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ORIGINAL RESEARCH

V.M. Nikolaev, N.M. Krasnova, A.S. Asekritova,O.V. Tatarinova, I.V. Bure, D.A. Sychev

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ANALYSIS OF THE EXPRESSION LEVEL OF CIRCULATING MICRORNAS IN THE BLOOD OF PATIENTS WITH ALZHEIMER'S DISEASE

Over the past few decades, there has been a steady decline in fertility worldwide, while life expectancy has been increasing. This is leading to an ageing population. In today's aging world, cognitive disorders and dementia in the elderly are key problems. Thus studying the regulation of the molecular mechanisms of age-related cognitive impairment is an urgent task. Fourteen elderly and senile individuals with Alzheimer's disease participated in this study. The expression of circulating microRNAs at all stages was determined using kits from Qiagen (Germany).

A study was conducted to determine the expression level of circulating microRNAs: hsa-mir-483, hsa-miR-132, hsa-mir-29c, hsa-mir-193b in the blood serum of elderly and senile people suffering from Alzheimer's disease.

The data obtained by us indicates that in patients suffering from Alzheimer's disease, the levels of these micro-RNAs depended on age and the degree of cognitive impairment. Circulating mir-132-5p microRNA was detected in the blood serum of senile people suffering from moderate dementia, in contrast to elderly people with mild degree of dementia.

Keywords: Alzheimer's disease, cognitive impairment, circulating microRNAs, β-amyloid, tau protein.

Introduction. Over the past few decades, there has been a steady decline in fertility worldwide, while life expectancy has been increasing. This leads to an aging population, which is becoming a global phenomenon and perhaps one of the most significant social changes of the 21st century. In today's aging world, cognitive disorders and dementia in the elderly are key issues.

In Russia, the population of patients with Alzheimer's disease is 1 million 248 thousand people. However, less than 10% of the estimated number of patients with dementia has been officially registered [2, 3].

Alzheimer's disease is a neurodegenerative disease characterized by a gradual, barely noticeable onset in pre-senile or elderly age, a steady progression of memory and higher brain functions disorders leading to dementia, with the formation of a characteristic complex of neuropathological, neuroimaging and biochemical signs [2].

Many risk factors lead to the development of Alzheimer's disease, which are conditionally divided into modifiable and unmodifiable. The risk of developing Alzheimer's disease increases in the presence of risk factors such as low intellectual activity, physical inactivity, obesity, smoking, uncontrolled hypertension, hyperlipidemia, diabetes mellitus, etc. [1]. Elderly and senile age, a family history of Alzheimer's disease and the carriage of genetic polymorphisms, the presence of the e4 allele of apolipoprotein E, female gender, and a history of traumatic brain injuries are among the unmodifiable risk factors for the development of this disease.

The current hypothesis of the development of the disease suggests that β-amyloid or amyloid plaques initiate a pathophysiological cascade leading to the accumulation of intracellular tau protein, which spreads through the cerebral cortex, directly triggering the process of neurodegeneration and the development of clinical manifestations of Alzheimer's disease [5].

Currently, an active search is underway for effective markers of the molecular mechanism of disease development. Research in recent decades has clearly demonstrated the important role of microRNAs in the development of the pathogenesis of Alzheimer's disease through post-transcriptional control of gene expression.

The aim of the study was to determine the expression level of circulating microRNAs: hsa-mir-483, hsa-miR-132, hsa-mir-29c, hsa-mir-193b in the blood serum of elderly and senile people suffering from Alzheimer's disease.

Materials and methods of research. This study was conducted at the Geriatric Center of the Republican Clinical Hospital No. 3 (RCH No. 3) in Yakutsk. 14 people with Alzheimer's disease were randomly selected (Table 1). The diagnosis was es-Tableished in accordance with the clinical recommendations "Cognitive disorders in the elderly and senile" approved by the Ministry of Health of the Russian Federation in 2020 [2]. The study was approved by the local Ethics Committee of the M.K. Ammosov Northeastern Federal University. Voluntary informed consent to participate in the study was obtained from each patient and/or guardians/relatives.

In the study, patients were divided into two age groups, age correlated with the degree of cognitive impairment. Venous blood sampling was performed in the morning, on an empty stomach. To obtain the serum, the blood was centrifuged at 3000 rpm for 7 minutes (4 °C). Biological samples were frozen and stored at a temperature of -85 ^{0} C. before the study.

Before the start of total RNA isolation, plasma was purified from cellular debris,

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apoptotic cells and blood platelets by double centrifugation: the first - 800 rpm, the second - 12,000 rpm.

The expression level of the following microRNAs was determined in the blood serum of all examined patients: hsa-mir-483, hsa-miR-132, hsa-mir-29c, hsa-mir-193b. To quantify microRNAs in real time, in accordance with the recommendations of Qiagen, the authors developed primers (Table 2). The sequences of microRNA primers were taken from the microRNA database: https://www.mirbase.org.

Total RNA extraction was performed by the trizol-chloroform method. Total RNA was subjected to reverse transcription according to the protocol of the manufacturer of the miRCURY LNA RT Kit (art. 339340, "Qiagen"). After that, real-time PCR was performed using the miRCURY LNA SYBR Green PCR kit 200 (art. 339345, "Qiagen"). Reverse transcription and polymerase chain reaction were performed on a BioRad CFX96 device (Bio-Rad, USA).

Exogenous microRNA - cel-miR-39-3p belonging to Caenorhabditis elegans (RNA Spike-In Kit, For RT and miRCURY LNA miRNA PCR Assay art. 339390 and YP00203952, respectively) was used as a control for the samples, with respect to which the concentration of the studied microRNAs were derived. The microRNA expression levels were calculated using the ΔCt method as follows: ΔCt = average Ct value References microRNA (cel-miR-39-3p) - average Ct value (microRNA of interest). The level of relative microRNA expression corresponded to the value of 2^ (ΔCt).

Statistical analysis was performed using the SPSS 18.0 for Windows program ("SPSS, Inc.", Chicago, IL, USA). The differences between the groups were assessed using the Mann-Whitney U-test. The comparison of the indicators was carried out using the chi-square test. Correlations were determined using Spearman's rank correlation. A statistically significant difference was considered to be the value of $p<0.05$.

Results and discussion. Among all the microRNAs studied by us, statistically significant differences between elderly and senile individuals were observed in the content of mir-132. mir-132 was not detected in the blood of elderly people, while in senile people the expression level of circulating microRNA reached 0.035±0.002 cu (Figure).

The levels of circulating mir-193b in the blood of elderly and senile people did not change statistically, but we discovered that the content of mir-193b in the blood of senile people tended to decrease.

The level of circulating mir-29c and mir-483 tended to increase in the group of elderly people, but did not reach statistic significance.

We analyzed academic sources on the nature of changes in the level of microRNAs in patients suffering from moderate cognitive impairment and Alzheimer's disease (Table 3).

Many studies have shown that the level of circulating miR-132 increases in the blood in neurodegenerative diseases such as Alzheimer's disease [26], Parkinson's disease [27], multiple sclerosis [8] and amyotrophic lateral sclerosis [21], this fact emphasizes its connection with

Table 1

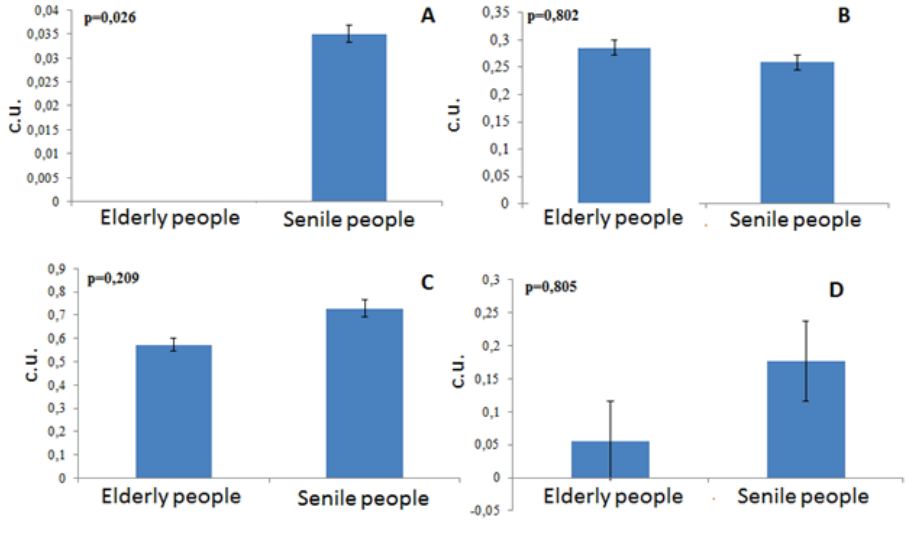
Brief description of the patients included in the study

Research Group	Elderly patients	Senile patients
Number of patients, n	7	7
Sex, n	Male - 4 Female - 3	Male - 5 Female - 2
Age at the moment of research, years	61.71±10.35	82.14±2.76
Concomitant diseases, n	Angina pectoris - 1 Hypertension - 6	Hypertension - 1 Angina pectoris - 2 Encephalopathy - 4
The stage of development of Alzheimer's disease according to the Clinical Dementia Rating (CDR) scale, n	1 point - 6 2 points - 1	2 points - 7
Bartel index, n	100 points - 1 96 points - 6	61 points - 7

Table 2

Sequences of primers used in the study

microRNAs	Праймеры
hsa-miR-483-5p	*5'- AAG ACG GGA GGA AAG AAG GGA-3'*
hsa-miR-132-5p	*5'- ACC GTG GCT TTC GAT TGT TAC TAA A -3'*
hsa-miR-29c-5p	*5'- GAC CGA TTT CTC CTG GTG TTC -3'*
hsa-miR-193b-5p	*5'- GGG TTT TGA GGG CGA GAT GAA -3'*



Expression levels of circulating microRNAs: mir-132 (A), mir-193b (B), mir-29c (C), mir-483 (D) in the blood serum of patients with Alzheimer's disease

Table 3

A brief review of studies on the expression of microRNAs (mir-29c, mir-193b, mir-483) in patients with cognitive impairment

microRNAs	Number of examined	Sample	Difference	Sources
mir-29c	AD (n = 20), Ctrl (n = 20)	Serum	↓	[24]
mir-193b	MCI (n = 43), AD (n = 51)	Plasma	↓	[13]
mir-483	AD (n = 20), MCI (n = 20), Ctrl (n = 20)	Plasma	↑	[15]
	AD (n = 20), MCI (n = 34), Ctrl (n = 37)	Plasma	↑	[14]

Note. AD - Alzheimer's disease; Ctrl – individuals in the control group; MCI-moderate cognitive impairment.

Table 4

Predicted/confirmed target genes of hsa-mir-132-3p involved in the pathogenesis of Alzheimer's disease

microRNA	Gene	Transcript binding site in an untranslated area	Cumulative PCT
mir-132	*MAPT*	4113-4119	0.5
	PTBP2	57-63	0.51
	PTBP2	372-378	< 0.1
	PTBP2	4506-4512	< 0.1
	SIRT1	1680-1686	0.38
	SIRT1	1614-1620	< 0.1
	MAPK1	1379-1386	0.78
	MAPK1	2225-2232	0.77
	MAPK1	8111-8118	< 0.1

neuropathological processes and determines its potential as a biomarker of neurodegenerative diseases.

It should be noted that human mir-132 consists of two homologous microRNAs: hsa-mir-132-5p and hsa-mir-132-3p. Mir-132 is evolutionarily conservative and has the same sequence and structure in humans, rats, mice, monkeys and other species. Mir-132 has tissue specificity and is highly expressed in nerve-related tissues [28].

To determine the molecular mechanisms by which mir-132-5p may be involved in the development of Alzheimer's disease, we used the TargetScan Release 7.1 database to predict mir-132-5p binding targets (Table 4). Analysis using the TargetScan database showed that mir-132 directly targets gene transcripts: *MAPT* (Tau protein) and *PTBP2* (protein 2 binding the polypyrimidine tract). This suggests that an increase in the level of mir-132 may have protective properties, since it reduces the amount of tau protein, however, overexpression of this microRNA changes the ratio of tau protein isomers 4R:3R in neuronal cells, which can lead to the development of neurodegenerative diseases [6].

According to the TargetScan database, in the human body, mir-132 suppresses the expression of three gene transcripts: *SIRT1* (sirtuin-1 deacetylase) and *MAPK1* (mitogen-activated protein kinase). The protein expressed by the *SIRT1* gene has protective properties: it protects the brain of mice from neurodegenerative diseases [12], and also demonstrates the phenotype of delayed aging and an increase in life expectancy [16]. The results obtained by Hadar et al. practically confirm the involvement of mir-132 in the regulation of transcript expression of the *SIRT1* gene [11]. It has been esTableished that in Alzheimer's patients, the MAPK1 enzyme *is* activated at an early stage [19], which indicates the involvement of this enzyme in the pathological process. In a study by Deng et al. Activation of mir-132 expression has been shown to improve the cognitive functions of rats with Alzheimer's disease by inhibiting the MAPK1 signaling pathway [7].

In addition, a study by Wang et al. has shown that a decrease in the level of mir-132 leads to an increase in the amount of the nitric oxide synthase-1 (NOS1) enzyme and triggers excessive production of nitric oxide followed by aberrant S-nitrosylation (SNO) of specific proteins associated with neurodegeneration and tau pathology, such as cyclin-dependent kinase-5. This leads to an increase in tau protein phosphorylation and the development of neurodegenerative diseases [23].

Walgrave et al. has shown that the pathogenesis of Alzheimer's syndrome leads to a deficiency of mir-132 in mouse brain tissue, and the addition of mir-132 alleviates memory deficiency in Alzheimer's disease [22]. Smith et al. and Xie et al. have found that mir-132 deficiency in the mouse brain leads to increased tau protein expression, phosphorylation and aggregation in mice [18, 25].

Thus, the data obtained by us indicate that in the body of patients suffering from Alzheimer's disease, the levels of micro-RNA: hsa-mir-483, hsa-mir-132, hsa-mir-29c, hsa-mir-193b depended on age and degree of cognitive impairment. Circulating mir-132-5p microRNA was detected in the blood serum of senile people suffering from moderate dementia, in contrast to elderly people with mild degree of dementia.

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GLYCEMIC CONTROL AND BLOOD LIPID PARAMETERS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN KABUL CITY OF THE REPUBLIC AFGHANISTAN

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The purpose of this study was to evaluate glycemic control and its relationship with lipid parameters in patients with type 2 diabetes mellitus at the Noble Clinic OPD of Kabul-Afghanistan. The cross-sectional study involved 1486 patients with type 2 diabetes with at least 1 year of diabetes experience (897 women and 589 men) aged 18 years and older, who visited the clinic between March 2020 and April 2021.

7.7% of patients had adequate glycemic control (HbA1c less than 7%). High levels of H b A1c were statistically significantly associated with the duration of the disease and high levels of blood lipids, while no dependence was esTableished on the gender, age of patients, body mass index and the presence of obesity. It is necessary to study the factors that determine glycemic control, the correction of which will improve metabolic parameters and reduce the risk of developing complications in diabetes.

Keywords: type 2 diabetes mellitus, glycemic control, lipid profile, dyslipidemia, Afghanistan.

Introduction. Diabetes mellitus (DM) is a chronic disease often complicated by microvascular and macrovascular complications. According to the International Diabetes Federation (IDF), the global prevalence of diabetes among people aged 20–79 years in 2021 was estimated at 10.5% (537 million people) and is expected to rise to 12.2% (783 million people) in 2045. [9].

Maintaining optimal blood glucose concentrations helps prevent serious complications leading to disability, mortality, and decreased quality of life for patients [1]. Despite a large arsenal of drugs, insufficient glycemic control still remains a problem in real clinical practice [6; 12; 15]. Thus, according to a 2022 systematic review including 12 studies (5765 patients) with type 2 diabetes, the prevalence of insufficient glycemic control ranged from 45.2% to 93% [6]. A systematic review of 34 studies of patients with type 2 diabetes treated with insulin found that 76% of patients did not achieve good glycemic control [15].

The aim of the study was to evaluate glycemic control and its relationship with lipid parameters in patients with type 2 diabetes mellitus at the Noble Clinic OPD Kabul-Afghanistan.

Materials and methods. The article presents the results of a cross-sectional study conducted at the Noble Clinic OPD (NOPDC) in the Afghan capital Kabul. The study protocol was approved by the ethics committee of the Institutional Review Board of the Ethics and Research Committee of Kabul University of Medical Sciences, KUMS (RIB protocol number: 22 dated December 7, 2021). The study was conducted among 2000 patients with diabetes mellitus with at least one year of disease experience who visited the Noble Clinic OPD between March 2020 and April 2021. Of these, 514 were excluded due to failure to meet inclusion criteria or refusal to participate in the study. All participants signed informed voluntary consent to participate in the study.

Inclusion criteria: 1. An esTableished diagnosis of type 2 diabetes mellitus (according to the ADA criteria of the American Diabetes Association); 2. Men and women over 18 years of age.

Exclusion criteria: 1. Patients in serious condition; 2. Pregnant women; 3. Patients with other types of diabetes; 4. Patients who refused to participate in the study.

The following information was extracted from outpatient records: gender, age, laboratory data (total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), glycated hemoglobin (HbA 1c), fasting glucose); height, body weight, diabetes experience. All patients took lipid-lowering drugs.

Fasting blood samples were collected by a trained technician using standard lipid measurement methods. Height and weight were measured at the time of enrolment by two well-trained technicians.

The target levels were taken to be an HbA1c level of less than 7.0% and a fasting glucose level of less than 7 mmol/L [1]. The level of glycated hemoglobin (HbA 1c) is considered the most reliable criterion characterizing the state of carbohydrate metabolism [1].

Statistical methods of analysis. IBM software was used to analyze the study data SPSS Statistics, v.26.

Categorical variables are presented as frequencies and percentage distributions in the format n (%), quantitative variables as mean with standard deviation (M (SD)) or quartile distribution (Me (Q_1-Q_3)). When comparing groups, Pearson χ^2 and Mann-Whitney tests were used. At p values <0.05, differences were considered statistically significant. Spearman's rank correlation analysis was used to assess the relationship between quantitative variables. The kappa coefficient was used to assess the agreement between the two criteria. The sensitivity and specificity of the test were also assessed with 95% confidence intervals.

Results. The study involved 1486 patients with type 2 diabetes (897 women and 589 men). The average age of the population was 55.3 (10.9) years. Men and women did not differ significantly in age (p=0.740). The average age of women was 55.4 (10.4) years, men - 55.2 (11.8) years.

The average length of experience with type 2 diabetes was 8.3 (3.2) years. In men, the average duration of diabetes was statistically significantly shorter than

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in women (8.1 and 8.5 years, respectively, p = 0.008). The quartile distribution of HbA1c in men and women was not statistically significantly different (p=0.895) and corresponded to 9.4% (7.9-11.4).

Table 1 presents the characteristics of those examined with different levels of glycated hemoglobin (HbA1c). Overall, across the entire sample, 7.7% of patients had an HbA1c level of less than 7%. Men and women did not differ statistically significantly in the proportion of individuals with optimal levels of glycated hemoglobin (p=0.141). There were no statistically significant differences in the average age of patients in the two groups (p=0.084). Among young people, the proportion of patients with HbA1c less than 7% was slightly higher than in other age groups, but the differences did not reach a statistically significant level (p = 0.144). Statistically significant differences were esTableished in the average duration of the disease at different levels of glycemia according to H b A1c (p < 0.001) . The average length of service in the group of patients with H b A1c less than 7% was 5.8 years versus 8.5 years in the group with high levels of glycated hemoglobin (p < 0.001) . This relationship is reflected in the proportion of patients achieving target H b A1c levels. Thus, in 26% of patients with a disease experience of up to 5 years, the level of H b A1c corresponded to the target (less than 7.0%), while among patients with an experience of 10 years or more, the proportion of such persons was 2.8% (<0.001) . Spearman's rank correlation coefficient between H b A1c level and disease duration was 0.35, p < 0.001.

Thus, based on the assessment results, glycemic control should be considered unsatisfactory in more than 90% of patients. Patients with a short history of the disease more often achieved the target level of H b A1c.

Table 2 presents the characteristics of those examined depending on the level of fasting glycemia. The proportion of people with an optimal level of fasting glycemia (less than 7 mmol/l) was generally 12.4%; no statistically significant differences were found between men and women (p = 0.668), patients of different ages (p = 0.353) and length of disease (p=0.355). Thus, there were no statistically significant differences in these characteristics between the two groups.

Spearman's rank correlation coefficient between the H b A1c fraction and fasting glucose level was 0.54, p < 0.001 (Table 3). When divided into groups by age, a stronger relationship between H b A1c and fasting glucose levels was ob-

Table 1

Characteristics of patients depending on H b A1c level

Group		HbA1c (%)		p
		<7,0 (n=115)	≥7 (n=1371)	
Women	n (%)	62 (6.9)	835 (93.1)	0.141
Men	n (%)	53 (9.0)	536 (91)	
Both sexes	N (%)	115 (7.7)	1371 (92.3)	
Age, years				
Women	M (SD)	53.6 (12.4)	55.5 (10.2)	0.060
Men	M (SD)	53.1 (13.9)	55.4 (11.6)	0.227
Both sexes	M (SD)	53.3 (13.1)	55.5 (10.8)	0.084
Age group, years				
20-44	n (%)	26 (11.5)	201 (88.5)	0.144
45-59	n (%)	48 (7.0)	636 (93.0)	
60-74	n (%)	35 (6.9)	470 (93.1)	
75 and older	n (%)	6 (8.6)	64 (91.4)	
Length of diabetes mellitus, years				
Women	M (SD)	5.7 (3.3)	8.7 (2.9)	<0.001
Men	M (SD)	5.9 (3.8)	8.3 (3.3)	<0.001
Both sexes	M (SD)	5.8 (3.5)	8.5 (3.1)	<0.001
Groups by diabetes experience, years				
Up to 5	n (%)	54 (26.0)	154 (74.0)	<0.001
5-9	n (%)	47 (6.1)	723 (93.9)	
10 or more	n (%)	14 (2.8)	494 (97.2)	
Groups by body mass index category				
<25 kg/m2	n (%)	19 (7.5)	235 (92.5)	0.929
25-29.9 kg/m2	n (%)	52 (7.6)	636 (92.4)	
≥30 kg/m2	n (%)	44 (8.1)	500 (91.9)	

Note: M (SD) - mean (M), standard deviation (SD); p is the achieved level of significance when comparing groups (Pearson $\chi^{2\,test}$).

Table 2

Characteristics of patients depending on the level of fasting glycemia

Group		Fasting glucose, mmol/l		p
		<7.0 (n=185)	≥7 (n=1301)	
Women	n (%)	109 (12.2)	788 (87.8)	0.668
Men	n (%)	76 (12.9)	513 (87.1)	
Both sexes	N (%)	185 (12.4)	1301 (87.6)	
Age, years				
Women	M (SD)	54.9 (10.4)	55.4 (10.4)	0.828
Men	M (SD)	56.5 (12.6)	54.9 (11.7)	0.278
Both sexes	M (SD)	55.6 (11.3)	55.3 (10.9)	0.579
Age group, years				
20-44	n (%)	34 (15.0)	193 (85.0)	0.353
45-59	n (%)	75 (11.0)	609 (89.0)	
60-74	n (%)	68 (13.5)	437 (86.5)	
75 and older	n (%)	8 (11.4)	62 (88.6)	
Length of diabetes mellitus, years				
Women	M (SD)	8.2 (2.8)	8.5 (3.0)	0.310
Men	M (SD)	8.0 (3.4)	8.1 (3.4)	0.916
Both sexes	M (SD)	8.2 (3.0)	8.4 (3.2)	0.401
Groups by diabetes experience, years				
Up to 5	n (%)	23 (11.1)	185 (88.9)	0.355
5-9	n (%)	105 (13.6)	665 (86.4)	
10 or more	n (%)	57 (11.2)	451 (88.8)	
Groups by body mass index category				
<25 kg/m2	n (%)	29 (11.4)	225 (88.6)	0.851
25-29.9 kg/m2	n (%)	88 (12.8)	600 (87.2)	
≥30 kg/m2	n (%)	68 (12.5)	476 (87.5)	

served in the group of patients 75 years and older (r = 0.67, p < 0.001). The proportion of H b A1c positively correlated with the length of the disease in all age groups, except for persons 75 years and older.

When analysing the consistency between indicators of diabetes compensation in terms of H b A1c level and fasting glucose level, it was found that in the group as a whole, the estimates coincided in 82.6% of cases (kappa coefficient = 0.049, p = 0.049).

If we consider the HbA1c level as the "gold standard" for assessing compensation in diabetes, then the sensitivity of fasting glycaemia ≥ 7 mmol/l in diagnosing decompensation is 88.0% (86.2-89.7%), specificity 18.3% (95% CI 12.3-26.3%).

Analysis of the relationship between the level of H b A1c and body mass index did not show the presence of certain patterns. A statistically significant weak negative correlation between H b A1c and body mass index was observed only in the group of people 75 years of age and older (r = -0.28, p = 0.019).

Among all those examined, the proportion of people with an optimal level of H b A1c was 7.5% for low and normal body weight (body mass index <18.5 kg/m2) , among people with overweight (body mass index 18. 5-24.9 kg/m2) – 7.6%, among obese individuals (body mass index ≥30 kg/m2) –8.1% (p=0.929).

Lipid metabolic disorders are common in diabetes mellitus because key enzymes and lipid metabolic pathways are affected due to deficiencies in insulin production and secretion [8].

In the present study, men and women differed statistically significantly in triglyceride levels (p=0.002) and HDL cholesterol (<0.001). There were no strong correlations between age and blood lipid parameters. The maximum Spearman rank correlation coefficient (r) was 0.14, <0.001 for total cholesterol. A weak pos-

Table 3

Spearman's rank correlation coefficients between H b A1c with diabetes experience, glucose level and body mass index

Age group, years	N	Fasting glucose, mmol/l		Diabetes experience, years		BMI, kg/ m^2	
		r	p	r	p	r	p
20-44	227	0.53	<0.001	0.45	<0.001	0.02	0.716
45-59	684	0.54	<0.001	0.42	<0.001	0.03	0.374
60-74	505	0.52	<0.001	0.35	<0.001	0.004	0.929
75 over	70	0.67	<0.001	0.08	0.491	-0.28	0.019
All ages	1486	0.54	<0.001	0.35	<0.001	0.009	0.735

Note: r is the Spearman rank correlation coefficient; p is the achieved level of significance of the correlation coefficient.

Table 4

Lipid spectrum indicators at different levels of HbA1c *

Indicator, mmol/l	HbA1c, %		p
	<7.0	≥7.0	
Women			
	n=62	n=835	
Triglycerides	2.5 (2.0-2.8)	3.0 (2.5-3.6)	<0.001
Total cholesterol	5.8 (5.5-6.4)	6.9 (6.1-8.1)	<0.001
HDL cholesterol	1.2 (1.0-1.3)	1.3 (1.2-1.4)	<0.001
LDL cholesterol	3.6 (3.0-3.9)	4.1 (3.5-5.0)	<0.001
VLDL cholesterol	1.2 (0.9-1.4)	1.5 (1.2-1.8)	<0.001
Cholesterol is not HDL	4.7 (4.4-5.1)	5.6 (4.9-6.7)	<0.001
Men			
	n=53	n=536	
Triglycerides	2.5 (2.1-3.1)	3.1 (2.6-4.0)	<0.001
Total cholesterol	5.9 (5.3-7.2)	7.0 (6.1-8.3)	<0.001
HDL cholesterol	1.2 (1.0-1.4)	1.4 (1.2-1.6)	<0.001
LDL cholesterol	3.6 (3.1-4.5)	4.1 (3.5-4.8)	0.004
VLDL cholesterol	1.2 (1.0-1.4)	1.5 (1.2-1.9)	<0.001
Cholesterol is not HDL	4.8 (4.2-5.7)	5.6 (4.9-6.7)	<0.001

Note: * data are presented as median (Me) and interquartile range (Q_1-Q_3) in Me format (Q_1-Q_3); p — achieved level of significance when comparing groups (Mann-Whitney test).

