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G.M. Bodienkova, E.V. Boklazhenko, M.O. Shchepina

RELATIONSHIP BETWEEN THE *RS6265* POLYMORPHISM OF THE *BDNF* GENE AND SERUM CONCENTRATIONS OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN PATIENTS WITH VIBRATION DISEASE

Vibration syndrome is an occupational disease characterized by polymorphic clinical symptoms and involving disorders of the nervous, vascular, immune, and musculoskeletal systems of the upper and lower extremities. The versatility of brain-derived neurotrophic factor (BDNF) is emphasized by its contribution to a range of adaptive neuronal responses encompassing long-term potentiation and depression, some forms of short-term synaptic plasticity, and homeostatic regulation of intrinsic neuronal excitability. Many stressful and harmful working conditions are known to be associated with decreased BDNF expression in the CNS. In recent decades, a number of studies have emphasized the contribution of the *rs6265 BDNF* gene polymorphism to impaired post-transcriptional processing and secretion of BDNF. At the same time, there is no information in the literature about the effect of the *rs6265 BDNF* gene single nucleotide polymorphism on neurotrophin serum concentration in subjects with VS.

The aim of the study is to determine the effect of the *rs6265 BDNF* gene polymorphism on the serum level of brain-derived neurotrophic factor in patients with VS.

Material and methods. BDNF serum concentrations were determined by solid-phase enzyme-linked immunoassay. DNA was extracted from the whole blood. The *rs6265* polymorphic locus of the *BDNF* gene was typed by real-time polymerase chain reaction.

Results. The highest level of neurotrophic factor in the group of patients with VS was registered in persons with G/G genotype, the lowest protein content was found in carriers of G/A and A/A genotypes of the *rs6265 BDNF* gene polymorphism. During the analysis of interrelations between the polymorphic variant of the *BDNF* gene and the content of neurotrophin in the blood serum of patients with VS, it was found that carriage of the A allele is associated with lower protein concentrations and 4.79 times reduces the risk of its hyperproduction, having a protective effect (dominant model). In addition, each copy of the rare allele reduces the risk of increased neurotrophin concentrations (log-additive model).

Conclusion. As a result of the study, it was found that there is some association of the *rs6265 BDNF* gene polymorphism with the BDNF serum level in patients with VS.

Limitations of this study include the number of the persons who were examined in all groups, especially in the comparison group.

Keywords: vibration syndrome, brain-derived neurotrophic factor, single nucleotide polymorphism *rs6265*, *BDNF* gene.

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Introduction. Vibration syndrome (VS) has been one of the leading positions among occupational diseases. The clinical picture of VS is characterized by polymorphic clinical symptoms and includes disorders of nervous, vascular, immune systems and musculoskeletal apparatus of upper and lower extremities. In this regard, the urgent task is to improve methods of early diagnosis of the disease.

Brain-derived neurotrophic factor (BDNF) is among the universal key proteins of the nervous system that is involved in many vital processes of neuronal adaptation and regulation of intrinsic excitability. The universality of BDNF is emphasized by its contribution to a number of adaptive responses of neurons, including long-term potentiation and depression, some forms of short-term synaptic plasticity, and regulation of intrinsic neuronal excitability. Many stressful and harmful conditions are known to be associated with decreased BDNF expression in the CNS and increased free radicals [16]. It should be noted that we have previously shown that in patients with VS the BDNF content varied depending on the stage of the disease. The increase of the neurotrophin concentration is parallel to the worsening of the severity of the pathological process that indicates the progression of the disease [1].

Recent decades studies have emphasized the contribution of the *rs6265 BDNF* gene polymorphism to impaired posttranscriptional processing and secretion of BDNF [8, 12, 14]. This mutation results in the substitution of valine (Val) for methionine (Met) in the 66th codon of the pro-domain encoding region. The mutation is thought to disrupt the function and distribution of the protein by interrupting its folding, dimerization, and intracellular transport, as well as interfering with activity-dependent release of BDNF [10]. The interaction between BDNF and sortilin is impaired, which subsequently leads to a deficiency of the mature form of the protein in carriers of the A allele of the *rs6265 BDNF* gene polymorphism. Also, this allele can affect intercellular transport and secretion of neurotrophin, forming homo- and heterodimers that are less efficiently sorted and secreted from

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neurons [3]. As a consequence, carriage of the minor allele is associated with reduced synaptic plasticity, impaired memory and learning ability, and increased susceptibility to neurodegenerative and psychiatric diseases [13].

At the same time, there is no information in the literature about the effect of the *rs6265* single nucleotide polymorphism of the *BDNF* gene on the serum concentration of the neurotrophin in individuals with VS. The present study is relevant due to the fact that the mechanisms of genetic regulation of BDNF production have not been sufficiently investigated. All this will further provide an opportunity to identify individuals at increased risk of developing disorders in the nervous system in workers with VS.

The aim of the study is to determine the effect of the *rs6265 BDNF* gene polymorphism on the serum level of brain-derived neurotrophic factor in patients with VS.

Material and methods. The study included 100 men with VS (mean age 51.56±0.67 years, mean work experience in conditions of vibration exposure 25.11±0.74 years) who were examined in the clinic of the Institute in 2023. The diagnosis of occupational disease was established by occupational pathologists in accordance with the International Classification of Diseases 10th revision. The occupations of persons with VS are represented by assemblers, assembly fitters, tunnel sinkers, heavy truck drivers, crane drivers, tractor drivers, excavator and bulldozer operators. The criteria to include the participants into the study were the presence of the diagnosis of VS established during the work, absence of comorbid pathology, and the exclusion criteria were concomitant acute and chronic diseases. The comparison group consisted of 40 conditionally healthy men who were 53,15±1,87 years old (according to the data of complex examination), and who were not in contact with harmful production factors. All the persons taking part in the study were Russians living in the Irkutsk Region. Data on ethnicity were obtained with the help of a specially designed questionnaire.

Venous fasting blood was drawn in the morning into Improvacuter vacuum tubes with coagulation activator SiO_2 (Improve Medical, China) for immunoenzymatic analysis and Improvacuter tubes with anticoagulant K_3-EDTA (Improve Medical, China) for molecular genetic studies. Then it was centrifuged at 1500 rpm for 15 min on a CM-6MT centrifuge (ELMI, Latvia). The serum was selected for enzyme immunoassay and the cell fraction was selected for molecular genetic studies, then they were aliquoted and the samples were stored at –70°C.

Serum concentrations of BDNF were determined by solid-phase enzyme-linked immunoassay ("sandwich" variant) by using the test system "Human Free BDNF Quantikine ELISA Kit" (Cat. No. DBD00, R&D Systems, USA) according to the manufacturer's instructions. The results were read with the help of an ELx800 automatic photometer (Bio-Tek Instruments, USA).

DNA extraction was performed by using DNA-Extran-1 reagent kit (Cat. No. EX-509-100, Syntol, Russia) according to the manufacturer's methodology. The *rs6265* polymorphic locus of the *BDNF* gene was typed by polymerase chain reaction with real-time detection of results on a CFX96 amplifier (Bio-Rad, USA). The test system (Cat. No. NP-623-100) produced by Syntol (Russia) was used to determine the genotypes. The parameters of the thermal cycle were performed in accordance with the reagent kit instructions.

Statistical processing of the results was performed by using Statistica 10.0 program (StatSoft, USA). The following parameters were used to describe quantitative features: arithmetic mean (M) and a standard error of mean (m) for age and work experience under vibration exposure conditions, the median (Me) and interquartile range (Q25–Q75) for BDNF concentration (pg/mL). The Mann-Whitney U-criterion was used to evaluate differences in BDNF content between groups. While analyzing the frequency distribution of the *rs6265 BDNF* gene polymorphism, the observed frequency of genotypes was checked against the expected one by using an online calculator (https://wpcalc.com/en/equilibrium-hardy-weinberg/). The significance of differences in the distribution of genotype and allele frequencies was assessed by using Fisher's exact test (df=1). The search of the *rs6265 BDNF* gene polymorphism associations with the disease, and serum concentration of neurotrophin was done in the online program SNPstats (https://www.snpstats.net/). The odds ratio (OR) with 95% confidence interval (95% CI) was calculated by using the logistic regression method according to 5 probable inheritance models (codominant, dominant, recessive, overdominant, and log-additive). The found differences between the groups were considered statistically significant at $p<0.05$.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki (as amended in 2000), the "Rules of Good Clinical Practice in the Russian Federation" approved by the order of the Ministry of Health of the Russian Federation №200n from 01.04.2016, and the voluntary informed consent signed by the participants. The work was approved by the local ethical committee of the Institute (Minutes No. 5 of 21.03.2023).

Results and discussion. While estimating genotype and allele frequencies of the *rs6265 BDNF* gene polymorphism in the group of patients with VS, the following values were obtained: G/G (abs. 60) – 60.0%; G/A (abs. 37) – 37.0%; A/A (abs. 3) – 3.0%; G (abs. 157) – 78.5%; A (abs. 43) – 21.5%. The frequencies of genotypes and alleles were also determined in the comparison group: G/G (abs. 24) –60.0%; G/A (abs. 15) – 37.5%; A/A (abs. 1) – 2.5%; G (abs. 63) – 78.7%; A (abs. 17) – 21.3%. The analysis of genotype frequency distribution of *rs6265 BDNF* gene polymorphism in the group of patients with VS and the comparison group for their compliance with the Hardy-Weinberg equilibrium showed that the observed genotype frequencies of the studied polymorphic variant of the gene corresponded to the expected frequencies ($\chi^2=0.65$, $p=0.420$; $\chi^2=0.50$, $p=0.480$, respectively). It is necessary to note that the allele frequencies of the studied polymorphic locus of the *BDNF* gene in individuals with VS and the com-

Table 1

Serum concentration depending on the genotypes. Me (Q25–Q75)

BDNF concentration (pg/mL)			Significance level p
Grops	G/G	G/A+A/A	
Patients with VS	395.49 (304.18-977.70)	309.25 (252.09-446.87)	**0.008**
Comparison group	354.14 (347.23-381.31)	234.99 (197.84-267.72)	**0.032**

Note: p is the level of significance for Mann-Whitney U-criterion. differences are significant at $p<0.05$.

parison group are comparable with the data obtained for European and Russian populations [2, 11]. No statistically significant differences were found between the compared groups with respect to genotype (G/G p=0.573; G/A p=0.552; A/A p=0.678) and allele frequencies (G, A p=0.551). When calculating the odds ratio, no association of genotypes with the disease was found.

While comparing BDNF serum concentrations between the groups, statistically significant differences were established: a higher neurotrophin level was registered in individuals with VS (366.20 (281.89–617.63) pg/mL) relatively to the protein concentration values in the comparison group (272.89 (234.99–353.14) pg/mL; p=0.048).

When dividing individuals of both groups into subgroups depending on the genotypes of the *rs6265 BDNF* gene polymorphism, BDNF level significantly differed. Individuals with G/A and A/A genotypes were combined into one subgroup to reveal the role of the minor allele. The highest level of neurotrophic factor was registered in individuals with G/G genotype (395.49 (304.18–977.70) pg/mL) in the group of patients with VS, the lowest protein content was found in carriers of G/A and A/A genotypes (309.25 (252.09–446.87) pg/mL). The concentration of neurotrophin in the comparison group also differed depending on genotypes: in individuals with G/G genotype it amounted to 354.14 (347.23–381.31) pg/mL, in individuals with G/A and A/A genotypes had 234.99 (197.84–267.72) pg/mL, respectively (Table 1).

Individuals with VS were divided into two groups basing on the BDNF median concentration obtained in the comparison group: patients with concentration <273.0 and ≥273.0 pg/mL (Table 2). According to the results of the regression analysis, the dominant and log-additive inheritance models are the most correct for the *rs6265 BDNF* gene polymorphism, as they are characterized by the lowest value of the Akaike information criterion (AIC=113.4). The analysis of interrelations between the polymorphic variant of the *BDNF* gene and neurotrophin content in serum of patients with VS showed that carriage of the A-allele is associated with lower protein concentrations and it decreases the risk of its hyperproduction by 4.79 times, having a protective effect (OR=4.79; 95% CI 1.87–12.24; p=0.0007; dominant model). In addition, each copy of the rare allele reduced the risk of increased neurotrophin concentration (OR=4.0; 95% CI 1.72–9.33; p=0.0007; log-additive model).

The results of our study are in agreement with the literature results [4, 5], whose authors made the following conclusions: homozygous or heterozygous individuals with allele A have lower plasma BDNF levels compared to carriers of the normal G/G genotype, which can be explained by impaired intracellular transport of pro-BDNF, which leads to decreased production of mature BDNF in cells of allele A carriers. Also Gallinat et al. reported that in healthy individuals, the rare A allele is associated with lower serum BDNF concentration [6]. The G allele that is associated with increased BDNF secretion may be a risk allele for the development of some neuropsychiatric diseases [15]. In patients with Parkinson's disease, the maximum protein level was found in carriers of G/G and G/A genotypes of the *rs6265* polymorphic locus of the *BDNF* gene, while the minimum concentration was observed in carriers of the A/A genotype [9]. Carrying the A allele increases the risk of BDNF level reduction almost 10 times in patients with thyroid pathology, while the presence of the G allele, on the contrary, prevents its concentration reduction; however, a decreased level of the neurotrophin in serum of individuals with hypothyroidism of different genesis was observed in carriers of all three genotypes compared to the control group [7].

At the same time, there are opposite opinions in the literature: Terracciano et al., Li et al. found that the *rs6265* polymorphic variant of the *BDNF* gene does not directly affect the level of BDNF in serum [8; 14]. BDNF expression can also be reduced as a result of posttranscriptional processes or epigenetic mechanisms, such as DNA methylation or histone acetylation [10].

Conclusion. As a result of this study, it was found that there is some associa-

Table 2

Associations between genotypes of the rs6265 BDNF gene polymorphism and BDNF serum level in patients with VS

Genetic model	Genotype	Patients with BDNF concentration		OR (95%CI)	p	AIC
		<273.0 pg/mL, abs. (%)	≥273.0 pg/mL, abs. (%)			
Codominant	G/G	10 (34.5)	50 (70.4)	1.00	**0.0027**	115.1
	G/A	17 (58.6)	20 (28.2)	**4.53 (1.74–11.79)**		
	A/A	2 (6.9)	1 (1.4)	9.25 (0.76–113.24)		
Dominant	G/G	10 (34.5)	50 (70.4)	1.00	**0.0007**	113.4
	G/A–A/A	19 (65.5)	21 (29.6)	**4.79 (1.87–12.24)**		
Recessive	G/G–G/A	27 (93.1)	70 (98.6)	1.00	0.2000	123.2
	A/A	2 (6.9)	1 (1.4)	4.76 (0.41–55.16)		
Overdominant	G/G–A/A	12 (41.4)	51 (71.8)	1.00	**0.0033**	116.3
	G/A	17 (58.6)	20 (28.2)	**3.87 (1.54–9.74)**		
Log-additive	G/G–G/A–A/A	–	–	**4.00 (1.72–9.33)**	**0.0007**	113.4

Notes. Table 2 shows odds ratio and 95% confidence interval OR (95% CI); p – value of the level of statistically significant difference; AIC – Akaike information criterion value.

tion of the *rs6265 BDNF* gene polymorphism with BDNF serum level in patients with VS. Individuals with normal G/G genotype had a higher level of neurotrophin, while carriers of G/A and A/A genotypes had a lower BDNF content. The results of regression analysis indicate that carriage of the G allele prevents a decrease in BDNF concentration, while the presence of the A allele reduces the risk of neurotrophin hyperproduction. The risk of protein concentration reduction was increased by 4.79 times in carriers of the A-allele. The obtained results expand our ideas about genetic features that may predetermine the sensitivity of patients with VS to the production of brain-derived neurotrophic factor.

The results we obtained are preliminary and require further study due to the low frequency of certain genotypes and insufficient number of subjects in the groups.

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INTRAPARTUM FETAL HYPOXIA: SEARCH FOR MATERNAL PREDICTORS OF PATHOLOGY

A retrospective analysis of the medical records of 203 women who gave birth at full term in a second-level obstetric hospital was carried out in order to study the characteristics of the medical history, the course of gestation and the outcome of childbirth with intrapartum fetal hypoxia (IHF, distress). **Materials and methods:** postpartum women were divided into 2 groups: group 1 (control) - 36 people (17.73%) without intrapartum fetal hypoxia (IHF) (average gestational age at the time of birth - 39.4 weeks), group 2 (main) - 167 patients (82.27%) with IHF (average period - 40.4 weeks). **Results and Conclusion.** Postpartum women of group 2 (with IGP) were younger than women of group 1 (28,16±5,52 years and 30.25±4.94 years, respectively, p = 0,01). In the obstetric and gynecological history of patients in group 2, primiparous women were more often noted (61%) with a large number of previous pregnancies (2.59). Gynecological pathology in the anamnesis was 2.4 times more likely to be detected in patients of group 2 with a significant predominance in the structure of inflammatory diseases of the cervix, uterine fibroids, endometrial polyp, and polycystic ovary syndrome. In the main group, pregnant women were significantly more likely to be diagnosed with respiratory diseases (21.4%), somatization disorder (F45 - neurocirculatory dystonia) (20.96%), obesity and other hyperalimentation (18.56%), subclinical hypothyroidism (13.77%). Myopia from childhood is 2.24 times more likely to be established as a concomitant diagnosis in group 2 postpartum women. In the main group, there were significantly more nicotine-dependent pregnant women (7.78%). Our data are consistent with domestic and foreign studies and indicate that further systematic study of maternal prognostic factors of fetal distress during childbirth is necessary to develop preventive pregravid programs.

Key words: full term pregnancy, fetal hypoxia, fetal distress, preconception risk factors

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Introduction. Statistics from the Russian Federation show that the country is in a demographic crisis [1]. The medical side of this issue poses an urgent task for the medical community: a personalized approach to the management of each pregnancy, careful and safe delivery. The most difficult problem of modern obstetrics is intrauterine fetal hypoxia (fetal distress), which is the cause of up to 40% of stillbirths and neonatal mortality [2, 5, 8].

The development of acute intrauterine hypoxia is caused by impaired blood supply to the fetus; the most common cause of the development of this condition during pregnancy is premature placental abruption or thrombosis of the placental vessels; during childbirth - pathology of uterine contractility [3, 7]. The result of perinatal hypoxia is damage to various organ systems, primarily the central nervous system, which is not only a medical, but also a social problem [1, 9, 13]. Many questions regarding the causes of fetal distress are controversial. According to a number of authors, the effectiveness of calculating antenatal risk factors for fetal distress is low, and anamnesis data and past infectious diseases are not modifiable and have little specificity for the development of intrapartum fetal hypoxia (IHF) [4, 9]. However, the number of cases included in the studies is small; at the same time, the authors point to a significant incidence of obesity and early reproductive age in mothers of newborns with intrapartum fetal hypoxia (IFH) [4, 10]. Other researchers have identified a high frequency of complicated somatic and obstetric-gynecological history in IGP [3, 5, 6, 14]. Additional research is required to explain these discrepancies.

To date, there are no published systematic data on low- and average-risk pregnant women for perinatal and maternal mortality that analyze pre-conceptional risk factors for intrapartum fetal hypoxia (IHF) at full term.

The purpose of our study was to assess the causes of intrapartum fetal hypoxia (IHF) during full-term pregnancy in a second-level obstetric hospital, if possible, to provide medical care while analyzing preconception risk factors.

Materials and research methods. A retrospective analysis of medical documentation (birth history, individual card of the pregnant and postpartum women) was carried out for 203 women who gave birth in an obstetric hospital of the second group (level) where medical care was available (GBUZ TO “Materni-

Table 1

Characteristics of the obstetric history of postpartum women, n (%)

Study criterion	1 group, control (n=36)	2 group (n=167)	P
Primigravidae	1 (2.78%)	91 (54.49%)*	p<0.001
Multipregnant women / - number of pregnancies in history (M±SD)	35 (97.22%) / 1.97±0.92	76 (45.51%)* / 2.59±1.82*	p<0.001
- 1 / 2 pregnancy	14 (38.89%) / 9 (25.00%)	30 (17.96%)* / 16 (9.58%)*	p=0.01 / p=0.03
- 3 / 4 pregnancy	11 (30.56%) / 1 (2.78%)	9 (5.39%)* / 8 (4.79%)	p=0.002 / p=0.27
- 5 / 6 pregnancy	0 (0%) / 0 (0%)	6 (3.59%)* / 4 (2.40%)*	p=0.007 / p=0.02
- 7 / 8 pregnancy	0 (0%) / 0 (0%)	2 (4.19%) / 1 (0.60%)	p=0.08 / p=1.16
Primipara	5 (13.89%)	102 (61.08%)*	p<0.001
Multiparous	31 (86.11%)	65 (38.92%)*	p<0.001
- number of births in history (M±SD)	1.69±0.78	1.75±1.03	
- 1 / 2 st births	13 (36.11%) / 13 (36.11%)	36 (21.56%)* / 16 (9.58%)*	p=0.04 / p=0.002
- 3 / 4 or more births	5 (13.89%) / 0 (0%)	7 (4.19%)* / 6 (3.79%)	p=0.04 / p=0.06
Complicated obstetric history:			
Medical abortion / Number of abortions in history (M±SD)	6 (16.67%) / 1.17±0.41	33 (19.76%) / 1.82±1.29	p=0.33
Spontaneous miscarriage	3 (8.34%)	14 (8.38%)	p=0.49
Regressive pregnancy	2 (5.56%)	9 (5.38%)	p=0.37
Ectopic pregnancy	2 (5.56%)	4 (2.39%)	p=0.18

Note: * – p < 0.05 when comparing the 1st and 2nd groups.

ty Hospital No. 3", Tyumen). Depending on the presence of fetal hypoxia during childbirth (FH), postpartum women were divided into 2 groups: group 1 (control) - 36 women (17.73%) without intrauterine fetal hypoxia during childbirth (average gestational age at the time of birth - 39.4 weeks), group 2 (main) - 167 pregnant women (82.27%) with a diagnosis: Labor and delivery complicated by fetal stress [distress] (O68 (Labor and delivery complicated by abnormality of fetal acid-base balance) – code: International Statistical Classification of Diseases and Related Health Problems - ICD-10) (average period - 40.4 weeks). Participants in group 1 were selected by using systematic random sampling method.

Type of study: continuous cross-section of all postpartum women diagnosed with: O68 Labor and delivery complicated by abnormality of fetal acid-base balance for 2021. (total births - 3482 cases, the frequency of this pathology during this period was 4.8%). There were no perinatal deaths in either group during the study period. Criteria for inclusion in the main group: availability of medical documentation on clinical observation for pregnancy in the antenatal clinic (exchange card of a pregnant woman, parturient woman and postpartum woman (form N 113/u-20)) and birth history (medical record of a pregnant woman, parturient woman and postpartum woman receiving medical care in a hospital setting (form N 096/1y-20)). Criteria for non-inclusion in both groups: multiple pregnancy.

Statistical processing of the research results was carried out using software packages: Microsoft Excel 2010, SPSS 25.0. Statistical analysis included univariate analysis with Student's t test and Fisher's exact test, and p < 0.05 was considered significant.

Results and Discussion. When analyzing the age of postpartum women, a significantly younger age was revealed in patients of group 2 (with IHF) 28,16±5,52 years. Women whose births occurred without IHF (control groups) were on average 2 years older (30.25±4.94 years, p = 0,01) and had a history of childbirth 2.2 times more often. When studying the social characteristics of postpartum women of both groups, no static differences were revealed: a greater number of women were employed (group 1 - 66.67%, group 2 - 67.07%) and were urban residents (group 1 - 69.44%, group 2 - 77.84%).

Table 2

Characteristics of gynecological pathology experienced by postpartum women, n (%)

Gynecological pathology	1 group, control (n=36)	2 group (n=167)	P
Vaginitis / Inflammatory diseases of the cervix	2 (5.56%) / 5 (13.89%)	22 (13.17%) / 46 (27.54%)*	p=0.05 / p=0.02
Endometrial polyp / Uterine fibroids	0 (0%) / 0 (0%)	4 (2.40%)* / 15 (8.98%)*	p=0.02 / p<0.001
Polycystic ovary syndrome	0 (0%)	7 (4.19%)*	p<0.001

Table 3

Characteristics of somatic pathology of postpartum women, n (%)

Extragenital pathology	1 group, (n=36)	2 group (n=167)	P
Diseases of the respiratory system	1 (2.78%)	36 (21.4%)*	p<0.001
Somatization disorder (neurocirculatory dystonia)	2 (5.56%)	35 (20.96%)*	p=0.001
Obesity and other hyperalimentation	0 (0%)	31 (18.56%)*	p<0.001
Subclinical hypothyroidism	0 (0%)	23 (13.77%)*	p<0.001
Myopia	5 (13.89%)	52 (31.14%)*	p=0.007
Pathology of the kidneys, ureters, bladder	0 (0%)	20 (11.98%)*	p<0.001
Diseases of the musculoskeletal system	0 (0%)	9 (5.39%)*	p=0.001
Atrioventricular block, first degree (tachycardia, arrhythmias)	0 (0%)	5 (2.99%)*	p=0.01
Essential (primary) hypertension	0 (0%)	3 (1.80%)*	p=0.04
Chronic viral diseases (HIV / hepatitis)	0 (0%)	7 (4.19%)*	p=0.004
Nicotine addicts / Drug addicts	0 (0%) / 0 (0%)	13 (7.78%)* / 1 (0.60%)	p=0.0001 / p=0.16

The number of primigravidas in group 2 (patients with intrauterine fetal hypoxia) is 19.6 times greater than in postpartum women without IHF (p < 0,001). Also in group 2 there was a 31.47% greater number of pregnancies in the anamnesis compared to group 1 (puerperas without IHF) (p < 0,001). The proportion of primiparous women in group 2 was significantly higher by 4.7 times compared to group 1 (61.08% and 13.89%, respectively). The proportion of primiparous women in group 2 was significantly higher by 4.7 times (table 1).

Intrapartum hypoxia during full-term pregnancy more often occurred in younger parturients and, in most cases, primigravidas, which has been repeatedly noted in various studies, including analyzes of the consequences of severe fetal asphyxia and long-term neurological disorders in children [4, 10, 14].

Gynecological pathology (table 2) in the anamnesis was 2.4 times more likely to be detected in patients of group 2 with a significant predominance in the structure of inflammatory diseases of the cervix, uterine fibroids, endometrial polyp, and polycystic ovary syndrome. Other gynecological diseases did not differ in frequency. Infertility was noted in 3 patients of the main group (p = 0,04); assisted reproductive technologies were not used in patients of both groups.

An important fact, from our point of view, is the large number of primiparous women with IHF (group 2), which is 4.7 times higher than in group 1, with simultaneously high rates reflecting a burdened obstetric and gynecological history: multipregnant women with no birth in history (61.08%), having had medical abortions, inflammatory diseases of the cervix, uterine fibroids, endometrial polyp, polycystic syndrome ovaries. Many authors who previously searched for risk factors for fetal distress and hypoxic-ischemic encephalopathy of newborns associated the absence of a history of childbirth with an increased incidence of placental disorders that develop against the background of pre-existing gynecological pathology and a history of induced abortions [4, 6, 10, 12, 14].

When analyzing chronic extragenital pathology (table 3), it was revealed that in patients of group 2, respiratory diseases (21.4%), somatization disorder (F45 - neurocirculatory dystonia) (20.96%), obesity and overweight were diagnosed significantly more often than in the control group body (18.56%), subclinical hypothyroidism (13.77%). These extragenital diseases differ from the average population and can be caused by women living in a sharply continental climate and a moderate iodine deficiency zone (southern Western Siberia) [11]. The influence of nicotine addiction on the development of respiratory diseases is undeniable (7.7% of women in group 2 noted a history of smoking), therefore, this pathology is diagnosed 8.6 times more often in postpartum women with IHF.

Diseases such as allergies, anemia, varicose veins of the lower extremities, pathology of the liver, stomach and intestines did not have significant differences in the studied groups.

Among the patients in group 2, the history significantly indicated more often chronic respiratory diseases (by 8.6 times), myopia (by 2.24 times), diseases of the musculoskeletal system (by 5.39%), which is not described in the literature data. Predictable risk factors were identified: nicotine addiction in women of group 2 (7.78%, p = 0,0001) and chronic viral diseases (HIV/hepatitis) (4.19%, p = 0,004) [3, 4, 5, 9]. In a study that studied the group of fetal asphyxia during childbirth at gestational ages of 27–39 weeks (Taranushenko T.E. et al. (Krasnoyarsk)), the proportion of women who smoked was even higher than 18% [5].

Thus, a detailed maternal history is important and may provide a pathway to preventative strategies for future fetal distress.

Conclusion. Analyzing the above, we came to the following conclusions. In women whose childbirth was complicated by intranatal fetal hypoxia:

1. in the obstetric and gynecological history, primiparous women (61%) with a large number of previous pregnancies (2.59) were noted with greater frequency;
2. gynecological pathology in the anamnesis was 2.4 times more likely to be detected in patients of group 2 with a significant predominance in the structure of inflammatory diseases of the cervix, uterine fibroids, endometrial polyp, and polycystic ovary syndrome;
3. extragenital pathology is most often represented by respiratory diseases (21.4%), somatization disorder (F45 - neurocirculatory dystonia) (20.96%), obesity and other hyperalimentation (18.56%), subclinical hypothyroidism (13.77%). Myopia from childhood is 2.24 times more likely to be established as a concomitant diagnosis in group 2 of postpartum women;
4. in the main group, there were significantly more nicotine-dependent pregnant women (7.78%).

Potentially modifiable preconception risk factors include medical abortion, chronic inflammatory diseases of the genitals, diseases of the lungs and airways, obesity and overweight, thyroid disease, and maternal smoking. Our data are consistent with domestic and foreign

studies and indicate that further systematic study of pre-conceptual maternal prognostic factors of fetal distress in labor is required in order to develop preventive pregravidarial programs.

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OPTIMIZING EARLY DETECTION OF UTERINE CANCER IN WOMEN WITH RISK FACTORS

The article describes the stages of early detection of uterine body cancer in patients with morbid obesity. It has been proven that genetic testing for oncogenic mutations of endocervical canal scrapings with a negative cytological conclusion regarding cervical cancer is effective for subsequent screening of uterine body cancer. In morbid obesity, the diagnostic sensitivity of mutation screening for uterine body cancer increases when examining endocervical canal scrapings. When oncogenic mutations are detected in samples from the endocervical canal, the next step is recommended to conduct a cytological examination of endometrial biopsies with sampling using brush technology.

Keywords: uterine body cancer, morbid obesity, oncogenic mutations, liquid cytology, endometrial biopsy.

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Introduction. Among oncogynecological diseases, uterine cancer is the most common in countries with a high level of economic development and the second most common worldwide [1]. At the same time, there is a steady trend of constant growth in the prevalence of uterine cancer in the world, despite the improvement of the preventive and diagnostic system for timely detection of endometrial tumor pathology [4].

Obesity is a recognized risk factor for uterine cancer. The correlation between obesity and cancer of the uterine body is the closest in comparison with malignant diseases of other localization [2]. Based on a meta-analysis of thirty randomized prospective studies, each increase in body mass index (BMI) by 5 kg/m^2 is associated with a 54% increased risk of developing uterine cancer with a 95% confidence interval of 47 to 61% [7]. Given that

the prevalence of obesity among women is growing every year everywhere in all countries, the development of effective tactics for early detection of uterine cancer in women with increased body weight is an urgent task. In morbid obesity with a BMI exceeding more than 40 kg/m2, women, due to psychological problems, are poorly motivated to regularly visit gynecologists, which affects the detection of more advanced forms of uterine body cancer in the initial diagnosis of cancer [8]. In addition, morbid obesity increases the risk of death of patients with uterine cancer by 6 times [3]. Therefore, the development of methods for early diagnosis of uterine cancer in women with morbid obesity is aimed at solving an important socio-medical problem.

Scraping of the cervical epithelium and endocervical canal in liquid cytology is traditionally used to diagnose cervical cancer. Meanwhile, in the last decade, the biological material obtained during the Pap test, in case of a negative result for cervical cancer, has been used to diagnose cancer of the uterine body or ovaries [9]. At the same time, the DNA concentration of circulating tumor cells, oncogenic mutations are determined in endocervical scrapings, and a mass spectrometric analysis of the protein profile is performed [6,9]. The basis for an additional search was the results of cytological, histological and molecular genetic studies confirming that in endometrial or ovarian cancer, circulating cancer cells from tumors of other localization are concentrated in the cervical canal of the uterus [5].

Since the Pap test during gynecological examinations is performed much more often than an aspiration biopsy of the endometrium, and in liquid cytology, stabilizing solutions do not destroy cells and preserve them, the standard technique may have a much wider potential than the traditional format of its use. Expanding the diagnostic tasks when using a single biologicalcsubstrate is especially important for the contingent of patients who are provoked in relation to uterine cancer by a risk factor in the form of morbid obesity and who experience psychological obstacles to frequent and thorough examinations by gynecologists.

In connection with the above, **the aim of the work** was to develop a step-by-step complex diagnostic algorithm for early detection of uterine cancer in patients with morbid obesity.

Materials and methods. The work includes the results of the examination of 378 patients of the main group with verified uterine body cancer, who were divided into two subgroups depending on the presence of morbid obesity. The 1st subgroup included 103 women with morbid obesity (BMI over 40 kg/m^2), and the 2nd subgroup included 275 patients without obesity (BMI from 18,5 to 30 kg/m^2). Cancer of the uterine body was verified by the results of targeted curettage of the uterine walls, followed by histological examination of samples. The control group included 226 women of similar age, but without cancer pathology, based on the results of preventive examinations during a dispensary examination. The 1st control subgroup consisted of 47 women with morbid obesity and the 2nd control subgroup - 179 patients without obesity.

The criteria for inclusion of patients in the main group were as follows: newly diagnosed uterine cancer, endometrial histological type, collection of diagnostic material from the endocervical canal and endometrial biopsy before starting specific antitumor treatment, BMI in the range of 18,5-30 kg/m^2 and more than 40 kg/m^2, written informed consent to inclusion in the study.

Exclusion criteria: BMI in the range of 30-40 kg /m^2, cervical cancer, infection with human papillomavirus based on the results of a study of scrapings from the cervix, tumors of a different localization in relation to the uterine body, decompensation of somatic diseases.

During the study, the ethical principles of the Helsinki Declaration of the World Medical Association were observed, and the approval of the Local Ethical Committee of the Federal State Budgetary Institution " National Medical Research Center of Oncology " of the Ministry of Health of the Russian Federation was obtained.

The age of women in the 1st main group was 59,7±0,85 years (range from 32 to 79 years), the 2nd main group – 62,3±0,49 years (range from 29 to 84 years), the 1st control group – 58,6±0,66 years (range from 33 to 76 years) and the 2nd control group – 59,4±1,12 years (range 37-78 years). There were no intergroup differences in age between the groups.

BMI in the 1st main group corresponded to 41,8±1,71 kg/m^2, the 2nd main group – 24,7±1,92 kg/m^2, the 1st control group – 40,9±1,67 kg/m^2, and in the 2nd control group – 22,3±1,38 kg/m^2. In all patients of the 1st main and 1st control groups, the presence of insulin resistance syndrome was noted.

In women of the main and control groups, a sample from the endocervical canal was obtained using a brush brush from the Cytoscreen kit (Hospitex, Italy). The resulting material was stabilized with a special solution "Cyto-screen solution", the cells were washed off in a shakere, and the density of the cell suspension was determined by nephelometry. Cytological examination of the stained smear on glass was performed using light microscopy. Human papillomavirus infection was determined by immunocytochemical method.

For endometrial sampling Tao, a Tao-Brush IUMC brush (Cook Medical Inc., USA) was used. Previously, the length of the uterine cavity was determined using a uterine probe. The limiter was set to the intended insertion depth and a brush in a cover was carefully inserted through the cervix to the level of the uterine floor. Then the outer shell was pulled back, and the brush was rotated five times 360° clockwise and counterclockwise. Next, the outer cover was returned back to the brush and the selection device was removed from the uterine cavity. A sample of endometrial tissue was placed in a stabilizing solution.

DNA was isolated from a buffer with tissue samples of the endocervical canal and endometrium, following the manufacturer's recommendations, using the QIAamp DNA micro DNA purification kit (Qiagen). The quantity and quality of the isolated DNA were determined, the samples were stored at a temperature of -80°C until the implementation of the laboratory stage. Further, the presence of oncogenic mutations in the genes *AKT1, APC, BRAF, CDKN2A, CTNNB1, EGFR, FBXW7, FGFR2, KRAS, MAPK1, NRAS, PIK3CA, PIK3R1, POLE, PPP2R1A, PTEN, RNF43*, and *TP53* biological samples of the endocervix and endometrium was evaluated by three multiplex PCRs using the SSafe-Sequencing System (SSE-SeqS) technology. At the same time, segments with a length from 110 to 142 bp of the studied genes was amplified using 139 pairs of primers. This approach made it possible to identify non-overlapping amplicons and detect low-frequency mutations by assigning a unique identifier to each matrix molecule. PCR fragments with the same unique identifier were considered mutant only if 95% or more contained the same mutation.

The mutation screening test was considered positive in the study of samples obtained with the PAP test or the TAO test if at least one of the genes was found to have a mutation. In addition, the results of cytological studies of biological samples obtained using brush-brush PAP and Tao were taken into account.

Statistical analysis of the study results was performed using STATISTICA 12.0 software (StatSoft, USA).

Results and discussion. In all patients of the main and control groups, cytological examination of scrapings from the cervix and endocervical canal tested negative for detection of cervical cancer and infection with human papillomavirus. When determining oncogenic mutations in cells concentrated in the endocervical canal, positive results in the 1st main subgroup were detected in 82,5% (n=85), and in the 2nd main subgroup in 72,4% (n=199) (Table 1). Consequently, in patients with verified uterine cancer, the detection of mutations of genes that contribute to the development of tumors in biological samples from the endocervical canal was high. The number of patients suffering from uterine cancer with a positive Pap test result for oncogenic mutations was higher (p=0,042) compared to patients without morbid obesity. In the control groups of healthy women, the detection of oncogenic mutations in endocervical canal scrapings was rare regardless of the presence of morbid obesity (Table 1).

The results of cytological examination of endometrial biopsies revealed uterine body cancer in the 1st main subgroup in 83,5% (n=86), and in the 2nd main subgroup in 82,2% (n=86) (Table 2). No intergroup differences were found based on the results of cytological examination of endometrial biopsies depending on the presence of morbid obesity (p=0,76). In the control group, cytological examination of endometrial biopsies showed no positive results, which indicated 100% specificity of the test (Table 2).

The results of the mutation screening test in the study of endometrial biopsies in the 1st main group were similar to the results of the cytological study. In the 2nd main subgroup, the results of the genetic study allowed us to obtain positive results regarding the detection of uterine cancer in an additional 10 women compared to the cytological conclusion (Table 3).

Table 1

Number of patients with positive and negative results of the test for mutational screening of uterine cancer in the study of endocervical canal scrapings in clinical groups

Group	PAP Test Mutation Screening	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	85	4
	Negative	18	43
	Total	103	47
2 Subgroup (no MO)	Positive	199	7
	Negative	76	172
	Total	275	179

Note: UC -uterine cancer, MO - morbid obesity

Table 2

Number of patients with positive and negative results of detection of uterine cancer in cytological studies and endometrial biopsies in clinical groups

Group	TAO Test	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	86	0
	Negative	17	47
	Total	103	47
2 subgroup (no MO)	Positive	226	0
	Negative	49	179
	Total	275	179

Table 3

Number of patients with positive and negative results of the mutation screening test in the study of endometrial biopsies in clinical groups

Group	TAO Test Mutation Screening	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	88	0
	Negative	15	47
	Total	103	47
2 subgroup (no MO)	Positive	236	0
	Negative	39	179
	Total	275	179

Table 4

Informative value of mutational screening of uterine cancer in the study of endocervical canal scrapings and endometrial biopsies

Test Parameters	PAP test Mutation screening		TAO test Mutation screening	
	1 main subgroup (UC+MO)	2 main subgroup (UC)	1 main subgroup (UC+MO)	2 main subgroup (UC)
Diagnostic sensitivity, %	82,5	72,4	85,4	85,8
Diagnostic specificity, %	91,5	96,1	100,0	100,0
Diagnostic accuracy, %	85,3	81,7	90,0	91,4
AUC	0,870	0,842	0,927	0,929
Positive predictive value, %	95,5	96,6	100,0	100,0
Negative predictive value, %	70,5	69,4	75,8	82,1

Note: UC – uterine cancer, MO - morbid obesity, AUC – area under the ROC curve

The informative value of the test for mutational screening of uterine cancer in the study of endocervical canal samples and endometrial biopsies is presented in Table 4.

Of course, diagnostic accuracy in detecting uterine cancer was higher when cytological and genetic studies of endometrial biopsies were performed simultaneously (90% in the 1st main subgroup and 91,4% in the 2nd main subgroup). However, it should be noted that the effectiveness of genetic testing for oncogenic mutations in endocervical canal samples in detecting uterine cancer was high (in the 1st main subgroup 85,3% and in the 2nd main subgroup 81,7%). This circumstance allows us to recommend conducting a genetic study of the substrate obtained during the Pap test to detect cancer of the uterine body. Additional mutational screening after liquid Pap cytology using cervical scrapings is particularly important in women who are compromised for risk factors, including morbide obesity. After detection of oncogenic mutations in the endocervical scraping, the next step is to conduct cytological examination of endometrial biopsies obtained using a brush-brush Tao. Additional genetic testing of endometrial biopsies after receiving a cytological conclusion does not increase diagnostic efficiency, so its implementation is not economically justified.

Conclusions

1. In morbid obesity, the diagnostic sensitivity of mutational screening for endometrial cancer using endocervical canal scrapings is higher than in non-obese patients (82,5% versus 72,4%, p=0,042), which should be taken into account when organizing a step-by-step examination of women.
2. In case of a negative cytological conclusion regarding cervical cancer in patients with morbid obesity, the next recommended step is screening for endometrial cancer using genetic testing of endocervical canal scrapings for oncogenic mutations.
3. In case of detection of oncogenic mutations in endocervical canal samples, a cytological examination of endometrial biopsies taken using brush technology is indicated as a further step in diagnosing endometrial cancer.
4. The developed step-by-step complex diagnostic algorithm is effective for the early detection of endometrial cancer in patients with morbid obesity.

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RELATIONSHIP OF THE TYPE AND POSITION OF MUTATION IN THE *FBN1* GENE WITH CLINICAL MANIFESTATIONS OF MARFAN SYNDROME IN CHILDREN

Marfan syndrome (OMIM # 154700) is an inherited connective tissue disease caused by mutations in the FBN1 gene, characterized by marked clinical variability, the causes of which are poorly understood.

The aim of this study was to determine the association of the type and localization of the *FBN1* gene mutation with the severity of clinical manifestations of Marfan syndrome in a Russian cohort of children.

Results: for the first time in a Russian cohort of children, the association between the type and localization of the *FBN1* gene mutation and the severity of clinical manifestations was demonstrated: LoF mutations lead to greater damage to the cardiovascular and skeletal systems; missense mutations lead to greater damage to the eyes. Mutations in exons 1-10 lead to the earliest onset of skeletal changes (foot (p=0.016) and chest (p=0.036) deformities), mutations in exons 11-20 - to the earliest appearance of lens ectopia (p=0.034), with less severe dolichostenomelia (p=0.041) and less frequent formation of aortic dilatation (p=0.035). Mutations in exons 21-35 are accompanied by the earliest manifestation of spinal deformity (p=0.02). Mutations in exons 51-66 less often lead to lens ectopia (p=0.001).

Keywords: *FBN1* gene, missense mutations, LoF (loss of function) mutations, TGFβ (transforming growth factor β), children, Marfan syndrome

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Introduction. Marfan syndrome (OMIM # 154700) is an autosomal dominant connective tissue disease with a prevalence of 1:5000 [2] in the population, based on mutations in the *FBN1* gene encoding fibrillin-1, a component of the extracellular matrix. A distinctive feature of Marfan syndrome is the marked variability of clinical manifestations.

Since the discovery of the *FBN1* gene in 1991 [5], studies have been conducted on laboratory animals with Marfan syndrome to study the influence of the type of *FBN1* gene mutation on clinical manifestations. In mouse models with LoF (loss of function) mutations, pronounced aortic and skeletal damage was proved [8]. Myxomatous thickening of atrioventricular heart valves was detected in mice with missense mutations [7]. The explanation for the variability of symptoms in mice with different types of *FBN1* gene mutations was differently changed activity of TGFβ (transforming growth factor β) signaling pathway, which is one of the main pathogenetic mechanisms of complications in Marfan syndrome [4-6]. In laboratory animals, mice with LoF mutations have been shown to have more altered TGFβ signaling pathway activity than missense mutations, resulting in variable clinical manifestations.

In the last decade of the XXI century, studies of the effects of the type and localization of the *FBN1* gene mutation were conducted on large groups of patients with Marfan syndrome of different ages. It has been confirmed that LoF mutations have a greater impact on the aorta than missense mutations [1-3], including a larger average diameter of the aortic root, a higher risk of aortic dissection or the need for surgical intervention. Also, patients with LoF mutations, in contrast to patients with missense mutations, were found to have taller stature, more severe arachnodactyly and dolichostenomelia, and a higher incidence of thoracic and high palate deformities [1-3]. At the same time, patients with Marfan syndrome with missense mutations had a higher incidence of lens ectopia [3]. Moreover, it was proved that patients with Marfan syndrome with missense mutations with cysteine loss, in contrast to patients with missense mutations without cysteine involvement, had larger aortic dimensions and a higher incidence of arachnodactyly [3].

In addition to the type of *FBN1* gene mutation, the relationship between the localization of *FBN1* mutation and clinical symptoms in Marfan syndrome has been studied. By now it has been proved that localization of *FBN1* gene mutation in exons 24-32 leads to especially severe clinical manifestations. The presence of a missense mutation with cysteine loss in

these exons aggravates the course of the disease with a higher frequency of surgical interventions on the aortic and mitral heart valves, a higher frequency of surgical correction of the visual organ, and more pronounced skeletal deformities [1-3]. The influence of other localizations of *FBN1* gene mutations has not been proven yet.

Thus, the study of the influence of the type and position of the *FBN1* gene mutation on the severity and spectrum of clinical manifestations in Marfan syndrome contributes to a better understanding of the pathogenesis of the disease and, consequently, to the search for new targets for therapy. This study makes it possible to determine the criteria of prognosis of the course of the disease, which is especially important in children. Reasoned planning of targeted dispensary monitoring of sick children will ensure early diagnosis of emerging complications and their timely treatment.

The aim of this study was to determine the association of the type and localization of the *FBN1* gene mutation with the severity of clinical manifestations of Marfan syndrome in a Russian cohort of children.

Patients and methods. Patient cohort. From October 2021 to December 2023, 72 children, aged 0 to 18 years, with clinical signs of Marfan syndrome were consecutively hospitalized at the Clinical Genetics Department of the Veltischev Institute. All children were evaluated using the revised Ghent criteria [10]. Marfan syndrome was confirmed in 72 children. The mean age in the group was 12 years; 35 girls and 37 boys were included in the study.

Clinical research methods. All patients had a thorough history of the disease, in particular, the age of onset of organ system lesions characteristic of Marfan syndrome. All children underwent a physical examination with calculation of the connective tissue systemic lesion score [10]. According to the Ghent criteria, a score of ≥7 is diagnostically significant and belongs to the large Ghent criteria.

Functional studies of the cardiovascular system. All children underwent transthoracic echocardiography with evaluation of cardiac and vascular anatomy with calculation of the Z criterion for aortic root dimensions.

Molecular genetic study. Molecular genetic study was performed on all 72 (100%) children. Full genome sequencing in Evogen laboratory, thanks to the financial support of the Genome of Life charitable foundation, was performed n=25 (32%) in the group. Full-exome sequencing was performed n=10 (14%) in the group. Study of a panel of 166 genes responsible for bone pathology - n=29 (43%) in the laboratory of the Medical and Genetic Research Center named after Academician N.P. Bochkov. Target sequencing of FBN1 gene - n=8 (11%) in the group.

Statistical analysis. Statistical analysis of the data was performed using IBM SPSS Statistics 26.0 program.

Results. Molecular genetic study revealed LoF mutations in 42 (58%) children, which included large deletions, including complete absence of *FBN1* gene, splice site mutations, frameshift mutations, nonsense mutations. Missense mutations were identified in 30 (42%) children, among which: 14 with cysteine loss and 16 without cysteine involvement.

Depending on the localization of the *FBN1* gene mutation, children were divided into 5 groups: 1) group of children with mutations in exons 1 through 10, total - 11 (15%) children, including: with LoF mutations - 4(36%), with missense mutations - 7(64%); 2) group of children with mutations in exons 11 through 20, total in the group - 14 (19%) children, of which with LoF mutations - 8 (57%), with missense mutations - 6 (43%); 3) a group of children with mutations in exons 21 through 35, total in the group - 10 (14%) children, among which with LoF mutations - 5 (50%), with missense mutations - 5 (50%); 4) group of children with mutations in exons 36 through 50, total in the group - 18 (25%) children, among them with LoF mutations - 12(67%), with missense mutations - 6(33%); 5) group of children with mutations in exons 51

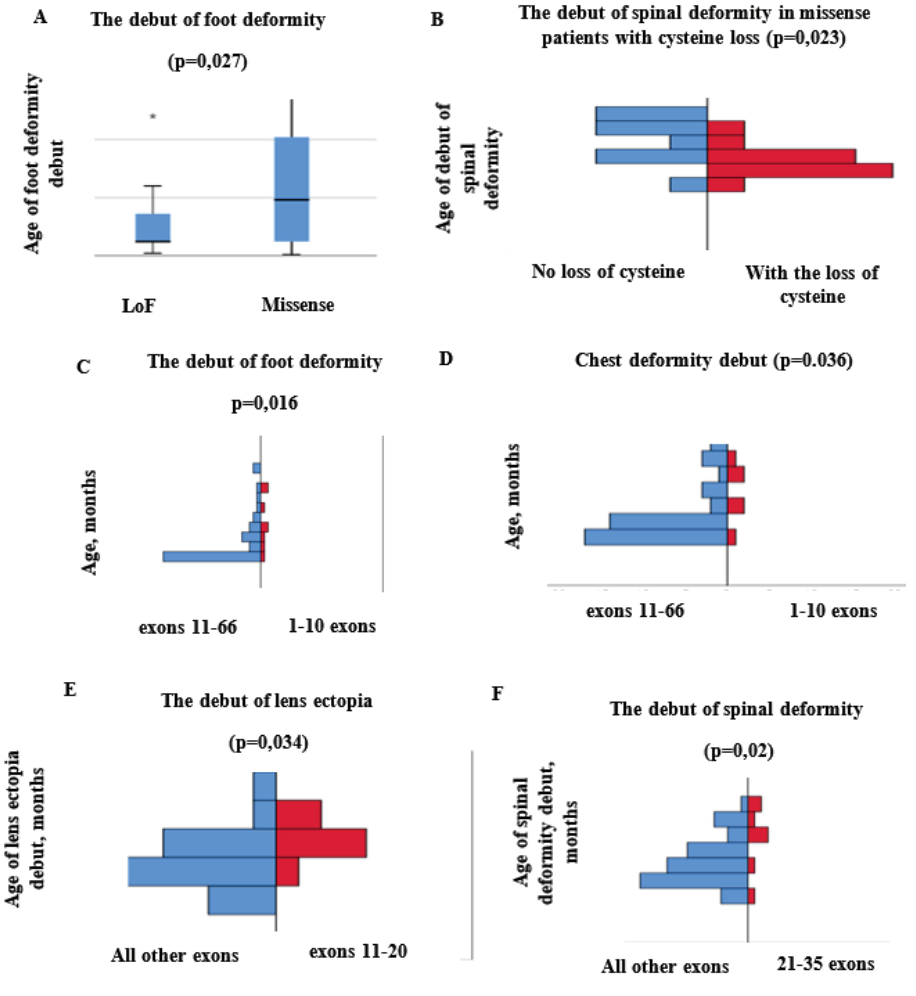

Fig. 1. Statistically significant differences between the compared groups regarding the debuts of clinical features: 1A - comparison of children with missense and LoF mutations by age of foot deformity debut; 1B - comparison of children with missense mutations with and without cysteine loss by age of spinal deformity debut; 1C and 1D - comparison of children with mutations in exons 1-10 with the rest of the children by time of spinal (1C) and thoracic (1D) deformity debuts; 1E - comparison of children with mutations in exons 11-20 with the rest of the children by time of debut of lens ectopia; 1F- comparison of children with mutations in exons 21-35 with the rest of the children by age of debut of spinal deformity.

through 66, total in the group - 19 (26%) children, among them with LoF mutations - 13(68%), with missense mutations - 6(32%) children.

To determine the influence of mutation type and localization on the spectrum of clinical manifestations in children with Marfan syndrome, we compared groups of 1) children with LoF and missense mutations, 2) children with missense mutations with and without cysteine loss, and 3) groups of children formed according to the localization of the mutation in the *FBN1* gene.

Study of the age of debut of clinical manifestations in different FBN1 gene mutations. Regarding the debut of clinical signs, it was revealed that children with LoF mutations, in contrast to children with missense mutations, have significantly earlier onset of foot deformities (up to 3 years of age) (p=0.027) (Figure 1A); children with missense mutations with cysteine loss, in contrast to children with missense mutations without cysteine involvement, have earlier onset of spinal deformities (up to 6 years of age) (p=0.023) (Figure 1B). Children with mutations in exons 1-10 show earlier deformities of both feet (up to 3 years of age) (p=0.016) (Figure 1C) and chest (up to 5 years of age) (p=0.036) (Figure 1D); children with mutations in exons 11-20 manifest lens ectopia earlier than others (up to 5 years of age) (p=0,034) (Figure 1E); with mutations in exons 21-35, spinal deformity is detected earlier than others (up to 6 years of age) (p=0,02) (Figure 1F).

Study of the severity of clinical manifestations in different FBN1 gene mutations. When examining the severity of cardiovascular damage, it was found that children with LoF mutations had larger aortic root sizes compared to children with missense mutations (p=0.003) (Figure 2A), and were significantly more likely to have aortic dilatation (Z-criterion for aortic size ≥3) (p=0.02). Children with missense mutations with cysteine loss had larger aortic root size compared to children with missense mutations without cysteine involvement (p=0.046) (Figure 2B). Children with mutations in exons 11-20 were less likely than others to have aortic dilatation (p=0.035). A negative effect of missense mutations was revealed in the form of greater mitral valve damage (p=0.04).

Regarding the severity of skeletal lesions, it was shown that children with LoF mutations more often than those with missense mutations had foot deformities (p=0.01), keeled chest deformity (p=0.004), and more pronounced dolichostenomelia (p=0.023) (Figure 2C). Children with mutations in exons 11-20 showed less pronounced dolichostenomelia (p=0.041) (Figure 2D).

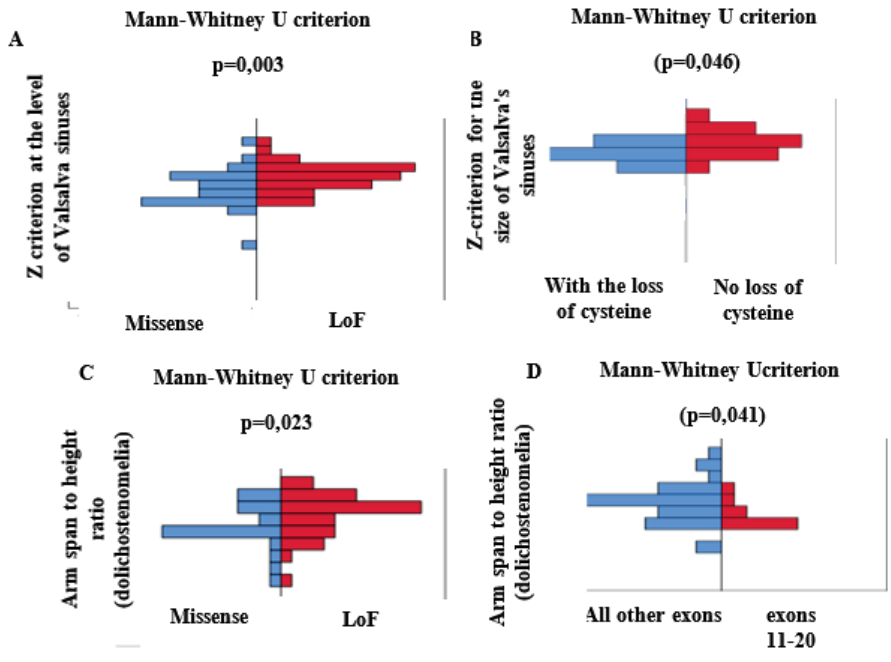

Fig. 2. Statistically significant differences between the compared groups with respect to clinical features: 2A, comparison of children with missense and LoF mutations with respect to aortic size at the level of Valsalva sinuses; 2B, comparison of children with missense mutations with and without loss of cysteine with respect to aortic size at the level of Valsalva sinuses; 2C, comparison of children with missense and LoF mutations with respect to dolichostenomelia; 2D, comparison of children with mutations in exons 11-20 with the rest of the children with respect to dolichostenomelia.

With regard to vision, it was found that: children with missense mutations were significantly more likely than those with LoF mutations to have lens ectopia (p=0.006); children with LoF mutations were more likely than those with missense mutations to have severe myopia (p=0.001). Children with mutations in exons 51-66 had lens ectopia less often than the others (p=0.001).

Discussion of the results. The study yields both new correlations and confirmation of previously found correlations.

In the present study, children with LoF mutations have been shown to have larger aortic dimensions and greater skeletal damage than children with missense mutations. From the pathogenetic point of view, the relationship between this spectrum of clinical manifestations and LoF mutations can be explained by extrapolating the results of studies of mice with Marfan syndrome, which showed that the activity of TGFβ signaling pathway is more altered in LoF mutations than in missense mutations [4,7]. In contrast, lens ectopia is more common in missense mutations, according to the results of this study. It is known that the cinnova ligament, which anchors the lens, consists only of fibrillin microfibrils. In missense mutations, defective fibrillin-1 is synthesized, which leads to the formation of a failed cinnova ligament, resulting in lens ectopia. Consequently, impaired structural function of fibrillin-1 underlies this manifestation.

In addition to a better understanding of the pathogenesis of Marfan syndrome, the correlations identified may help to shape the prognosis of the disease. Thus, according to the results of our study, children with LoF mutations have an earlier debut and frequency of foot deformities and larger aortic dimensions. Given that skeletal signs manifest earlier than cardiovascular manifestations [9], children with early manifestation of foot deformity (before 3 years of age) and suspected Marfan syndrome should be recommended to be seen by a pediatric cardiologist as early as possible without waiting for the results of molecular genetic testing. Similarly, children with early onset of spinal deformity (before 6 years of age) and suspected Marfan syndrome should be recommended for pediatric cardiology follow-up, as early spinal cord involvement is characteristic of children with missense mutations with cysteine loss, who also have greater aortic involvement than children with missense mutations without cysteine involvement.