Table 5

Glycemic control in patients with type 2 diabetes in selected countries

A country	Population	Criterion	Frequency, %	Source
Jordan	N=287, 18 years and older	HbA1c <7%	42	[14]
Brazil	N=338, 18 years and older	HbA1c <7%	53	[7]
Jakarta	N=126, 18 and older years	HbA1c ≤7%	45.2	[5]
Saudi Arabia and the people of the Tabuk region	N=697, 18 years and older	HbA1c <7%	18.5	[4]
Southwestern Cameroon	N=131, 30 and older	HbA1c <7%	19.1	[10]
Ethiopia	N=124, 30-83 years old	HbA1c <7%	39.5	[3]
Iraq	N=520, 18 years and older	HbA1c <7%	23.5	[13]
Pakistan	896, 18-75 years old	HbA1c <7%	14.5	[2]
China	N=13972, 18 years and older	HbA1c <7%	44	[11]

itive correlation was noted between the duration of diabetes and the content of triglycerides (r=0.20, p <0.001), total cholesterol (r =0.23, p <0.001), VLDL cholesterol (r =0.21, p <0.001), not HDL cholesterol (r =0.23, p <0.001).

The level of H b A1c positively correlated with the content of triglycerides (r=0.31, p<0.001), total cholesterol (r=0.30, p<0.001), LDL cholesterol (r=0.22, p<0.001), cholesterol VLDL (r=0.30, p<0.001), non-HDL cholesterol (r=0.30, p<0.001).

Comparison of groups of patients with different H b A1c levels showed that glycemic compensation of diabetes is accompanied by an improvement in the metabolic profile (Table 4).

Discussion. The work assessed the control of glycemic levels depending on gender, age and duration of type 2 diabetes mellitus, as well as its relationship with the blood lipid profile in patients of one of the clinics in the Republic of Afghanistan. It was found that only 7.7% of patients had the target H b A1c level, which is significantly lower than in studies conducted with similar criteria in other countries (Table 5). The reasons for poor glycemic control in this population are unknown. A systematic review including 12 studies found that factors influencing glycemic control may include educational level, gender, body mass index, obesity, diabetes history, hypertension, number of antidiabetic medications, diabetes treatment regimens, medication adherence and exercise [6].

Glycemic control was better in patients with recent onset of the disease. Patients with type 2 diabetes with H b A1c levels≥7.0% had statistically significantly higher blood lipid levels than patients with H b A1c <7.0%. Moreover, this also applied to the level of HDL cholesterol among both men and women (Table 4), which requires further study.

Thus, the present study revealed that insufficient glycemic control was observed in 92% of patients with type 2 diabetes. High levels of H b A1c were statistically significantly associated with the duration of the disease and high levels of blood lipids, while no dependence was esTableished on the gender, age of patients, body mass index and the presence of obesity. It is necessary to study the factors that determine glycemic control, the correction of which will improve metabolic parameters and reduce the risk of developing complications in diabetes.

Limitations of the study. A limitation of the study is the recruitment of participants from only one center, which affects the generalizability of the study results. At the same time, Noble Clinic OPD (NOPDC), located in the capital of Afghanistan, Kabul, is one of the large centres that receives patients from all over Afghanistan. Also, the completeness of the assessment is affected by the lack of data on factors possibly associated with glycemic control, such as education level, income, comorbidities, patient adherence to treatment, drug therapy, and others.

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PREVALENCE OF STEREOTYPIES AMONG ADULTS WITHOUT NEUROLOGICAL DISORDERS AND INTELLECTUAL DECLINE

Stereotypies, along with tics, are the most common hyperkineses, especially among children. It has been esTableished that stereotypies can occur among children with normal development. At the same time, we found only one article on the prevalence of stereotypies among relatively healthy adults. **The aim of the study** is to assess the prevalence and nature of stereotypies among adults without neurological and intellectual disorders and to determine its relationship with tics and associated psychiatric symptoms. Material and methods. We have created an online questionnaire that includes 32 questions about the presence of movement disorders and their characteristics, assessment of anxiety, depression and attention level. 80 people were studied, including 21 men and 59 women, the median age was 23.0 [22.0; 26.0] years. **The results of the study.** Of the 80 people who participated in the study, signs of stereotypies, motor and/or vocal tics were identified in 60 people (75%). Each of them had from 1 to 15 symptoms (median – 3.5 [3.0; 6.0]). In 59 (73.8%) people, the revealed motor symptoms were regarded as stereotypies, in 10 (12.5%) people – motor tics, in 6 (7.5%) – vocal tics. In 4 people (5.0%), motor tics were combined with vocal tics, which is typical for Tourette's syndrome. Participants with violent movements were more likely to have a high level of anxiety (53.3% vs. 10%), which often indicated obsessive-compulsive symptoms (41.7% vs. 15.0%), and they also performed worse on the Schulte Table test (40.0 sec vs. 31.5 sec). In-person examination of respondents demonstrated a high level of sensitivity and specificity of the questionnaire in relation to stereotypies (100% and 66.7%, respectively), but a low level of sensitivity to tics (33.3%) with 100% specificity. **Conclusion.** Stereotypies are quite common among the adult population, even in the absence of organic brain damage and cognitive decline, and in about half of the cases they are combined with obsessive-compulsive symptoms and anxiety.

Keywords: stereotypies, motor tics, vocal tics, obsessive-compulsive symptoms, anxiety.

Stereotypies, along with tics, are the most common hyperkineses, especially among children [6]. Stereotypies are repetitive and aimless movements that have a certain pattern and can be stopped by distraction. These include both simple movements in the form of stamping with your foot, twisting your hair, biting your nails, and complex movements – flapping your arms, rotating your hands, swaying your torso, orofacial movements, as well as self-harming behavior [4, 11, 13].

Stereotypies are often observed in various mental disorders and diseases of the nervous system. Thus, according to the meta-analysis, 21.9–97.5% (median – 51.8%) of children with autism spectrum disorder (ASD), regardless of gender, have stereotypies, and they are associated with a younger age, lower level of intelligence and severity of ASD [16]. Other causes of the development of stereotypies can be schizophrenia, affective disorders, oligophrenia, genetic diseases (most often Rett syndrome), as well as neurological diseases such as epilepsy, Tourette syndrome, Parkinson's disease [14].

However, simple stereotypies can be observed in 20-70% of cases, and complex stereotypies – in 3-4% of cases of normally developing children [13]. They do not differ phenotypically from pathological stereotypies, they are most often manifested by thumb sucking, body swaying and nail biting and are more often identified in boys (3:2 ratio) [7]. Such stereotypies, observed more often in children under 2 years of age, are associated with the maturation of the neuromuscular pathways and insufficient maturity of the inhibitory effect of the cortex, especially the frontal lobes [1].

If the prevalence and phenomenology of stereotypies in normally developing children have been studied well enough, then this cannot be said about adults. Stereotypical motor disorder in intellectually intact adults without mental disorders was first described in 1996 by Castellanos F. et al. So, out of 20 respondents, 12 people had signs consistent with DSM-IV SMD. 11 of the 12 subjects had a history of affective or anxiety disorder [8].

Tics are semi-spontaneous, sudden, rapid, repetitive, irregular movements or vocal tics in response to an imperative urge, a sensory feeling that leads to the need to make a particular movement (the so-called "premonitory urge") [2]. Motor and vocal tics are the basis of Tourette's syndrome and occur mainly in children, adolescents and young people (under 18 years of age) and, as a rule, tend to regress. They are more common in boys than in girls, but in adulthood this predominance is less pronounced [9].

The aim of the study is to assess the prevalence and nature of stereotypies among adults without neurological and intellectual disorders and to determine its relationship with tics and associated psychiatric symptoms.

Materials and methods of research. The study was conducted on the premises of the Department of Neurology and Psychiatry of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Based on the aim of the study, we created an online questionnaire that includes 32 questions and is divided into the following sections:

1. General information: gender, age, ethnicity, employment, information about parents and siblings, information about previously diagnosed neurological and somatic diagnoses, information about taking medications, information about bad habits, information about academic performance at school and university.
2. Signs of stereotypies and tics. The patients had to note certain motor phenomena that they observed. The questions were based on the Yale Global Tic Severity Scale (Leckman et al., 1989), in addition, willpower suppression, the presence of premonitory urge, duration and frequency of motor phenomena, cessation during distraction, influence on

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daily activity, aggravating and reducing factors were evaluated.

3. Obsessive-compulsive symptoms based on the Yale Brown Obsessive-Compulsive Scale (Goodman et al., 1989).

4. Assessment of anxiety and depression on the HADS scale (Hospital Anxiety and Depression Scale).

5. Evaluation of the attention function according to the Schulte Table test.

Participants had the opportunity to provide contact details to send the results of their research, as well as to clarify the specified information.

The object of the study were students of years 4-6 of a medical university. Before starting the survey, each respondent was instructed on the basic terminology.

Criteria for inclusion in the study: 1) age 18 and older; 2) voluntary consent to participate. Exclusion criteria: 1) age under 18 years; 2) the presence of epilepsy and other paroxysmal disorders; 3) the presence of cognitive impairment that prevents the analysis of the data obtained; 4) the presence of diseases of the nervous system accompanied by the development of chorea, dystonia, tremor, paresis, and paralysis.

A total of 80 people participated in the study, including 21 men (26.3%) and 59 women (73.7%). The median age of the respondents was 23.0 [22.0; 26.0] years, all were university students, two participants were employed at the same time (2.5%). By ethnicity, the majority of participants were Yakuts (66 people, 82.5%), Russians – 5 people (6.3%), another ethnic group – 9 people (11.2%).

Based on the analysis of these motor symptoms, all participants were divided into two groups. The first (main) group consisted of persons with motor symptoms that can be attributed to tics and/or stereotypies, the second (control) group consisted of persons without motor phenomena.

During the study, none of the respondents were recommended to take medications and other therapeutic manipulations. If a motor phenomenon was present, the report included the nature of hyperkinesis (stereotypies, tics), the presence of associated mental symptoms (obsessive-compulsive symptoms, signs of anxiety and depression) and the recommendation of an in-person consultation with a specialist (neurologist or psychiatrist).

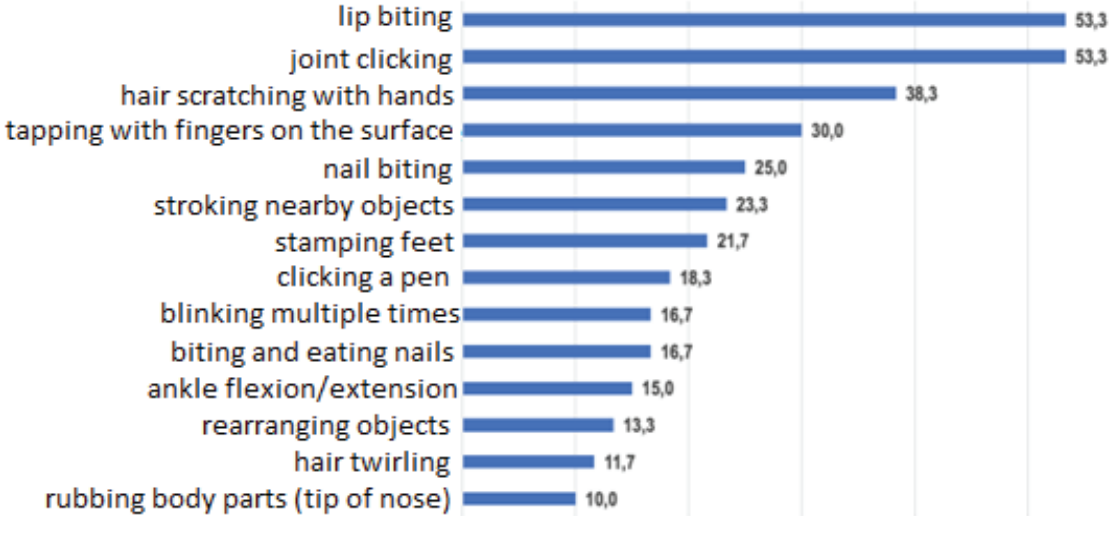
To check the sensitivity and specificity of the created questionnaire from among the respondents, we invited a group of volunteers for an in-person examination, who underwent a neurological examination and a thorough analysis of existing hyperkinesis.

Statistical processing was carried out in the SPSS Statistica 25.0 program. Since the distribution of most of the studied quantitative indicators differed from the normal one, their descriptive statistics are given in the form of the median, the 25th and 75th quartiles (Me [Q1; Q3]), and the Mann-Whitney U-test was used to compare the two groups of quantitative data. Qualitative data are presented in the form of frequencies, for comparison of binary data, a contingency Table was used with the calculation of the Pearson $\chi 2$ criterion or the Fisher exact criterion, depending on the assumed minimum value. To determine the strength of the connection between two nominal variables, Cramér's V criterion was calculated. The differences at $p \leq 0.05$ were considered statistically significant.

The results of the study. Of the 80 people who participated in the study, signs of stereotypies, motor and/or vocal tics were identified in 60 people (75%). Each of them had from 1 to 15 symptoms (median – 3.5 [3.0; 6.0]). The most common motor symptoms were lip biting (53.3%), joint clicking (53.3%), hair scratching with hands (38.3%) and tapping with fingers on the surface (30.0%). Figure 1 shows the frequency of the identified hyperkineses.

In 59 (73.8%) people, the revealed motor symptoms were regarded as stereotypies, in 10 (12.5%) people – motor tics, in 6 (7.5%) – vocal tics. In 4 people (5.0%), motor tics were combined with vocal tics, which is typical for Tourette's syndrome. However, none of the respondents with this combination of signs had such a diagnosis, one participant was diagnosed with residual encephalopathy, and another was diagnosed with intracranial hypertension. A combination of motor tics and stereotypies was found in 9 (11.3%) people, and a combination of all three signs (motor tics, vocal tics, stereotypies) – in 3 (3.8%) people.

The respondents with hyperkineses did not differ from the representatives of the control group in age and the age of the mother at the time of birth. In the main group, 17 (28.3%) people had at least one neurological diagnosis in their medical history, and in the control group, 3 (15.0%) people ($p = 0.234$). Moreover, in both groups, intracranial hypertension was most often diagnosed: in 10 (16.7%) people of the main group and 2 (10.0%) people of the control group ($p = 0.47$). Attention deficit hyperactivity disorder



Frequency distribution of hyperkineses (in % of all responses).
Note: symptoms observed in less than 10% of patients are not included.

(ADHD) was noted in only one respondent with stereotypies.

The respondents of both groups did not differ statistically in the frequency of rheumatism, helminthiasis, and viral hepatitis. At the same time, anemia was noted by 32 (53.3%) representatives of the main group and only 3 (15.0%) representatives of the control group (p = 0.003; V= 0.335). Of the respondents in the main group, 1 (1.7%) people took antidepressants, 1 (1.7%) people took neuroleptics, 3 (5.0%) people took tranquilizers. Among the respondents of the control group, the use of these drugs was not registered. Although smoking was more often registered in the main group (40% versus 20%), no statistically significant difference was achieved.

Representatives of the main group more often ended their semester with good and excellent grades (93.3% vs. 75.5%, V = 0.25; p = 0.025), although they did not differ in academic performance from representatives of the control group.

The analysis of associated psychiatric disorders showed (Table 2) that the respondents of the main group had a statistically significantly higher level of anxiety, and anxiety was detected in 32 (53.3%) people, whereas among the control group – only 2 (10.0%) people. Obsessive-compulsive symptoms were found in 25 (41.7%) representatives of the main group and only in 3 (15.0%) representatives of the control group (p = 0.023). The most common symptoms among the main group were the desire to double-check (13 people, 21.7%), the need for symmetry (9 people, 15.0%) and the need for excessive cleanliness (8 people, 13.3%). Of the 25 people with obsessive-compulsive symptoms, 23 people noted the meaninglessness of rituals, but could not get rid of them on their own. In addition to anxiety and obsessive-compulsive symptoms, the respondents of the main group were slower at passing the Schulte Table test (40.0 [33.0; 54.5] sec versus 31.5 [27.5; 51.0] sec, p = 0.032).

Out of 80 people, 10 people agreed to take part in an in-person neurological examination. In 7 people who, according to the results of an online survey, hyperkineses were regarded as stereotypies, as a result of the analysis of complaints, analysis, neurological examination, the nature of hyperkinesis was confirmed. On the contrary, among the three people who were assigned to the control group, one respondent revealed stereotypies during an in-person examination. Thus, the sensitivity of our questionnaire in relation to stereotypies was 100%, the specificity was 66.7%.

The questionnaire's sensitivity to ticks was significantly lower. Thus, tics were identified in only one patient out of three volunteers with hyperkineses. But at the same time, none of the control group had been identified with tics. Consequently, the sensitivity was 33.3%, and the specificity was 100%.

Discussion. Our study shows the widespread prevalence of stereotypies among adults without neurological diseases and intellectual disabilities. Tics and stereotypies are two of the most common non–directional motor behaviors, which in some cases can coexist. If in mild manifestations they decrease over time and do not require active intervention, in severe cases they can persist further into adulthood and affect daily activity [15].

A recent systematic review revealed that 23% of children aged 8 to 31 years with stereotypical motor disorder have concomitant tics, 37.6% of patients have ADHD and 16.5% have obsessive-compulsive symptoms. And 8% of children with Tourette's syndrome have stereotypies [6]. Consequently, stereotypies, tics, ADHD and obsessive-compulsive disorder may have a common pathophysiological basis. According to our data, a

Table 1

General characteristics of the respondents

Parameter	Main group (n=60)	Control group (n=20)	p-level
Age, years	23.0 [22.0; 25.0]	25.5 [23.0; 27.0]	p = 0.043
Males, abs. (%)	14 (23.3)	7 (35.0)	p = 0.304
Age of the mother at the time of the respondent's birth, years	29.0 [24.2; 35.75]	31.0 [22.5; 36.75]	p=0.854
Neurological diagnosis since childhood, abs. (%)	7 (11.7)	2 (10.0)	p = 0.838
Neurological diagnosis in medical history, abs. (%)	17 (28.3)	3 (15.0)	p = 0.234
Somatic diagnosis in medical history, abs. (%)	39 (65)	8 (40)	p = 0.05
Smoking, abs. (%)	24 (40)	4 (20)	p = 0.104
Excellent and good grades as of last semester, abs. (%)	56 (93.3)	15 (75)	p = 0.025; V = 0.251

Table 2

Associated psychiatric symptoms in respondents

Parameter	Main group (n=60)	Control group (n=20)	p-level
HADS, anxiety, points	7.0 [5.0; 10.0]	4.0 [2.25; 5.75]	p < 0.001
Anxiety, abs. (%)	32 (53.3)	2 (10.0)	p = 0.001; V = 0.38
HADS, depression, scores	5.0 [3.25; 8.0]	4.0 [2.0; 6.75]	p=0.151
Depression, abs. (%)	22 (36.7)	5 (25.0)	p = 0.339
Obsessive-compulsive symptoms, abs. (%)	25 (41.7)	3 (15.0)	p=0.023
Schulte Table test, sec.	40.0 [33.0; 54.5]	31.5 [27.5; 51.0]	p=0.032

combination of tics and stereotypies was observed in 11.3% of cases.

Tics and stereotypies, along with akathisia, restless legs syndrome, obsessive-compulsive disorder, tardive dyskinesia and some levodopa-induced dyskinesias, are combined into the general term "acasitic spectrum disorders", since their development is based on an imperative need to make movements and, probably, a single pathophysiological mechanism [3].

Long-term observation of stereotypies in children without mental retardation and ASD showed that in the vast majority of cases (81%) they develop before 24 months and are more often associated with ADHD (30%), tics (18%) and OCD (10%) [12]. In almost all cases, stereotypies have a protracted course. Thus, a survey of 49 children and adolescents aged 9 to 20 years revealed that during the entire observation period (range from 6.8 to 20.3 years) stereotypies persist in 48 (98%) people, including 9 (19%) people - for more than 15 years. However, 37 people noted an improvement in symptoms, and 10 people's symptoms remained at the same level [17].

Tics in the vast majority of cases begin at the age of 5 to 8 years, occur three times more often in men, characterized by cranio-caudal spread with the first tics in the form of blinking, movement of the nose, face, whereas the muscles of the trunk and limbs are involved later, the peak of tics occurs at the age of 10 to 13 years, after then their severity gradually decreases [5].

Freeman R. and colleagues observed 42 children (11 girls and 31 boys) with a stereotypical motor disorder, but without self-harming disorder, mental retardation, and ASD. Among them, ADHD was found in 16 people, tics in 18 people, including Tourette's syndrome in 11 people, OCD in 2, obsessive-compulsive behavior in 3 people. The first signs of stereotypies appeared at the age of 17 months, and the diagnosis was esTableished on average at the age of 6 years. The authors observed 39 children for more than 6 months, and 25 people's symptoms improved, including 4 children whose stereotypies were completely stopped. The family history was positive in 13 children [10]. According to the results of our study, representatives of the main group, which mainly included patients with stereotypies, were more likely to have obsessive-compulsive symptoms and anxiety, and were slower at passing the Schulte Table tests.

Attention is drawn to the lack of a diagnosis of Tourette's syndrome in individuals who note all the symptoms of the disease, such as motor and vocal tics.

An interesting finding of the study was the more frequent indication of anemia in the main group of individuals. We conducted a search in PubMed databases, eLibrary.ru, Google Academy, however, we did not find any scientific articles discussing the relationship of anemia with stereotypies or tics. The only disease from the group of "acasitic" disorders that can be caused by iron deficiency is restless legs syndrome [18].

The strength of our research is the high sensitivity of the created questionnaire in relation to stereotypies. Undoubtedly, most respondents, especially when identifying anxiety or obsessive-compulsive symptoms that reduce daily activity, need to consult a neurologist or psychiatrist for an in-person examination. In our study, we were able to show a fairly wide prevalence of stereotypies among adults.

The study also has a number of limitations. First of all, it is the identification of signs using a questionnaire. At the same time, in-person examinations revealed its rather high sensitivity to stereotypies, but low sensitivity to tics. Secondly, we did not take into account the age of hyperkineses development. Thirdly, we limited ourselves to obsessive-compulsive symptoms. However, the last point is quite justified, since the diagnosis of obsessive-compulsive disorder undoubtedly requires face-to-face consultation with a psychiatrist.

Conclusion. Stereotypies are identified not only among children with normal development, but are also quite common among the adult population, even in the absence of organic brain damage and cognitive decline, and in about half of all cases they are combined with obsessive-compulsive symptoms and anxiety. Although active treatment may not be required in all cases, with the influence of stereotypies, tics, obsessive-compulsive symptoms on daily activity, the development of stigmatization, pharmacotherapy or psychotherapy may be options for improving a person's condition.

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THE RATE AND STRUCTURE OF THE ASSORTATIVE MARRIAGES AMONG DEAF INDIVIDUALS IN THE REPUBLIC OF BURYATIA

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It is currently accepted that the reproductive capabilities of deaf people increase over time, and marriages between deaf people occur according to the principle of assortativity, which in total can lead to an increase in the frequency of one major autosomal recessive form of deafness. In this regard, the purpose of this work was to analyze the share and structure of assortative marriages based on deafness in the Republic of Buryatia. The sample of deaf individuals consisted of 201 people (113 female and 88 male) aged from 21 to 77 years (mean age 46.7 ± 7.9 years). For analysis of the marriage structure of deaf people, information was available for 168 marriages. Individuals were considered married if they had a registered marriage and/or if they had common children. An assortative marriage (AM) was a marriage in which both partners were deaf. An AM in which all the children were deaf was considered non-complementary, and an AM in which all the children were hearing was considered complementary. Marriages in which there were both hearing and deaf children were designated as segregating. An analysis of the marriage structure of deaf people showed that the proportion of marriages between deaf individuals in Buryatia is 81.8% (122 out of 149 marriages analyzed), and in 18.2% of cases (27 marriages) marriages were concluded between deaf and hearing people. Among all AM, the share of complementary marriages was 86.9% (106 out of 122), non-complementary - 5.7% (7 out of 122) and segregating 7.3% (9 out of 122). It was revealed that with a high frequency of AM, the marital structure was characterized by a high proportion of complementary and low proportion of non-complementary and segregating AM, which may be explained by the peculiarities of the genetic structure of hereditary forms of hearing loss in the Republic of Buryatia.

Keywords: hereditary hearing loss, assortative marriages, sign language, autosomal recessive deafness 1A (DFNB1A), Buryatia.

Introduction. The inventor of the telephone, Alexander Graham Bell, first suggested in 1883 that frequent marriages between deaf individuals could lead to an increase in the occurrence of hereditary forms of hearing loss. In the 2000s, this assumption was revisited by Walter Nance, who formulated the hypothesis that the reproductive opportunities of deaf individuals increase over time, and marriages between deaf individuals occur not randomly but according to the principle of assortative mating. This could lead to an increase in the frequency of the "connexin" form of deafness, caused by pathogenic variants of the *GJB2* gene. Subsequent computer modeling supported this hypothesis, showing that increased reproductive opportunities and intensive assortative mating could indeed double the frequency of the most common "connexin" deafness form in the United States in less than 200 years, after the introduction of sign language. This hypothesis was further supported by evidence from the dynamics of the socio-demographic structure of individuals with hearing impairments in the United States from the 19th to the 20th centuries, as well as from other computational experiments on the computer modeling of the spread of hereditary hearing loss.

Nance's hypothesis suggests that the effect of assortative mating is limited to the most common form of recessive hearing loss because, with frequent assortative mating, critical is the proportion of marriages in which both partners have the same genetic etiology of hearing loss and have a 100% chance of having deaf children. According to this hypothesis, such marriages are called non-complementary. Accordingly, in populations where one major recessive form of hearing loss predominates, intensive assortative mating marriages for deafness may lead to greater transmission of pathogenic alleles in subsequent generations.

Earlier studies have shown that the proportion of assortative marriages between deaf individuals in Yakutia is 77.1%, among which 24% are non-complementary (hearing loss in both spouses is caused by recessive pathogenic variants of the *GJB2* gene). Agent-oriented computer modeling of the spread of the "connexin" form of deafness in Yakutia showed that in the presence of assortative marriages, the proportion of recessive mutant homozygotes almost doubled within the first four generations. These data suggest that assortative marriages between deaf individuals in Yakutia may lead to an increase in the frequency of hereditary "connexin" hearing loss, as previously shown for the population of the United States.

Therefore, the aim of this study was to analyze the proportion and structure of assortative marriages for deafness in the previously unstudied neighboring region of Eastern Siberia - the Republic of Buryatia.

Materials and methods. Specialized surveys were conducted with deaf individuals belonging to the Buryat branch of the All-Russian Society of the Deaf (Ulan-Ude city) with the help of sign language interpreters. The sample of deaf individuals consisted of 201 individuals (113 women and 88 men) aged 21 to 77 years (mean age 46.7±7.9 years). The

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ethnic composition of the sample of deaf individuals was as follows: Buryats - 98 people (48.7%), Russians - 85 people (42.3%), and others (individuals of mixed ethnic backgrounds, as well as occasional representatives of other nationalities) - 18 people (8.9%).