The correlations between the debut and the spectrum of clinical signs with

the localization of the *FBN1* gene mutation identified in this study can also help in planning the dispensary follow-up of children with Marfan syndrome. For example, children with mutations in exons 1-10 should be monitored by an orthopedic traumatologist for foot and thoracic deformities, and children with mutations in exons 21-35 should be monitored for spinal deformities. Earlier observation by an ophthalmologist is recommended for children with mutations in exons 11-20 due to the risk of lens ectopia.

Conclusion. The study of the influence of the type and localization of the *FBN1* gene mutation on the severity and spectrum of clinical manifestations in Marfan syndrome may contribute to a better understanding of the pathogenesis of this disease, the formation of prognosis of its course and planning of dispensary follow-up. In the present study, for the first time in a Russian cohort of children with Marfan syndrome, the influence of the type and localization of the *FBN1* gene mutation on the clinical manifestations of the cardiovascular, ocular, and skeletal systems was proved. Further study of the influence of the patients' genotype on other organ systems in this disease is planned.

Conflict of interest. The authors declare that there are no obvious and potential conflicts of interest related to the publication of this article. Parents of all children participating in the study signed informed consent.

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Z.S. Huseynova

INFLUENCE OF UTERINE FIBROID ON UTERINE BLOOD FLOW, MENSTRUAL FUNCTION AND FEATURES OF REPRODUCTIVE HEALTH DISORDERS IN WOMEN

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The study was conducted on women aged 18-45 years old with uterine fibroids and impaired reproductive function. In patients with uterine fibroids, menarche began at an earlier age and cyclic bleeding was more often observed, causing posthemorrhagic anemia. Reproductive function disorders were caused by infertility and miscarriages. Indicators of S/D, RI, PI of the uterine artery in the presence of fibroids were lower than in the group of healthy women. In group I, primary infertility predominated, and in group II, secondary infertility prevailed. Thus, risk factors for reproductive potential in women with uterine fibroids have been studied, early diagnosis has been established, and it has been determined that it is important to choose adequate treatment tactics to achieve the realization of reproductive desires.

Keywords: uterine fibroids, benign diseases of the uterus, reproductive potential disorders, dopplerography of the uterine arteries.

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Introduction. Uterine fibroids are among the most common benign tumors affecting the female reproductive system. The detection rate of uterine fibroids in women reaches 60% by age 35 and more than 80% by age 50 [13]. The presence of myomatous nodes adversely affects the reproductive function of women and negatively affects the somatic health of patients and their quality of life [1]. In addition, risk factors for the development of uterine fibroids include race and ethnicity, family history, early menarche and late menopause, obesity, stress, hypertension, exposure to environmental toxins, and vitamin D deficiency [7,9]. Most women with uterine fibroids do not have any special complaints, but a third of patients experience serious symptoms such as uterine bleeding with secondary anemia, pelvic pain, infertility and recurrent miscarriages [8]. Ultrasonography, preferably transvaginal, is the first-line method for diagnosing uterine fibroids [5]. Approximately 60% of patients with uterine fibroids experience clinical mani-

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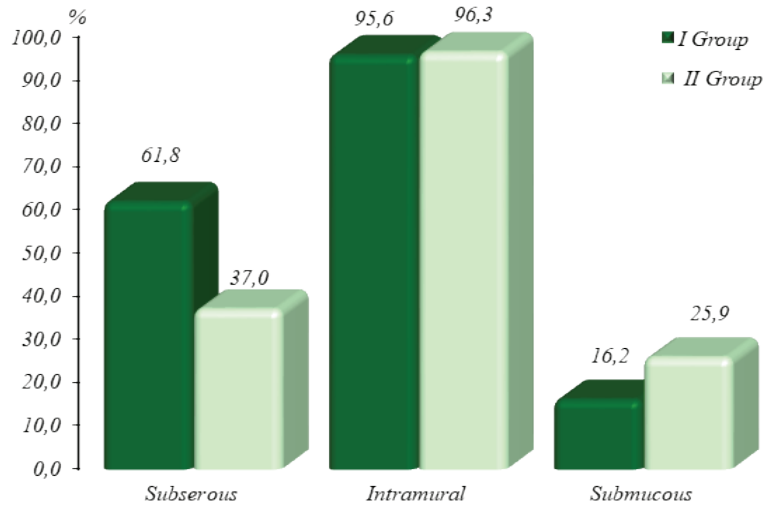
festations of the disease, which depend on the location and size of the fibroids [1]. Uterine fibroids, depending on their location in the uterus, cause habitual miscarriages and infertility [6]. Infertility, both primary and secondary, is a common occurrence with this disease. According to research, the incidence of uterine fibroids in women of reproductive age is up to 40%, and infertility associated with uterine fibroids occurs in 5–10% of women [12]. Several mechanisms have been proposed to explain the negative impact of uterine fibroids on fertility, including increased uterine motility, neuroendocrine action of the uterine fibroid pseudocapsule, and changes in the expression of genes involved in endometrial receptivity [3]. A growing number of studies highlight the possible negative impact of uterine fibroids on fertility and reproductive outcomes. It is generally accepted that the closer the myoma is to the uterine cavity and the endometrium, the more it can negatively affect fertility, reducing the chances of successful implantation and pregnancy [4]. It is advisable to perform myomectomy before planning pregnancy, and conservative treatment carried out at the stage of preoperative preparation and in the postoperative period is effective and helps to preserve and improve fertility [2].

Purpose: to study the features of reproductive potential disorders in patients with uterine fibroids, to promote the effectiveness of its optimal restoration.

Materials and methods. The study included women with benign diseases of the uterus and reproductive disorders who applied to the Maternity Hospital No. 5 named after Shamama Alaskarova, the Clinical Medical Center and the antenatal clinic of the Maternity Hospital No. 5 to receive medical services in 2017-2022. Uterine fibroids were identified in 96 women out of 200 such patients aged 18-45 years. They were divided into two groups: I – with the presence of isolated uterine fibroids (68 women) and II – with myomatous nodes in association with such benign uterine pathologies as adenomyosis, hyperplasia and endometrial polyps (28 women). The control group included 50 practically healthy women.

In the process of a comprehensive examination, along with clinical and anamnestic methods, instrumental research methods were used. The medical history of each patient was obtained by interview using a structured questionnaire. All women included in the study underwent ultrasound examination (transvaginal) and Doppler ultrasound of the uterine arteries in the first phase of the menstrual cycle. Using transvaginal ultrasound, the size of the uterus, the number, size and location of myomatous nodes, as well as the resistance index (RI), pulsation index (PI), and systole-diastolic ratio (S/D) in the uterine arteries were assessed.



The frequency of different localization of myomatous nodes in patients with impaired reproductive potential

Quantitative and qualitative data were subjected to statistical processing using the methods of variational (Student-Bonferroni t-test and Mann-Whitney U-test) and discriminant (Pearson Chi-Square test) analyzes in the statistical package SPSS-26. The null hypothesis was rejected at the P < 0.05 level.

Results and discussion. In our prospective study, the average age of patients with uterine fibroids and reproductive dysfunction was 32.1±0.5 and 32.3±0.5, and in the control group – 31.7±0.7. The initial diagnosis of uterine fibroids was made using transvaginal ultrasound examination in the first phase of the menstrual cycle. Ultrasound examination determined the location, nature, quantity and size of uterine fibroids and myomatous nodes (Figure).

The average size of various myomatous nodes located in the uterus in group I was 60.4±2.9×58.7±2.4, and in group II was 52.0±4.4×51.2±4.0.

In group I, menarche began on average at 12.9±0.1 years, that is,

Table 1

Characteristics of reproductive disorders and pregnancy complications in women with uterine fibroids

Indicators		group I		group II		P
		n	%	n	%	
Infertility	primary	27	39.7	8	29.6	P_{I-II}=0.104
	secondary	14	20.6	11	40.7	
Duration infertility	2 years	3	7.3	0	0 .0	P_{I-II}=0.023*
	3-5 years	20	48.8	5	26.3	
	>5 years	18	43.9	14	73.7	
Spontaneous miscarriages	weren't	34	50.0	17	63.0	P_{I-II}=0.256
	early	27	39.7	7	25.0	
	late	7	10.3	3	10.7	
Non-developing pregnancy	wasn't	48	70.6	21	77.8	P_{I-II}=0.481
	was	20	29.4	6	22.2	
Recurrent miscarriages	weren't	42	61.8	19	70.4	P_{I-II}=0.432
	were	26	38.2	8	29.6	
Premature birth	weren't	47	69.1	21	77.8	P_{I-II}=0.401
	were	21	30.9	6	22.2	

Note: the statistical significance of the difference between indicators: PI – group with isolated uterine myoma (I) according to Wilcoxon (Mann-Whitney); PII – groups with myoma of the uterus in combination with one of the other benign pathologies of the uterus (II) according to Wilcoxon (Mann-Whitney). * – «0»- the hypothesis is rejected (p < 0.05).

Table 2

Indicators of blood flow in the uterine arteries, revealed by dopplerometry

Indicators	groups	N	M	±m	Me	Q1	Q3	$P_к$	P_I
S/D - right	control	50	5.76	0.19	5.62	4.94	6.32		
	group I	68	4.26	0.13	4.25	3.47	4.95	<0.001*	
	group II	27	4.69	0.16	4.75	4.18	5.43	<0.001*	0.017*
S/D - left	control	50	6.29	0.20	6.02	5.23	7.24		
	group I	68	4.62	0.11	4.58	4.10	5.13	<0.001*	
	group II	27	4.80	0.13	4.85	4.28	5.11	<0.001*	0.271
RI- right	control	50	0.818	0.007	0.820	0.800	0.840		
	group I	68	0.752	0.007	0.765	0.710	0.800	<0.001*	
	group II	27	0.786	0.007	0.790	0.770	0.820	<0.001*	0.005*
RI- left	control	50	0.834	0.005	0.835	0.810	0.860		
	group I	68	0.773	0.006	0.780	0.755	0.800	<0.001*	
	group II	27	0.785	0.006	0.790	0.770	0.800	<0.001*	0.382
PI- right	control	50	2.17	0.05	2.20	1.89	2.36		
	group I	68	1.69	0.03	1.71	1.64	1.82	<0.001*	
	group II	27	1.76	0.06	1.72	1.68	1.85	<0.001*	<0.001*
PI- left	control	50	2.35	0.06	2.33	1.96	2.68		
	group I	68	1.79	0.02	1.77	0.69	1.92	<0.001*	
	group II	27	1.86	0.06	1.78	1.72	1.83	<0.001*	<0.001*

Note: the statistical significance of the difference according to Wilcoxon (Mann-Whitney) with indicators: Pк – control group (K) according to Wilcoxon (Mann-Whitney); PI – group with isolated uterine myoma (I) according to Wilcoxon (Mann-Whitney); * – "0" hypothesis is rejected ($p < 0.05$)

earlier than in other groups. In group II, menarche began on average at 13.4±0.1 and in the control group at 13.0±0.1, the difference between the control with the first and control with the second groups was p=0.006* and p=0.030*, respectively. On average, the duration of menstruation lasted 8.0±0.3 days in group I, 7.4±0.4 days in group II and 5.7±0.1 days in the control group (P<0.001*). Among menstrual cycle disorders, menorrhagia prevailed over other disorders in both groups with uterine fibroids and was observed in 51.5% of patients in group I and in 70.4% of patients in group II. Metrorrhagia was observed in 36.8% of patients in group I and in 25.9% of patients in group II, and dysmenorrhea was observed more often in group I (30.9% and 14.8%, respectively). Posthemorrhagic anemia was observed in both groups with uterine fibroids. Thus, first degree anemia was detected in 57.4% of patients in group I, in 44.4% of patients in group II, second degree anemia - in 14.7% of patients in group I, in 11.1% of patients in group II, and third degree anemia - in 2.9% of patients in group I and 11.2% in group II.

As can be seen from the table, in the group with isolated uterine myomas, compared to group II, such obstetric complications leading to impaired reproductive potential prevailed, such as spontaneous abortions, non-developing pregnancy and premature birth, but no significant difference between the groups was revealed (Table 1). At the same time, 55.9% of women with uterine fibroids did not develop complications during pregnancy and childbirth.

To clarify the role of blood supply to the uterus in patients with uterine fibroids, spectral dopplerometry was performed in the uterine arteries. Basically, they compared indicators such as resistance index (RI), pulsation index (PI), and systolic-diastolic ratio (S/D). Table 2 shows the results of spectral dopplerometry of the uterine arteries, which may be related to the identified disorders of the reproductive potential.

There was no significant difference in age between groups in our study. In most patients with uterine fibroids, menarche began at an early age, and menstrual irregularities in the form of menometrorrhagia were observed, causing posthemorrhagic anemia. According to the studies conducted previously [5] and our study, menstrual dysfunction was mostly observed as menorrhagia. Although most uterine fibroids are asymptomatic, their location and size can affect pregnancy and childbirth [15]. Submucosal, intramural and subserosal fibroids have different effects on fertility and are mainly associated with submucosal lesions leading to implantation defects [14]. Failure to realize reproductive desire was more often observed in women with intramural myomatous nodes that deform the uterine cavity and submucosal uterine fibroids. During our study, in patients with uterine fibroids, primary infertility prevailed in group I, secondary infertility prevailed in group II, and the duration of infertility was 3-5 years in group I, and more than 5 years in group II. This difference between the results of the duration of infertility is associated with the deeper influence of combined pathology on reproductive dysfunction in group II. It should be emphasized that uterine fibroids affect not only fertility, but also pregnancy outcomes [12]. Thus, in our study, pregnancy complications were more common in patients with uterine fibroids, such as early and recurrent miscarriages, as well as premature birth. When Doppler monitoring of blood flow in the uterine arteries was performed in patients with uterine fibroids and reproductive disorders, a significant change in Doppler parameters was observed compared to healthy women. According to a previous study, increasing uterine volume increases blood flow and decreases Doppler readings due to decreased vascular resistance [11]. These data correspond to the results of our study, where in both groups with uterine fibroids and reproductive dysfunction, Dopplerographic indicators of the uterine arteries - IR, PI and S/D - were lower than in healthy patients. Thus, the effect of uterine fibroids

on the blood supply to the uterus is characterized by a change in the established Doppler parameters.

Conclusions:

- in women with uterine fibroids, menarche began at an early age, and menorrhagic disturbances of menstrual function were more often observed, causing posthemorrhagic anemia;
- the clinical course of the disease in women with uterine fibroids depends not on the patient's age, but on the number, size and location of myomatous nodes;
- in patients with isolated uterine fibroids, primary infertility prevailed;
- secondary infertility and duration of infertility prevailed in patients in whom fibroids were found along with other benign diseases of the uterus;
- in patients with uterine fibroids, early, recurrent miscarriages and premature births were more common;
- with Doppler ultrasound of the uterine artery, IR, PI and S/D indicators in women with uterine fibroids were lower than in healthy patients;

In the end, we can conclude that timely assessment of clinical symptoms and early diagnosis in women with uterine fibroids can become the basis for pathogenetically based treatment, which can lead to improving women's lives, restoring menstrual function and achieving reproductive desire.

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CHARACTERISTICS OF METABOLIC INDICATORS OF BODY STUDENTS DOING BOXING

The assessment of metabolic parameters in students engaged in boxing at the training stage was carried out. According to the results of the study, normal functional parameters of the body, BMI, and satisfactory AP were established. According to biochemical parameters, the group of athletes showed an excess of the range of normal values of CK, HDL, a decrease in LDL and the de Ritis coefficient (CDR), in the beginner group – an increase in CDR and a decrease in VLDL. Significant differences between the groups were found in the values of TG, VLDL ($p<0.005$), HDL glucose and KA ($p<0.05$). Conclusion. The athletes showed metabolic indicators indicating formed adaptive and metabolic changes to training loads in comparison with the beginner group.

Keywords: students, athletes, beginners, metabolic, biochemical parameters, boxing

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Introduction. Each meal supplies our metabolic pathways with new metabolites, but nothing changes the rate of metabolic reactions as much as intense exercise [18]. The three main pathways of metabolism – energy metabolism, anabolism, and catabolism – are profoundly altered in response to exercise [20]. Studies of biochemical parameters in blood serum and functional

systems of the body provide insight into the development of adaptation, the level of exposure to a stress factor and the degree of recovery of the body during intense physical activity [5, 19]. Understanding by coaches and scientists of the physiological adaptation of martial arts athletes can provide valuable information for adjusting training programs that help improve the performance of athletes [17].

The purpose of the study: to characterize the metabolic parameters of the body of students engaged in boxing during the training period.

Materials and methods of research. 36 young men of the NEFU named after M.K. Ammosov of indigenous nationality who are engaged in boxing at the training stage (average age 20.5 (19.25; 23) years) were examined. 23 of them had a sports category or the title of KMS and MC (athletes), 13 had been engaged in boxing for more than 1 year, had no sports category (beginners). The study was conducted in compliance with the ethical medical and biological requirements set out in the Helsinki Declaration. Determination of biochemical parameters (aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CK), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), glucose, total cholesterol (TCH), HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides (TG), uric acid (MC), urea, creatinine, total protein, and albumin were measured in blood serum using a Labio – 200 biochemical analyzer. Blood sampling was performed from 8 a.m. to 10 a.m. from the ulnar vein, after a 12-hour abstinence from eating. The following indicators were calculated: the de Ritis coefficient (CDR=AST/ALT), the index of muscle tissue damage according to the formula (MDI=CK/AST) and the coefficient of atherogenicity (KA= (TH –HDL)/HDL). The anthropometric measurement of body length (P, cm) was performed using a height meter and body weight (MT, kg) on an electronic scale (Massa-K, Russia). The body mass index was calculated using the formula: BMI = weight (kg)/height 2 (m²). Blood pressure was measured in a state of relative muscle rest on the right arm in a sitting position after a 5-minute rest using an automatic blood pressure monitor PRO-33 with the recording of the average value of 3 measurements. The adaptive potential (AP) was calculated according to the formula of R.M. Baevsky (1987): AP=0.011*HR+0.014*SBP+0.008*DBP+ 0.009*MT-0.009*H+0.014*A-0.27, where HR is the heart rate at relative rest, SAD is systolic pressure (mmHg), DBP-diastolic pressure (mmHg),H-height (cm), MT-body weight (kg), A-age (years). Interpretation: below 2.60-satisfactory adaptation, 2.60-3.09-tension of adaptation mechanisms, 3.10-3.49-unsatisfactory adaptation, 3.50 or more-failure of adaptation. The results of the study were processed using the IBM SPSS Statistics 22.0 program. Statistical hypotheses about the distribution law of a normal population and the parameters of a normal distribution were tested using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. The analysis data is presented in the table as Me (median) and the interquartile range of the first (Q1) and third (Q3) quartiles (quartiles 25 and 75%). The statistical significance of the data obtained was checked using the nonparametric Mann-Whitney criterion (U). The results were considered statistically significant when the achieved significance level was $p<0.05$.

Results and discussion. According to the results of the study, SBP, DBP, heart rate, and calculated BMI in both compared groups were in the range of normal values (systolic pressure less than 120 mmHg and diastolic pressure less than 80 mmHg [11], heart rate 60-80 beats per minute according to WHO, BMI within -18.5-25 kg/m²) (Table 1). It has been established that physical activity has a positive effect on the cardiovascular system of athletes as a result of the adaptive response of the myocardium [9]. There was a significant decrease in blood pressure during all types of training [14]. At the same time, athletes of various qualifications had SBP and heart rate above normal values; DBP above normal values was noted in athletes of speed-power and jet-power sports [9]. It was shown that the proportion of athletes with an increased blood pressure response increased with age. According to some authors, in competitive athletes, during physical activity testing, an increased blood pressure reaction was diagnosed in 6.8% -19.6% of athletes without known hypertension [16].

The AP value makes it possible to assess the level of physical fitness, as well as the functional maturity of hormonal and vegetative links in the regulation of homeostasis [4]. Among the students we examined, the median values of adaptive potential were satisfactory in both groups compared – 2.05 (1.9; 2.3) and 2.0 (1.87; 2.15). It has been shown that positive adaptive changes occur due to the stressful effects of physical exertion during the training process [1]. The obtained functional indicators (SAD, DBP, HR), BMI and AP of the examined contingent, corresponding to normal values, are most likely related to the study during the training period. It is believed that the signs of the development of adaptation or disadaptation during physical exertion in athletes and non-athletes may be metabolic features [8].

Numerous studies have proven that blood counts can serve as markers of the metabolic response to physical activity in professional and non-professional athletes and assess the level of metabolic potential [15]. During the study of biochemical parameters of blood serum in the group of athletes, an excess of the range of normal values of CK, HDL, a decrease in LDL and CDR values was found, in the group of beginners – an increase in CDR (AST/ALT) and a decrease in VLDL values (Table 2). Significant differences in TG and VLDL values were found between the compared groups ($p<0.001$), glucose, HDL, and KA ($p<0.05$). The urea value was also found at the lower limit of the reference values for beginners (2.6 (1.79; 3.53)) and not high for athletes (3.17 (2.51; 4.33)).

Table 1

The average values of age, length and body weight, SBP, DBP, heart rate, BMI and AP in the compared groups (Iu (Q25; Q75))

Indicator	The Athletes (n=23)	Beginners (n=13)	p
Age, years	20.5 (19; 23)	20 (18.75; 21.5)	0.987
Height, m	174.25 (171.75; 176.78)	178.15 (173.45; 180.78)	0.348
Body weight, kg	64.725 (59.3; 72.25)	72.5 (68.35; 78.05)	0.531
SBP, mmHg	116 (112; 127)	117 (108.75; 130)	0.608
DBP, mmHg.	70.5 (64.75; 74)	73.5 (65.75; 75.25)	0.087
Heart rate, beats per minute	61.5 (56.5; 65)	64.5 (60; 73.75)	0.161
BMI, kg/m²	20.35 (19.3; 22.45)	21.6 (19.88; 25.53)	0.373
AP, units	2.05 (1.9; 2.3	2.0 (1.87; 2.15)	0.553

According to literature data, a gradual increase in the level of enzymes in the blood serum during intensive physical training is an adaptive reaction of the body [3]. An increase in the level of CK is also noted during the recovery period [21]. Among athletes, an increase in the value of this enzyme indicates a higher intensity of physical activity compared to beginners.

As a rule, prolonged training leads to an increase in the concentration of urea in the blood [10]. It has been shown that an increase in the urea content in the blood is crucial for muscle activity. During short-term operation, it is insignificant, and during prolonged operation, the load can increase 4-5 times [5].

However, a low urea content may indicate an anabolic orientation of the processes, minimal use of protein as an energy substrate (during gluconeogenesis) and a higher energy supply to muscles. The level of urea in blood serum as the most important indicator of protein metabolism with values less than 5.75 mmol/l reflects the ability of athletes to better tolerate the training and competitive loads [10]. Low urea values in some athletes may be associated not only with this statement, but also with insufficient intake of protein-containing foods and sports nutrition.

Table 2

Biochemical parameters of blood serum (Me (Q25; Q75))

Indicator	The Athletes (n=23)	Beginners (n=13)	p
LDH (225-450 U/l)	351 (326; 381)	350 (306.5; 399.5)	0.934
CPK (< 190 U/l)	200 (115; 283)	165 (109.5; 254)	0.521
ALP (< 258 U/l)	225 (190; 292)	209 (193.5; 286.5)	0.961
GGT (11 – 50 U/l)	20 (18; 36)	21 (18.5; 27.5)	0.754
ALT (< 30 U/l)	17 (13; 23)	16 (10.5; 20.5)	0.355
AST (< 40 U/l)	23 (20; 25)	24 (21; 31)	0.180
CDR (1.3 – 1.5)	1.26 (1.08; 1.47)	1.71 (1.11; 2.12)	0.103
IPMT, units	8.32 (7.35; 12.57)	5.45 (4.79; 10.34)	0.103
MK (men 268-488 µmol/l)	263 (204; 291)	278 (239.5; 325.5)	0.236
Urea (2.5 – 8.3 mmol/l)	2.6 (1.79; 3.53)	3.17 (2.51; 4.33)	0.063
Creatinine (50 – 120 µmol/l)	98 (92; 100)	96 (92.5; 100)	0.586
Glucose (3.3 – 5.5 mmol/l)	4.9 (4.6; 5.4)*	4.5 (4.1; 5.1)	0.013
Total protein (65 – 85 g/l)	76.2 (75; 80)	75 (73; 77.5)	0.141
Albumin (34 – 48 g/l)	47 (45; 49)	46 (45; 48)	0.319
TG (0.5-1.7 mmol/l)	0.82 (0.70; 1.22)**	0.54 (0.44; 0.65)	<0.001
TC (3.6-6.5 mmol/l)	4.24 (3.85; 4.68)	3.99 (3.43; 4.36)	0.134
HDL-C (0.78-2.2 mmol/l)	2.48 (2.15; 2.72) *	1.98 (1.44; 2.21)	0.005
LDL cholesterol (1.68-4.53 mmol/l)	1.24 (0.95; 1.68)	1.78 (1.14; 2.19)	0.070
VLDL cholesterol (0.26-1.5 mmol/l)	0.38 (0.33; 0.56)**	0.25 (0.21; 0.30)	<0.001
KA (<3.5)	0.6 (0.5; 0.86)*	1.25 (0.57; 1.79)	0.046

Note. * – differences are significant, p<0.05, ** – differences are significant, p<0.001

The CDR value exceeding the normal range in the beginner group is associated with the predominance of catabolic processes. At the same time, a decrease in the urea value against the background of an increase in the CDR value in the beginner group may indicate unformed metabolic rearrangements of the body. In athletes, the CDR value is slightly reduced, which is associated with the predominance of anabolic metabolic processes, indicating an excellent functional state and good adaptive reserves of the body sufficient to overcome intense and prolonged physical exertion [22].

According to sources, exercise and training also cause adaptation of glucose metabolism, which improves glucose utilization in athletes and helps reduce insulin resistance in non-athletes [19]. The mechanism of biological reliability in muscular activity consists in excessive mobilization of carbohydrates from the depot, which is necessary to meet the energy needs of other functional systems, prevent hypoglycemic conditions, etc. With a decrease in glucose levels during physical work, the energy supply of other functional systems that ensure the vital activity of the body will decrease [2]. The established significant difference between the groups in glucose levels may be due to the difference in the intensity of the training process and the high consumption of carbohydrate-containing foods among athletes.

The lipid status of athletes' blood deserves special attention. In professional athletes, the lipid status was found to be more favorable compared to the sex- and age-appropriate population leading a sedentary lifestyle [8, 12]. Athletes have lower levels of TG, LDL, and comparable or higher HDL levels in the blood [12, 19]. HDL is an anti-atherogenic particle that ensures the release of cells from excess cholesterol. LDL is known to contribute to the formation of atherosclerotic plaques [13]. The above statements explain the high HDL values, low LDL and TG values close to the lower limit of normal values in the group of athletes, as well as lower HDL and high CA compared to athletes in the beginner group. It has been shown that a significant part of cholesterol in athletes is involved in the biosynthesis of steroid sex hormones and corticosteroids, in the formation of blood cells (erythrocytes), the secretion of sebaceous glands and bile acids [7]. Positive changes in the lipid profile in athletes are also associated with the rheological properties of blood [6]. Along with this, VLDL values are lower than the reference values in the beginner group, possibly due to the intensity of the training process and insufficient intake of saturated fatty acids from food.

Conclusion. According to the results of the study of boxing students, metabolic changes characterized by the predominance of anabolic processes, optimal lipid profile and characteristic enzymemia in athletes were revealed, which allow us to assert the formed adaptive and metabolic rearrangements to training loads, as well as the incompleteness of metabolic rearrangements in the beginner group, manifested by low values of urea, VLDL and an increase in CDR.

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STUDY OF COAGULATION HEMOSTASIS IN RATS UNDER CONDITIONS OF INDUCED GENERAL MODERATE HYPOTHERMIA

The use of induced hypothermia in clinical practice can lead to coagulopathy, increasing the risk of peri- and postoperative bleeding. The aim of this study was to investigate the effect of cooling the body to moderate hypothermia on the hemostatic system in rats. Activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT) were determined upon reaching a rectal temperature of 32°C and after prolonged two-hour hypothermia while maintaining the animal's temperature at the same level. It was shown that cooling the animals to moderate hypothermia resulted in an increase in activated partial thromboplastin time, thrombin time, and prothrombin time, indicating the development of hypocoagulation shifts and impairment of the secondary hemostasis. With prolonged hypothermic exposure, a decrease in APTT, TT, and PT parameters from the achieved values was observed, which probably indicates some suppression of coagulation reactions with prolonged exposure to moderate hypothermia. It is suggested that impaired thrombin generation may be a key factor in hypothermia-induced coagulopathy.

Keywords: moderate hypothermia; hemostatic system; rats.

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Introduction. All organs and tissues are involved in the formation of an urgent response to general hypothermia. However, under conditions of general hypothermia, the state of the cardiovascular system is key to ensuring the adequate functioning of other organs and systems [10; 18; 26]. Maintaining adequate tissue perfusion relies heavily on the hemostatic system [2;19].

Numerous studies have shown that maintaining the body in a state of mild hypothermia can have a protective effect on damaged brain tissue [14; 25; 28; 29]. However, hypothermia used in surgical practice to protect against ischemic damage, for example, during aortic surgery with circulatory arrest, often leads to coagulopathy, which is one of the main life-threatening complications [12]. Low body temperature alters platelet aggregation and reduces the activity of enzymes in the coagulation cascade [22; 23], these changes inevitably increase the risk of perioperative bleeding.

It is considered [26; 27] that in a hypothermic state, blood clotting is reduced, primary and secondary hemostasis are impaired, and platelet function is decreased. A number of animal studies confirm the weakening of hemostasis markers during hypothermia [20; 23; 33], however, some studies [17; 24] using hypothermia in experimental models of trauma and/or hemorrhagic shock did not show this. Other researchers show [9] that increased bleeding at moderately reduced temperatures (33°–37°C) is primarily the result of a platelet adhesion defect, rather than reduced enzyme activity or platelet activation. However, at temperatures below 33°C, both reduced platelet function and reduced enzyme activity likely contribute to coagulopathy.

It is noted [7] that hypothermia leads to a decrease in circulating blood volume, causing hemoconcentration, manifested by an increase in blood viscosity and hematocrit, and prolonged vasoconstriction (small venous vessels are most affected) leads to frostbite and thrombus formation. The risk of thrombosis also increases in the presence of postoperative hypothermia in a patient who has undergone prolonged surgery accompanied by blood loss [31].

Studies of blood drawn at normal body temperature and then incubated at various temperatures have yielded conflicting results [1; 21]. These studies showed that temperature has an ambiguous effect on the activating and inhibiting reversible reactions of hemostasis. Thus, hypothermia reduces the rate of the platelet shape change reaction from discoid to spherical, however, activation of human platelets by various agonists leads to acceleration of their aggregation.

Thromboelastography, as a method determining the dynamics of interaction of all components of hemostasis, revealed [13; 30; 34] a decrease in coagulation with delayed thrombus formation during hypothermia. In healthy subjects, progressive delay in thrombus formation began only when the temperature dropped below 30°C [16]. It was confirmed [11] that blood clotting disorders during hypothermia were associated with a decreased clot formation rate, reduced clot strength, and impaired fibrinolysis.

In-depth studies of the hemostatic system under various environmental conditions, including hypothermic states, are conducted in our country by Barnaul researchers, who have demonstrated a stereotypical stress response of the hemostatic system in response to a single threshold stressor [8]. Furthermore, it was found [5] that during sequential cooling with immersion hypothermia, changes in the hemostatic system are phased, transitioning from hypocoagulation (in mild hypothermia) to thrombinemia (in moderate and deep hypothermia), with subsequent disappearance of signs of coagulation activation at ultra-deep hypothermia. With immersion cooling of rats to a rectal temperature of 30°C, an increase in platelet aggregation ability and the concentration of soluble fibrin-monomer complexes was registered [4], with a decrease in their polymerization time, which characterizes a shift in the hemostatic potential of blood towards hypercoagulation. When cooling animals in air to a rectal temperature of 30°C, platelet aggregation ability significantly decreased relative to normothermia.

The contradictory conclusions of researchers regarding the effect of hypothermia on hemostasis can be explained by the methods of achieving hypothermia, its duration, and the degree of temperature reduction. The use of hypothermia in the clinic unequivocally indicates [29] that very mild hypothermia (up to 35°C) does not affect coagulation, and at lower temperatures, moderate platelet dysfunction may begin.

The aim of this study was to investigate the effect of cooling the body to moderate hypothermia on the hemostatic system. The objectives included determining hemostasis parameters (APTT – activated partial thromboplastin time, TT – thrombin time, PT – prothrombin time) upon reaching a rectal temperature of 32°C and after prolonged two-hour hypothermia while maintaining the rectal temperature at the same level.

Materials and Methods. Experiments were performed on male Wistar rats weighing 300-320 g from the biocollection “Collection of laboratory mammals of different taxonomic affiliations” of the I.P. Pavlov Institute of Physiology of the Russian Academy of Sciences. All procedures performed in this study complied with ethical standards approved by the legal acts of the Russian Federation, the principles of the Basel Declaration, and the recommendations of the Commission for the Control over the Keeping and Use of Laboratory Animals at the I.P. Pavlov Institute of Physiology of the Russian Academy of Sciences (Protocol No. 12/19 of December 19, 2022).

Anesthetized rats (urethane, i.v., 1000 mg/kg) were cooled using ice packs. The time to reach the target Tr was 30 min, after which the ice packs were removed, and the animals were kept at room temperature on a thermostatically controlled mat to maintain the required Tr. To assess hemostasis parameters (APTT, PT, TT), blood was collected from the hepatic sinus in the norm (group 1, control, n=7), upon reaching a rectal temperature (Tr) of 32°C (group 2, n=8), and after 2 hours of maintaining Tr at 32°C (group 3, n=8).

As additional criteria for platelet functional activity, PDW (platelet distribution width) and MPV (mean platelet volume) were measured. Platelet count, PDW, and MPV were determined using an automated hematology analyzer Mindray BC-30 Vet (Mindray Animal Care, China). Blood for hematological analysis was stabilized with EDTA solution at a concentration of 2 mg/ml of whole blood.

For the study of the coagulation link of hemostasis, 5 ml of blood was collected into a tube containing 0.11 M (3.8%) sodium citrate solution (blood-to-citrate ratio 9:1) and centrifuged for 10 min at 3000 rpm. PT, TT, and APTT were determined using a CoaTest-4 coagulometer (NPC “Astra”, Ufa, Russia) with standard DDS reagents from Diakon (Pushchino, Russia).

For statistical data processing, the STATISTICA 6.0 software package was used; the Mann-Whitney non-parametric test was used to identify differences between groups. The critical significance level p for testing statistical hypotheses was taken as 0.05. All experimental data are presented as mean ± standard error of the mean (M ± SE).

Results and discussion. Coagulopathy, often observed in accidental hypothermia and acidosis, can be caused by a decrease in the number and/or function

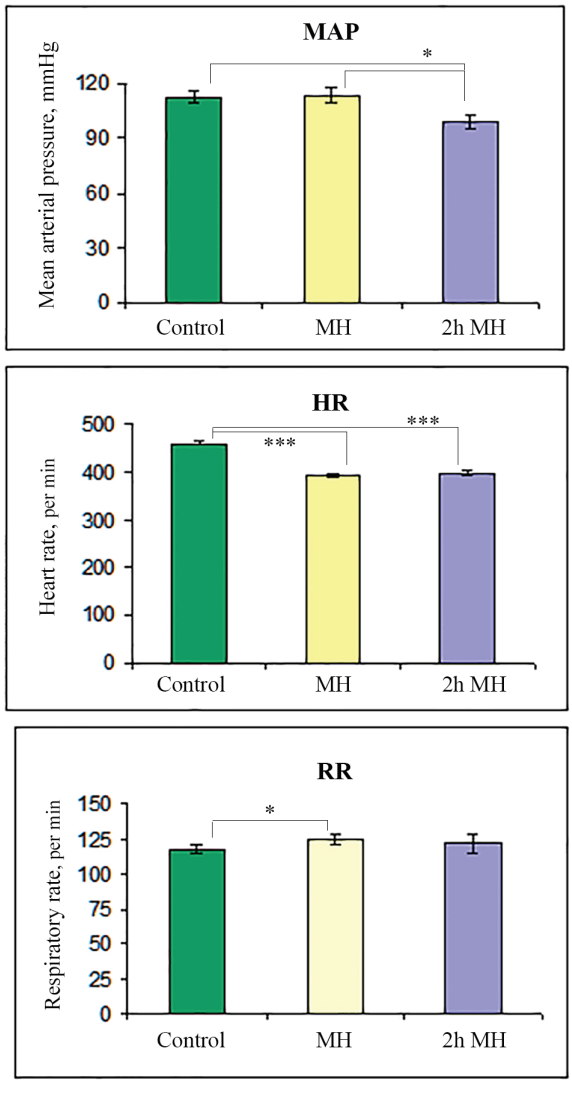

Fig. 1. Effect of moderate hypothermia on SAP, HR, and RR.
Note: MH – moderate hypothermia upon reaching Tr 32°C; 2h MH – prolongation of moderate hypothermia at Tr 32°C for 2 hours.

of platelets, thrombin and fibrinogen synthesis/degradation, and also by a specific effect on various blood clotting factors [20]. We developed our experimental hypothermia model to investigate whether, compared to normothermia, induced general hypothermia alters the coagulation link of hemostasis, which could lead to increased bleeding when using body cooling in the clinic.

Unlike mild hypothermia [32], moderate hypothermia significantly suppresses hemodynamic responses, especially when using general anesthesia. In our experiment, when cooling anesthetized rats to a rectal temperature (Tr) of 32°C (Fig. 1), a 15% decrease in heart rate (HR) ($p<0.001$) compared to the norm and a 14% increase in respiratory rate (RR) ($p<0.05$) were noted, while systolic arterial pressure (SAP) did not change. Prolonging hypothermia at Tr 32°C for two hours led to a 13% decrease in SAP ($p<0.05$), while no further changes in HR and RR occurred.

In this study, we determined a number of parameters of the coagulation link of hemostasis (APTT, TT, PT). Thrombin time (TT) reflects the interaction of thrombin with fibrinogen – the final stage of blood clotting. Prothrombin time (PT) measures the time required for clot formation in the presence of a thromboplastin-calcium mixture, which ensures the functioning of the extrinsic pathway of fibrin formation. Activated partial thromboplastin time (APTT) measures the time required for clot formation in the presence of an activator of the intrinsic pathway of blood coagulation and calcium, and assesses the ability to form fibrin through the sequential interaction of a number of blood clotting factors [3].

The results of this study allow us to conclude that lowering body temperature to moderate hypothermia significantly affects the activity of the extrinsic and intrinsic pathways of blood coagulation in rats. When assessing coagulation hemostasis parameters in rats cooled to Tr 32°C (group 2), it was established (Fig. 2) that APTT was prolonged by 29%, TT by 41%, and PT by 17% ($p<0.001$). With the prolongation of moderate hypothermia (group 3), APTT and PT returned to normal, while TT remained elevated (by 30% above normal).

The study [4] showed a phased nature of changes in the hemostatic system depending on the duration of a single cold exposure necessary to achieve a particular degree of hypothermia. The hypocoagulation shifts recorded in the initial stages of hypothermia are replaced

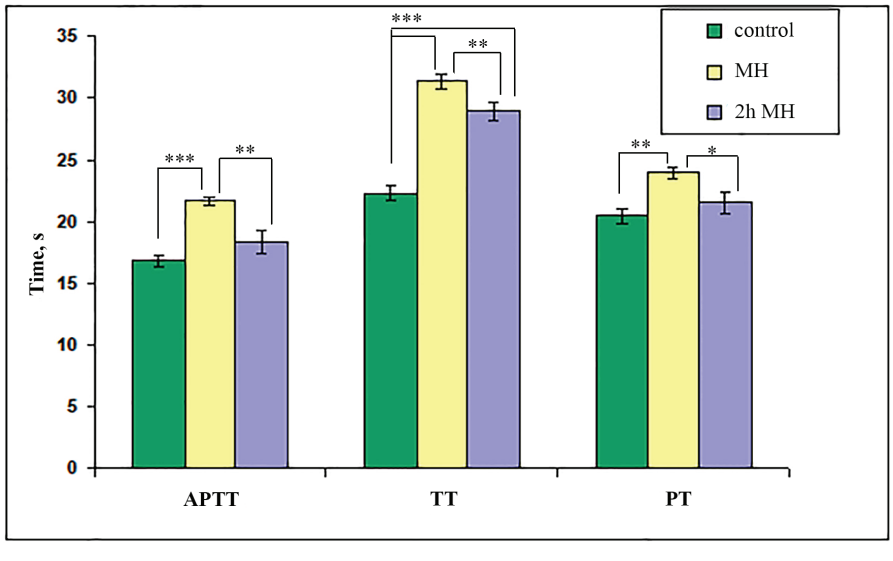

Fig. 2. Changes in activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time (PT) during moderate hypothermia in rats

by the development of a thrombotic readiness state as body temperature decreases. In our experiment, when Tr decreased and was maintained at 32°C, we observed similar changes in APTT, TT, and PT, indicating hypocoagulation shifts at moderate hypothermia.

A study investigating coagulation hemostasis at a higher Tr in rabbits [32] showed that short-term mild hypothermia affects the blood clotting mechanism to a clinically insignificant extent. With the use of mild hypothermia [15] in patients with traumatic brain injury over two days, prolongation of PT and APTT was observed, and when the duration of temperature exposure was increased to five days, PT and APTT decreased significantly (more than 35%), which likely indicates a dependence of the coagulation link of hemostasis on the duration of induced hypothermia. Our study at a lower Tr also showed a dependence of APTT and TT on the duration of hypothermic exposure.

Hypothermia reduces the activity of enzymes in the coagulation cascade reactions [18]. Enzymes, like all biochemical reactions, slow down with decreasing temperature. In general, impaired thrombin generation is one of the main factors contributing to coagulopathy during hypothermia. The slowing of this key enzyme's activity leads to disruption of the entire blood coagulation cascade, increased clotting time, and increased bleeding risk. Analysis of kinetic curves characterizing thrombin generation and the formation of the thrombin-antithrombin complex [22] showed that hypothermia in the temperature range from 36°C to 31°C gradually slowed thrombin generation, as evidenced by clotting time, time to reach the thrombin peak, and prothrombin time, which increased in all subjects. Our work also supports the idea that impaired thrombin generation may be a key factor in hypothermia-induced coagulopathy, since the maximum changes in the coagulation link of hemostasis during hypothermia concerned the increase in thrombin time both upon reaching Tr 32°C and with the prolongation of moderate hypothermia at Tr 32°C for 2 hours.

Results obtained in vitro in isolated hypothermic platelets [35] showed a temperature-dependent decrease in thrombin generation: in hypothermic platelet samples, thrombin generation was 25% (33°C) and 68% (23°C) lower compared to normothermic platelet samples. These results lead to the conclusion that with hypothermia, proper microvascular hemostasis may be initially delayed due to a delay in the thrombin initiation phase, i.e., moderate hypothermia leads to a delay in thrombin generation in the initial stage. Our study confirmed that induced hypothermia primarily affects the rate of thrombin formation; these changes are likely temporary.

Hypothermia significantly affects both blood clotting and hemorheology. According to [18], the increase in blood viscosity with decreasing body temperature leads to hematological concentration and increased hematocrit. In our study, we also obtained an 8% increase in hematocrit upon reaching Tr 32°C (group 2), and a 15% increase with prolonged hypothermia (group 3).

Cold stress, stimulating the release of catecholamines such as adrenaline and noradrenaline, can lead to increased vascular resistance and reduced blood flow in peripheral vessels [6]. As a result, platelets may be retained in the vessels, which can contribute to their destruction and a decrease in their number in the blood. In addition, thrombocytopenia during hypothermia can occur due to platelet sequestration [18], and this, in turn, can lead to uneven distribution of platelets in the vessels. In our work, we recorded a significant decrease in the number of platelets (by 80% in group 2 and by 92% in group 3, $p<0.001$). Accordingly, the risk of bleeding in the cold may increase due to a decrease in the number of platelets themselves, and, consequently, the ability of platelets to adhere and form thrombi. It should be noted that the values of the mean platelet volume and platelet distribution width by volume with hypothermic exposure differed insignificantly from the initial values (within 5-9%).

Thus, it has been shown that a number of enzymatic reactions of the coagulation cascade are inhibited by induced general moderate hypothermia, as evidenced by the significant prolongation of PT, APTT, and TT with a decrease in Tr in rats to 32°C and the preservation of the increased TT value with the prolongation of moderate hypothermia at Tr 32°C for 2 hours. We believe that when diagnosing and managing patients with reduced body temperature, the prolongation of blood clotting time and the risks of perioperative bleeding should be taken into account.

Conclusions:

1. With single, short-term cooling of anesthetized rats to Tr 32°C (to the stage of moderate hypothermia), an increase in activated partial thromboplastin time, thrombin time, and prothrombin time occurs, indicating the development of hypocoagulation shifts and impairment of secondary hemostasis.

2. During maintenance of Tr at 32°C for two hours, a decrease in APTT, TT, and PT parameters from the achieved values is observed, which probably indicates some alteration of coagulation reactions with prolonged exposure to moderate hypothermia.

3. Upon reaching the boundary of moderate hypothermia, the main changes may be associated with impaired thrombin generation, which may be a key factor in hypothermia-induced coagulopathy.

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Author has no conflict of interest to declare.

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FRAILTY INDEX AND ITS ROLE IN EMERGENCY SURGERY OF ACUTE ABDOMINAL DISEASES IN ELDERLY PATIENTS

Frailty is an important predictor of adverse outcomes in elderly patients with acute abdominal diseases requiring surgery. Preoperative assessment of frailty can significantly improve the prognosis of surgical outcomes and postoperative recovery.

Objective: To study the influence of frailty on the immediate and long-term results of surgical treatment in elderly patients with acute diseases of the abdominal cavity.

Materials and methods: The study involved 154 patients over the age of 62 with acute diseases of the abdominal organs who underwent surgical treatment. Patients were divided into two groups based on the Edmonton Frail Scale (EFS). Complications were classified according to the Clavien-Dindo system. The short- and long-term results of surgical treatment were assessed.

Results: The postoperative period was more complicated in patients with high frailty index. The ICU days were more for patients with the frailty score more than 7. They demonstrated delayed initiation of active movement and food intake, as well as a higher incidence of postoperative complications. 2nd and 3rd Grade ccomplications according Clavien-Dindo classification were significantly higher in patients with a high frailty index in the postoperative short-term. However, 1st Grade complications were more common in patients without frailty. In the group with a high frailty index, unsatisfactory long-term results were observed, including an increased risk of rehospitalisation (readmission) and a decreased functional status.

Conclusion: Frailty assessment plays a key-role in improving postoperative outcomes in elderly patients with acute abdominal diseases. Further research is necessary to develop methods that can mitigate the negative impact of frailty on surgical outcomes.

Keywords: elderly, frailty assessment, emergency surgery, abdominal diseases, outcomes/results.

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Introduction. Understanding the role of frailty is of utmost importance in emergency surgery, particularly in elderly patients with acute diseases of the abdominal cavity. Acute abdominal diseases such as appendicitis or intestinal obstruction pose a significant health threat to the elderly population due to age-related physiological changes and comorbidities. Treatment of such conditions often requires urgent surgical intervention, and the presence of frailty may complicate treatment tactics and may affect outcomes in patients [1–3].

Frailty often characterised by reduced physiological reserve and increased vulnerability to stressors is a major challenge in surgical treatment.

Elderly patients with increasing frailty may experience decreased functional status, delayed wound healing, and increased susceptibility to postoperative complications such as infections and delirium. In addition, preoperative frailty assessment is critical for risk stratification and informed decision-making regarding the feasibility of surgical intervention and approaches to perioperative care [4–7].

This article presents a comparative study of two groups of elderly patients with acute abdominal diseases and an examination of the impact of frailty on surgical outcomes. By assessing frailty degrees using validated tools such as the Edmonton Frail Scale, we aim to elucidate the association between frailty and the surgical complication rate, mortality and healthcare utilization.

Materials and methods. The research is based on the examination of patients over the age of 62 with acute surgical diseases of the abdominal organs. Along with routine examinations, all patients were assessed for their "frailty index" according to the Edmonton scale. In 68 patients, the frailty index was calculated to be below 7, indicating no signs of frailty according to the Edmonton scale. Among patients who applied in 2021, 86 people had a frailty index greater than 7, indicating the presence of senile frailty. The comparison of patients without frailty with patients whose frailty index was higher than 7 were performed. The results of surgical treatment of acute surgical diseases of abdominal organs in elderly patients with and without frailty were compared.

The anthropometric indicators of patients without frailty were as follows: the average age of patients was 69.3±0.8, ranging from 62 to 87. Among patients without frailty, men predominated (n=48; 70.6%).

The number of women was approximately three times less (n=20; 29.4%).

The average age of patients with a frailty index of more than 7, i.e., with signs of frailty, was 69.7 ± 0.71, ranging from 62 to 87. Among patients with frailty, men accounted for n=54; 62.8%, while women n=32; 37.2%.

The incidence of main diseases as an indication for surgery, was compared in patients with a frailty index above 7 and without fragility. The analysis showed that patients with hernias prevailed in the group without frailty. The incidence of hernias in the group without frailty was 69.1%, but in patients with a fragility index above 7 this figure was 50%. The difference in the incidence of hernias between the groups was statistically significant ($p<0.05$). However, when analysing the incidence of gallstone disease, the opposite trend was observed. The incidence of gallstone disease in the group without frailty was only 11.8%, while in the group of patients with a high frailty index this figure was 26.7%. The incidence

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of gallstone disease in patients with a frailty index above 7 was statistically significantly higher than in the group without frailty (p<0.05). The results of the frequency of occurrence of other major disease groups in patients without frailty and with a frailty index above 7 were as follows: perforated ulcer (4.4% and 9.3%), gastrointestinal bleeding (0 and 3.5%), acute intestinal obstruction (7.4% and 7%), acute appendicitis (7.4% and 3.5%). The differences in the frequency of occurrence of these major diseases between the groups were statistically insignificant (p>0.05).

The incidence of acute diseases of the abdominal cavity among the comparable groups is presented in Table 1.

The Edmonton Frail Scale (EFS), a widely used instrument to measure alterations related to frailty, was used to assess the frailty degree in elderly people [8]. The scale consists of 10 items, each rated on a scale of 0 to 1 or 0 to 2, depending on the specific question. Questions include assessment of cognitive status, functional independence, functional performance, continence, social support, and medication use. The total score ranges from 0 to 17, with higher values indicating greater frailty [9].

Both groups of patients were treated by the same hospital team, ensuring consistency in the surgical approach and postoperative care. All patients underwent surgery for medical reasons. The types of surgical procedures performed in patients with and without frailty were shown in the Table 2.

The statistical analysis using the Chi-Square test showed the following results: Pearson Chi-Square test value = 11.679; p-value = 0.020. Since p < 0.05, it can be stated that there is a statistically significant difference in the number of operations between the groups. Likelihood ratio value = 12.155; p-value = 0.016. This result also confirms the significance of the differences (p < 0.05). Linear by linear relationship = 1.064; p-value = 0.302. This result shows that the linear relationship is not significant. Thus, the differences are due to the distribution by categories.

Postoperative results were compared between groups. The main criterion for assessment was the frequency of postoperative complications. The Clavien-Dindo classification was used to rank the severity of surgical complications. This system, developed by Dr. Pierre Clavien and Dr. Daniel Dindo in 2004, has become a standard tool for reporting and comparing surgical outcomes across studies and institutions. The classification divides complications based on their clinical severity and the necessary interventions for treatment. According to this classification, complications are divided into the following grades:

Grade I–any deviation from the normal postoperative course without the need for pharmacological or surgical treatment and interventions.

Grade II – requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and total parenteral nutrition (TPN) are also included.

Grade III – requiring surgical or endoscopic intervention:

IIIa–intervention not under general anaesthesia, i.e. local anaesthesia.

IIIb–intervention under general anaesthesia.

Grade IV – life-threatening complications (including those affecting the brain) requiring intensive care management:

IVa – single organ dysfunction (including dialysis);

IVb –multi-organ dysfunction.

Fatal outcomes are classified as Grade V.

The Clavien-Dindo classification provides a standardised and objective way of assessing the severity of postoperative complications. This facilitates comparisons between different studies and helps clinicians and researchers better understand the impact of surgical interventions on patient outcomes [10].

Secondary assessment criteria included the duration of stay in the intensive care unit, hemodynamic parameters, respiratory rate, time to the onset of independent feeding, and time to the first bowel movement.

Table 1

The Incidence of Acute Diseases of the Abdominal Cavity

	Frailty index <7	Frailty index >7	Significance
Complex hernia	47 (69.1)	43 (50)	p<0.05
Calculous cholecystitis	8 (11.8)	23 (26.7)	p<0.05
Perforated ulcer	3 (4.4)	8 (9.3)	p>0.05
GI (gastrointestinal bleeding)	0	3 (3.5)	p>0.05
Obstructive ileus/Intestinal obstruction	5 (7.4)	6 (7)	p>0.05
Acute appendicitis	5 (7.4)	3 (3.5)	p>0.05

Table 2

The types of surgical procedures

Surgical Procedure	Patients without frailty: number (%)	Patients with frailty index >7: number (%)	Significance
Hernioplasty	46 (67.6)	41 (47.7)	p<0.05
Cholecystectomy	9 (13.2)	23 (26.7)	p<0.05
Stomach surgery	2 (2.9)	9 (10.5)	p<0.05
Ileus surgery	6 (8.8)	11 (12.8)	p<0.05
Appendectomy	5 (7.4)	2 (2.3)	p<0.05

Statistical analysis. All numerical indicators obtained during the study were arranged in order of variation, and the mean value and standard error (M±m) were calculated for each row. A non-parametric method, i.e., the Wilcoxon (Mann-Whitney) criterion (U) was used to determine differences between group indicators. All statistical procedures were performed using the IBM SPSS 22 program.

Research results and their discussion. Immediate postoperative results: Comparative analysis in the immediate postoperative period revealed significant differences between the two groups. The average duration of stay in the intensive care unit after surgery in patients without frailty was 2.52 ± 0.22 days. Patients with a high frailty index spent an average of 4.16±0.32 days in the intensive care unit (minimum 1 and maximum 16 days), which indicates a more severe course of the postoperative period. The difference in the duration of stay in the intensive care unit was statistically significant (p<0.001).

The groups were compared in terms of the time it took to start active movements, independent food intake, and ability to communicate during treatment in the surgical hospital. Patients with a frailty index of less than 7 required an average of 1.59±0.11 days to start active movements after surgery. In patients with a frailty index greater than 7 this period increased to 2.7±0.25 days (p<0.001). In addition, patients without frailty received oral nutrition on average 1.8±0.13 days after surgery. In patients with a high frailty index, 2.9 ± 0.24 days were required to initiate oral nutrition.

It took a significantly longer time for weakened patients to begin food intake (p<0.001). Another important observation was the comparison of time to the first bowel movement. In the group of patients with a high frailty index, this occurred after 2.98±0.26 days, while in the other group – after 1.87±0.14 days. Patients with a high frailty index had a higher rate of complications in the short-term postoperative period. These complications ranged from surgical site infections to postoperative delirium, suggesting an increased vulnerability of frail patients to surgical stressors. Table 2 shows the complication rates in both groups according to the Clavien-Dindo classification.

In addition, clinical indicators of patients with a high frailty index was significantly suboptimal, highlighting the challenges in managing this cohort during the acute phase of recovery. It was found that cases of shortness of breath occurred more often in patients with a high frailty index. The respiratory rate in patients with frailty was significantly higher (20.2±0.29 per minute, p<0.05) compared to patients without frailty (14.8±0.13 per minute). Pain intensity in patients without frailty was lower compared with the other group. The time of the surgical wound healing was shorter in the group of patients without frailty.

The average duration of hospital stays for patients without frailty came to 3.7±0.25 days, which was statistically significantly less (p<0.001) than for patients with a high frailty index, which came to 5.3±0.32 days.

Long-term postoperative results:

In addition to the immediate postoperative period, the influence of frailty also affected the long-term results of surgical interventions. All patients were invited to the clinic 30 days after surgery for examination. Patients with a high frailty index faced persistent challenges including longer hospital stays, increased risk of rehospitalisation (readmission), and deterioration of functional status compared with their healthy counterparts. These results highlight the complex relationships between frailty and surgical outcomes, which indicates the need for individual strategies for managing patients in the preoperative period.

As can be seen from Table 3, the incidence of complications of grades 1, 2 and 3a during the first 30 days after discharge was statistically significantly higher in the group with a high frailty index.

Discussion. This study examines the impact of frailty on surgical outcomes in elderly patients with acute abdominal diseases. One of the strongest aspects of our study is the comprehensive assessment of frailty using the Edmonton Frail Scale (EFS), a validated instrument that covers multiple aspects of frailty such as cognitive status, functional independence, and social support. We managed to establish a relationship between frailty and surgical outcomes by dividing patients into groups based on their preoperative frailty index.

However, our study has several limitations. First, the sample size of 154 elderly patients may limit the generalisation of our findings to broader populations. Additionally, the single-centre study design may introduce biases related to institutional practices and patient demographics. Even though we used the Clavien-Dindo classification to categorise postoperative complications, the subjective nature of some criteria may cause variability in the assessment.

Our results highlight the significant impact of frailty on surgical outcomes in elderly patients with acute diseases of the abdominal cavity. Patients with frailty experienced longer intensive care unit stays, delayed postoperative recovery, and higher rates of postoperative complications compared to the group without frailty.

Complications of the first degree of severity according to the Clavien-Dindo

Table 3

Rate of surgical complications within 7 days after surgery

CDC Grades	Frailty index <7		Frailty index >7		p
	n	%	N	%	
Grade 1	29	42.6	4	4.7	<0.001*
Grade 2	24	35.3	48	55.8	<0.05*
Grade 3a	12	17.6	28	32.6	<0.05*
Grade 4b	3	4.4	6	7.0	>0.05

Note: *<0.05 difference is reliable.

Table 4

Shows the surgical complication rate 30 days after surgery

Clavien-Dindo complications	Frailty index <7		Frailty index >7		p
	n	%	n	%	
Grade 1	21	30.9	47	54.7	<0.001*
Grade 2	4	5.9	16	18.6	<0.05*
Grade 3a	3	4.4	17	19.8	<0.001*
Grade 4b	2	2.9	2	2.3	>0.05

Note: *<0.05 difference is reliable.

classification were more often recorded in the group of patients without frailty, without requiring drug treatment and intervention. A statistically significant difference ($p<0.05$) was found when comparing the incidence of grade 1 complications between the groups. Severity complications of Grades 2 and 3 were predominant in patients with a high frailty index. Severity complications of Grade 2 were recorded in 48 patients (55.8%), and Grade 3 in 28 patients (32.6%). Only the difference in severity complications of Grade 4B was not statistically relevant between the groups.