For the analysis of marriage structure, information was available for 168 individuals, which included 149 marriages (including remarriages). Individuals were considered married if they had a registered marriage and/or shared children. An assortative marriage (AM) was considered a marriage in which both spouses were deaf. A non-complementary marriage was considered an AM in which all children were deaf, while a complementary marriage was considered one in which all children were hearing. Marriages in which there were both hearing and deaf children were designated as segregating.

Statistical analysis between groups was performed using the chi-square test with Biostatd software (McGraw-Hill, Inc. Version 3.03). Differences were considered statistically significant at $p<0.05$.

The examinations provided for within the framework of this research were conducted after obtaining informed written consent from the participants. The research was approved by the local biomedical ethics committee at the Yakut Scientific Center of Complex Medical Problems (Yakutsk city) in 2019 (Protocol No. 7 dated August 27, 2019).

Results and discussion. The analysis of the marriage structure of deaf individuals showed that the proportion of marriages between deaf individuals in Buryatia is 81.8% (122 out of 149 analyzed marriages), while in 18.2% of cases (27 marriages), marriages were contracted between deaf and hearing individuals. Among all assortative marriages, the proportion of non-complementary marriages was 5.7% (7 out of 122), segregating marriages 7.3% (9 out of 122), and complementary marriages 86.9% (106 out of 122) (Table 1).

We compared the proportion of assortative marriages in Buryatia with data from 10 other studied regions worldwide, for which the proportion of marriages between deaf individuals was calculated (Table 2). As a result, the proportion of marriages between deaf individuals in Buryatia (81.8%) was one of the highest, indicating the presence of positive assortative mating based on the "deafness" trait. A high proportion of assortative marriages between deaf marital partners, along with widespread use of sign language, is one of the main characteristics of consolidated deaf communities (deaf culture). A similarly high proportion of AM marriages is considered characteristic of countries where deaf people actively use sign language: Northern Ireland (UK) - 89.3%, USA - 79.5%, Sweden (Narke region) - 99%. In contrast, in countries where the introduction of sign language has occurred relatively recently, the proportion of AM is much lower: Tunisia - 10-30%, Mongolia - 37.5%, Turkey - 46.8% (Table 2).

Table 1

The marital structure of hearing-impaired individuals in the Republic of Buryatia

Total marriages	n (%)
Всего	149 (100)
Assortative marriages:	122 (81.8)
- Non complementary	7 (5.7)
- Segregating	9 (7.3)
- Complementary	106 (86.9)
Non assortative marriages	27 (18.2)

As seen from Table 2, two regions in Russia (Buryatia and Yakutia) also have a high proportion of AM marriages in relation to deafness, likely associated with a longer history of sign language use. For example, the first school for the education of deaf people based on sign language was esTableished in Yakutsk in 1951, whereas in Mongolia, the first similar school was opened in Ulaanbaatar only in 1995.

Next, we compared the proportion and structure of assortative marriages in Buryatia with those in Yakutia, where a

Table 2

The proportion of assortative marriages in Buryatia compared to available literature data

Region	Proportion ofAM	References
Russia, Republic of Buryatia	81.8	[This study]
Russia, Republic of Sakha (Yakutia)	77.1	[1]
USA	79.5	[13]
United Kingdom, Northern Ireland	89.3	[17]
Sweden, Narke	99.0	[8]
Sweden, Varmland	10.0	
India	56.6	[16]
Turkey	46.8	[18]
Mongolia	37.5	[12]
Tunisia	10.0-30.0	[9]

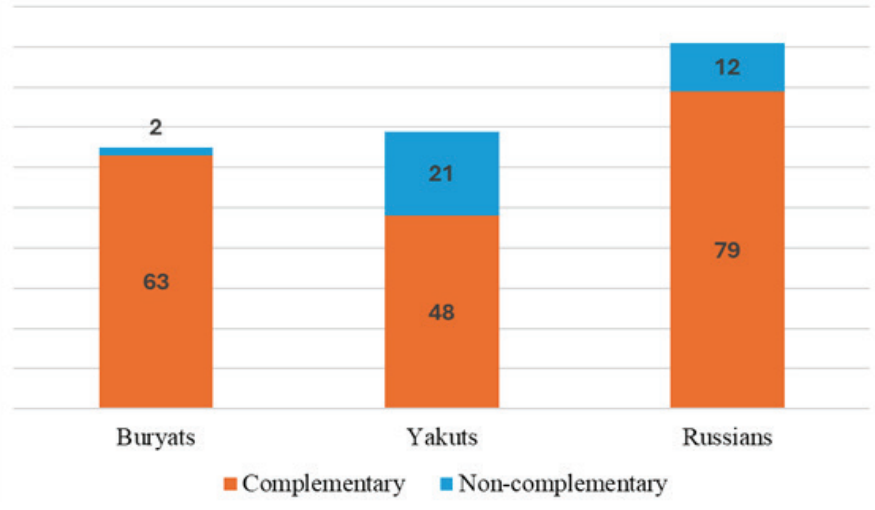
Note: Regions where the proportion of assortative marriages was below 60% are highlighted in gray.

Table 3

Comparative analysis of the proportion and structure of assortative marriages for deafness in Buryatia and Yakutia

Region	Assortative marriages	Non-complementary marriages	Complementary marriages	Segregating	References
Republic of Buryatia	122 out of 149 (81.8%)	7 out of 122 (5.7%)	106 out of 122 (86.9%)	9 out of 122 (7.3%)	[This study]
Republic of Sakha (Yakutia)	81 out of 105 (77.1%)	19 out of 81 (23.5%)	62 out of 81 (76.5%)	24 out of 81 (29.6%)	[1]
$\chi 2$	0.86	**13.69**	3.65	**17.71**	-
p	>0.05	**<0.001**	>0.05	**<0.001**	-

Note: statistically significant differences ($p<0.05$) are highlighted in bold.



Proportion of complementary and non-complementary assortative marriages by ethnicity

Table 4

Comparative analysis of the contribution of the connexin deafness (DFNB1A) among patients with hearing impairments among Buryats and Yakuts

Ethnicity	DFNB1A proportion	References
Buryats	4 out of 79 (5.1%)	[19]
Yakuts	29 out of 55 (52.7%)	[1]
$\chi 2$	**36.69**	-
p	**<0.001**	-

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

previous analysis of assortative mating among people with hearing impairments was conducted [1]. The comparative analysis of the proportion and structure of assortative marriages for deafness in Buryatia and Yakutia is presented in Table 3. The proportion of assortative marriages for deafness in Buryatia - 81.8%, was comparable to the proportion of assortative marriages in Yakutia - 77.1% ($\chi 2$= 0.86, *p*>0.05). However, the structure of assortative marriages differed significantly, as the proportion of non-complementary assortative marriages in Buryatia (5.76%) was four times lower than in Yakutia, where non-complementary marriages accounted for - 23.5% ($\chi 2$= 13.69, *p*<0.001). Additionally, the proportion of segregating marriages in Buryatia (7.36%) was also four times lower than in Yakutia (29.6%) ($\chi 2$= 17.71, *p*<0.001), while the proportion of complementary marriages in Buryatia (86.9%) and Yakutia (76.5%) did not differ statistically ($\chi 2$= 3.65, *p*>0.05) (Table 3).

In the analysis of marriages by ethnic belonging, it was found that the maximum proportion of non-complementary assortative marriages was identified among the Yakuts (30%, 21 out 69 AM), while average values were found among the Russians (13%, 12 out 91 AM), and the minimum proportion of non-complementary assortative marriages was identified among the Buryats (3% - 2 out 65 AM) (Figure).

The significant difference in the proportion of non-complementary and segregating marriages, despite the similar frequency of assortative marriages for deafness in Buryatia (81.8%) and Yakutia (77.1%), may be explained by the peculiarities of the genetic structure of hereditary forms of hearing loss in these neighboring regions of Eastern Siberia. When comparing the contribution of pathogenic variants of the *GJB2* gene, which underlie the "connexin" form of hearing loss (DFNB1A, OMIM #220290), it was found that among Buryat patients (5.1%), its contribution was ten times lower than the contribution of this form of hearing loss among Yakut patients (52.7%) ($\chi 2$=36.69, *p*<0.001) (Table 4).

Previously, it was shown that the relatively high proportion of non-complementary and segregating marriages in Yakutia is associated with the prevalence of a major "connexin" form of hearing loss in this region of the world (47% of non-complementary marriages were registered among deaf individuals with DFNB1A) [1]. Currently, this region of Eastern Siberia is known as the largest local hotspot for the accumulation of the allelic form of this disease, associated with the pathogenic variant of the c.-23+1G>A splicing site of the *GJB2* gene, which formed over 800 years ago as a founder effect [6]. Analogous to the previously obtained results in Yakutia, the low proportion of non-complementary and segregating assortative marriages in Buryatia likely suggests the absence of dominance not only of the "connexin" form (contribution of DFNB1A - 5.1%, one of the lowest contributions in the world) [19], but also of any other predominant autosomal recessive form of hearing loss in the Buryat population. In turn, this almost completely negates the effect described by Walter Nance of fixation of pathogenic autosomal recessive alleles associated with assortative marriages for deafness among the indigenous population of the Baikal region.

Conclusion. In the Republic of Buryatia, a high proportion of assortative marriages (AM) for deafness (81.8%) was identified, indicating a high consolidation of deaf communities. Despite the high frequency of AM, the marriage structure was characterized by a high proportion of complementary (86.8%) and a low proportion of non-complementary (5.7%) and segregating assortative marriages (7.3%), which is likely associated with the peculiarities of the genetic structure of hereditary forms of hearing loss in the Republic of Buryatia.

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AGE AND GENDER CHARACTERISTICS OF THE CHEMICAL ELEMENTS IN THE HAIR OF RESIDENTS OF UFA CITY

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The formation of the elemental status of the human body living in a certain region de-pends on the biogeochemical, ecological and geographical factors of the area, nutrition, and pro-fession. The content of chemical elements in the body and their ratio are an indicator of human health. For residents of the city of Ufa, a large industrial center of the Republic of Bashkortostan, References intervals for the concentration of macro- and microelements in hair have been developed. However, to identify deficiencies, excesses or imbalances of chemical elements in the body, it is necessary to take into account gender and age differences. In this regard, the purpose of this work was to study the age and gender characteristics of the content of macro- and microelements in the hair of residents of a large industrial city. The content of 12 chemical elements in the hair of residents of the city of Ufa of the age groups - 18-29 years, 30-44 years, 45-65 years and over 65 years old was determined by atomic absorption spectrometry using devices with flame and electrothermal atomization.

In all age groups, a deficiency of zinc and copper was detected in the hair of both men and women against the background of excess chromium, lead and manganese. Median concen-trations of iron, magnesium, cadmium, mercury and arsenic are within the 25-75 centile range. A deficiency of calcium in the hair of men under 65 years of age was revealed; in women it was found in the range of References values. An excess of 4-11% of the upper limit of permissible Ni content in men was esTableished. There is a tendency towards higher accumulation of cadmium, lead and arsenic in the hair of the male population. In women over 65 years of age, the minimum levels of essential elements are determined - calcium, magnesium, zinc and copper, in men of this age - copper, iron and manganese. Toxic elements cadmium, lead and arsenic accumulate to their maximum at 65 years of age and older.

The results of the study can be used as an additional method for determining the charac-teristics and time of onset of various diseases, as well as for the medical correction of diselementoses and enriching diets with essential micronutrients.

Keywords: macroelements, microelements, hair, age, residents of Ufa.

Introduction. The study of the elemental status of the population is a very promising scientific direction in connection with the growing pollution of the environment with metals and their importance for the functioning of the body. The role of elements for the human body is beyond doubt, for example, calcium is involved in all types of metabolism (protein, mineral, fat, carbohydrate, en-ergy). With its deficiency, metabolic processes are disrupted, bones, muscles, nervous and cardi-ovascular systems suffer, and the immune system weakens [2]. A lack of magnesium can lead to diseases of the nervous system, heart, gallbladder, kidneys, pancreas, cause diabetes mellitus, and atherosclerosis [11]. Iron is a vital element for the growth, division, differentiation and vital activity of body cells, but if consumed in excess, it can cause irreversible damage to cellular structures [7]. A lack of zinc in the body is manifested by the development of skin diseases, de-creased immunity, mental disorders, delayed growth and sexual development [16]. Due to the absence of clinical symptoms in adults, zinc deficiency is a serious problem worldwide. Copper and manganese are part of many enzymes that participate in the redox reactions of the body [8]. With a lack of copper, brittle bones, neutropenia, and arterial aneurysms can develop. Manganese affects growth, reproduction, hematopoiesis, immunity, metabolism, and plays a significant role in protecting the body from the harmful effects of peroxide radicals.

Residents of different regions are characterized by the formation of elemental status, which depends both on the state of the environment and occupational exposure, as well as on the quality of nutrition, lifestyle and other factors.

The city of Ufa, a large industrial center of the Republic of Bashkortostan, is character-ized by a high risk of pollution of atmospheric air, water bodies, and soil with toxic metals asso-ciated with the activities of oil refining enterprises, mechanical engineering, and the intensity of traffic flow [1, 3, 5, 10]. This largely determines the load of metals on the body of residents of the capital of the republic.

Based on previously conducted studies, a database of References values for the elemental composition of biological media (blood, hair) was formed [4]. Among biological media, hair is the most informative and accessible material for analyzing the content of chemical elements in the human body [18, 20]. However, to diagnose diselementosis, it is necessary to take into ac-count the gender and age characteristics of a person, since with age the body becomes more sus-ceptible to the effects of macro- and microelements [6]. In addition, age-related differences in the content of chemical elements in biological media in women and men may explain different susceptibility to certain diseases [15]. An analysis of the literature data showed multidirectional changes in the age-related changes in the content of macro- and microelements in the hair, lead-ing with age not only to a deficiency, but also to an excess of certain elements [6, 15, 19].

Aim of the work: to study the age and gender characteristics of the content of mac-ro- and microelements in the hair of residents of a large industrial city.

Materials and methods. The study involved residents of the city of Ufa who had lived in the area for at least five years and had no professional contact with salts of heavy metals. The examinations were approved by the bioethical commission of the Ufa Research Institute of Oc-cupational Medicine and Human Ecology, protocol No. 01-11 dated November 15, 2022. Hair samples were collected from 296 clinically healthy individuals (125 men and 171 women) with their written informed consent. Samples were

Table 1

The content of chemical elements in men's hair, median (25th and 75th percentile), µg/g

Chemi-cal ele-ment	Age group					
	18-29 years old n=34	30-44 years old n=39	45-65 years old n=31	References values (25 and 75 percentile)	Over 65 years old n=21	References values (25 and 75 percentile)
Ca	429 (347; 623)	489 (398; 658)	475 (376; 611)	**494; 1619**	539 (473; 721)	**354; 1122**
Mg	34 (29; 46)	42 (34; 51)	43 (35; 59)	**39; 137**	38 (29; 42)	**32; 113**
Fe	19.7 (14.0; 27.1)	21.3 (13.2; 28.0)	24.5 (15.9; 29.9)	**11; 24**	15.9 (11.5; 19.5)	**12; 25**
Zn	108 (105; 127)	117 (114; 126)	120 (112; 150)	**155; 206**	120 (113; 141)	**145; 196**
Cu	8.6 (7.4; 10.0)	11.0 (9.1; 12.1)	9.0 (7.0; 11.0)	**9; 14**	6.9 (6.8; 10.0)	**9; 12**
Mn	1.00 (0.72; 1.81)	0.85 (0.66; 1.06)	1.40 (1.10; 1.67)	**0.32; 1.13**	0.80 (0.65; 0.93)	**0.31; 1.29**
Cr	0.74 (0.42; 1.06)	0.99 (0.87; 1.32)	1.63 (1.49; 1.78)	**0.32; 0.96**	1.97 (1.42; 2.01)	**0.20; 0.60**
Ni	0.57 (0.50; 0.62)	0.59 (0.48; 0.66)	0.55 (0.48; 0.60)	**0.14; 0.53**	0.53 (0.39; 0.58)	**0.14; 0.51**
Cd	0.084 (0.076; 0.147)	0.078 (0.052; 0.123)	0.090 (0.078; 0.090)	**0.02; 0.12**	0.066 (0.041; 0.093)	**0.02; 0.13**
Pb	2.63 (2.41; 3.42)	3.32 (2.80; 3.83)	2.44 (2.25; 2.99)	**0.38; 1.40**	3.78 (2.73; 4.20)	**0.50; 1.67**
Hg	0.252 (0.202; 0.307)	0.168 (0.136; 0.204)	0.176 (0.156; 0.187)	-	0.181 (0.176; 0.188)	-
As	0.023 (0.015; 0.034)	0.026 (0.020; 0.032)	0.042 (0.040; 0.054)	**0.00; 0.56**	0.077 (0.062; 0.086)	**0.00; 0.98**

collected in paper bags, hair was cut from the back of the head, and stored in a dry place at room temperature until analysis. The content of the chemical elements calcium (Ca), magnesium (Mg), iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), chromium (Cr), nickel (Ni), cadmium (Cd), lead (Pb), mercury (Hg) and arsenic (As) after sample preparation were determined by atomic absorption spectrometry using devices with flame and electrothermal atomization in accordance with current regulatory documents.

Statistical processing of the results was carried out using the IBM SPSS Statistics 21.0 software package. The normality of distribution was checked using the Kolmogorov-Smirnov test. Multiple comparisons of the content of chemical elements in the hair of the studied study groups were performed using the Kruskal-Wallis test. To esTableish differences between two in-dependent samples (women and men) in terms of element content, the Mann-Whitney test was used. Differences were accepted as statistically significant at p<0.05.

When processing the data, four age groups of the surveyed were identified: 18-29 years, 30-44 years, 45-65 years and over 65 years. The research results, presented as a median with an interquartile range of 25-75 percentiles, were compared with the References values of concentra-tions of chemical elements given in the work of A.V. Skalny (2003) [12].

Results and discussion. The results of a study of the content of chemical elements in the hair of the male and female population of the city of Ufa, divided by age groups, are presented in Tables 1 and 2.

When considering the results of studies on chemical elements, it was esTableished that women's hair contains more calcium than men's in all age groups, except for people over 65 years of age (p<0,0001). The calcium content in the hair of the female population decreases with age (H=19,03; p<0.0001). The median value of calcium concentration in the hair of men in age groups up to 65 years is beyond the lower limit of the physiological norm (494 μg/g). In persons over 65 years of age – within normal limits.

The concentration of magnesium in the hair of city residents, both men and women, is at the lower limit of the physiological norm and no significant changes are observed with age (H=3,69; p=0,297 – men; H=1,39; p=0,708 – women).

The iron content in hair in all age groups is within the References values. The minimum values were observed in those examined aged 18-29 years and over 65 years.

There is a deficiency of zinc in the hair of those examined relative to physiological stand-ards; with age, the median values do not undergo significant differences (H=2,53; p=0,470). In women's hair under 65 years of age, the level of zinc is higher than in men's, but the differences are statistically insignificant (p=0,185).

Copper deficiency was identified in all age groups of those examined, with the exception of men 30-44 years old.

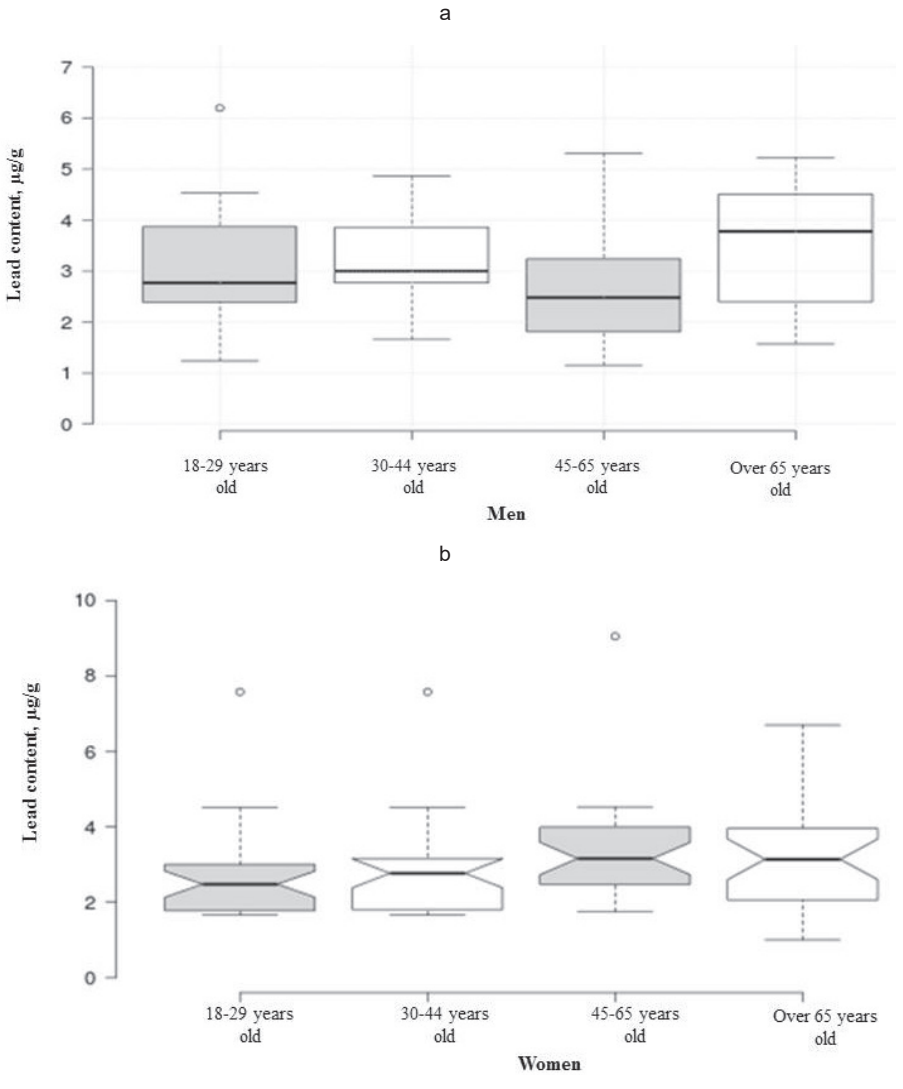
The manganese content in the female population up to 65 years of age decreases from 1.41 to 0.90 μg/g; after 65 years, an increase is observed to 1.08 μg/g. In men, maximum concen-trations were detected at the age of 45-65 years (1.40 μg/g). It should be noted that the median concentrations of manganese in the hair of city residents are quite high, and in women aged 18 to 29 years and men 45-65 years old, they are 25% higher than the upper limit of the physiological level.

An increased content of chromium was found in the hair of those examined. In men under the age of 30, the metal level is within the physiological norm - 0.74 μg/g; with age, its concentration increases to 1.97 μg/g. In women, the highest chromium content in hair (2.85 μg/g) was

Table 2

The content of chemical elements in women's hair, median (25th and 75th percentile), μg/g

Chemi-cal ele-ment	Age group					
	18-29 лет n=47	30-44 лет n=57	45-65 лет n=37	References values (25 and 75 percentile)	Over 65 years old n=30	References values (25 and 75 percentile)
Ca	1049 (875; 1493)	636 (317; 897)	875 (364; 1027)	**494; 1619**	387 (286; 692)	**354; 1122**
Mg	44 (34; 68)	39 (34; 63)	42 (31; 54)	**39; 137**	34 (27; 49)	**32; 113**
Fe	14.6 (12.6; 18.6)	17.1 (14.4; 19.0)	16.8 (14.4; 19.0)	**11; 24**	15.2 (11.3; 19.1)	**12; 25**
Zn	126 (115; 145)	123 (113; 137)	128 (117; 138)	**155; 206**	116 (109; 125)	**145; 196**
Cu	8.1 (6.4; 10.9)	8.7 (7.4; 10.6)	8.6 (7.4; 10.6)	**9; 14**	7.4 (6.6; 10.2)	**9; 12**
Mn	1.41 (0.71; 1.64)	1.14 (0.70; 1.64)	0.90 (0.69; 1.62)	**0.32 1.13**	1.08 (0.83; 1.11)	**0.31; 1.29**
Cr	0.99 (0.80; 1.31)	2.85 (1.04; 3.32)	1.25 (1.07; 1.54)	**0.32; 0.96**	1.23 (1.11; 1.49)	**0.20; 0.60**
Ni	0.44 (0.36; 0.52)	0.52 (0.42; 0.59)	0.45 (0.35; 0.55)	**0.14; 0.53**	0.40 (0.14; 0.48)	**0.14; 0.51**
Cd	0.069 (0.064; 0.074)	0.075 (0.063; 0.125)	0.075 (0.035; 0.109)	**0.02; 0.12**	0.075 (0.067; 0.087)	**0.02; 0.13**
Pb	2.48 (1.78; 3.01)	2.77 (1.81; 3.16)	3.16 (2.48; 4.00)	**0.38; 1.40**	3.27 (2.61; 3.58)	**0.50; 1.67**
Hg	0.142 (0.109; 0.266)	0.198 (0.128; 0.342)	0.204 (0.171; 0.336)	-	0.199 (0.196; 0.211)	-
As	0.023 (0.014; 0.030)	0.023 (0.017; 0.032)	0.030 (0.026; 0.033)	**0.00; 0.56**	0.047 (0.036; 0.054)	**0.00; 0.98**



Lead content in hair of residents of Ufa depending on age: a – for men, b – for women

found in the age category of 30-44 years.

The maximum concentrations of nickel were found in those examined aged 30-44 years, regardless of gender. In all age groups, both men and women, the nickel content is within the upper limit of the permissible level of the element.

Increased concentrations of chromium and nickel in hair are probably due to the geo-ecological characteristics of the region and the spectrum of emissions from industrial enterprises in the city.

The concentration of cadmium in the hair of the male population increases maximally at the age of 45-65, and after 65 years it decreases slightly. In women, no significant differences were found with age (H=1,65; p=0,648). For all respondents, cadmium levels were below the upper physiologically accepTable level.

The lead content in the hair of the city population exceeds the permissible values, but is below the "level of concern" equal to 5 µg/g, which indicates excessive intake of the element into the body [13]. High concentrations of lead in the human body may be associated with industrial pollution and vehicle emissions [17]. In Ufa residents, the maximum accumulation of lead was found in the hair of men and women over 65 years of age. Concentrations of more than 6 µg/g were also recorded in the hair of some men aged 18-29 years (Fig. a)

Research has revealed an increase in lead content in women's hair with increasing age (Fig. b). The maximum values (9.05 µg/g) were determined in the age group 45-65 years.

According to the literature, the background level of mercury in hair varies from 0.5 to 1 µg/g [14]. In the hair of Ufa residents, the concentration of mercury is in the range of 0.1 - 0.33 µg/g. The maximum content of mercury in the hair of men was determined at the age of 18-29 years, in women it accumulates at the age of 45-65.

The arsenic content in the hair of city residents is within the physiological norm; it in-creases with age in both men and women from 0.023 to 0.077 µg/g (H=12,25; p=0,007) and from 0.023 to 0.047 µg/g (H=8,79; p=0,032), respectively. Arsenic is a carcinogen of the first hazard class, and therefore an increase in its concentration in older age groups can lead to an increase in cancer [6].

Studies conducted to study the content of chemical elements in the hair of different age groups of the population of the city of Ufa showed reduced levels of zinc and copper in all age groups. Against the background of copper deficiency, increased levels of manganese were found, a microelement that is its antagonist. Probably, the esTableished low concentrations of zinc and copper in the hair of Ufa residents were formed due to insufficient intake of these elements from food products, but they may also be a consequence of the accumulation of lead, cadmium, mer-cury, manganese and iron in the body.

Iron and nickel were significantly higher (p=0,001 и p=0,011, respectively) in the hair of men compared to the hair of women over the entire age period. Women's hair contains more cal-cium, and the average content of the element decreases with age, which is consistent with litera-ture data [9]. The magnesium content is within the References values. Regarding toxic elements, the maximum concentrations of lead and arsenic were found in respondents over 65 years of age. There is a tendency towards higher accumulation of cadmium, lead and arsenic in the hair of the male population. The mercury content is higher in the hair of women, with the exception of those aged 18-29 years.

Conclusion. Thus, significant differences have been esTableished in the content of micro- and macro-elements in the hair of residents of the large industrial city of Ufa, depending on gen-der and age. The results of the study are quite informative and can be used as an additional method to determine the characteristics and time of onset of various diseases, as well as for med-ical correction of diselementoses and enrichment of diets with essential micronutrients.

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CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN THE REPUBLIC OF SAKHA (YAKUTIA)

A retrospective epidemiological study based on the data of the republican register of systemic lupus erythematosus of the Department of Cardio-Rheumatology of the Pediatric Center RH No.1 – M.E. Nikolaev National Centre of Medicine is presented in the article. The peculiarities of the clinical course and therapy of the disease were analyzed taking into account the ethnicity of the patients. It was found out that the incidence of SLE **is higher among the residents of the Republic of Sakha (Yakutia) compared to the neighboring regions of the Russian Federation.**

Keywords: systemic lupus erythematosus, children, Sakha, Russian, Yakutia.

Introduction. Juvenile systemic lupus erythematosus is one of the most common systemic connective tissue diseases in children with multisystem involvement, serious prognosis, and unpredicTable course [26,8,3]. The severity of the course of SLE in children and adolescents is due to a higher incidence of kidney, CNS, and blood system damage, as well as more severe damage to these organs and systems [22].

The literature data demonstrate a wide variability in the prevalence of systemic lupus erythematosus in children. The prevalence of SLE in children and adolescents is thought to vary according to ethnicity and age [18]. The true prevalence of this disease can be judged only by the results of epidemiologic studies [1,7,2]. According to foreign contemporary sources, the incidence of JUSLE is 0.3-0.9/100,000 children per year [18,28]. The prevalence of JUSLE in children from 1 to 9 years of age ranges from 1.0-6.2, and in 10-19 years of age - from 4.4 to 31.1 cases per 100,000 children [15,16]. The peak of the disease occurs at the age of 10-13 years [6,18]. At the same time, patients with a very early disease debut (up to 5 years of age) usually have an atypical disease pattern (e.g., absence of autoantibodies), a more severe course, and a poor prognosis [16].

The diagnosis of systemic lupus erythematosus is made on the basis of clinical and laboratory findings. There are several classification criteria: ACR 1977, SLICC 2012, EULAR 2019. According to the Russian clinical guidelines for the management of patients with SLE, the diagnosis can be esTableished using the criteria of ACR 1977, SLICC 2012.

The European Alliance of Associations for Rheumatology 2019 criteria are the most relevant in the world literature, but they are not currently included in clinical guidelines for the management of patients with SLE. Therefore, they can be used as confirmatory criteria, but they cannot be used as the sole criteria for diagnosis. These criteria include an entry criterion - the presence of a positive antinuclear factor (ANF) titer on HER-2 cells greater than 1:80 [8]. EsTableishing the diagnosis of SLE requires the presence of at least one clinical criterion and ≥10 points (if the inclusion criteria are met). The criteria are summarized in Table 1.

The main goals of SLE therapy are to minimize damage to involved organs and systems, prevent exacerbations during remission, and improve patients' health-related quality of life [26,13].

Current standards for the management of SLE include combinations of GCS, disease-modifying antirheumatic cytostatic (DMARD) and antimalarial drugs; however, the place of biological therapy has not yet been defined. According to current recommendations, the starting therapy for SLE includes the use of antimalarials at any disease activity [6,8]. The use of systemic glucocorticosteroids can alleviate the course of the disease; it is recommended as pulse therapy with subsequent transition to oral administration in highly active disease course [8]. Prolonged use of GCS has serious consequences, therefore, minimizing their use is required. However, no uniform regimens and rates of reduction until their withdrawal have been developed so far, with the exception of lupus nephritis [26,24,20].

Among the cytostatic drugs used in the therapy of SLE the following are considered: mycophenolate mofetil/mycophenolic acid, azathiprine, methotrexate, cyclosporine and cyclophosphamide.

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Table 1

EULAR 2019 classification criteria for SLE [8]

Clinical criteria	Points
Constitutional criteria:	
- fever (> 38.3° C)	2
Hematological criteria:	
- leukopenia (< 4000/μl)	3
- thrombocytopenia (< 100,000/μl)	4
- autoimmune hemolysis Evidence of autoimmune hemolysis (presence of reticulocytosis, low haptoglobin, increased indirect bilirubin, increased LDH) and a positive direct Coombs test should be presented	4
Psychoneurological criteria:	
- delirium Characteristic features: 1) change in consciousness or level of excitability with a decrease in the ability to focus, 2) development of symptoms from several hours to 2 days, 3) changes in the severity of symptoms during the day, 4a) acute/subacute change in cognitive functions (for example, memory loss or confusion) or 4b) changes in behavior, mood or affect (eg, anxiety, sleep/wake cycle reversal)	2
- psychosis Characteristic features: 1) illusions and/or hallucinations 2) absence of delirium	3
- convulsions (generalized or partial)	5
Damage to skin and mucous membranes:	
- scarless alopecia	2
- oral ulcers	2
- subacute cutaneous lupus erythematosus (SCLE) or discoid lupus erythematosus (DLE)	4
- acute cutaneous form of SLE	6
Damage to the serous membranes:	
- pleural effusion or pericardial effusion (as determined by radiography, CT or MRI)	5
- acute pericarditis Two or more signs must be presented: 1) pericardial pain in the chest (usually acute, worsening with inspiration, decreasing with bending forward), 2) pericardial friction noise, 3) ECG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion according to ultrasound, x-ray, CT, MRI	6
Musculoskeletal manifestations:	
- joint damage: 1 Synovitis involving ≥ 2 joints, characterized by swelling or effusion or 2 Tenderness in two or more joints and at least 30 minutes of morning stiffness	6
Kidney disorders:	
- proteinuria (> 0.5 g/24 hours)	4
- lupus nephritis according to kidney biopsy (class II or V according to ISN/RPS 2003)	8
- lupus nephritis according to kidney biopsy (class III or IV according to ISN/RPS 2003)	10
Immunological criteria	Points
Antiphospholipid antibodies:	
- antibodies to cardiolipin (IgA, IgG or IgM) in medium or high titer - or antibodies to β2-glycoprotein I (IgA, IgG or IgM) - or lupus anticoagulant	2
Complement system proteins:	
- low C3 level or low C4 level	3
- low level of C3 and low level of C4	4
SLE-specific antibodies	
- AT to Sm antigen - AT to dsDNA	6

Initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) is recommended to initiate disease remission and thus shorten the duration of GCS. These drugs are considered as first-line therapy for the treatment of SLE with moderate to active disease [6,8]. In turn, treatment with cytostatic drugs may be accompanied by such adverse events as damage to the blood system, liver and kidneys, as well as an increased risk of infertility and cancer [8,22]. In connection with the above, it is necessary to change the therapy regimen. The use of biologic drugs allows to achieve remission faster and minimize side effects of cytostatic therapy [12]. Several biologic agents have been approved for the treatment of SLE: belimumab, which is approved for use in adults and children; anifrolumab, which is approved in adult practice; and rituximab, which has not yet been officially approved despite its known clinical efficacy [10,17]. Rituximab, a chimeric antibody against CD20; currently has conflicting about its efficacy. On the one hand, in the largest RCTs, the efficacy of rituximab was not different from that of standard therapy [14]. On the other hand, many non-randomized studies, including domestic studies, have shown its efficacy [26,21,9,4,5].

In recent years, the rapid development of rheumatology has made it possible to achieve persistent remission in children with systemic lupus erythematosus using biological therapy [11].

The Republic of Sakha (Yakutia) having a centralized system of rheumatological care for children can be a region for conducting in-depth epidemiological studies based on registers and monitoring of rheumatic diseases. The article presents the data of the regional register of systemic lupus erythematosus in children of the Republic of Sakha (Yakutia) according to the data of the cardio-rheumatology department of the Pediatric Center of the State Budgetary Institution of the Republic of Sakha (Yakutia) "RH № 1-NCoM named after M.E. Nikolaev". The description of clinical and epidemiological characteristics of this disease will allow to improve the routing of these patients and to choose the most effective treatment.

Materials and Methods. In order to describe the clinical and epidemiological characteristics of systemic lupus erythematosus in the Republic of Sakha (Yakutia), we analyzed the data of the regional register according to the data of the Cardio-Rheumatology Department of the Pediatric Center of the State Budgetary Institution of the Republic of Sakha (Yakutia) "RH № 1-NCoM named after M.E. Nikolaev" as the head institution of the diagnostics of the disease. A total of 21 children diagnosed with systemic lupus erythematosus were registered.

Results. By the end of 2023, according to the data of V.M. Argunova, Chief External Rheumatologist of the Far Eastern Federal District, the largest number of children with systemic lupus erythematosus in the regions of the Far Eastern Federal District was registered in the Republic of Sakha (Yakutia) - 21 children, in Primorsky Krai - 4, in the Republic of Buryatia - 3, in Amur Oblast - 1, in Khabarovsk Krai - 1.

The prevalence of systemic lupus erythematosus in the regions of the Far Eastern Federal District is presented in Table 1. As shown in Table 2, the highest prevalence of SLE is registered in the Republic of Sakha (Yakutia) (7.88 cases per 100,000 children), Primorsky Krai (1.23), Republic of Buryatia (1.15), Amur Oblast (0.63), Khabarovsk Krai (0.39).

In the Republic of Sakha (Yakutia) on the basis of the cardio-rheumatology department of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) " RH № 1-NCM named after M.E. Nikolaev" a register of patients with systemic lupus erythematosus is being formed.

Distribution of children with systemic lupus erythematosus:

Yakutsk - 8 children;

rural area: Ust-Aldan District - 2, Megino-Kangalassky District - 1, Namsky District - 1, Suntarsky District - 1, Nyurbinsky District - 1, Verkhnevilyuysky District - 1;

industrial zone: Mirninsky - 2, Aldansky - 1, Lensky - 1,

mixed zone: Khangalassky - 1;

Arctic zone: Anabarsky - 1.

Most patients live in the central part of the Republic of Sakha (Yakutia), including the city of Yakutsk - 8 (38%), rural zone - 7 (33%), industrial zone - 4 (19%), mixed zone -1 (4.7%), Arctic zone - 1(4.7%).

According to the register - 12 (57.1%) children are Sakha, 9 (42.9%) are Russian.

The most frequent cases are girls - 16 out of 21 children (76.2%), 5 of them are boys (23.8%), which corresponds to the published data [2,7]. At the same time, the number of male patients in the group of Sakha children is higher compared to Russian children and makes up 1/3 of patients.

The most frequent clinical manifestations of the disease in the general group were skin lesions (100%), alopecia (33.3%), mucous membrane lesions (42.8%), joints (76.2%), nervous system (23.8%), hematologic and immunologic disorders (71.4 and 100%, respectively). Lupus nephritis was detected in 4 (19%) patients. Severe serositis was rare - 19%.

Treatment of children with systemic lupus erythematosus was carried out strictly according to clinical recommendations. 90.4% of patients were prescribed glucocorticoids, in 28.5% of patients pulse therapy with methylprednisolone was carried out in the debut. Hydroxychloroquine was given to 95% of children, mycophenolic acid to 52.3%. Genetically Engineered Biological Drugs were administered to eleven patients: nine children received rituximab and two received belimumab.

Rituximab was prescribed in cases of aggressive and highly active course of SLE with kidney, central nervous system or blood system damage in the presence of resistance to standard therapy, as well as in cases of glucocorticosteroid toxic-

Table 2

Prevalence of systemic lupus erythematosus in the FEFD regions

Republic of Sakha (Yakutia)	Absolute number	Child population according to census data, 2020	Prevalence 100,000 child population
Primorsky Region	21	266 293	7.88
Republic of Buryatia	4	323 962	1.23
Amur Province	3	260 067	1.15
Khabarovsk Region	1	157 007	0.63
Хабаровский край	1	250 201	0.39

Table 3

Clinical and epidemiologic characteristics of children with systemic lupus erythematosus in the Republic of Sakha (Yakutia)

	Sakha, n (%)	Russian, n (%)	Total, n (%)
Total	12	9	21
Boys	4 (33)	1 (11)	5 (23)
Girls	8 (66)	8 (88)	16 (76)
City	5 (41)	6 (66)	11 (52)
Rural	7 (58)	3 (33)	10 (47)
Clinical characteristics			
Skin lesions including alopecia	12 (100)	9 (100)	21 (100)
Mucous membrane lesions	3 (25)	6 (66)	11 (52)
Joint lesions	9 (75)	7 (77)	16 (76)
Nervous system lesions	3 (25)	2 (22)	5 (23)
Hematologic disorders	9 (75)	6 (66)	15 (71)
Immunologic disorders	12 (100)	9 (100)	21(100)
Kidney lesions	4 (33)	1 (11)	5 (23)
Pleurisy	2 (16)	2 (22)	4 (19)
Treatment			
Glucocorticosteroids	12 (100)	7 (77)	19 (90)
Pulse therapy with methylprednisolone	3 (25)	3 (33)	6 (28)
Hydroxychloroquine	11 (91)	8 (88)	19 (90)
Mycophenolic acid	8 (66)	3 (33)	11 (52)
Rituximab	7 (58)	2 (22)	9 (42)
Belimumab	0 (0)	2 (22)	2 (9)

ity and inability to withdraw GCS on the background of standard therapy.

Characteristics of children in the general group and subgroups of Russian and Sakha children are presented in Table 3.

Discussion. Systemic lupus erythematosus is one of the most severe diseases and unpredicTable connective tissue diseases in childhood. One of its main features is the possibility of affecting any organs and systems.

In this study, all children had skin lesions, more than ¾ of the observed patients had arthritis manifestations, which coincides with the data of other studies [4,23].

CNS involvement was noted in 23% of patients, which coincides with the data of a foreign study [23]. However, this figure is significantly lower than the data of Russian studies, in which CNS involvement was noted in more than 50% of patients [4,5]. The frequency of lupus nephritis in our group of patients was also 23%, which is significantly lower compared to the frequency of renal damage in SLE in other studies [4,5,21,23,29]. Separately, we would like to note that kidney lesions were more frequent in Saha children, while the frequency of central nervous system lesions was the same in the two groups. Hematologic disorders were slightly more frequent in Sakha children.

Laboratory changes, namely immunologic activity were noted in 100% of cases. The above clinical data have been reported by other authors [11,23].

Regarding epidemiologic data, in our cohort of patients, girls suffer 3 times more often from the disease compared to boys, which correlates with the data of modern studies [25,19]. The prevalence of SCD in the Sakha Republic correlates with the data of world studies [15,16].

Therapy with systemic glucocorticosteroids was received by 90.4% of patients, which corresponds to the tactics of patient management according to the data of modern domestic and foreign clinical recommendations. Pulse therapy with methylprednisolone was received by 28%, which is significantly lower compared to domestic studies [4]. Also, hydroxychloroquine was prescribed as a baseline therapy in our cohort of patients in almost all patients; mycophenolic acid preparations were received by more than 50%. Genetically engineered biologic therapy was received by 11 of 21 patients, among whom 9 were treated with rituximab, which is used only as an off-label agent according to current guidelines [27].

In the Sakha subgroup, all children received hormonal therapy, while only 3/4 of the Russian patients received it. Also in the subgroup of Sakha children, the proportion of children receiving mycophenolic acid and rituximab is higher, which allows us to indirectly judge about a more severe course of the disease in this subgroup.

Conclusion. Systemic lupus erythematosus is one of the most important diseases of childhood. The prevalence of this disease in the pediatric population of the Sakha Republic is higher than in neighboring regions, but correlates with the results of studies in Asian populations. According to the register data, the majority of patients live in the central part of the republic, including Yakutsk, while the smallest number of patients live in Khangalassky (mixed zone) and Anabarsky districts (Arctic zone). The most frequent clinical manifestations are skin, joints and mucous membranes. Affection of vital organs: CNS, kidney llesions are noted in 1/4 of patients. Patients from the Republic of Sakha (Yakutia) received genetically engineered biological therapy more often. Further epidemiologic studies are needed to compare the results of juvenile SLE with epidemiologic data in adult patients of the Republic of Sakha (Yakutia) with systemic lupus erythematosus.

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GLUTATHIONE AND LIPID PEROXIDATION LEVELS IN THE BLOOD OF LUNG CANCER PATIENTS

Lung cancer is one of the most commonly diagnosed malignant tumors worldwide and is characterized by high mortality. Lipid peroxidation plays a very important role in the development and progression of lung cancer. In this regard, the purpose of this study was to evaluate the status of lipid peroxidation and the glutathione system in patients with lung cancer depending on the histological form and stage of the disease.

In this work, 100 people with lung cancer with various histological forms and stages of the disease were examined. The intensity of free radical oxidation of lipids was assessed by the accumulation of malondialdehyde. The indicators of the glutathione system were assessed by the concentration of the reduced form of glutathione and the activity of enzymes: glutathione peroxidase, glutathione reductase, glutathione transferase.

Our data indicate that as the clinical stage of lung cancer develops, the level of lipid peroxidation increases, against the background of inhibition of the glutathione system (decreased glutathione reductase activity). Higher levels of malondialdehyde in patients with adenocarcinoma suggest that tumor development may be more closely related to oxidative stress.

Keywords: lipid peroxidation, antioxidant protection, lung cancer, adenocarcinoma, squamous cell carcinoma, large cell carcinoma, small cell lung cancer.

Introduction. Lung cancer ranks first in the structure of cancer incidence worldwide [27]. This disease has one of the lowest rates of 5-year survival among oncopathologies [27]. Lung cancer is a multifactorial disease, in the development of which both exogenous (smoking, asbestos, radon, arsenic, nickel, cadmium, chromium, polycyclic aromatic hydrocarbons, chloromethyl ether, smoke from wood fuel, climatic factors, etc.) and endogenous (chronic diseases, hereditary predisposition, age hormonal shifts) factors play a significant role [21,26]. It should be noted that smoking is one of the most significant risk factors for the development of lung cancer [5]. According to Bade BC, Dela Cruz CS, 2020, if we examine lung cancer in people who have never smoked, then this disease would rank seventh in the world among oncopathologies [6].

According to many domestic and foreign authors, the initiation of free radical reactions plays an important role in the development of lung cancer [2,3,4]. Many of these exogenous and endogenous factors stimulate the development of oxidative stress in lung tissue. It should be noted that unlike other organs, due to anatomical and physiological characteristics, the lung is directly affected by a powerful oxidizer – oxygen.

Lung tissues have a fairly powerful protective system (antioxidant system) that suppresses the development of oxidative stress, the main link of which is the glutathione system. Glutathione is an intracellular tripeptide, which, in addition to antioxidant protection, performs a large number of important functions: participates in the detoxification of xenobiotics [1], promotes repair of damaged DNA [7]; provides active amino acid transport [23]; participates in the modulation of the immune response [20]; regulates the redox status of the cell [19], etc. Glutathione is a key coenzyme of enzymes (glutathione peroxidase, glutathione reductase, glutathione transferase) included in the glutathione system. The functioning of enzymes: glutathione peroxidase (an enzyme involved in the utilization of lipoperoxides and hydrogen peroxide) and glutathione transferase (an enzyme involved in the detoxification of electrophilic xenobiotics) depends on the immediate concentration of the reduced form of glutathione. The main pool of the reduced form of glutathione is supported by glutathione reductase. Information on the role of the glutathione system and lipid peroxidation, depending on the stage of the disease and the development of various histological forms of lung cancer, is scarce.

In this regard, the purpose of this study was to assess the state of the glutathione system and lipid peroxidation in the blood of lung cancer patients, depending on the histological type of tumor.

Material and methods. This work was carried out in 2024 on the premises of the Department of Epidemiology of Chronic Noncommunicable Diseases of the Yakut Science Centre of Complex Medical Problems in cooperation with the Yakut Republican Oncology Centre. In the study, 100 people with lung cancer were examined. The general characteristics of the patients are shown in Table 1.

The protocol of the study was approved by the local Committee on Biomedical Ethics at the Yakut Science Centre of Complex Medical Problems No. 52 dated 03/24/2021, decision 1.

The control group was selected based on age, gender and ethnicity. It included 60 volunteers, selected based on age. The main criterion for selection to the control group was the absence of any oncological diseases.

The study material was venous blood, which was taken on an empty stomach from the ulnar vein. The intensity of free radical lipid oxidation was determined by spectrophotometric methods based on the accumulation of TBK-active products in blood serum (TBK-AP) [11]. The following indicators of the glutathione system were determined in the hemolysate of red blood cells: glutathione peroxidase activity [17], glutathione reductase activity [10], glutathione transferase activity [14], reduced glutathione level [29]. The hemolysate of red blood cells was prepared

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by diluting the purified erythrocyte mass with distilled water in a ratio of 1* 20.

Statistical processing of the obtained data was carried out using the SPSS 23 statistical software package for Windows. Standard methods of variational statistics were used: calculation of means, standard errors, 95% confidence interval. The distribution of the sample for "normality" was evaluated using the Kolmogorov-Smirnov single-sample criterion. The reliability of the differences between the means was assessed with a normal "distribution" using the Student's t criterion for independent samples, and with a different from the "normal" distribution using the Mann-Whitney criterion. The

Table 1

Brief description of the examined patients

Histological forms of lung cancer		Small cell lung cancer, n	Adenocarcinoma, n	Squamous cell lung cancer, n
All (n)		18	26	50
Sex	M	10	22	42
	F	8	4	8
Age		67.000±1.527	64.600±1.080	66.666±2.677
Stage	First	0	2	2
	Second	0	4	6
	Third	4	10	24
	Fourth	14	10	18

Table 2

The level of indicators of the glutathione and malondialdehyde system in patients with lung cancer and those without oncopathology

Groups	Control group (n=60)	Больные с онкопатологией легких			
		Stage 1 (n=4)	Stage 2 (n=12)	Stage 3 (n=40)	Stage 4 (n=44)
GPx U/ml	10.169±0.496	12.065±1.735	9.628±0.1529	11.605±1.103	11.385±1.001
GR U/ml	11.821±0.883	4.548±0.576	**2.935±0.744***	**3.024±0.342*.****	**4.179±0.570*.***.****
GST U/ml	4.050±0.066	1.488±0.504	**1.705±0.265***	**2.058±0.197***	**1.931±0.225***
GSH mcmol/L	2.285±0.072	2.965±0.206	2.704±0.199	2.205±0.365	2.148±0.404
MDA mcmol/l	1.109±0.067	1.999±0.123	**2.127±0.136***	**2.748±0.249*.****	**2.846±0.239*.*****

Note: * p<0.05 compared with the control group; ** p<0.05 compared with patients of stages 2 and 3; *** p<0.05 compared with patients of stages 2 and 4; **** p<0.05 compared with patients of stages 3 and 4.

Table 3

Indicators of the glutathione system and the level of malondialdehyde, depending on the histological form of lung cancer 1-2 stages of the disease

Histological form	GPx U/ml	GR U/ml	GST U/ml	GSH mcmol/L	MDA mcmol/l
Adenocarcinoma (n=6)	9.955±2.034	2.628±0.214	1.309±0.446	2.4233±0.303	1.958±0.198
Squamous cell lung cancer (n=8)	11.528±1.701	3.577±1.020	1.835±0.278	2.207±0.539	1.944±0.116
Small cell lung cancer (n=0)	-	-	-	-	-

Table 4

Indicators of the glutathione system and the level of malondialdehyde, depending on the histological form of lung cancer, stages 3-4 of the disease

Histological form	Control group (n=60)	Adenocarcinoma (n=20)	Squamous cell lung cancer (n=42)	Small cell lung cancer (n=18)
GPx U/ml	10.169±0.496	11.335±1.474	12.068±0.969	11.418±1.988
GR U/ml	11.821±0.883	5.218±1.096 *	4.164±0.555 *	4.324±0.554 *
GST U/ml	4.050±0.066	1.808±0.202 *	1.889±0.205 *	2.441±0.234*.**
GSH mcmol/L	2.285±0.072	2.730±0.332	2.900±0.208 *	2.885±0.283 *
MDA mcmol/l	1.109±0.067	2.913±0.051 *	2.593±0.316 *	2.295±0.205*.***

Note: * p<0.05 compared with the control group; ** p<0.05 compared with adenocarcinoma and squamous cell carcinoma; *** p<0.05 compared with adenocarcinoma.

data in the Tables are presented in the form M±m, where M is the mean, m is the error of the mean. The probability of validity of the null hypothesis was assumed at $p<0.05$.

Results and discussion. According to the data obtained, the concentrations of malondialdehyde and reduced glutathione in the blood of lung cancer patients were 1.9 times higher, p=0.010 (2.187±0.091mmol/l) and 1.2 times (2.122±1.332mmol/l), compared with people without cancer. The activity of glutathione peroxidase in the blood of patients was 1.1 times higher (11.290±0.647U/ml), and the activity of glutathione reductase and glutathione transferase were significantly lower by 2.8, p=0.000 (4.131±0.354U/ml) and 2.1, p=0.001 (1.937±0.131U/ml) times, respectively.

The data obtained by us indicate an intensification of free radical processes in the body of patients with lung cancer, as indicated by an increase in the level of the final product of lipid peroxidation – malondialdehyde and, considering the inhibition of the glutathione system, a decrease in the activity of glutathione reductase, which is consistent with literary sources [18].

The values of the biochemical parameters taken into account by us in patients, depending on the severity and in relatively healthy individuals who do not have cancer, are presented in Table 2.

The data obtained indicates that in the blood of patients with lung cancer, even in patients where the cancer is in its initial stage, the indicators of glutathione transferase and glutathione reductase activity, as well as the concentration of malondialdehyde, significantly changed compared with those without cancer. Although the indicators we take into account are not specific to this pathology, they can probably be used as additional indicators of prognostic value for early diagnosis of lung cancer. However, additional research is needed to confirm these results.

Histologically, lung cancer is divided into two groups: small cell carcinoma and non-small cell carcinoma. Non-small cell lung cancer can be divided into three histological forms: adenocarcinoma, squamous cell carcinoma and large cell carcinoma [30]. The level of biochemical parameters, taking into account the histological form and severity of the disease, is presented in Tables 3 and 4.

Due to the fact that lung cancer is very difficult to detect in its early stages, there isn't enough stage 1-2 patients to judge the statistical significance of differences in groups with various histological forms of this pathology.

In the analysis of patients with cancer stages 3-4, significant differences in the activity of glutathione reductase, glutathione transferase and malondialdehyde concentrations were revealed between lung cancer patients with different histological types and the control group (Table 4). The average value of malondialdehyde in patients with small cell lung cancer was 1.3 times lower than in patients with adenocarcinoma. In patients with small cell carcinoma, the activity of glutathione transferase was 1.3 times higher than in the group of patients with adenocarcinoma and squamous cell lung cancer. There were no statistically significant differences in other biochemical parameters between different histological forms of lung cancer.