However, in the high frailty index group, the rate of Grade 4b complications came to 7%, which was higher than in relation to the other group (4.4%).

These results emphasize the importance of preoperative frailty assessment for risk stratification and decision-making regarding surgical strategy and perioperative care.

Furthermore, our study provides valuable information on the long-term consequences of frailty in the context of surgical repair. Patients with a high frailty index experienced persistent problems: rehospitalisation, and decreased functional status, highlighting the need for individual strategies in the preoperative and postoperative periods. Despite the assistance provided, 6 patients died, and the 30-day mortality rate came to 3.9%.

Our results are consistent with previous studies demonstrating the negative impact of frailty on surgical outcomes in elderly patients. A study by Makarii et al. (2010) found that frailty was associated with increased postoperative complications and mortality in elderly patients who underwent surgery [11]. Similarly, Robinson et al. (2019) reported that frailty was a major predictor of adverse outcomes after emergency abdominal surgery in elderly patients [12].

However, some studies have shown contradictory results regarding the association between frailty and surgical outcomes [13–16]. For example, Amini et al. (2018) found no substantial differences in the rate of postoperative complications between frail and healthy elderly patients who underwent planned surgical procedures [17].

These discrepancies may be related to differences in study populations, frailty assessment tools, and types of surgical interventions.

Conclusion. Our study stresses the critical role of frailty assessment in optimization of surgical outcomes in elderly patients with acute abdominal diseases. Despite some limitations, our results provide valuable insights into the complex interactions between frailty, surgical stressors, and postoperative recovery. Additional research is needed to confirm our findings in larger multicentre samples and explore potential interventions to mitigate the impact of frailty on surgical outcomes.

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CORRELATION ANALYSIS OF THE IMMUNOLOGICAL AND CLINICAL PARAMETERS OF PATIENTS WITH ENDO-PERIODONTAL LESIONS

In the practice of therapeutic dentistry, the most difficult from the point of view of diagnosis and prediction of treatment results are patients with simultaneous pulp and periodontal lesions in the same segment вdue to the fact that their anatomical, embryonic and functional relationships determine a high probability of joint participation in the pathological process. Inflammatory processes occurring in the pulp and periodontal tissues can lead to cause both auto- and heterosensitization of the body, which, in turn, leads to a decrease in its immune defense. The aim of the study was to determine the effectiveness of studying the level of cytokines in the diagnosis of endo - periodontal lesions. Materials and methods. We compared clinical and immunological parameters in 82 patients with endo-periodontal lesions and 47 periodontologically healthy individuals aged 23-54 years. The clinical examination included assessment of hygiene status using the Green–Vermillion Simplified Hygiene Index (OHI-S), as well as periodontal status determined by the bleeding index (SBI) and Russell periodontal index (PI) and PMA. The state of local immunity was determined by the level of pro-inflammatory (TNF-α, IL - 1ß , IL-6) and anti-inflammatory (IL-4, IL-10) cytokines and IgA. The result of the study revealed a correlation between the severity of inflammatory processes in periodontal tissues and the level of pro-inflammatory cytokines. We found statistically significant differences in the concentrations of TNF-α and IL-6 in the oral fluid of patients with endo - periodontal lesions depending on the severity of periodontal damage, which underlines the role of these cytokines in the progression of the disease. The study of periodontal status and its relationship with the level of cytokines in the oral fluid revealed important correlations that indicate the prospects of using immunological markers for the diagnosis and prediction of the course of periodontal diseases.

Keywords: periodontal disease, endo-periodontal lesions, cytokines, local immunity.

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Introduction. The modern scientific paradigm is based on the belief that the properties of the whole can be explained based on the properties of the parts. All sicentific research begins with the study of the function of isolated organs, cells, or molecules. It is important that an integrated approach to the interpretation of patient examination data, as well as dynamic treatment results, can provide a new understanding of the nature of the disease as a violation of harmony in a living system.

In the practice of therapeutic dentistry, patients with simultaneous pulp and periodontal lesions in the same segment are the most difficult from the point of view of diagnosis and prediction of treatment results, due to the fact that their anatomical, embryonic and functional relationships determine a high probability of joint participation in the pathological process [5,9,]. The spread of infection from pulp to periodontal and vice versa is a complex process involving several pathways, often working synergistically, which leads to a high probability of developing inflammatory diseases. There are various hypotheses about the ways and mechanisms of infection spread. One of the most studied methods is spreading through the dentinal tubules. A significant role is also assigned to the hematogenic pathway. Bacteria, due to their ability to adhere and form biofilms, spread in both apical and coronal directions. Another way is to spread through the palato-gingival furrows, which can serve as a reservoir for pathogenic microflora. Also, we should not forget about the role of lateral tubules, which often go unnoticed during endodontic treatment and significantly complicates the complete rehabilitation of the focus of infection, contributing to the relapse of the disease. The infection can also migrate through the alveolar bone, causing osteolysis. [5,9]. The mechanism of this process is related to the body's immune response to infection, including the activation of osteoclasts. Finally, the common lymphatic system, which connects all structures of the maxillofacial region, is of great importance [1,2].

Currently, it is proved that the cause of endo-periodontal lesions (EPL) is the association of microbial communities – biofilms. As a result of bacterial contamination, first of all, the epithelium is damaged, there by provoking an increase in periodontal permeability for pathogenic microorganisms and their metabolic products, which initially leads to inflammation of periodontal tissues and subsequently to bone destruction[3,4,7].

Inflammatory processes occurring in the pulp and periodontal tissues can cause both auto-and heterosensitization of the body, which, in turn, leads to a decrease in its immune defense. In the current pathogenesis of EPL, it is recognized that immune components play an important role. Studies show that assessment of the local immune status of the oral cavity in inflammatory diseases of the mouth can be useful both for diagnosis and for predicting the consequences of diseases[5,6].

Immunocompetent cells responsible for protecting the body can also initiate destructive processes. The protective function is that the lack of the immune system often leads to pulp and periodontal pathologies. The destructive function is manifested through the ability of immune cells to secrete cytokines, which causes the destruction of connective tissue and bone resorption. This suggests

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that early elimination of bacterial contamination may increase the chances of developing immunological reactions that do not lead to bone loss[8, 10].

Modern studies have confirmed that a decrease in the reactivity of the immune system is associated with dystrophic changes and impaired regeneration processes in periodontal tissues. The level of cytokines in saliva can serve as an indicator of the activity of macrophages and monocytes located in the oral mucosa[1,7].

Some studies indicate that minimal amounts of pro-inflammatory cytokines are necessary for the formation of an inflammatory focus and subsequent recovery. At the same time, high levels of IL-1β and IL-6 may indicate a chronic inflammatory process. Scientists suggest that an imbalance in the level of cytokines plays a key role in the development of chronic inflammatory reactions, which gives cytokines significant diagnostic and prognostic value[4,7].

The aim of our study was to determine the effectiveness of studying the level of cytokines in the diagnosis of endo-periodontal lesions.

Materials and methods. The study was conducted on the basis of the dental clinic of the Kazan State Medical University of the Ministry of Health of the Russian Federation. The sample included 129 people aged 23-54 years, who sought dental care, who were divided into two groups depending on the presence of endo-periodontal lesions (EPL): the main group and the comparison group. The main group included 82 patients who had a combination of endodontic and periodontal lesions in one sector during clinical examination, including 30 men (36.4%) and 52 women (63.6%). The comparison group consisted of 47 patients with healthy periodontitis, including 25 men (55.6%) and 22 women (44.4%). The clinical examination included assessment of hygiene status using the Green–Vermillion Simplified Hygiene Index (OHI-S), as well as periodontal status determined by the bleeding index (SBI), Russell periodontal index (PI) and PMA. The state of local immunity was determined by the level of pro-inflammatory (TNF-α, IL - 1ß, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines and IgA, using an enzyme-linked immunosorbent assay, with the inclusion of a set of reagents from Vector-Best LLC (Russia) according to generally accepted rules in the Central Research Laboratory FEDERAL State Budgetary Educational Institution Of Higher Education Of The Ministry Of Health Of The Russian Federation. Statistical analysis was performed using the IBM SPSS Statistics 20 program To assess the diagnostic significance of quantitative features in predicting a certain outcome, the method of ROC-curve analysis was used.

Results and their discussion. Data analysis showed that the differences between the groups by gender did not reach statistical significance (p=0.198). The average age of participants in the main group was 38.5 years (Q1-Q3: 33.0-47.0 years), while in the control group it was 23 years (Q1-Q3: 22.0-25.0 years). The differences in age between the study groups were statistically significant (p<0.001), which indicates a significantly older age of patients with EPL.

Comparison of the studied groups was also carried out by the level of cytokines in saliva. The results of the analysis clearly demonstrated the presence of statistically significant differences in the levels of all studied cytokines in the oral fluid of participants, which depended on the presence of EPL (p<0.001). The study of cytokine levels in patients with EPL made it possible to identify promising markers for early diagnosis and assessment of the severity of the disease. Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine that is considered in numerous studies as a key mediator of immune inflammation in various human pathologies. Comparing the level of TNF-α in patients with EPL and healthy persons, it was found that its concentration in the oral fluid of patients with EPL was significantly higher than in the control group. Accordingly, the level of TNF-α in the oral fluid, equal to 2.0 pg/ml, can serve as a dividing value. This makes it possible to classify patients according to the presence of EPL with 100% diagnostic efficiency. (Table 1).

Analysis of interleukin-10 (IL-10) concentrations showed that values of ≤ 2.05 pc/ ml predict a high risk of developing EPL. IL-10 levels above this threshold were associated with a low probability of disease. However, IL-10 is only one of many factors involved in the pathogenesis of EPL. Its role is complex and multifaceted: IL-10, being an anti-inflammatory cytokine, can both suppress inflammation and promote its development, depending on the balance with other cytokines and the conditions of the immune response.

Table 1

Comparative analysis of cytokine content in oral fluid depending on the presence of EPL

Cytokines	of the study groups				p
	Main		Comparison		
	Me	Q_1-Q_3	Me	Q_1-Q_3	
TNF, pkg/ml	17.38	11.85-24.71	1.24	1.01-1.62	<0.001*
IL-10, pkg / ml	1.0	0.69-1.38	3.85	3.07-5.14	<0.001*
IgA, g / l	5.23	3.92-6.79	1.96	1.61-2.87	<0.001*
IL-6, pkg / ml	8.91	6.17-11.46	2.25	1.23-3.66	<0.001*
IL-1β, pkg / ml	9.86	8.34-13.28	1.85	1.21-2.92	<0.001*
IL-4, pkg / ml	12.58	8.39-19.73	2.54	1.08-3.57	<0.001*

* - differences in indicators are statistically significant (p<0.05)

Table 2

Data from ROC analysis of the relationship between the level of cytokines in the oral fluid and the presence of EPL

Cytokines	cut-off	Area under the ROCcurve (S_{xy})		Diagnostic efficacy	
		S_{xy}±m	95% ДИ	Se, %	Sp, %
TNF, pkg / ml	2.0	1.0	1.0-1.0	100.0	100.0
IL-10, pkg / ml	2.05	0.95±0.03	0.89-1.0	99.1	88.9
IgA, g / l	3.18	0.92±0.03	0.87-0.98	84.5	83.3
IL-6, pkg / ml	4.69	0.95±0.02	0.91-0.99	91.8	83.3
IL-1β, pkg / ml	4.08	0.98±0.01	0.95-1.0	93.6	94.4
IL-4, pkg / ml	4.86	0.98±0.01	0.96-1.0	94.5	94.4

Further analysis expanded the range of markers studied to include IL-6, IL-4, IL-1β, and IgA. Evaluation of the prognostic value of these indicators showed that TNF-α shows the greatest correlation with the development of EPL, followed by IL-10, IL-4, and IL-1β. This indicates an important role of pro-inflammatory cytokines in the development and progression of the disease. It is important to note that high levels of IgA in saliva do not always correlate with the severity of the disease, which may be due to its diversity of isotypes and its role in various immune mechanisms. (Table 2).

For a more in-depth study of the pathophysiological mechanisms of EPL, a correlation analysis of the relationship between cytokine levels and dental indices was performed: periodontal Russell index (PI), gum bleeding index (SBI), and PMA. The results of the analysis revealed statistically significant direct correlations between PI values and TNF-α, IL-6, IL-1β, and IL-4 concentrations in patients suffering from EPL. This indicates a strong relationship between the severity of inflammatory processes in periodontal tissues and the level of pro-inflammatory cytokines.

Correlations between SBI and cytokine concentrations (TNF-α, IL-10, IL-6, IL-1β, IL-4) were also statistically significant, but were characterized by a low density. This may indicate that gum bleeding is only one indicator of the inflammatory process, while a comprehensive analysis should take into account a wide range of different biomarkers.

An increase in the PI, PMA, and SBI indices significantly correlated with high levels of TNF-α, IL-6, and IL-1β, as well as with lower levels of IL-4 and IgA. These results confirm the multifactorial nature of periodontal inflammation, which includes both pro-and anti-inflammatory cytokines. The levels of TNF-α, IL-10, IL-4, and IL-1β demonstrated the greatest prognostic significance for assessing the risk of developing chronic inflammation. (Table 3). In particular, TNF-α occupies a leading position in the ranking of prognostic markers.

Moreover, there were statistically significant differences in the concentrations of TNF-α and IL-6 in the oral fluid of patients with EPL, depending on the severity of periodontal damage (PI), which emphasizes the role of these cytokines in the progression of the disease. TNF-α, being a powerful pro-inflammatory cytokine, stimulates the production of other inflammatory mediators, and IL-6 plays a key role in regulating the inflammatory response and the body's systemic response to infection. Understanding this relationship opens up new opportunities for developing personalized therapies focused on controlling the levels of these cytokines.

Table 3

Data of correlation analysis of the relationship between the level of cytokines in the oral fluid and dental indices

Cytokines	Dental indexes							
	OHI-S		PI		PMA		SBI	
	ρ_{xy}	p	ρ_{xy}	p	ρ_{xy}	p	ρ_{xy}	P
TNF	0.027	0.779	0.286	0.002*	0.093	0.334	0.251	0.008*
IL-10	-0.085	0.376	0.034	0.728	-0.074	0.444	0.188	0.049*
IgA	0.006	0.953	-0.009	0.928	-0.012	0.902	-0.006	0.949
IL-6	-0.084	0.383	0.332	<0.001*	0.058	0.545	0.235	0.014*
IL-1β	0.039	0.684	0.274	0.004*	0.077	0.422	0.221	0.02*
IL-4	-0.06	0.536	0.224	0.019*	0.118	0.219	0.211	0.027*

* - the correlation is statistically significant ($p<0.05$)

Conclusion. The study of periodontal status and its relationship with the level of cytokines in the oral fluid revealed important correlations that indicate the prospects of using immunological markers for the diagnosis and prediction of the course of periodontal diseases. The obtained data confirm the high informative value of the analysis of cytokines in the oral fluid for the diagnosis and monitoring of the treatment of periodontal diseases. Determination of TNF-α, IL-1β, IL-6, IL-10, and IL-4 levels in mixed saliva can serve as an additional tool for evaluating the effectiveness of therapy and predicting the risk of complications. It is important to note that using only the applied indices may not be sufficient to fully assess the severity of periodontitis and predict its course. An integrative approach that combines clinical assessment with laboratory methods for determining cytokine levels allows you to get a more complete and reliable picture of the periodontal condition and make more informed treatment decisions.

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FEATURES OF GENETIC MARKERS OF OXIDATIVE STRESS AND FUNCTIONAL LABORATORY PARAMETERS IN COMORBID PATIENTS WITH CAROTID ATHEROSCLEROSIS

The features of the dependence of the degree of atherosclerotic stenosis of the carotid arteries on the expression level of oxidative stress marker genes in patients with atherosclerosis and comorbid pathology were studied. The association of decreased expression of the genes encoding antioxidant defense factors *GSTP1, NRF2, HMOX1* with ultrasound signs with increasing severity of atherosclerotic stenosis of the carotid arteries; an inverse correlation between the expression of the *HMOX1* gene and the degree of stenosis of the right internal carotid artery, between the level of expression of the *GSTP1* gene and the degree of stenosis of the left internal carotid artery; a direct correlation between the diameter of the right common carotid artery and the level of total cholesterol and low-density lipoprotein cholesterol in the blood serum were revealed. The knowledge gained can be used to develop a new medical technology for predicting the progression of atherosclerosis.

Keywords. Carotid atherosclerosis, gene expression, antioxidant protection, dyslipidemia, ultrasound duplex scanning.

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Introduction. In modern clinics, the incidence of atherosclerosis (AS) occurring in comorbidity (CM) conditions is increasing [1, 3, 6]. Depending on the localization and severity of AS, certain clinical and morphological manifestations are formed [6, 7]. Starting with endothelial dysfunction followed by a specific cascade of intra- and intercellular reactions, AS can form one of the pathogenetic platforms of cardiovascular CM [9]. Risk factors for endothelial damage, early stages of AS include: hypercholesterolemia, hyperhomocysteinemia, elevated cytokine levels (interleukins-1 and -8, tumor necrosis factor alpha), and oxidative stress (OS) [6]. The study of genes – markers of oxidative stress (OS) and the antioxidant defense system, such as Nrf2, is actively developing. Nrf2 – (Nuclear factor etythroid 2-related factor 2) is a transcription factor with antioxidant effects associated with the pathogenetic mechanisms of some forms of cardiovascular pathology (CVP) [15]. Nrf2 regulates the biosynthesis, utilization and regeneration of glutathione, thioredoxin and NADPH, as well as the production of reactive oxygen species and NADPH oxidase to maintain cellular redox homeostasis [20]. Studies have shown the possibility of therapeutic effects in atherosclerosis by activating the NrF2-dependent anti-inflammatory effect [11] and the inhibitory effect of the Keap/Nrf2 system on macrophage ferroptosis [13]. Nrf2 can reduce the risk of chronic diseases associated with atherosclerosis due to the corrective effect on endothelial function [14]. In OS, destruction of cell membranes occurs due to lipid peroxidation processes, reduction of antioxidant activity, as well as phospholipase hydrolysis. When the endothelium is damaged, the production of active oxygen species is activated, which have a vasoconstrictor effect, providing an increased tone of smooth muscle cells. A vasomotor form of endothelial dysfunction (ED) occurs, which is important in the mechanisms of both a systemic increase in blood pressure and local angiospasm, which emphasizes its role in the pathogenesis of cardiovascular diseases; dyslipidemia is closely associated with the activation of lipid peroxidation mechanisms and radical formation. Hypercholesterolemia leads to a decrease in NO production and a decrease in its vasodilating effect. On the surface of LDL in the intima of blood vessels, the LOX-1 receptor is present, the elevated level of which in patients with hypercholesterolemia and arterial hypertension (AH) is combined with a decrease in NO-dependent vasodilation and, accordingly, the progression of vascular damage [9]. The most common clinical method for diagnosing atherosclerotic blood flow disorders in the main arteries is ultrasound duplex scanning of arteries [4]. However, this method is financially expensive and difficult to apply for developing approaches to predicting the progression of AS.

In this regard, the study of the characteristics of atherosclerotic changes and the state of the Nrf2-dependent antioxidant system in comorbid patients with AS is relevant.

The purpose of the study. To study the features of the dependence of the degree of atherosclerotic stenosis of the carotid arteries on the level of expression of genes - markers of oxidative stress in patients with atherosclerosis and comorbid pathology.

Material and methods of research. The study included 51 patients of the Clinic of the Federal Research Center for Fundamental and Translational Medicine (FRC FTM). The sample included: 29 patients with verified carotid atherosclerosis with stenosis of more than 30%, randomly selected according to the established criterion, 22 patients for comparative analysis, without carotid atherosclerosis or with minor atherosclerotic changes in the carotid arteries without stenosis. The age of the patients studied ranged from 30 to 80 years. The average age was 64.9 ± 7.2 years. 52% of patients included in the

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study were men, 48% were women. An assessment was made of the presence of diagnosed diseases reflected in the main and concomitant diagnoses in the medical records during hospitalization of patients, as well as a comparative analysis of the presence of pathologies in each of the two groups of patients. Verification of diagnoses in patients was carried out in accordance with current clinical guidelines. The patients underwent diagnostic duplex scanning of the neck vessels (Vivid E9, GE, USA) to determine the diameter of the common carotid arteries (CCA), internal carotid arteries (ICA), the thickness of the intima-media complex, peak systolic blood flow velocity and the percentage of stenosis of the CCA and ICA. The level of the lipid spectrum of the blood was determined in the serum taken in the morning on an empty stomach; the indicators of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), alpha cholesterol and triglycerides (TG) were determined. The measurements were carried out on a biochemical analyzer "BECKMAN COULTER AU480"

The expression level of polymorphisms of the gene of the antioxidant defense system *NRF2, HMOX1, GSTP1, NQO1* was determined in a group of comorbid patients with atherosclerosis with varying degrees of verified stenosis of the carotid arteries, as well as in a comparison group by PCR (polymerase chain reaction), using a CFX96 amplifier (Bio-Rad Laboratories). Work on determining gene expression was carried out on the basis of the "laboratory of molecular mechanisms of free-radical processes" of the FRC FTM (head of the laboratory and chief researcher - MD Elena Bronislavovna Menshchikova). RNA was isolated using a special ready-made reagent kit ("Lira" from BioLabMix). The obtained RNA samples were subjected to the reverse transcription procedure to obtain cDNA using a special reagent kit "Reverta-L" ("Amplisens" by Helicon) according to the instructions. The comparative expression of mRNA of the genes *NRF2, HMOX1, GSTP1, NQO1* was studied using the real-time PCR method on a CFX96 amplifier (Bio-Rad Laboratories). The housekeeping gene *GAPDH1* was used as a reference. The amplification reaction was carried out as follows: a 20 μl PCR reaction mixture was prepared containing: 10 μl Biomaster HS-qPCR SYBR Blue (2x) reaction mixture (high-throughput recombinant HS-Taq DNA polymerase, deoxynucleoside triphosphate mixture, PCR buffer, MgCl, SYBR Green I, inert dye), forward and reverse primers, DNA template, sterile water. Amplification was performed according to the following program: 5 minutes at 95 °C for preliminary denaturation, then 40 cycles: 10 seconds at 95 °C for denaturation, 15 seconds at 60 °C for primer annealing, fluorescent signal collection, 20 seconds at 72 °C - elongation. The mRNA expression level of genes was calculated according to the 2-ΔΔCT method and normalized relative to the reference housekeeping gene Gapdh1. The 2-ΔΔCT method is widely used as a relative quantification strategy for quantitative analysis of real-time PCR data. The method used is a convenient way to calculate relative gene expression levels between different samples, allowing direct use of threshold cycles (Ct/Cq) obtained by the real-time PCR system on a thermocycler for calculation.

Statistical analysis of the data was performed using the statistical software package "STATISTICA 10.0" (StatSoft Incorporated, USA). Normal distribution of indicators was estimated using the Kolmogorov-Smirnov criterion. Parametric and nonparametric statistics methods were used. Quantitative parameters were described by calculating arithmetic means and standard error of the mean (M±SE). Qualitative parameters were described by calculating the frequency of occurrence of a feature (n (%)). The t-test for comparison of independent variables was used to analyze the statistical significance of differences in quantitative indicators. Spearman correlation analysis was performed. Differences were considered statistically significant at a significance level of $p<0.05$.

Results and discussion. In the main group of patients, the average values of expression of the antioxidant defense genes *Nrf2* (0.67±0.21) and *HMOX1* (0.75±0.21) were statistically significantly lower than in the comparison group (Table 1).

In the main group of examined patients, a more frequent occurrence of expression of the antioxidant defense genes *NRF2, GSTP1, HMOX1* below the reference values than within or above the reference values was revealed: *NRF2* - in 57% (Fig. 1, a), *GSTP1* - in 86% (Fig. 1, b), *HMOX1* - in 77% (Fig. 1, c). The level of expression of the *NQO1* gene in the main group was higher than the reference values in 60% of those examined.

A comparative analysis of the incidence of comorbid pathology in the examined patients was performed: hy-

Table 1

Differences in gene expression in the main and comparison groups

Groups	*NRF2**	*HMOX1**
Main group	0.67±0.21	0.75±0.21
Comparison group	1.20±0.38	2.05±0.21

Note. * - statistical difference between the parameters of the main and comparison groups, $p<0.05$.

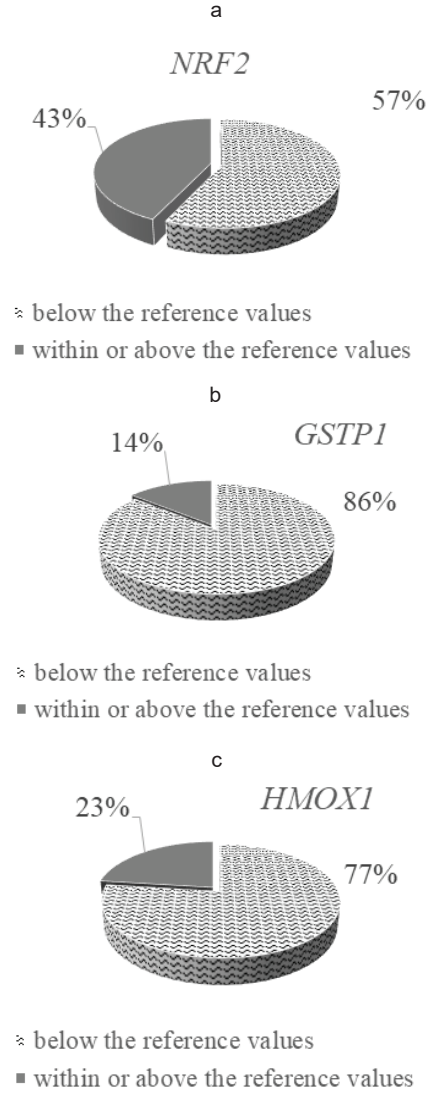

Fig. 1. Distribution of the expression level of antioxidant defense genes in relation to reference values in the main group of patients: a - *NRF2*, b - *GSTP1*, c - *HMOX1*

pertension, coronary heart disease; previous acute myocardial infarction, acute cerebrovascular accident, type 2 diabetes mellitus (Fig. 2). The average comorbidity index for the above-mentioned diseases (1 point for each nosological form) was calculated for each patient and the average value in the groups was calculated. In the main group, the comorbidity index was statistically significantly ($p<0.05$) higher (3.24±0.27) than in the comparison group (1.06±0.25) (Fig. 2). The incidence of nosological forms in the groups was as follows: in the main group, hypertension was present in all subjects, in the comparison group - in 62.5% of patients, which is 37.5% more than in the main group. Ischemic heart disease was 69.5% more common in the main group than in the comparison group: 88.2% and 18.7%, respectively. Acute myocardial infarction in the anamnesis was more common in the main group than in the comparison group (12.5%) (70.5%). Acute cerebrovascular accident in the anamnesis was 16.8% of cases in the main group, which is 10.55% more common than in the comparison group (6.25%). Type 2 diabetes mellitus was 41.2% in the main group; there were no patients with type 2 diabetes in the comparison group (Fig. 2).

Maximum degree of stenosis of the carotid arteries in the main group of examined patients was up to 81%, the average degree of stenosis of the common and internal carotid arteries was from 31% to 45%.

In the main group, the average lipid spectrum values did not exceed the reference values: TC 3.65 mmol/l [3.27; 4.74], LDL 2.4 mmol/l [1.94; 2.91], TG 1.41 mmol/l [0.87; 2.67], at the same time, significant direct correlations were revealed between the level of TC, LDL in the blood serum and the diameter of the common carotid artery, the level of TG and the diameter of the internal carotid artery (Table 2), which is explained by an increase in the rigidity of the vascular wall with a shift in lipid values towards the proatherogenic side, even within the reference values. In the main group, an inverse correlation was found between the expression of the *GSTP1* gene and stenosis of the left internal carotid artery ($r = -0.59$; $p <0.05$) (Table 2), an inverse correlation was found between the expression of the *HMOX1* gene and the severity of stenosis of the right internal carotid artery ($r = -0.45$; $p <0.05$).

The study showed the relationship between the degree of atherosclerotic stenosis of the carotid arteries, the level of expression of antioxidant defense genes

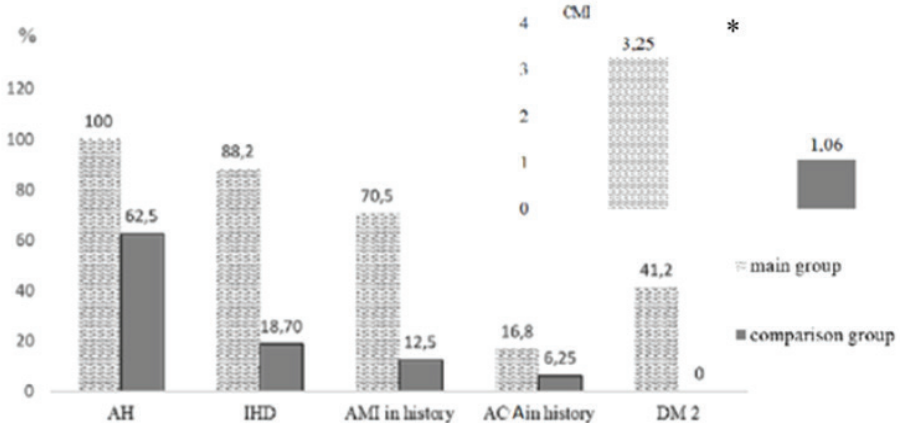

Fig. 2. Incidence of comorbid pathology in the main group and the comparison group: ICI – comorbidity index (in points), AMI – acute myocardial infarction; CHD – ischemic heart disease: ACC – acute cerebrovascular accident: DM 2 – diabetes mellitus type 2, * - $p < 0.05$

and some indicators of lipid metabolism in patients with comorbid pathology. In modern clinical practice, the incidence of cardiovascular pathology increases in conditions of comorbidity, which is most important in patients with cardiovascular pathology [8]. Combined pathology is associated not only with an increase in the number of patients with several diseases, but also the difficulties of organizing diagnosis and treatment, with the severity of the condition of these patients, "masking" different nosologies with similar syndromes, predicting the course of diseases and the difficulties of preventing complications, therefore accurate diagnosis is important using new modern methods [2]. Hypertension, the most common CM in the examined patients, is a multifactorial disease [5]. The pathogenesis of hypertension is closely related to atherosclerosis and lipid metabolism disorders [17]. Oxidation of low-density lipoproteins to oxidized LDL (oxLDL) under conditions of oxidative stress is one of the stages of the pathogenetic cascade of atherosclerosis [10], which is a manifestation of the pathogenetic relationship between OS and dyslipidemia. Increased secretion of chemokines by endothelial cells and increased expression of adhesion proteins on their surface allow them to recruit monocytes into the intima of the arteries, and monocytes differentiate into macrophages, which subsequently phagocytize lipids and form foam cells that undergo necrosis and apoptosis, forming the lipid necrotic nucleus of atherosclerotic plaque. Damaged endothelial cells during OS secrete growth factors to activate smooth muscle cells (SMC), which migrate through fenestration in the inner elastic membrane and phagocytize lipids mediated by surface lipoprotein lipase receptors, forming foam cells derived from SMC. In the late stages of AS, SMCs secrete extracellular matrix (collagen and elastin), forming fibrous capsules that increase the instability of atherosclerotic plaques [18]. An important role in regulating the cell response to OS is played by the Nrf2, which is a member of the Cap'collar (CNC) family of transcription factors – Bzyb (basic leucine lightning proteins) with 7 functional domains, participating in the regulation

Table 2

Correlations of ultrasound, laboratory parameters and the level of gene expression in the main group of patients

Indicators	expression of *GSTP1*	Diameter of the right CCA	Diameter of the left ICA
Stenosis of the left internal carotid artery	-0.59*	-0.51	0.37
Total serum cholesterol	-0.35	0.55*	0.26
Low-density lipoproteins	-0.13	0.53*	0.45
Triglycerides	0.02	0.32	0.58*

Note. CCA – common carotid artery; ICA – internal carotid artery; * - statistical significance of the indicator $p <0.05$

of their stability or transcriptional activity. [19]. Nrf2 is associated with the ubiquitin ligase complex Keap1/Cu13 (Kelch-like epichlorohydrin-associated protein 1/ Cullin 3, which inhibits its activity. Under oxidative stress or similar stimuli, cysteine residues are modified in Keap1 and protein binding with the Nrf2 is stopped. After exiting the complex, Nrf2 enters the nucleus and forms a heterodimer with the small protein Maf (Nrf2-Maf) [16]. The formed heterodimers combine with the elements of the antioxidant response (ARE) in the initiation domain in a sequence-specific manner [19], promoting the transcription of antioxidant enzymes.

Thus, the fact that a decrease in the expression of antioxidant protection genes contributes to the development and progression of atherosclerosis in CVP has been confirmed in studies, however, there is little clinical evidence on the involvement of the Keap1/Nrf2/ ARE regulatory system in atherogenesis in comorbid patients with atherosclerosis. The results obtained in this study of a decrease in the expression of the Nrf2 transcription factor gene, and the genes of antioxidant protection proteins as arterial stenosis increases clinically confirm the hypothesis of their involvement in the pathogenesis of atherosclerosis.

Conclusion. Low expression rates of genes *Nrf2, GSTP1, HMOX1* are associated with a greater severity of atherosclerotic stenosis of the carotid arteries in patients with comorbid pathology. In a group of patients with carotid atherosclerosis and severe or moderate stenosis of the carotid arteries, an inverse correlation was found between the expression of the *GSTP1* and *HMOX1* genes and the degree of stenosis. The new fundamental data obtained can be used to develop a new medical technology for predicting the progression of atherosclerosis.

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DIAGNOSTIC AND TREATMENT METHODS

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COMPARATIVE EVALUATION OF THE LOCATION OF OCCLUSAL LANDMARKS ON THE ORTHOPANTOMOGRAM AND TELEROENTGENOGRAM

A comparative analysis of the location of occlusal landmarks on orthopantomogram and teleradiogram in normal and occlusive pathology was carried out, which has a high level of information value in planning orthopedic treatment in patients with defects of dental arches and dental-alveolar anomalies of occlusion. In the course of comparative analysis of orthopantomogram and teleradiogram data, it was determined that the infradental-occlusal horizontal, as a rule, was parallel to the gnathic horizontal. The ratio of the size of the alveolar-articular line (Cond-A) to the size of the segment crossed by the articular circle line on the teleradiogram was 1.50±0.09. At the OPG, when analyzing linear parameters, it was noted that the ratio of the distance from the "Cond" point to the intersection with the aesthetic median vertical to the segment of the articular circle intersected by the line was 1.61±0.1, which was close in value to the Fibonacci number. This circumstance allowed the use of the principle of the "golden section" in determining the radius of the circle in anomalies of the position of the molars in the vertical direction. A comparative analysis of the location of occlusal landmarks on the orthopantomogram and teleradiogram in normal and occlusion pathology showed that both methods of X-ray examination can be used in the clinic of prosthetic dentistry in the diagnosis of dental-alveolar forms of occlusal anomalies and for the selection of treatment methods for patients with defects of dental arches that are not limited on the distal side of the arch. In addition, the intersection point of the occlusal lines and infradental-occlusal horizontals, which are located in the same way on both types of X-rays, which makes both methods of X-ray examination acceptable in the clinical practice of dental prosthetics.

The results obtained reveal that when constructing the occlusal line, it is most appropriate to use its parallelism with the gnathic horizontal, connecting the supramental point Downs with the lower diameter of the articular circle. At the same time, the use of parallelism of the infradental-occlusal horizontal with the gnathic line of the lower jaw in the clinic of prosthetic dentistry makes it possible to use them in determining the position of the distal occlusal point.

Keywords: orthopantomography; teleradiography; occlusal line; articular horizontal; distally unlimited defects of dental arches

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Introduction. Methods for assessing the condition of the maxillofacial region based on X-ray data are widely used in the clinical practice of dentists [8,11]. In the presented works, the authors carried out a detailed comparison of the X-ray and morphometry data of native skull specimens with a complete set of teeth of permanent occlusion. Data on the ratio of the sizes of the upper and lower jaws, taking into account odontometric indicators, were noted.

In the clinical examination of patients, teleradiography is an irreplaceable method of examination, in which the position of the structures of the maxillofacial region in relation to linear landmarks is assessed. The most significant and controversial issues of orthodontics and prosthetic dentistry are the methods of constructing and analyzing the occlusal plane [1]. In the presented scientific study, recommendations are given to focus on the position of the mandibular plane when constructing the alveolar-occlusal horizontal of the lower jaw. The author used the obtained landmark for further construction of the occlusal horizontal and determined their stable position regardless of the type of jaw growth and the size of the mandibular angle.

The works of researchers comparing the position of the mandibular plane on orthopantomograms and teleroentgenograms of the same patients deserve attention [10]. In this study, the author showed various options of constructing the mandibular plane and revealed certain regularities when comparing the marked horizontal on different types of roentgenograms. However, this study was limited only to the position of the mandibular horizontal, and the starting point of the orthopantomograms was the constructive point of the angle of the mandible, without taking into account the proportionality of the branch and the body of the organ under study. At the same time, the study was carried out in people with a physiological occlusal norm.

Specialists draw attention to the need for a comprehensive examination of patients with various dental pathologies, including X-ray, functional and laboratory methods. The effectiveness of such studies was demonstrated by the authors using the examples of diagnosis and treatment of dental patients in combina-

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tion with somatic pathology, in particular, diabetes mellitus and connective tissue dysplasia [3,5].

The analysis of the position of the occlusal plane is significantly complicated by numerous variants of anomalies of the maxillofacial region, in which the position of key teeth of different classes changes, which in its turn affects the condition of hard tissues and the periodontal complex [6,14].

When assessing the position of the occlusal plane when it deviates from the azimuth of the pupillary horizontal, the researchers recommend evaluating teleroentgenogram in direct projection and orthopantomography data [9]. This type of anomaly is recommended by the authors to be defined by the term "transversal occlusion". This study was carried out taking into account the growth of the jaws. However, relatively stable landmarks for the construction of the occlusal line are not shown, and the features of the temporomandibular joint, which determines the biomechanics of the mandible, are not taken into account.

This feature was noted by specialists studying the spatial arrangement of the bone elements of the mandibular joint, taking into account the trusal types of dental arches and the location of anterior teeth in the gnathic complex [2]. In the presented material, experts noted the effect of occlusal balance of the anterior teeth on the shape of the articular fossa and the location of the mandibular head in it.

The issues of proportionality of dental arches and the size of the craniofacial complex are presented in the classifications of specialists in the analysis of the physiological occlusal status [4,7,12]. However, in the course of the study, the authors compared the biometrics of the dental arches with the morphometry of the head and face, which did not allow assessing the position of the teeth relative to the occlusal horizontal in the structure of the gnathic complex. Nevertheless, a comparative analysis of the parameters of the head and dental arches determines the algorithm for predicting the size of dental arches in anomalies [13].

Data on the position of the structures of the maxillofacial region of the head relative to the location of stable anatomical landmarks were shown by the specialists and the features of different periods of ontogenesis were noted [15]. Information is presented on the variability of the position of the teeth relative to the occlusal plane in various anomalies and variants of bite height reduction [16].

Nevertheless, we did not find information about the position of the teeth relative to the occlusal plane, built considering the location of the elements of the mandibular joint, on teleroentgenograms and orthopantomograms at the same time, which determined the purpose of the work.

Research objective: To conduct a comparative analysis of the location of occlusal landmarks on orthopantomogram and teleroentgenogram in normal conditions and malocclusion.

Material and methods of research. In the course of the retrospective study, the analysis of teleroentgenograms (TRG) and orthopantomograms (OPG) of the same young people with physiological occlusion, necessary for the development of a method of comparative analysis, was carried out. For this purpose, 38 clinical cases were analyzed. At the second stage, similar data were analyzed in 23 individuals with distally unlimited defects of the dental arches, in whom vertical occlusion anomalies were identified, in particular, the protrusion of antagonists. This study made it possible to clarify the diagnosis and determine the tactics of therapeutic measures.

For the convenience of analysis, scaled (1:1) photographs of X-ray images were placed in the Power Point program, after which point landmarks were placed, among which the main ones were those that were placed on the TRG and OPG. The main points on the TRG and OPG, in accordance with the purpose of the work, were articular ones (Cond), installed in the upper part of the jaw head. The infradental point (Id) was located on the TRG in the upper part of the alveolar part on the vestibular side near the incisor neck. On the OPG, the indicated landmark was located along the midline between the incisors-anthemers in their cervical part. Of the chin points, the most rational was considered to be the setting of the "gnation" (Gn) point. On the OPG, the point was located in the lower part of the jaw body along the midline. On the TRG, this landmark was projected on the lower point of the chin, protruding anteriorly. On the second lower molar in the distal part of the occlusal surface, an occlusal point "hPOcP" was installed on both TRG and OPG.

The auxiliary points on the TRG in our study were landmarks for the construction of the skull base line (N-Se), the nasal vertical of the face (n-sn), the Dreyfus line, and the occlusal line (hPOcP-vPOcP). Besides, the points of the apical bases ("A" and "B") and the supramental point (sm) on the skin of the chin were marked (Fig. 1).

The use of Microsoft PowerPoint allowed the construction and combination of lines and shapes to enable comparative analysis.

The analysis of the location of occlusal landmarks is based on the construction of an articular circle, the radius of which was the distance from the apex of the articular head to the occlusal point of the distal odontomer of the second molar (Cond-hPOcP) and the construction of the circle was carried out both on the TRG and on the OPG on both sides. The occlusal line on the TRG connected the anterior and distal occusal points. On the OPG, the distal points were connected by a straight line. An infradental-occlusal line connected the "Id" point with the distal molar points "hPOcP". The lower gnathic horizontal was drawn from the gnathion point (Gn) to the position point of the lower diameter of the circle on one side of the TP and on both sides of the OPG (Fig. 1).

The line connecting the articular points was an auxiliary landmark on the OPG. On TRG, the nasal vertical and the Dreyfus line were used to clarify the position of the points of the apical bases of the jaws when the projection of the tips of the incisor roots on the alveolar bone was not clear. At the same time, the subspinal point Downs ("A") was located at the intersection of the perpendicular to the Dreyfus line coming out of the subnasal cutaneous point "sn". When determining point “B”, a perpendicular was constructed to the nasal vertical, which passed through the supramental point “sm” to the junction with the alveolar part of the jaw. In the TRG, point "A" was used to build the alveolar-articular radial line, and point "B" was connected to the lower diameter of the circle, obtaining the lower alveolar line.

After drawing the X-ray images, linear and angular parameters were evaluated. The distance from the "Cond" point to the point of intersection with the articular circle line was measured on the OPG. The angles formed by the median aesthetic vertical and the infradental-occlusal horizontal, as well as the angle of inclination of the gnathic line to the specified vertical, were measured. The parallelism of the articular and occlusal lines was assessed.

On TRG, the ratio of the alveolar-articular radial line with the segment crossed by the articular circle was determined. The angles of deviation of the horizontal lines of the TRG from the Dreyfus vertical were determined and the parallelism

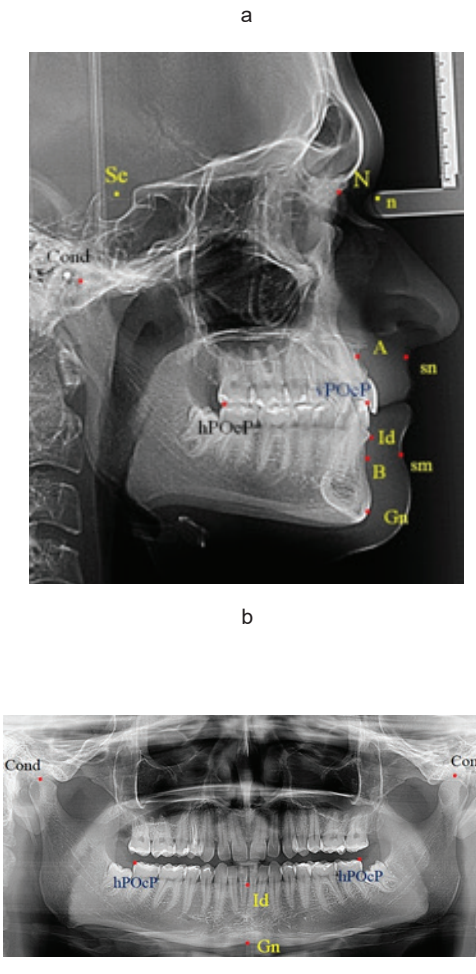

Fig. 1. Location of the main points on the TRG (a) and OPG (b)

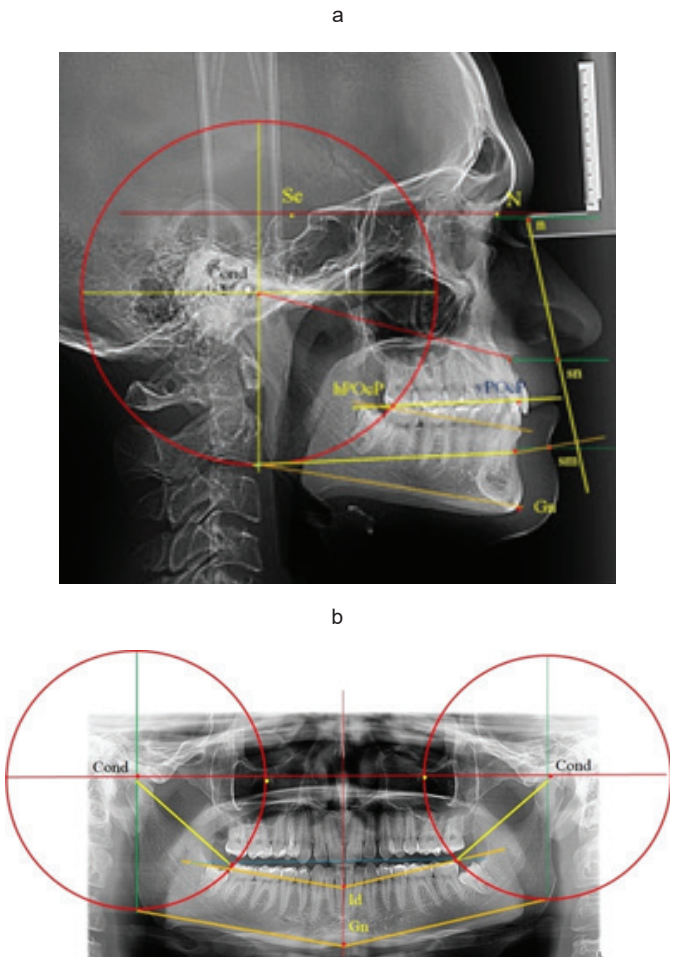

Fig. 2. Methodology of comparative analysis of the location of occlusal landmarks on the TRG (a) and OPG (b)

of the lower alveolar horizontal and the occlusal line was estimated. The location of the infradental-occlusal horizontal in relation to the gnathic line was also compared.

Numerical indicators were evaluated in Microsoft Excel, calculating mean values with a representativeness error index (M±m) to determine reliability according to Student.

Results and discussion. In the course of a comparative analysis of the TRG and OPG data, it was determined that the infradental-occlusal horizontal, as a rule, was parallel to the gnathic horizontal, both on the TRG and OPG. Parallelism of the TRG occlusal line with the inferior alveolar line was also noted. On the OPG, the articular horizontal at physiological occlusion was parallel to the occlusal intermolar horizontal (Fig. 3).

When analyzing the linear parameters on the TRG, it was noted that the ratio of the size of the alveolar-articular line (Cond-A) to the size of the segment crossed by the articular circle line was 1.50±0.09. This coefficient can be used to determine the radius of the articular circle in case of abnormal deviation of the distal occlusal point in people with occlusal anomalies and in the presence of dental arch defects in the distal region.

When measuring angular parameters, a significant variability of indicators was revealed. However, a comparative analysis revealed certain patterns.

At the OPG, when analyzing linear parameters, it was noted that the ratio of the distance from the "Cond" point to the intersection with the aesthetic median vertical to the segment of the articular circle crossed by the line was 1.61±0.1, which was close in value to the Fibonacci number. This circumstance allowed the use of the principle of the "golden section" in determining the radius of the circle in anomalies of the position of the molars in the vertical direction.

The differences in the value of the angle formed by the median aesthetic vertical and the infradental-occlusal horizontal, as well as with the angle of inclination of the gnathic line to the specified vertical, did not exceed one and a half degrees, and the difference in the indicators for the group accounted for 0.87±0.62 degrees. The result proved the parallelism of these lines and the possibility of using the gnathic horizontal as a reference point for the construction of the infradental-occlusal line in occlusal anomalies.

A similar situation was observed on the TRG when analyzing the slope of these contours with the Dreyfus vertical. In addition, the differences in the value of the angles formed by the Dreyfus vertical with the occlusal line and the lower alveolar horizontal accounted for 1.04±0.91 degrees. Thus, the lower alveolar horizontal can be used to predict the location of the occlusal line in malocclusion.

It is noteworthy that the point of intersection of the occlusal line with the infradental-occlusal horizontal was located on the distal occlusal point of the second molar, which will make it possible to determine the position of the distal occlusal point in case of dental-alveolar deformity of antagonists.

A comparative analysis of the results of the study of roentgenograms of patients with distally unrestricted defects of the dentofacial arches showed correspondence in the location of the occlusal

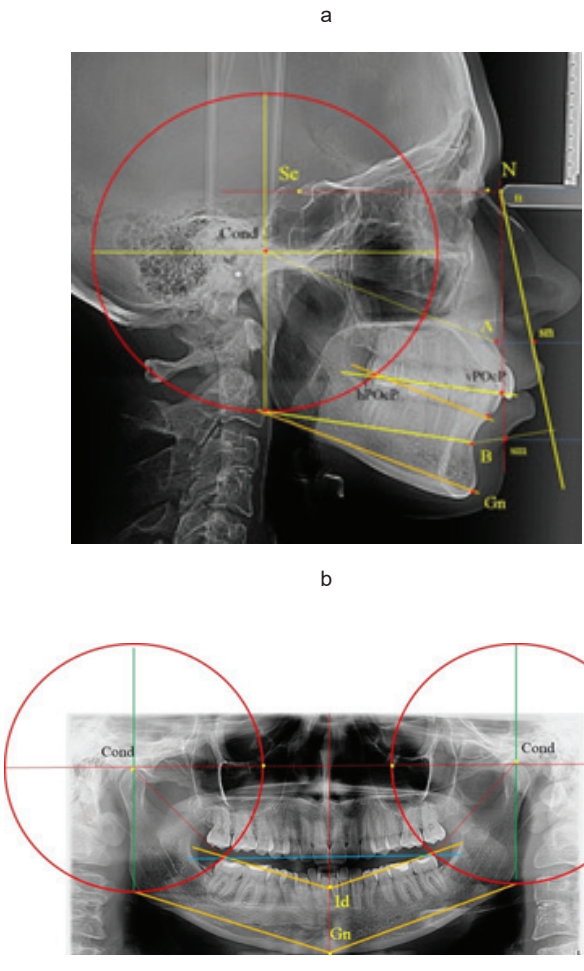

Fig. 3. Comparative analysis of the location of occlusal landmarks on TRG (a) and OPG (b) in physiological occlusion

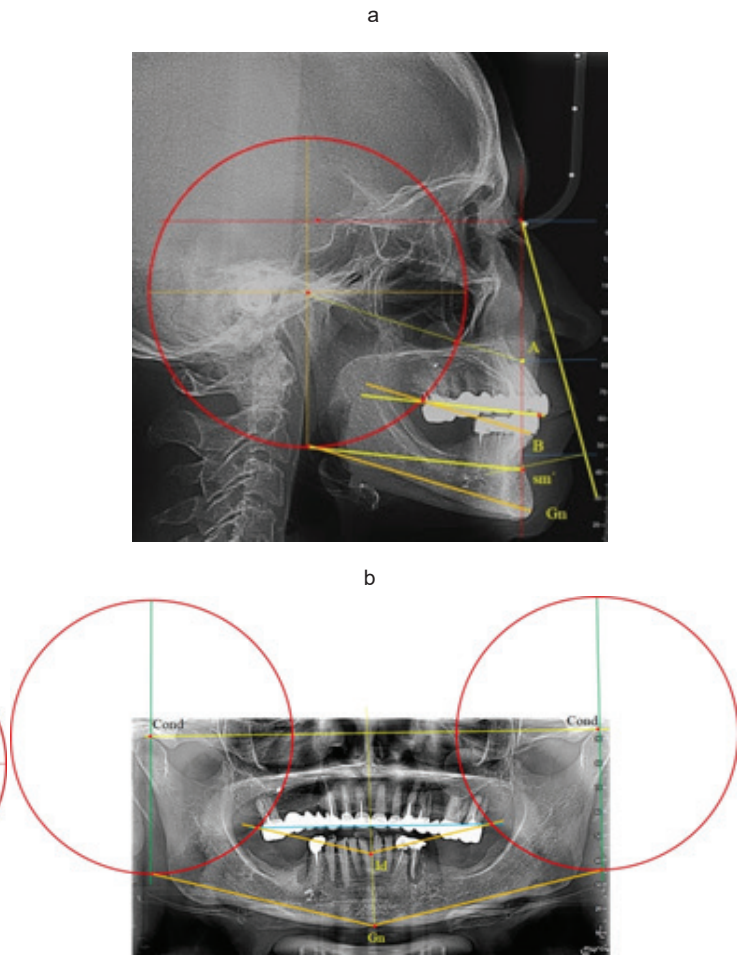

Fig. 4. Comparative analysis of the location of occlusal landmarks on TRG (a) and OPG (b) in pathological occlusion

landmarks of the TRG with the data of the analysis of orthopantomograms.

In the course of the study, the same algorithm for constructing diagnostic lines and figures was used as in people with the physiology of bite ratios. The radius of the articular circle on the TRG was determined by the ratio of the "Cond-A" size to the coefficient of 1.5. But the OPG radius was calculated through the ratio of half the value of the interarticular distance to the Fibonacci number (1.618). Infradental-occlusal horizontals were drawn in parallel with the gnathic lines in both images (Fig. 4).

Attention is drawn to the point of intersection of occlusal lines and infradental-occlusal horizontals, which were located in the same way on both types of X-rays, which makes both methods of X-ray examination acceptable in the clinical practice of dental prosthetics.

Conclusion. Thus, a comparative analysis of the location of occlusal landmarks on the orthopantomogram and teleradiogram in normal and occlusion pathology showed that both methods of X-ray examination can be used in the clinic of orthopedic dentistry in the diagnosis of dental-alveolar forms of occlusion anomalies and for the selection of treatment methods for patients with dental arch defects not limited on the distal side of the arch. When constructing the occlusal line, it is most expedient to use its parallelism with the gnathic horizontal, connecting the supramental point Downs with the lower diameter of the articular circle. The parallelism of the infradental-occlusal horizontal with the gnathic line of the mandible allows their use in determining the position of the distal occlusal point.

The authors declare that there is no conflict of interest.

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METHOD OF TREATMENT OF CHRONIC PERIODONTITIS OF MEDIUM SEVERITY WITH DYSBACTERIOSIS

Chronic periodontitis is the most widespread stomatologic disease, leading to tooth loss, disorder of occlusion, temporomandibular joint and dento-mandibular system function, etc. At the same time, chronic periodontitis is more severe clinically when the balance of microflora is disturbed, which determines the need to restore endoecological balance in the treatment of chronic periodontitis. In this regard, studies aimed at solving this problem are relevant and have scientific and practical importance in clinical periodontology. Purpose of the study. To improve the effectiveness of complex treatment of chronic periodontitis with the substantiation of rational approach to the correction of dysbiotic state and to develop practical recommendations. Study material. A clinical and epidemiological study was conducted in groups with dysbiosis (n=504) and without dysbiosis (n=732) aged from 15 to 74 years. At the same time, the developed method for the treatment of chronic generalized periodontitis was used in 328 patients aged 35 to 48 years with concomitant gastrointestinal diseases and laboratory-established grade 2 dysbiosis of the large intestine. A randomized group, a blinding group and a placebo-control group were formed according to the modern concept of evidence-based medicine. In the course of complex treatment to restore oral dysbiosis, a therapeutic paste was used locally with administration into the periodontal pocket based on synbiotic “Bifikin Forte” 20 billion CFU, oil solution of vitamin “A” and zinc oxide with subsequent fixation with protective dressing “Parasept”. In addition, oral administration of synbiotic “Bifikin Forte” 20 billion CFU was prescribed. Results. Application of synbiotic in complex treatment of chronic periodontitis promotes stimulation of growth of beneficial bacteria and reduction of pathogenic microflora in periodontal pocket with subsequent reduction of intensity of inflammatory process, edema and bleeding of periodontal tissues. Positive properties of the therapeutic paste according to the developed method allow its application in clinical dentistry as an alternative method of treatment of chronic localized and generalized periodontitis of medium severity with dysbiosis of the second degree. In this case the developed method causes the increase of clinical effectiveness of treatment of periodontal diseases characterized by inflammatory-destructive process of periodontal tissues, prevention of chronic foci of infection in the maxillofacial region.

Keywords: periodontal tissues, inflammatory process, bleeding, gingival edema, gastrointestinal tract, dysbiosis, oral cavity, synbiotic, treatment, prevention.

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Introduction. Modern research determines the multifactorial development of chronic periodontitis, which, when carrying out etiopathogenetic therapy and prevention, cause some difficulties [3]. The development of the inflammatory process is mainly associated with the aggressive impact of periodontopathogenic microorganisms with disturbances in the oral cavity microbiota, impairment of function of the dentoalveolar system [6]. In addition, poor oral hygiene, the presence of gastrointestinal diseases, decreased immunity, etc. have an important role in the pathogenesis of chronic periodontitis [1; 9]. [1; 9]. At the same time, gastrointestinal dysfunctions accompanied by intestinal dysbacteriosis cause a pronounced course of chronic periodontitis due to the activation of virulence of periodontopathogenic microflora [8].

Complex treatment of periodontal diseases involves the use of a wide range of different means and methods of therapy, prevention and rehabilitation, which separately can lead to a short-term clinical effect [5; 7]. At the same time, the use of various means in clinical periodontology is often insufficiently effective, especially in the presence of microflora disorders [4].

To date, the positive properties of using synbiotics in the therapy of chronic periodontitis have been studied [2]. However, the problems of eliminating dysbiosis and the positive effect of probiotics and prebiotics on the microflora of the periodontal pocket have not been completely solved [4]. In this regard, studies

aimed at solving the above problems are relevant.