Studies by previous authors indicated that the concentration of malondialdehyde increases in the blood of patients with lung cancer [18,28]. Some authors claim that an increase in lipid peroxidation is associated with clinical tumor progression [13,25]. The data obtained by us are consistent with the fact that as the stage of lung cancer increases, there is an increase in lipoperoxide processes in patients. However, in the study by Xiang M, Feng J, Geng L, 2019, the authors found no significant differences in the levels of total oxidant status and oxidative stress index. [31]

There are conflicting data on antioxidant protection in patients with oncopathology, some claim activation of the antioxidant system [9,15], other authors report a decrease in antioxidant protection [22,24]. Our study showed that there is no significant change in the level of the reduced form of glutathione in the blood of lung cancer patients, however, there is an inhibition of the glutathione system due to a decrease in the activity of the enzyme that restores glutathione from its oxidized form – glutathione reductase. We also noted a significant decrease in the activity of glutathione transferase. Depending on the stage of lung cancer, we noted a significant increase in the level of reduced glutathione in its initial stage by 1.3 times.

Conclusion. In conclusion, the available data indicate that as the clinical stage of lung cancer develops, during inhibition of the activity of the enzyme glutathione reductase, the level of lipid peroxidation increases. The higher level of malondialdehyde in patients with adenocarcinoma suggests that oxidative stress plays a fairly important role in the development of this tumor.

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ASSOCIATION OF THE *FTO* GENE POLYMORPHISM (RS9939609) WITH BODY MASS INDEX IN THE YAKUT POPULATION

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The study is devoted to studying the relationship between the rs9939609 polymorphism of the FTO gene and body mass index (BMI) in the Yakut population. The sample consisted of 521 participants of Yakut nationality without diabetes mellitus and not registered with a dispensary, aged from 18 to 75 years, 222 women and 299 men. An analysis of the distribution of frequencies of occurrence of alleles and genotypes was carried out, as well as an analysis of BMI indicators in groups with different genotypes of the rs9939609 polymorphism of the FTO gene, during which similarities were found in the ratios of allele frequencies with populations of East and South Asia. Statistical analysis using the Kruskal-Wallis test with multiple analysis Dunn's test with Bonferroni correction and the odds ratio (OR) with the significance test with Yates' correction within the study showed a weak association of obesity with the risk allele A when comparing the group with normal BMI and the combined group of obesity + pre-obesity p = 0.043.

Keywords: obesity, FTO, rs9939609 polymorphism, Yakut population, BMI.

Introduction. Obesity is one of the most common health problems throughout the world, including the population of Yakutia. It is characterized by excess accumulation of fat in the body, which can have serious consequences for a person's health. Obesity is caused by a combination of genetic, psychological, behavioral and environmental factors, such as diet, level of physical activity and lifestyle. Large weight gain leads to the risk of developing a variety of serious diseases, including diabetes, cardiovascular disease and some types of cancer [11]. Addressing the problem of obesity requires a comprehensive approach, including lifestyle changes, a balanced diet and increased physical activity. Developing and implementing effective interventions to prevent obesity is a critical public health challenge [4, 5].

Genome-wide association studies (GWAS) have identified at least 52 obesity susceptibility loci at the population level [10]. The FTO (Fat Mass and Obesity-Associated) gene encodes a protein that plays a role in regulating appetite and metabolic processes. FTO belongs to the superfamily of Fe(II)- and 2-oxoglutarate-dependent dioxygenases and plays a role in the demethylation of RNA and single-stranded DNA [9, 15]. A number of animal studies have shown that FTO expression occurs in the hypothalamus, predominantly in the arcuate, paraventricular, dorsomedial and ventromedial nuclei, which are key brain regions that control appetite [13,15]. The rs9939609 polymorphism is one of the most studied variants in the FTO gene and is associated with the risk of obesity [8]. The association of FTO variants with obesity was confirmed by a study by Church Ch. et al. (2010) in mice, they found that increased FTO expression leads to increased fat mass and obesity due to hyperphagia. The authors suggest that at-risk single nucleotide polymorphisms (SNPs) in the human FTO gene may enhance FTO expression [12]. Research by Daya M et al. (2019) found that individuals with the T to A polymorphism of the FTO rs9939609 gene show a pReferences for high-calorie foods, such as high-fat foods, which leads to weight gain due to changes in gene expression FTO in the hypothalamus [11].

Although there has been a lot of research into genetic susceptibility to obesity in recent years, research findings may also differ among different peoples and ethnic groups. Studying individuals from different ethnic groups can help us better understand the genetic factors that influence susceptibility to obesity and improve our understanding of the different findings across different populations [1, 3].

The purpose of this study was to study the association of T/A polymorphism rs9939609 of the FTO gene in the Yakut population and its relationship with BMI in people without diabetes.

Materials and research methods. The study was conducted in the laboratory of hereditary pathology of the department of molecular genetics of the Yakut Scientific Center for Complex Medical Problems (YSC KMP). For the study, DNA samples were used from the bioresource collection of the YSC KMP using the UNU “Genome of Yakutia” (reg. No. USU_507512). All study participants gave written consent. The study protocol was approved by the local biomedical ethics committee at the YSC KMP.

The sample consists of 521 randomly selected participants of Yakut nationality without diabetes, aged from 18 to 75 years, 222 women and 299 men. The main criterion for dividing into groups was body mass index (BMI) and the absence of diabetes mellitus. Body mass index (BMI) was assessed using the Western Pacific Region (WPRO) criteria for Asian residents [16]. With a BMI <18.5%, body weight was considered insufficient, within 18.5–22.9% – normal, within 23.0–24.9 kg/m2 – overweight. In the range of 25.0–29.9 kg/m2, class I obesity was diagnosed, ≥ 30.0 kg/m2 – class II obesity, ≥ 35.0 kg/m2 – class III obesity, ≥ 40.0 kg/m2 – obesity IV degree. Three groups

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were formed: a group with normal BMI, a group with overweight and a general group with obesity of all degrees.

For molecular genetic analysis, DNA extraction was carried out from whole blood using a commercial DNA extraction kit "Newteryx" (Russia, Yakutsk).

The study of single nucleotide polymorphisms was carried out using the polymerase chain reaction (PCR) followed by restriction fragment length analysis (RFLP). The conditions for amplification and restriction are presented in Table 1.

Interpretation of genotyping results was performed based on different band patterns of the region with the rs9939609 polymorphism (Figure).

The analysis of the obtained data was carried out using the Microsoft Office Excel 2010 program. To examine the association between unfavorable allele frequency and obesity, we used a four-field contingency Table and applied the χ-square test with Yates' correction. To assess the significance of the odds ratio, the boundaries of the 95% confidence interval (CI 95%) were calculated.

Comparison of mean BMI values depending on the genotype was carried out using the Kruskal-Wallis test with the method of multiple comparisons according to Dunn's test using the Bonferroni correction. For the analysis, we used the online calculator Statistics Kingdom [6]. Results were considered significant at $p < 0.05$.

Results and discussions. Analysis of the odds ratio of allele frequencies showed some connection between allele A in the compared groups of obesity and normal BMI (OR = 1.643; CI 1.083-2.492; p = 0.054), but did not reveal significant differences between samples with pre-obesity and normal BMI (OR = 1.65; CI = 0.967-2.816; p = 0.174). At the same time, in the combined sample of obesity + preobesity, an association of the A allele with obesity was revealed (OR = 1.644; CI 1.101-2.455; p = 0.043). (Table 2).

In the analysis of BMI scores (Table 3), the Kruskal-Wallis H test indicated that there was a significant difference in mean BMI scores between genotypes in the entire sample (p = 0.037). However, when considering each individual sample, no significant differences were found.

Table 4 presents the frequencies of alleles and genotypes of the rs9939609 polymorphism in various populations; data were taken from a database of 1000 genomes [7]. On average, in all populations, the A allele occurs in 34% of cases, and the T allele in 66%.

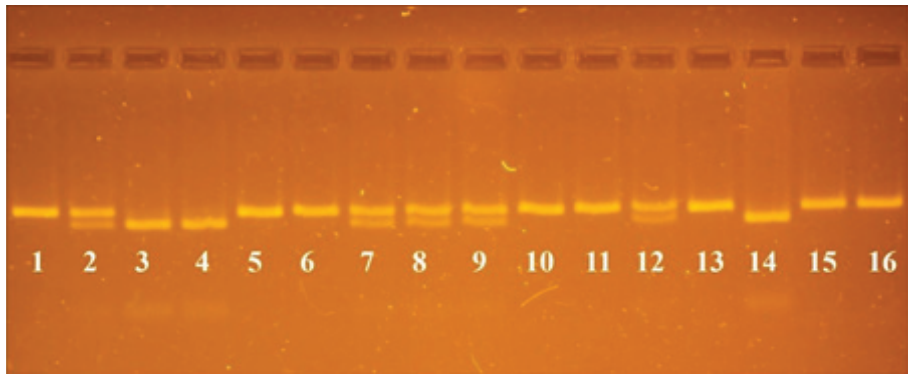
When comparing the obtained frequencies of alleles and genotypes of other populations of the world [7] with the Yakuts, similarities were revealed with the Vietnamese population of Ho Chi Minh City in East Asia, the Pakistani population of Lahore, the Gujarati Indian population in Houston and the Bengali population in Bangladesh in South Asia (Table 4).

The association of the rs9939609 FTO polymorphism with BMI and other indicators associated with obesity has important clinical implications, as it may be associated with the presence of several components of the metabolic syndrome [3]. A study by Boyarinova M.A. et al (2018) found that the presence of the A allele reduced the likelihood of metabolic health in obese patients. The presence of the TT genotype of the FTO gene in obesity is probably associated with the formation of a metabolically healthy obesity phenotype [2]. Our study involved only healthy individuals who were not regis-

Table 1

Conditions for PCR-RFLP analysis

Gene	Primer sequence	Length of amplification bp.	Annealing temperature	Restriction endonuclease	Length of restriction fragments bp.
FTO	5'-TGGGCCTGAAGTCCGAGGGT-3'	182 п.н.	65ºC	*Zrm I*	*TT*– 182 *AT* – 182, 154, 28 *AA* – 154, 28



Electrophoregram of polymorphism rs9939609 of the FTO gene on 4% agarose gel after RFLP: 1, 5, 6, 10, 11, 13, 15 and 16 – TT genotype (182 bp); 2, 7, 8, 9 and 12 – AT genotype (182, 154, 28 bp); 3, 4 and 14 – AA genotype (154, 28 bp)

Table 2

Frequency distribution of alleles and genotypes of polymorphism rs9939609 of the FTO gene with odds ratios (OR)

Sample	n	Genotypes, %			Alleles, %		OR	p
		TT	AT	AA	T	A	(ДИ 95 %)	
Pre-obesity	93	51.6	40.9	7.5	72.0	28.0	1.65	0.17
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	(0.967-2.816)	
Obesity	290	51.7	41.4	6.9	72.4	27.6	**1.643**	**0.05**
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	**(1.083-2.492)**	
Pre-obesity + Obesity	383	51.7	41.3	7.0	72.3	27.7	**1.644**	**0.04**
Normal BMI	138	63.8	29.7	6.5	78.6	21.4	**(1.101-2.455)**	

Note: OR (95% CI) – odds ratio with 95% confidence interval, p – significance with Yates correction, BMI – body mass index.

Table 3

BMI indicators for different genotypes of the rs9939609 polymorphism of the *FTO* gene

Показатель		Генотип			p
		TT	AT	AA	
Normal BMI	Number of patients	88	41	9	0.536
	Body mass index (kg/m²)	21.0±0.174	21.0±0.175	21.4±0.541	
Pre-obesity	Number of patients	48	38	7	0.075
	Body mass index (kg/m²)	23.9±0.187	23.8±0.194	24.3±0.192	
Obesity	Number of patients	150	120	20	0.192
	Body mass index (kg/m²)	29.8±0.073	30.7±0.082	31.9±1.247	
Pre-obesity+ Obesity	Number of patients	198	158	27	0.435
	Body mass index (kg/m²)	28.4±0.066	29.1±0.070	29.9±1.126	
Entire sample	Number of patients	286	199	36	**0.037**
	Body mass index (kg/m²)	27.1±0.056	27.4±0.066	27.8±0.185	

Note: p according to the Kruskal-Wallis test

Table 4

Frequency of occurrence of alleles and genotypes of the rs9939609 polymorphism of the *FTO* gene in different populations

Population	Subpopulation	Alleles. %		Genotypes. %		
		T	A	TT	TA	AA
All		66	34	45.7	40.6	13.7
African (AFR)		51	49	25.6	50.1	24.4
	African Caribbean in Barbados	51	49	27.1	46.9	26
	African Ancestry in Southweast US (ASW)	54	46	29.5	49.2	21.3
	Esan in Nigeria (ESN)	54	46	27.3	52.5	20.2
	Gambian in Western Division. The Gambia (GWD)	55	45	33.6	42.5	23.9
	Luhya in Webuye. Kenya (LWK)	44	56	21.2	46.5	32.3
	Mende in Sierra Leone (MSL)	49	51	18.8	61.2	20
	Yoruba in Ibadan. Nigeria (YRI)	48	52	21.3	53.7	25
American (AMR)		74	26	54.8	38	7.2
	Colombian in Medellin. Colombia (CLM)	66	34	43.6	44.7	11.7
	Mexican Ancestry in Los Angeles. California (MXL)	77	23	57.8	39.1	3.1
	Peruvian in Lima. Peru (PEL)	92	8	85.9	11.8	2.4
	Puerto Rican in Puerto Rico (PUR)	64	36	37.5	52.9	9.6
East Asian (EAS)		83	17	70	26.2	3.8
	Chinese Dai in Xishuangbanna. China (CDX)	85	15	73.1	23.7	3.2
	Han Chinese in Bejing. China (CHB)	84	16	72.8	23.3	3.9
	Southern Han Chinese. China (CHS)	86	14	76.2	20	3.8
	Japanese in Tokyo. Japan (JPT)	83	17	68.3	28.8	2.9
	Kinh in Ho Chi Minh City. Vietnam (KHV)	77	23	59.6	35.4	5.1
European (EUR)		59	41	37.2	19.9	42.9
	Utah residents with Northern and Western European ancestry (CEU)	56	44	30.3	50.5	19.2
	Finnish in Finland (FIN)	61	39	41.4	38.4	20.2
	British in England and Scotland (GBR)	61	39	37.4	47.3	15.4
	Iberian populations in Spain (IBS)	63	37	43.9	37.4	18.7
	Toscani in Italy (TSI)	54	46	32.7	42.1	25.2
South Asia (SAS)		71	29	50.1	42.1	7.8
	Bengali in Bangladesh (BEB)	72	28	50	44.2	5.8
	Gujarati Indian in Houston. TX (GIH)	76	24	57.3	36.9	5.8
	Indian Telugu in the UK (ITU)	70	30	49	41.2	9.8
	Punjabi in Lahore. Pakistan (PJL)	72	28	51	42.7	6.2
	Sri Lankan Tamil in the UK (STU)	66	34	43.1	46.1	10.8
Yakut population		74	26	54.9	38.2	6.9

tered for any diseases, which could have played some role in the obtained results on the frequencies of alleles and genotypes of the rs9939609 polymorphism of the FTO gene. A limitation of the study is also the lack of data, particularly on lifestyle factors such as diet and daily activity patterns.

Conclusion. This study showed similarity in the frequencies of alleles and genotypes of the rs9939609 polymorphism of the FTO gene between the populations of South and East Asia with the Yakut population. Also, an analysis of the odds ratio of allele frequencies showed a significant association of allele A with the risk of obesity, while the analysis of BMI indicators for different genotypes did not reveal statistically significant differences in individual groups, however, when multiple analysis of Dunn's test with Bonferroni correction in the entire sample, there was a significant association between the risk allele A and also BMI indicators. From the results of the study, we can assume a weak connection between obesity and the studied polymorphism in the Yakut population.

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DIAGNOSTIC AND TREATMENT METHODS

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METHOD OF FIXING FULL REMOVABLE PROSTHESES ON THE TOOTHLESS UPPER JAW USING SERIES-CLOSED VALVE ZONES

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There has been an increase in the ratio of elderly and senile people to the general population who need prosthetics. At the same time, complete teeth loss leads to various anatomical-topographical changes in the denture bed in the elder age group. Meanwhile, there are insufficient researches aimed at improving the fixation and stabilization of complete removable dentures, which determined the direction of our study. The aim of this research was to increase the degree of retention of complete removable dentures by creating additional valve zones, taking into account the individual anatomical-topographical variability of the denture bed structure of the maxilla. **Material and Methods.** Prosthetics of 115 people aged from 60 to 93 years old with complete teeth loss on the upper jaw was carried out. Prosthetics were performed by the method of determining the locations of individual valve zones in the area of the pliable mucous membrane of the denture bed on the edentulous upper jaw, including the use of a digital model of the denture bed obtained by cone-beam computed tomography (CBCT) with the use of a contrast agent and subsequent analysis in 3D graphics editors. **Results.** Additional retention elements were determined with the individual anatomical-topographical variability of the location of the malleability zones, places of exit of the neurovascular bundles and places with dense mucosa on the upper jaw to improve the retention of the prosthetic structure. At the same time, the obtained results characterize the increase in the efficiency of functional retention of complete removable prostheses due to the creation of consecutive concentrically closed valve zones, which create negative pressure zones medial to the borders of the prosthetic bed. Discussion. The developed method provides conditions for increasing the efficiency of retention and functionality of complete removable plate prostheses on the upper jaw due to accurate determination of individual anatomical-topographical features of the prosthetic bed, thickness of the mucous membrane, places of exit of neurovascular bundles, torus and exostoses. The probability of vascular compression with microcirculation disturbance and traumatization of soft tissues adjacent to the prosthetic structure was significantly reduced. The method minimizes alternating loads in the area of torus and exostoses in the area of maxillary tubercles, which significantly reduces the probability of fracture of the base of a full removable plate prosthesis. **Conclusion.** Our method in case of depressurization of external valve zones increases the degree of retention and stabilization of complete removable orthopedic constructions on the upper jaw during the operation. At the same time, retention is provided by additional internal valve zones located in places where there is sufficient pliability and there are no neurovascular bundles and exostoses.

Keywords: upper jaw, anatomy and topography, complete teeth loss, denture bed, full removable plate prosthesis, retention, prosthetic efficiency.

Introduction. Recently, the ratio of elderly and senile age people to the general population who need prosthetics has increased [1, 2]. The main etiologic factors of tooth loss in these age groups are the prevalence of dental caries and its complications, inflammatory processes of periodontal tissues, which require further improvement of therapeutic and preventive measures [2, 5, 6,]. Meanwhile, tooth loss in the older age group leads to various anatomical-topographical changes in the prosthetic bed area, which are associated with significant atrophy of the alveolar processes and their changing relations with the maxillary sinuses and the base of the pear-shaped hole, mandibular canal, making it difficult to plan and manufacture prosthetic structures. At the same time decompensated forms of general medical pathologies make the use of dental implants impossible. Meanwhile, production of removable prostheses is the main method of medical and social rehabilitation of patients in these clinical cases. In this regard, orthopedic rehabilitation of patients with the complete removable plate prostheses requires an individual approach taking into account the above-mentioned changes in the alveolar process and oral mucosa [7, 8]. Today, there are no researches improving prostheses fixation and stabilization, which determined the direction of our study.

The research objective is to increase the degree of retention of complete removable plate prostheses by creating additional valve zones taking into account the individual anatomical-topographical variability of the structure of the maxillary denture bed.

Materials and methods. Prosthetics of 116 people aged from 60 to 93 years old, males - 23,53±1,38% (27) and females - 76,47±0,43% (89) with complete upper jaw teeth loss was carried out. The research was conducted at the clinic of M.K.Ammosov North-Eastern Federal University, the center of radiological diagnostics "Voxel" (Yakutsk) and the dental clinic "Harmony" (Yakutsk).

Prosthetics were performed by the developed method of determining the location of individual valve zones in the area of the pliable mucous membrane of the denture bed on the edentulous maxilla using a digital model of the prosthesis boundaries obtained by cone-beam computed tomography with the use of contrast agent and subsequent analysis in 3D graphics editors (Patent for Invention № 2792541 from 22.03.2023) [4]. For this purpose, a digital model of the prosthesis boundaries was used based on the results of cone-beam computed tomography ("OnDemand 3D Dental" ("KaVo Russia" LLC Ace Dental RUS)) with the

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use of a barium sulfate contrast agent "Barium sulfate" [4]. Bar-VIPS barium sulfate contrast agent (manufacturer LLC Firm VIPS-Med 141190 Russia, Moscow Region, Fryazino, Zavodskoy Str., 3A, Tel (495)22-181-22 internet: www.vipsmed.ru. Registration number in the state Registration number in the state register of medicines R No000178/0, date of registration 18.02.2011) and subsequent analysis in 3D graphics editors ("Blender 2.91 References Manual"). Informed voluntary consent was obtained from all patients during the study.

Statistical processing was carried out according to standard methods of variation statistics. Calculation of the sample volume and its size (sample size) were carried out by the method of K.A. Otdelnova (1980), which stipulates the necessary volume of clinical material to obtain reliably significant data [3]. At the same time, the research indicators were representative. Correlation analysis of the obtained results was carried out with the determination of the Spearman's coefficient (rs) in the software package "SPSS", version 22 of IBM SPSS license."

Clinical studies were conducted on the basis of the ethical principles of the Helsinki declaration (1964) and the decision of the local ethical committee of Medical Institute of M.K. Ammosov NEFU" (protocol No29 of 08.04.2021).

Results and discussion. The main purpose of the developed method is to increase the retention of complete removable prosthetic constructions taking into account individual anatomical-topographical features of the prosthesis boundaries on the upper jaw. In this case, to determine the optimal locations of the valve zones, CBCT was performed, where tomography was carried out with the use of the contrast agent "Bar-VIPS". For this purpose, the patient's oral cavity was filled with a contrast agent suspension, which is obtained by adding 240 g of powder to 60 ml of boiled water while stirring for 3 min, where the volume of the resulting suspension is 120 ml. The suspension was then held in the mouth by the patient without swallowing and tomographic examination was performed (Fig.1). Processing of the obtained series of images in "Dicom" format was converted into "Stl" format (Fig.2 a, b, c, d) of the digital model of the maxilla, where we identified areas with pliable mucosa with the help of neural network (Fig.3), avoiding the location of the maxillary greater palatine and incisor aperture, and areas of irregularities of the medial palatine suture and maxillary tubercles, where masks were formed in

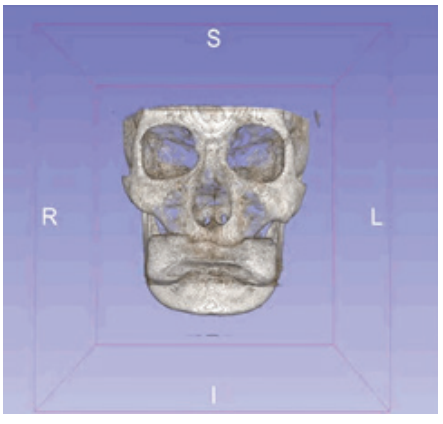
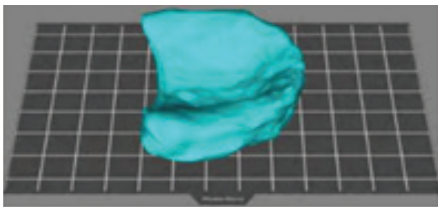


Fig. 1. CT result with contrast agent of the oral cavity in ".dcm" format

a



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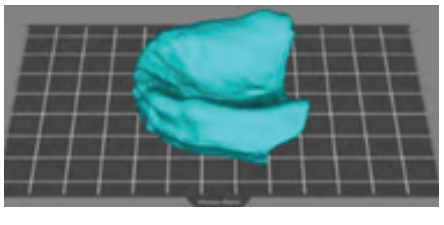

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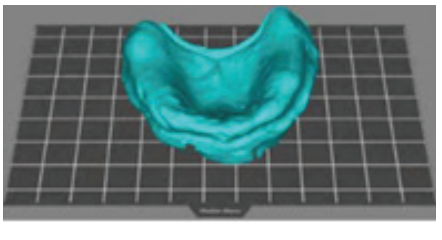

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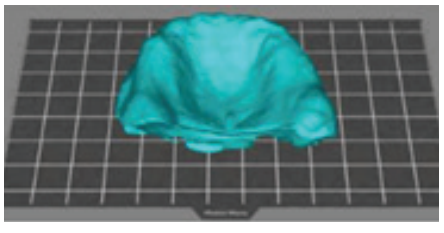


Fig. 2. Obtaining a volumetric digital model of the edentulous maxilla on the basis of cone-beam tomography (a - left view, b - right view, c - front view, d - back view)

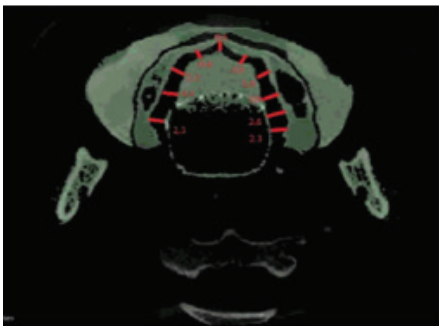


Fig. 3. Zones identification of the supple mucosa of the denture bed in the area of the lateral sections of the middle third of the hard palate

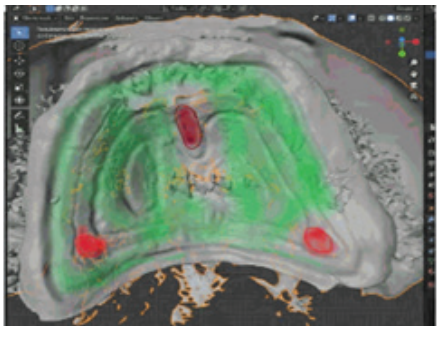


Fig. 4. Formed consecutive closed valve thickenings of the custom tray surface facing the denture bed (red color indicates places in the area of exit of neurovascular bundles and places with thinned mucosa, green color - places favorable for the formation of valve zones).

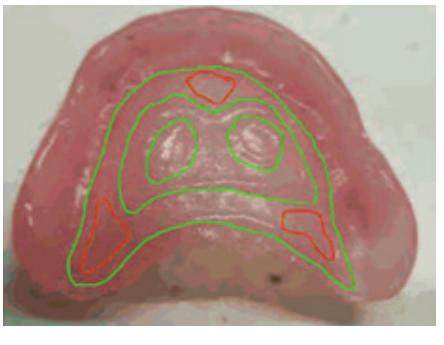
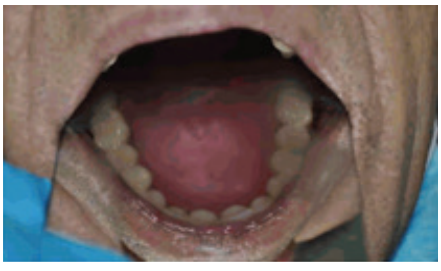


Fig. 5. Finished prosthesis made on the model obtained by impression with formed consecutive valve zones, taking into account individual anatomical variability of the topography of the soft tissues of the prosthetic bed

the "Stl" array of the model, in places of sufficient mucosa suppleness of the denture bed mucosa, medial to the external borders of the denture bed. Based on the masks, 3D modeling of the individual spoon was performed in the 3D graphics editor ("Blender 2.91 References Manual"). Then, at a distance of 2-5 mm towards the center of the denture bed from the attachment of the soft palate curtain

a



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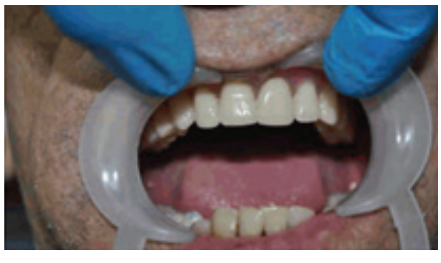

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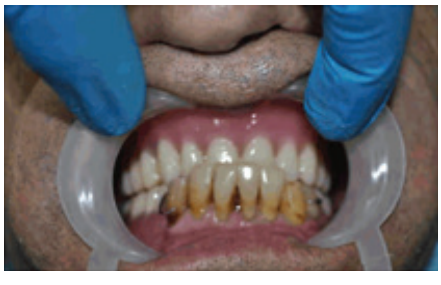

Fig. 6. View of the finished denture in the oral cavity (a – palatal surface, b – front view, c – view of the upper complete denture in bite position)

and the center of the alveolar process apex, "in the projection of the mask allowing compression, a roughness was placed on the surface of the spoon in the form of a roller with a height of 0.1 to 0.8 mm, where the height of the valve depended on the thickness of the mucous membrane, 2-5 mm away from the mask prohibiting compression in the area of the vessels and irregularities of the bone base of the denture bed. If the mask allowing compression was of sufficient size, the area with the valve zone was located again at a distance of 2 to 5 mm from the previous one. In the area of the mask prohibiting compression, decompression technological openings were designed in the areas of adhesion of the thinning mucosa, torus and exostoses (Fig. 4). Then the individualized spoon was printed using additive technologies, followed by fitting in the patient's oral cavity. Further stages of producing of complete removable orthopedic constructions were carried out according to generally accepted technologies.

Clinical case: Patient P., 68 years old, came to the Clinic of the North-Eastern Federal University named after M.K. Ammosov with the diagnosis: complete loss of teeth due to chronic periodontal disease of the upper jaw. Schroeder class 2, Supple class 1. From the anamnesis he had been previously prosthetized with full removable prosthetic constructions, for the last six months he notes unsatisfactory fixation of removable prosthesis, violation of food intake. Two days ago, while cleaning the denture, the patient dropped the denture, resulting in a fracture of the base.

After dental examination, the patient was offered to produce a full removable plate prosthesis according to our new method, where the patient's consent to participate in a scientific clinical study was obtained. Then the patient underwent CBCT with Bar-VIPS oral contrasting. Further, after the analysis of the prosthetic bed, taking into account his individual anatomical-topographical variability, three consecutive valve zones and three areas where the prosthetic bed is not in contact with the surface of the mucous membrane of the upper jaw in the area of exit of neurovascular bundles were formed (Fig. 5). After that, a digital model of the individual spoon was formed and then printed by the stereolithographic printer "Anycubic". The subsequent stages of producing of a complete removable orthopedic structure were carried out according to the well-known technology. At the same time dynamic control of the patient during 5 months characterizes the absence of necessity of prosthetic bed correction. In addition, the patient reports satisfactory fixation of the prosthesis and absence of discomfort on the upper jaw (Fig. 6 a, b, c).

Conclusion. The developed method of determining consecutively located concentrically closed valve zones with contrasting of the oral cavity provides the increase of fixation efficiency and function of complete removable plate prostheses on the upper jaw with a personalized approach of anatomical-topographical features of the prosthetic bed, thickness of the mucous membrane, places of exit of neurovascular bundles, torus and exostoses. At the same time the probability of vascular compression with microcirculation disturbance and traumatization of soft tissues to which the prosthetic construction adjoins is significantly reduced. In addition, the developed method minimizes alternating loads in the area of torus and exostoses in the area of maxillary tubercles, which significantly reduces the probability of fracture of the base of the full removable plate prosthesis. The sequential arrangement of the valve zones reduces the likelihood of tipping of the prosthesis in the event of a breach of the tightness of the external valve zones, since concentric sequential valve zones are provided inside the borders of the prosthetic bed, which preserve retention. It improves the quality of dental care and increases the living standard of patients.

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MODERN METHOD OF SURGICAL TREATMENT OF EPITHELIAL COCCYGEAL TRACT

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There are several theories of the origin of epithelial coccygeal diseases: empirical, neurogenic, ectodermal and acquired. Most Russian scientists consider this pathology to be congenital, while foreign colleagues tend to believe that it is a consequence of injuries to the sacrococcygeal area. This disease occurs quite often, affecting more than 5% of the adult population, including children and adolescents, significantly impairing the quality of life, which affects all aspects of their life.

Conservative methods of treatment include sclerotherapy and obliteration of the cavity with silver nitrate or hydrochloric acid, which is not used today, since a positive result of treatment of the epithelial - coccygeal course is not achieved, because the cause of the disease is not eliminated.

Surgical treatment is the most effective method of treating epithelial coccygeal stroke. Surgical treatment, despite the simplicity of its execution, is quite scrupulous. The high incidence of complications after surgery and the long period of disability often disappoint surgeons. The resulting rough scar has an undesirable cosmetic effect, and the probability of recurrence remains quite high. The problem of creating and implementing new methods of treating pilonidal disease remains relevant in our time.

Keywords: epithelial coccygeal tract, pilonidal cyst, surgical treatment methods.

The epithelial-coccygeal passage (ECC), epithelial-coccygeal cyst (ECC) is located in the subcutaneous adipose tissue in the area of the interstitial space. The ECC cavity communicates with the environment through the fistula passages, both primary and secondary. [1,5]. Infection in the primary fistula passages causes ECC inflammation and abscess formation [2, 10]. This disease most often develops in young, able-bodied males, whose age ranges from 16 to 45 years. The ratio between men and women is 4:1[5, 10]. According to statistics, the incidence of ECH reaches 2% of all surgical pathology [18]. At the same time, ECC inflammation reaches 15% of the total number of surgical purulent-septic diseases [5, 8, 6]. The most effective method of treating this pathology is surgical.

In the middle of the 19th century, A. Anderson first described the technique of radical excision of the ECC within healthy tissues in a letter to the Boston Medical Journal [6]. However, when a cyst or ECC is excised, a rough and deep postoperative wound is formed, and therefore surgeons' disputes about wound closure do not subside. In turn, this leads to the search for new ways of surgical treatment of ECC [10].

All surgical aids in the treatment of ECC are divided into three main groups: the first group is open: with the use of various dressings and vacuum therapy by secondary tension, the postoperative wound regenerates [2]. The second group is closed: the postoperative wound is sutured tightly (using nodular sutures or Donatti sutures), partial suturing of the postoperative wound using various plastic surgery techniques (according to Karydakis or Bask) [10,11,3].

The third group is semi-open: a drainage tube is installed into the cavity of the postoperative wound or a drainage channel is formed, after which the postoperative wound is sutured (excision of the epithelial coccygeal passage with sutures along the Moshkovich) [6].

One of the methods of treating epithelial coccygeal stroke using vacuum therapy is described by Benderwald F.P. [11]. After excision of the fistula passage, a removable drainage bandage is applied, and round-the-clock vacuum therapy with a negative pressure of 125 mmHg is carried out in a constant mode. The dressing is changed every two days. The course of vacuum therapy lasts from 4 to 9 weeks. Vacuum therapy is discontinued after complete granulation of the wound, and complete wound healing occurs within 9-22 weeks.

Healing of an infected postoperative wound takes quite a long time and, as a result, a rough postoperative scar forms after healing. As a result, most surgeons use two-stage surgical treatment for ECC inflammation in the acute phase. At the first stage, the abscess is opened, then the abscess cavity is sanitized (consisting of daily rinses, ointments on a water-soluble basis are injected into the abscess cavity). After these manipulations, the inflammatory process is stopped and the patient undergoes radical surgical treatment [3, 11].

In Russia, the technique of marsupialization and plastic surgery of a wound defect using a skin flap transplant will be widely used [4]. The marsupialization method was first proposed by L. Buie in 1937, and this technique was subsequently modified several times. [16]. One of the commonly used methods of marsupialization is excision of the ECC and further suturing of the postoperative wound with Moshkovich sutures [6].

According to A.V. Kibalcic, the incidence of true relapses after radical excision of the ECC is no more than 6% [12], and 94% are false relapses caused by infectious complications - hair entering the wound cavity, the healing of which is complicated by the development of a purulent process. Basically, ECH recurs in the area of the interdigital fold along the midline. The cause of relapses, according to many authors, is the high position of the buttocks, deep interdigital fold, obesity, as well as thick hair in this area. Due to the extensive and deep postoper-

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ative wound and uneven healing, cavities are formed that contribute to the development of infection and the formation of rough postoperative scars in 10-40% of patients [11,3].

Recently, new technologies have been sought and developed using various physical factors that affect inflammatory processes in the sacrococcygeal region. In recent years, special attention has been paid to laser therapy, which is actively being introduced into the treatment of various pathologies. This becomes possible thanks to the development of high-energy lasers that deliver radiation directly to the pathological focus through flexible light guides, which makes it possible to actively use them for conducting intracranial and intracavitary therapeutic manipulations [5]. However, during these operations, the cavity of the fistula does not decrease, which can lead to a relapse in the future.

Based on the above, the search for the most effective methods of surgical treatment of ECC is an urgent problem of both coloproctology and surgery in general.

The aim of the study was to improve the results of treatment of patients with ECC by developing and implementing a minimally invasive method of laser obliteration of the epithelial coccygeal passage.

Material and methods. The paper describes the results of treatment of 52 patients with ECH who were in the surgical department of the CHUZ CB "RZD-Medicine" in Astrakhan from 2021 to 2023. The age of the patients ranged from 25 to 45 years. The average age of patients was 35 years - the working-age population. There were certain criteria for including patients in the ongoing study. First of all: clinically and diagnostically confirmed diagnosis of ECC, recurrence of ECC, the presence of primary and secondary fistula openings. Patients with ECC abscess were not included in the study.

Pronounced thick hair in the coccygeal region was observed in 36 (69.2%) patients, overweight in 16 (30.8%) patients. As a percentage, 49 (94.2%) men and 3 (5.8%) women participated in the study.

All patients were hospitalized as planned. Before hospitalization, outpatients were examined: General blood test, general urine test, biochemical blood test, coagulogram, chest X-ray and blood test for hepatitis HBsAg and HCV. The patients underwent ultrasound examination of soft tissues in order to exclude hidden foci of inflammation and determine the size of the ECC (Fig.1). All the subjects underwent preoperative preparation, including shaving of the surgical intervention zone and preoperative antibacterial therapy. The criteria for the effectiveness of treatment were: the duration of the operation, the duration of the pain syndrome in the postoperative period, the severity of the pain syndrome, which we determined using a 5-point International Visual Analog Scale (VAS) of pain; the duration of hospitalization, the time of recovery, the frequency of relapses and patient satisfaction with the results of the operation, which were revealed using a questionnaire.

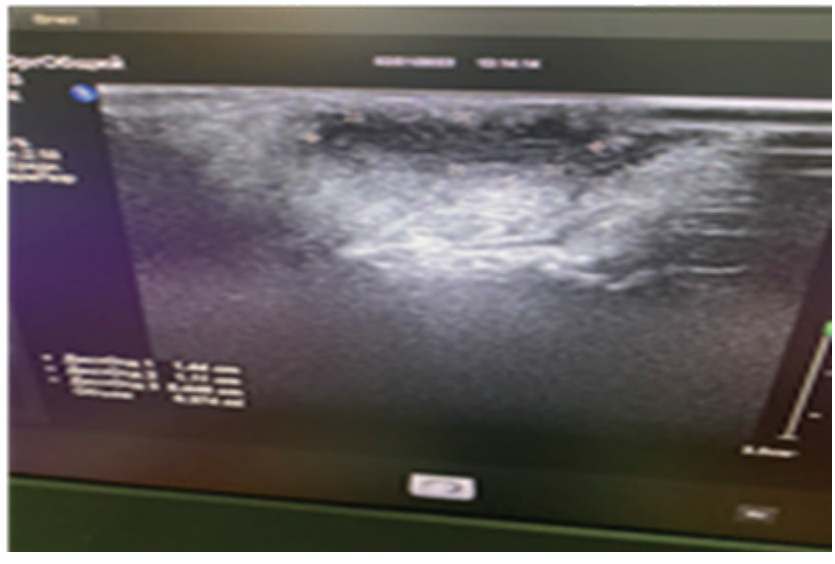

Fig. 1. Sonogram of the epithelial coccygeal passage before surgery

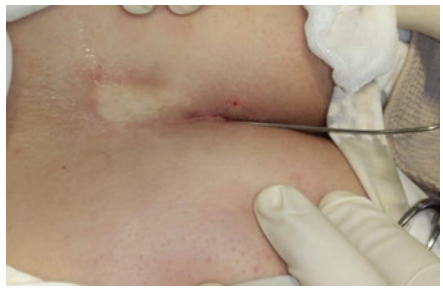

Fig. 2. Revision of the fistula passage with a button probe

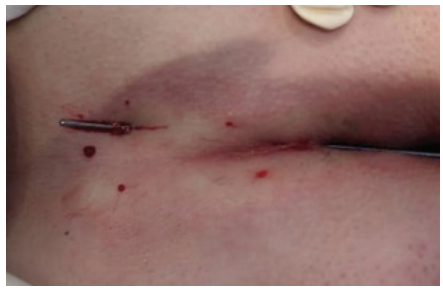

Fig. 3. Creation of a "coupling" that reduces the cavity of the fistula

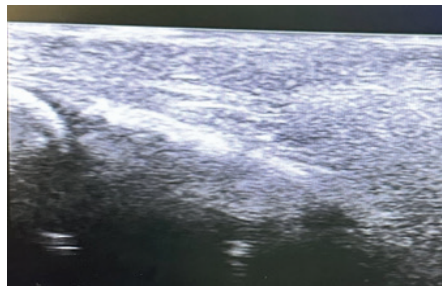

Fig. 4. Sonogram of the intervertebral region one year after surgery

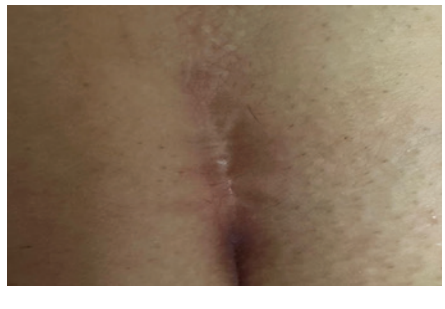

Fig. 5. Postoperative area 1 year after surgery

The main stages of the minimally invasive method of treatment of the epithelial coccygeal course proposed by us (patent No. 2767889 dated 03/22/2012) are presented below. The operation begins with local anesthesia. After excision of the primary fistula opening, a button probe is used to inspect the fistula passage with the removal of a contraperture at the upper point of the fistula (Fig. 2). Then, with a Volkmann spoon, the contents of the fistula passage with granulations are processed and removed. Next, the cavity is

washed with a solution of aqueous chlorhexidine. The next step, under ultrasound control using tumescent (infiltration) anesthesia, is to create a "coupling" that reduces the fistula cavity (Fig. 3). Next, the fistula cavity is coagulated with a laser in continuous mode with a wavelength of 1470 nm, with a power of 9 W, at a speed of 1 mm/ s (Fig. 4.5).

Results and discussion. The duration of the operation was 10-12 minutes, the severity of pain on the VAS scale was no more than 2 points. In patients, tension and swelling of soft tissues in the surgical area decreased on 2-3 days, and fistulas closed on the 4th-5th day. During ultrasound examination, a connective tissue scar formed at the ECC site after 2 months. The average duration of inpatient treatment was 3 days. Recovery of working capacity was noted on 5-6 days.

Of the 52 patients, a relapse occurred in 2 (3.8%) patients 3 months after surgery, which was associated with the period of mastering and implementing this technique, which required repeated laser obliteration. Long-term results a year after surgery were studied in 47 patients, there were no relapses.

Conclusions. A porTable compact laser with a wavelength of 1470 nm was used to treat epithelial coccygeal stroke. Laser radiation with a long wavelength of 1470 nm, due to its physical properties, has a pronounced sanitizing and coagulating effect on epithelial coccygeal passages.

The main advantage of the proposed method is:

1. Our use of a tumescent coupling to reduce the cavity of the fistula passage, increases the area of tissue contact with the working surface of the laser, which allows a single and radical procedure for laser ablation of the cavity without repeated interventions.

2. This technique can be applied in all forms of ECC, since the operation is performed directly under the control of ultrasound, which eliminates the possibility of leaving additional or false strokes, brush congestion.

3. Non-intense pain syndrome, good cosmetic effect, reduced inpatient treatment and reduced disability, minimally invasive this technique makes it more promising in the treatment of this pathology.

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THE EXTERNAL AUDIT AS A TOOL FOR IMPROVING MEDICAL CARE

Based on the results of the expert assessment of the medical records of children who received treatment in the 24-hour hospital, the following was revealed: 75% (2021) and 25% (2022) of patients were unreasonably hospitalized; there was an overlap between the flows of patients with infectious and somatic pathology; records in the medical history do not reflect a complete review of the patient and the dynamics of observation; there is no justification of the diagnosis and prescription of medications; the time of observation, transfers and examination of patients is not indicated; when consulting with other specialists, there are no records in the medical history of the patient; there is a lack of justification and interpretation of instrumental and laboratory tests, etc. The identified problems should be taken into account when developing organizational measures for improving medical care for children in hospital.

Keywords: children, pediatric hospital, in-patient medical records, expert assessment, check-list.

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Introduction. The Article 4 of the Federal Law No. 323-FL “On the Fundamentals of Health Protection of Citizens in the Russian Federation” defines the priority of children's health protection among the basic principles of health protection [7]. In modern conditions, the medical and demographic indicators of children's health are characterized by a low birth rate, high morbidity rates, early chronicity of pathological processes, and an increase in the number of children classified as health group 3 according to the results of preventive medical examinations. In this regard, improving the quality of medical care for children is of paramount importance in the organization of children's health care [3, 6].

In-patient medical care is the most resource-intensive type of medical care. Therefore, it is necessary to control the validity of hospitalization and the quality of inpatient care. Rationality of resource utilization is carried out by means of expert assessment of inpatient treatment cases. Based on the results obtained, measures are developed to improve the quality and availability of medical care for children with optimal resource utilization [1, 2, 5, 8].

Purpose. To analyze the organization of in-patient medical care for children in one of the regional pediatric clinical hospitals of the North-Western Federal District.

Materials and Methods. The Federal Statistics Surveillance Form N 30 “Information on Medical Organization” was studied. Medical records of the in-patients hospitalized in 2021 and 2022 were evaluated according to the check-list developed in accordance with the clinical recommendations. The sample was formed on the basis of the order of the Ministry of Health of the Russian Federation No. 231n dated March 19, 2021 “On Approval of the Procedure for Control of the Amount, Timing, Quality and Conditions of Medical Care Provision under Compulsory Medical Insurance to Insured Persons, as well as its Financial Support” and amounted to 3% of the number of cases of in-patient medical care (n=820) accepted for payment [4]. Analytical, statistical, and expert evaluation methods were used.

Results and Discussion. Within the framework of organizational and methodological activities in the profile of “Pediatrics” the staff of the National Medical Research Center of St. Petersburg State Pediatric Medical University (hereinafter - NMRC) conducted an external audit of one of the regional pediatric clinical hospitals of the North-Western Federal District.

The Regional Children’s Clinical Hospital is a multidisciplinary health care institution providing children with medical care at all levels - primary outpatient and inpatient care, specialized outpatient and inpatient care, and high-tech care. The medical organization works 24 hours a day as an emergency hospital for pediatrics, pediatric surgery and traumatology.

It interacts with all central district hospitals of the region, providing consultative and visiting medical care.

In 2022, the staff composition of the hospital was 952 people, including 145 physicians, 358 nurses. Over the two years, the percentage of physicians' staffing by individuals decreased, while there was an increase in staffing by employed positions, both among physicians and mid-level medical staff (Table 1). The compatibility ratio among physicians was 1.7 in 2021 and 1.9 in 2022, and among nurses it was 1.1 and 1.2, respectively.

The in-patient department has a 24-hour ward, a day hospital, a 24-hour trauma center, and a consultative and diagnostic polyclinic. The hospital has 16 therapeutic and 10 auxiliary departments of different profiles, providing inpatient care to patients from newborn to 18 years of age.

The structure of the 24-hour hospital includes the following departments:

- **Infectious-box department** for 5 boxes, where 30 beds of round-the-clock stay are deployed. Main areas of activity are:
  - hospitalization and treatment of patients with suspected infectious diseases or general somatic pathology with a concomitant infectious disease;
  - treatment of patients who have had contact with infectious patients;
  - treatment of diagnostically unclear patients;
  - treatment of children for social reasons (from disadvantaged families);
  - treatment of children under 6 years of age with acute viral infection.
- Infection Ward for Infants with 50 beds. The department is multidisciplinary with an infectious regime. All nosological forms of children from birth to 1.5 years of age are treated.
- The Department of Pathology of Newborns and Premature Babies No. 1 has 30 boxes (20 single and 10 double boxes). Since 2012 the department accepts children with weight over 2000 g and gestation period over 34 weeks (late premature babies who do not need nursing in a cuvette,) because it is equipped with only one cuvette.
- The Department of Pathology of Newborns and Premature Babies No. 2 (Department of Premature Babies) has 35 round-the-clock beds and maternity wards for mothers of children in the Department of Anaesthesiology and Intensive Care No. 2. There are 30 joint stay boxes in the structure of the department. There are four round-the-clock nursing posts that function there, while the standard is 8 posts.
- Pediatric Department №1 has 35 beds: 10 for patients with gastropathology, 20 for patients with bronchopulmonary pathology, 5 pediatric beds. Children aged from 1 year 6 months to 18 years are treated in the department.
- Pediatric Department No. 2 with 45 beds: 20 nephrology, 5 cardiology, 5 rheumatology, 15 endocrinology. In addition, there are 4 day hospital beds: 1 nephrology, 1 rheumatology, 2 endocrinology.
- Dermatovenerology Department for 12 beds, 10 beds of round-the-clock hospitalization and 2 beds of day hospitalization. There are 9 double boxes in the department, two boxes are allocated for children under one year of age, two boxes for day hospitalization, there are 5 reserve beds.
- Anesthesiology-Reanimation Department No. 1 is mainly for children over 1 month of life with 12 beds. The beds are assigned to specialized departments. There are no separate resuscitation beds!
- Anesthesiology-Reanimation Department No. 2 for newborns and premature babies for 6 beds.

In 2021, 13,544 children were treated at the hospital and in 2022, 14,117 children received treatment.

When analyzing the work of these departments, the following problems were identified:

- routing of emergency room patients with crossing of flows in case of admission of planned, emergency and respiratory pathology was violated;
- irrational use of isolation (Melzer) boxes during the period of spread of new coronavirus infection;
- routing of children from the infectious diseases ward (1st floor) with respiratory pathology to the infectious diseases ward for infants (2nd floor) was disrupted;
- patients with infectious pathology and somatic pathology were crossed on the infectious ward;
- placement of children of neonatal age (without infectious pathology) on the department with respiratory pathology;
- children with infectious pathology were assisted by pediatricians, as there were no infectious disease doctors on the staff;
- medical services were provided to adults in the absence of a license;
- biomaterials from patients were stored in the refrigerator of the treatment room.

Check-lists were developed for expert assessment of cases of medical care in the conditions of the Regional Children's Clinical Hospital, taking into account the current clinical recommendations. The evaluation was based on the study of patients' medical records.

In 2021, when analyzing the medical records of in-patients, attention is drawn to the following:

- in the presence of informed voluntary consent, the types of medical manipulations are not always indicated;
- diary records do not contain a complete description of the patient and the dynamics of observation;
- there is no chronology in keeping the medical history: indicating the time of observation, transfers and examination of patients;
- there are no temperature sheets, with the dynamics after the use of antipyretics;
- there is no justification for medical manipulations, as well as unjustified prescription of manipulations that are not included in the standards of medical care;
- in the presence of severe concomitant pathology - there is no record of a consulting physician, which does not comply with clinical recommendations and standards;
- there is no interpretation of instrumental examinations;
- there is no interpretation of laboratory examination;
- there is no justification of the diagnosis and rationale for prescribing medications, which leads to non-compliance with clinical recommendations;

Table 1

Staffing level of the Regional Children's Clinical Hospital (%)

Positions	Staffing by individuals (%)		Staffing by employed positions (%)	
	2021	2022	2021	2022
Physicians	57.4	53.0	97.4	98.8
Mid-level medical staff	78.5	79.0	89.6	96.4

- concomitant pathology is not fully included in the final diagnosis;
- the validity of hospitalization was only 25% (Table 2).

There was also a discrepancy between diagnoses in the medical history and in the discharge epicrisis (15%), the severity of the disease was not indicated in the medical history (22%), there was no calculation of nutrition for children under 1 year of age (12%), no calculation of infusion therapy (9%), in the presence of infectious pathology there was no bacteriological examination (sputum, urine) to identify the pathogen (14%).

In the examined hospital, electronic document management is not fully implemented, in particular, there is no information system for maintaining the patient's medical history.

Based on the results of the 2021 audit, the administration of the Children's Regional Clinical Hospital was recommended:

- to conduct training sessions on the implementation of clinical protocols, recommendations and standards of medical care from the position of validity of hospitalization in a 24-hour hospital;
- to strengthen work in the quality control system for completing primary medical documentation;
- to consider patient routing, in particular, to examine options for transferring infectious patients to a separate hospital building;
- to unify primary documentation (medical record of an inpatient) for all departments of the hospital;
- to train medical staff in additional educational programs to improve their qualifications;
- to provide training in the professional retraining program for specialists in the field of “infectious diseases”;
- to strengthen and implement control over compliance with clinical recommendations;
- to improve the medical information system, introduction of electronic medical history;
- to create templates for records of dynamic observation of an inpatient, consultations of specialized doctors, heads of departments, temperature list, etc. before the introduction of the electronic medical history;
- to provide re-equipping the hospital with the necessary medical equipment;
- to provide staffing positions for specialists of medical and nursing personnel.

The repeated audit conducted by NMRC specialists in 2022 showed the

Table 2

Comparative analysis of in-patient medical record check-list results in 2021 and 2022

№	Characteristic	% or point (from 0 to 20)	
		2021	2022
1	Justification for hospitalization (% of all reviewed case histories)	25	75
2	Availability of informed consent from parents or guardian (% of all reviewed medical records)	100	100
3	Availability of justification of diagnoses (% of all reviewed medical records)	60	100
4	Quality of rationale for diagnosis (number of points for every 10 medical records reviewed)	10	16
5	Availability of medical and life medical record data (% of all verified medical records)	60	100
6	Incomplete collection of medical record (number of points for every 10 medical records reviewed)	8	14
7	Presence of a plan of treatment and examination of patients in the examination of the head of the department (% of all checked medical records)	100	100
8	Presence of treatment and examination plan in the dynamics of observation (% of all checked medical records)	30	80
9	Quality of completion of treatment and examination plans (number of points for every 10 checked medical records)	10	16
10	Availability of justification of medication prescriptions (% of all checked medical records)	65	85
11	Quality of justification of medication prescriptions (number of points for every 10 medical records reviewed)	0	10
12	Presence of a protocol of MC for medications that are not included in Vital and Essential Drugs (% of all medical records where the medications were used)	100	100
13	Presence of polypragmasy (% of all reviewed medical records)	0	0
14	Compliance with clinical guidelines and protocols (% of all reviewed medical records)	100	100
15	Quality of application of clinical guidelines (examination and treatment) (number of points for every 10 medical records reviewed)	12	20
16	Availability of assessment of results of laboratory tests (% of all reviewed medical records)	85	100
17	Quality of evaluation of laboratory tests (number of points for every 10 medical records reviewed)	12	18
18	No examination, if necessary, of other specialists (Physiotherapy Treatment, infectious disease specialist, nephrologist, ENT, etc.)	20	8
19	No examination by an anesthesiologist before anesthesia benefit (% of all MRs where anesthesia was administered)	0	0
20	Neurological status normal, without neurologist examination (% of all MRs where a neurologist was required)	0	0

effectiveness of the implementation of the recommended measures. Thus, the proportion of justifiably hospitalized in 24-hour inpatient care increased 3 times to 75%, all audited records had justification of diagnosis (60% in 2021), complete medical and life history (60% in 2021), evaluation of laboratory results (85% in 2021). There was a 2.7-fold increase in the proportion of case histories containing treatment and examination plans in the dynamics of follow-up (80% in 2022; 30% in 2021). There was a 2.5-fold decrease in the number of case histories that did not have records of consultations during examinations by other specialists (20% in 2021; 8% in 2022). Justification of medication prescriptions was available in 85% of case histories against 65% in 2021 (Table 2).