Materials and methods of research. A clinical and epidemiological study was conducted in groups with dysbiosis (n=504) and without dysbiosis (n=732) aged from 15 to 74 years. In accordance with the requirements of the modern concept of evidence-based medicine, a randomized (study) group (n=328) with grade 2 dysbiosis, a blinded (comparison) group (n=31) without dysbiosis with moderate chronic periodontitis, and a placebo control group (n=29) without dysbiosis with moderate chronic periodontitis, where no treatment or preventive measures were taken, were formed, where the age of the subjects ranged from 35 to 48 years. The study group used the developed method for treating chronic generalized periodontitis (application for patent for invention No. 2024126815 dated 12.09.2024, a positive decision received on the grant of a patent dated 27.12.2024). At the same time, in accordance with the requirements of the modern concept of evidence-based medicine, a randomized (study) group (n=328) with dysbiosis of the second degree of severity, a blinded (comparison) group (n=31) without dysbiosis with chronic periodontitis of the middle degree of severity and a placebo-control group (n=29) without dysbiosis with chronic periodontitis of the middle degree of severity, where no treatment and preventive measures were carried out, were formed. Inclusion criteria in the study were patients with chronic generalized periodontitis of medium severity with established diagnosis of second-degree dysbiosis with concomitant GI pathologies, non-inclusion criteria were patients with chronic generalized periodontitis of mild and severe severity , without dysbiosis and exclusion criteria were patients who expressed unwillingness to participate in the study. The research was conducted in the dental polyclinic and microbiological laboratory of the Clinic of the Federal State Autonomous Educational Institution of Higher Education “North-Eastern Federal University named after M.K. Ammosov”, as well as in the inpatient department of gastroenterology and bacteriological laboratory of the State Budgetary Institution of RS (Ya) “Yakutsk Republican Clinical Hospital”.

Retrospective and prospective analysis of case histories with the results of clinical and laboratory and objective studies of gastroenterologists was carried out in the inpatient setting. Oral pathological processes were studied with the analysis of periodontal tissue diseases according to the CPI (1978) periodontal index in groups with dysbiosis (n=504) and without dysbiosis (n=732). Oral hygiene index by IGR-U (1964) in groups with dysbiosis (n=464) and without dysbiosis (n=716) was studied. Periodontal index according to A. Russell (1956) was also determined in groups with dysbiosis (n=318) and without dysbiosis (n=237). The dental examination card recommended by WHO (2013) was used for the study. In addition, based on the results obtained, the need for dental care of the examined patients was determined using the method of P.A. Leus (1987).

Complex treatment in the main group was carried out using the developed method of treatment of chronic periodontitis of medium severity with dysbiosis of the second degree. In order to reduce the number of pathogenic microbial associations in the gingival biotope and to restore the oral cavity microbiocenosis in the patients of the main group for local treatment, therapeutic paste with synbiotic “Bificin Forte” 20 billion CFU was used (state registration certificate AM.01 .11.01.01.003.R.000001.01.24), vitamin “A” oil solution (State Register of Medicinal Products Reg. No. RN 001778/01) and zinc oxide (State Register of Medicinal Products Reg. No. FS-001204, Safety Data Sheet in accordance with GOST 30333-2007 ROTI®nanoMETIC ≥99%, 25 nm, Article no: 8278, Version: GHS 1.0 ru), where their mass percentages are 54-55, 33-35 and 10-13%. The components were mixed until a thick cream-like consistency was obtained, then the prepared paste was introduced into the periodontal pocket and it was fixed with a protective dressing “Parasept” (registered in the Federal Service for Supervision in the Sphere of Health Care No. FSR 2007/00142, TU 9391-067-45814830-2002 dated November 16, 2020. In this case, the daily procedure is associated with a single injection of the therapeutic paste into the periodontal pocket, the course includes 8-10 procedures. In addition, “Bifikin Forte” 20 billion CFU was administered orally, 1 capsule daily for 3-4 weeks. The comparison group was treated with liquid synbiotic “Normoflorin®-D”, which was injected into the periodontal pocket in the volume of 0.2 ml daily for 12-14 days, followed by supragingival applications of this product for 15 minutes. In addition, patients were recommended to take 20 ml of synbiotic orally 2 times a day before meals for 30 days. For microbiological study the material from periodontal pocket (inflammatory focus) was obtained using a thin probe-tampon, which was placed in liquid transport medium “Amiesa”. The material was examined by real-time PCR with hybridization-fluorescence detection. The average number in statistical processing was expressed in lg CFU, where 101 CFU=1 lg CFU (CFU - colony-forming unit, microbial cell).

Approval of the local ethical committee of the Medical Institute of the Federal State Educational Institution of Higher Education “Ammosov North-Eastern Federal University” was obtained for the comprehensive clinical and laboratory examination (Minutes No. 15 of October 31, 2018, decision No. 2). All participants gave voluntary informed consent before conducting the studies.

Statistical processing of the obtained materials was performed using the program “SPSS-22”. The estimation of the sample volume of clinical material and its sufficient size (sample size) was carried out according to K.A. Otdelnova (1980).

Results and discussion. To date, the improvement of therapeutic and prophylactic measures for periodontal diseases is of great scientific and practical importance. In view of the above, we evaluated the prevalence and intensity of periodontal tissue diseases in the examined age groups with and without dysbiosis (Table 1). Thus, the average prevalence of periodontal diseases in the examined age groups without dysbiosis is 88.58±0.06%, while in the group with dysbiosis 90.78±0.06% ($p<0.05$). At the same time, the maximum prevalence of periodontal diseases was found in the age group 45-54 years, where the index in the group without dysbiosis was 95.67±0.08%, and with dysbiosis - 97.33±0.04% ($p<0.05$), and the minimum level was found in the age group 65-74 years - 72.54±0.77%, and with dysbiosis -73.79±0.69% ($p>0.05$), which is associated with the presence of individuals with complete tooth loss in the groups. Meanwhile, in the indices of healthy individuals without periodontal disease sextants, there is a definite pattern of maximum decrease with age, where it was 10.46±1.56% in 15-year-old adolescents without dysbiosis and 6.54±0.14% ($p<0.05$) with dysbiosis, which decrease to the level of numerical values of 0.79±0.07% and 0.21±0.10% ($p>0.05$) in the groups of 65-74 years, respectively. Such symptom as bleeding in 15-year-old adolescents without dysbiosis was 38.93±0.88% and with dysbiosis was 41.32±1.16% ($p<0.05$%), and in the age group of 65-74 years without dysbiosis was 6.99±1.84% and with dysbiosis was 7.28±1.77% ($p>0.05$). Meanwhile, the presence of supra- and sub-gingival tar-

Table 1

Clinical characterization of the frequency and structure of periodontal diseases in groups with and without oral dysbiosis

Age groups	Number examined	Prevalence rate (%))	CPI (%)			
			Healthy	Bleeding	Supra- and subgingival stones	Periodontal pocket
15 years	with dysbiosis (n=84)	93.46±0.14	6.54±0.14	41.32±1.16	39.94±1.19	12.20±1.81
	dysbiosis-free (n=124)	89.54±0.18 p<0.05	10.46±1.56 p<0.05	38.93±0.88 p<0.05	38.78±0.88 p>0.05	11.83±1.35 p>0.05
20-34 years	with dysbiosis (n=95)	93.59±0.13 p<0.05	6.41±1.92 p>0.05	30.27±1.30 p>0.05	45.81±0.98 p<0.05	17.51±1.56 p>0.05
	dysbiosis-free (n=220)	91.23±0.10	5.78±1.14	28.54±0.75	43.51±0.57	15.83±0.91
35-44 years	with dysbiosis (n=148)	95.77±0.06 p<0.05	4.23±1.48 p>0.05	14.18±1.26 p>0.05	41.83±0.83 p>0.05	39.76±0.86 p>0.05
	dysbiosis-free (n=234)	93.96±0.07	6.04±1.09	13.88±0.93	40.92±0.61	39.16±0.63
45-54 years	with dysbiosis (n=113)	97.33±0.04 p<0.05	2.67±1.80 p>0.05	9.03±1.63 p>0.05	34.63±1.15 p>0.05	53.67±0.80 p>0.05
	dysbiosis-free (n=95)	95.67±0.08	4.33±1.97	8.31±1.79	33.87±1.27	53.49±0.86
65-74 years	with dysbiosis (n=64)	73.79±0.69 p>0.05	0.21±0.10 p>0.05	7.28±1.77 p>0.05	16.74±1.52 p>0.05	49.77±0.64 p>0.05
	dysbiosis-free (n=59)	72.54±0.77	0.79±0.07	6.99±1.84	16.37±1.57	49.18±0.65
Averages	with dysbiosis (n=504)	90.78±0.06 p<0.05	4.01±0.70 p<0.05	20.39±0.58 p<0.05	35.79±0.46 p<0.05	34.58±0.47 p<0.05
	dysbiosis-free (n=732)	88.58±0.06	5.48±0.55	19.33±0.47	34.69±0.38	36.31±0.37
Age groups	**Number examined**	**CPI (sextant)**				
		Healthy	**Bleeding**	**Supra- and subgingival stones**	**Periodontal pocket**	**Unaccounted sextants**
15 years	with dysbiosis (n=84)	0.44±0.12 p>0.05	2.20±0.08 p>0.05	2.85±0.07 p>0.05	0.38±0.12 p>0.05	0.13±0.13 p>0.05
	dysbiosis-free (n=124)	0.42±0.09	2.17±0.06	2.83±0.05	0.37±0.09	0.21±0.10
20-34 years	with dysbiosis (n=95)	0.24±0.11 p>0.05	1.83±0.08 p>0.05	2.72±0.06 p>0.05	1.11±0.10 p>0.05	0.10±0.12 p>0.05
	dysbiosis-free (n=220)	0.22±0.06	1.81±0.05	2.75±0.03	1.09±0.05	0.13±0.07
35-44 years	with dysbiosis (n=148)	0.13±0.09 p>0.05	1.05 ±0.76 p>0.05	2.41±0.05 p>0.05	2.13 ±0.05 p>0.05	0.28 ±0.08 p>0.05
	dysbiosis-free (n=234)	0.12±0.09	1.04±0.07	2.34±0.05	2.15±0.05	0.35±0.08
45-54 years	with dysbiosis (n=113)	0.09±0.10 p>0.05	0.41±0.10 p>0.05	1.20 ±0.08 p>0.05	2.83±0.05 p>0.05	1.47 ±0.08 p>0.05
	dysbiosis-free (n=95)	0.08±0.12	0.39±0.11	1.21±0.09	2.81±0.06	1.51±0.09
65-74 years	with dysbiosis (n=64)	0.03 ±0.15 p>0.05	0.16±0.15 p>0.05	0.57±0.14 p>0.05	3.09 ±0.07 p>0.05	2.15±0.10 p>0.05
	dysbiosis-free (n=59)	0.04±0.16	0.15±0.16	0.55±0.09	3.05±0.05	2.21±0.10
Total	with dysbiosis (n=504)	0.18±0.04 p>0.05	1.13±0.03 p>0.05	1.95±0.02 p>0.05	1.90±0.02 p>0.05	0.98±0.03 p<0.05
	dysbiosis-free (n=732)	0.17±0.03	1.11±0.02	1.93±0.02	1.89±0.02	0.88±0.03

Note: the degree of reliability is determined in groups with and without dysbiosis

tar in the age group of 65-74 years without dysbiosis was 16.37±1.57% and with dysbiosis was 16.74±1.52% (p>0.05), and in the age group of 20-34 years without dysbiosis was 43.51±0.57% and with dysbiosis was 45.81±0.98% (p<0.05). The presence of periodontal pocket in those aged 15 years without dysbiosis was 11.83±1.35% (p>0.05%) and with dysbiosis was 12.20±1.81% and in the age group of 45-54 years without dysbiosis it was at 53.49±0.86% and with dysbiosis was 53.67±0.80% (p>0.05).

It should be noted that there are certain clinical symptomatic features in the intensity of the course of periodontal diseases in the examined age groups, where the index of healthy sextants in the age group 65-74 years was 0.04±0.16% in persons without dysbiosis and 0.03±0.15% (p>0.05) with dysbiosis, and in 15-year-olds without dysbiosis 0.42±0.09% and with dysbiosis 0.44±0.12% (p>0.05%), respectively. Meanwhile, the bleeding symptom in 65-74 year olds without dysbiosis was 0.15±0.16% and with dysbiosis was 0.16±0.15% (p>0.05), and in 15 year olds without dysbiosis was 2.17±0.06% and with dysbiosis was 2.20±0.08%, which characterizes the aggressive course of periodontal diseases

Table 2

Oral hygiene status in the surveyed groups of adolescents and adults

Age	Number of people surveyed	Dental plaque	Dental calculus	OHI-S Green-Vermillion
15 years	with dysbiosis (n=84)	2.71±0.06	1.18±0.02	3.89±0.08
	dysbiosis-free (n=124)	1.67±0.02*	1.24±0.02*	2.91±0.05*
20-34 years	with dysbiosis (n=110)	1.73±0.03	1.75±0.03	3.48±0.06
	dysbiosis-free (n=164)	1.31±0.01*	1.63±0.02*	2.94±0.04*
35-44 years	with dysbiosis (n=148)	2.14±0.03	1.68±0.02	3.82±0.05
	dysbiosis-free (n=234)	2.09±0.02	1.63±0.01*	3.72±0.04*
45-54 years	with dysbiosis (n=122)	2.44±0.04	1.88±0.03	4.32±0.07
	dysbiosis-free (n=194)	2.41±0.03	1.85±0.02	4.26±0.05
Total	with dysbiosis (n=464)	2.25±0.01	1.62±0.01	3.87±0.02
	dysbiosis-free (n=716)	1.85±0.01**	1.59±0.01**	3.44±0.02**

Note: –* significant differences among groups with dysbiosis and without dysbiosis; –**significant differences in the mean values of groups with dysbiosis and without dysbiosis.

Table 3

Comparative characterization of the effectiveness of the developed therapeutic paste at the stages of treatment of medium severity chronic periodontitis with second degree dysbiosis

Types of microorganisms	Quantity, lg CFU before treatment			Quantity, lg CFU by the end of treatment		
	Study group (n=328)	Comparison group (n=31)	Placebo-control group (n=29)	Study group (n=328)	Comparison group (n=31)	Placebo -control group (n=29)
Tannerella forsythensis	7 ±0.02	8 ±0.08	7±0.04	3 ±0.05	4 ±0.21	7±0.04
Treponema denticola	8 ±0.04	7 ±0.08	8±0.09	3 ±0.05	5 ±0.13	8±0.09
Streptococcus oralis	8 ±0.02	7 ±0.13	7±0.04	5 ±0.03	4 ±0.21	7±0.04
S. sanguis	7 ±0.03	8 ±0.17	8±0.09	3 ±0.04	4 ±0.21	8±0.09
S. aureus	8 ±0.04	8 ±0.13	7±0.04	3 ±0.05	5 ±0.17	7±0.04
S. suis	7 ±0.01	8 ±0.17	8±0.09	5 ±0.02	4 ±0.17	8±0.09
S. constellatus	8 ±0.04	8 ±0.13	8±0.09	3 ±0.05	5 ±0.17	8±0.09
S. vestibularis	7 ±0.02	8 ±0.21	8±0.09	4 ±0.03	3 ±0.21	8±0.09
S. parasanguinis	7 ±0.03	6 ±0.08	6±0.18	3 ±0.04	4 ±0.17	6±0.18
S. cristatus	7 ±0.02	7 ±0.13	8±0.09	4 ±0.03	4 ±0.17	8±0.09
Average for the genus Streptococcus	7.40 ±0.02	7.5 ±0.14	7.5±0.11	3.75 ±0.04	4.12 ±0.19	7.5±0.11
Candida dubliniensis	7 ±0.01	8 ±0.13	7±0.04	5 ±0.02	5 ±0.13	7±0.04
Fusobacterium nucleatum	8 ±0.02	8 ±0.08	8±0.09	5 ±0.03	6 ±0.13	8±0.09
Neisseria sicca	8 ±0.01	8 ±0.04	7±0.04	6 ±0.02	7 ±0.08	7±0.04
N. elongata	6 ±0.02	7 ±0.08	8±0.09	3 ±0.03	5 ±0.08	8±0.09
N. mucosa	7 ±0.03	8 ±0.13	8±0.09	3 ±0.04	5 ±0.13	8±0.09
N. flava	8 ±0.01	7 ±0.08	7±0.04	6 ±0.02	5 ±0.17	7±0.04
Average for the genus Neisseria	7.25±0.02	7.5 ±0.08	7.5±0.11	4.5±0.03	5.5 ±0.13	7.5±0.11

with age. Meanwhile, the conducted clinical study revealed a significant decrease in the index of supra- and sub-gingival dental calculi, where in 15-year-olds it was 2.83±0.05% in the group without dysbiosis and 2.85±0.07% with dysbiosis, while in the age group of 65-74 years without dysbiosis it was 0.55±0.09% and with dysbiosis - 0.57±0.14%, respectively. Meanwhile, a similar trend is determined in periodontal pocket data, where in the group of 65-74 year olds without dysbiosis it was 3.05±0.05%, with dysbiosis - 3.09±0.07%, and in 15 year olds without dysbiosis 0.37±0.09%, with dysbiosis - 0.38±0.12%. Meanwhile, the opposite trend of increase in the indices of unaccounted sextants is determined in the age groups 20-34 years and 65-74 years without dysbiosis, where the indices amounted to 0.13±0.07% and 2.21±0.10%, and with dysbiosis - 0.10±0.12% and 2.15±0.10%, respectively, confirming that periodontal diseases are the main etiologic factor of tooth loss.

The examined age groups have a high prevalence rate and unfavorable tendency of clinical course of periodontal diseases with age, their clinically more severe course is determined in groups of persons with oral dysbiosis. The identified clinical features dictate the need for further research aimed at improving periodontal care for the population.

In the structure of etiologic factors of inflammatory processes of periodontal tissues, plaque, which is closely related to the state of oral hygiene, is of great importance. Taking into account the above-mentioned, we studied the state of oral hygiene (Table 2). The obtained results of oral hygiene condition in the examined age groups of adolescents and adults determine an unfavorable situation, which is associated with the presence of dental plaque and calculus identified in this study. Thus, in the age groups with dysbiosis 15 and 20-34 years old, a poor hygienic state is determined compared to the groups without dysbiosis ($p<0.05$), where satisfactory oral hygiene was detected. At the same time, plaque and tartar data in these age groups are interpreted as satisfactory levels. In the age group 35-44 years with and without dysbiosis, the plaque and calculus data show satisfactory levels. However, the data of total IGR-U index in this surveyed group is evaluated as poor hygiene. Whereas, in the group of 45-54 years old with dysbiosis and without dysbiosis according to the data of dental plaque and calculus, as well as the total values of hygiene index, the poor hygiene state was established.

It should be noted that the average plaque index in persons with dysbiosis (2.25±0.01) is characterized as a poor hygienic state, and without dysbiosis the index was within 1.85±0.01, which is interpreted as a satisfactory level. The data of tartar index in all examined age groups with dysbiosis and without dysbiosis characterize a satisfactory hygienic state of the oral cavity. The obtained average total values of IGR-U in the examined groups with dysbiosis and without dysbiosis characterize poor levels of hygienic condition of the oral cavity. In this case, in groups with dysbiosis the given plaque expresses a poor level, and in groups without dysbiosis the indicator is defined as a satisfactory value, and for tartar indicators in groups with dysbiosis and without dysbiosis is defined as a satisfactory level.

Before the treatment of chronic periodontitis of medium severity of the developed method, the data of periodontal index according to Russell in groups with dysbiosis were -3.9 and without dysbiosis - 3.2, which when interpreted characterizes periodontitis of medium severity.

The analysis of the conducted complex treatment of chronic periodontitis of medium severity in patients with second-degree dysbiosis of the large intestine characterizes the presence of certain clinical features. Thus, the microflora of the periodontal pocket is represented by grampositive and gramnegative aerobic and anaerobic microorganisms, as well as yeast-like fungi of the genus Candida. Among anaerobes, gram-negative bacteria of the genus Tapperella, Treponema and Fusobacterium predominated in patients. The aerobic component was represented by numerous species of Gram-positive streptococci and Gram-negative Neisseriaceae. Species composition and average content of microorganisms in the study group, comparison group and placebo control group before and after treatment are presented in Table 3.

The results obtained after one month of complex treatment of chronic periodontitis of medium severity in the study group using the developed therapeutic paste indicate a certain restoration of periodontal pocket microbiota and reduction of opportunistic microflora in the oral cavity. Thus, the number of Tannerella forsythensis amounted to 3 lg CFU, Treponema denticola also 3 lg CFU, the average index for Streptococcus genus decreased to 3.75 lg CFU, for Neisseria genus - to 4.5 lg CFU, the content of fungi of the genus Candida and Fusobacteria decreased not so significantly and

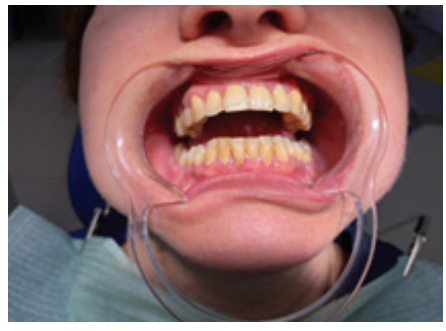

Fig. 1. A patient with chronic generalized periodontitis of moderate severity with dysbiosis of the second degree before treatment

Fig. 2. Therapeutic paste for the treatment of chronic periodontitis of moderate severity with dysbiosis of the second degree

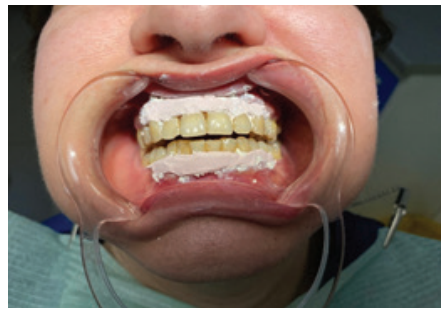

Fig. 3. The introduction of a therapeutic paste into a periodontal pocket with a protective bandage "Parasept" for periodontitis of moderate severity with dysbiosis of the second degree

Fig. 4. The condition of periodontal tissues after a course of therapy with a therapeutic paste with the synbiotic "Bificin Forte" 20 billion CFU in chronic generalized periodontitis of moderate severity with dysbiosis of the second degree

amounted to 5 lg CFU for both microorganisms. Thus, it can be seen that treponemes and streptococci turned out to be the most sensitive to the therapeutic effect. The similar tendency of dynamic changes of clinical picture and positive change of microflora balance are noted in patients of the comparison group. At the same time in the placebo-control group quantitative indicators of periodontal pocket microbiota remain respectively unchanged.

Dynamic change in the balance of periodontal pocket microflora in the study group was accompanied by the manifestation of positive changes in periodontal tissues at the stages of the complex treatment already on the 3rd day in the form of reversal of the inflammatory process with subsequent reduction of periodontal tissue edema and disappearance of gingival bleeding. After the inflammatory process of periodontal tissues subsided, some patients underwent surgical methods of treatment, which included open curettage or flap operations. At the end of the procedure, recommendations were given on rational oral hygiene and visits to the dentist at the place of residence 3-4 times a year for preventive examination, where treatment courses were repeated if indicated.

Pearson's chi-square analysis characterizes the presence of a relationship between the compared categorical variables, where the correlation of periodontal pocket depth and bleeding symptom is determined (r=0, 79), Streptococcus ogalis and Neisseria sicca (r=0,49), Streptococcus sanguis and Treponema denticola (r=0,52), Tannerella forsythensis and Fusobacterium pucleatum (r=0,81), which causes a pronounced reverse development of periodontal tissue inflammation when using the developed method. Clinical efficacy of treatment is confirmed by Varimax factor analysis.

A clinical example. Patient S., 44 years old, turned to the dental clinic of the Clinic of the Northeastern Federal University named after M.K.Ammosov. Complaints: the presence of soft and hard dental deposits, tooth mobility with manifestations of bleeding gums during meals and when brushing teeth.

Objective: external examination – the configuration of the face is unchanged, the skin is without features, the regional lymph nodes are not enlarged, the opening is free, TMJ dysfunction on the left, the red border of the lips is without features; examination of the oral cavity – the mucous membrane of the gums in the area 1.6,1.5, 2.5, 2.6, 3.1, 3.2, 3.3, 4.1, 4.2 and 4.3 hyperemic, edematous, bleeding during probing, the depth of periodontal pockets in the area 3.1, 3.2, 3.3, 4.1, 4.2, 4.3 it is 3.6 mm without separation, the mobility of teeth in the antero-posterior direction, the Kulazhenko test is positive and is 9 seconds (Fig.1).

According to the data provided by the inpatient discharge: the patient underwent inpatient treatment 3 months ago in the gastroenterological department of the Yakut Republican Clinical Hospital for exacerbation of gastric ulcer and duodenal ulcer, where dysbiosis of the second degree was detected.

Diagnosis: chronic periodontitis of moderate severity with dysbiosis of the second degree.

Treatment: the initial stage of therapeutic and preventive measures included professional oral hygiene and oral hygiene training. Local and general treatment is prescribed. A therapeutic paste was applied topically (Fig.2) based on the powder of the synbiotic "Bificin Forte" 20 billion CFU, an oil solution of vitamin A and zinc oxide by injection into the periodontal pocket with its fixation with a protective bandage "Parasept" for 3-5 hours (Fig.3). Additionally, Bificin Forte synbiotic was prescribed 20 billion CFU orally, 1 capsule per day for 3-4 weeks.

After the course of treatment, the patient objectively determines the reverse development of the inflammatory process with a decrease in swelling, disappearance of symptoms of bleeding and hyperemia of periodontal tissues (Fig.4). At the same time, the patient was referred to preventive courses of treatment to a gastroenterologist and consultation with a therapist, obstetrician-gynecologist and endocrinologist. The patient has been registered at the dispensary. Turnout for a repeat appointment in 2-3 months.

Conclusion. The developed method of treating chronic periodontitis of moderate severity in patients with dysbiosis of the second degree helps to reduce the number of pathogenic microbial associations in the gum biotope and restore the microbiocenosis of the oral cavity, followed by the manifestation of positive changes in periodontal tissues. At the same time, at the stages of complex treatment, the reverse development of the inflammatory process is clinically determined on the 3rd day, which confirms the clinical effectiveness of the developed treatment method, preventing further complications of inflammatory processes of periodontal tissues. In this regard, this method has prospects for its application in clinical periodontology.

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STUDY OF THE ANTITUMOR ACTIVITY OF 2-(1,1-DIMETHYL-1H-BENZO[E]INDOLIN-2-YL)-5,6,7-TRICHLORO-1,3-TROPOLONE IN COMBINATION WITH TEMOZOLOMIDE ON THE U87 GLIOBLASTOMA MODEL IN VIVO

Glioblastoma remains one of the most aggressive and treatment-resistant brain tumors, highlighting the need for novel therapeutic approaches. This study aimed to evaluate the antitumor efficacy of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone in combination with temozolomide (TMZ) in subcutaneous xenografts of U87 glioblastoma cells in Balb/c Nude mouse line. The animals were divided into three groups: (1) TMZ monotherapy (20 mg/kg), (2) combination therapy with tropolone and TMZ (20 mg/kg each), and (3) an untreated control group. Tumor volumes were measured three times weekly, and tumor growth inhibition (TGI%) along with relative tumor mass were calculated at the end of the experiment. On day 25, the mean tumor volumes were as follows: 443.02±52.16 mm³ in the monotherapy group, 395.80±41.98 mm³ in the combination therapy group, and 1331.43±65.65 mm³ in the control group. The results demonstrated that the combination of tropolone and temozolomide significantly suppressed tumor growth compared to the control group. Furthermore, the tumor volume in the combination therapy group was smaller than in the TMZ monotherapy group, although the difference was not statistically significant. The findings revealed that combination therapy resulted in a greater reduction in tumor volume and relative tumor mass compared to TMZ monotherapy, with TGI rates of 70.27% versus 66.72%, respectively. Histological analysis confirmed marked cellular dystrophic changes in tumors subjected to combination therapy. These results suggest a potential synergistic interaction between tropolone and temozolomide, which may enhance the efficacy of glioblastoma treatment.

Keywords: glioblastoma, U87 cell line, tropolone, temozolomide, immunodeficient mice, antitumor activity, chemotherapy.

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Introduction. Glioblastoma is the most aggressive and lethal form of primary brain tumor. It is characterized by rapid growth, diffuse infiltration, and resistance to conventional therapeutic interventions. Despite strides in surgical techniques, radiation therapy, and chemotherapy, the prognosis for patients remains dismal, with a median survival of a mere 14.6 months [15]. Temozolomide (TMZ), a standard alkylating drug in the treatment of glioblastoma, has seen its efficacy diminished by resistance and adverse effects, underscoring the need for novel therapeutic approaches [15].

Several studies have investigated combination strategies with various compounds to enhance the action of TMZ, including histone deacetylase (HDACis) inhibitors and PI3K/AKT/mTOR signaling pathways, as well as natural compounds such as curcumin and resveratrol. These approaches show synergy with TMZ, enhancing its pro-apoptotic action and increasing tumor cell sensitivity [9].

Tropolones, low-molecular compounds with a unique structure and pronounced antitumor properties, attract particular attention. They inhibit key enzymes such as MMP and HDAC and are able to induce apoptosis, inhibit angiogenesis, and regulate the levels of reactive oxygen species in tumor cells. Some tropolones derivatives exhibit antiproliferative and proapoptotic effects, making them promising for the treatment of glioblastoma in combination with TMZ [2, 4–6].

Purpose of the study – to evaluate the antitumor activity of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone in combination with temozolomide against subcutaneous xenografts of U87 glioblastoma cell culture in immunodeficient Balb/c Nude mice.

Materials and methods. In the present experiment, 18 female Balb/c Nude mice were utilized. These mice were

maintained in a pathogen-free environment with unlimited access to food and water. The mice in all of the studied groups were weighed at the beginning and at the conclusion of the experiment. All experimental procedures were carried out in accordance with the rules of the European Convention for the Protection of Vertebrate Animals Used for Experiments or Other Scientific Purposes (ETS 123, Strasbourg, March 18, 1986) and were approved by the Biotic Commission of the National Medical Research Centre for Oncology of the Ministry of Health of Russia.

Human glioblastoma cell line U87 was cultured in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin at 37°C in a humidified atmosphere containing 5% CO2. U87 cells (5 × 10^6) were injected subcutaneously into the right flank of each mouse in a mixture of serum-free DMEM and Matrigel Matrix.

The studied tropolone derivative, 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122(2)), synthesized at the SFEDU Research Institute of Physical Chemistry, was administered orally 3 times a week for 3 weeks [5]. Temozolomide (TMZ) was dissolved in 0.9% NaCl solution and administered intraperitoneally daily for 3 weeks. The drugs were administered regardless of food and water intake.

After the tumors reached an average volume of ~100 mm³, the mice were divided into three groups (n = 6), with the average volume of subcutaneous xenografts between the groups not differing by more than 10%: group 1 – TMZ (20 mg/kg), group 2 – a combination of TMZ and tropolone (20 mg/kg each), group 3 – control group.

Tumor growth was measured every three days, starting with the first administration of the drugs. Tumor volume was calculated using the formula:

$$V = LW^2/2,$$

where V is the tumor volume (mm³), L and W are the length and width of the tumor (mm).

To assess antitumor activity, the tumor growth inhibition index (TGI%) was used:

$$TGI\ (\%) = (Vk - Vo) / Vk \times 100,$$

where Vk and Vo are the average tumor volume (mm3) in the control and experimental groups, respectively.

The experiment lasted 25 days. The euthanasia procedure was performed by decapitation, after which the tumor material was extracted. The tumors were weighed to calculate the relative mass using the formula:

$$m_{rel}\ (\%) = (m_t / m_b) \times 100$$

where m_t is the tumor mass (g), m_b is the animal's body mass (g).

For histological analysis, the obtained tumor material was stained with hematoxylin and eosin.

Data are presented as mean ± standard error of the mean (SEM). Statistical analysis of data was performed using Statistica 10. Comparisons between groups were performed using one-way analysis of variance (ANOVA). A p value of <0.05 was considered statistically significant.

Research results and discussion. The experiment assessed the effect of temozolomide and its combination with the studied tropolone on the growth of glioblastoma tumors. The results showed a significant effect on tumor growth compared to the control group (Figure 1).

On the 7th day of the experiment, a statistically significant decrease in tumor volume was noted in the experimental groups compared to the control group. By the end of the 25-day period of drug administration, the average tumor volume in the group receiving the combination of tropolone and TMZ (group 2) was 395.80±41.98 mm³. This value was lower than in the TMZ monotherapy group (group 1443.02±52.16 mm³) and the control group (group 3, 1331.43±65.65 mm³).

In the TMZ monotherapy group, tumor growth was slower than in the control group, confirming the antitumor activity of the drug. In combination therapy, a more pronounced effect was noted, suggesting a synergistic or additive mechanism. However, no statistically significant differences were found between the monotherapy and combination groups, indicating similar efficacy of the approaches.

TMZ therapy at a dose of 20 mg/kg significantly reduced the relative tumor mass compared to the control group (Figure 2). In Group 1, the relative tumor mass was 1.12±0.30%, and the TGI index reached 66.72%, indicating a pronounced antitumor effect of the drug. Figure 3 shows tumor nodes of mice from the experimental and control groups, which allows for a visual assessment of the sample sizes.

In the combination therapy group, the relative tumor mass decreased to 0.95±0.17%, and TGI was 70.27%. This confirms the more pronounced effect of combination therapy, possibly due to the synergistic effect of the interaction of tropolone and TMZ.

After completion of therapy, tumor nodes were subjected to histological analysis (Figure 4).

Histological analysis of the specimen revealed a malignant tumor, the structural characteristics of which are consistent with those of glioblastoma. The presence of minor foci of necrosis was observed in the relevant fields of view. Furthermore, dystrophic changes of individual tumor cells were observed in tumor samples exposed to temozolomide. Concomitant exposure to both temozolomide and the other agent resulted in more pronounced dystrophic changes in cells and signs of karyopyknosis in

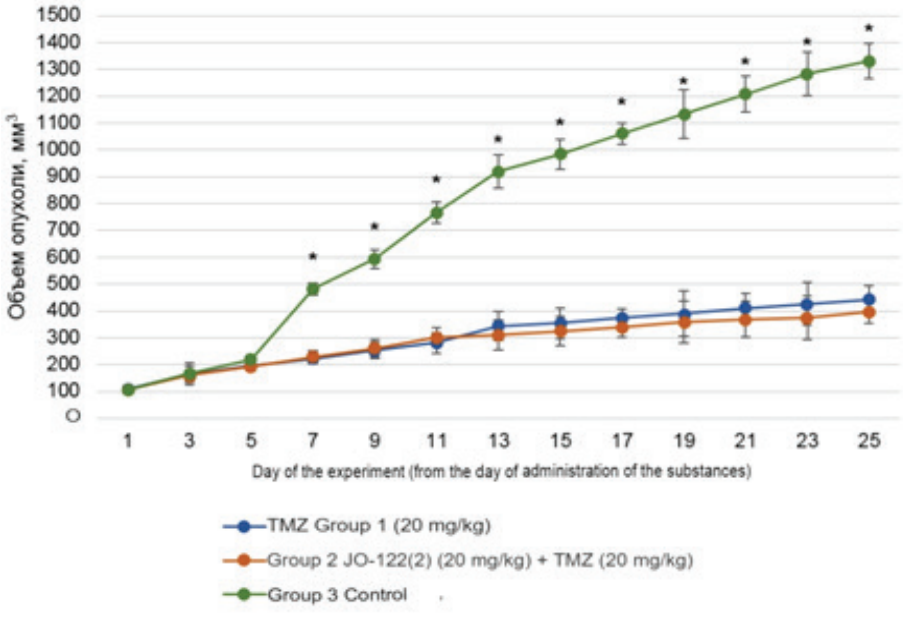

Fig. 1. Average tumor node volumes in Balb/c Nude mice over time. * – statistically significant differences from groups 1 and 2 (p<0.05).

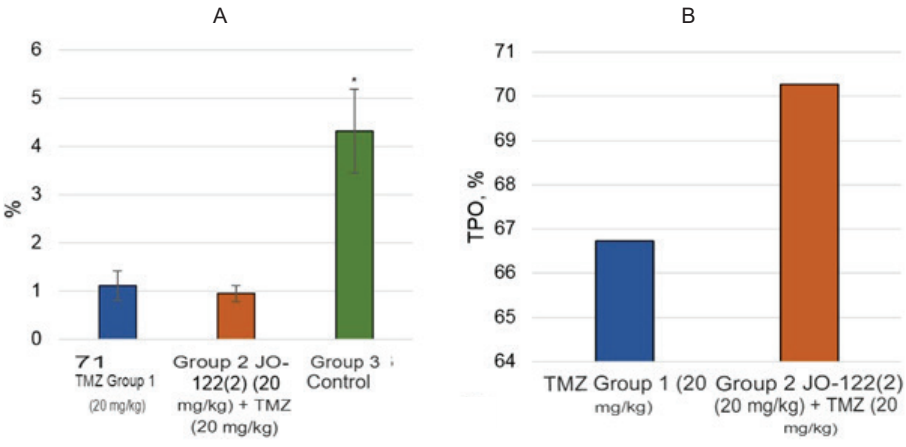

Fig. 2. Relative tumor mass (A) and tumor growth inhibition (TGI) (B) indices in the experimental and control groups

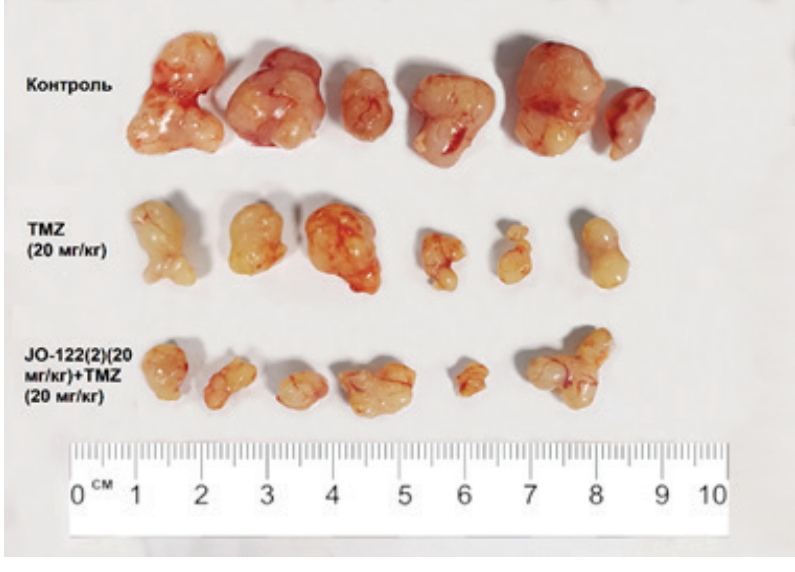

Fig. 3. Tumor nodes of mice from the experimental and control groups

individual tumor nuclei. These findings may indicate induction of cell death due to the combined therapy.

The analysis showed that the administration of TMZ and the combination with tropolone was well tolerated: the body weight and condition of the animals remained stable, and there were no signs of toxicity.

The results of the study demonstrate the potential of the new tropolone derivative as a therapeutic agent for the treatment of glioblastoma. In particular, its combination with temozolomide resulted in an increase in the TGI index, a decrease in tumor weight and characteristic histological changes. These data indicate a possible interaction between tropolone and temozolomide, which may improve therapeutic results and possibly allow a reduction in the dose of temozolomide to reduce its side effects.

It is noteworthy that the dose of temozolomide (TMZ) used in this study was 20 mg/kg (60 mg/m² [12]), which is lower than the standard clinical dose of 75–100 mg/m² [15]. Such a reduction may significantly reduce the severity of side effects of the drug.

Tropolone derivatives are known to have high cytotoxic activity. For example, one of the tropolones showed a pronounced cytotoxic effect on gastric adenocarcinoma (AGS) cells, surpassing fluorouracil (5-FU) even at lower concentrations [4]. In addition, it demonstrated significant efficacy against primary glioma cell cultures [3] and was almost ten times more effective than 5-FU on the SW620 cell line [1]. Its antiproliferative effect on A431 epidermal carcinoma cells was also revealed [7].

The mechanisms underlying the proposed synergy between tropolone and temozolomide require further study. Tropolones are thought to induce caspase-dependent apoptosis and suppress antiapoptotic proteins (e.g., Bcl-2), whereas temozolomide induces apoptosis via DNA damage. Co-administration of the drugs may also enhance p53-dependent apoptosis [2,11,14].

Tropolones also inhibit the Wnt/β-catenin pathway, limiting tumor cell proliferation and migration, and increase reactive oxygen species, causing DNA damage. Temozolomide complements these effects by enhancing oxidative stress [8, 10–11]. In addition, tropolones increase endoplasmic reticulum stress, promoting cell death [13].

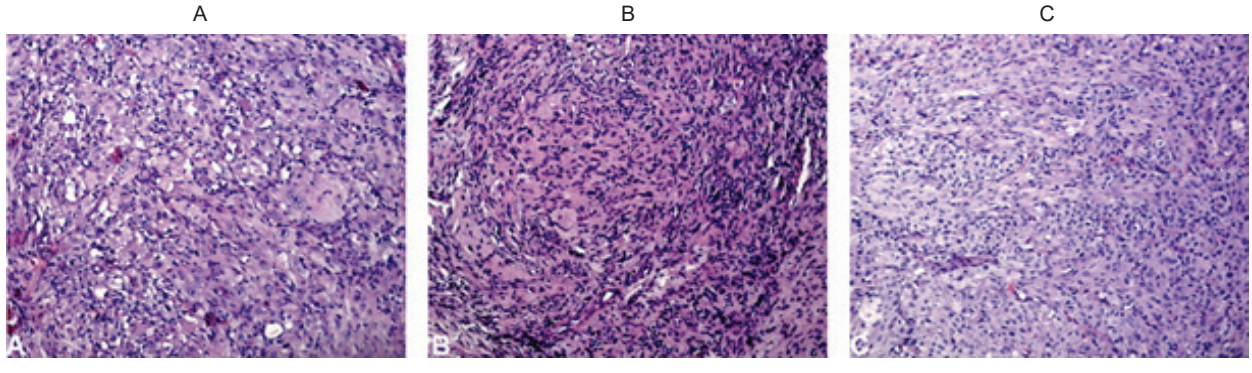

Fig. 4. Histological preparations of subcutaneous xenografts of the U87 glioblastoma cell line. A – 1st group; B – 2nd group; C – 3rd group (control). Magnification ×200

Despite the encouraging results, limitations of the study remain, such as the use of only one glioblastoma cell line and a subcutaneous xenograft model that does not fully recapitulate the brain tumor microenvironment. Transcriptomic and proteomic analyses are needed to clarify the mechanisms of tropolone-temozolomide interaction.

These data provide a basis for further evaluation of tropolones in combination therapy for glioblastoma, opening up opportunities to improve treatment efficacy and reduce side effects.

Conclusion. The findings indicate the promise of tropolone derivatives in conjunction with temozolomide for the treatment of glioblastoma. The efficacy of this combination is likely attributable to a synergistic effect involving the activation of caspase-dependent apoptosis, the suppression of antiapoptotic proteins, and the enhancement of oxidative stress. Moreover, the potential to reduce the dosage of temozolomide enables the mitigation of its toxicity. However, further studies are needed to confirm these results, including investigating the molecular mechanisms of tropolone and TMZ interaction and evaluating efficacy in other glioblastoma models. These data provide a basis for developing new approaches to glioblastoma treatment and improving the efficacy of existing therapies.

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CREATION OF A HETEROTOPIC PDX MODEL OF UVEAL MELANOMA

Uveal melanoma, the second most prevalent form of the disease after cutaneous melanoma, exhibits a lower prevalence rate. Treatment options for uveal melanoma may include enucleation, exenteration, radiation therapy, brachytherapy, or systemic therapy. However, these methods do not guarantee a complete cure, and half of the patients subsequently develop metastases, which still carry an unfavorable prognosis. Therefore, preliminary selection of therapeutic candidates in preclinical studies is important. The reliability and potential of preclinical study results depend on the tumor model's reflection of the fundamental biological characteristics of uveal melanoma. The objective of our study was to develop a subcutaneous PDX model of uveal melanoma, which will be utilized to generate uveal melanoma metastases.

In the course of our research, we developed a collection of three heterotopic PDX models of uveal melanoma. Histological examination of these models revealed their correspondence to the donor tumors. According to the results of our study, the first-generation tumor engraftment rate was 37.5% (3/8). We also assessed the growth dynamics of the obtained PDX models. The analysis revealed that the growth rate of the first-generation xenografts obtained from patients was low, with a doubling time of 42 days. To sustain the growth of the PDX model, the tumors obtained from the first-generation mice were systematically transplanted into the subsequent group of mice. Our findings demonstrate that the first-generation models successfully engrafted in the second-generation mice. Furthermore, it was observed that the growth rate of the tumor node was higher in the second generation compared to the first generation.

Keywords: uveal melanoma, PDX, tumor models.

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Introduction. Uveal melanoma, the second most prevalent form of the disease after cutaneous melanoma, manifests as the most common primary intraocular neoplasm [4]. This neoplasm originates from melanocyte cells residing within the intraocular structures, including the choroid, ciliary body, and/or iris. The predominant location of the disease is the choroid (90%), followed by the ciliary body (6%) and iris (4%) [8].

A multitude of factors have been identified as contributing to an increased likelihood of developing uveal melanoma. These factors include, but are not limited to, light eye and skin color, the presence of dysplastic nevus syndrome, ocular melanocytosis, and xeroderma pigmentosum [2]. Furthermore, research has demonstrated a positive correlation between prolonged exposure to natural and artificial ultraviolet radiation and the likelihood of developing uveal melanoma. [11].

Treatment of uveal melanoma may include enucleation, exenteration, radiation therapy, brachytherapy (placement of radioactive sources directly into the tumor), or systemic therapy (chemotherapy, targeted therapy) [11]. However, these strategies do not always lead to complete recovery. In fact, half of the patients subsequently develop metastases, the prognosis for which remains unfavorable [6].

Currently, there are no effective treatment options for patients with advanced or metastatic uveal melanoma. Therefore, innovative therapeutic approaches are needed to improve treatment outcomes [1].

In recent years, preclinical models created by direct implantation of tumor material obtained from patients into immunodeficient mice (patient derived xenografts - PDX) have been considered the most preferable for oncology research, since they most accurately reproduce the characteristics of a human tumor compared to other model systems [3].

PDX models serve as an experimental tool, facilitating a deeper understanding of the molecular processes underlying diseases and identifying promising targets for therapeutic intervention. In the context of oncology research, the use of PDX models of uveal melanoma allows for a broader understanding of the mechanisms of disease progression and metastasis.

Furthermore, such models enable the testing of new therapeutic approaches and the identification of optimal combinations of treatments. Consequently, this may result in enhanced prognoses for patients afflicted with metastatic uveal melanoma [5].

In this regard, the objective of our study was to develop a subcutaneous PDX model of uveal melanoma, as well as to assess the growth dynamics and histology of the obtained tumor nodes, with the aim of further refining this model to create a metastasis of uveal melanoma.

Materials and methods. *Animals and their managment.* In the course of the experiment, female Balb/c Nude mice aged 12-14 weeks, with an average weight of 27-30 g, were utilized. These animals were obtained from the in-house breeding vivarium of the Testing Laboratory Center of the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation. The mice were housed in individual ventilated cages and provided with food and water ad libitum. All manipulations carried out within the framework of the study 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 (ETS 123, Strasbourg, March 18, 1986). The study protocol was approved by the local bioethics committee of the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation.

Tumor samples. A total of eight patients receiving treatment at the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation provided samples of uveal melanoma. Informed consent for the transfer of biological material was obtained from all patients.

Anesthesia. The surgical manipulations performed on the animals in this experiment were carried out using intramuscular injection anesthesia of the veterinary drugs "Xyla" (20 mg/kg) and "Zolelil-100" (50 mg/kg).

Technique of creating a heterotopic (subcutaneous) model of uveal melanoma by transplanting a tumor fragment from a patient to the right side. We previously obtained samples of uveal melanoma tumor material from patients following enucleation of the eye or orbital exenteration. The tumor material was transported to the vivarium within 15 minutes of removal in DMEM nutrient medium containing 10% gentamicin. Tumor material obtained from one patient was implanted in a group of three mice. Upon reaching the requisite depth of anesthesia, the animals were incised along the right side of the skin, followed by the introduction of sterile closed blunt scissors into the subcutaneous space to separate the peritoneum from the skin, thereby creating a subcutaneous pocket. The isolated tumor material was then implanted without causing trauma to the abdomen. The surgical wound was sutured using an interrupted suture, and all surgical interventions were performed under sterile conditions. The second generation was created in a similar manner.

Assessment of tumor node growth. The linear dimensions of tumor nodes were measured using a caliper weekly, starting from the 14th day after implantation of tumor material into immunodeficient mice. The volume of the tumor node was calculated using the formula:

$$V=LW^2/2,$$

where L, W are the linear dimensions of the tumor.

Observations and measurements of tumor nodes were performed for 4 months, starting from the date of implantation of tumor material.

Euthanasia. Euthanasia was performed by decapitation followed by tumor node collection at the end of the observation period.

Histological examination. The tumor node was fixed in a 10% formalin solution for 24 hours. After this procedure, the material was placed in paraffin for further preparation of histological microsections, which were stained with hematoxylin and eosin according to the standard technique. Using a ZEISS Axio light microscope, a histological study of the human donor tumor and tumor material of the PDX models was performed.

Research results and their discussion. Animal models are indispensable tools in the study of tumor growth and metastasis, as well as the evaluation of novel treatment methods. The reliability of research findings is contingent upon the selection of an appropriate model that accurately reflects the pathogenesis of the disease [10].

In the 2023–2024 period, a total of

Results of heterotopic implantation of uveal melanoma in Balb/C Nude mice

Code of xenograft procedures	Age	Sex	Method of obtaining material	Tumor localization	Stage	TNM stage	Results of heterotopic implantation
PDX-UM-01	66	F	Enucleation of the left eye	At 5-6 o'clock Posterior lateral wall of the eyeball	II	T3aN0M0	-
PDX-UM-02	76	F	Orbital exenteration of the left eye	At 7-8 o'clock Posterior lateral wall of the eyeball	II	T2aN0M0	+
PDX-UM-03	64	M	Enucleation of the right eye	In all quadrants Diffuse spread	III	T4aN0M0	+
PDX-UM-04	47	F	Orbital exenteration of the right eye	At 2-4 o'clock Along the nasal surface	II	T3aN0M0	-
PDX-UM-05	67	M	Orbital exenteration of the right eye	At 8-9 o'clock Left temporal region	II	T2aN0M0	-
PDX-UM-06	50	F	Orbital exenteration of the left eye	At 7-9 o'clock Posterior lateral wall of the eyeball	II	T3aN0M0	+
PDX-UM-07	70	F	Orbital exenteration of the left eye	In all quadrants Diffuse spread	III	T3bN0M0	-
PDX-UM-08	62	M	Enucleation of the right eye	In all quadrants Diffuse spread	III	T4bN0M0	-

Note: "+" – successfully engrafted material; "-" - lack of successful engraftment of the material.

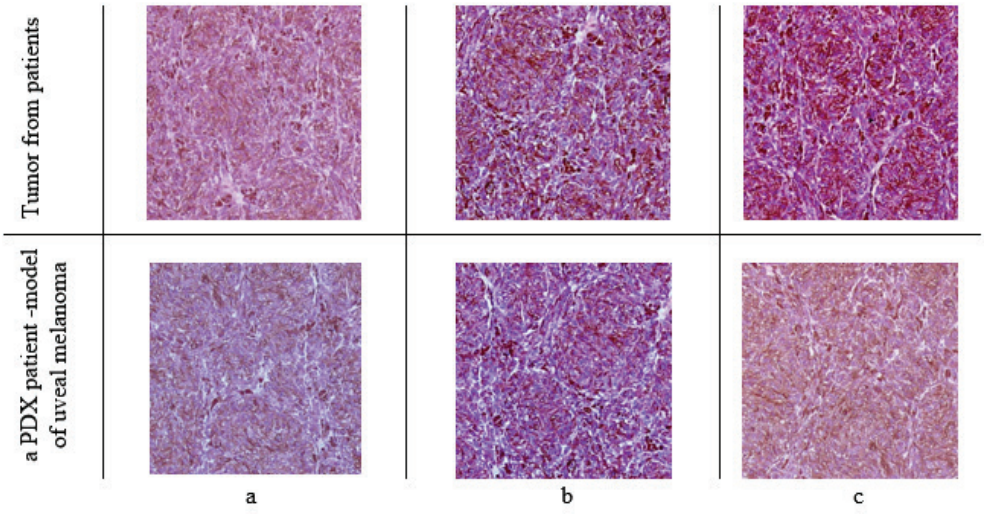

Fig. 1. Histological preparations of patient tumors and corresponding PDX models of uveal melanoma (a - PDX-UM-02; b - PDX-UM-03; c - PDX-UM-06)

eight patients diagnosed with uveal melanoma were enrolled in the study. These patients were treated at the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation. The patients' tumor samples were then implanted subcutaneously into the right side of Balb/C Nude mice (n = 3). The success of the engraftment process was determined by the volume of the tumor node, which had to reach a minimum of 60 mm³ for the tumor to be considered successfully engrafted. The observation period was four months, during which the absence of tumor growth was noted. In the event that no growth of tumor nodes was observed during this time, the xenotransplantation procedure was assessed as ineffective. It is noteworthy that all uveal melanoma samples were obtained during the surgical stage of treatment and implanted within 30 minutes post-surgery. The average age of the sample donor patients was 63 years (range, 47–76 years). The distribution of gender among the donor patients was as follows: 37.5% male and 62.5% female. The tumor donor patients did not receive neoadjuvant chemotherapy or radiotherapy. The majority of patients were diagnosed with stage II disease, and a total of 3 PDX models of human uveal melanoma were obtained from tumor samples from 8 patients. The detailed patient characteristics and tumor xenotransplantation results are presented in Table 1. The success rate of primary tumor engraftment obtained from patients was 37.5%, as shown in Table.

Next, samples of donor tumors and corresponding successfully engrafted xenogeneic (PDX) tumors were subjected to histological examination.

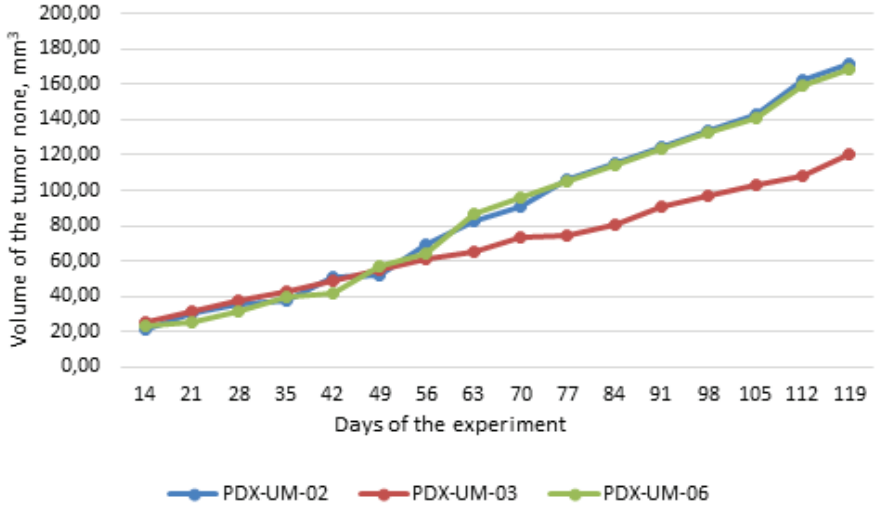

Fig. 2. Dynamics of tumor node growth in 1st generation (passage) PDX models of human uveal melanoma

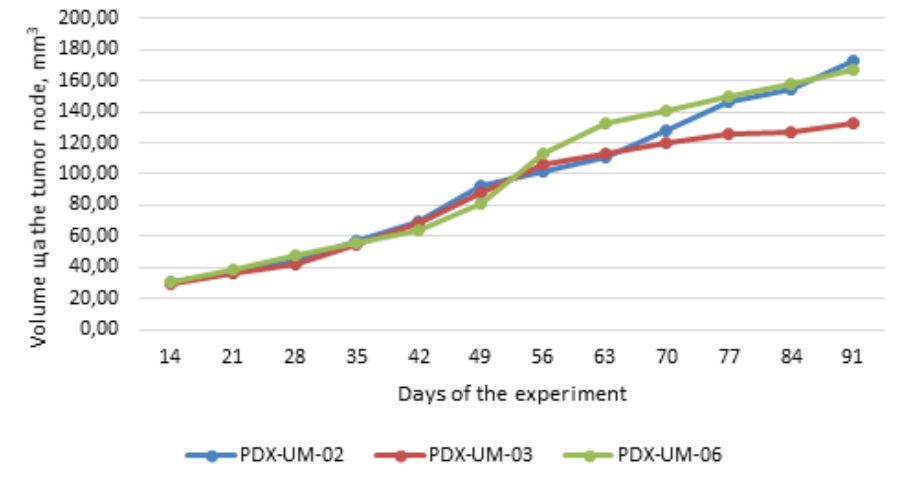

Fig. 3. Dynamics of tumor node growth in 2nd generation (passage) PDX models of human uveal melanoma

A histological examination revealed that xenotransplanted heterotopic (subcutaneous) tumors in mice exhibited a histotype consistent with the corresponding donor tumors. The models obtained consisted of epithelioid cells with a high content of pigment, melanin, and moderate cellular atypia. The preparations also contained mitotic division figures. It is noteworthy that the models retained the same degree of pigmentation as the original tumors from the patients.

The results of our study indicate that the rates of successful engraftment of the first generation tumor were 37.5% (3/8) when implanted into a heterotopic (subcutaneous) site, which is comparable to the results of the work of N émati F. et al., where the efficiency of implantation of human uveal melanoma samples was 28% (25 out of 90); in the work of Heegaard S. et al., the efficiency rates were slightly lower – 13%.Furthermore, histopathological analysis revealed that model samples obtained from these tumors also demonstrated characteristic features of uveal melanoma [7, 9].

In this study, we evaluated the growth dynamics of the obtained PDX models. According to the results presented in Figure 2, it can be concluded that the growth rate of the first-generation xenografts obtained from patients was quite low, with the doubling of the tumor volume occurring in 42 days.

In order to sustain the expansion of the PDX model, tumors obtained from the first generation mice were successively transplanted to the subsequent group of mice. The first generation models obtained were effectively established in the second generation mice. Furthermore, it was observed that the tumor node growth rate was higher than in the first generation. A twofold increase in tumor volume was observed on day 35. (Figure 3).

A comprehensive analysis of tumor node growth dynamics revealed that the heterotopic PDX models of uveal melanoma, obtained by us, exhibited a relatively low growth rate. This finding suggests that the biological properties of xenotransplanted tumors, specifically their proliferative and tumorigenic potential, may be a contributing factor. Additionally, the probable influence of the microenvironment on the growth of xenogenic tumors must be considered, given that in heterotopic xenotransplantation, samples develop in the subcutaneous site in a microenvironment that is not conducive to uveal melanoma. The aforementioned facts underscore the necessity for further research in this area.

Conclusion. In the course of the research, PDX models of uveal melanoma were obtained. These models can be used in experimental studies in the field of oncology. They can be used to study the fundamental aspects of the pathogenesis of uveal melanoma. They can also be used to create a model of uveal melanoma metastasis. Furthermore, they can be used to evaluate effective tumor drugs.