Conclusion. To improve the organization of medical care for children in the conditions of the regional clinical hospital it is advisable to conduct both internal and external audits in order to objectively assess the current situation in the hospital and identify priority problems. Based on the results obtained, external auditors develop recommendations on the basis of which management decisions are made by the hospital administration to be implemented in the activities of the medical organization and to be monitored in dynamics in terms of their effectiveness.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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THE ROLE OF *Ile105Val* POLYMORPHISM OF THE *GSTP1* GENE IN THE DEVELOPMENT OF ALLERGIC PATHOLOGY IN THE CHILDREN POPULATION OF THE INDUSTRIAL CENTER OF WESTERN URAL

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Introduction. A modern approach to the diagnostic support of patients with allergic diseases involves the introduction of innovative developments in the field of precision medicine, the development, identification and use of reliable biomarkers, including the determination of individual genetic variability in living conditions at various territories of the Russian Federation. **The aim** of the study is to investigate the role of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in the development of allergic pathology and its connection with the characteristics of the formation of the immune profile in the child population of the industrial center of the Western Urals. **Materials and methods.** The observation group consisted of 34 children with allergic pathology. The comparison group included 37 children, relatively healthy, without allergies. Markers of hypersensitivity and cytokine status were studied using enzyme-linked immunosorbent assay. Genotyping was performed using real-time polymerase chain reaction. **Results.** In the group of children with allergic pathology, an increase in the eosinophilic-lymphocyte index was shown by 1.8 times, total IgE concentration by 4.7 times, a change in the level of serum cytokines IL-10 by 1.3 times and IL-4 by 1.8 times relative to the comparison group (p=0.005-0.038). Genetic analysis of the *Ile105Val* polymorphism of the *GSTP1* gene revealed a 2.0-fold increase in the frequency of the homozygous *AA* genotype in the observation group (p=0.01). Allele *A* was associated with the development of allergies in the examined children (OR=2.36; 95% CI=1.16-4.79), while allele *G* had a protective value (OR=0.33; 95% CI= 0.12-0.89). An increase in the concentration of total IgE and blood eosinophils in carriers of the *AA* genotype was shown to be 4.6 times and 1.9 times, respectively, relative to owners of the *AG* and *GG* genotypes (p=0.013-0.031). **Conclusion.** Allele *A* and genotype *AA* of the polymorphic variant *Ile105Val* of the *GSTP1* gene in children with allergic pathology act as sensitivity markers associated with the formation of allergies, a significant increase in total IgE, blood eosinophils and the anti-inflammatory cytokine IL-4, and can be considered as promising indicators of pathophysiological conditions associated with risk of development of atopic processes (allergic pathology) in children (RR=1.61; 95% CI=1.06-2.44) living in the Western Urals.

Keywords. Genetic polymorphism; *GSTP1* gene; immunoglobulin E; eosinophils; IL-4.

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Introduction. The prevalence of allergic diseases, including asthma, atopic dermatitis, allergic rhinitis, conjunctivitis, chronic rhinosinusitis and food allergies, accounts for more than 40% of the population in industrialized countries, and is constantly increasing in developing countries, reducing people's quality of life. The significant increase in the number of allergy cases is due to factors such as environmental pollution, climate change, loss of biodiversity, urbanization, and changing lifestyles and eating habits. The variability of the population's sensitivity to the adverse effects of chemicals is associated with the level and duration of exposure, which significantly depend not only on the development of industry and the type of production, but also on the geographical features and meteorological conditions of the region, as well as concomitant diseases, period of life and genetic predisposition to exposure to xenobiotics [5, 6].

The ability to metabolize xenobiotics is determined by the level of activity of enzyme in biotransformation systems, which depends on the sex, age and genetic characteristics of the organism. Glutathione-S-transferases (GSTs) belong to a multigene family of enzymes that metabolize a wide range of exogenous and endogenous electrophilic compounds, with a high degree of gene polymorphism, which determines the individual level of enzymatic activity. All human tissues express GST, but each tissue has a unique expression profile. Studies show the dominance of GSTP1 (π class) in the respiratory tract, its role in antioxidant protection and the association of polymorphism of this enzyme with the development of allergic inflammation [3, 16].

The aim of the study is to investigate the role of the Ile105Val polymorphism of the GSTP1 gene (rs1695) in the development of allergy pathology and its connection with the characteristics of the formation of the immune profile in the child population of the industrial center of the Western Urals.

Materials and methods. We examined the school-age children of a large industrial center of the Perm region; the observation group included 34 children with allergic pathology: allergic rhinitis, allergic contact dermatitis, atopic dermatitis, asthma with a predominance of the allergic component. The comparison

group included 37 relatively healthy children. The groups were comparable by gender, age, and ethnicity (p>0.05). All legal representatives of the examined children signed voluntary informed consent to participate in the study.

Quantitative indicators of leukocyte fractions were studied using a hematology analyzer "Drew-3" (USA). The content of total IgE, interleukins (IL-6, IL-4, IL-10), tumor necrosis factor (TNFalfa), interferon gamma (IFNgamma) was determined by commercial test systems (Vector-Best, Xema, Russia) using the enzyme immunoassay method on an analyzer "Elx808IU" (BioTek, USA). DNA for genetic analysis was isolated using the sorbent method. The *Ile105Val* polymorphism of the glutathione-S-transferase *GSTP1* gene (rs1695) was studied by real-time polymerase chain reaction on a thermal cycler "CFX96" (Bio-Rad, USA) using SNP-screen kits (Synthol, Russia).

The collected data were analyzed using Statistica 10.0 software (Statsoft, USA). The results are presented as the arithmetic mean and standard error of the mean (M±m) or frequency (%). In the absence of a normal distribution, a normalizing log-transformation was used. The significance of differences between groups in quantitative characteristics was determined using Student's t-test, qualitative variables were compared using the chi-square test (χ^2), differences were considered significant at the p<0.05 level. Genetic analysis data were processed in the "Gene-Expert" program, and genotype frequencies were calculated using the Hardy-Weinberg equilibrium. Allele frequency data were analyzed by logistic regression analysis with calculation of odds ratio (OR), relative risk (RR) and 95% confidence interval (95% CI).

Results and discussion. The identified features of the immune profile of children in the group with allergic pathology (Table 1) indicate characteristic changes in cellular parameters with an increase in the number of blood eosinophils by 1.5 times and the eosinophil-lymphocytic index by 1.8 times relative to the comparison group (p=0.012-0.037), while the References range for this indicator was exceeded in 97.1% of the studied samples. The level of general sensitization in terms of total IgE content significantly exceeded the comparison indicators, on average 4.7 times (p=0.005). Serum levels of cytokine mediators also significantly increased relative to the levels of the comparison group in terms of IL-10 content by 1.3 times and IL-4 and INFgamma by 1.8 times, respectively (p=0.008-0.038).

The genetic analysis of the *Ile105Val* polymorphism of the *GSTP1* gene (Table 2) revealed a 2.0-fold increased frequency of occurrence of the homozygous *AA* genotype in the group of examined children with allergic pathology relative to the comparison group (additive model: p=0.01). In this case, carriage of the *A* allele can be considered as a marker of sensitivity associated with the development of atopic diseases (OR=2.36; 95% CI=1.16-4.79), while the *G* allele probably performs a protective function (OR=0.33; 95% CI=0.12-0.89). The distribution of allele and genotype frequencies corresponded to Hardy-Weinberg equilibrium (χ^2=0.02-0.22; p=0.64-0.88). Calculation of the relative risk showed an increase in the probability of developing allergic health disorders by 1.7 times in owners of the *A* allele compared with carriers of the *G* variant in the examined group (RR=1.61; 95% CI=1.06-2.44).

A study of hypersensitivity markers in children with allergic pathology associated with carriage of the *Ile105Val* polymorphic variant of the *GSTP1* gene (Table 3)

Table 1

Basic and immune parameters in examined children with allergic diseases

Parameter	Observation group	Comparison group	p
Age, years	11.41±0.59	11.26±0.32	0.838
Gender, girls/boys, %	61.8/38.2	62.2/37.8	1.000
Total IgE, IU/cm^3	201.99±108.63	43.27±18.27	0.005
Eosinophils, %	4.18±1.20	2.70±0.67	0.037
Eosinophilic-lymphocytic index	0.105±0.033	0.059±0.014	0.012
IL-10, pg/cm^3	3.60±0.62	2.78±0.47	0.038
IL-4, pg/cm^3	1.70±0.54	0.92±0.20	0.008
IL-6, pg/cm^3	2.23±1.05	1.49±0.25	0.167
INFgamma, pg/cm^3	1.82±0.56	1.02±0.22	0.009
TNFalfa, pg/cm^3	2.09±0.64	1.55±0.26	0.122

Table 2

Results in the study of the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695) in children with allergic pathology

Genotype, allele	Observation group, %	Comparison group, %	p	OR (95% CI)
Multiplicative model (chi-square test)				
A	73.5	54.1	0.02	2.36 (1.16-4.79)
G	26.5	45.9		0.42 (0.21-0.86)
Additive model (Cochran-Armitage test for linear trends)				
AA	52.9	27.0	0.01	3.04 (1.13-8.17)
AG	41.2	54.1		0.60 (0.23-1.52)
GG	5.9	18.9		0.27 (0.05-1.39)

Table 3

Features of hypersensitivity indicators in children with allergic pathology associated with the *Ile105Val* polymorphism of the *GSTP1* gene (rs1695)

Показатель	Genotype		p
	AA	*AG+GG*	
Total IgE, IU/cm^3	320.04±193.40	69.17±39.57	0.013
Total IgE >100.0 IU/cm^3	61.1%	25.0%	0.045
Eosinophils, %	5.33±2.12	2.88±0.70	0.031
Eosinophils >3.0%	55.6%	18.8%	0.039

determined significantly higher levels of total IgE concentration and relative content of blood eosinophils, increased by 4.6 times and 1.9 times respectively in carriers with the *AA* genotype relative to those with heterozygous *AG* and variant homozygous *GG* genotypes (p=0.013-0.031). The proportion of samples exceeding the References value in carriers of the *AA* genotype was significantly higher, by 2.4 times for total IgE and 3.0 times for blood eosinophil content, 61.1% and 55.6%, respectively (p=0.039-0.045).

Allergic diseases are mediated by the specific influence of environmental factors and an imbalance of innate and adaptive immune reactions with the development of a pathological allergic inflammatory process [4]. It is believed that environmental changes, associated primarily with an increase in the level of chemical contamination, are the leading factor in the rapid spread and progression of allergic pathology [15]. Many pollutants exhibit oxidative properties, promoting the activation of free radical oxidation processes and the development of oxidative stress, which in turn can also provoke the progression of allergies through the regulation of signaling pathways (NF-κB) and activation of the production of proinflammatory mediators (IL-6, IL-1, TNF), increasing the expression of the corresponding genes even at very low levels of exposure [13, 14].

GSTP1 is the main enzyme of this group in the lung epithelium, which accounts for up to 90% of the activity; therefore, genetic polymorphism of the GSTP1 coding sequence is crucial in the implementation of antioxidant protection and detoxification of aerogenic chemical compounds. The GSTP1 gene is mapped to chromosome 11q13.2 and consists of seven exons and six introns. The *Ile-105Val* polymorphism of the *GSTP1* gene (rs1695) is located in the coding region near the ligand-binding site, in which adenine (A) is replaced by guanine (G) at position 313 of exon 5 (*313A>G*), which leads to the replacement of the amino acid isoleucine (Ile) by valine (Val) in codon 105 and changes in the physicochemical properties and secondary structure of the protein, modification of the catalytic activity of the enzyme [17].

Studies show an association of the *Ile105Val* polymorphism of the *GSTP1* gene with an increased risk of decreased pulmonary function, asthma and allergies as a result of exposure to exhaust gases and industrial pollutants, and variant genotypes are prone to earlier development of symptoms and a more severe course of various forms of allergic pathology [1, 9]. At the same time, data regarding individual polymorphic variants of *Ile105Val GSTP1* are quite contradictory due to differences in study design, exposure level, gender, age and ethnicity of participants. Various polymorphic variants of *GSTP1* gene can significantly differ in the level of expression, changes in the catalytic activity of the enzyme or substrate specificity, and also depend on the level of exposure to toxicants [7, 18]. For example, the Val-variant of the GSTP1 enzyme exhibits greater catalytic activity towards diol epoxides of polycyclic aromatic compounds and lower catalytic activity towards 1-chloro-2,4-dinitrobenzene compared to the Ile-variant. Factors such as the possibility of gene interactions with other components of the antioxidant defense system (other *GST* or *NQO1* genotypes) or environmental factors should be taken into account. It has been shown that the protective effects of *GSTP1* genotypes on the negative effects of diesel exhaust particles, observed at lower levels and exposure patterns, can be reversed when children are exposed to multiple environmental stressors at an early age [10]. The current inconsistency in research results may therefore be explained by variations in enzyme activity towards different pollutants and depending on specific environmental conditions or research methodology.

It is worth noting a number of scientific works that are consistent with our results and indicate a possible protective role of the *G* allele (*Val*) and a decrease in the frequency of the *GG* genotype in patients with atopy [2]. An increased risk of asthma in children carrying the *IleIle* (*AA*) genotype has been reported in both areas with high and low levels of air pollution [11]. Controlled human exposure studies examining the effect of *GSTP1* polymorphism on the association between exposure to exhaust air pollution and respiratory disease and allergy also showed increased allergic inflammation, elevated IgE and histamine levels in carriers of the *AA* genotype [12].

A modern approach to patients with allergic diseases must combine accurate diagnosis and personalized treatment, new developments in the field of precision medicine, phenotyping and endotyping of diseases, as well as the identification and use of reliable biomarkers, including the determination of individual genetic variability in conditions of exposure to harmful factors of production and the environment [8]. The results obtained in this research require further study due to the limited sample size, taking into account possible gene and gene-environment interactions and population characteristics of the examined group.

Conclusion. A study of the association of the genetic polymorphism *Ile105Val* of the *GSTP1* gene with the development of allergic pathology in children showed a shift in the vector of immune regulation towards Th2-inflammatory responses – an increase in the production of total IgE, the number of blood eosinophils and IL-4 (p=0.005-0.037). The identified shift in immune parameters in children with allergic pathology was reliably associated with individual genetic variability in *Ile105Val* polymorphism of the *GSTP1* gene, and the *A* allele of *Ile105Val* polymorphism acts as a marker of sensitivity (OR=2.36; 95% CI=1.16-4.79) and the risk of allergy formation (RR=1.61; 95% CI=1.06-2.44) and can be considered as a promising prognostic criterion, a marker of individual risk of developing atopic processes in children in industrialized areas of the Western Urals.

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EPIDEMIOLOGICAL PREVALENCE OF MEASLES IN THE RUSSIAN FEDERATION, NEIGHBOURING AND FOREIGN STATES

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This article analyzes the statistical studies results of the epidemiological prevalence of measles infection in Russia, neighboring and foreign countries for the period from 2017 to 2023. A comparative characteristic of the measles incidence has been carried out in the Russian Federation, Ukraine, Georgia, Kazakhstan, and the USA. The effect of immunization results on morbidity is shown. The increasing risks of outbreaks of morbidity associated with migrations and import processes during the import of the causative agent of measles infection have been identified.

The reasons for the lack of vaccination against measles among the entire population are considered. Data on vaccination coverage among residents of the Russian Federation are provided. Social groups that are less resistant to outbreaks of the disease due to the lack of immunization have been identified. All risks and possible complications due to high morbidity among the entire population are reflected. The restrictive measures influence related to the unfavorable epidemiological situation of COVID-19 was noted. The relationship is presented between the introduced restrictive measures related to the new coronavirus infection and the reduction of measles outbreaks among different countries, as well as the general incidence. The prevention importance is shown among children and adults, as well as the importance of timely detection of new measles infection outbreaks.

Keywords: measles; morbidity; epidemiological situation, vaccination.

Introduction. Measles is a highly contagious acute viral disease that is transmitted by airborne droplets and can lead to serious complications and death.

The incubation period of measles infection ranges from 9 to 17 days. Infected people are contagious from 4 days before the appearance of the rash and up to 4 days after the appearance of the rash in vaccinated people.

Measles virus is transmitted by airborne droplets through aerosolised secretions, as a part of the contents of the nasopharynx, secretions from coughing, sneezing, talking, breathing. The pathogen can spread considerable distances with airflow.

The disease begins with fever and usually at least one of three symptoms: cough, rhinitis and conjunctivitis. Filatov-Koplik spots are small whitish-gray dots surrounded by a corolla of hyperemia. They are located on the mucous membrane of the cheeks opposite the second molars and make it possible to clinically diagnose measles a day or two before the rash appears.

The rash appears in 3-4 days after the onset of fever, first on the face and behind the ears. Then it spreads to the trunk and extremities, coinciding with the development of the adaptive immune response. Fever and catarrhal symptoms usually peak along with the rash, which persists for 3-4 days. Measles in vaccinated patients occurs in a mild form, there is no stage in the manifestation of infection.

Diagnostic studies of measles consist of the collection of anamnesis, examination, assessment of the manifestation of the main symptoms of the disease, as well as laboratory and instrumental methods of investigation.

Specific prevention. The main method of protecting the population from measles, rubella and mumps is vaccination.

Immunization of the population against measles, rubella, and mumps is carried out within the framework of the National Calendar of Preventive Vaccinations and the Epidemic Indications Preventive Vaccination Calendar.

Children and adults who received vaccinations under the National Preventive

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Vaccination Schedule and whose blood serum did not detect antibodies to the relevant pathogens in standard serology tests receive additional vaccinations against measles and rubella (or) mumps according to the instructions for immunobiological drug use (hereafter referred to as "ILP").

For immunization, ILPS is used, registered and approved for use on the territory of the Russian Federation in accordance with instructions for its use.

In order to maximize coverage of vaccinations for measles, rubella and mumps in the population of the Russian Federation, efforts are being made to identify people who have not had these infections and have not received vaccinations among hard-to-reach groups (migrants, refugees, internally displaced people, nomadic populations) and to immunize them in accordance with the National Immunization Schedule.

To ensure population immunity to measles, rubella, and mumps, sufficient to prevent the spread of infection among the population, vaccination coverage of the population in the territory of the municipality should be:

- vaccination and revaccination against measles, rubella, mumps in children at decreed ages - at least 95%;
- vaccination against rubella in women aged 18-25 years - at least 90%;
- vaccination against measles in adults aged 18-35 years - at least 90%;
- vaccination against measles of persons of decreed professions aged 18-55 years - at least 90%. [8].

Materials and Methods. In the analysis of the epidemiological situation, materials from the official websites of the US and European health care organisations, WHO, as well as data from Rospotrebnadzor were used. Statistical processing of the material was carried out by using the MS EXCEL software package for the Microsoft Office 2020 operating system.

Objectives:

- to summarise the results of the spread of the epidemic process in Russia, neighbouring and foreign countries;
- to determine the main difficulties in conducting vaccine prophylaxis of measles infection, cite the reasons preventing its elimination in the country and modern conditions, as well as possible ways to eliminate them;
- to analyse the level of prevalence of measles infection on the territory of the Russian Federation and assess the vaccination coverage rate;
- to analyse the reasons for late vaccination.

Results and discussion. The epidemiological situation of measles in the Russian Federation

Considering the epidemiological situation of measles in the Russian Federation and other countries of the world since the 1990s, it can be noted that the level of morbidity is characterized by dynamic wave-like rises with a periodicity of 7-10 years and subsequent declines after the introduction of anti-epidemic measures [5].

Between 2017 and 2023, new wave-like outbreaks of infection can be observed both in the Russian Federation and in other countries [2, 3, 4, 5, 6, 7]. All this is happening for various reasons that can include increased migration between neighboring countries, increased parallel imports, and weakened anti-epidemiological measures related to the new coronavirus infection. All this requires a direct analysis of the incidence and its spread associated with new outbreaks of measles. Data on cases in the period 2017-2023 are presented in Fig.1 and Table 1.

Analyzing the reported data from 2017 to 2019, there is an increase in incidence. Between 2019 and 2021, on the contrary, there is a sharp number decrease of infections due to the epidemiological situation connected with the new coronovirus infection (COVID-19) in the world and in the country. All this was accompanied by the imposition of measures such as restrictions on the movement of citizens, self-isolation, mask regime, bans on mass events, closure of borders, and restrictions on trade with neighboring countries [5, 6, 7]. All of these restrictions slowed the spread of the new infection and also reduced the risks associated with the spread of measles.

According to the data for the period from 2022 to 2023, there is an increase in the incidence of the disease. There is a tendency to "restore" the indicators of the "pre-COVID" period.

Specific prophylaxis is one of the effective measures to protect the population from measles and other infections. However, its effectiveness will depend on the immune coverage of the population, which should be at least 75% of the country's population. And in the case of measles it should be 95%. Indicators of immunization of the RF personnel are presented in Table 2.

Analyzing the data from 2017 to 2023, overall vaccination coverage among under 24 months and 6 years old children, and 18-35 years old adults exceeded the regulated level (at least 95%) nationwide. Nevertheless, measles outbreaks continued to be observed. The epidemic process of measles was supported by people who were not vaccinated and those with an unknown vaccination history, accounting for 82.4% of cases. Those who had been vaccinated once and twice participated in the epidemic process equally, at 8.8% each, indicating the effectiveness of vaccination [7]. Imported cases of measles are shown in Figure 2.

A pronounced upward trend in imported measles cases was observed in the periods from 2017 to 2019, and from 2020 to 2022 there was a sharp decrease. The deterioration of the epidemiological situation of measles is facilitated by an increase in the number of children and adults in many territories who have not been vaccinated with HCV, mainly due to refusals of vaccination, including during vaccination according to epidemiological indications [3]. The largest number of cases, as well as imported cases of measles, occurred in 2019. According to the Federal State Budgetary Institution "MNIIEM named after G.N. Gabrichevsky" Rospotrebnadzor imported 231 cases of measles from 41 countries on the territory of 40 subjects of the Russian Federation. Measles was most often imported from Ukraine (49), Azerbaijan (24), Thailand (24), Georgia (21), Turkey (16), Uzbekistan (17), Kyrgyzstan (12) [4]. The decline in morbidity is caused by a reduction in tourism, the closure of borders with neighboring countries, as well as a decrease in imports [5].

Due to the closure of borders due to the COVID-19 pandemic in 2020, the long-term trend of increasing the number of imported cases did not persist, but the import of measles cases from neighboring countries still prevailed (in 2020 - about 70% of all imported cases) [5].

However, from 2022 to 2023, an increase in imported measles cases was observed again, due to the cancellation of anti-epidemic measures aimed at preventing the spread of the new coronavirus infection and an increase in parallel imports and tourism.

Kazakhstan. In recent years, there has been an increase in the number of measles cases in the Republic of Kazakhstan. For example, from 2018 to 2019, the number of cases increased from 576 to 13326 [10].

One of the main reasons for the aggravation of the epidemiological situation was insufficient immunisation of the population due to refusals and medical contraindications to preventive vaccinations.

The main share of morbidity that made up 58.3 per cent (7,775 cases) was noted among unvaccinated children, who accounted for, of whom 3,703 (47.6%) were under one year old and

4,072 (52.4%) due to medical withdrawals and refusals.

Among those who fell ill, 2,405 people (18 %) were vaccinated against measles, 1,273 (52.9 %) of them received one dose of vaccine and 1,132 (47.1 %) of them received two doses.

Analysing the morbidity of different population groups, the main share of infections was in children from 1 to 4 years old, which corresponded to 4257 (31.9%) and children under 1 year were corresponded to 3879 (29.1 %).

Smaller proportion of patients was observed in the age group of 20-29 years (14.7 %.), 30 years and older (11.9%).

At the end of 2019, 21 cases of measles-related deaths were reported, 19 (90.4 %) of them were children.

According to the US Centers for Disease Control and Prevention (CDC), 12,985 cases of measles were recorded in Kazakhstan from May to October 2023 [18].

In a study by Yerdesov et al., 2023, the cyclical nature of measles outbreaks in Kazakhstan is noted, often correlating with a drop in vaccination rates and aggravated by seasonal factors [11].

Thus, the number of new measles outbreaks in the Republic of Kazakhstan has increased in recent years. Unvaccinated children accounted for the bulk of the cases. Mostly children under 1 year of age were ill due to not reaching the vaccination age and medical refusals, as well as unvaccinated adults.

Ukraine. Ukraine is one of the most endemic territories with measles infection. This is a serious public health problem that needs to be continuously monitored.

The largest recent outbreak occurred between 2017 and 2019. More than 115,000 people were infected in Ukraine during this period, and 41 of those who became ill died. The incidence peaked in 2018 and 2019 with up to 53219 cases of infected people. In 2019, this figure increased even further to 57282. The increase in infections was due to people who were not vaccinated or did not complete the immunisation course. According to the latest data, 65-67 per cent of those who fell ill were children and 33-35 % were adults in Ukraine.

Ukraine has risks of new measles outbreaks due to low vaccination coverage, which implies increased susceptibility to the virus in the country.