Conflict of interest: The authors declare that they have no conflict of interest.

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HEALTHY LIFESTYLE. PREVENTION

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CHARACTERISTICS OF SLEEP PATTERNS IN ADOLESCENTS IN SIBERIA

Background. Disruption of sleep patterns has a negative impact on mental and physical health, which is especially important in adolescence, when intensive growth and development of the whole organism is observed. The frequent problematic use of smartphones among teenagers, as well as the ever-increasing academic pressures and multitasking of modern life, contribute to this, where sleep takes a backseat.

Purpose. Assess the main indicators of sleep patterns, taking into account gender, age and ethnicity in adolescents aged 12-18 in three large cities of Central Siberia: Krasnoyarsk (the studied ethnic group is Caucasians), Abakan (the studied ethnic groups is Khakass) and Kyzyl (the studied ethnic groups is Tuvans).

Materials and methods. The study involved 5332 adolescents aged 11-18. There were 3,797 from Krasnoyarsk, 1,339 - from Abakan, and 200 – from Kyzyl. There were 4,499 Caucasians, 376 - Khakass, and 173 - Tuvans. Teenagers were asked to answer the following questions: what time did you usually go to bed? How long (minutes) did it usually take to fall asleep? What time did you usually wake up?

Results. In all the studied cities of Siberia, adolescents had a late bedtime (at 11 pm and later) and a decrease in sleep duration below established age norms (less than 9 hours in the group of children 11-14 years old, and less than 8 hours in the group 15-18 years old). This corresponds to the situation in other regions of Russia, as well as abroad. In Krasnoyarsk there was a later bedtime, longer night sleep latency and, accordingly, shorter sleep duration compared to Abakan and Kyzyl. Girls, compared to boys, and the older age group (15-18 years), compared to the younger one (11-14 years), had significantly more pronounced disturbances in all sleep parameters in all studied cities, except Kyzyl: they went to bed later, fell asleep longer, got up earlier, and had shorter sleep duration.

Conclusion. The findings show Siberia adolescents have disturbance in sleep patterns: late going to bed and a decrease in sleep duration compared to age norms, which requires preventive measures. Gender, age and ethnic differences were identified also: girls, the older age group (15-18 years) and Caucasians had more severe sleep disturbances.

Keywords: teenagers, sleep duration, time to wake up, night sleep latency, Khakass, Tuvans, Caucasians

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Relevance: The importance of sleep in adolescence can hardly be overestimated, as this period is a time of intensive growth and development of the whole organism both at the physical and psychosocial levels. Full-fledged sleep is necessary for recovery and rest after daytime activity and increased academic load in modern schoolchildren [27]. During sleep there is systematization of the received information, repair of tissues and hereditary material of cells, synthesis of immunoglobulins, production of neurotransmitters and hormones [5, 11]. After sleep, improvement of memory and attention is noted, and performance increases [27]. Sleep reduces the effects of stress and the level of neurotization, slows down aging processes, and improves skin quality [8, 10]. While sleep disorders lead to numerous negative consequences. The risk of cardiovascular [13] and oncologic pathology, metabolic syndrome and obesity [14], anxiety-depressive disorders [18], neurodegenerative diseases [10] increases, immunity decreases. Adolescents have poorer school performance, increased irritability and aggression, and problems in relationships with peers [24].

According to the recommendations of the US National Sleep Foundation, children should sleep 9-11 hours before the age of 14 and 8-10 hours after the age of 14 [19]. However, according to the results of population studies, the established norms are often not observed [3, 7, 21, 26]. Moreover, in the last decade, marked by the widespread introduction of the Internet into everyday life, this trend has intensified. The negative impact of Internet addiction on sleep was confirmed by our previous study [2].

In addition, the sleep schedule is greatly influenced by cultural and national traditions that determine the degree of freedom and obedience of adolescents in the family, respect for the authority of elders and established rules of behavior [20, 21]. Also of great importance is the degree of urbanization and economic development of the area of residence, the availability of various institutions of further education and entertainment, which can affect the bedtime. For example, significant racial and ethnic differences in sleep duration and quality have been found among American schoolchildren: African-Americans and Hispanics had shorter sleep duration compared to their white peers [21].

Many authors have noted the dependence of sleep disorders on gender, and

the results obtained are quite contradictory. According to some data, girls have a later bedtime, and they are more likely to suffer from insomnia and other sleep disorders [7, 13]; according to other data, late bedtime and shorter sleep duration are characteristic of the male sex [1, 4]; and third researchers find no differences between them [3].

At the same time, in Russia, there is insufficient data on the prevalence of sleep disorders in adolescents, their dependence on gender and age. Studies on ethnic differences of sleep disorders in different regions of Russia were not found in the available literature.

Thus, the aim of our study was to evaluate the main indicators of sleep patterns taking into account gender, age and ethnicity in adolescents 12-18 years old in three large cities of Central Siberia: Krasnoyarsk (predominantly Caucasians), Abakan (predominantly Khakas) and Kyzyl (predominantly Tuvinians).

Materials and Methods: The study is a cross-sectional (one-stage) observational case-control study of a school sample in three large cities of Siberia. It was approved by the ethical committee of FGBU FIC KSC SB RAS "Research Institute of MPS" of Krasnoyarsk. In advance, parents were asked to fill in informed consents for the examination of children, on the basis of which 5332 adolescents aged 11-18 years were examined: in Krasnoyarsk - 3797, in Abakan - 1339 and in Kyzyl - 200, of which 4499 were Caucasians, 376 were Khakassians and 173 were Tuvinians. The sex and age characteristics of the groups are presented in Table 1.

To assess sleep parameters, adolescents were asked to answer questions characterizing their sleep patterns over the past month, excluding weekends: What time did you usually go to bed? How long (minutes) did it usually take you to fall asleep? At what time did you usually wake up?

Statistical processing of the results was carried out in a computer program - STATISTICA-10. All quantitative data are given in the form of medians with 25-75 centile interval Me (25%-75%), and qualitative features are given in the form of percentages with indication in brackets of the ratio of the absolute number of children with this feature to the total number of children in the study group % (abs/total). The Mann-Whitney test was used to compare quantitative traits, and Pearson's chi-square was used to compare qualitative traits.

Results: The analysis of the main indicators of sleep in adolescents according to the city of residence, sex and age is presented in Table 2.

The data obtained indicate pronounced differences between boys and girls in all the studied sleep parameters: girls are characterized by a later bedtime, longer time spent on falling asleep, with an earlier rise, which leads to a total reduction in the duration of sleep, compared to boys. The greatest gender differences in sleep characteristics were observed in Krasnoyarsk, to a lesser extent in Abakan, and none at all in Kyzyl.

Reliable differences were also observed when comparing different age groups. Younger schoolchildren (11-14 years old) went to bed earlier and got up later, and their sleep duration was longer. Only in Kyzyl, there were no reliable differences in bedtime between age groups. The time taken to fall asleep did not differ between age groups.

Significant differences were found among adolescents in the main parameters of sleep depending on the city of residence. Later bedtime was noted in Krasnoyarsk. Abakan and Kyzyl did not differ in this indicator. The time taken to fall asleep was also the longest in Krasnoyarsk, followed by Abakan, and Kyzyl in third place. The earliest time to wake up was in Abakan, while in Krasnoyarsk and Kyzyl they got up at the same time. As a result, the total duration of sleep in Krasnoyarsk and Abakan practically did not differ, while in Kyzyl it was significantly longer.

When comparing the sleep patterns of boys in different cities, the following was noted. Their sleep duration did not differ reliably. They went to bed reliably earlier in Abakan, and in Krasnoyarsk and Kyzyl they went to bed at the same time. It took significantly more time to fall asleep in Krasnoyarsk. We woke up reliably earlier in Abakan.

When comparing the sleep patterns of girls in different cities, there were also differences. The longest sleep duration was observed in Kyzyl, followed by Abakan, and the least sleep was observed in Krasnoyarsk. Krasnoyarsk was the city where the girls went to bed the latest. The longest time to fall asleep was noted there, followed by Abakan and then Kyzyl. The earliest rise time was in Abakan, and Krasnoyarsk and Kyzyl did not differ by this indicator.

When comparing the age group of 11-14 years old in different cities, the following points were highlighted. The total duration of their sleep did not differ significantly. This group went to bed the earliest in Abakan, then in Kyzyl and the latest in Krasnoyarsk. It took the longest time to fall asleep in Krasnoyarsk, somewhat less time in Abakan, and the fastest to fall asleep in Kyzyl. Abakan was the first to wake up, while in Krasnoyarsk and

Table 1

Descriptive statistics of the main studied groups. % (absolute value)

	Krasnoyarsk	Abakan	Kyzyl	Всего	p
	1	2	3		
Total sample. n	**3793**	**1339**	**200**	**5332**	
Boys	46.8 (1774)	47.3 (633)	41 (82)	46.7 (2489)	p1-2=0.753 p1-3=0.109 p2-3=0.096
Girls	53.2 (2019)	52.7 (706)	59 (118)	53.3 (2843)	
11-14 years	52.9 (2006)	39.1 (524)	56.5 (113)	49.6 (2643)	**p1-2<0.001** p1-3=0.320 **p2-3<0.001**
15-18 years	47.1 (1787)	60.9 (815)	43.5 (87)	50.4 (2689)	
Boys. n	**1774**	**633**	**82**	**2489**	
11-14 years	52.5 (932)	36.5 (231)	57.3 (47)	48.6 (1210)	**p1-2<0.001** p1-3=0.395 **p2-3<0.001**
15-18 years	47.5 (842)	63.5 (402)	42.7 (35)	51.4 (1279)	
Girls. n	**2019**	**706**	**118**	**2843**	
11-14 years	53.2 (1074)	41.5 (293)	55.9 (66)	50.4 (1433)	**p1-2<0.001** p1-3=0.568 **p2-3=0.004**
15-18 years	46.8 (945)	58.5 (413)	44.1 (52)	49.6 (1410)	
Children 11-14 years. n	**2006**	**524**	**113**	**2643**	
Boys	46.5 (932)	44.1 (231)	41.6 (47)	45.8 (1210)	p1-2=0.326 p1-3=0.309 p2-3=0.627
Girls	53.5 (1074)	55.9 (293)	58.4 (66)	54.2 (1433)	
Children 15-18 years. n	**1787**	**815**	**87**	**2689**	
Boys	47.1 (842)	49.3 (402)	40.2 (35)	47.6 (1279)	p1-2=0.297 p1-3=0.208 p2-3=0.106
Girls	52.9 (945)	50.7 (413)	59.8 (52)	52.4 (1410)	

Table 2

Characteristics of the main sleep indicators depending on city of residence, sex and age, Me (25%-75%)

Groups	Number	Bedtime	Time to fall asleep	Rising time	Sleep duration in min	Sleep duration in hours
Krasnoyarsk						
total	3797	23.2 (22.5-24)	15 (10-21.5)	7 (6.7-8)	465 (405-530)	7.8 (6.8-8.8)
Boys	1776	23 (22.5-24)	10 (10-20)	7 (6.8-7.8)	473 (420-533)	7.9 (7-8.9)
Girls	2021	23.5 (22.7-24)	15 (10-25)	7 (6.5-7.7)	455 (390-520)	7.6 (6.5-8.7)
p		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
11-14 years	2025	23 (22.5-24)	15 (10-25)	7.3 (6.8-8.8)	500 (443-560)	8.3 (7.4-9.3)
15-18 years	1795	23.5 (23-24)	12 (10-20)	7 (6.5-7.2)	435 (380-475)	7.3 (6.3-7.9)
p		**<0.001**	0.130	**<0.001**	**<0.001**	**<0.001**
Abakan						
total	1339	23 (22.3-23.8)	10 (7-20)	6.9 (6.5-7.3)	470 (420-519)	7.8 (7-8.7)
Boys	633	23 (22.2-24)	10 (5-15)	7 (6.7-7.3)	475 (430-530)	7.9 (7.2-8.8)
Girls	706	23 (22.5-23.8)	10 (8-20)	6.7 (6.5-7.1)	462 (415-508)	7.7 (6.9-8.5)
p		0.608	**<0.001**	**<0.001**	**<0.001**	**<0.001**
11-14 years	524	23 (22-23.5)	10 (7-20)	7 (6.7-8)	500 (450-555)	8.3 (7.5-9.3)
15-18 years	815	23 (22.5-24)	10 (7-20)	6.8 (6.5-7)	455 (407-491)	7.6 (6.8-8.2)
p		**<0.001**	0.122	**<0.001**	**<0.001**	**<0.001**
Kyzyl						
total	200	23 (22.5-23.7)	10 (5-15)	7 (6.5-8)	482.5 (440-532)	8 (7.3-8.9)
Boys	82	23 (22.5-24)	10 (5-15)	7 (6.5-8)	485 (440-530)	8.1 (7.3-8.8)
Girls	118	23 (22.5-23.5)	10 (7-15)	7 (6.5-8.1)	480 (432.5-533.5)	8 (7.2-8.9)
p		0.606	0.124	0.987	0.993	0.993
11-14 years	113	23 (22.5-23.8)	10 (5-15)	7.5 (7-8.8)	515 (470-545)	8.6 (7.8-9.1)
15-18 years	87	23 (22.5-23.5)	10 (7-15)	6.8 (6.5-7.2)	455 (415-504)	7.6 (6.9-8.4)
p		0.809	0.756	**<0.001**	**<0.001**	**<0.001**
Comparison of overall samples		**p1-2<0.001** **p1-3=0.012** p2-3=0.186	**p1-2<0.001** **p1-3<0.001** **p2-3=0.022**	**p1-2<0.001** p1-3=0.398 **p2-3<0.001**	p1-2=0.180 **p1-3=0.003** **p2-3=0.009**	p1-2=0.180 **p1-3=0.003** **p2-3=0.009**
A comparison of the boys		**p1-2<0.001** p1-3=0.712 p2-3=0.198	**p1-2<0.001** **p1-3<0.001** p2-3=0.235	**p1-2<0.001** p1-3=0.203 p2-3=0.241	p1-2=0.652 p1-3=0.388 p2-3=0.439	p1-2=0.652 p1-3=0.388 p2-3=0.235
Comparison of girls		**p1-2<0.001** **p1-3=0.002** p2-3=0.560	**p1-2<0.001** **p1-3<0.001** **p2-3=0.025**	**p1-2<0.001** p1-3=0.743 **p2-3<0.001**	p1-2=0.099 **p1-3<0.001** **p2-3=0.003**	p1-2=0.099 **p1-3<0.001** **p2-3=0.003**
Comparison of groups of 11-14 year olds		**p1-2<0.001** p1-3=0.568 **p2-3=0.035**	**p1-2<0.001** **p1-3<0.001** p2-3=0.077	**p1-2<0.001** p1-3=0.960 **p2-3=0.003**	p1-2=0.819 p1-3=0.183 p2-3=0.119	p1-2=0.819 p1-3=0.183 p2-3=0.119
Comparison of groups 15-18 years old		**p1-2<0.001** **p1-3=0.001** p2-3=0.844	**p1-2<0.001** **p1-3<0.001** p2-3=0.139	**p1-2<0.001** p1-3=0.123 p2-3=0.533	**p1-2<0.001** **p1-3=0.001** p2-3=0.661	**p1-2<0.001** **p1-3=0.001** p2-3=0.661

Kyzyl there were no significant differences in rising time.

When comparing the age group of 15-18 years old in different cities, reliable differences were also revealed. In Krasnoyarsk, sleep duration was 20 minutes shorter than in Abakan and Kyzyl, where this indicator did not differ. Bedtime was also the latest in Krasnoyarsk, with no differences in Abakan and Kyzyl. Also in Krasnoyarsk it was significantly more time spent on falling asleep. Getting up was the earliest in Abakan, and the latest time to get up was in Krasnoyarsk.

Discussion: The study revealed significant differences in the main sleep patterns between different urban (ethnic) populations, as well as gender and age differences.

The data obtained indicate marked differences between boys and girls in all studied sleep parameters: girls are characterized by a later bedtime, longer time spent falling asleep, and earlier rising, which leads to an overall shorter sleep duration compared to boys. This is most likely due to their greater impressionability, emotionality and tendency to experience events more deeply, which requires more time to calm down and fall asleep. Perhaps, girls are more responsible (anxious) and spend more time on preparing lessons. Also, this may be the reason for earlier rising to have more time to get ready for school, to tidy up and not to be late for lessons.

The greatest gender differences in sleep characteristics were observed in Krasnoyarsk, to a lesser extent in Abakan and completely absent in Kyzyl. That is, there is a dependence on the degree of urbanization and material status, availability of various entertainment and additional clubs, as well as, probably, on the level of education of parents, way of life and traditions that influence approaches to upbringing and the degree of obedience of adolescents.

Similar results were obtained by Korean researchers who also studied adolescents 12-18 years old: girls went to bed at 24 (±1.2) hours and boys at 23.8 (±1.1) hours, girls woke up at 6.8 (±0.6) hours and boys at 6.9 (±0.6) hours, total sleep duration in girls was 6.7 (±1.4) hours and in boys 7.1 (±9.8) hours, p=0.001 [13]. Also in a study by Organek K.D.M. et al. boys reported more sleep than girls [7]. In Japan, also during isolation for coronavirus infection, later bedtime was reported in girls [25]. However, other researchers obtained the opposite result, in which later bedtime was reported in men and boys, although girls got up earlier, as we did [1].

Also, researchers from Polar, a company that produces a program for recording various sleep parameters, report later bedtime and shorter sleep duration in men. According to their sleep monitoring data, women slept 22 minutes longer than men in 28 countries [4]. Evidence is also provided that gender differences change with age. For example, in a large-scale Brazilian study including 65,837 adolescents 12-17 years of age, the average sleep duration up to age 14 years was longer in boys than in girls, and vice versa from age 15 years. However, there are studies that found no differences at all in sleep duration between boys and girls. For example, in the Republic of Karelia in a sample of 539 people aged 10 to 18 years, no significant sex differences were found, although the results of the Pittsburgh Sleep Quality Inventory (PSQI) survey showed that girls had a higher total score, indicating worse sleep quality than boys [3].

When comparing different age groups in our study, there were also significant differences: younger schoolchildren (11-14 years old) went to bed earlier and got up later, and thus their sleep duration was longer.

The same results were obtained by many researchers. In the Republic of Karelia in the interval from 10 to 18 years of age, the difference in sleep duration time amounted to 3 hours 24 min [3]. Brazilian researchers compared the age groups of children at 12 and 17 years old, the difference in sleep duration in them amounted to about 1 hour [14]. This decrease in sleep duration in adolescence can be explained by puberty factors, in which there is a slowdown in melatonin secretion, especially in the late stages, which leads to a delay in the sleep phase, later bedtime and awakening [12]. Also increased work activity and academic workload among older adolescents, increased availability of gadgets contribute to this situation. In a recent systematic review, digital media use has been shown to be associated with shorter sleep duration and poorer sleep quality [16]. This was confirmed in our previous study: adolescents with ID had late bedtime, late awakening, shorter nighttime sleep duration, longer falling asleep and frequent night awakenings, and greater daytime sleepiness [2].

In addition, we found significant differences among adolescents in the main parameters of sleep depending on the city of residence. Sleep duration and all its regime moments suffered the most in Krasnoyarsk (especially in girls, as more susceptible to emotional problems), which is probably associated with greater opportunities and greater accessibility of various entertainment organizations, sports sections and institutions of additional education, leading to greater workload of children. The influence of national traditions in terms of child rearing and accepted norms of behavior, in particular the degree of parental authority and control over adolescents, is also possible.

Differences in sleep duration and other sleep parameters in different nationalities have also been reported in studies by many authors. For example, according to anonymous sleep monitoring in 28 countries conducted by Polar (the manufacturer of the Polar Sleep Plus program for detailed sleep analysis), it was found that the longest sleep duration is in Estonia: 7 hours 36 minutes, and the shortest - in Japan: 6 hours 33 minutes. The earliest time to go to bed is 23:09 in Australia and 22:45 in South Africa. The latter are the earliest to rise in the morning - at 6:06. Lateest to bed in Hong Kong - 00:52 and Spain 00:45. [4]. Also in the U.S., a number of studies have been conducted to investigate racial-ethnic differences in sleep characteristics between children of national minorities (Hispanics, Asians, and African Americans) and representatives of the white race [21]. At the same time, almost all authors registered a decrease in sleep duration in these groups of children by an average of half an hour or more compared to white children [6, 7, 22]. At the same time, the decrease in sleep time was mainly due to a later bedtime [6]. The authors suggest that this is due to racial-ethnic discrimination of children, which makes them susceptible to the influence of stress [15], as well as to the influence of cultural, national characteristics and social status, including long distances to school, which requires earlier rising and, consequently, reduced sleep [21].

In addition, it should be noted that in all the cities of Siberia studied by us, in most cases the established physiological norms of sleep for adolescents are not observed. The median bedtime is 23 hours, while the desirable norm is up to 22 hours, and the sleep duration time is also insufficient. In all cities, this indicator does not meet the age-specific norms recommended by the National Sleep Foundation (9-11 hours before 14 years of age and 8-10 hours after 14 years of age) [19]. Even in Kyzyl, where the highest value of this indicator is observed, children do not get almost half an hour of sleep. Moreover, this situation is observed not only in Russia, but also around the world. For example, Norwegian schoolchildren aged 16-17 years sleep on average 7 hours and 36 minutes

during school days [23]. Sleep duration of less than 8 hours was also observed among adolescents in Poland, Latvia, Estonia, and Greece [23]. In Japan, among schoolchildren aged 12-17 years, 28.7% of boys and 32.6% of girls had less than 6 hours of sleep per night [9]. Although in some European countries and in the USA, high school students sleep at least 8 hours [23]. According to other data, one third of high school students in the USA also sleep less than 8 hours [22].

The decrease in sleep duration in our study was mainly due to late bedtime. Many authors have identified late bedtime as a factor predisposing to the development of cardiovascular pathology, depression, cognitive impairment and increased body mass index [13, 26]. The use of smartphones before bedtime is considered to be one of the causative factors, which due to exposure to short-wave (blue) light reduces melatonin production by 14-15% and thus delays the onset of sleep [17].

Conclusion:

Thus, considering the results obtained, the following conclusions can be drawn:

1. Differences between the studied cities of Siberia in the frequency of occurrence of sleep disorders in adolescents have been established: in Krasnoyarsk (Caucasians) there was a later bedtime, more time was required to fall asleep, and, accordingly, a shorter duration of sleep was registered, compared to Abakan (Khakassians) and Kyzyl (Tuvinians).

2. Gender and age differences in sleep patterns were revealed: girls, compared to boys, and the older age group (15-18 years old), compared to the younger (11-14 years old), had significantly more pronounced violations of all sleep parameters in all cities studied, except Kyzyl: they went to bed later, fell asleep longer, got up earlier, had a shorter sleep duration.

3. In all Siberian cities under study, adolescents have late bedtime (at 23 hours and later) and reduced sleep duration below the established age norms (less than 9 hours in the group of 11-14 year olds, and less than 8 hours in the group of 15-18 year olds), which corresponds to the situation in other regions of Russia and abroad.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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ANALYSIS OF ILE105VAL POLYMORPHISM ASSOCIATIONS OF *GSTP1* GENE WITH IMMUNE REACTIVITY MARKERS, OXIDANT STATUS AND REGULATION OF APOPTOSIS IN THE CHILDREN'S POPULATION OF THE KRASNOYARSK REGION IN THE CONDITIONS OF BIOEXPOSURE OF ALUMINIUM

An important task in the context of environmental pollution and the accumulation of heavy metals, including aluminum, is the development of sensitive diagnostic tests, including the search of genetic markers of susceptibility, which make it possible to identify high-risk groups and justify preventive measures to reduce health damage. **The aim of the study** was to assess the role of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in the processes of cell death regulation in the child population under conditions of bioexposure to aluminum. **Materials and methods.** Preschool children (average age 5.34±0.10 years) were examined, 37 children permanently residing in the zone of influence of emissions from a non-ferrous metallurgy enterprise formed the observation group, and 27 children from the conditionally clean territory were included in the comparison group. Aluminum in urine was analyzed by mass spectrometry with inductively coupled plasma. Apoptosis indicators were studied by flow cytofluorometry. SNP genotyping was performed by real-time PCR. **Results.** The level of aluminum contamination in the urine of children in the observation group exceeded similar indicators in the comparison group by 1.53 times (p=0.004). A change in the ratio of immune cell populations was observed (a decrease in $CD3^+$- and $CD4^+$-lymphocytes, p=0.000-0.010) against the background of a violation of the overall oxidant-antioxidant balance (p=0.004-0.042). We identified the proapoptotic effects of the glutathione system associated with the increased frequency of *G* allele of the *GSTP1* gene (rs1695), with the balance sheet of regulatory proteins Bcl-2/Bax (decrease by 2.78 times, p<0.001) and an increase in the number of apoptotic Annexinv-$FITC^+7ADD^-$-cells by 2.59 times (p=0.016). Based on the results of the study, a hypothesis on the role of GSTP1 was formulated as an expression product *GSTP1* gene (rs1695), in the regulation of the processes of programmed cell death with an increased level of contamination of biological media with aluminum. **Conclusion.** Thus, the *G* allele (*105Val*) of the phase II detoxification gene of glutathione-S-transferase *GSTP1* can be considered as a marker of sensitivity in the examined group and can form an increased risk of immune disorders (RR=2.03; 95%CI=1.03-3.99), including dysregulation of cell death processes, under conditions of bioexposure to aluminum.

Keywords. Genetic polymorphism; *Ile105Val GSTP1;* apoptosis; oxidative stress; aluminum.

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Introduction. Aluminum is one of the most common non-essential chemical elements, making up more than 8% of the earth's crust, and the intensive development of the aluminum industry, caused by the growing consumption of the metal, leads to an increase in the level of exposure and the likelihood of developing adverse physiological effects, including diseases of the skeletal system, metabolic syndrome, neurodegenerative disorders, oncopathology [2]. The immunotropic effect of the metal is realized through general toxic properties, including prooxidant, proinflammatory, proapoptotic activity in relation to various cell lines and tissues, through the complication of cell signaling pathways, the release of cytokines, DNA damage and epigenetic changes [12].

Under conditions of a high level of accumulation of xenobiotics, the functional state of the enzyme biotransformation systems, which carry out metabolic transformations of toxic compounds, is of great importance [5]. Phase II enzymes of the xenobiotic detoxification system of glutathione-S-transferases (GST) neutralize electrophilic compounds by conjugation with glutathione, participate in the metabolism of endogenous substrates (hormones, lipids, pros-

taglandins), providing cell resistance to free radicals and DNA damage, and also participate in cellular signaling, regulation of the cell cycle [8]. The GSTP1 enzyme (π class) plays an important role in the elimination of airborne toxicants, and its participation in antioxidant protection and the relationship of individual polymorphic variants of the *GSTP1* gene are actively studied with a predisposition to various pathological conditions, including cardiovascular, atopic, lymphoproliferative diseases [1].

The aim of the study was to assess the role of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in the processes of cell death regulation in the pediatric population under conditions of bioexposure to aluminum.

Materials and methods. The study was conducted with the participation of preschool children (mean age 5.34±0.10 years). A total of 64 children were examined, Russians (56% boys and 44% girls), of which 37 children formed the observation group, permanently residing in the zone of influence of emissions of the non-ferrous metallurgy enterprise (Krasnoyarsk city), and 27 children were included in the comparison group from a conditionally clean territory (Divnogorsk city, Krasnoyarsk region). The formed groups were comparable in age and gender characteristics, ethnicity (p>0.05). All legal representatives of the examined children signed voluntary informed consent to participate in the study.

The content of aluminum in urine was studied by mass spectrometry with inductively coupled plasma on an Agilent 7500cx mass spectrometer (Agilent Technologies Inc., USA). Lipid hydroperoxides were studied by enzyme immunoassay using commercial test systems (Elabscience, China). Antioxidant activity of plasma was determined colorimetrically on a 5400-PE Ekros spectrophotometer (Russia). Apoptosis indices (regulatory proteins Bcl-2 and Bax, p53), lymphocyte fractions by membrane CD markers were studied by immunofluorescence using labeled monoclonal antibodies on a FACSCalibur flow cytofluorometer (Becton Dickinson, USA). Lymphocyte apoptosis was detected by binding to Annexin V-FITC and the vital dye 7-AAD (7-amino-actinomycin D) with determination of the stage of early apoptosis (AnnexinV-FITC$^+$7AAD$^-$-cells) and late apoptosis or necrosis (AnnexinV-FITC$^+$7AAD$^+$-cells) using commercial kits (Becton Dickinson, USA). The testing of the polymorphic marker *Ile105Val GSTP1* (rs1695) was performed using the SNP-screen kits (Synthol, Russia) by PCR with real-time

Table 1

Markers of immune reactivity and oxidative status in examined children with contamination of biological media with aluminum and in the comparison group

Parameter	Observation group (n=37) Me[IQR]	Comparison group (n=27) Me[IQR]	p
Aluminum [urine], mg/dm^3	0.0069[0.0054]*	0.0045[0.0036]	**0.004**
Leukocytes, 10^9/dm^3	5.5[1.9]	6.2[1.1]	**0.045**
CD3+-lymphocytes, %	67[5]	75[7]	**<0.001**
CD4+-lymphocytes, %	37[11]	41[9]	**0.010**
Plasma antioxidant activity, %	31.77[6.34]	37.39[9.55]	**0.004**
Lipid hydroperoxides, μmol/dm^3	227.5[90.2]	198.8[68.7]	**0.042**

Note: p – level of significance of intergroup differences according to the Mann-Whitney criterion. *-reference level of aluminum content in urine <0.006 mg/dm^3.

Table 2

Genetic analysis of the Ile105Val polymorphism of the *GSTP1* gene (rs1695) in examined children with contamination of biological media with aluminum and in the comparison group

Genotype, allele	Observation group (n=37), %	Comparison group (n=27), %	OR (95%CI)
AA	43.2	70.4	0.32 (0.11-0.92)
AG	45.9	25.9	2.43 (0.83-7.13)
GG	10.8	3.7	3.15 (0.33-29.93)
AA+AG	89.2	96.3	0.32 (0.03-3.01)
AG+GG	56.8	29.6	**3.12 (1.09-8.92)***
A	66.2	83.3	0.39 (0.17-0.93)
G	33.8	16.7	**2.55 (1.08-6.04)****
	RR(95%CI)=2.03(1.03-3.99)		
p^{HWE}	0.83	1.00	

Note: OR – odds ratio; RR – relative risk; CI – confidence interval; HWE – Hardy-Weinberg equilibrium. *χ^2=4,64; p=0,031, **χ^2=4,69; p=0,030.

Table 3

Features of apoptosis regulation markers in the examined children of observation group associated with the Ile105Val genotypes of the *GSTP1* gene

Parameter	*AA* (n=16) Me[IQR]	*AG+GG* (n=21) Me[IQR]	p
AnnexinV-FITC + 7AAD–-cells, %	0.64[1.07]	1.66[10.76]	**0.016**
AnnexinV-FITC+7AAD+-cells, %	2.14[3.51]	8.85[23.62]	**0.017**
Bcl-2, %	9.17[4.22]	4.0[5.7]	**0.047**
Bax, %	5.54[5.63]	10.43[9.96]	**0.036**
Bcl-2/Bax	1.50[0.69]	0.54[0.26]	**<0.001**
p53, %	9.63[6.46]	13.3[9.4]	0.478

Note: p – level of significance of intergroup differences according to the Mann-Whitney criterion.

detection on a CFX96 thermal cycler (Bio-Rad, USA).

The results of the study were processed in the Statistica 10.0 software product (Statsoft, USA). The frequencies of alleles and genotypes were calculated in the Gen-Expert online calculator. The results of the study are presented as a median and interquartile range (Me[IQR]) or frequency (%). Comparisons were made using the Mann-Whitney U-test and the chi-square test (χ^2), the odds ratio (OR) and the relative risk (RR) were calculated with the definition of the boundaries of the 95% confidence interval (95%CI). The construction of the "exposure marker – effect marker" models was performed using the method of logistic regression analysis with calculation of the Fisher criterion (F) and the determination coefficient (R^2). Differences were considered significant at $p<0.05$.

Results and discussion. The study revealed shifts in functional indicators in the group of examined children against the background of contamination of biological media with aluminum (Table 1). According to the results of chemical analysis, the level of contamination of biological media in terms of aluminum content in urine was 1.53 times higher in the observation group compared to the comparison group (p=0.004). A violation of the oxidant-antioxidant balance was revealed in children of the observation group with an increase of lipid hydroperoxide content by 14% and a decrease in the total antioxidant activity of plasma by 1.2 times according to the values in the comparison group (p=0.004-0.042). The change in the ratio of immunocompetent cell populations in the observation group was associated with a general decrease in the number of leukocytes and a decrease in the subpopulations of $CD3^+$- and $CD4^+$-lymphocytes by 11-13% relative to the comparison group (p=0.000-0.045).

The results of genetic analysis of the *Ile105Val* polymorphism of the *GSTP1* gene (Table 2) showed a lower frequency of occurrence of the homozygous *AA* genotype (by 1.63 times) and higher frequencies of homozygous and heterozygous genotypes for the allele *G* (*105Val*), by 1.92 times in the group of examined children relative to the comparison group (p=0.031). The frequency of the allele *G* exceeded the indicators in the comparison group by 2.02 times (p=0.030). The probability of the risk of negative health consequences in carriers of the *G* allele (rs1695) of *GSTP1* detoxication gene in the observation group increases by 2.03 times (RR=2.03; 95%CI=1.03-3.99).

Analysis of the distribution of apoptosis markers depending on the carriage of polymorphic variants *Ile105Val* of the *GSTP1* gene (Table 3) revealed excess levels of apoptosis in the observation group in carriers of homozygous and heterozygous genotypes for the *G* allele, relative to those with the *AA* genotype, on average by 2.59 times for the AnnexinV-$FITC^+7AAD^-$-cells indicator and by 4.14 times for the AnnexinV-$FITC^+7AAD^+$-cells indicator (p=0.016-0.017). Dysregulation of cell death processes was observed with a 2.78-fold decrease in the overall ratio of Bcl-2/Bax regulatory proteins (p<0.001), associated with carriage of the *G* allele of the *Ile105Val GSTP1* polymorphism.

Mathematical modeling showed the probability of changes in cellular homeostasis markers depending on an increase in the level of contamination of biomedia with aluminum (Table 4). Models of "exposure marker - effect marker" dependencies revealed a reliable relationship between elevation in the concentration of aluminum in the urine and a decrease in the lymphocyte fraction and total antioxidant activity of plasma (R^2=0.474-0.568; p=0.012-0.027). The probability of an increase in apoptotic AnnexinV-$FITC^+7AAD^-$-cells enhances with the level of bioexposure to aluminum (R^2=0.949; p<0.001).

Aluminum is a widespread metal with high reactivity towards cells and tissues of living organisms. Al^{3+} ions are able to influence the activity of key metabolic pathways, compete with Mg^{2+} for phosphate sites in critical biological enzymes such as ATPase, interfere with the functioning of second messenger systems; stimulate the production of reactive oxygen species (ROS), which disrupt mitochondrial metabolism, damaging the mitochondrial membrane and activating apoptosis processes, while the prooxidant effects of aluminum are associated with changes in the expression of regulatory proteins Bcl-2/Bax, a significant increase in the reactivity of Bax, caspase-3 and c-Jun N-terminal kinase (JNK), which through the regulation of transcription factors (c-Jun and ATF2, p53) affects changes in the cell cycle, repair of DNA damage and/or programmed cell death [7, 9]. Aluminum has also been shown to induce down-regulation of the Nrf2/Keap1 signaling pathway, which likely mediates the inhibitory effect of the metal on the antioxidant system and promotes ROS accumulation [6].

Glutathione-S-transferases catalyze and promote excretion of many xenobiotics, as heavy metals, including aluminum, via conjugation with glutathione. Several studies have found a significant decrease in glutathione-S-transferase activity and glutathione levels after aluminum exposure, and higher urinary aluminum concentrations were associated with lower enzyme activity [4], while differential susceptibility to heavy metals was associated with glutathione-S-transferase gene polymorphisms, enzymatic activity deficiencies, and decreased detoxification in the context of oxidative stress [11].

The *Ile105Val* polymorphism (rs1695) of the *GSTP1* gene, located on chromosome 11q13, is a missense mutation and is localized near the active center of the enzyme. The substitution of adenine (A) for guanine (G) at position 313 of exon 5 determines the exchange of the amino acid isoleucine (Ile) for valine (Val) at codon 105 and leads to a modification of the catalytic properties [14]. It is believed that the 105Val variant has low thermal sta-

Table 4

Parameters of the "exposure marker – effect marker" models in the examined children of the observation group

Exposure marker	Effect marker	Direction of change of the indicator	b_0	b_1	F	R^2	p
Aluminum [urine]	Lymphocytes	Decrease	-4.92	574.57	7.24	0.474	**0.027**
	Plasma antioxidant activity	Decrease	5.67	-804.54	10.56	0.568	**0.012**
	AnnexinV-FITC+ 7AAD–-cells	Increase	2.50	-630.84	109.41	0.949	**<0.001**

Note: b0, b1 – parameters of the mathematical model; F – Fisher criterion; R2 – determination coefficient; p – level of statistical significance of the model.

bility and reduced functional activity due to steric changes in the substrate-binding site, which can lead to a decrease in the ability to detoxify and an increase in the accumulation of toxic substances [3].

The important role of glutathione-S-transferases in the regulation of signaling pathways responsible for the stress response, cell proliferation and apoptosis is determined through interaction with stress-associated MAP kinases, when GSTP1 acts as a chaperone, forming complexes with JNK, and negatively regulates signaling that induces apoptosis (c-Jun and AP1). The *G* allele variant (*105Val*) of the *GSTP1* gene can increase JNK activity and disrupt the protective function of cells. In addition, GSTP1 modulates NF-κB-mediated regulation of transcription of target genes that mitigate the effects of oxidative stress through IκBa, when an increase in ROS promotes the dissociation of GSTP1 and the activation of signaling pathways that ensure cell survival, increased antioxidant activity and ROS elimination, which can ultimately reduce ROS-induced JNK-mediated signaling [10, 13].

Based on the results of the study, we formulate a hypothesis about the role of GSTP1, as a product of the expression of the *GSTP1* gene (rs1695), in the regulation of cell death processes at an increased level of contamination of biological media with aluminum, taking into account the features of its metabolism, the effect of the enzyme on the oxidant-antioxidant status and the regulation of intracellular signaling pathways. Further study of this issue is necessary due to the small sample size of the examined population, possible age and ethnic characteristics, intergenic interactions and epigenetic modifications affecting various aspects of the cellular homeostasis regulatory system.

Conclusion. Thus, the conducted study allowed us to establish the risk of developing apoptosis dysregulation under conditions of aluminum bioexposure and its association with the *G* allele (*105Val*) of the *GSTP1* gene (RR=2.03; 95%CI=1.03-3.99), the carriage of which can be considered as a specific indicator that allows us to differentiate high-risk groups for the purposes of optimizing treatment and preventive measures for the development of immunoregulatory disorders in children under conditions of excessive aluminum bioexposure.

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SEROLOGICAL AND MOLECULAR DIAGNOSTICS OF COMBINED INFECTION "BRUCELLOSIS + TOXOPLASMOSIS" AMONG THE POPULATION OF AZERBAIJAN

This article presents the results of a study on the diagnosis of the combined infection "brucellosis + toxoplasmosis" among the population of Azerbaijan. The aim of this study was to investigate the frequency and characteristics of detection of dual infection "brucellosis + toxoplasmosis" among samples received by the Special Dangerous İnfections Control Center. The results of the conducted study may have great scientific and practical significance both for fundamental science and for clinical practice. The analysis of the results of studies of the Special Dangerous İnfections Control Center's laboratory of blood samples received in 2019-2021 from 3208 patients with suspected brucellosis who sought medical treatment in the country was carried out. Serological and molecular testing was carried out by generally accepted methods in accordance with the rules in BSL2.

Keywords: *Brucella, Toxoplasma gondii*, antibodies, combined infection, laboratory diagnostics, seroprevalence

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Introduction. Brucellosis and toxoplasmosis, which have serious health consequences, are considered neglected zoonotic diseases with a worldwide distribution, which are endemic in Azerbaijan [7, 8]. It is known that both brucellosis and toxoplasmosis have common nonspecific clinical symptoms, such as fever, weakness, muscle pain, and others, which significantly complicates the differentiation of diseases only on the basis of clinical data. Moreover, in both infections, diagnosis presents some difficulties due to the imperceptible course of the disease, similarity of clinical manifestations, late appeal of the population to medical institutions.

In Azerbaijan, brucellosis is recognized as a particularly dangerous disease, which requires emergency notification within 24 hours to the relevant medical structures and the electronic monitoring system for infectious diseases [8]. Every year, about 20% of all initially notified suspected cases of brucellosis remain unconfirmed based on the results of laboratory testing. Parallel testing for other infections, including toxoplasmosis, is not provided for by the rules of laboratory diagnostics adopted in the country. Toxoplasmosis infection in the country, as well as in many other countries, is often detected in connection with problems in pregnant women, such as miscarriages, premature births, etc. [3, 9, 13].

Given the similar risk factors for human infection, such infections can be detected both on their own and in combination with others. Combined infection with these infections can enhance pathogenesis and cause a more severe course of the disease. [1, 10]. Dual infection in the form of toxoplasmosis + brucellosis is rarely registered among people around the world, however, this should not reduce interest in the study in connection with the search for effective ways to differentiate one infection from another, as well as to exclude the loss of cases and their adequate treatment [2, 5]. In Azerbaijan, possible co-infection with brucellosis and toxoplasmosis among humans has been identified for the first time. Considering the above, the study of laboratory diagnosis of co-infection "brucellosis + toxoplasmosis" is important for both fundamental science and clinical practice, and can help improve the diagnosis, therapy and prevention of infectious diseases.

The purpose of this study was to study the frequency and characteristics of detection of the dual infection "brucellosis + toxoplasmosis" among samples received by the Center for Control of Particularly Dangerous Infections (CCPDI).

Material and methods. The study included the results of laboratory tests of blood samples performed at the Center for the Control of Particularly Dangerous Infections (CDOCI), where medical institutions of the republic send material from patients with suspected brucellosis. The material from patients with suspected brucellosis was collected upon patient's application before the start of antibiotic therapy. A total of 3208 blood samples were examined. All tests were carried out in a laboratory of the second level of biological safety (BSL-2) in accordance with the order of the Ministry of Health No. 64 "Rules for Control and Supervision of Particularly Dangerous Infections". Accounting, storage, transfer, transportation of biological material suspected of having the causative agent of brucellosis, and waste disposal were carried out in accordance with the biosafety rules implemented in the CCPDI.

The descriptive characteristics of patients with suspected brucellosis are presented in Table 1.

Blood serum was tested for the presence of antibodies to the causative agent of brucellosis using the following tests: plate agglutination reaction (Heddleson reaction) and test tube agglutination reaction (Wright reaction) using the test system "Brucella-reagent" manufactured by ZAO "ECOlab" (RF); and Roze Bengal - with the ADR® Roze Bengal test manufactured by "Mediko Kimya Ltd." (Turkey). Antibodies to the causative agent of brucellosis in blood serum were also determined by the ELISA method using the NovaLisa TM Brucella IgM - ELISA test systems manufactured by "RayBiotech" (USA). The ELISA results were recorded on an automatic ELISA reader Thermo Scientific Multiscan FC (SN 357-904086).

To detect antibodies to toxoplasma, ELISA test systems from Novatec Im-

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mundiagnostica GMBH (Almaniya) were used. ELISA results were recorded using an automatic ELISA reader Thermo Scientific Multiscan FC (SN 357-904086).

Molecular detection of *Toxoplasma gondii* was performed using the AmpliSens® Toxoplasma gondii – FRT PCR Kit in real time on the Real Time Biorad CFX 96 apparatus.

Testing of samples and interpretation of results were carried out in accordance with the kit manufacturer's instructions.

Statistical significance was calculated using the χ2 method or Pearson's exact test for comparing differences in variables [6]. A significance level of $p<0.05$ was taken as statistically significant changes.

Results and discussion. 3208 blood serum samples were studied, of which 2810 (87.6%) belonged to patients with chronic brucellosis, 398 (12.4%) - to newly registered cases of brucellosis. Of these, 294 (72.4% of all newly registered samples) were positive for brucellosis infection, and 448 (13.0% of all chronically infected samples) were samples taken from repeat patients.

The results of the study of IgG and IgM seroprevalence among the studied blood samples to *Brucella* and *Toxoplasma gondii* for the study period are presented in Table 2.

As can be seen from Table 2, antibodies to *Brucella* and *Toxoplasma gondii* were detected in a very small number of samples. However, the obtained results allowed us to discover some patterns. For example, the seropositivity of men with IgG to Brucella was higher (63.4% of all positive results). Statistically revealed differences are significant and reliable – $\chi2=6.80$, $p = 0.009$. For IgM, the picture is completely opposite - 64.3% of all positive results occurred in women. However, the results obtained are not statistically significant ($\chi2=0.64$, $p=0.422$). According to the results of the test for seropositivity for antibodies to Toxoplasma gondii, the proportion of women prevailed for both IgG and IgM (75.0% and 57.4%, respectively).

Gender differences in IgM, both statistically insignificant ($\chi2=0.92$, $p=0.339$) and statistically significant in IgG ($\chi2=8.7$, $p=0.004$), can be explained by the characteristics of the immune response, which depend on gender. Women may have a more pronounced humoral response in the early stages of infection (IgM), while men may have a more robust response (IgG). In addition, a high proportion of IgG in men to Brucella may indicate previous or chronic forms of infection, which may be associated with constant exposure to the pathogen in certain professions (farmers, hunters).

By age groups, seropositive samples for IgG to Brucella were distributed almost evenly ($p>0.05$). However, for IgM, the largest proportion of seropositive samples were in the age groups “10-19 years” and “60 years and older” - 28.6% of all positive samples each. The prevalence of the studied indicators in the age group “60 years and older” may indicate long-term exposure to risk factors or a chronic course of infections, since both pathogens, Brucella spp. and Toxoplasma gondii, can remain in the body for a long time. As some authors point out, the key aspect in this case may be occupational risks of infection [1, 6].

As for seropositivity to Toxoplasma gondii, the largest proportion for both IgG and IgM is typical for the age group “20-29 years” (28.0% and 24.1%, respectively). At this age, the immune system may still be active enough to respond in the form of IgG and IgM antibodies, which makes it possible to detect both current and past infection.

Analysis of tested samples at the place of residence of patients showed that for IgG to Brucella, the proportion of seropositives was higher in rural residents (54.5% of all positive, $\chi2 = 0.64$, $p = 0.422$). For IgM, on the contrary – in urban residents (71.4% of all positive, $p<0.05$). However, these differences did not have statistical significance - $\chi2=1.79$, $p=0.181$.

Samples from patients living in dis-

Table 1

Descriptive characteristics of patients who applied to the Central Clinical Particularly Dangerous Infections (CCPDI). with suspected brucellosis

Study years	Total patients	Males (%)	Females (%)	Average age of patients
2019	1689	951 (56.3)	738 (43.7)	32.5±0.6
2020	738	410 (55.5)	328 (44.5)	33.4±0.6
2021	781	416 (53.3)	365 (46.7)	32.1±0.4
Total	3208	1777 (55.4)	1431 (44.6)	32.7±0.4

Table 2

Seroprevalence of IgG and IgM among the studied blood samples to *Brucella* and *Toxoplasma gondii* for 2019-2021

Variables	N=3208	*Brucella* antibody test results, (%)		*Toxoplasma gondii* antibody test results, (%)	
		IgG	IgM	IgG	IgM
		101	14	36	54
by gender	men	64 **(63.4)**	5 (35.7)	9 (25.0)	23 (42.6)
	women	37 (36.6)	9 **(64.3)**	27 **(75.0)**	31 **(57.4)**
by age categories	0-9 years	9 (8.9)	0	1 (2.8)	5 (9.3)
	10-19 years	20 **(19.8)**	4 **(28.6)**	2 (5.6)	6 (11.1)
	20-29 years	15 (14.6)	2 (14.3)	10 (28.0)	13 **(24.1)**
	30-39 years	14 (13.9)	1 (7.7)	5 (13.9)	10 (18.6)
	40-49 years	13 (12.9)	1 (7.7)	2 5.6)	6 (11.1)
	50-59 years	14 (13.9)	2 (14.3)	5 (13.9)	9 (16.7)
	60 years and older	16 (15.8)	4 **(28.6)**	11 **(30.6)**	5 (9.3)
by place of residence	city	46 (45.5)	10 **(71.4)**	13 (36.1)	15 (27.8)
	district	55 **(54.5)**	4 (28.6)	23 **(63.9)**	39 **(62.2)**

Table 3

Frequency of detection of specific antibodies to brucellosis, toxoplasmosis and combined infection "brucellosis + toxoplasmosis" for 2019-2021

Specific antibodies	Absolute number	Percentage of all samples tested
IgG to *Brucella*	101	3.1
IgG to *Toxoplasma gondii*	36	1.1
IgG to *Brucella* +*Toxoplasma gondii*	48	1.5
IgM to *Brucella*	14	0.4
IgM to *Toxoplasma gondii*	54	1.7
IgM to *Brucella* +*Toxoplasma gondii*	2	0.1

tricts and villages were seropositive for both IgG and IgM to Toxoplasma gondii (63.9%; $\chi 2=2.26$, $p=0.133$ and 62.2%; $\chi 2=9.88$, $p=0.002$, respectively). This may be explained by the presence of infected people in an environment where both pathogens (Brucella and Toxoplasma gondii) circulate, which also increases the likelihood of co-infection.

The results of molecular diagnostics for detection of *Toxoplasma gondii*, despite the small proportion of positive results, are of undoubted interest for both epidemiologists and clinicians. Positive PCR results for *Toxoplasma gondii* were found in 89 (2.8% of all tested samples). As some authors point out [3, 6, 9, 13], toxoplasmosis in an organism with good immunoresistance rarely produces typical manifest forms: in 95-99% of cases, this disease is asymptomatic and remains undiagnosed due to the absence of pathognomonic signs. Thus, the obtained data allow us to talk about the advisability of testing for toxoplasmosis if brucellosis is suspected, especially with a negative result. Dolgikh T.I. and other authors indicate that molecular diagnostics allows detection of genetic material of toxoplasma in blood, cerebrospinal fluid and biopsies and has high diagnostic value in acute and congenital toxoplasmosis, as well as in monitoring patients with weakened immunity. The diagnostic value of PCR increases when combined with serological methods. [4, 11, 12]. The frequency of positive tests for the combined infection "brucellosis + toxoplasmosis" among all those tested during the study period is presented in Table 3.

The demographic characteristics of patients in whose samples a combined infection of "brucellosis + toxoplasmosis" was detected were almost identical: by gender, the ratio of men to women with the parallel presence of IgG and IgM antibodies to Brucella + Toxoplasma gondii was 1:1. By age group: the largest proportion of samples with co-infection "brucellosis + toxoplasmosis" was from patients in the age category "20-29 years". The average age of these patients was 33.3±0.4 years. By place of residence - 68.8% are residents of districts and villages, which may be due to the constant exposure of these individuals to these infections during their daily activities on farms or private farms. The presence of IgG antibodies to both pathogens may also indicate past exposure, while detection of IgM (especially in combination with a high IgG titer) may be a marker of an active process.

Seropositivity for IgG to Brucella or Toxoplasma gondii does not necessarily indicate the presence of an active infection. Many authors consider this fact to be a sign of the host's humoral immune response to pathogens. [10, 13] Conversely, the combined infection "brucellosis + toxoplasmosis" can aggravate the course of the disease. For example, toxoplasmosis may modulate the immune response, which may contribute to a more protracted or severe course of brucellosis.

In addition, the presence of antibodies, especially the IgG class, can be associated not only with infection, but also with vaccination (in the case of brucellosis). This requires confirmatory tests (eg PCR or culture) to make an accurate diagnosis. In this study, out of 33 cultures, only 78.8% were Brucella melitensis and only 21.2% were Brucella abortus. This proportion indicates a higher epidemiological significance of Br.melitensis in the country, which may be due to the spread among sheep and goat owners, as well as the lack or insufficient vaccination of animals. In 8 samples, the results were positive for both IgG and IgM to *Brucella*, which may indicate reinfection with brucellosis in these patients at the time of testing.

Thus, given the medical significance of the studied zoonoses and based on the data obtained, it is possible to recommend conducting more extensive studies of the population in order to establish the scale of the problem of combined infection "brucellosis + toxoplasmosis". The results of such studies will help in conducting campaigns to raise awareness and prevention programs for individuals at risk.

Conclusions.

1 Among those who applied to the Center for the Control of Particularly Dangerous Infections, 398 cases for diagnosis of brucellosis (12.4%) were initially notified, and 2810 (87.6%) were chronic. The majority of patients were male (55.4%), and 58.8% of patients lived in the capital or major cities, indicating a significant proportion of the urban population in the overall disease burden. The average age of those who applied was 35.3±1.6 years for initially notified cases and 32.3±1.4 years for chronic cases.

2 Combined seropositivity of IgG antibodies to Brucella and Toxoplasma gondii was detected in 1.5% of all tested samples.

3 Combined seropositivity of IgG antibodies to Brucella and Toxoplasma gondii is more common in rural residents (63.4%) and can complicate the course of the disease. This fact emphasizes the need for further research into risk factors and the introduction of comprehensive diagnostic approaches for the timely detection and treatment of such cases.

Limitations. This study could not consider potential risk factors associated with brucellosis and toxoplasmosis, such as consumption of dairy products, contact with animals, consumption of undercooked meat, exposure in the workplace, source of drinking water, etc. It was also not possible to study the epidemiological history and establish a connection with the clinical manifestations of the described co-infection due to the limited information provided in the standard referral form for laboratory testing.

The authors declare no conflict of interest.

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TOPICAL ISSUE

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ANALYSIS OF MORTALITY AMONG PATIENTS WITH COGNITIVE DISORDERS

The structure of mortality among patients with the established diagnosis of dementia was evaluated and analyzed who seek medical help at the Yakut Republican Neuropsychiatric Dispensary for the period from 2019 to 2024. Totally 213 fatal cases were analyzed in patients with the diagnose F00 - F03. The average age of death in men diagnosed with dementia was 76.08 +8.73 years, and among women this indicator was 80.3+8.77 years. When analyzing the immediate cause of death in patients with dementia, cerebral edema was indicated in the first place (16.43%), other specified forms of pulmonary heart failure were diagnosed in the second place on the death certificate (15.96%), and acute respiratory failure was in the third place (15.49%). Among the initial causes of death, the most common cause of death was coronary heart disease (22.06%), pneumonia of various origins (15.9%) was in second place, and diagnoses that were included in the category of brain damage (encephalopathy) were most often in third place, which amounted to 15.03%. Among the initial causes of death among patients with dementia, it is extremely rare to be diagnosed with dementia (6.07%), which strongly affects mortality statistics.

Keywords: mortality, Alzheimer's disease, dementia, diagnosis

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Introduction: The problem of cognitive disorders and dementias that develop in the elderly and senile age, is currently, the most urgent problem for the entire world community. If we talk about the most common form of dementia in Alzheimer's disease, then its prevalence is extremely high, so five percent of people aged 65 to 74 years, 13.2% of people aged 75 to 84 years and 33.4% of people aged 85 years and older suffer from Alzheimer's disease. Dementia is a multi-factorial syndrome characterized by a significant cognitive decline, which manifests itself in the deterioration of memory, language, and other abilities that prevent independence [10]. В конUltimatelyитоге, dementia is fatal, although many people also die и from other diseases before dementia becomes fatal. Studies show that people aged 65 and older survive an average of four to eight years after being diagnosed with Alzheimer's dementia, but some live up to 20 years. Severe dementia often causes complications such as immobility, difficulty swallowing and malnutrition, which significantly increase the risk of acute conditions that can lead to death. One such condition is pneumonia (a lung infection), which is the most commonly identified direct cause of death in older adults with Alzheimer's disease or other types of dementia.

Compared with people with Alzheimer's disease, a diagnosis of any non-Alzheimer's dementia was associated with a higher risk of all-cause mortality, shorter survival time from diagnosis, and younger age at death, with the highest risk of death in patients with Lewy body dementia [9].

The variability of mortality rates was determined by the number of samples, the conditions of research and the differences in the time frame of the analyzed periods. In the conditions of Russian reality, the methodological equipment of this kind of research suffers for various reasons, primarily due to the lack of reliable mortality rates for Alzheimer's disease and other dementias in the official statistics of causes of death [5, 8]. As shown by domestic researchers in the field of demography, mortality from Alzheimer's disease in the Russian Federation in all age groups is many times lower than in foreign countries [1].

Materials and methods: The cases of fatal outcome in patients who applied to the Republic of Sakha (Yakutia) "Yakut Republican Neuropsychiatric Dispensary", from December 2020 to April 2024 with a diagnosis of dementia (F00 - F03) were analyzed. Death certificates were taken from the RT-MIS medical information system. Statistical processing of the study results was carried out using the Statistica 6.0 program. The analysis used Spearman's rank correlation analysis, the Mann-Whitney and Kolmogorov-Smirnov coefficients, and the Student's t-coefficient. Differences were considered statistically significant at a p value of <0.05.

Results: A total of 213 cases of fatal outcomes we reanalyzed in patients with a diagnosis of F00-F03 who applied for medical care in the Republic of Sakha (Yakutia) "Yakut Republican Neuropsychiatric Dispensary", from 2020 to 2024. (including the month of April). In total, during this period of time, 674 patients with these diagnoses applied to the polyclinic department of the Republic of Sakha (Yakutia) "Yakut Republican Neuropsychiatric Dispensary", hence 31.6%, that is, every third patient had died by the time of the control section. The median age at death was 78, 78.65+8.73 years. There were 112 women (52.6%) and 101 men (47.4%). Death occurred in a medical institution in 122 cases (57.3%), at home in 54 cases (25.3%), the rest of the deaths occurred in social service institutions (boarding houses), mainly commercial, which accounted for 17.3% (37 cases). When analyzing the nosological structure of dementia, vascular dementia was diagnosed most often in deceased patients – 72 people, then F02.8 (other mixed dementias) was diagnosed most often in 67 deaths, senile dementia was diagnosed in third place in frequency, which amounted to 62 cases, and finally diagnoses such as dementia in Alzheimer's disease, frontotemporal dementia and dementia in Parkinson's disease were exhibited in nine, two and one cases, respectively (which accounted for a total of 5.6% of the total number of cases). Residents of Yakutsk predominated among the dead (92%). Of all the deceased patients, only 15 people had previously received inpatient treatment at Republic of Sakha (Yakutia) "Yakut Republican Neuropsychiatric Dispensary", often this was the only hospitalization and in only one clinical case of frontotemporal dementia, the patient was hospitalized more than 3 times in the psychiatric department of the dispensary. I would like to note, that not a single fatal case occurred in a round-the-clock psychiatric hospital, all patients were in somatic departments of various profiles (most of them in the palliative care department). Severe psychotic symptoms were detected only in 28 cases (13.1%), and were expressed in recurrent visual hallucinations, gross behavioral disorders, and pronounced physical and verbal aggression. In most cases, patients and their relatives sought the advice of a psychiatrist to register a disability group and an individual habilitation program (obtaining individual personal hygiene products, absorbent products), as well as to determine the type of social service institution for the patient's permanent stay. Subsequently, an autopsy was performed in 50.7% (108 people) of fatal cases, the rest – 105 patients (49.3%) were not subjected to pathological anatomical examination. Among the patients who died in hospitals in 38 cases (31.4%), that is, in every third case, an autopsy was not performed. To analyze directly the main causes of death in patients with dementia, it is necessary to understand what the immediate cause and the original cause of death are. Thus, the immediate cause of death is a morphological state of organ changes that led to the development of irreversible functional disorders and made it impossible to continue human life as a single living organism, when the initial cause is a disease or injury that caused a chain of events that directly led to death. When analyzing death certificates, the immediate and initial cause of death were used in the study. The immediate causes of death are shown in table 1.

Initial causes of death were grouped by major ICD – 10 diagnoses and presented in table 2.

All patients were divided into 5 age groups by age at the time of death (from 50-59 years; 60-69 years; 70-79 years; 80-89 years; older than 90 years). The minimum age of death for a diagnosis of dementia was 53 years, and the maximum age was 99 years. Thus, the first group consisted of 9 people (4.2%), the second age group – 31 people (14.5%), the third group – 61 patients (28.7%), the fourth – 78 patients (36.6%) and the fifth – 34 people (15.9%) (see Diagram).

Spearman's correlation analysis revealed significantи correlations between gender and age of death ($r=-0.238$ $p<0.05$), as well as between such signs as death in hospital and autopsy ($r=0.507$ $p<0.05$). When comparing the subgroups of traits between men and women, a significant correlationwas found between age and diagnosis in the subgroup of women (Kolmagorov – Smirnov test) $p<0.05$. No more-differences were found between the subgroups of men and women.

Discussion of results: an Analyzing the results obtained, first of all, it is necessary to pay attention to the fact that the average age at the time of death in patients with an established diagnosis of dementia c is 78.65+8.73. The average age of death in men diagnosed with dementia was 76.08 +8.73 years, among women this indicator was 80.3+8.77* years, that is, women diagnosed with dementia died significantly more often at a later age than men. This is due to gender differences in life expectancy in the Russian Federation, which is also reflected in life expectancy in patients with age-associated pathologies.

The nosological structure showed, that vascular dementia is most often diagnosed (33.8%), that is, in every third patient. It should be noted, that almost always the diagnosis of vascular dementia is made in the presence of a history of acute cerebral circulatory disorders, while there are not always clear indications of a vascular catastrophe. The second most frequent diagnosis was organic dementia (31.4%), which was mainly made in the absence of any significant reasons for the development of cognitive decline (for example, cerebral circulation disorders, severe TBI, etc.). In essence, this diagnosis does not reflect to any extent the main nosological affiliation of dementia, but rather is simply a kind of "working" diagnosis, although in fact any other nosological form of dementia may be within the framework of this diagnosis. It can also be mentioned that not all pa-

Table 1

Immediate causes of death in patients with dementia

Direct cause	Number of patients	%
G93. 6 Cerebral edema	35	16.43
I27. 8 Other specified forms of pulmonary heart failure	34	15.96
J96. 0 Acute Respiratory failure	33	15.49
I50. 0 Congestive Heart failure	20	9.38
I50 Left Ventricular failure	10	4.69
R64 Cachexia	9	4.22
I25. 1 atherosclerotic heart disease	7	3.28
I67. 8 Other specified brain vascular lesions	6	2.8
I50. 9 Unspecified heart failure	5	2.34
A41.9 Sepsis unspecified	4	1.87
I24. 8 Other forms of acute coronary heart disease	4	1.87
I42. 9 Cardiomyopathy unspecified	4	1.87
A41. 8 Other specified sepsis	3	1.4
J81 Pulmonary edema	3	1.4
R65.3 the Syndrome of systemic inflammatory non-infectious origin with organic disorders	3	1.4
J18.0 unspecified Bronchopneumonia	3	1.4
F01.8 Other vascular dementia	3	1.4
C80.9 Malignant neoplasm of unspecified	3	1.4
I26.0 Pulmonary embolism with mention of acute pulmonary heart	2	0.93
I25.5 Ischemic cardiomyopathy	2	0.93
F01.2 Subcortical vascular dementia	2	0.93
T71 Asphyxiation	1	0.46
I48.0 Paroxysmal form of atrial fibrillation	1	0.46
T51.1 Toxic effect of methanol	1	0.46
R57.8 Other types of shock	1	0.46
T79.4 Traumatic shock	1	0.46
S06.5 Traumatic subdural hemorrhage	1	0.46
A16.2 TB lung without mention of bacteriological or histological confirmation	1	0.46
J85.1 Abscess of lung with pneumonia	1	0.46
K72.0 Acute and subacute hepatic failure	1	0.46
K72.1 Chronic liver failure	1	0.46
J96.1 Chronic respiratory failure	1	0.46
I69.3 the Consequences of cerebral infarction	1	0.46
G93.5 compression of the brain	1	0.46
I61.8 Other cerebral hemorrhage	1	0.46
I21.4 upper subendocardialnah Acute myocardial infarction	1	0.46
I21.0 Acute transmural infarction of the anterior wall of the myocardium	1	0.46
I46.9 heart failure unspecified	1	0.46
I42.0 Dilated cardiomyopathy	1	0.46

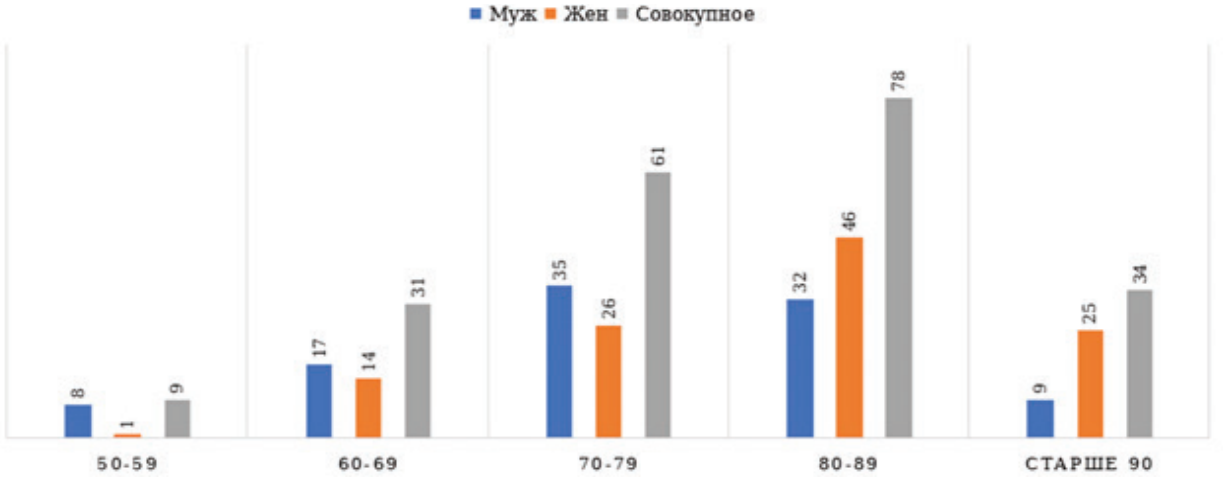
Table 2

Underlying causes of death in patients with dementia

Initial cause of death	Количество больных	%
I 25. Coronary heart disease	47	22.06
J12-18. Pneumonia	34	15.9
G 93. Brain damage	32	15.03
U 07. COVID- 19	19	8.9
I 60-69.Stroke	14	6.57
From 00-97. Neoplasms	9	4.22
F 01. Vascular dementia	9	4.2
I 21. Myocardial infarction	8	3.75
I 11. Hypertension	6	2.8
E 11. Type 2 diabetes mellitus	4	1.87
F 00. Alzheimer	4	1.87
J 44. COPD	4	1.87
A15-19. Tuberculosis	3	1.4
L 89. Pressure sores	2	0.93
R 64. Cachexia	1	0.46
I 82. Thrombosis	1	0.46
T 95. Burn disease	1	0.46
D 69. Thrombocytopenic purpura	1	0.46
M 86. Osteomyelitis	1	0.46
G 00. Meningitis	1	0.46
I 71. Aortic aneurysm	1	0.46
K 40 -46. Hernia	1	0.46
I 35. Aortic stenosis	1	0.46
K 85. Acute pancreatitis	1	0.46
J 09 -18. Influenza	1	0.46
N 30. Cystitis	1	0.46
K 74. Cirrhosis	1	0.46
K 56. Intestinal obstruction	1	0.46
T00-07. Injury	1	0.46
K 65. Peritonitis	1	0.46
F 10. Alcoholism	1	0.46
G 20. ParkaNson's disease	1	0.46

tients undergo MRI diagnostics (according to our data, only8.5% of patients had a mention of passing or passed to a state institution), but perhaps most patients undergo MRI in commercial institutions. The available MRI findings were quite uninformative for differential diagnosis of different types of dementia, and contained only general conclusions about neurodegeneration. In fact, in terms of the frequency of occurrence of various forms of dementia, dementia in Alzheimer's disease should be in the first place, when as in our study, its specific weight was only 4.2% of the total number [2].

When analyzing the immediate cause of death in patients with dementia, brain edema was indicated in the first place (16.43%), the second place in the death certificate indicated the diagnosis of other specified forms of pulmonary heart failure (15.96%), and the third place was acute respiratory failure (15.49%). Among the initial causes of death, the most common cause of death was ischemic heart disease (22.06%), followed by pneumonia of various origins (15.9%), and the third most common diagnosis was made under the heading of brain damage (encephalopathy), which was 15.03%. The results obtained differ from the data of other domestic researchers, which indicate somatic diseases only in half of the cases, and the remaining part falls on the end stage of dementia [5]. In our study withered of initial causes of death, only 13 cases were diagnosed with dementia (4 cases of Alzheimer's disease and 9 cases of vascular dementia), which is actually very small. In fact, the diagnosis of dementia, namely dementia in Alzheimer's disease and mixed forms (vascular dementia + dementia in Alzheimer's disease) should be made much more often at pathoanatomical sections, since only in this case it is possible to conduct a



The distribution of mortality rates across different age groups. (Man – blue, women – orange, general – gray)

histological examination of brain tissues that confirms the diagnosis of Alzheimer's disease. But again, the presence of a pathoanatomical study without taking into account the clinical picture (the presence of a cognitive defect) is not a criterion that determines the main diagnosis. In vivo analysis of brain tissues is not performed in Russia, and the only analysis that verifies the diagnosis of Alzheimer's disease, namely the analysis of spinal fluid for biomarkers of neurodegeneration (beta-amyloid and tau protein), is laborious and practically inaccessible in practical medicine [6, 7, 4]. Most likely, the diagnoses included in the category G93should have been encrypted on the death certificate as end-stage of various forms of dementia. The direct causes of death in the framework of somatic pathology obtained in our study generally do not differ from the main causes of death among the elderly population (cardiovascular pathology is in the first place, and pneumonia is in the second placeи) [3]. Possibly a specific one the role is played by the fact that in the RT –MIS information system, the visit of a psychiatrist to a neuropsychiatric dispensary is hidden from doctors of other specialties, but all updated diagnoses are usually reflected for all medical institutions.

A certain contribution to the causes of death of patients with dementia was made by a new coronavirus infection, so in the immediate causes of death, acute respiratory failure was in third place, and among the immediate causes of death, a new coronavirus infection was indicated in 19 cases (8.9%). Most likely, there were more deaths from больше, потомуNCVI, because the virus is not always tested positive. In such cases, the primary cause of death was unspecified or viral pneumonia.

Analyzing the causes of mortality in patients with dementia, I would also like to say that in fact, the diagnosis of dementia in MS (I) has certain difficulties, firstly in terms of territorial features (a large territory with a low population density), and secondly, insufficient availability of specialized medical care and primary outpatient screening (lack of specialists patients with cognitive disorders), as well as low awareness of the population about cognitive disorders, as well as the possibilities of modern pharmacotherapy. All this ultimately leads to insufficient diagnosis of dementia mainly due to Alzheimer's disease, which should make up the largest share in the nosological structure.

Conclusions:

1. Among the initial causes of death among patients with dementia, it is extremely rare to be diagnosed with dementia (6.07%), which strongly affects mortality statistics, although according to foreign data, Alzheimer's disease is one of the five main causes of death in citizens over 65 years of age [9, 10]. Perhaps, in some cases, the end-stage of dementia is indicated under the ciphers that encode various types of encephalopathies. Among the somatic causes of death in patients with dementia, diseases of the cardiovascular system and various forms of pneumonia are in the first place.

2. Low diagnosis of dementia in Alzheimer'srdisease among cases of severe cognitive decline. In general, the diagnosis of dementia aspa syndical diagnosis in neurology and psychiatry does not cause any difficulties, but differential diagnosis is very difficult and requires a comprehensive approach that takes into account the results of instrumental research methods, primarily magnetic resonance imaging, as well as the features of the neurocognitive profile described by a clinical psychologist.

The need for further research on the course of dementia, including its outcomes in MS (I), as well as the maintenance of registers, is an important goal for obtaining evidence-based statistical indicators. These data should be taken into account when providing various types of medical and social care to dementia patients and their families at all stages of the disease.

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S.S. Sleptsov, S.S. Sleptsova, M.P. Dutkin, L.N. Afanasyeva

IMPROVEMENT OF WORK ON SUICIDE PREVENTION IN THE ARCTIC ZONE OF YAKUTIA

Introduction. Despite the declining overall suicide mortality rate in Yakutia, this issue remains acute in the Arctic zone оnf the republic. Research in this area should rely on primary medical documentation to develop effective suicide prevention programs.

Objective. To identify individuals at risk based on hospital documentation from the Arctic zone of Yakutia to improve regional suicide prevention programs.

Materials and Methods. This study utilized materials from the Yakut Republican Medical Information-Analytical Center (YRMIAC) covering 2013–2023, 263 medical death certificates of suicide victims, and forensic examination documents provided by central district hospitals (CDHs) in the Arctic zone of the Republic of Sakha (Yakutia) (AZ RS(Y)). Additional data on the number of children of the deceased and presumed causes of suicide were also requested. Statistical analysis was conducted using IBM SPSS Statistics v.26.

Results and Discussion. An analysis of suicides in the Arctic Zone of Yakutia from 2013 to 2023 revealed significant factors such as alcoholism, unemployment, and low education levels. Most suicide victims experienced depression or emotional crises, highlighting the need for comprehensive prevention programs. Improving monitoring and data collection in medical institutions of the AZ RS(Y) is key to combating this issue effectively. Recommendations include developing a regional suicidology registry and enhancing medical personnel training to work with high-risk patients.

Conclusion. The primary cause of excessive suicide mortality in the Arctic is not ethnocultural but socio-economic factors. Addressing this issue requires creating a suicidology registry and targeted prevention programs, which are crucial for improving the mental health of Yakutia's population.

Keywords: suicides, suicidal behavior, mortality, gender differences, suicide prevention, Yakutia, Arctic zone.

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Introduction. The issues of suicide prevention remain topical all over the world. According to WHO data, suicide takes the lives of more than 700 thousand people annually, and the average global mortality rate (per 100 thousand of us) as of 2019 was equal to 9.2. In the world ranking of countries, the Russian Federation ranked 9th with an indicator of 25.1 [6]. The data on suicides among men are even more tragic - the world average was at the level of 12.6, and for the Russian Federation - 43.6 (6th place in the world). At the same time, it should be noted that all over the world, including Russia, including the Republic of Sakha (Yakutia), the overall mortality rate from suicides has a pronounced downward trend. Thus, if in 2000-2001 in Yakutia it was at the level of 39.4, then by 2023 it has gradually decreased to 13.2.

However, it is important to realize that for a long time a significant contribution to regional suicide rates has been made by the data obtained in the Arctic zone of the Republic of Sakha (Yakutia), which unites 13 uluses with a total population of about 64 thousand people. Thus, from 2010 to 2023, this coefficient in the Arctic Zone of the Republic of Sakha (Yakutia) exceeded the national average by an average of 2 times. Undoubtedly, this problem has been covered in scientific literature, but it should be recognized that so far the research has been based solely on the data of state statistics [2, 3]. In this regard, the aim of the work is to identify possible suicides from the risk group based on the data of primary documentation of hospitals of the RS(Ya). The obtained data will be used to improve suicide prevention programs in the region.

Materials and methods of research: The materials of the Yakutsk Republican Medical Information and Analytical Center (YARMIAC) for 2013-2023, as well as data from 263 medical certificates of suicide deaths and related documents of forensic medical examinations (RME) provided by central district hospitals (CDH) of AZ RS(Ya) were used. In addition, information on the number of suicidal children and the presumed cause of suicide was also requested. Statistical analysis was conducted using IBM SPSS Statistics v.26.

Results and Discussion. From 2013 to 2023, there were a total of 335 suicides in the Yakut Arctic, of which we were able to obtain more detailed information on 263 cases (78.5%). The absence of information on some suicides is explained by 2 reasons. Firstly, some of them actually lived outside their district, so their postmortem epicrises were not received by the Arctic CDCs (for a similar reason, the data received from some ulus CDCs, e.g. Verkhnekolymsk CDC, shows that the number of suicides exceeds the data indicated in the YARMIAC data). Second, in some CDCs, documentation is extremely poor. For example, in Anabarsky ulus, with a population of only 3.5 thousand people, 38 suicides were committed in 11 years, that is, in some years (e.g., 2014-2015) the standardized mortality rate from the considered cause reached 265 people/100 thousand people. Nevertheless, the data on only 2 cases were preserved in the specified CRB (table 1). In spite of the presence of a full-time psy-

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chiatrist-drug addict, cases of suicides are insufficiently recorded in the CRBs of Bulunskiy ulus. By the way, 32 cases of suicides were recorded in this ulus from 2010 to 2012.

In general, the share of suicides committed in the Yakut Arctic from the total number of suicides in the region averages 12.4%. Considering that no more than 6.4% of Yakutia's population currently lives in this territory, such figures are alarming. Of the 263 cases, 138 (52.5%) occurred in the provinces, 111 (42.2%) - in ulus centers, in 14 cases information about the place of death was not specified.

A significant part of the deceased was represented by men (n = 201 or 76.4%). Nevertheless, the gender ratio was 3.2 : 1, whereas in most regions of the Russian Federation the proportion of men is 4-5 or more times higher [5]. At the same time, the overwhelming majority of men were people of working age - the total share of people from 18 to 59 years of age amounted to 82.1%. A similar picture is also observed in the female sex, but the share of girls is significantly higher than in boys (table 2).

The distribution by ethnicity is as follows: Sakha - 171 people or 65.0%, representatives of indigenous minorities - 57 people or 21.7% (including 34 Evenks, 20 Evens, 2 Chukchi, 1 Yukagir), representatives of non-indigenous ethnicity, mainly Russians - 33 people or 12.5%, nationality was not specified in 2 people (0.8%). A positive strong correlation ($r = 0.81$, $p = 0.001$) was established between the share of non-indigenous population living in the uluses and the share of the latter among suicides (Figure). For example, in Verkhnekolymsky ulus, where 55% of non-indigenous people live, 15 suicides were recorded, 8 of which, or 60%, were committed by Russians. In other words, socio-economic factors, rather than ethno-cultural component, play a greater role in the formation of this indicator in the AZ of RS(Ya), which was previously noted in the works of N.B. Semenova [7, 8].

Table 3 shows that the majority of suicides had secondary general or secondary vocational education, while only 4.6% had higher education. This fact once again confirms that a high educational level is associated with a more favorable socio-economic position of a person in society and, as a consequence, is to a certain extent a protective factor of suicide risk. Therefore, it is not surprising that 1/3 of suicides (80 people) were unemployed. There were 33 pensioners (12.5%), employees of various budgetary institutions - 106 people (40.3%), schoolchildren and students - 25 people (9.5%).

We also found that among suicides the share of married persons amounted to 32.3%, and those who had children, including minors - 25.1%. Thus, 44.7% (21 persons) of fathers and 45.0% (9 persons) of mothers were under 35 years of age. Out of the total number of mothers, 5 women had two children each, and 7 women had many children, i.e. from 3 to 7 children. The share of widowed and divorced men and women was insignificant.

The research has revealed in the Yakut Arctic the majority (76.2%) of suicide victims chose self-hanging (table 4). In second place is self-shooting, occupying up to 18.4% of the total structure of suicide methods. Undoubtedly, such a high rate is associated with the availability of firearms among the residents of the Far North. For comparison, in other regions of the Russian Federation, death by self-shooting was chosen by no more

Table 1

Dynamics of completed suicides in AZ RS(Ya) and mortality rates per 100 thousand inhabitants

District	years											in total	information collected in CRC
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023		
Abyisky	2	2	1	6	1	1	0	0	2	1	3	19	19
Allaihovsky	2	3	1	1	2	0	1	2	1	0	1	14	14
Anabarsky	3	9	9	4	0	2	2	4	3	0	2	38	2
Bulunsky	3	6	3	3	2	2	0	5	3	4	3	34	19
Verkhnekolymsky	1	1	2	1	0	1	0	0	0	1	2	9	15
Verkhoyansky	7	5	6	5	6	9	5	7	3	1	1	55	45
Zhigansky	1	2	1	1	2	0	3	2	1	0	3	16	19
Momsky	0	2	1	4	2	1	0	1	1	2	0	14	10
Nizhnekolymsky	2	0	1	1	1	0	0	3	3	2	3	16	10
Olenyoksky	4	3	0	0	4	2	0	2	2	1	0	18	18
Srednekolymsky	6	2	6	7	8	7	8	6	5	1	4	60	61
Ust-Yansky	4	1	4	3	2	1	3	2	0	3	0	23	24
Ev.-Bytantaysky	1	1	3	0	4	1	3	2	3	0	1	19	7
Total for AZs of RS(Ya)	36	37	38	36	34	27	25	36	27	16	23	335	263
Share of AZ RS(Ya), %	10.5	11.2	11.4	12.4	12.7	11.7	11.3	18.0	13.8	9.7	17.4	12.4	-
AZ RS(Ya)	51.2	53.5	55.3	52.5	49.8	39.8	36.9	53.2	40.0	24.9	35.8	51.2	-
RS(I)	35.8	34.5	34.7	30.2	27.7	23.9	22.9	20.5	19.8	16.5	13.2	35.8	-

Table 2

Age and gender structure of suicides

Gender	Gender Age category											
	12-17		18-44		45-59		60-74		75-90		total	
	n	%	n	%	n	%	n	%	n	%	n	%
Men	11	5.5	133	66.2	32	15.9	20	10.0	5	2.4	201	100
Women	8	12.9	40	64.5	7	11.3	5	8.1	2	3.2	62	100
Both sexes	19	7.2	173	65.8	39	14.8	25	9.5	7	2.7	263	100

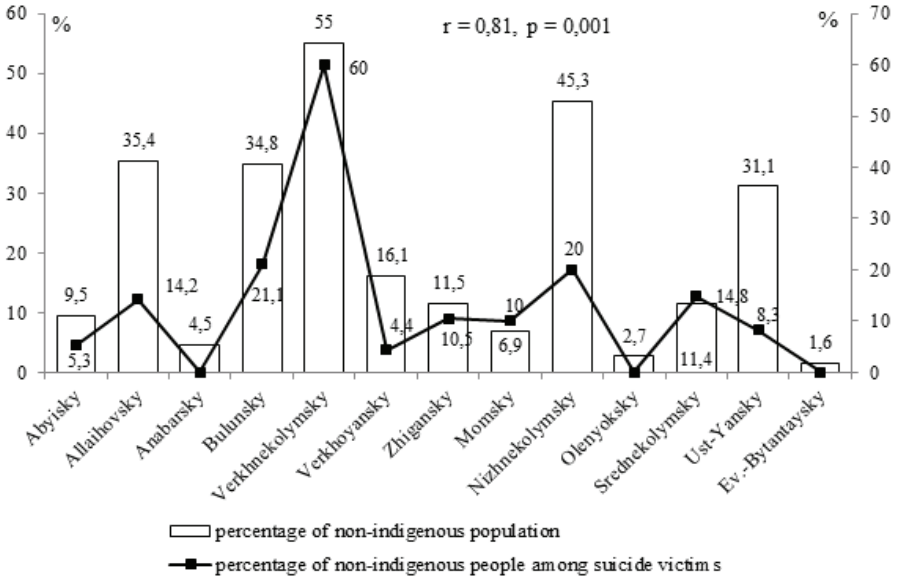
than 7.8% of men [9]. In women, self-cutting (9.7%) and poisoning (8.1%) rank second.

The study of suicide seasonality has long been of interest to researchers. Thus, more than a century ago, the classic of Western sociology Emile Durkheim noticed that «in spring people take their own lives more often than in fall» [4]. Some Russian researchers came to similar conclusions later [1, 10, 11]. In our data we obtained a similar pattern - from March to May there is an increase in suicides, which can be associated with a sharp contrast between the state of internal confusion of the suicidal person and the increase in social activity of people at this time (tab. 5). In our opinion, the decrease in the number of fall suicides is influenced by preparatory work for wintering and the beginning of hunting season, and some.

The study of suicide seasonality has long been of interest to researchers. Thus, more than a century ago, Emile Durkheim, a classic of Western sociology, noted that «people take their own lives more often in spring than in fall» [4]. Some Russian researchers came to similar conclusions later [1, 10, 11]. In our data we obtained a similar pattern - from March to May there is an increase in suicides, which can be associated with a sharp contrast between the state of internal confusion of the suicidal person and the increase in social activity of people at this time (table 5). In our opinion, the decrease in the number of autumn suicides is influenced by preparatory work for wintering and the beginning of the hunting season, and some rise in December and January is presumably associated with alcohol consumption during the New Year holidays.

Studies examining the association of suicide with the day of the week are highly inconsistent. For example, A.J. Kposowa et al. [13], based on the analysis of more than 20 thousand cases of suicide, found that the highest risk is on Wednesday (24.6%), L. Bradvik [12] named Sunday as such a day (31%), M. Plöderl [14] showed that the risk of suicide is higher at the beginning of the week and decreases by the weekend. No pronounced pattern was found in our study. The time of death was indicated in 131 cases (49.8 %), of which 39 cases occurred from 6 : 00 to 12 : 00, 47 - from 12 : 00 to 18 : 00, 26 - from 18 : 00 to 00 : 00, 19 - from 00 : 00 to 6 : 00. Thus, the majority of suicides occur in the morning and afternoon.

It is well known that the majority of suicides are related to the use of psychoactive substances, but in a significant part



Proportion of non-indigenous population living in uluses and their share among suicides

Table 3

Some indicators of the social status of suicides

Indicator	Men		Women		Both sexes	
	n	%	n	%	n	%
Education						
higher education	7	3.5	5	8.1	12	4.6
secondary vocational	36	17.9	15	24.2	51	19.4
secondary general	125	62.2	29	46.8	154	58.6
basic general	1	0.5	1	1.6	2	0.8
school students	11	5.5	8	12.9	19	7.2
no data	21	10.4	4	6.5	25	9.5
Occupation						
employees of budgetary institutions	88	43.8	18	29.0	106	40.3
pensioners	25	12.4	8	12.9	33	12.5
unemployed	63	31.3	17	27.4	80	30.4
individual entrepreneurs	2	1.0	-	0.0	2	0.8
school pupils and students	14	7.0	11	17.7	25	9.5
no data	9	4.5	8	12.9	17	6.5
Marital status						
married	71	35.3	14	22.6	85	32.3
divorced	3	1.5	2	3.2	5	1.9
single	112	55.7	36	58.1	148	56.3
widows/widowers	2	1.0	1	1.6	3	1.1
no data	13	6.5	9	14.5	22	8.4
Presence of children						
available	46	22.9	20	32.3	66	25.1
not available	77	38.3	24	38.7	101	38.4
no data	78	38.8	18	29.0	96	36.5

of the deceased (42.9%, or 113 people), the results of blood alcohol concentration tests in the were not indicated in the documents. Alcohol intoxication at the time of death was documented in 74 cases (including 56 men and 18 women), the absence of alcohol influence was proved in 76 cases (including 51 men and 25 women). On the question about the supposed reason of suicide the answers were received for 83 people, from which in 43 cases (51,8 %) death was connected with the long-term depressive state of the suicidal person, 25 (30, 2 %) - with family quarrels (mainly against the background of alcohol abuse), 10 (12.0 %) - with se-

Table 4

Structure of ways of committing suicide in AZ RS(Ya)

Method of suicide	Men		Women		Both sexes	
	n	%	n	%	n	%
Self-hanging	156	77.6	45	72.6	201	76.2
Poisoning	2	1.0	5	8.1	7	2.7
Jumping from height	1	0.5	3	4.8	4	1.5
Self-shooting	37	18.4	3	4.8	40	15.2
Self-cutting	4	2.0	6	9.7	10	3.8
Self-immolation	1	0.5	-	-	1	0.4
Total	201	100	62	100	263	100

Table 5

Distribution of suicide cases by months and days of the week in AZ RS(Ya)

Month	n	%	Day of week	n	%
January	28	10.7	Monday	40	15.7
February	16	6.1	Tuesday	39	15.3
March	23	8.8	Wednesday	34	13.3
April	31	11.9	Thursday	27	10.6
May	31	11.9	Friday	39	15.3
June	23	8.8	Saturday	39	15.3
July	25	9.6	Sunday	37	14.5
August	23	8.8			
September	10	3.8			
October	17	6.5			
November	13	5.0			
December	21	8.0			

Note: 2 cases were missing in the data by month, 8 cases were missing by day of the week.

rious illness (mainly cancer), 4 (4.8 %) - with a difficult life situation (death of close relatives, friends), 1 (1.2 %) - with schizophrenia.

Conclusion: Suicidal behavior of residents of the Arctic zone of Yakutia requires special attention. But, unfortunately, in small societies the work to identify potential suicides, which should be considered all alcohol-dependent citizens or people with mental disorders, is not done properly for a number of reasons. For example, there is an acute shortage of examinations of the population by psychiatrists and narcologists, which is clearly evident from the data of state statistics, according to which the primary incidence of mental disorders in the AZ RS(Ya) for the last two decades is 3-4 times lower than in the Russian Federation on average. Preventive work is weak, and documents on committed suicides are often filled in poorly. Therefore, it is necessary to create a regional suidologic register and increase the level of training of medical staff to work with patients at risk.

Based on the collected material, we can assert that the root cause of suicide mortality in the AZ RS(Ya) should be considered a socio-economic factor rather than an ethno-cultural one. The main risk group includes single young childless men of working age with secondary general or secondary vocational education, alcohol abusers, often unemployed or employed in various budgetary organizations. But at the same time the presence of a person's family and children, including minors, is not a guarantee that he will refuse a rash act - every third suicide victim was married, every fourth - had children. That is, it is obvious that the problem of suicides has a complex character, for the solution of which, first of all, it is necessary to develop effective prevention programs, the basis of which is formed by the data of scientific research of both medical-biological and socio-economic directions.

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FEATURES OF THE IMMUNE STATUS IN PRACTICALLY HEALTHY AND CANCER-AFFECTED RESIDENTS OF THE EUROPEAN NORTH WITH A HIGH CONTENT OF DOPAMINE IN PERIPHERAL VENOUS BLOOD

The study was conducted of 65 practically healthy people and 122 people suffering from oncological pathology of the gastrointestinal tract of various localization to study the immune status of practically healthy and oncological residents of the European region with an increased content of dopamine in peripheral venous blood. Thus, for the first time, it was established that the state of the immune status of residents of the European North with an increased content of dopamine in peripheral venous blood, in accordance with the state of health имеет, has significant deviations in people suffering from oncological pathology compared to practically healthy residents of the territories of the European North. Thus, the average dopamine content in practically healthy people and in people suffering from cancer pathology, is 33.1±3.93 and 133.66±8, respectively, чthe frequency of recording elevated dopamine concentrations in practically healthy people and in people suffering from cancer pathology is 7.69±0.23 % and 59.84±0.63 %, respectively. The average blood levels of transferrin and IgE in people suffering from oncological pathology are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune responses is established, i.e. the interaction of the immune system with the tumor, which represents a balance between the processes of immune activation and immune suppression and violation of the mechanisms of regulation of components of the immune system that occur in people with malignant tumors.

Keywords: dopamine, immune status, oncological pathology, cytotoxic lymphocytes, transferrin, IgE, autoantibodies to DNA and RNA, CIC, autoantibodies to phospholipids (IgM), autoantibodies to phospholipids (IgG)

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A survey of 65 practically healthy people and 122 people suffering from oncological pathology of the gastrointestinal tract of various localization was conducted to study the immune status of practically healthy and oncological residents of the European North with elevated dopamine levels in peripheral venous blood. Thus, for the first time, it was established that the state of immune status in residents of the European North with an increased dopamine content in peripheral venous blood, in accordance with the state of health, has significant deviations in people suffering from oncological pathology compared with practically healthy residents of the European North. Thus, the average dopamine content in practically healthy people and in people suffering from oncological pathology is 33.1±3.93 and 133.66±8, respectively, the frequency of increased dopamine concentrations in practically healthy people and in people suffering from oncological pathology is 7.69±0.23% and 59.84±0.63%, respectively. The average blood transferrin and IgE levels in people suffering from cancer are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of the other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune reactions has been established, i.e. the interaction of the immune system with the tumor, representing a balance between the processes of immune activation and immune suppression and a violation of the mechanisms of regulation of the components of the immune system that occur in people with malignant tumors.

Introduction. Dopamine is interesting from the point of view of science because it performs various functions in the human body. It not only helps to think, move, form feelings, and make choices, but also

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contributes to the development of certain diseases. It is possible that dopamine affects the metabolism of cancer cells and promotes their progression and growth, and blocking dopamine receptors significantly slows down the growth of tumor formations. Researchers at Vanderbilt University Medical Center have identified the effects of dopamine on breast cancer growth. Studies conducted in mice have shown that inhibition of specific receptors contributes to the suppression of tumor development. This discovery opens up new opportunities for the development and implementation of effective cancer treatment methods. In some areas of science, dopamine is not well understood. It was necessary to find out whether the production of "stress dopamine" or any other factors that increase and accelerate the development of the disease, how they affect and change other immunological parameters of the blood, предстояло выяснить. It was of considerable interest to study elevated dopamine concentrations and compare them with immune responses in practically healthy and oncological patients of the European community with elevated dopamine content in peripheral venous blood. There is a well-known fact that in malignant neoplasms there is a violation of the immune defense.

Dopamine is a hormone and neurotransmitter, that cis synthesized from L-DOPA. This hormone is produced in the neurons of the brain located in the middle and medulla oblongata and is involved in the transmission of nerve impulses between cells. The dopaminergic system has a clear zonal distribution of dopamine neurons. Dopamine synthesized outside the central nervous system (adrenal glands, kidneys, and intestines) is not involved in the transmission of nerve impulses, but is involved in the regulation of the cardiovascular and other body systems. Up to 90% of dopamine is secreted in the gut [12,1-6]. Acting on the peristalsis of the ventricle and intestines, slows it down. It plays a significant role in the work of the pancreas, because it reduces the production of insulin by its cells (islets of Langerhans), kidneys, thereby accelerating the excretion of sodium and urine. Dopamine is involved in regulating the activity of the immune system and has a significant effect on the function of immune cells (reduces the activity of lymphocytes). Many immune cells express dopamine receptors that are bound to dopamine and this allows them to actively respond to dopamine and suggests that dopaminergic immune regulation is an important part of normal immune function. The dopamine concentration that immune system cells are exposed to in various anatomical regions is not yet clear [14]. So, бliterally, dopamine, as a key neurotransmitter , plays a huge role in the work of many body systems and a key role in a number of diseases, including cancer. All this suggests that dopamine plays an important role in the immune system.

The aim of the study is to study the features of the immune status in practically healthy and oncological residents of the European Region with a high content of dopamine in peripheral venous blood.

Materials and methods. An immunological examination of 65 practically healthy people living in the city of Arkhangelsk, who at the time of the examination had no history of acute and chronic pathology, was performed. As a comparison group, we took 122 people with a history of oncological pathology of the gastrointestinal tract of various localization. The age of the surveyed people was 41-70 years. The examination was carried out by a doctor in the medical company Biolam, Arkhangelsk. We have studied and analyzed the material carried out by employees of the laboratories of the Institute of Physiology of Natural Adaptations UB of the N. P. Laverov Federal State Budgetary Institution of the Russian Academy of Sciences of the Ural Branch of the Russian Academy of Sciences for several years. The study was conducted in accordance with the provisions of the Helsinki Declaration and was approved by the Ethics Committee of the N. P. Laverov Federal Research Center for Integrated Arctic Studies of the Ural Branch of the Russian Academy of Sciences (Protocol No. 5 of 27.11.2020). The survey was conducted with the written consent of respondents.

Blood sampling for the study was performed in the morning hours (8-10), on an empty stomach. Blood serum was separated from the formed elements (erythrocytes) by centrifugation (separation of the liquid part of blood from cells in order to prepare the biomaterial for subsequent analysis).

The complex of immunological research included the study of hemograms in blood smears stained by the Romanovsky-Giemse method. The concentrations of dopamine in the blood serum were studied by an enzyme-linked immunosorbent assay (IBL Hamburg, Germany). The level of cytotoxic lymphocytes (CD4+), transferrin (Bender MedSystems, Germany), immunoglobulin E (IgE) was evaluated using the test-kit 'Biosourse' (USA), circulating immune complex (CIC) using the test kit of the chemical company Reakompleks (Chita). The content of antibodies to double-stranded DNA (anti-dsDNA), ribonucleoprotein-(anti-RNP) (Bio-Rad, USA) was studied using Multiscan MS (Labsystems,-Finland) and Evolis (USA) analyzers and antibodies to phospholipids (IgM, IgG) using diagnostics of their production kits 'Biosourse' (USA).

Statistical analysis of the research results was carried out using the application software package "Microsoft Excel 2010" and "Statistica 7.0" (StatSoft, USA). The boundaries of the normal distribution of indicators were determined. The data distribution was compared with normal values using the Shapiro–Wilk test. The distributions of the results turned out to be similar to the normal one, so for describing the data the average arithmetic mean (*M*) and standard error of the mean *(m)* were calculated. Quantitative values between groups were compared using the Student's t-test. The differences were considered statistically significant at the significance level of the t-test $p < 0.05$-0.001.

Results and discussion. Changes in immunological parameters and the state of the immune status were found both in practically healthy people and in people suffering from oncological pathology of the gastrointestinal tract of various localization. Namely, an increase in the average blood content of dopamine, and immunoglobulin E and transferrin, both in practically healthy people and in people suffering from cancer (Table 1). Neurotransmitters are involved in many physiological and pathophysiological functions of the body, in the formation of the immune system, antimetastatic and antitumor resistance of the body. It is known from the literature that an imbalance in the system of excitatory and inhibitory neuro-transmitters affects the development and progression of malignant tumors [11]. Neurotransmitters can act as powerful regulators of many cell functions in the production of growth factors and factors that promote metastasis. They also modulate proliferation, migration, and the formation and development of new vessels in tumors, and, accordingly, their involvement in the formation and progression of oncological diseases cannot be excluded [15]. The average content of other immunological markers slightly exceeded the physiological limits. Immunoglobulin E (IgE) belongs to a class of immunoglobulins that are found in blood and in small amounts, but one of the most important factors of the immune

Table 1

Average content of both dopamine and immunological parameters in peripheral venous blood in practically healthy and cancer-affected residents of the European North with a high content of dopamine in peripheral venous blood, (M±m)

Study parameters	Average content in practically healthy people, n=65, (M±m)	Average content in in people with oncological pathology of the gastrointestinal tract, n=122, (M±m)	Physiological limits
Dopamine, pg/ ml	33.1±3.93	133.66±8.2***	>30 пг/мл
Cytotoxic lymphocytes CD3+ CD8+, ×109 cells/l	0.39±0.02	0.44±0.03*	0.2-0.4
Transferrin, g / l	3.09±0.17	5.06±0.15**	1.5-3.5
Immunoglobulin E (IgE), u/ml	53.34±7.21	119.89±35.77***	<100
CEC, g/ l	2.97±0.64	4.03±0.38*	<2.0
Anti-dsDNA , u/ ml	53.95±7.47	68.0±13.66*	<50.0
Anti-RNP, u/ml	0.83±0.1	1.13±0.1*	<1.0
Antiphospholipids IgM, u/ ml	4.18±0.59	5.91±0.57*	<10.0
Antiphospholipids IgG, u/ml	6.54±1.25	7.16±0.9*	<10.0

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

system. It reacts first to the penetration of a foreign antigen into the body and causes the development of an allergic reaction (type I). It also participates in the response to infection with parasites and at the same time directly interacts with the pathogen's antigens. In oncological diseases, the content of reagins increases. It is possible that the immune response to the complex of tumor antigens is accompanied by an antibody formation reaction with an increase in the m content of serum immunoglobulins and IgE, including [2]. Transferrin is a plasma protein that transports iron ions. Participates in the provision of innate immunity. It is known that in iron-deficient anemia, the level of transferrin in the blood increases [11-3]. The development of anemia is typical for patients with cancer [5]. Anemia occurs in 40-60 % of patients with malignant tumors of various localizations. The decrease in hemoglobin levels in cancer patients may be due to both the use of various methods of chemotherapy and radiation therapy, which have an overwhelming effect on hematopoiesis, and iron deficiency, which can be observed in chronic blood loss, reduced iron absorption and suppression of the process of red blood cell formation, which is typical for cancer patients. [6]. Iron deficiency occurs with blood loss, and transferrin transports iron ions in the body. Thus, the level of transferrin may be elevated in the blood.

The frequency of registration of elevated concentrations of cytotoxic lymphocytes, transferrin, immunoglobulin E,

Table 2

Frequency of registration of elevated dopamine concentrations and immunological parameters in peripheral venous blood in practically healthy and cancer-affected residents of the European North with a high content of dopamine in peripheral venous blood. %

Parameters studied	Frequency of registration of elevated concentrations in healthy subjects. n=65 %	Frequency of registration of elevated concentrations in people with cancer pathology of the gastro- intestinal tract. n=122 %	Physiological limits
Dopamine. PG/ml	7.69±0.23	59.84±0.63***	>30 пг/мл
Cytotoxic lymphocytes CD3+ CD8+. ×109 cells/l	23.08±0.39	90.77±0.78***	0.2-0.4
Transferrin. g/l	16.92±0.34	58.46±0.62***	1.5-3.5
Immunogobulin E (IgE). IU/ml	9.23±0.25	41.54±0.53***	<100
CEC. g/l	15.39±0.32	96.92±0.8***	<2.0
Anti-dsDNA. IU/ml	12.31±0.29	58.46±0.62***	<50.0
Anti-RNP. IU/ml	1.54±0.1	49.23±0.57***	<1.0
Antiphospholipid IgM. u/ml	4.62±0.18	12.31±0.29***	<10.0
Antiphospholipid IgG. IU/ml	9.23±0.25	18.46±0.35***	<10.0

circulating immune complexes, anti-dsDNA, anti-RNP, and autoantibodies to phospholipids was revealed depending on the increased content of dopamine in peripheral venous blood in practically healthy people and in people with malignant neoplasms of the gastrointestinal tract of various localization (Table 2). The obtained data were compared with the physiological limits. An increase in the frequency of registration of cytotoxic lymphocytes, transferrin, circulating immune complexes and *anti-RNP* in peripheral blood was found in practically healthy people. The content of other immunological parameters was slightly increased, but did not exceed the limits of the physiological norm. People suffering from cancer have a high frequency of elevated concentrations of all the studied parameters.

An increase in the concentration of cytotoxic lymphocytes can be observed in viral and bacterial infections, as well as during recovery from a severe infectious disease. But, in addition, an increased content of cytotoxic lymphocytes can also be observed in oncological pathology. Reactions to the antigen, in the form of graft rejection, cell-mediated cytotoxicity, as well as autoantigens and tumor, include lymphoproliferation and, as a result, an increase in the content of activated lymphocytes (CD25+, CD71+, HLA), NK (CD16+, CD56+), Th (CD4CD4+) and cytotoxic suppressors ((CD8+) [3]. T-cytotoxic lymphocytes cause lysis of tumor cells and spontaneous tumor breakdown. However, there is an opinion that these cells themselves are not related to the tumor cytotoxicity reactions; on the contrary, they are able to block activated specific cytotoxic T cells [11-0].

Circulating immune complexes (CICS) are compounds that are formed when antibodies meet antigens in the blood. Their role is to bind and neutralize foreign antigens and then eliminate them from the body. High concentrations of circulating immune complexes can be observed in practically healthy people [1]. An increase in CEC is also characteristic of autoimmune, infectious diseases and allergic reactions of type III. An increase in circulating immune complexes is also characteristic of oncological pathology [7]. The content of circulating immune complexes in the blood serum is constantly under the control of phagocytosis of blood mononuclears, and when the formation of CIC is out of control of phagocytes, respectively, an increase in the content of CIC is observed in the blood serum and this gives them toxic properties [8]. It is known from literature sources that a high frequency of phagocyte activity is recorded in oncological diseases [4].

It is known, that autoantibody concentrations are directly related to the activity of inflammation and are most pronounced in case of systemic complications [9]. Nearly always extremely high levels of autoantibodies, especially to dsDNA are detected in malignant neoplasms. It is possible that the main effect and purpose of increased concentrations of antibodies to nucleoproteins is to destroy tumor cells, since on proliferating cells the concentrations of various receptor structures that can bind antibodies to autoantigens, are much higher.

Phospholipid antibodies are proteins that the body produces in response to phospholipid antigens present in cells. It is possible that in the development of a number of diseases, antibodies to phospholipids IgM and IgG affect the appearance and development of certain diseases. The relatively high level of elevated concentrations of antiphospholipids IgM and IgG attracts attention, and it is possible that this process is somewhat more important in oncological pathology, since the most often detected increase in antibodies to antigens in other pathological conditions.

Conclusion. The state of the immune status of residents of the European North with a high content of dopamine in peripheral venous blood has significant deviations in people, with oncological pathology of the gastrointestinal tract of various localization, compared with practically healthy residents of the territories of the European North. Thus, the average dopamine content in practically healthy people and in people with oncological pathology, is 33.1±3.93 and 133.66±8, respectively; the frequency of registration of elevated dopamine concentrations in practically healthy people and in people with oncological pathology, is 7.69±0.23 % and 59.84±0.63 %, respectively. The average blood levels of transferrin and IgE in people with cancer are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune responses, i.e., the interaction of the immune system with the tumor, which is a balance between the processes of immune activation and immune suppression, and a violation of the mechanisms of regulation of immune system components that occur in people with malignant tumors, is established.

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The author declares that there is no conflict of interest.

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SCIENTIFIC REVIEWS

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RADIAL SCAR OF THE BREAST AS A MASK OF MALIGNANT NEOPLASMS

In order to study the radial scar as a mask of malignancy, a literature review was conduct-ed. It was found that the difficulty in diagnosing the radial scar is due to its morphological simi-larity to a malignancy and associated intraductal epithelial proliferations. To exclude a malignan-cy and intraductal proliferations, immunohistochemical visualization of the intact myoepithelial cell layer is used, as well as cellular heterogeneity of intraductal proliferations using markers such as p63, basal cytokeratins, smooth muscle actin, basal cytokeratins, and estrogen receptor. It was found that in the case of a combination of a radial scar with atypia or other high-risk lesions of the mammary gland, the likelihood of its transformation into malignant lesions of the mammary gland increases.

Keywords: radial scar, breast, radiation sclerosing lesion, B3 lesions, ductal carcinoma in situ

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Radial scar is part of a group of breast lesions [16] with uncertain malignant behavior [3], also known as high-risk or B3 lesions [9] with a borderline to variable histologic spectrum, risk of associated malignancy [7, 9, 15] and account for 5 to 12% of initial biopsy findings [27, 28].

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The most commonly used classification of breast lesions worldwide is the B-classification [28, 29], which was introduced in 1999 by a collaborative group of 23 European pathologists for the assessment of breast needle biopsy findings [14].

At the 3rd International Consensus Conference in 2022, six most relevant B3 lesions were discussed - benign but of uncertain biological potential [7], atypical ductal hyperplasia, squamous epithelial atypia, classic lobular neoplasia, radial scar, papillary lesions without atypia, and phyllodes tumors [29]. This group of breast lesions is difficult to classify histologically [3] and they are considered optional precursors to malignancy [9, 30]. In turn, the frequency of B3 lesions with a total risk of malignant development varies from 9.9% to 35.1% [7, 10, 14].

The main problem with B3 lesions is the possibility of underestimation of lesion malignancy [27, 33]. According to the study by Chou R et al., [14], the overall rate of transition to malignancy of B3 lesions was 26.4%, which is consistent with the data of other authors. Thus, according to Richter-Ehrenstein C. et al. [10], approximately a third of puncture biopsies of breast lesions classified as B3 detected during screening are precancerous or malignant after removal.

The diagnosis of a radial scar is problematic because of its morphological resemblance to malignancy and complicates differential diagnosis because of its association with other proliferative lesions.

Immunohistochemistry with visualization of the intact myoepithelial cell layer is of critical importance for differentiating the radial scar from invasive carcinomas and associated intraductal epithelial proliferations [33].

The prognosis of malignancy of a radial scar depends on the presence or absence of associated atypia. If atypia is absent on histological analysis, the probability of malignancy increases with larger lesions, the presence of calcifications, and advanced age [16, 21, 25].

The purpose of the study: analysis of publications devoted to the study of radial breast scar as a mask of malignancy.

In this review, we examined the literature sources devoted to the study of radial breast scar. A comprehensive search

was conducted in the electronic databases PubMed, Web of Science, Google Scholar for 2009-2024. The key words for the search included: radial scar, mammary gland, radiation sclerosing lesion, B3 lesions, ductal carcinoma in situ. The duration of the studies in the analyzed publications ranged from 4 to 20 years, and the number of radial scars confirmed by biopsy was 1801.

A microscopic method was also used, conducted on the basis of the OGBUZ "Belgorod Pathoanatomical Bureau" during our own studies. The material was fixed for 24 hours in 10% neutral buffered formalin, then it underwent histological processing in a closed-type histoprocessor Thermo Scientific Excelsior AS (sequential dehydration, degreasing and impregnation of tissue with paraffin). From the manufactured paraffin blocks, 4-μm-thick sections were made using a semi-automatic rotary microtome Thermo Scientific HM340e. Sections were stained with hematoxylin and eosin, antibodies Chromogranin (clone LK2H10, manufacturer Cell Marque, USA), Cytokeratin 20 (Ks20.8, Cell Marque, USA), Cytokeratin cocktail (AE1/AE3, Cell Marque, USA), Ki-67 (30-9, Ventana, USA), Synaptophysin (MRQ-40, Cell Marque, USA), TTF-1 (86763/1, Cell Marque, USA). To obtain images, a Hamamatsu nanozoomer s60 scanner was used.

Radial scar (RS) is a benign lesion of the mammary gland, consisting of a central fibroelastotic stromal core imitating a scar, with outgoing ducts, lobes of varying degrees of proliferative and cystic changes, located in a stellate configuration [17] and a lesion less than 10 mm in size [9]. According to the studies of Kraft E. et al. [18], the average lesion size was 6.0 mm (range 2-39). As noted by Turkyilmaz Z. et al. [4] and Fenoglio et al. [5], in their studies the average size of RS was 1.08 cm (0.2-3). Similar results were obtained by Grabenstetter A. et al. [19] - 9 mm (range 2-41). With sizes greater than 10 mm, a lesion that exhibits the same features as RS is called a complex sclerosing lesion and occurs with a frequency of 0.6 to 3.7% [17], although it is often used to describe larger and disorganized lesions and these terms are often used interchangeably [29]. Typically, complex sclerosing lesions include multiple patterns of epithelial proliferations such as sclerosing adenosis, sclerosing papillomas, common ductal hyperplasia, and cysts [22].

Regardless of the size and surface area of the mammary gland, RS are clinically hidden and not palpable [9, 17]. Turkyilmaz Z. et al. [4] explain the palpability of mammary gland lesions by the combination of RS with other benign mammary gland lesions, such as fibroadenomas and papillomas.

This pathology usually occurs in premenopausal women, rarely before 40 years and after 60 years [4, 26]. The etiology of RS remains unclear, although several theories have been proposed, such as Trombadori CML. et al. [17], suggested that RS may begin as a reaction to an unknown injury that heals with focal areas of fibrosis and elastosis, contracting in the center and forming a characteristic stellate appearance. The pathogenesis is also unknown: possible causes include a localized inflammatory reaction and chronic ischemia with subsequent slow infarction [5, 6, 9, 17], previous injuries and surgeries may be of great importance in the pathogenesis of RS [21].

RS can be single, multiple or manifest as clusters [5]. According to Bao JJ. [1], the registered frequency of RS, detected on screening mammograms, is 0.3-0.9 per 1000 examined women, which is consistent with the data of the studies of Yan et al. [11, 22] 0.03%-0.8% of breast biopsy results.

For the first time, a radial scar as "sclerosing papillary proliferation" was described by Fenoglio C. and Lattes R. in 1974 [5]. In turn, in 1975 Hamperl H. [8] described RS or cicatricial obliterating mastopathy and proposed the term "radial scarring or scar".

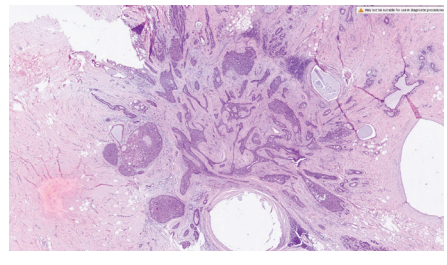
Microscopic (histological) description. The central sclerotic zone imitating the scar [9, 17, 25] is associated with fibroelastotic change [23], surrounded by elastic fibers [9], consists of fibrosis and elastosis with ducts and lobes radiating outward between the bands of sclerotic tissue, suggestive of obliterating mastopathy [9], accompanying by peripheral cysts, peripheral proliferative lesions and calcifications [33]. The central scar area [9] often contains small trapped obliterated ducts [9, 17], which consist of double epithelial and myoepithelial rows [5] and are morphologically similar to invasive carcinoma [31], making diagnosis difficult [4]. Especially because of the creamy yellow elastic center, which is common to both, and the fibroelastic area with engulfed ducts [4, 5].

Thus, RS poses a challenge due to its morphological resemblance to malignancy and complicates differential diagnosis due to its association with other proliferative lesions [17]. Our study confirms the authors' opinion that in RR, the mammary gland ducts are irregular in shape, with pronounced cellular proliferation, intraductal hyperplasia and metaplasia (fig. 1 a-c).

Immunohistochemistry is crucial for differentiating RS from invasive carcinomas and associated intraductal epithelial proliferations [33]. For this purpose, immunohistochemical visualization of the intact myoepithelial cell layer [1] is used using various markers (including p63, basal cytokeratins) and clarification of intraductal/intraacinar proliferations using basal cytokeratins and the estrogen receptor [30, 33]. Our immunohistochemical study confirms the authors' opinion (fig. 2 a-d).

On mammographic images, radial scars have a pointed outline with a trans-

a



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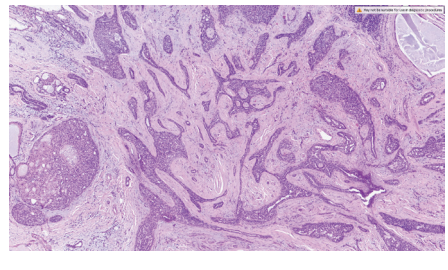

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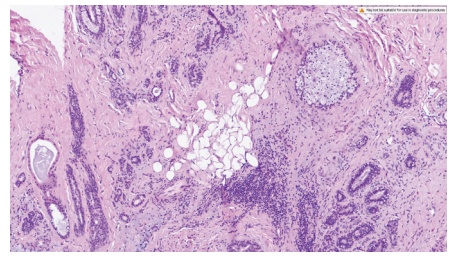
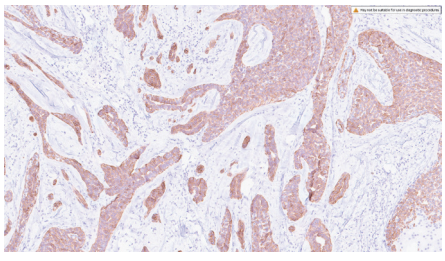


Fig. 1. Patient, 21 years old.
a - the specimen contains breast tissue with a pathological focus in the form of central pronounced stromal sclerosis, areas of periductal cicatricial fibrosis, isolated tubular structures, as well as predominantly radially oriented ducts deformed due to fibrosis with typical intraductal hyperplasia and focal apocrine metaplasia;
b - in the duct lumen there is pronounced cellular proliferation, forming typical ductal hyperplasia, irregularly shaped ducts, imitating invasive malignant tumor growth;
c - foci of pronounced chronic inflammatory infiltration, accumulations of xanthomatous cells in the duct lumen; (magnification a x25, b x50, c x100, staining: hematoxylin and eosin)

a



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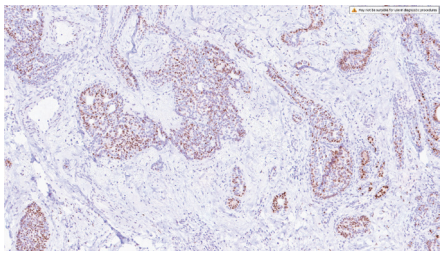

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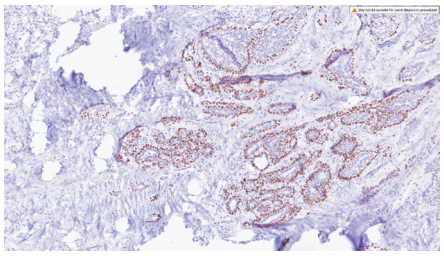

d

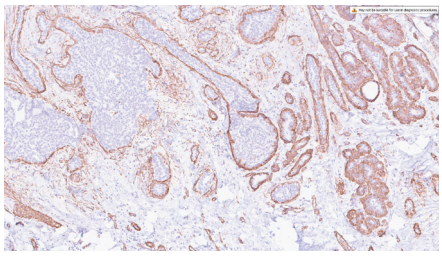

Fig. 2. Patient, 21 years old.
a - intraductal proliferator cells are diffusely stained (stain: cytokeratin 5);
b - antibody to estrogen receptors unevenly stains the nuclei of intraductal proliferator cells (stain: estrogen receptor);
c - P63 stains the nuclei of the preserved layer of ductal myoepithelial cells (stain: p63).
d - smooth muscle actin stains the preserved layer of ductal myoepithelial cells (stain: SMA), (magnification a, b, c, d x100)

lucent center and can look like an architectural distortion, which can be associated with microcalcifications [23, 24, 32]. Thus, Fenoglio et al. [5] found microcalcification in 51.3% of cases on mammograms, and a pointed lesion in 43.2%.

It is worth noting that atypia or other high-risk breast lesions found in combination with RS are serious risk factors for malignancy with an incidence rate, defined as the rate of transformation into malignant or other high-risk breast lesions, varying between 0-20% [2, 12, 14, 20]. In turn, according to Phantana-Angkool et al. [23], the rates of radial scar transformation into malignancy in the final pathology vary from 0 to 40%, which is consistent with the results of Yan et al. [22].

In their study, Rakha et al. [13] found that in patients with RS associated with atypia, it was associated with atypical ductal hyperplasia in 69.43% of cases, while lobular neoplasia was observed in 21.66%.

Yan et al. [11] in contrast, found that the majority 80.1% (117 of 146) of all RS did not have concomitant atypia or malignancy, and only 19.9% (29 of 146) had concomitant atypia detected on initial biopsy. As a result of their study, they concluded that the incidence of increased malignancy in RS without atypia is low and amounts to 0.9% (one of 117 [95% CI: 0.02, 4.7]), and with concomitant atypia - 14% (four of 29).

Turkyilmaz et al. [4] in their study studied the relationship between the number of RS and atypia, the number of RS and the patient's age and did not find a significant relationship, there was also no relationship and between RS size and atypia. In their study, the most common lesion accompanying RS was sclerosing adenosis (39.1%), which is consistent with the results of Fenoglio et al. [5].

It should be noted that the prognosis of RS depends on the presence of concomitant atypia. The risk of subsequent breast cancer associated with RR, detected in pathology with and without atypia, ranges from 1.1-3.0 to 2.8-6.7%, respectively. If atypia is absent in histological analysis, the likelihood of malignancy increases with large sizes (> 10 mm), calcifications, and old age [9, 16, 21, 25].

Conclusion. Based on the results of the analysis, it was established that radial scar is part of a group of breast lesions with uncertain malignant behavior. The diagnosis of a radial scar is problematic due to its morphological similarity to malignancy and complicates differential diagnosis due to its association with other proliferative lesions. Immunohistochemistry is critical to exclude malignancy when there is no associated atypia and when radiographic and histologic findings are consistent, which we confirmed with our research.

Patients with a radial scar with atypia have a higher risk of malignancy. Further studies are needed to determine in which patients radial scar excision can be safely avoided.

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THE USE OF 3D PRINTING FOR PREOPERATIVE PLANNING AND INDIVIDUALIZATION OF TREATMENT IN TRAUMATOLOGY AND ORTHOPEDICS: CONCEPTUAL EVOLUTION AND DEVELOPMENT PROSPECTS

3D printing technology in orthopedic surgery and traumatology opens up wide opportunities for improving preoperative planning and personalization of treatment, which leads to an improvement in the quality of medical care. This review focuses on modern advances in the use of 3D printing to create models, implants, and instruments that adapt to the individual anatomical characteristics of the patient. The benefits of 3D printing include improving the accuracy of surgical procedures and reducing operational risks through personalized solutions. At the same time, the review highlights key obstacles to the introduction of technology into clinical practice, such as high costs and the need for standardization of processes. Despite these challenges, 3D printing has significant potential to transform medical approaches and teaching methods, which opens up prospects for creating more effective and personalized therapeutic techniques in the field of orthopedics and traumatology.

Keywords: orthopedic surgery, 3D printing, traumatology, implants, 3D modeling, surgical instruments.

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Introduction. Three-dimensional (3D) printing, also known as additive manufacturing or rapid prototyping, has been around for several decades and is recognized as an effective method of manufacturing orthopedic instruments and implants [63,35,53]. In recent years, interest in 3D printing in the field of orthopedics has grown again, due to cost reductions, increased availability of 3D printers, printing materials and software, as well as the desire to provide more personalized treatment to patients. This development has led to the concept of "local printing" or "on-site printing of medical care" (PPC). Regardless of who manufactures

the devices, traditional companies or PPC, the advantages of 3D printing are obvious. [46, 31, 16, 36].

This technology makes it possible to develop instructions and surgical instruments adapted to the specifics of each individual anatomical model, which makes it possible to perform volumetric and accurate 3D measurements [38]. Individualized instruments help surgeons simulate operations, accurately measure necessary adjustments in osteotomy, plan fracture repair, calculate the volume of required allografts, and apply this technology in many other fields [25]. The purpose of this review is to present an approach to understanding this technology and its key principles.

Materials and methods. A literature search was conducted in the following databases: Web of Science, Scopus, PubMed (MEDLINE), eLibrary.RU and Cochrane Database of Systematic Reviews. Keywords such as "3D printing in orthopedic surgery", "three-dimensional printing and traumatology", "additive manufacturing in orthopedics", "personalized implants in traumatology", "3D printing and surgical instruments", "internal printing and medical care" were used to select relevant publications.

As a result of the search, 5005 publications were found. After removing 1,702 duplicates, the selection process was continued with 3,303 potentially suitable studies. When checking the titles and annotations, 3089 articles were excluded. The full texts of the remaining 214 articles were analyzed in detail, and the final list included 64 works. The PRISMA block diagram is shown in the figure (Figure).

In the table (table.1) All demographic and technical data are listed. Among the 64 selected studies, both randomized controlled trials, meta-analyses, and systematic reviews were reviewed. Special attention was paid to the quality of the methodology and the approaches used in the research. The obtained results allowed us to draw reasonable conclusions about the influence of the studied factors, as well as to identify areas requiring further research.

Historical background. The origins of three-dimensional printing can be traced back to the time when the art of sculpture was born in the Stone Age. Humanity, existing in a three-dimensional world, has always sought to reproduce this reality in different materials. In 1859, Francois Willem created the first 3D scanning technology in France, calling it "photosculpture." Photographs taken with a 360-degree viewing angle were used to create silhouettes of a person or object, which were then transferred to the desired scale thanks to the pantograph and served as the basis for creating a three-dimensional sculpture. In 1892, Joseph Blanter patented in the United States a technology for creating three-dimensional topographic maps that used a layer-by-layer accumulation method similar to the concept of modern 3D printers. Almost a hundred years later, in Japan, Hideo Kodama proposed the idea of creating 3D prototypes by injecting photopolymers that harden under the influence of ultraviolet rays. However, the first person to create a real 3D printer was Charles Hull in 1984 in the USA, and he is considered the founder of 3D printing [61]. In 1988, Hull introduced the first 3D printer on the market, called the SLA-250 [33].

Since 2007, patents have been issued, and interest in the topic of 3D printing has increased markedly. Affordable, open-source printers were developed that could self-replicate. The first mention of the use of this technology in the healthcare sector appeared at the beginning of the 21st century [35, 44]. In the period from 2009 to 2011, there was a change of emphasis in publications: from simple printing for preoperative planning to the production of surgical instruments and even implants [63].

The use of 3D printing in orthopedic surgery and traumatology. All over the world, orthopedic surgeons, specialists in related fields and scientists are actively using 3D printing to create models, instruments, implants, orthoses and prostheses adapted to each patient. 3D bioprinting technologies are also used to create skeletons of bones and cartilage, covering almost all aspects of orthopedic traumatology, from the head to the feet (Table 2).

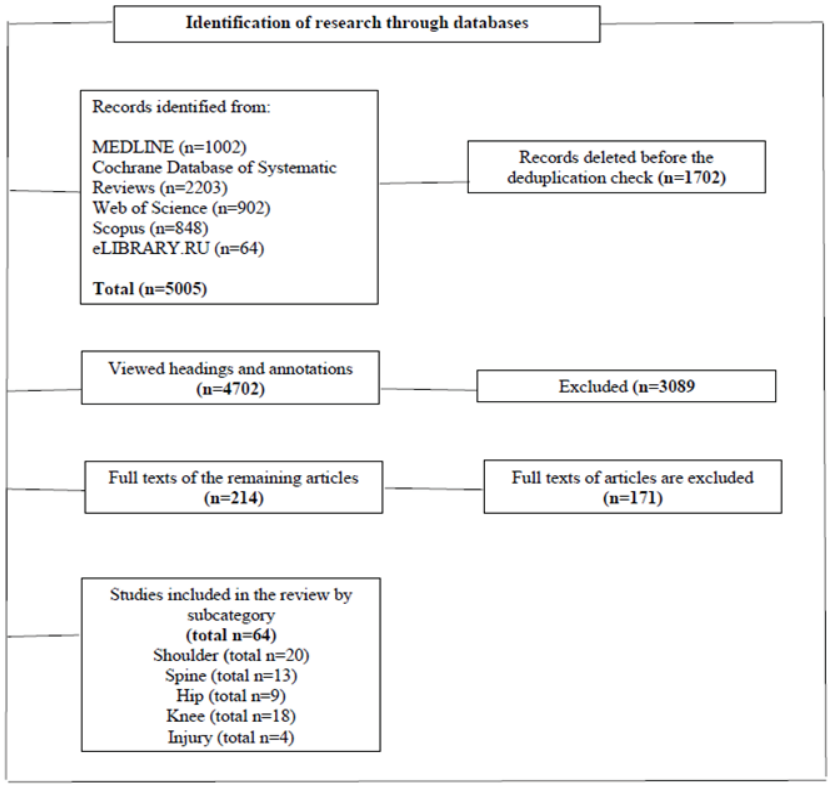
Based on the presented table, we note that the use of 3D models allows surgeons to visualize complex anatomical structures in advance, such as the proximal humerus, acromion, and pelvis, which contributes to more accurate and efficient operations. In particular, for the distal humerus and elbow, printing plates, templates and guides optimize the surgical process, increasing its predictability and reducing the risk of complications. Personalized navigation templates for ankle ligament repair improve the results by taking into account the individual anatomical features of the patient. In addition, 3D printing technologies promote innovations in reconstructive approaches, as in the case of the hand and thumb model, which opens up new possibilities for restoring the functions of complex joints and bone structures. In general, the use of 3D printing in orthopedics contributes to improving the quality of medical care, reducing operational risks and improving patient rehabilitation.

The main advantages and disadvantages of 3D printing in orthopedic surgery and traumatology. Orthopedics and traumatology are among the medical fields where 3D planning has significantly influenced practice, especially in the treatment of injuries and oncological orthopedics. An analysis of the literature in the field of orthopedics shows a noticeable increase in the number of publications devoted to this topic [55, 24, 25, 20, 12]. The main use of 3D technologies is related to preoperative planning, as well as the development of individual implants and guiding devices. Among the most commonly used materials for 3D printing are titanium, acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA).

In preoperative preparation, 3D printing opens up new possibilities for improving accuracy that are unattainable using traditional methods. This is especially true for the treatment of fractures, where it is important to model the recovery process in advance. Significant improvements have been noted in studies such as the work of Izatt and his colleagues: surgeons indicated that in 65% of cases anatomical details on biomodels were more noticeable than with standard visualizations, and in 11% they were unique only to 3D models [57]. These achievements emphasize the importance of 3D modeling, since improving the understanding of anatomical structures can directly affect the choice of materials and the location of implants, which is confirmed by the research of Wu and Shao [54].

Continuing the topic of precision, the research of Iannotti and co-authors demonstrate that the use of individual instruments in orthopedics, for example, in shoulder replacement, significantly improves the positioning of components [59]. Other papers, such as the Buller study, describe how arthroplasty guides allow experienced surgeons to reduce orientation deviations by 9 degrees, thereby increasing the accuracy of operations [56].

The integrated use of 3D printing and computer navigation complements procedures, as shown in the Chen study: the use of these technologies improved the accuracy of implant placement during reconstructive operations on pelvic bones by 3-5 times [23]. This also led to a reduction in radiation exposure and blood loss, which was noted during bone surgeries such as calcaneal and tibial.



Preferred reporting elements for systematic reviews and meta-analyses (PRISMA)

One of the biggest advantages of 3D technology remains personalization. Dekker and colleagues emphasize that individual implants based on precise parameters of the patient's anatomy significantly improve treatment results, for example, in complex deformities of the foot [39]. In addition, the prospects of bioprinting open up new horizons in the creation of biomaterials for tissue regeneration, as indicated in the works of Tan and co-authors [53]. As can be seen from these advantages, 3D printing technology is transforming orthopedics and traumatology, enabling precise preoperative planning and the creation of customized surgical instruments and implants, which significantly increases the accuracy and effectiveness of procedures.

However, despite the significant advantages, the use of 3D printing in medicine is fraught with certain difficulties that must be taken into account for the successful integration of this technology into medical practice [61, 25]. The disadvantages of 3D printing are similar to the disadvantages of any innovative technology, including high costs and lack of data, which is especially important in the economically limited and controversial field of medicine, where customized medical implants are manufactured. In addition, considerable time and resources are required to train medical professionals to use this technology in practice. Standardization and regulatory issues also require special attention to ensure the safety and effectiveness of the products [60].

Despite these challenges, the continued improvement of 3D technologies and the accumulation of experience in their application promise significant improvements in the quality of medical care and expanded treatment options, making the future of medicine more personalized and effective.

Application of additive 3D printing technologies in the diagnosis and treatment of pathologies of the musculoskeletal system. The use of additive 3D printing technologies for the diagnosis and therapeutic intervention in various pathologies of the human musculoskeletal system, including fractures, bone neoplasms, arthrosis of large joints, as well as congenital and acquired deformities and other conditions.

One of the most urgent tasks of modern medicine is the treatment of patients with bone diseases. The inci-

Table 1

Demographic and technical information on research using 3D printing in orthopedic surgery and traumatology

Link	Country	Category	Visualization method
Parratte et al. [31]	USA	Spine	CT
Gauci et al. [46]	France	TSA	CT
Wang et al. [16]	China	THA	CT
Yamamura et al. [43]	Japan	TKA	CT
Ferretti et al. [55]	Italy	THA	CT
Hendel et al. [24]	USA	TSA	CT
DeVloo et al. [58]	Belgium	TKA	MRT
Sariali et al. [50]	France	TKA	CT
Cui et al. [32]	China	Spine	CT
Roh et al. [38]	South Korea	TKA	CT
Dasari et al. [13]	USA	TSA	CT
Mohar et al. [47]	Slovenia	Spine	CT
Van Genechten et al. [36]	Belgium	TKA	CT
Matsukawa et al. [41]	Japan	Spine	CT
Moya et al. [64]	Mexico	TSA	MRT
Zheng et al. [25]	China	TKA	CT
Zhang et al. [30]	China	Pelvic area	CT
Chen et al. [23]	China	Spine	CT
Cho et al. [15]	South Korea	Spine	CT
Zheng et al. [18]	China	Pelvic area	MRT, CT
Rosenzweig et al. [14]	Canada	TSA	CT
Pehde et al. [29]	USA	TKA	CT

Note* CT - computed tomography; MRT- magnetic resonance imaging; THA - total hip replacement; TKA - total knee replacement; TSA - total shoulder replacement.

dence associated with both primary bone tumors and metastases to the musculoskeletal system is increasing annually. More than 2,900 cases of cerebral palsy and previously diagnosed osteogenic sarcomas are registered annually. In addition, many malignant neoplasms are prone to metastasis to bone tissue. In a study conducted on the basis of the Volga Scientific Research Medical University of the Ministry of Health of Russia, the results of surgical treatment of 22 patients with tumors of the long bones of the upper extremities were analyzed. After the tumors were removed, all patients underwent simultaneous bone transplantation. To eliminate the defects, individual implants made of bone replacement material using 3D printing technologies were used.

In the postoperative period, all patients noted a decrease in pain and an improvement in the function of the upper extremities. During the entire follow-up period, there were no X-ray confirmed cases of implant displacement. A year after surgery, patients with benign tumors showed the following results: according to the SF-36 questionnaire, the average score was 71.4 ± 6.6, according to the visual analog scale (VAS) - 2.5 ± 1.5 points, and according to the MSTS scale (Society's assessment of Tumors of the Musculoskeletal System) — 65.1 ± 8.3%. In patients with malignant changes, the indices were: SF-36 — 39.2 ± 4.3 points, VAS — 4.8 ± 1.4 points, and MSTS — 41.8 ± 5.2% [3].

The study conducted by Berasi C.C. and co-authors examines the experience of using individual titanium hip cups created using a 3D printer in revision arthroplasty in patients with critical bone loss. The authors analyzed 28 operations performed in 26 patients, among which 4 patients needed repeated revisions. The causes of unsuccessful outcomes were 2 cases of periprosthetic infections, 1 case of loosening of the femoral component of the endoprosthesis and 1 case of fracture of the prosthesis [20].

The individual implants demonstrated good durability, with no signs of migration or weakening over an average follow-up period of 2.5 years. The researchers concluded that the results of using the implants are comparable to the use of anti-intrusive cells and extension cords. In cases of significant damage to the acetabulum accompanied by pelvic dissociation, the use of individual implants may be more effective [12].

The positive results of patient treatment were also noted in a study evaluating the use of individualized guides for positioning during resection, created using 3D printing and prototyping. The authors showed that operative planning using these individual guides and physical modeling of the tibia and femur leads to a statistically significant normalization of the axis of the lower extremities in all patients. Applications of individual guides include cases with a history of inflammatory diseases or deformities, as well as the need for hip or hip replacement. Their use may be preferable when it is necessary to avoid opening the bone marrow canal. This is especially true in the presence of massive bone defects, large osteophytes in the posterior condyles of the femur, or with pronounced restriction of movement in the knee joint [5].

The number of applications of additive technologies, such as 3D printing, is increasing annually in the field of creating individual orthotics and orthopedic insoles. In the study [10], methods for the production of such insoles using 3D printing were developed. The researchers successfully achieved their goals and demonstrated that a statistically significant improvement ($p < 0.05$) was recorded not only according to the AOFAS questionnaire, but also according to the results of biomechanical examinations of patients. In addition, the use of custom-made orthopedic insoles using 3D printing has shown that they help to restore the load on the lower extremities, reduce pain and bring gait closer to the physiological norm, contributing to improving the quality of life of patients [10].

The study by Karyakin N.N. and Gorbatov R.O. [3] presents the results of the development of technologies for creating individualized orthoses for immobilizing joints of the upper extremities using 3D printing. This technology includes measuring the biometric parameters of the corresponding area and determining the necessary force for immobilization, on the basis of which a 3D model of the orthosis is created. The subsequent production process is carried out using an FDM 3D printer. The created orthoses have demonstrated high efficiency in immobilization, providing excellent radiological and clinical treatment results. They have a number of advantages over traditional manufacturing methods: individual adaptation depending on the biometric parameters of the patient and the type of pathology, light weight, fast application, resistance to moisture and heat exchange between the damaged area and the environment [11].

Despite the positive results of the application, the local implementation of additive technologies faces a number of difficulties related to the complexity of the technological processes themselves [1]. First, there is the high cost of 3D printing equipment and supplies, which can be a significant barrier for small medical facilities and laboratories. Secondly, the technology itself requires specific train-

Table 2

Results of 3D printing application in various fields of orthopedic surgery and traumatology

Anatomical area	Applications of 3D printing
The proximal humerus	A 3D model used for planning [64]
Acromion	A 3D model used to adjust the shape of the plate [25]
Collarbone	A 3D model designed for planning and preparing plates [61]
Distal humerus and elbow	Plates for 3D printing, 18 templates and guides, as well as 3D models [61]
Distal radius	Surgical planning of osteotomies using 3D modeling [25]
Arm	Experimental 3D modeling for planning thumb reconstruction, including vascularized bone flaps and navicular plates [64]
The basin	A 3D model used for preparation and planning [61]
Distal femur	A 3D model used for preparation and planning [61]
ACL Reconstruction	An arthroscopic instrument for creating the femoral tunnel of the ACL, adapted to the ethnic characteristics of the patient based on MRI data [25]
Proximal tibia	A 3D model used for preparation and planning [61]
Tibial pylon and ankle	A 3D model used for preparation and planning [61]
The ankle	Personalized navigation template for ankle ligament repair [64]

ing from specialists and the ability to work with digital models and programs that prepare data for the printer. Thirdly, standards and protocols for the use of additive technologies in medicine are still insufficient, which makes it difficult to integrate these technologies into everyday medical practice.

Nevertheless, the experience of using polymer models of the pelvis is actively discussed in the scientific literature on pelvic bone fractures. These models play a key role in preoperative preparation, allowing surgeons to carry out rational planning and preliminary modeling of surgical plates. This makes it possible to reduce risks and improve the results of operations [11].

In turn, the research led by Cai L. and his co-authors demonstrate that the inclusion of 3D models in the preoperative planning process significantly reduces both the radiation load and the duration of the operation. This is especially important when performing minimally invasive vascular osteosynthesis, which is necessary to correct unstable fractures [12].

After analyzing publications on 3D technologies, Krettek C. and Bruns N. also came to the conclusion that the level of evidence of these works is low and contains many methodological shortcomings, such as limited samples of clinical examples and lack of long-term efficacy data [40]. Nevertheless, they emphasize the importance of the research conducted, as additive technologies offer enormous potential for the medical industry, opening up opportunities for personalized medicine and improving the effectiveness of surgical interventions.

Customized tools created by 3D printing. The PSI concept, or tools adapted to each patient, is actively used in scientific publications and research. In the world literature, it is customary to designate this area with a term reflecting an individualized approach to medical procedures. These dual devices are being developed on the basis of data obtained from computer models, which significantly improves the efficiency of their use.

With the use of 3D printing technology, such instruments become an integral part of surgical operations, providing a more rational intervention to increase accuracy. This becomes especially important in the context of oncoortopedic operations, where a high degree of accuracy and adaptability is required.

The term PSI refers to a unified concept encompassing special surgical instruments, including templates and manuals that are widely used in the planning and execution of medical procedures. In some situations, however, it may be necessary to perform radical resection of the tumor, which requires the use of more aggressive surgical methods.

In his study, Buller L. and his colleagues are comparing two control groups of patients. In one group, the installation of the swivel component was carried out using the standard method. In the second group, PSI technologies were used, which provide an individual approach and increase the accuracy of the installation [56]. The results showed that in patients whose treatment included the use of PSI, the average deviation of angles such as anteversion and tilt was significantly smaller, indicating a more optimal displacement of the components. This confirms the effectiveness of PSI not only in hip replacement, but also in more complex operations such as the installation of transpedicular screws in the spine, where precision and individual approach are important.

PSI technologies are actively used for radical resections in the treatment of malignant tumors in the pelvic bones [34]. François Gouin and his team performed pelvic bone tumor removal in 11 patients using PSI [28]. After the operations were completed, a histological examination of the removed tissue was performed. Macroscopic analysis and comparison of postoperative CT images with preoperative CT data made it possible to evaluate the accuracy of performed surgical interventions. The results showed that in all cases, the edges of the resections were classified as R0, which confirms the complete removal of the tumor tissue. At the same time, the average accuracy of resection, determined by comparing X-ray images, was 2.5 mm.

Individual navigation templates for installing transpedicular screws in the cervical spine. In recent years, the number of publications on the use of transpedicular fixation in the cervical spine has increased significantly. This is explained by the fact that from a biomechanical point of view, this technology demonstrates exceptional stability and, in some cases, may be the only effective method of correcting pathologies [45, 28, 37]. In response to the current need, alternative methods have emerged, such as the use of new surgical technologies in spinal neurology. One of such innovative approaches is the development of individual navigation templates created using 3D printing, which allow precise installation of implantable screw structures [23, 55].

There was also interest in this area in the Russian Federation: the first mention of the methodological approach was presented at a conference in 2018, where a clinical case of a patient with C2 vertebral neoplasia was considered [4]. Continuing to study this issue, in 2019, Kovalenko R. A. and his colleagues published a study discussing the use of templates for installing transpedicular screws in the subaxial and upper thoracic spine [6]. They reported that out of 88 installed screws, the accuracy of compliance with Class 1 and 2 was 97%. In addition, implantation safety level 0 was achieved in 79 cases (89.77%), level 1 in 5 cases (5.68%) and level 3 in 2 cases (2.27%).

Earlier, in 2015, Abumi K. and his colleagues demonstrated the successful implementation of this technique by installing 80 transpedicular screws in the subaxial cervical spine using three types of individual 3D navigation matrices for each vertebra. These matrices provided accurate identification of entry points, drilling direction, and navigation when installing screws [26]. Of the 80 installed screws, 78 turned out to have a safety level of 0. It was also noted that the absence of the need for retraction of the paravertebral muscles in the middle part of the cervical region allowed the use of additional instruments for the removal of soft tissues [34].

However, several researchers point out potential errors related to the insufficient accuracy of adapting the navigation pattern to the spine [4]. Especially in the subaxial region, where a significant angle of convergence may require an additional incision to ensure the correct direction of the tool. Sometimes it is also necessary to modify a part of the navigation template in order to successfully install the screws on the opposite side [48].

Thus, innovative approaches in 3D navigation and customized templates significantly improve the accuracy and safety of transpedicular screw implantation in difficult cases. However, further research and technology improvements are needed to minimize possible errors and expand their application in clinical practice.

The use of navigation guidance templates in the field of orthopedics. In recent years, advanced technologies in the field of orthopedics have been developed and actively applied, expanding the capabilities of surgeons in the treatment of spinal diseases. One of these methods is the use of navigation guidance patterns, which significantly improve the accuracy of implant placement. These patterns are especially important in cases such as the correction of scoliosis in children, where the accuracy and safety of the procedure are crucial [4, 2].

An analysis of the use of guiding navigation patterns in the field of orthopedics shows how transspedicular fixation is becoming the main method of surgical stabilization of the spine. In a study conducted by A.V. Kosulin and his colleagues, the use of individual navigation patterns for installing transpedicular screws in children with spinal deformities was studied. The study showed that 3D models were created on the basis of preoperative computed tomography, according to which polylactide (PLA) navigation templates were developed and manufactured on a 3D printer [7]. During the operations, templates were used to accurately position the screws. The results showed that 93.7% of the screws were installed with high accuracy inside the bone, confirming the effectiveness and safety of the method. The use of this method allows not only to improve the stability and effectiveness of surgical interventions, but also to significantly speed up the recovery process of patients. This technology opens up new possibilities for individualizing treatment and optimizing surgical procedures in pediatric orthopedics.

Complementing these findings, the authors Kokushin D.N., Vissarionov S.V., Baindurashvili A.G. and colleagues conducted a study evaluating the use of guiding templates (SHN) for the installation of transpedicular screws (TV) in children with congenital scoliosis. The second version of the monosegmental SHN proved to be the most effective, which ensured the correct installation of 93.7% of the screws. This made it possible to increase the accuracy of the procedure and minimize the risks of malformation, without the occurrence of neurological disorders in the postoperative period. The authors emphasized the importance of taking into account anatomical and morphological features when planning the installation of TV in children [8].

It should be noted that the publication by Kovalenko R.A. and co-authors focused on the use of individual navigation patterns for installing screws in the subaxial cervical and upper thoracic spine. The study determined the risk of implantation, while in 79 cases (89.77%) the screws were installed without deviations (grade 0), in 5 cases (5.68%) there was a slight deviation (grade 1), and in 2 cases (2.27%) serious deviations (grade 3) were detected. The matrix was designed taking into account three points of contact on the arches of the vertebrae and joints, as well as on the spinous process, with the guide tubes fixed with stiffeners. The channel for installing the screw was formed by means of a drill bit or a Kirchner wire, which was guided through the tube. The development and application of such matrices can significantly reduce the risk of implantation errors, which is of key importance for increasing the safety and effectiveness of surgical intervention [6].

Discussion. The use of 3D physical models in medical practice provides a number of advantages over traditional imaging techniques such as CT and MRI, as well as virtual reconstructions. For example, studies by Auricchio and Marconi confirm that three-dimensional printing is actively being implemented in orthopedics and traumatology to improve preoperative planning and modeling of complex anatomical structures [21]. This is consistent with our findings that physical models can reduce errors caused by a limited understanding of volume, viewing angle, and lighting when working with two-dimensional images.

The study by Sheth and colleagues pays special attention to the use of 3D printing as part of preoperative planning for shoulder joint instability [51]. This correlates with our observations that physical models help surgeons more accurately assess anatomical abnormalities, for example, when correcting hip joint deformities and other complex interventions. Other studies, such as the work of Mazzarese and colleagues and Smoczok et al., note the potential of 3D printing in implant modeling and the development of retainers made of absorbent polymers, which proves the possibility of improving surgical correction and adapting instruments to the individual needs of the patient [42, 52]. Finally, the work of Trauner [62], Kang and colleagues [22] emphasize that 3D printing not only changes the approach to surgical intervention planning, but also promotes training and improves the skills of novice surgeons, which is also one of the key conclusions of our study. Overall, a variety of research shows that 3D printing has significant potential to transform orthopedic practice and education.

Thus, in the field of orthopedics and traumatology, 3D printing technology allows surgical procedures to be planned in advance, this possibility can lead to improved intervention results and shorter surgery time. 3D-printed models can be a useful tool for training aspiring surgeons, improving the quality of training and speeding up the learning process.

Conclusion. An analysis of the scientific literature has shown that the use of 3D printing in orthopedic surgery and traumatology opens up new horizons for individualizing treatment and improving the quality of medical care. The technology promotes more accurate preoperative planning, allows you to create models and tools adapted to the patient, which reduces operational risks and improves the results of operations. However, for the successful integration of 3D printing into clinical practice, it is necessary to overcome a number of challenges, including high costs, the need to train specialists and the development of standards. Despite these obstacles, the continued improvement of technologies and the accumulation of experience in their application can significantly improve the effectiveness and personalization of medical interventions, making future medical practices more accurate and safer.

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CAPILLAROSCOPY AS A METHOD OF DIAGNOSTICS OF SYSTEMIC DISEASES IN CHILDREN

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The article presents current data on the possibility of using capillaroscopy as a method of diagnostics of systemic diseases. Capillaroscopy can be widely used in pediatrics due to the following advantages: simplicity, non-invasiveness, relatively low cost, and possibility of repeated examination.

Keywords: capillaroscopy, microcirculation, pediatrics, rheumatology, systemic connective tissue diseases, Raynaud's syndrome, systemic scleroderma, juvenile dermatomyositis.

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Capillaroscopy is a noninvasive method of microcirculation examination based on visualization of capillaries through the skin, which plays a key role in the differential diagnosis of primary and secondary Raynaud's phenomenon, and has been successfully used for diagnosis of diseases such as systemic scleroderma, juvenile dermatomyositis. It can also be used for their staging and activity assessment. Capillaroscopy can also be useful for evaluating the microcirculation in other rheumatic diseases such as systemic lupus erythematosus, antiphospholipid

syndrome, juvenile idiopathic/rheumatoid arthritis, and Sjögren's syndrome.

Current capillaroscopy development began in the 1980s with the introduction of videocapillaroscopy, which allowed digital image analysis. By this time, standardized criteria and protocols for the evaluation of capillaroscopic images in adults have been developed [19, 24, 27, 29, 30]. However, there are still not enough studies devoted to the peculiarities of capillaroscopy in children, although in recent years there have been active works on its standardization for juvenile patients [23, 33].

The capillaroscopy method is informative in systemic diseases. Capillaroscopic signs of microangiopathy include [29]:

– change in capillary density (normal capillary density is 7 mm);
– changes in capillary diameter (in normal capillary diameter, as a rule, does not exceed 20 microns);
– presence of avascular areas – avascular areas are defined in the absence of 2 or more consecutive capillaries;
– microhemorrhages – visualized as small dark spots representing hemosiderin depots;
– neoangiogenesis – new capillary formation (newly formed capillaries can be represented as spiral, branching or bush-like capillaries);
– disorganization of the architectonics of the capillary network of the nail bed;
– changes in capillary distribution and multidirectional orientation of capillary loops. This type of changes is one of the characteristic elements of microcirculatory system damage in systemic connective tissue diseases.

Capillaroscopy is actively used to diagnose systemic diseases such as systemic scleroderma, systemic lupus erythematosus, dermatomyositis and other autoimmune diseases. The method allows to detect early changes in microcirculation, often characteristic for these diseases, which is important for timely diagnosis.

In children, as in adults, the normal capillaroscopic picture of the nail bed is represented by a parallel and regular arrangement of a distal row of capillaries, shaped like an open hairpin or the letter U, with a thinner shoulder representing the arterial branch and a thicker shoulder representing the venous branch, and a density of 7-17 per millimeter, averaging about 9 capillaries per millimeter.

New data on capillaroscopy in healthy children have recently been published. The Bergkamp study found differences in capillary density in children with different skin color: children with darker skin had significantly lower capillary density (up to 5.9 cap/mm) [11].

This important finding for clinicians will help to correctly interpret what is (ub)normal in patients with different ethnic backgrounds.

The main features in children are greater visibility of the subpapillary venous plexus, fewer capillary loops per millimeter, and a higher frequency of atypical capillary loops. These differences should be known and taken into account when evaluating capillaroscopy in children with rheumatic diseases [13].

As for pathologic changes, one of the main ones found in rheumatic diseases is microbleeding, indicating a violation of capillary integrity.

According to an international study, microhemorrhages on capillaroscopy in children were significantly more common in juvenile dermatomyositis (85.3%), systemic sclerosis (84.6%), and systemic lupus erythematosus (80.0%) compared with healthy children (39.2%) [23].

A summary of microcirculatory changes in rheumatologic diseases is presented in Table.

Capillaroscopy is effective in the differential diagnosis of primary (idiopathic) and secondary Raynaud's syndrome. Raynaud's syndrome (RS) represents episodes of transient ischemia due to vasoconstriction of arteries, precapillary arterioles and cutaneous arterio-venous shunts under the influence of cold temperature and emotional stress [2].

Primary Raynaud's syndrome is a benign functional condition and is characterized by a normal capillaroscopy picture. Primary RS reveals a functional disorder in the form of a marked decrease in blood flow velocity. It should be emphasized that the diagnosis of the primary condition cannot be based solely on capillaroscopy. It also requires the absence of inflammatory changes in the blood and normal level of antinuclear antibodies, as well as the absence of any other clinical symptoms.

Russian and foreign literature recommends performing capillaroscopy every 12-24 months in primary RS because 10% of these patients develop connective tissue disease, sometimes decades later [1, 15, 22, 25, 36].

Secondary RS is characterized by changes in the number, size and shape of capillary loops, signs of capillary destruction, reduction of the capillary network [1].

In scleroderma, capillaroscopy reveals changes characteristic of this disease – giant capillaries, microaneurysms, hemorrhages [33, 34]. Systemic scleroderma (SSD) is a diffuse systemic autoimmune disease of connective tissue, which is manifested by microcirculatory vascular lesions and processes of increased fibrosis [4].

Possible changes in microcirculation in various rheumatologic diseases

Disease	Changes visible on capillaroscopy
Primary Raynaud's syndrome	A marked decrease in blood flow velocity
Raynaud's secondary	Changes in the number, size and shape of capillary loops Signs of capillary destruction Capillary network reduction
Systemic scleroderma	Giant capillaries Microaneurysms Hemorrhages
Systemic lupus erythematosus	Increase in capillary loop length Increased tortuosity Well visualized subpapillary plexus Dilated capillaries without avascular areas
Dermatomyositis	Megacapillaries Capillary loss Disorganization of the capillary array Bushy capillaries Winding capillaries Hemorrhages
Sjögren's syndrome	Twisted, irregular capillaries
Antiphospholipid syndrome	Change in capillary diameter Symmetrical microhemorrhages
Juvenile idiopathic arthritis / rheumatoid arthritis	Absence of pronounced structural changes of capillaries Possible presence of single dilated capillaries Moderate increase in capillary network density Preservation of the general architectonics of the capillary pattern

The characteristic feature of SSD is a long progressive course with specific changes in the skin, musculoskeletal system, internal organs (lungs, digestive tract, heart, kidneys) [4, 7].

Systemic scleroderma causes capillary abnormalities that develop in a well-defined sequence called scleroderma pattern, which correlates with internal organ damage.

Three patterns of scleroderma are distinguished: "early", "active" and "late", which reflect the progressive nature of the disease. "Early" pattern is characterized by the presence of giants (homogeneously enlarged capillaries with normal morphology and a diameter of 50 μm or more) and does not show reduced density. "Active" and "late" models always show reduced density (less than 7 capillaries/mm). In the "active" model, capillary loss is combined with giant capillaries, and in the "late" model, capillary loss is combined with abnormal shapes [33, 34].

The three defined patterns are consistent and dynamic as the disease progresses and can be easily recognized by qualitative evaluation of capillaroscopic images (Figure).

There is a Fast Track algorithm [34]: a fast, simple and robust algorithm for distinguishing a "scleroderma pattern" from a "non- scleroderma pattern". This algorithm includes three rules: 1) normal capillary density (greater than 7) and the absence of giant capillaries allows the capillaroscopic pattern to be classified as a "non-scleroderma pattern"; 2) extremely reduced capillary density (less than three capillaries) together with abnormal shapes or the presence of giant capillaries allows the capillaroscopic pattern to be classified as a "scleroderma pattern"; 3) if the imaging results do not meet rule 1 or rule 2, the image is automatically sorted as a "non-scleroderma pattern".

The capillary abnormalities seen in juvenile and adult SSD are similar. Several studies have reported the simultaneous presence of giant capillaries and avascular areas in >60% of children with juvenile SSD (13).

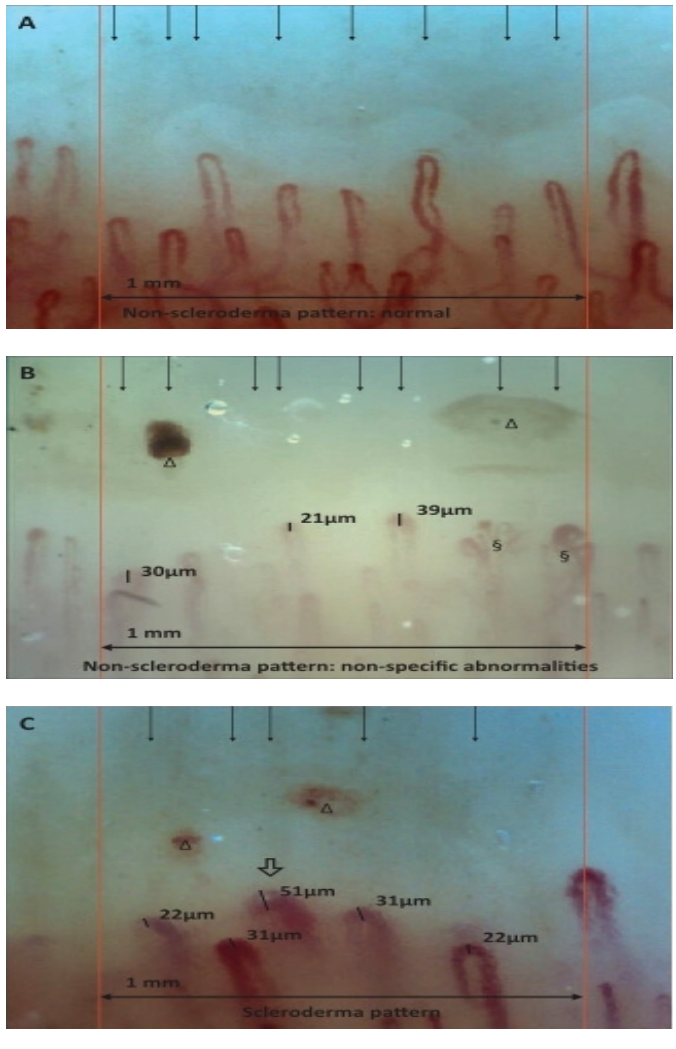
The international multicenter study by Melsens et al. (2023) analyzed differences in capillaroscopic characteristics in different juvenile rheumatic diseases. The authors found out that in juvenile systemic sclerosis there was a significant decrease in capillary density to 5.2 capillaries/mm compared to the values of healthy children (8.5 capillaries/mm), as well as an increase in the number of dilated capillaries (1.8/mm vs. 0.5/mm in healthy children) [23].

Capillaroscopy of the nail bed may be a useful method to evaluate microvascular changes in patients with SLE, but the sensitivity of the capillaroscopic method is lower in patients with SLE than in patients with systemic scleroderma, for whom a reliable algorithm exists to distinguish a "scleroderma pattern" from a "non-scleroderma pattern". Microvascular involvement is an important feature of SLE.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of connective tissue arising on the basis of genetically determined imperfection of immunoregulatory processes characterized by hyperproduction of autoantibodies and their components, and the emergence of immune inflammation, the consequence of which is multi-organ damage [3]. SLE is considered to be one of the urgent medical problems among the pediatric and adolescent population. Due to multi-organ damage, wave-like course, accompanied by many nonspecific manifestations (weight loss, fever, increased general fatigue), the early diagnosis of SLE is still a difficult and urgent task [6, 35].

E.I. Alexeeva et al. determined that this pathology rarely debuts in children under the age of 5 years, the rise in morbidity is noted at the age of 8-9 years, and the peak occurs at the age of 14-25 years (average age of debut 11-12 years) [5].

Cutulo M. et al. described a variaty of capillaroscopic patterns in SLE: nor-



Standardized evaluation of native videocapillaroscopy images according to the international consensus of the EULAR study group on microcirculation in rheumatic diseases: A – example of "normal" stereotypic pattern: 8 capillaries/mm, no dilatations, no giant capillaries, no abnormal shapes, no microhemorrhages, interpretation: normal pattern (non-sclerodermic); B – example of "non-specific" pattern: 8 capillaries/mm, presence of 3 dilatations/mm, no giant capillaries, presence of two abnormal shapes, microhemorrhages present, interpretation: non- specific changes (non-sclerodermic pattern); C – example of "sclerodermic" pattern: 5 capillaries/mm, presence of giant capillaries, no abnormal shapes, microhemorrhages present, interpretation: active sclerodermic pattern [33]

mal pattern (with normal distribution of typical capillaries), nonspecific pattern (including abnormalities that do not meet the definition of scleroderma pattern) and scleroderma pattern (giant capillaries, hemorrhages, avascular areas) [28].

Five studies included in one systematic review attempted to identify a specific pattern of SLE based on the following features: increased capillary loop length, increased tortuosity, well visualized subpapillary plexus, dilated capillaries without avascular areas.

In children, as in adults with SLE, capillary changes predominantly consist of abnormal capillary morphology and hemorrhages (up to 88% of patients with juvenile SLE). Dutch researchers noted that the number of capillary hemorrhages correlates with disease activity (according to SLEDAI) [9, 31].

There are few published studies on capillary abnormalities in juvenile dermatomyositis. Dermatomyositis is an autoimmune disease characterized by lesions of the transverse striated muscles and skin. Dermatomyositis results from a "humoral attack" against muscle capillaries and small arterioles.

Researchers Garra V., Danese N., Rebella M. in their study recorded abnormal capillaroscopy findings in 70% of patients with dermatomyositis [16]. In more than 60%-80% of cases, the pattern is similar to that in systemic scleroderma. Juvenile dermatomyositis (JDM) shows more bush- like capillaries on capillaroscopy compared to juvenile SSD [13].

The diagnosis of dermatomyositis requires at least 2 of the following criteria: megacapillaries, capillary loss, disorganization of the capillary array, bushy capillaries, tortuous capillaries, and hemorrhages [12].

A large cross-sectional study including 58 patients reported capillary changes in patients with JDM with a mean disease duration of 16.8 years, comparing "active" and "inactive" patients. In this study, capillary density in JDM was significantly lower than in healthy controls. Low capillary density (mean 5.9 capillaries/mm) and neovascular (late) pattern, more common in "active" patients with JDM, were associated with disease activity and its cutaneous and muscular manifestations [8].

Both "active" (90%) and "inactive" (78%) patients showed a capillaroscopic picture of scleroderma, with late-onset scleroderma observed in patients with the active form of JDM [8].

According to K. Melsens et al., similar changes to systemic scleroderma were also found in juvenile dermatomyositis, where the capillary density was 6.3 capillaries/mm, and the number of dilated capillaries reached 1.5/mm, with a greater number of abnormal capillary forms (0.9/mm) [23].

Capillaroscopy can be used in Sjögren's syndrome. Sjögren's syndrome is a systemic autoimmune disease of unknown etiology characterized by damage to external secretion glands: primarily lacrimal, salivary, sweat, and sebaceous glands.

Approximately 30% of patients with Sjögren's syndrome (SS) develop Raynaud's syndrome [18]. The study led by Capobianco KG et al. included 40 patients with primary SS (16 with RS, 14 without RS and 10 with anticentromere antibodies), 20 with scleroderma (control group) and 40 healthy subjects. Patients with SS and RS had a higher incidence of microvascular abnormalities than patients without RS. Capillaroscopic signs of scleroderma were found in 80% of patients with anticentromere antibodies [10].

Another study by Spanish scientists involved 136 patients with primary SS. Capillaroscopy was normal in 41%, nonspecific changes were identified in 27%, and a scleroderma pattern in 10% of the subjects. In addition, changes on capillaroscopy were more common in patients with SS and RS - 40% vs. 10% [26].

A study by Lercara A. showed that reduced capillary density is also observed in patients with juvenile SS, and an association between capillary hemorrhages and low levels of the C3 fraction of complement was found. Raynaud's syndrome was observed in only 8% of patients in this cohort, although the sample size was quite small [21].

Capillaroscopy findings in antiphospholipid syndrome (APS) are nonspecific, and a characteristic pattern has not yet been defined [14]. The core of APS is a non-inflammatory vasculopathy. In the study by Alina Dima et al, capillary diameter was significantly smaller in patients with APS than in controls, although no differences in capillary density and blood flow velocity were found. Another study reported the presence of symmetrical microhemorrhages on capillaroscopy analysis, and these changes were particularly significant in patients with both IgG and IgM anticardiolipin antibodies [12].

Schonenberg-Meinema D. et al. describe the following capillaroscopic findings in juvenile idiopathic arthritis (JIA) [32]:

- absence of pronounced structural changes in capillaries;
- possible presence of single dilated capillaries;
- moderate increase in capillary network density;
- preservation of the general architectonics of the capillary pattern.

Juvenile idiopathic arthritis is arthritis of unspecified cause, lasting more than 6 weeks, developing in children under 16 years of age, when other joint pathology is excluded (according to ILAR classification) [20].

These changes may be more noticeable during the active phase of the disease.

It is also worth noting that a "scleroderma-like" pattern is not seen in patients with juvenile arthritis.

Thus, capillaroscopy is a promising and feasible investigation in children because it is a simple, non-invasive, accessible, easy to perform and easily repeatable procedure, and the best method to evaluate microangiopathy [12].

In the future, the development of digital technologies and the introduction of artificial intelligence (AI) will allow the automation of capillary image analysis, which will improve diagnostic accuracy and expand the use of capillaroscopy in clinical practice.

Steps are already being taken in this direction, as reflected in an article describing the use of AI to evaluate capillaroscopy in patients with JDM[17].

Despite several advances in nail bed capillaroscopy, the lack of uniformity in its application remains a problem due to differences in ethnic groups, types of devices used, and parameters evaluated.

Nail lunula capillaroscopy is not always easy to perform in children, and effective cooperation with the patient is mandatory. Pediatric patients may require a longer time to develop trust and more convincing reassurance that the procedure will be painless.

Conclusion. Capillaroscopy is an important diagnostic method, especially in the context of rheumatologic systemic diseases. This type of diagnosis has also found application in pediatric practice. The normal appearance of nail bed capillaries in children is similar to that of healthy adults, but there are a number of differences, such as fewer capillary loops per millimeter, greater visibility of the subpapillary venous plexus, and a greater frequency of isolated hemorrhages and atypical capillaries. These differences should be considered when evaluating the nail bed in children with rheumatologic diseases.

The capillaroscopy method can be widely used in pediatrics due to its ad-

vantages – simplicity, non-invasiveness, relatively low cost, and the possibility of repeated examination. Despite its limitations, this method continues to evolve, offering physicians new opportunities for diagnosing and monitoring diseases. Modern technology will help improve the accuracy and availability of capillaroscopy in the future.

The authors declare that there is no conflict of interest.

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POINT OF VIEW

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PREVALENCE OF PATHOLOGICAL EMOTIONAL STATES AND PSYCHOMETRIC PROPERTIES OF THE DASS 42 QUESTIONNAIRE AMONG THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

The aim of the study was to assess the prevalence of pathological emotional states and psychometric properties of the DASS 42 questionnaire in two groups of the population of the Republic of Sakha (Yakutia): employees of ALROSA diamond mining company in Mirny town and residents of two rural areas. The results of the study showed that women had higher scores on all scales of the DASS 42 questionnaire than men, and a higher frequency of anxiety (40 and 18%, respectively, p <0.001) and signs of stress (28 and 13%, respectively, p = 0.003). No statistically significant dependence of scale scores and the frequency of psychoemotional disorders on age and place of residence was found. The questionnaire showed reliability and construct validity, the absence of cross-cultural differences in the perception of test questions among different groups of the population of the Republic of Sakha (Yakutia). The results of the study of the psychometric characteristics of the DASS-42 questionnaire indicate the possibility of its use as a tool for screening depression, anxiety and stress among the population of Yakutia.

Keywords: depression, anxiety, stress, DASS 42, psychometric properties, Republic of Sakha (Yakutia)

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Introduction. According to the Global Burden of Disease study 2021, anxiety and depressive disorders are common in all age groups worldwide, and their contribution to the overall disease burden is increasing [8]. The underlying burden of these diseases is measured in terms of years lived with disability (YLD) and disability-adjusted life-years (DALY). In terms of YLD, depressive disorders were the second most common and anxiety disorders were the sixth most common among all diseases in 2021. Age-standardized DALYs increased by 16.4% for depressive disorders and 16.7% for anxiety disorders between 2010 and 2021 (GBD, 2021) [7, 8]. The Republic of Sakha (Yakutia) is a region with extreme climatic conditions, where factors such as cold, seasonal decrease in natural light, insufficient level of socio-economic development, and low quality of life contribute to the development of stress, anxiety and depression [2, 11-13]. To develop effective strategies in the field of mental health, it is necessary to assess the situation in different population groups, which requires the use of reliable tools for diagnosing these conditions. In this regard, the aim of the study was to assess the prevalence of depression and anxiety disorders, as well as the psychometric properties of the DASS 42 questionnaire in population groups of the Republic of Sakha (Yakutia).

Materials and methods. The analysis included data from two groups of the population aged 20 and older: employees of ALROSA diamond mining company in Mirny town - 252 people and residents of the rural Churapchinsky and Tattinsky districts of Republic of Sakha (Yakutia) - 114 people, a total of 366 people (267 women and 99 men), examined according to a single protocol. The questionnaire was filled out in paper form. One of the sections of the program was an assessment of the psychoemotional state of respondents using the Depression, Anxiety, and Stress Scale-42 (DASS-42). DASS-42 contains three scales designed to diagnose depression, anxiety, and stress [9, 10]. The analysis also used the Results of the 2020 All-Russian Population Census [1].

Statistical data processing was carried out using IBM SPSS Statistics, v.26 software. Categorical variables are presented as frequencies and percentage distribution in the format n (%), quantitative variables as quartile distribution (Me (Q1-Q3)). Pearson $\chi 2$, Mann-Whitney, Kruskal-Wallis criteria were used to compare groups. Spearman's rank correlation analysis was used to assess the relationship between quantitative or ordinal vari-

ables. Cronbach's alpha was calculated to assess the reliability of the test. Factor analysis was conducted using the principal component method. The critical value of the statistical significance level (p) was taken to be 5%.

Results and discussion. Women and men were comparable in age, the median values and interquartile ranges of age were 47 (41–58.5) years for men and 47 (38.5–61) years for women (p=0.896). Women were statistically significantly more likely to have higher scores on the three scales of the DASS 42 questionnaire (Table 1).

An assessment of the distribution of the value of the total score for each of the 3 scales showed that symptoms of anxiety of varying severity were detected in 34%, signs of depressive disorders in 17%, and stress in 24% of the respondents. The high prevalence of anxiety, depression and stress among residents of northern territories than among residents of other latitudes has been confirmed in other studies [2, 11-13]. This is associated with a complex of factors, such as climatic, biological and socio-economic. For example, lack of sunlight and disruption of circadian rhythms, vitamin D deficiency, limited opportunities for socialization and physical activity, low quality of life, limited access to medical and psychological care, stress due to changes in traditional lifestyles, social transformations, sleep disorders, and others [2, 11-13].

Distribution by gender showed signs of depressive disorders in 18% of women and 14% of men (p = 0.385), anxiety symptoms in 40% of women and 18% of men (p <0.001), stress in 28 and 13%, respectively (p = 0.003). Table 2 shows the distribution of respondents by the severity of the disorders identified. Moreover, no statistically significant differences in the frequency of severe (severe and very severe) disorders were found between men and women. Overall, 43% of women and 21% of men (p <0.001) have signs of either depression or anxiety, with stress symptoms observed in 28% and 13%, respectively (p=0.003).

Numerous studies in different countries and cultures have shown a high frequency of depression indicators among women [4, 8]. This was also noted in the Yakut population by other researchers [3]. The reasons for these differences continue to be studied in the context of the influence of social attitudes, changes in ovarian hormone levels, etc. [4].

The scores of the three scales of the questionnaire showed a weak negative correlation with the age of the respondents (Table 3). Comparison of age

Table 1

Scores and Internal Consistency of the DASS 42 Questionnaire

Indicator	Women	Men	Both sexes	P
Depression				
Me (Q1; Q3)	4 (1–8)	2 (0–6)	4 (1–8)	< 0.001
Cronbach's Alpha	0.88	0.88	0.88	
Anxiety				
Me (Q1; Q3)	6 (3–11)	3 (1–7)	5 (2–10)	< 0.001
Cronbach's Alpha	0.84	0.85	0.85	
Stress				
Me (Q1; Q3)	9 (4–15)	4 (1–11)	8 (3–14)	< 0.001
Cronbach's Alpha	0.92	0.93	0.93	

Note. Data are presented as median (Me) and interquartile range (Q1; Q3). In Tables 1-2: p is the achieved level of statistical significance of differences when comparing men and women.

Table 2

Distribution of respondents by categories of the DASS 42 questionnaire scales depending on gender

Sex	Scores				
	Normal	Midl	Moderate	Severe	Extremely severe
Depression					
Women	219 (82.0)	21 (7.9)	20 (7.5)	6 (2.2)	1 (0.4)
Men	85 (85.9)	9 (9.1)	3 (3.0)	2 (2.0)	0 (0.0)
Both sexes	304 (83.1)	30 (8.2)	23 (6.3)	8 (2.2)	1 (0.3)
p	0.569				
Anxiety					
Women	159 (59.6)	23 (8.6)	54 (20.2)	19 (7.1)	12 (4.5)
Men	81 (81.8)	7 (7.1)	5 (5.1)	6 (6.1)	0 (0.0)
Both sexes	240 (65.6)	30 (8.2)	59 (16.1)	25 (6.8)	12 (3.3)
p	<0.001				
Stress					
Women	192 (71.9)	32 (12.0)	31 (11.6)	9 (3.4)	3 (1.1)
Men	86 (86.9)	9 (9.1)	3 (3.0)	0 (0.0)	1 (1.0)
Both sexes	278 (76.0)	41 (11.2)	34 (9.3)	9 (2.5)	4 (1.1)
p	0.019				

Note: Data are presented as n (%).

Table 3

Correlations between the scales of the DASS 42 questionnaire

Scale		Age	Depression	Anxiety	Stress
Depression	r	-0.14	1	0.77	0.78
	p	0.006		<0.001	<0.001
Anxiety	r	-0.14	0.77	1	0.76
	p	0.009	<0.001		<0.001
Stress	r	-0.19	0.78	0.76	1
	p	<0.001	<0.001	<0.001	

Note: In Table 3-4: r is the value of the Spearman correlation coefficient, p is the significance level of the correlation coefficient.

groups did not reveal statistically significant differences in the scores of the scales and the frequency of pathological emotional states.

A strong positive correlation of 0.76–0.78 was observed between the scores of the scales of the questionnaire.

The psychometric properties of questionnaires include reliability, validity, and sensitivity to change. The format of this study allows us to study reliability in the form of internal consistency and construct validity of the questionnaire. Cronbach's alpha was calculated to check the internal consistency of the test. When including all 42 questions, the Cronbach's alpha value in the group as a whole was 0.95 (0.95 for women, 0.96 for men), indicating a high degree of consistency of the characteristics describing the object. In a similar analysis within each of the 3 scales, Cronbach's alpha was 0.88 for depression, 0.85 for anxiety, and 0.93 for stress (Table 1).

To test the validity of the original subscales, a factor analysis was performed using the principal component method; the Varimax method with Kaiser normalization was used to rotate the factors. The suitability of the original data for factor analysis was determined by the Kaiser-Meyer-Olkin (KMO) test value, which was 0.94. The three-factor solution contained 48% of the total variance, and the four-factor solution accounted for 52%.

To assess the construct validity of the DASS 42 questionnaire, an analysis of the correlations between the questionnaire scale scores and external criteria was performed, which were questions on the frequency of sleep disorders (Table 4). These questions had the following wording:

1. How often over the past 4 weeks have you had problems falling asleep?

2. How often over the past 4 weeks have you had frequent awakenings during the night?

3. How often over the past 4 weeks have you woken up too early in the morning?

Respondents assessed their condition using the following gradations: “Never” - 1; “Sometimes” - 2; “Often” - 3; “Almost always” - 4; “Constantly” - 5.

The choice of sleep disorders for studying the construct validity of the questionnaire was due to the information about the two-way relationship between sleep disorders and depression, anxiety disorders. Just as depression (anxiety) can lead to insomnia, so insomnia can lead to depression and anxiety. 90% of patients with depression and 50% of people with anxiety complain of sleep disorders [5, 6].

Table 4

Correlations between the scores of the DASS 42 questionnaire scales and external criteria

Scale		External criteria		
		Frequency of problems with falling asleep	Frequency of frequent awakenings during the night	Frequency of waking up too early in the morning
Depression	N	365	364	363
	r	0.251	0.194	0.087
	p	<0.001	<0.001	0.100
Anxiety	N	365	364	363
	r	0.285	0.265	0.191
	p	<0.001	<0.001	<0.001
Stress	N	365	364	363
	r	0.221	0.196	0.087
	p	<0.001	<0.001	0.097

Table 5

Agreement rates between the DASS 42 questionnaire scale scores in 2 groups

Scale	Groupe 1: employees of ALROSA, Mirny	Groupe 2: residents of the Churapchinsky and Tattinsky districts
The share of people for whom Russian is their native language according to the 2020 All-Russian Population Census	78.8%	0.27-0.58%
Cronbach's Alpha		
Depression	0.89	0.88
Anxiety	0.84	0.87
Stress	0.93	0.93
All questions of the questionnaire	0.96	0.95

The analysis showed that depression scores positively correlate with the frequency of disorders for questions 1 and 2 (Table 4). Anxiety correlated with the frequency of all three types of sleep disorders. Stress scores showed the same correlation as depression.

In addition to the gender and age aspects, this study assessed the cross-cultural aspect of the Russian-language version of the questionnaire. The group of workers from the Mirny district (group 1) represents the urban population, and residents of the Churapchinsky and Tattinsky districts represent the rural population (group 2). According to the 2020 All-Russian Population Survey, among those who indicated their native language, Russian was indicated as their native language by 78.8% in the Mirny district. In the Tattinsky district, it was 0.58%, and in the Churapchinsky district, it was 0.27% [1]. The analysis did not reveal statistically significant differences in the frequency of depression, anxiety, and stress between the groups ($p > 0.05$). At the same time, it cannot be ruled out that there may be some differences in the perception of the questions related to belonging to different cultures. In this regard, the internal consistency of the questionnaire as a whole, as well as the questions of individual scales, was studied in these groups. The analysis showed that Cronbach's alpha showed high consistency in both groups and showed virtually no differences (Table 5).

Conclusion. Thus, our study of the groups of urban and rural population of the Republic of Sakha (Yakutia) using the DASS-42 questionnaire revealed symptoms of anxiety of varying severity in 34%, signs of depressive disorders - in 17%, stress - in 24% of respondents. At the same time, women were characterized by higher scores on all scales of the

DASS 42 questionnaire than men, and a higher frequency of anxiety (40 and 18%, respectively, p <0.001) and signs of stress (28 and 13%, respectively, p = 0.003). The analysis did not reveal a statistically significant dependence of scale scores and the frequency of psychoemotional disorders on age and place of residence. The identified high frequency of pathological emotional states requires further research. The questionnaire showed reliability and construct validity, the absence of cross-cultural differences in the perception of test questions among different groups of the population of the Republic of Sakha (Yakutia). The results of the study of the psychometric characteristics of the DASS-42 questionnaire indicate the possibility of its use as a tool for screening depression, anxiety and stress among the population of Yakutia.

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The authors declare no conflict of interest.

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FATTY LIVER DISEASE AS A RISK FACTOR FOR HEMOSTASIS DISORDERS IN PATIENTS WITH COVID-19

Purpose of the study: To study the association of GERD with hemostasis disorders in COVID-19.

Methods: A retrospective analysis of the results of 760 autopsies in 2021 was conducted. The studies were conducted at the pathology department of the State Budgetary Healthcare Institution Irkutsk Regional Clinical Hospital of the Order of the Badge of Honor. The analysis of the obtained data was carried out in the Statistica 13 program.

Object of the study: medical documentation - "Act of pathological anatomical autopsy". Results: A retrospective analysis of 760 autopsies of patients with COVID-19 performed in 2021 was carried out. There were 370 men (49%), age 66 [57.0; 74.0]; 390 women (51%), age 68.5 [60.0; 76.0], women were significantly older than men (p = 0.015). Hemostasis disorders were detected in 227 (30%) cases, age 68 [59.0; 76.0]. There were 122 men (54%); women 105 (46%). p=0.015

Conclusions: 1) Hemostasis disorders were detected in 30% of those who died from COVID-19. 2) FLD was more common (19%) in those who died from COVID-19 and had hemostasis disorders than in those who died from COVID-19 without hemostasis disorders (12%) p = 0.019 3) PE was detected in 15% of those who died from COVID-19.

4) The risk of developing hemostasis disorders in those who died from COVID-19 and had FLD is 1.4 times higher than in those who did not have FLD, and the risk of developing PE is 1.7 times higher. The obtained results may indicate an association of GBP with hemostatic disorders in COVID-19

Keywords: fatty liver disease, pulmonary embolism, COVID-19, hemostasis disorder, thrombosis.

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Introduction. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in all countries, with a prevalence of 20-30% and continuing to increase [1]. Considering that it is far from always possible to clearly define the etiological factor in the development of fatty liver disease, and morphologically alcoholic and non-alcoholic fatty liver diseases are indistinguishable, many scientists use the term "fatty liver disease" or steatous liver disease [2].

In 2020, an international expert consensus statement was published proposing a new adaptive concept – MBD: Metabolic (dysfunction) associated fatty liver disease. The proposed interpretation of the disease makes it possible not only to emphasize the systemic and multifactorial pathogenesis of a unified lesion of the hepatic parenchyma (for example, the combination of dysmetabolic and alimentary-toxic), but also to personalize the scope and directions of therapeutic and diagnostic care for various clinical variants of CKD-associated comorbidity [13]. However, the 2024 clinical guidelines use the concept of non-alcoholic fatty liver disease.

The prevalence of CKD increases the interest of scientists in the study of pathology, which is accompanied by an annual increase in the number of publications on this topic. So, only on the pages of the PubMed electronic medical library for the period from 2000 to 2023, there are 38,854 publications on the request of "nonalcoolic fatty liver disease", of which 4,678 were published in 2023.

It has been observed and proven that NAFLD is associated with a lower life expectancy, the main cause of which is mortality from cardiovascular diseases, which has aroused the interest of cardiologists in this pathology [1, 3].

There is a link between CKD and the development of cardiovascular pathology, and one of the most important pathophysiological links is endothelial dysfunction (ED) [4]. It was found that the incidence of ED among patients with steatosis and steatohepatitis reaches 77% and 82%, respectively [5].

One of the basic mechanisms of endothelial dysfunction is a change in the synthesis and release of endothelial nitric oxide (NO), one of the most important regulators of the endothelial-vasal system. The leading cause of NO deficiency is considered to be the destruction or capture of NO by free radicals. The excessive formation of free radicals, which disrupt the endothelium-dependent relaxation of blood vessels and enhance the contractile reactions of smooth muscle, is triggered by the activation of chemical reactions, including lipid peroxidation (POL). At the same time, the formed POL products: malondialdehyde and 4-hydroxynonenal, trigger the formation of collagen, but already in the walls of blood vessels [6].

In the period from 2020 to the present, with the advent of the new COVID-19 coronavirus infection, which was characterized by a pandemic and was accompanied by high mortality, it was noted that a significant proportion of adverse outcomes were due to a catastrophe in the hemostatic system, including cerebral, coronary and mesenteric vascular thrombosis, one of the links in the pathogenesis of which is endothelial dysfunction. Scientific publications around the world report an increase in the incidence of pulmonary embolism (PE) among intensive care patients. In particular, it was shown that in 2020, during the COVID-19 pandemic, the incidence of PE among intensive care patients was 20.6%, which was more than three times higher than the number of similar cases in 2019 - 6.1% [7].

The suspected cause of vascular thrombosis in patients with COVID-19 is direct damage to the endothelium by the virus. The involvement of the intercellular substance in the inflammatory process and the subsequent effect on the subendothelial matrix containing tissue factor (TF) and collagen causes activation of the coagulation cascade along the external pathway. The effect of TF and collagen leads to the formation of thrombin and the conversion of fibrinogen into fibrin, which, together with platelet aggregates, forms blood clots [8].

The above proves that the mechanisms of hemorrhagic and thrombotic complications, including PE, in patients suffering from a new coronavirus infection have not been sufficiently studied and proven, the severity of the problem cannot be underestimated and research in this direction is actively continuing.

However, we were unable to find information on how susceptible hemorrhagic and thrombotic complications are in patients with CKD and COVID-19.

The aim of the study was to study the effect of CBP on hemostasis disorders in COVID-19.

Materials and methods. In order to study the association of fatty liver disease with hemostasis disorders in patients with COVID-19, a retrospective analysis of the results of 760 autopsies performed in 2021 at the Irkutsk Regional Bureau of Forensic Medical Examination was conducted. The concept of NAFLD was used in connection with the impossibility of differential diagnosis of NAFLD and ABP according to liver histology and insufficient anamnestic data.

The object of the study was medical documentation – the "Act of pathoanatomic autopsy", on the basis of which the causes of death, histological data of liver and cardiovascular system damage (vessels and myocardial condition) in people who died from COVID-19 were studied.

Inclusion criteria: the presence in the protocols of data on the morphological examination of the liver and heart muscle, blood vessels, a positive test for COVID-19.

Exclusion criteria: incomplete information about age, cause of death, and age under 17.

Statistical analysis of the obtained data was performed in the Statistica 13 for Windows program. The data in the groups were processed using classical methods for biomedical work using parametric and nonparametric statistical criteria (Student's t-test, Mann-Whitney U-test, Fisher's φ-test, χ2). To calculate the relative risk, a four-field conjugacy table was also constructed based on the number of subjects with certain values of factorial and performance characteristics.

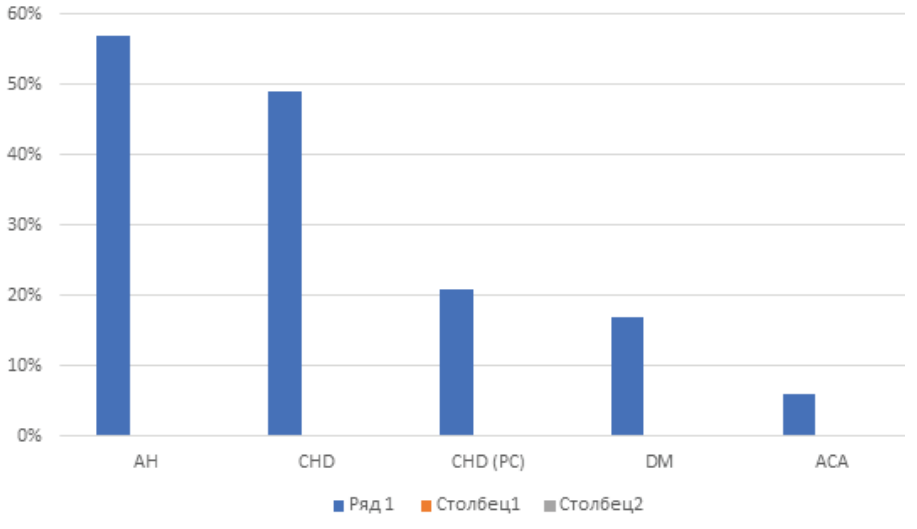
The boundaries of the confidence interval were calculated - 95% CI. The values of relative risk and the boundaries of the confidence interval were compared with unity.

Results. A rating analysis of 760 cases of COVID-19 infection in 2021 has been published. Male 370 (49%), age 66.0 [57.0; 74.0]; female 390 (51%), age of COVID-19 68.5 [60.0; 76.0], women were significantly older than men (p=0.015).

TBP was detected in 106 (14%) cases, men were 59 (57%), 47 (43%) women. Cardiovascular pathology and CKD were detected in 51 (48%) cases, of which hypertension accounted for 29 (57%), CHD – 24 (49%), PIC – 10 (21%), ONCC in 3 cases (6%), type 2 diabetes mellitus - 7 (17%) cases (Figure).

Hemostasis disorders among all those who died from COVID-19 were detected in 227 (30%) cases, age 68.0 [59.0; 76.0]. In men, hemostasis disorders were significantly more common than in women in 122 cases and 105, respectively (p=0.015).

Hemostasis disorders had the following manifestations: mesenteric thrombosis – 12 (2%); deep vein thrombosis of the lower extremities - 28(4%); ischemic stroke – 14 (2%); PE – 100 (13%); DIC syndrome -73 (10%).



Concomitant pathology of cardiovascular diseases and type 2 diabetes mellitus in patients with fatty liver disease and COVID-19

Overweight and obesity among all those who died from COVID-19 (n=760) were detected in 232 (31%) cases, and among those with hemostasis disorders (n=227) in 65 (29%) cases. There were no significant differences in the incidence of obesity among those who died from COVID-19 (depending on the presence or absence of hemorrhagic complications) (p=0.47).

Among those who died from COVID-19 with hemostasis disorders (n=227), CKD was more common in 42 (19%) than among non- of those who had (n=532) 64 (12%). The differences are significant (p=0.019).

To confirm the association of fatty liver changes with the development of hemostasis disorders, the relative risk was calculated (Table 1).

Calculations show that CKD is associated with impaired hemostasis in COVID-19. The risk of developing hemostasis disorders in the group of COVID-19 patients with PD is 1.4 times higher than in the group without PD.

When hemostasis was impaired in people with CKD and COVID-19 (n=106), PE was most common - in 24% (25) of cases, which is significantly more common than in people without CKD - in 14% (106) (p<0.05) (Table 2).

To confirm the association of CKD with PE in patients with COVID-19, the relative risk was calculated (Table 3).

Calculations have shown that RBP is associated with the development of PE in COVID-19. The presence of CKD in people with COVID-19 increases the risk of PE by 1.7 times.

Discussion: Currently, the incidence of CKD is pandemic and has a high prevalence. The liver plays a central role in metabolism and detoxification, as well as in protein synthesis, including coagulation factors. Endothelial dysfunction can affect the blood supply to the liver, exacerbating existing diseases. It is known that changes in liver function are observed in COVID-19, which may be associated with high levels of inflammatory cytokines, cytolytic effects, as well as microcirculation disorders. This can lead to increased levels of transaminases in the blood and more serious conditions such as acute liver damage. In addition, against the background of COVID-19, some patients have disorders in the hemostasis system [15].

There are many factors that can contribute to a hypercoagulable condition in patients with COVID-19. The main one is endothelial dysfunction, since damage to endothelial cells excessively activates platelets and the coagulation system [10].

As a result of our study, 30% (227) of those who died from COVID-19 had hemostasis disorders, which were more common in men (54% (122 cases) than in women (46% (105 cases)). Hemostasis disorders had the following manifestations: mesenteric thrombosis – 12 (2%); deep vein thrombosis of the lower extremities - 28 (4%); ischemic stroke – 14 (2%); PE – 100 (13%); DIC-73 (10%).

The predominance of these hemostasis disorders among men may be explained by lower levels of estrogens, which are known to have a protective effect on the endothelium (through genomic and non-genomic mechanisms) [15].

Accordingly, this contributes to a greater susceptibility to endothelial damage and activation of the calycrein-kinin system. In addition, activation in the hemostasis system predisposes a higher level of testosterone [15].

Previously, the association of endothelial damage with the risk of acute car-

Table 1

Relative risk of developing hemostasis disorders associated with fatty changes in the liver

	Violation of hemostasis	There are no hemostasis disorders
FLD	42(40%)	64(60%)
No FLD	185(28%)	469(72%)
The frequency difference is statistically significant p<0.05		
		ДИ 95%
Relative risk (RR) ± standard error of relative risk (S)	1.4±0.13	1.0-1.8

Table 2

Association of fatty liver disease with conditions associated with hemostasis disorders

	FLD (n=106)	No FLD (n=654)	p
Mesenteric thrombosis	3(3%)	9(1%)	0.26
Deep vein thrombosis	4(4%)	24(4%)	0.95
Ischemic stroke	0(0%)	14(2%)	-
PE	25(24%)	91(14%)	**0.011***
DIC syndrome	13(12%)	60(9%)	0.32

Note: p is the Chi-Square criterion, *- significant differences of p<0.05

Table 3

Relative risk of pulmonary embolism associated with fatty liver disease

	PE	No PE
FLD (n=106)	25 (24)	81 (76)
No FLD (n=653)	91 (14)	562 (86)
The frequency difference is statistically significant p=0.011		
		ДИ 95%
Relative risk (RR) ± standard error of relative risk (S)	1.7±0.2	1.1-2.5

diovascular disasters has been proven, so the relative risk of death from CVD in men with CVD is 1.4 times higher than in women [16], which places the male sex as a risk factor for vascular damage.

We found that acute cardiovascular disasters associated with hemostasis disorders in COVID-19 deaths were 1.4 times more common among people with CKD than without it, 19% (42) and 12% (64), respectively (p = 0.019). And the risk of PE in patients with fatty liver disease is 1.7 times higher.

Based on the results of our study, we concluded that CKD significantly increases the risk of dysfunction in the hemostatic system and, as a result, acute vascular catastrophes such as PE, venous thrombosis and mesenteric thrombosis in patients with COVID-19. This is confirmed by other studies that report both prothrombotic and hypofibrinolytic changes in the blood coagulation system in patients with CKD [15]. The researchers point to an increase in the level of blood coagulation factor (VIII) and an inhibitor of plasminogen activator-1, the most important regulator of the fibrinolytic system, as well as a decrease in the level of natural anticoagulants — proteins S and C. Studies of dynamic coagulation analysis, including thromboelastometry and thrombin generation, have confirmed the theory of prothrombotic imbalance in CKD, as well as the presence of more hemostatically active immature platelets, as evidenced by an increased average platelet volume [11]. These pathogenetic links cause hemostasis disorders in patients with CKD, and when infected with COVID-19, changes in the hemostasis system are aggravated, which causes an increased risk of thrombosis and thromboembolism.

Also, in such studies, the results were presented when COVID-19 infection worsens the course of CKD, manifested by increased activity of liver enzymes (AST, ALT, GGT), the severity of which varies from minor to moderate. It was found that liver dysfunction, determined by changes in the level of liver enzymes and albumin, was detected in 43% of patients with CKD and COVID-19 [12].

From the above, it can be concluded that liver damage can be considered as an independent predictor of higher mortality in patients with COVID-19.

Conclusions: Hemostasis disorders were found in 30% of those who died from COVID-19. CKD was more common (19%) in those who died from COVID-19 and had a hemostasis disorder than in those who died from COVID-19 without a hemostasis disorder (12%) (p = 0.019). Hemostasis disorders were more common in men (54%) than in women (46%) (p=0.015). In 24% of those who died from COVID-19 and had a concomitant disease with TB, the cause of death was PE. The risk of developing hemostasis disorders in those who died from COVID-19 and had CKD is 1.4 times higher than in those who did not have CKD, and the risk of developing PE in this group of patients is 1.7 times higher.

Conclusion: Fatty liver disease is a significant risk factor for hemostasis disorders in patients with COVID-19. Studies show that the presence of CKD is associated with dysregulation of inflammatory processes, which can significantly increase the likelihood of thrombosis.

Patients with CKD have elevated levels of pro-inflammatory cytokines, which can lead to platelet activation and decreased anticoagulant activity. These changes in hemostasis can be aggravated by concomitant diseases such as cardiovascular pathologies, which further increases the risks.

Therefore, it is important to carry out early diagnosis and regular monitoring of hemostasis in patients with CKD infected with COVID-19, as well as to apply individualized treatment approaches in order to minimize the risks of thrombosis and improve clinical outcomes. In the future, it is necessary to continue research in this area, which will allow for a deeper understanding of the mechanisms of interaction between TBD and COVID-19 in the context of hemostasis.

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CLINICAL CASE

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CLINICAL CASE OF RHEUMATIC CHOREA WITH CARDIAC INVOLVEMENT IN A 13-YEAR-OLD CHILD IN THE REPUBLIC OF SAKHA (YAKUTIA)

During the last two decades, the prevalence of acute rheumatic fever has significantly decreased to isolated cases nationwide. In this article, a clinical case of rheumatic chorea, with choreic hyperkinesis syndrome, in a 13-year-old child with cardiac involvement is described. Modern concepts of therapy of rheumatic chorea are presented.

Keywords: chorea, streptococcus, fever, myocarditis, children, Sakha, Yakutia.

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Introduction. Rheumatic chorea (syn. Sydenham's chorea, minor chorea) is a post-streptococcal immune-mediated inflammatory neuropsychiatric movement disorder. The disease has been known since the Middle Ages and was called "St. Vitus' dance" at the beginning of observation. In 1686 Thomas Sydenham described "a kind of convulsion which affects boys and girls from the tenth year of life to puberty". Sydenham's chorea, is a great diagnostic criterion for acute rheumatic fever (ARF). It debuts between 5 and 15 years of age, with a peak at 8-9 years of age [12], girls are more commonly affected [4,5,9].

Rheumatic chorea is an inflammatory postinfectious lesion of the CNS that occurs 4-8 weeks after a streptococcal infection, predominantly pharyngitis. Typically, bilateral involvement is noted, but approximately 20% of patients have hemichorea. The disease is a consequence of an autoimmune reaction following infection with " group A β-hemolytic streptococcus" (GABHS). The phenomenon of molecular mimicry is thought to underlie the pathogenesis of the disease. After frequent macroorganism contacts with GABHS, predisposed individuals develop autoreactive lymphocytes and antibodies directed against epitopes of group A β-hemolytic streptococcus that cross-react with human cells [8]. This cross-reactive immune reaction explains the heterogeneity of the symptoms of ARF, which is usually manifested by skin lesions (subcutaneous nodules, erythema annulare), joint pain, fever, and cardiac involvement (myocarditis, transient atrio-ventricular block, heart valve endocarditis).

The clinical picture is composed of choreic hyperkinesis, muscle hypotonia (up to imitation of paralysis), disorders of statics and coordination, vascular dystonia, emotional lability, and psychiatric disorders. The duration of the attack is 3-6 months, residual phenomena can be observed for a year.

The Jones criteria [3] are used to diagnose acute rheumatic fever (Table 1).

Differential diagnosis. The most difficult cases to diagnose are cases of isolated minor chorea. The circle of differential diagnosis includes PANDAS, obsessive-compulsive syndrome, transient tics, autoimmune encephalitis, systemic autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome), primary angiitis of the central

nervous system, Wilson-Konowalow disease [1].

The methods of treatment can be divided into three main groups: antibiotic therapy, symptomatic therapy and immunomodulatory therapy. Antibiotic therapy and antibiotic prophylaxis is currently the most studied method of treatment. Penicillin antibiotics are most commonly used; in case of penicillin intolerance, macrolides are used. Immunomodulatory therapy is used in severe and refractory cases, as well as in patients with severe side effects from symptomatic therapy [13,14] to shorten the duration of the disease and prevent complications [6,7]. There are different regimens for the use of glucocorticosteroids. For example, Fusco et al, suggested intravenous methylprednisolone for 5 days (25 mg/kg per day) followed by oral therapy with deflazacortin for 3 months (0.9 mg/kg per day) [2]. Paz et al. applied prednisolone (2 mg/kg/day, maximum dose 60 mg/day) [10]. Intravenous immunoglobulin and plasmapheresis are used as second-line therapy [11,12]. Anti-epileptic drugs, tranquilizers, and neuroleptics are used to control hyperkinesis [15] (Fig. 1)).

To provide a clinical case of rheumatic chorea with cardiac involvement in a 13 year old child is described below as a demonstration. The child, 13 years old, of Sakha nationality, was admitted on October 9, 2024 to the Reception and Diagnostic Department of the Pediatric Center of the Pediatric Center of the Republican Hospital No. 1-NCoM named after M.E. Nikolaev with complaints of: involuntary movement of the limbs, which the child cannot control, unable to hold objects (a spoon, a cup), slow response to speech, irritability, staring, speech disorders (speech is unintelligible), rapid fatigue, pain in the heart area, poor sleep, excessive tearfulness. Not only the writing abilities were disturbed in the girl, the child could not sit, stand. In the last 3 days bulbar disorders appeared - water was pouring out of the mouth, she could not swallow, did not eat, almost did not drink.

From the medical history: according to data reported by her mother, the girl has been suffering from frequent purulent sore throats since the age of 2 years, the last one was at the end of August 2024 with outpatient treatment. Since 10.09.2024 arthralgias appeared in the area of the right hand, legs, knee joints. After 4 days, swelling of the wrist joint appeared, in connection with which they applied to the district hospital. On 16.09.2024 she was examined by a neurologist, neurological disorders were excluded, reactive arthritis was diagnosed, nimesulide, pentoxifylline, amoxiclav were prescribed. Despite the therapy, arthralgias persisted, cough was added. From 30.09.2024 to 07.10.2024 with the diagnosis of acute bronchitis the girl received inpatient treatment in the children's department of the district hospital, where periodic uncontrolled, chaotic movements of the upper and lower limbs more on the right side were observed. According to the girl's statements, the compulsive movements occurred by themselves. Antibacterial (ceftriaxone), antiviral therapy, expectorant medications were carried out. The joint syndrome was eliminated. Despite the persistence of severe neurological symptoms and psychoemotional instability, the girl was discharged home.

After discharge from the hospital, the mother noticed that the child's hyperkinesias became more frequent and intensified. Due to the worsening of the condition, the parents applied to the district hospital again. On 08.10.2024, the girl was examined by a district neurologist and re-hospitalized to the children's department of the district hospital with a preliminary diagnosis of minor chorea. The pediatrician consulted the rheumatologist of the cardio-rheumatology department of the PC, who recommended urgent hospitalization in the department. She was urgently delivered by air ambulance to the cardio-rheumatology department of the PC.

Past medical history: Child from the 1st pregnancy, without pathology. Delivery was on time, independent. Birth weight was 3270 g, body length was 52 cm. Past diseases were acute respiratory viral infections, acute respiratory infections, chickenpox. Since 2 years purulent sore throats were up to 5 times a year, in 2024 they were almost monthly. Hereditary factor: mother is 34 years old, healthy, father is 37 years old, healthy. On the father's line: rheumatism in a native aunt. Allergologic anamnesis: food allergy - plum, apple, nectarine - of Quincke's edema type.

On admission: Height of 151 cm, weight of 47 kg, HR of 18 per min, saturation of 98%, HR of 108 beats per min, BP of 99/52 mm Hg. The condition was severe. The well-being was disturbed due to chaotic movements of the limbs, which the child did not control. Consciousness was clear, position in bed: constantly on the move. On examination she responded adequately, calmly. Not speaking, because the language “did not obey”. Appetite was reduced, she was not able to eat. Sleep was restless. In the neurologic status there were choreic storm, bulbar disorders. The physique was normosthenic. The musculoskeletal system was visually unchanged. Skin covers were flesh-colored, moderately moist, clean. Turgor of tissues was preserved. Cyanosis was absent. No edema. The mucous membranes were pink, moist, clean. The conjunctiva of the eyes was pale pink. Tears were present. The pharynx was not hyperemic. Palatine tonsils without plaque, scarred. Subcutaneous fatty tissue was moderately expressed, evenly distributed. Peripheral lymph nodes were not enlarged. Nasal breathing was free, without discharge. Auscultatory respiration was even, vesicular, no wheezing in all fields. Percutaneously the borders of the heart were not changed. Auscultating heart tones were clear, rhythmic, there were no coarse noises. The tongue was clean, moist. The abdomen was not enlarged, soft on palpation, accessible to deep palpation, painless. The liver on the edge of the rib arch. Spleen was not enlarged. The stool was formed. The area of the kidney projection was not externally changed, the symptom of effleurage was negative on both sides. Urination was free, painless. Urine was light-colored, transparent. There were no meningeal signs, focal neurological symptoms.

Neurological status: Consciousness was clear. During examination involuntary movements of eyeballs: rotation, involuntary sprawling movements of arms, legs, twitching of shoulders. Hyperkinesis increased with verticalization. Frequently changing postures. Pupils of rounded shape, equal. Photoreaction was lively. Eye slits were equal. The volume of eyeball movements was full, there was no nystagmus. The face was symmetrical. Tongue tip straight. (-) ROA. Muscle tone in the limbs was diffusely reduced. No paresis. Tendon reflexes from the limbs were alive, D=S. No pathologic or meningeal signs. Sensitivity was not disturbed. In Romberg's test she staggered. Ticotic hyperkinesis was widespread - chorea.

Paraclinically:

In the general blood test there was leukocytosis and acceleration of COE up to 29.00 mm/h. Biochemical blood test from 09.10.2024: hyperproteinemia, hypoalbuminemia, C-Reactive protein - 1.18 mg/l (0.00 - 10.00). Antistreptolysin-O level - 1522.20 IU/mL (0.00 - 200.00) on 30.09.2024 (Table 2).

ECG from 09.10.24: sinus rhythm.

Echocardiography from 10.10.24: AV insufficiency of 1 degree, MV 1-2 degrees, TV 1 degree. Ectopic attachment of MV chords. Heart cavities are not dilated. EF 69%. Splitting of pericardial sheets. Echocardiography dated 28.10.2024: AV

Table 1

The modified Jones criteria for the diagnosis of rheumatic fever

A. Evidence of prior GABHS infection of the pharynx for all patient groups	
Primary ARF	2 major criteria or 1 major plus 2 minor criteria
Recurrent ARF (with a history of verified ARF or existing chronic rheumatic heart disease)	2 major criteria or 1 major plus 2 minor criteria or 3 minor criteria
B. Major criteria	
Low risk populations	*Moderate or high risk populations*
Carditis clinical and/or subclinical	
Arthritis	
Polyarthritis	Monoarthritis or polyarthritis Polyarthralgia
Chorea	
Ring-shaped erythema	
Rheumatic nodules	
C. Minor criteria	
Low-risk populations	*Moderate or high risk populations*
Polyarthralgia	Monoarthralgia
Fever (≥38,5oC)	Fever (≥38,0oC)
Erythrocyte sedimentation rate (ESR) ≥ 60mm/h and/or C-reactive protein ≥ 30 mg/l	ESR ≥ 30 mm/h and/or C-reactive protein ≥ 30 mg/l
Age-adjusted PR interval prolongation on ECG (if carditis is a major criterion)	

insufficiency of 1-2 degree. Regurgitation on PA valve of 1 degree, on TV of 1 degree. Additional trabeculae in the LV cavity. Heart cavities are not dilated. Ejection fraction 71%.

MRI of the brain from 09.10.24: Topographic position of anatomical structures of cranio-vertebral transition is not disturbed. The middle structures of the brain are not displaced. In the frontal and parietal lobes on both sides subcortically, periventricularly there are foci of gliosis up to 3 mm in size. No changes in signal intensity from internal capsules, basal ganglia, thalamus were noted. The corpus callosum is of normal thickness and signal intensity. Brainstem and cerebellum have usual configuration and signal intensity. In diffusion mode at b=1000 no zones of acute ischemia or edema in brain structures were noted. The ventricular system is not dilated. Lateral ventricles are symmetrical. III and IV ventricles along the midline. There is no periventricular edema. Subarachnoidal convexital, cisternal spaces are not dilated. The pituitary gland is of normal size, its contours are smooth, clear, its structure is not changed. Pituitary pedicle along the midline. Chiasma and suprasellar cistern without features. Internal auditory canals are symmetrical, normal width on both sides. No pathologic formations were found in the area of the pontine cerebellar cisterns. Thickening of the mucosa of the maxillary sinuses on both sides, cells of the lattice labyrinth. The structure of orbits is not changed.

The cervical spine and spinal cord were imaged on a series of tomograms. Physiologic lordosis was preserved. The shape and structure of the cervical vertebral bodies were unchanged, and the relationship between the C1 and C2 vertebrae was intact. No pathologic changes in the signal intensity from the bone marrow of the vertebral bodies and paravertebral soft tissues were detected. The signal intensity from the intervertebral discs was not changed. The intervertebral discs did not protrude beyond the dorsal surface of the vertebral bodies. The nerve roots were intact. The spinal cord was located in the center of the spinal canal, had normal thickness and signal intensity. After contrasting the foci of pathologic accumulation of paramagnetic in the substance and in the brain membranes were not revealed. Conclusion: MR signs of residual encephalopathy. MR signs of bilateral maxillary sinusitis, ethmoiditis.

Ultrasound of abdominal cavity organs from 10.10.2024 without pathology.

Electroencephalography with activating tests from 10.10.24g: Bioelectrical activity of the brain is formed according to age. No pathologic, epileptiform activity was revealed.

Holter ECG monitoring from 15.10.24y: Conclusion: during the time of ECG monitoring the main rhythm was registered - sinus rhythm, episodes of supraventricular rhythm driver migration to unstable atrial rhythm mainly in the night hours. Episodes of marked and moderately - marked arrhythmias mainly in the night hours.

On the basis of complaints, anamnesis, clinical data, laboratory and instrumental investigations a clinical diagnosis was made: Main disease: Rheumatic chorea with heart involvement (I02.0): severe chorea. Carditis with mitral, aortic, tricuspidal valve lesions, mitral insufficiency of the 1-2 degree, aortic insufficiency of the 1st degree, tricuspidal insufficiency of the 1st degree. Arthritis. The III degree of activity. Complication: CHF of the 0-1 degree. FC 1. Associated diseases: chronic decompensated tonsillitis (J 35.0). Acute catarrhal sinusitis, acute catarrhal ethmoiditis (recovery) (J 01.8).

The child was examined by an otorhinolaryngologist on 09.10.2024: Acute catarrhal rhinosinusitis. Hypertrophy of the palatine tonsils of 1-2 degree.

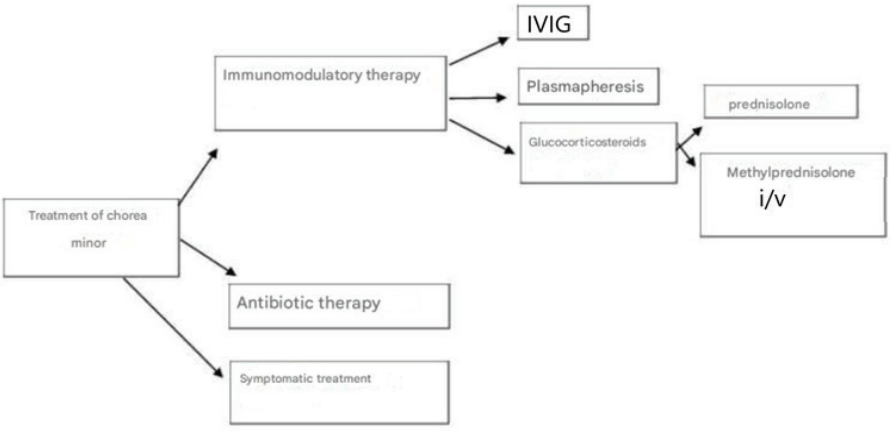

Table 2

Dynamics of laboratory indicators

Laboratory data	09.10.24	14.10.24	21.10.24	28.10.24	05.11.24
Erythrocytes x1012/l	4.92	5.23	5.28	5.09	4.97
Hemoglobin, g/l	120	126	130	127	126
Platelets x109/l	336	323	349	329	344
Leukocytes x109/l	5.85	9.38	12.32	8.38	9.21
COE, mm/hour	29.0	14.0	8.0	16.0	20.0
C-Reactive protein, mg/l	1.18				
Anti-streptolysin O	585.2				

In the dynamics the child was repeatedly consulted by a neurologist.

18.10.24. Consciousness is clear. During examination, involuntary movements of eyeballs: rotating, involuntary movements of hands in distal parts, twitching of shoulders. Pupils of rounded shape, equal. Photoreaction is alive. Eye slits are equal. The volume of eyeball movements is full, there is no nystagmus. The face is symmetrical. Tongue tip straight. (-) reflexes of oral automatism. Muscle tone in the limbs is diffusely reduced. No paresis. Tendon reflexes from the extremities are evoked, D=S. There are no pathologic and meningeal signs. Sensitivity is not disturbed. She is stable in the Romberg test. Finger-to-nose test is performed satisfactorily. Walking around the ward, gait is disturbed, with atactic component.

21.10.2024. In the dynamics of the neurological status during the examination involuntary movements in the hands, grimaces, gait with atactic component.

29.10.2024: Significant improvement in the neurological status, there are practically no involuntary movements. Hypotonia of muscles persists. There is staggering in the Romberg pose. 06.11.2024: according to neurological examination coordinator tests performs satisfactorily. Kernig's symptom is negative. She is stable in the Romberg pose.

The child received antibacterial (Ampicillin-sulbactam 1. 5 g 3 times a day intravenously, followed by prophylaxis with bicillin-5, immunosuppressive therapy with glucocorticosteroids (methylprednisolone 10 mg/kg per injection 500 mg #3, then per oral - prednisolone 1 mg/kg/day), carbamazepine (Finlepsin) 100mg*2 (5 mg/kg) in hospital with positive dynamics.

Walking well on discharge. Consciousness is clear. During examination, exophthalmos is not noticeable. No hyperkinesis. Pupils are rounded, equal. Photoreaction is lively. Eye slits are equal. The volume of eyeball movements is full, nystagmus is preserved. The face is symmetrical. Tongue tip slightly to the right Muscle tone in the limbs is reduced diffusely. No paresis. Tendon reflexes from the limbs are alive, D=S. No pathologic and meningeal signs. Sensitivity is not disturbed. Performance of coordinator tests, but with errors.

She was discharged with improvement under the supervision of a pediatrician, neurologist. Recommended: to continue therapy with carbamazepine, prednisolone, aspirin, bicillin. Re-hospitalization in 3 months.

Conclusion: rheumatic chorea is currently a very rare condition with which pediatric practitioners are not well acquainted. Rheumatic chorea is a neurologic disease that can cause involuntary movements in children and rarely in adults. The presence of cardiovascular involvement allows the diagnosis of rheumatic chorea and ARF, but cardiac involvement in the first few months of the disease may be nonmanifest and manifest only as instrumental findings. It is necessary to include cardiologic examination and search for streptococcal infection in all patients with hyperkinetic syndromes. Rational antibiotic therapy for infection caused by GABHS may reduce the likelihood of developing ARF.

The authors declare no conflict of interest.

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SHORT BOWEL SYNDROM IN CHILDREN

Short bowel syndrome (SBS) is a symptom complex caused by the absence of most of the small intestine with the development of mal digestion and malabsorption. The aim of the study is to describe our own clinical case of a child with SBS who achieved enteral autonomy without the use of a synthetic analogue of glucagon-like peptide-2.The presented clinical case shows that as a result of timely initiation of treatment, it was possible to stabilize the boy's condition and transfer him to enteral feeding without the use of a synthetic analogue of glucagon-like peptide-2.

Keywords: short bowel syndrome; parenteral nutrition; children; teduglutide.

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Introduction. Short bowel syndrome (SBS) is a symptom complex caused by the absence of most of the small intestine with the development of mal digestion and malabsorption [8]. In the Russian Federation, a registry of children with SBS has been created; in 2020, it included 220 patients [5].

The aim of the study is to describe our own clinical case of a child with SBS who achieved enteral autonomy without the use of a synthetic analogue of glucagon-like peptide-2.

Pathological physiology. The most common causes of SBS in children are congenital and perinatal diseases: necrotizing enteral colitis (NEC), middle gut incorrect rotation, gastroschisis and intestinal atresia, cytomegalovirus infection [16]. NEC is the basis for almost 30% of all cases of SBS. In most cases, patients are forced to be on parenteral nutrition (PN), which leads to various complications from various organs and systems [14]. After bowel resection, the body responds with a process called intestinal adaptation, which consists of adaptive changes in the preserved portion of the intestine; in children, this process begins soon after bowel loss and continues for several years [6, 15]. The first period is characterized by diarrhea with massive loss of fluid and electrolytes, which requires parenteral administration of these substances [8]. Later, epithelial hyperplasia occurs [17]. Patients with colon resection are at significant risk of dehydration [10]. Most sodium and water are absorbed through the colon, but nutrients with fermented carbohydrates are also absorbed. Patients with SBS can receive up to 50% of their nutritional needs through the colon [2, 9].

Clinic. The clinic is manifested by a violation of physical, psychic development, water-electrolyte and acid-base balance due to insufficient intake of micro- and macronutrients. The main signs of SBS include the following: diarrhea, abdominal pain, bloating, weight loss, dehydration, steatorrhea, edema, weakness, drowsiness, anemia, vitamin deficiency.

Treatment and prognosis. After the stage of surgical interventions, children are transferred to PN, first in the hospital, then at home. Survival after extensive bowel resections after 3 years is 87-89%, but most patients are forced to receive PN. The further principle of treatment is to achieve complete independence from PN. For this purpose, the use of a synthetic analogue of glucagon-like peptide-2 (GLP-2) is recommended [13]. GLP-2 is an intestinal growth factor produced by L-cells of the ileum and distal colon [10]. A synthetic analogue of GLP-2, teduglutide (T) increases the size of villi and the depth of crypts in the intestinal epithelium. In 2021, T was officially registered in our country and approved for use in children with SBS over 1-year-old [3]. It has been established that T allows to reduce PN, infusion time and even achieve a complete transition to enteral autonomy [7]. The ileum is more capable of increasing the surface area of the villi, the height of the villi and the depth of the crypts, as well as developing processes of increasing the length, diameter and motor function [11]. This part of the intestine, compared to the jejunum, specializes in the absorption of vitamin B12, bile acids, fluid and is able to effectively increase its absorption capacity [4].

Clinical case. Boy R., born on November 24, 2021 from the 3rd pregnancy, 2 births. The pregnancy proceeded against the background of chronic viral hepatitis C, chronic cervicitis, mild iron deficiency anemia, at 31 weeks' mild acute respiratory viral infection. Surgical delivery at a gestational age of 40 weeks. The reasons for the cesarean section were premature detachment of a normally located placenta of a severe degree without signs of external bleeding and acute fetal distress.

Physical development at birth: weight 2850 grams, length 50 cm, chest circumference 33 cm, head 34 cm. Apgar score: 1-3 points. The condition is severe due to respiratory disorders against the background of asphyxia, since birth he was on intravenous pulmonary bypass. In the neurological status, the syndrome of central nervous system depression, responded to the examination with tonic convulsions.

On the 3rd day of life, the dynamics are negative due to the abdominal syndrome (intestinal paresis of 2-3 degrees, gastric bleeding), hemodynamic disorders, and increasing respiratory failure. According to radiography, the presence of free air in the abdominal and pleural cavities were detected. A diagnosis of NEC stage 3B, peritonitis was made. After preoperative preparation, an operation was performed - drainage of the abdominal cavity in both iliac regions. The condition in the postoperative period was extremely severe.

After relative stabilization, a repeat operation was performed: laparotomy, revision of the intestine, stomach, total resection of the jejunum, subtotal resection of the colon, duodenal-ileum anastomosis "end to end", end ileostomy, sanitation, drainage of the abdominal cavity. During

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the operation, transfusion of filtered red blood cells (FRBC) was performed. In the postoperative period, the condition remained extremely severe for a long time, unstable, massive intensive therapy was carried out, the child suffered severe multiple organ failure. On the 12th day, enteral loading with water was started, from the 14th day - with the formula "Nutrilon pepti gastro" with a gradual expansion of the volume. At the age of 1 month 20 days, for further treatment, nursing of the child in the postoperative period, he was admitted to the early childhood department. The condition upon admission was severe due to intoxication, severe malabsorption syndrome, gross neurological symptoms, anemia, metabolic and trophic disorders. For a long time, the child's condition remained unstable, severe, the loss of intestinal contents through the stoma progressed. The dynamics showed an increase in intoxication, a sharp increase in acute phase proteins, an increase in leukocytosis in the blood, a decrease in the hemoglobin level to severe anemia, which required a FRBC transfusion, continuous infusion therapy for the purpose of partial PN. Against the background of intensive therapy, it was possible to expand nutrition to 2/3 of the volume of the physiological need, relieve the intoxication syndrome; positive dynamics were achieved in weight, a tendency towards an increase in the hemoglobin level was noted.

Considering the relative stabilization of the condition, the child was prepared for reconstructive surgical correction of the stoma. After preoperative preparation, on 03/10/2022, a reconstructive operation was performed: laparotomy, intestinal lysis, reconstructive resection of the ileum, hardware ileum connection "side to side". In the postoperative period, he was in the anesthesiology and intensive care department, received PP, pain relief, antibacterial therapy, and a FRBC transfusion was performed due to severe anemia. After relative stabilization of the condition, on March 17, 2022, he was again transferred to the early childhood department for further treatment and care. The condition in the postoperative period remained severe for a long time. The volume of nutrition was gradually expanded to the physiological need, which the child began to assimilate, positive weight dynamics were outlined. Cholestasis syndrome persisted for a long time, and was relieved by taking liver protectors during treatment. Neurological symptoms in the form of movement disorder syndrome persist. Therapy and nutrition were constantly corrected, the condition gradually stabilized. The child did not receive T, since in the Russian Federation the drug was registered only in the year of the patient's birth and was approved for use after 1 year, and he had not yet reached this age. The parents refused to raise the boy, and he was transferred to the Orphanage. Upon reaching the age of 1 year, from which the use of T is permitted, it was decided to abandon the use of the drug, since the child had already achieved enteral autonomy without it.

Currently, the patient is 3 years old. He is on complete enteral nutrition, gradually expanding his diet. Medications constantly receive enzymes, amino acid formula, iron preparations. Moderate delay in physical and psychic development persists. He continues to be raised in the Orphanage.

Conclusion. A distinctive feature of this case is that as a result of timely initiation of treatment, it was possible to stabilize the boy's condition, transfer to enteral feeding without the use of a synthetic analogue of glucagon-like peptide-2.

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CLINICAL CASE: FETO-FETAL TRANSFUSION SYNDROME IN A NEWBORN

This article presents a clinical case of feto-fetal transfusion syndrome (FFTS) in a newborn.

Feto-fetal transfusion syndrome (FFTS) is a severe complication of monochorionic multiple pregnancies that requires timely and accurate diagnosis, followed by fetoscopic laser coagulation of anastomoses to preserve the pregnancy. The presented clinical case of FFTS in a newborn highlights the importance of neonatologists and intensive care specialists being aware of the clinical features, diagnosis, and treatment of this condition. The development of FFTS in this case was due to a shared placenta, which likely led to the formation of transplacental vascular communications and circulatory imbalance between the placental vascular systems of the twin fetuses.

Keywords: Feto-fetal transfusion syndrome, newborn, donor, recipient, prematurity, twins, anemia-polycythemia syndrome.

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Introduction. Feto-fetal transfusion syndrome, or Twin-to-Twin Transfusion Syndrome (TTTS), is a severe complication of monochorionic multiple pregnancies associated with transplacental vascular communications and circulatory imbalance between the placental vascular systems of the twin fetuses [2].

All twin pregnancies should be considered at risk for FFTS until the type of placentation is determined [4]. The primary diagnostic method is fetal ultrasound. In the first trimester, signs indicating a high risk of developing this syndrome include discordance in nuchal translucency thickness, abnormal blood flow in the ductus venosus, and a size difference between the fetuses of more than 25% [2, 7].

In the presence of significant vascular anomalies in the placenta, hemodynamic relationships develop between the donor and recipient fetuses, leading to a disproportion in circulating blood volumes (CBV). Due to unbalanced transfusion, the donor fetus develops hypovolemia and anemia, along with growth restriction. A critical reduction in CBV is accompanied by progressive oliguria and anuria, severe oligohydramnios, which impedes normal lung maturation, and a high likelihood of antenatal fetal death. In the recipient fetus, the disproportionate circulation leads to a sharp increase in CBV, resulting in polycythemia and hypertrophic cardiomegaly. Hemodynamic decompensation leads to congestive heart failure. Increased renal blood flow and urine production lead to polyhydramnios, which increases the risk of premature rupture of membranes and preterm labor [2].

Although anastomoses and, consequently, blood shunting between fetuses occur in all monochorionic twins, FFTS typically develops only in diamniotic monochorionic twins. This is likely because monochorionic pregnancies have more bidirectional superficial anastomoses than diamniotic ones [3].

With expectant management, perinatal mortality in FFTS reaches 95% [1, 5, 6]. Treatment options for FFTS include fetoscopic laser coagulation of placental anastomoses, amnioreduction, selective reduction of one twin, or termination of pregnancy. Factors influencing the choice of treatment include gestational age, cervical length, and technical limitations for fetoscopy (placental location, cord insertion sites, and maternal anatomy).

Objective: To describe a clinical case of feto-fetal transfusion syndrome in a newborn.

Materials and methods: A retrospective analysis of the medical records of a patient in the neonatal intensive care unit (NICU) of the perinatal center of RBN№1-NCM was conducted.

Clinical case. A newborn boy from the 5th pregnancy and 4th delivery. In the first half of the pregnancy, the mother had a mild case of COVID-19 at 16 weeks without fever. She was treated on an outpatient basis with antiviral medications (Grippferon, Arpeflu).

At a routine ultrasound at 14.5 weeks, FFTS was suspected, and the mother was sent home with recommendations for weekly follow-up ultrasounds with fetometry.

At 18-19 weeks, she was hospitalized at the Central District Hospital. Ultrasound revealed a threatened miscarriage with a shortened cervix (<25 mm), abnormal blood flow in the uterine arteries, monochorionic diamniotic twins, and placental insufficiency: Doppler showed reversed diastolic flow. Oligohydramnios in the first fetus (amniotic fluid index <5 cm). Intrauterine growth restriction (IUGR) in the first fetus below the 10th percentile. The woman was referred to the Medical Genetic Center of GAU RS(Y) Republican Hospital №1, but she did not attend the consultation.

A telemedicine consultation was conducted with the National Medical Research Center for Obstetrics, Gynecology, and Perinatology named after Academician V.I. Kulakov. The recommendation was to monitor Doppler and maximum vertical pocket weekly until 27 weeks, with fetometry every 2

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weeks. No intervention was indicated at this stage.

At 23 weeks, ultrasound revealed: monochorionic diamniotic twins. IUGR in the first fetus below the 10th percentile. Placental insufficiency grade 1A. Marginal cord insertion in the first fetus. Pyelectasis in both fetuses. A tendency toward polyhydramnios in the second fetus. The woman was advised to have weekly ultrasounds, but she refused due to difficulty traveling from the district, citing icy conditions. She agreed to ultrasounds every 2 weeks.

At 31 weeks, a routine ultrasound revealed: monochorionic diamniotic twins at 31.2 weeks. Both fetuses in cephalic presentation. Placental insufficiency grade 2. Antenatal death of the first fetus. Tachycardia in the second fetus. Pericardial effusion in the second fetus. The woman was urgently referred to GAU RS(Y) Republican Hospital №1 for emergency delivery.

Histology of the placenta showed no inflammatory infiltration in the membranes or cords, trophoblastic dysfunction, and reduced vascularization. Vascular anastomoses were present.

Emergency delivery was performed at 31.2 weeks. The first twin, a boy, was delivered at 15:11, stillborn, weighing 1300g, length 41cm. On examination, the skin was burgundy-colored, with tight cord entanglement around the body. Autopsy findings: the cause of antenatal death of the first twin at 31.2 weeks was intrauterine hypoxia due to placental transfusion syndrome. Pathology of the fetus: first twin of monochorionic diamniotic twins. Tight cord entanglement around the body. Placental pathology: monochorionic diamniotic placenta. Trophoblastic dysfunction, reduced vascularization. Vascular anastomoses. Chronic placental insufficiency, mixed type. Edema of Wharton's jelly in the second cord.

The second twin, a boy, was born at 15:12, alive, premature, weighing 1540g, length 41cm, Apgar score 4/7. Condition was very severe at birth. He was admitted to the NICU from the operating room on nasal CPAP, accompanied by the NICU team in a transport incubator, with a preliminary diagnosis of respiratory distress syndrome (RDS) grade II, FFTS, donor? Prematurity 31.2 weeks. Congenital anemia at birth. Respiratory failure grade II. On admission, the infant was placed in a heated incubator and connected to an "IF" ventilator in "Biphasic" mode.

The infant's condition was severe due to severe RDS, FFTS (anemia-polycythemia syndrome), cardiovascular failure grade II A-B, respiratory failure grade III, severe congenital anemia, prematurity at 31 weeks, and very low birth weight.

Consciousness was moderately depressed. Pain score on N-PASS: 3. Anterior fontanelle was not tense. No seizures were observed. Neonatal reflexes were depressed. Muscle tone was reduced. Visible mucous membranes were pale pink, clean, and moist. Skin was pale pink, clean, and moderately moist. Warm to touch. Extremities were warm. Generalized edema was present. Breathing was assisted by mechanical ventilation; auscultation revealed uniform air-oxygen flow noise throughout all lung fields, with transmitted rales. Respiratory rate: 59/min. Silverman score: 3. Hemodynamics were relatively stable. Heart sounds were muffled and rhythmic. Heart rate: 114-118/min, with a tendency toward bradycardia. Microcirculation was not impaired. On total parenteral nutrition. Abdomen was soft, not distended, and accessible to palpation. Bowel sounds were present. Liver and spleen were not enlarged. No stool on admission. Urination was free into the diaper, with a diuresis of 13.4 ml/kg/h, indicating polyuria.

Echocardiography on day 0 revealed: congenital heart defect. Patent ductus arteriosus (0.29 cm), atrial septal defect (0.16 cm). Cardiac chambers were not dilated. Left ventricular contractility was normal. Ejection fraction: 86%. Abdominal ultrasound: a thin strip of free fluid near the spleen. Chest and abdominal X-ray: hypoventilation of the left lung.

On the first day of life, the infant's condition worsened due to respiratory failure, with a Silverman score of 5, increasing oxygen requirements, and tachypnea up to 90/min. The infant was switched to high-frequency oscillatory ventilation (HFOV) on a Leoni+ ventilator. HFOV parameters were adjusted: amplitude was reduced by 10%. A recruitment maneuver was performed. After 10 hours, due to the ineffectiveness of the recruitment maneuver and the infant's condition (hypotension, tachycardia), the infant was switched to S-IMV mode on the Leoni+ ventilator. Echocardiography revealed: congenital heart defect. Muscular ventricular septal defect (0.12 cm). Atrial septal aneurysm with shunt (0.36 cm). Patent ductus arteriosus (0.22-0.28 cm). Signs of pulmonary hypertension grade 1-2. Right ventricular hypertrophy. Mitral and tricuspid valve regurgitation grade 1. Mild dilation of the right ventricle, right atrium, and pulmonary artery. Ejection fraction: 75.4%. Neurosonography showed moderate periventricular hypoechogenicity.

Laboratory tests revealed: severe anemia with hemoglobin of 94 g/L. Blood transfusion with individual matching was indicated. Biochemical blood tests showed elevated liver enzymes and hyperbilirubinemia.

On the second day, heart rate increased to 200-215/min, and blood pressure reached 92/74/55 mmHg. Echocardiography showed: patent ductus arteriosus 0.18-0.21 cm. Left atrium: 1.2 cm, not dilated. Right ventricle: 0.92 cm, mildly dilated. Right ventricular anterior wall thickness: 0.34 cm. Mild right atrial hypertrophy: 1.4 cm, not dilated (Kushner). Estimated systolic pressure in the right ventricle: 40-42 mmHg. Pericardium: separation of pericardial layers up to 0.28 cm near the left ventricular apex, up to 0.27 cm near the right ventricular anterior wall, and up to 0.25 cm. Left ventricle (end-diastolic dimension 1.54 cm, end-systolic dimension 0.9 cm) was not dilated. Interventricular septal motion was normal. End-diastolic volume: 6.5 ml, end-systolic volume: 1.6 ml. Ejection fraction: 75.3%, fractional shortening: 40.2%.

Chest and abdominal X-ray: hypoventilation of the left lung. Uneven pneumatization of the intestines. Congenital heart defect. Cardiac shadow enlargement. Elevated high-sensitivity troponin: 74,200 ng/L.

On the third day, abdominal ultrasound revealed pyelectasis. After blood transfusion, red blood cell parameters improved, with hemoglobin of 121 g/L.

A telemedicine consultation was conducted with the National Medical Research Center for Obstetrics, Gynecology, and Perinatology named after Academician V.I. Kulakov. Recommendations included continuing the protective treatment regimen, respiratory therapy with monitoring of acid-base status and blood gases, analgesia, and antibiotic therapy with monitoring of inflammatory markers at 48-72 hours of life to confirm the diagnosis and decide whether to continue or stop antibiotics. Massive vasopressor and inotropic therapy was continued with blood pressure and echocardiography monitoring, considering pulmonary hypertension in the infant with FFTS. Therapy was adjusted with levosimendan 0.1-0.2 mcg/kg/min, dobutamine was gradually discontinued, and dopamine dose was reduced to 5-7 mcg/kg/min.

On the fifth day, blood pressure normalized, and heart rate decreased to moderate tachycardia of 180/min. Neurosonography revealed subependymal cysts in the left thalamo-caudal notch in the cyst formation stage. Periventricular hyperechogenicity.

On the sixth day, the infant was conscious, actively resisting the ventilator, and agitated. Inotropic therapy was discontinued, and the infant was extubated and switched to nasal CPAP on an IF ventilator in Biphasic mode. Red blood cell parameters normalized, with hemoglobin of 151 g/L, and high-sensitivity troponin decreased to 38,700 ng/L.

Echocardiography on day 9 showed: regurgitation grade 1. Left ventricle: not dilated. Atrial septum: 0.33 cm, hypertrophy, end-diastolic dimension 1.2 cm, posterior wall thickness 0.28 cm, end-systolic dimension 0.7 cm, ejection fraction 78%, fractional shortening 43%. Anterior wall thickness: 0.28 cm, mild hypertrophy. Tricuspid valve: thin leaflets. Minimal regurgitation. Estimated systolic pressure in the right ventricle: 20.0 mmHg.

On day 10, abdominal ultrasound showed improvement: parenchymal organs were normal, with mild meteorism.

On day 11, the infant was weaned off mechanical ventilation. Blood pressure and heart rate were within normal limits. On day 12, after stabilization, the infant was transferred to a specialized department for further care and treatment.

The infant received infusion therapy, respiratory support, and antibiotics (ampicillin-sulbactam). Central nervous system stimulation and apnea prevention were provided with caffeine citrate. Neurometabolic therapy included Cytoflavin. Inotropic therapy included levosimendan, dopamine, and dobutamine. Sedation and analgesia were provided with fentanyl and midazolam. Volume expander therapy included 0.9% sodium chloride solution.

Final diagnosis: Feto-fetal transfusion syndrome (anemia-polycythemia syndrome, edematous syndrome, severe congenital anemia (corrected), risk of cardiomyopathy). Respiratory distress syndrome: mild. Other cases of prematurity: Prematurity at 31 weeks. Second twin (monochorionic diamniotic twins). Complication: Respiratory failure grade 1. Associated conditions: Other cardiovascular disorders arising in the perinatal period: Congenital heart defect. Muscular ventricular septal defect 0.12 cm. Atrial septal aneurysm with shunt 0.36 cm. Intraventricular (non-traumatic) hemorrhage grade 1: subependymal cysts in the left thalamo-caudal notch in the cyst formation stage.

Conclusion. Feto-fetal transfusion syndrome (FFTS) is one of the most complex complications of monochorionic multiple pregnancies. A common complication in women with multiple pregnancies and antenatal death of one fetus is placental insufficiency, which inevitably leads to intrauterine growth restriction. In FFTS, significant vascular anomalies in the placenta lead to hemodynamic relationships between the donor and recipient fetuses, with a disproportion in circulating blood volumes.

According to studies by Logutova L.S. and Shilkina P.S., timely diagnosis and fetoscopic laser coagulation of anastomoses are the primary methods for preventing severe outcomes [2]. However, as noted by Mikhailov A.V. and colleagues, despite the presence of vascular anastomoses in all monochorionic twins, clinically significant FFTS does not always develop, which is related to the characteristics of blood circulation between the fetuses. Additional studies show that without treatment, mortality in FFTS can reach 95% [3]. Perinatal outcomes significantly improve with early detection and timely correction, such as fetoscopic laser coagulation of anastomoses, amnioreduction, or selective reduction of one fetus [3].

In this clinical case, FFTS was suspected at 14.5 weeks of pregnancy. The first twin was the recipient and died antenatally. The second twin was the donor. Clinical signs of FFTS appeared from the first day of life, including hypovolemia (elevated blood pressure on admission, tendency toward bradycardia), severe anemia, and cardiovascular abnormalities (tachycardia, hypertension, tachypnea).

Severe complications and fatal outcomes can be avoided with early diagnosis, optimal pregnancy management, and minimally invasive intrafetal correction methods such as laser coagulation of placental anastomoses, which can preserve the pregnancy, the lives of the mother and both fetuses, and reduce perinatal mortality. Management of such patients requires careful monitoring and control of fetal blood flow parameters, as recommended in modern clinical guidelines [1].

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