At the beginning of the outbreak of 2017-2019, the coverage of the population with measles vaccinations in Ukraine was 42%, which is two times less than the 95% regulated by WHO [19]. In 2021,

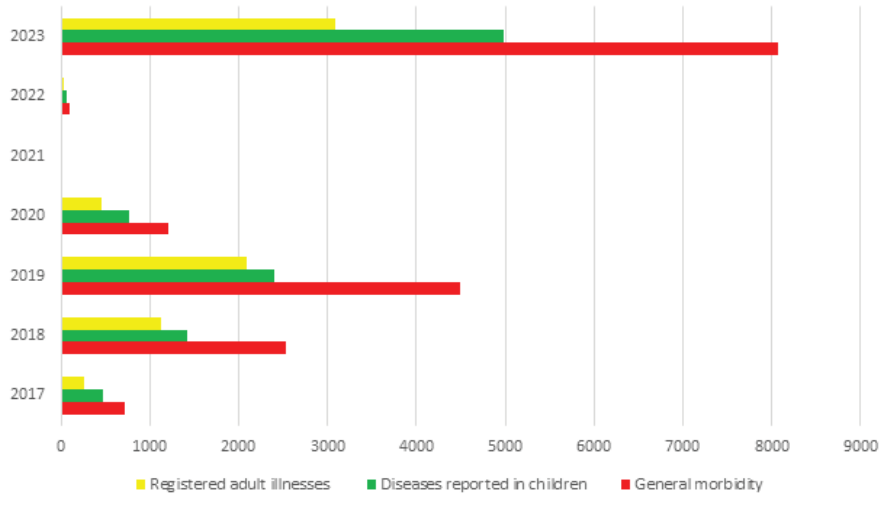

Fig. 1. Dynamics of measles incidence in the Russian Federation in 2017-2023 abs.units

Table 1

Results of measles outbreaks in the Russian Federation in 2017-2023 abs.units

Number of patients	2017	2018	2019	2020	2021	2022	2023
Recorded cases	721	2539	4491	1214	1	102	8073
Diseases reported in children	464	1414	2395	763	0	65	4989
Reported illnesses in adults	257	1125	2096	451	1	37	3084

Table 2

Indicators of vaccination coverage of the population of the Russian Federation for 2017-2023

Index	2017	2018	2019	2020	2021	2022-2023
Vaccination coverage of children at 24 months, %	97.69	97.1	97.66	97.28	97.34	97.44
Revaccination coverage of children at 6 years of age, %	97.05	97.02	96.62	96.09	96.4	96.52
Measles vaccination coverage of adults 18-35 years old, %	99.08	97.82	97.99	97.71	97.83	97.97

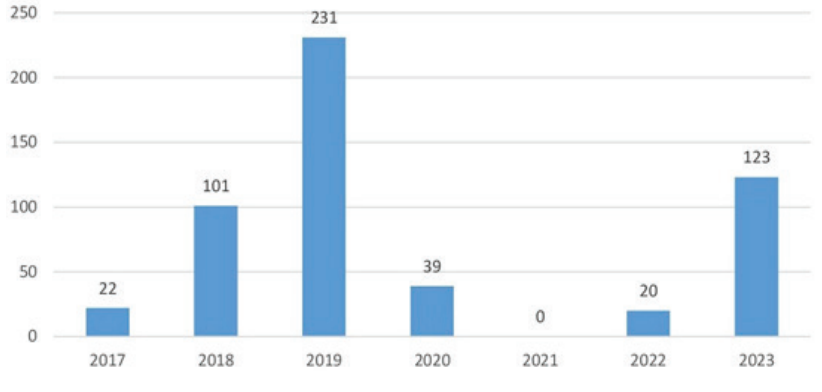

Fig. 2. Imported measles cases in the Russian Federation in 2017-2023

the vaccination coverage rate increased to 88%, and in 2022 it was only 74%, which led to a decrease in the immune layer and, accordingly, to an increase in the number of vulnerable populations [20].

Thus, new cases of measles occur periodically in Ukraine, which is the reason for insufficient vaccination rates among all segments of the population. Thus, due to the current situation, military actions and migration to other countries, there is an additional risk of outbreaks of measles infection outside the territory of Ukraine.

The U.S.A. Thanks to universal vaccination in the United States, measles was officially declared eliminated in 2000. According to the Centers for Disease Control and Prevention (CDC), 31 states reported 1,282 confirmed measles cases and 128 hospitalisations from January to December 2019, that is the highest reported number since 1992 [12].

Severe cases of measles require hospitalisation of patients. Based on historical data, CDC estimates that about 1 in 4 infected cases in the U.S. requires hospitalisation, and 1 in 1,000 cases is fatal. The number of hospitalisations fell sharply following widespread measles vaccination [12].

The 2019 measles outbreak in the U.S. was imported, and most of those who became ill were unvaccinated.

In light of increased mobility in this century, any under-immunized region is at risk of a measles outbreak due to social migration.

During the COVID-19 pandemic, routine immunisation rates are reported to have decreased in various parts of the world, including in the USA. Epidemiologists estimate that more than 27 million children worldwide missed their first dose of measles vaccine in 2020. A decrease in the level of routine vaccination is likely to lead to an upsurge in highly contagious diseases, including such as measles.

Measles in Europe. Despite the introduction of vaccination programmes in European countries, the increase in vaccination refusals and the lack of mandatory immunization strategies in a number of countries have led to various outbreaks throughout Europe [14].

In particular, in 2017, measles epidemics were observed in 28 European countries with 37 reported deaths. They were mainly detected in Romania (5,608 cases), Italy (5,098), Greece (967) and Germany (929 cases). Measles infections were also reported in European countries in 2018 (17,822 cases) and 2019 (13,199 cases).

In 2020, measles incidence decreased by 2,043 cases in all European countries due to restrictions implemented during the COVID-19 pandemic [14].

In 2022, 123 measles cases were registered in the EU/EEA countries, of which 75 (61%) were laboratory confirmed, 41 cases were registered as "possible" (33%), 5 cases as "probable" (4%) and 2 cases as "unknown" (<2%) [16].

In 2023, 2,361 cases of measles were reported in the EU/EEA countries, of which 1,607 (68%) were laboratory confirmed. The remaining 754 cases were registered as "probable" (29%), "possible" (3%) and "unknown" (<1 %) [16].

Twenty-three countries reported measles cases in 2023, while seven countries (Bulgaria, Greece, Iceland, Cyprus, Luxembourg, Malta, Slovenia) did not report any cases during this period, indicating a favorable epidemiological situation [16].

One country (Romania) accounted for 74% of all reported cases.

The spread of measles in Europe indicates that the eradication of infection has not yet been achieved.

In Europe, the persistent presence of measles each year highlights that eradication has not yet been achieved. This emphasizes the need to continue expanding vaccination efforts to control the disease and prevent future outbreaks.

Until March 2020, surveillance data confirm the classic cyclical pattern of measles prevalence.

Since March 2020, many European countries didn't report any cases of measles virus infection [15].

In Europe the average number of measles cases has a maximum value in 2019 (37.51 cases per million inhabitants) and a minimum value in 2020 (4.24 cases per million inhabitants) [15].

Based on WHO data, it can be assumed that COVID-19 containment measures have largely prevented the spread of other airborne diseases, as the epidemic trend that is usually observed has not been confirmed in 2020-2021 [15].

The resurgence of measles incidence is paradoxical in Europe in the last few years. Although national immunisation programmes offer an affordable and effective vaccine, but the results of epidemiological situation analysis show that more than 47000 people have contracted measles in WHO countries. Serbia, France, Greece and Italy were the most affected countries were [15].

Recent outbreaks, that are often transmitted nasocomialy and infect healthcare workers, were reported in several European countries, such as Ireland, Portugal, France, Sweden and Ireland, in which the virus has been eradicated according to WHO [15].

Transmission from unvaccinated patients from measles-endemic countries is the most common cause of outbreaks.

Lack of awareness of the infection, as well as the late appearance of the typical maculopapular rash characteristic of measles, 3-4 days after the onset of fever, increases the risk of disease with nasocomial and household transmission.

Between January and July 2018, measles caused 63 deaths in Europe, a rate of one to two cases per 1,000 cases. During the outbreak in France from October 2017 to July 2018, there were two deaths per 1,101 infected people. These figures appear to have been underestimated because of possible unconfirmed data, without virological laboratory results, and a higher prevalence of susceptible patients with risk factors for severe measles [15].

Migration of unvaccinated populations from the war zones increased the risk of the infection transmission with underdeveloped primary health care systems such as Syria and Pakistan in the Middle East. Other reasons are poor vaccination of hard-to-reach populations and national minority groups living in European countries [15].

Conclusion. The occurrence of measles outbreaks in the near abroad indicates the need to maintain vigilance against this infection [7]. And the constant annual detection of measles cases in Europe indicates that eradication has not yet been achieved, and underlines the need to further increase the number of vaccinations necessary to control the disease and prevent new outbreaks [14].

WHO information resources and the European Center for Disease Prevention and Control provided data to assess the solution to the problem of vaccination refusal and recommended evidence-based responses to increase and maintain the level of the immune stratum of the population.

There are good reasons to focus on the risk of measles in children who are unprotected or not immunized yet, as even newborns can be at risk when they are exposed to the virus. Infants born to vaccinated women have significantly lower antibody concentrations than those born to naturally immune women and may have no protection until the first MMR vaccination. In addition, under one year old children are seven times more likely to die than older children due to post-infectious complications such as pneumonia.

The current outbreaks in Europe affect both adult and pediatric populations. A large proportion of cases in the analysis of European measles outbreaks involved health care workers, and most were associated with the refusal to be vaccinated.

The of two doses of MMR vaccine is about 95%. Immunity to the measles pathogen acquired from immunization with live attenuated vaccine is much lower than the protection afforded by natural infection. A 2018 study reported that immunity wanes over time regardless of how it was acquired.

The route of transmission may be important because health care workers who are in close contact with primary measles patients and are exposed to high doses of virus appear to have a greater risk of infection.

Vaccination is the only way to prevent measles and eliminate the disease, and a great effort must be made to restore public confidence in vaccination. Currently, mandatory measles vaccination is included in national immunization programs in nine of the 28 European Union countries, but Italy has recently decided to opt out of mandatory MMR measles vaccination. The European Commission proposed to increase the cooperation between countries in the fight against diseases that can be prevented by vaccination against infections such as measles, whooping cough and seasonal influenza. The European Union proposals emphasize the importance of joint action to increase vaccination coverage and provide reliable and understandable information about vaccines to the public [14].

Since 2017, there has been a rise in measles incidence in the Russian Federation through 2019. The main reason was the decrease in attention to immunization against measles and, as a consequence, the formation of susceptible to the pathogen persons among the population shares.

The decline in morbidity occurred from 2020 to 2022, which is the result of anti-epidemic measures carried out in the country related to isolation in connection with COVID-19.

In 2023, there was a tendency for the incidence of measles to rise. Many domestic researchers have noted an increase in vaccination refusals over the past few years, which has contributed to a significant decline in the immune layer of the population prior to the 2017-2019 COVID-19 pandemic [9].

Another problem is the large influx of migrants from neighboring countries. Cultural and language barriers prevent the timely seeking of health care, which ultimately creates large groups of unvaccinated citizens. It contributes to the spread of infections among the local population [9].

Based on the epidemiological analysis of neighboring countries for the years 2017-2023, it can be seen that the rise in incidence and its cyclical nature is characteristic of many states, so the problem of measles virus is a worldwide problem. Maintaining vaccination rates for all segments of the population is the top priority in measles prevention and requires a coverage rate of at least 95%.

Imported cases with migration flows remain relevant in the Russian Federation and neighboring countries. This requires special attention from health authorities to take additional measures, including even such as checking certificates for measles vaccination.

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ERYTHROPOETIN AS A PREDICTOR OF EXTREMELY SEVERE COURSE OF NEW CORONAVIRUS INFECTION COVID-19 IN PREGNANT WOMEN

A comparative analysis of medical, social, clinical and laboratory parameters in pregnant women with a new coronavirus infection (NCI) COVID-19 of varying severity was carried out. For the first time, the level of serum erythropoietin was studied in this category of patients; for the first time, a statistically significantly lower level of erythropoietin was detected in pregnant women with extremely severe COVID-19. The threshold value of serum erythropoietin level was determined to predict the development of extremely severe COVID-19 in pregnant women.

Keywords: new coronavirus infection, COVID-19, pregnancy, extremely severe course, serum erythropoietin/

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Introduction. On 5th May, 2023 World Health Organization officially announced that Novel Coronavirus Infection (NCI) COVID-19 pandemic **no longer constitutes a public health emergency of international concern.** However, there is still a wide circulation of various SARS-CoV-2 virus variants [4]. NCI COVID-19 is a predominately respiratory disease with multisystem damage, especially in case of extremely severe disease course, accompanied by pronounced hypoxic effect on all the tissues and organs with the development of multiple organ dysfunction with potential early damage to the kidney parenchyma [9]. The decrease in oxygen saturation of the tissues stimulates the synthesis of erythropoietin (EPO) a glycoprotein hormone. Up to 90% of EPO in the body of an adult person is produced by peritubular fibroblasts of renal interstitium [5]. EPO activates the production of nitrogen oxide in the endothelium, thus effecting the lung vasoconstriction and improving the oxygen supply to the brain, heart and other organs and tissues [12]. Under physiological regulation EPO is capable of reacting against the pro-inflammatory cytokines TNFα and IL-1β, producing an anti-inflammatory effect [3, 13, 14]. Numerous studies have presented the data on adverse pregnancy outcomes in patients with NCI of various severity. Against the background of steady NCI course pregnant women may have sudden development of critical state. The majority of studies testify to a high risk of fetus distress in pregnant women with severe COVID-19, which is associated with the necessity of preterm labor, premature fetus birth, or potential prenatal/intrapartum fetus death [1, 10, 11, 15, 19]. That is why the studies devoted to the analysis of the NCI effect on pregnancy remain highly relevant. The determination of early predictors of the progression of the COVID-19 severity during gestation is of utmost importance.

The aim of the study: to assess the level of blood serum erythropoietin in pregnant women with novel coronavirus infection COVID-19 of various severity; determine its threshold value to predict extremely severe course of COVID-19 during gestation.

Materials and methods. A comparative prospective cohort study has been performed with subsequent retrospective analysis of the data from medical records (labor and delivery record, health card of

Laboratory parameters in pregnant women of the 1st-5th studied groups upon admission to the hospital

	1st group (n=7)	2nd group (n=21)	3rd group (n=10)	4th group (n=7)	5th group (n=20)	p (significance criterion)*,**
C-reactive protein (CRP), mg/l (N=0-5)	8 (5; 23)	25 (16; 39)	53 (20.3; 75)	45 (24; 84)	0 (0; 1.2)	p_{1-5}<0.001; $p_{1.5}$=0.001; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.2}$=0.044; $p_{1.3}$=0.006; $p_{1.4}$=0.009; p_{oc}<0.001
Procalcitonin (PCT), ng/ml (N≤0.1)	0.07 (0.06; 0.54)	0.08 (0.06; 0.16)	0.15 (0.08; 0.53)	0.25 (0.09; 0.92)	0.07 (0.06; 0.08)	p_{1-5}=0.004; $p_{2.5}$=0.095; $p_{3.5}$=0.004; $p_{4.5}$=0.001; $p_{2.4}$=0.013; p_{oc}=0.005
Ferritin, ng/ml (N=6-159)	46 (30; 87)	114 (60.5; 163)	110 (82.5; 283)	406 (112; 475)	14.5 (6.3; 37.8)	p_{1-5}<0.001; $p_{1.5}$=0.014; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.2}$=0.024; $p_{1.3}$=0.022; $p_{1.4}$=0.006; $p_{2.4}$=0.041; p_{oc}<0.001
D-dimer, ng/ml	646 (502; 950)	607 (405; 1116.5)	2063.5 (572.5; 2562)	3000 (1873; 3000)	252.5 (164;305)	p_{1-5}<0.001; $p_{1.5}$<0.001; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.4}$=0.017; $p_{2.4}$<0.020; p_{oc}<0.001
Lactate dehydrogenase (LDG), u/l (N=195-450)	324 (308; 480)	512 (363.5; 635.5)	617.5 (546.3; 700.3)	926 (592; 1469)	243.5 (89.8; 443.3)	p_{1-5}<0.001; $p_{2.5}$=0.001; $p_{3.5}$=0.002; $p_{4.5}$=0.001; $p_{1.2}$=0.015; $p_{1.3}$=0.002; $p_{1.4}$=0.004; $p_{2.4}$=0.014; p_{oc}<0.001
Erythropoietin (EPO), mlU/ml (N=8-30)	23 (17; 35)	16 (7.2; 21.5)	21 (12.8; 27.5)	4.7 (4.4; 9.3)	16.5 (11; 23.5)	p_{1-5}=0.002; $p_{4.5}$=0.001; $p_{1.2}$=0.046; $p_{1.4}$=0.002; $p_{2.4}$=0.005; $p_{3.4}$=0.002; p_{oc}=0.584

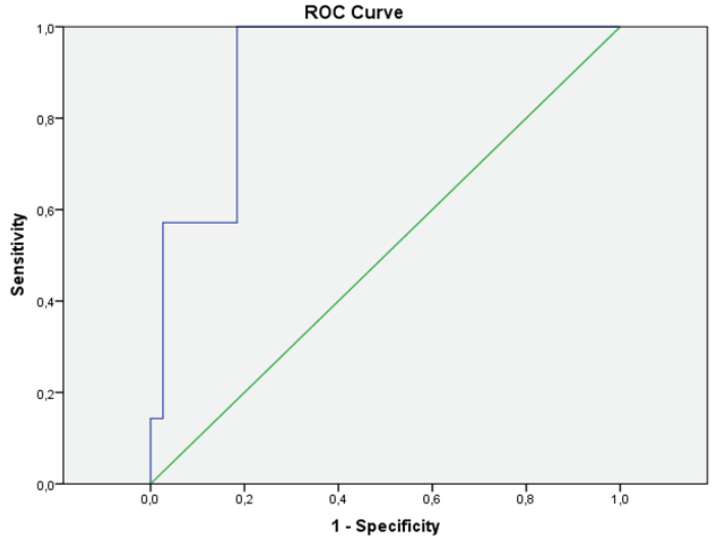
Note: * - subscript number denotes the number of the compared groups, ** - pmc – criterion of significance p between the main group and the comparison group

a pregnant and puerperant woman) of 65 pregnant women. Continuous sampling method has been used in the study. Medical and social, clinical and laboratory parameters were analyzed. The main group consisted of 45 patients with NCI hospitalized during the 3-4th wave of COVID pandemic (July 2021 – September 2021) to the maternity hospital of the State Budgetary Healthcare Institution Regional Clinical Hospital № 2, Chelyabinsk which has been repurposed to a COVID hospital for providing medical assistance to pregnant, parturient, and puerperant women with NCI, as well as to the newborns in the territory of the Chelyabinsk City and Chelyabinsk Region. The comparison group included 20 pregnant women with no indications of NCI/acute respiratory viral infection (ARVI) during the current pregnancy admitted to the maternity hospital of the State Budgetary Healthcare Institution Regional Clinical Hospital #3, Chelyabinsk in August-September 2021 in the 3rd trimester of gestation. At admission the pregnant women from the comparison group had negative SARS-CoV-2 PCR test from the oral and nasopharyngeal cavity, had no clinical signs of ARVI over the course of the current gestation. The COVID-19 severity was determined in accordance with the existing guidelines (Version 4(05.07.2021

r. https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/057/333/original/05072021_MR_Preg_v4.pdf, accessed on 26.10.2023). Patients with mild NCI comprised the 1st group (n=7), medium – the 2nd group (n=21), severe – the 3rd group (n=10), extremely severe – the 4th group (n=7), pregnant women of the comparison group - the 5th studied group (n=20). Main group inclusion criteria were: confirmed COVID-19 case (U07.1), antenatal care, availability and accessibility of the medical records to collect necessary data on gestation course. The non-inclusion criterion was probable/suspected COVID-19 case (U07.2/Z03.8). To evaluate the laboratory parameters the blood was sampled from the median cubital vein upon the studied patients' admission to the in-patient department. Blood serum EPO concentration was determined with ELISA technique with the use of the Erythropoietin-EIA-Best (Vector-Best, Russia) test-system. Optical density of the samples was registered on the photometer «Multisrkan ORIGINAL» (Labsystems, Finland). Statistical processing of the obtained results was performed in the IBM SPSS Statistics 19 software package. To describe quantitative data median and quartile were used, for qualitative data we used absolute and relative frequency. The data were analyzed with the use of non-parametric criteria depending on the type of the data and amount of comparison groups (Kruskal-Wallis test, Mann-Whitney test, Fisher's exact test). ROC-analysis was performed to assess the diagnostic significance of the serum erythropoietin level. The differences were considered statistically significant at $p< 0.05$.

Results and Discussion. Gestational age median upon admission was 29.4 (25.0; 39.0), 25.0 (19.5;37.0), 32.0 (26.8; 35.3), 32.0 (27.0; 32.4) and 40.0 (39.3;40.0) weeks ($p_{1-5}<0.001$; $p_{1,2}=0.395$; $p_{1,3}=0.961$; $p_{1,4}=0.949$; $p_{2,3}=0.409$; $p_{2,4}=0.770$; $p_{3,4}=0.768$; $p_{oc}<0.001$) for the 1st -5th group, respectively, without statistically significant differences between groups 1-4, with the predominance of NCI manifestation in the 3rd trimester of the gestation. Women from the 1st-4th group were hospitalized on the 6 (5;9), 6 (4,5;7), 3.5 (3;5,3), 4 (3;5) day, respectively, from the onset of NCI manifestation ($p_{1-4}=0.044$; $p_{1,2}=0.788$; $p_{1,3}=0.063$; $p_{1,4}=0.080$; $p_{2,3}=0.027$; $p_{2,4}=0.053$; $p_{3,4}=0.799$). The median of the lung tissue involvement according to the initial computer tomography (CT) was 0 (0; 0), 24 (16; 31), 31 (19; 56), 32 (15; 36) % ($p_{1-4}<0.001$; $p_{1,2}<0.001$; $p_{1,3}<0.001$; $p_{1,4}=0.001$; $p_{2,3}=0.143$; $p_{2,4}=0.670$; $p_{3,4}=0.591$) in the 1st - 4th group, respectively. There was no statistically significant differences between the parameter values in groups 2-4. The median of the maximum lung tissue involvement based on the CT data in the dynamics was 0 (0%), 25 (20;34), 53.5 (47.3;56.0) and 100.0 (84.0;100.0) in the 1st -4th group, respectively ($p_{1-4}<0.001$; $p_{1,2}<0.001$; $p_{1,3}<0.001$; $p_{1,4}=0.001$; $p_{2,3}=0.143$; $p_{2,4}=0.670$; $p_{3,4}=0.591$). The median of the hospital stay length was 5 (5; 8), 10 (7.5; 13.5), 15.5 (12.3; 16), 27 (23; 36) and 7 (6; 9) days in the 1st-5th group, respectively ($p_{1-5}<0.001$; $p_{1,2}=0.003$; $p_{1,3}=0.002$; $p_{1,4}=0.002$; $p_{2,3}=0.051$; $p_{2,4}<0.001$; $p_{3,4}=0.016$; $p_{oc}=0.001$). It shows the statistically significant increase in the length of the hospital stay with the increase in the NCI severity. One woman from the 2nd group underwent COVID-19 vaccination prior to the current pregnancy planning. In general, medical and social characteristics of the pregnant women of the 1st-5th group did not differ statistically significantly. The median of the age of the studied women was 31.0 (28.0; 36.0), 31.0 (27.5; 34.0), 31.0 (25.8; 33.5), 33.0 (29.0; 37.0) and 34.0 (30.5;36.8) in the 1st-5th group, respectively ($p_{1-5}=0.407$; $p_{oc}=0.086$). In general, in terms of the presence of somatic disease (4 (57.1%), 14 (66.7%), 10 (100.0%), 6 (85.7%), 18 (90.0%) cases, $p_{1-5}=0.060$; $p_{oc}=0.314$) and exacerbations of the course of the current gestation (6 (85.7%), 17 (81.0%), 8 (80.0%), 6 (85.7%), 18 (90.0%) cases, $p_{1-5}=0.945$; $p_{oc}=0.711$) no statistically significant differences between the pregnant women from the 1st-5th group were obtained.

We have registered high levels of the markers of the acute phase of the inflammation – C-reactive protein and ferritin, marker of the tissue destruction - LDH with the statistically significant difference in pregnant women with NCI, with much higher values in case of extremely severe course of the process (Table 1). It fully agrees with the results of other studies [7, 17, 18]. The level of procalcitonin that shows the risk of the development of COVID-19 complications (bacterial infection or septic state) was statistically significantly higher in the main studied group and it correlated with the NCI severity. The highest values of procalcitonin were registered in case of the extremely severe course of the process which agrees with the published papers data [2]. Statistically significantly high level of D-dimer in pregnant women with COVID-19 was observed, especially in those who had extremely severe course of the infection, relative to the healthy pregnant women, which is in line with the data of published studies [2, 8, 16]. According to the conclusions of the meta-analysis presented in Gungor Baris et al. (2021), the increase in the D-dimer level in dynamics is typical of more severe NCI COVID-19 and is associated with the risk of the lethal outcome [16]. No statistically significant differences between the levels of C-reactive protein, procalcitonin, ferritin, D-dimer, LDH was observed in women of the 3rd and 4th group. In our study for the first ever the level of the serum EPO in pregnant women with COVID-19 was analyzed upon admission to the hospital (Table 1). Statistically significantly lower levels of EPO were registered in group 4 relative to those in pregnant women from group 1-3 ($p_{1,4}=0.002$; $p_{2,4}=0.005$;



ROC-curve of the parameter "Blood serum erythropoietin, mIU/ml" in predicting extremely severe course of NCI COVID-19 in pregnant women

$p_{3,4}$=0.002) and women in the comparison group (p_{1-5}=0.002; $p_{4,5}$=0.001). Our results are similar to those presented in the studies by Yağcı S. et al. (2021), Viruez-Soto A. et al. (2021), Revin V.V. et al. (2022), who observed and reported low levels of serum EPO in non-pregnant patients (men/women) in the group of patients with severe COVID-19 course that required referring the patients to the intensive care unit, and in the group of people who died of NCI [6, 20, 21].

Table 1 Laboratory parameters in pregnant women of the 1st-5th studied groups upon admission to the hospital.

As a result of the conducted ROC-analysis, we esTableished that it is possible to predict the onset of the extremely severe course of NCI COVID-19 in pregnant women with 100% sensitivity and 81.6% specificity when the level of erythropoietin is ≤ 10.5 mIU/ml (on the 4th day from the onset of the disease). The score of the area under the ROC-curve was 0.920 with $CI_{95\%}$ [0.819; 1.000] (p=0.001). It testifies to high discriminating power of the method and possibility of its usage in practical activities (fig. 1).

Fig.1 ROC-curve of the parameter "Blood serum erythropoietin, mIU/ml" in predicting extremely severe course of NCI COVID-19 in pregnant women.

Conclusion. Statistically significantly lower level of blood serum erythropoietin is registered in pregnant women with extremely severe NCI. The development of extremely severe NCI COVID-19 could be predicted when the level of blood serum erythropoietin is ≤10.5 mIU/ml on the 4th day from the disease onset

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ARCTIC MEDICINE

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PARAMETERS FOR ASSESSING THE STATE OF CEREBRAL ENERGY EXCHANGE OF ELDERLY WOMEN LIVING IN THE ARCTIC ZONE OF THE RUSSIAN FEDERATION

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Neuroenergy exchange of the brain acts as a significant indicator affecting the preservation of neuropsychic activity in elderly age The aim of the study was to identify the features of the DC-potential level in various periods of old age in women living in the Arctic zone of the Russian Federation. The study involved 192 Northerners who were divided into age groups: 1 — 60-64 YO; 2 — 65-69 YO; 3 — 70-74 YO. The evaluation of cerebral energy exchange indicators was carried out by the hardware and software diagnostic complex "Neuroenergometer-KM" "Statokin". Registration of the DC-potential level was carried out monopolarly from 12 leads esTableished in accordance with the international scheme 10-20.

In the studied groups of elderly women, there is a change in the median values of the DC-potential level, demonstrating pronounced fluctuations in the distribution of brain energy consumption in the aging process. Brain metabolism decreases with age, but in old age there may be a multidirectional change between glucose metabolism and acid-base balance, indicating oxidative stress.

Then, at the age of 65-69, there is a gradual development of mental and physiological compensatory mechanisms, which leads to a relative normalization of neuroenergy exchange of the brain. The next increase in the DC-potential level of the brain begins to be traced at the age of 70-74 years. Probably, it is at this age that the decline of physiological compensatory processes begins to occur.

The obtained results made it possible to identify the peculiarities of the distribution of the DC-potential level in women of different age groups and to esTableish normative values. The developed standards will improve the quality of diagnostics of the functional state of the brain in women living in the Arctic Zone of the Russian Federation, and will also allow timely monitoring brain functional changes in aging.

Keywords: cerebral energy exchange, DC-potential level, gerontogenesis, brain, cents, women, elderly age.

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Introduction. Currently, in the most developed countries, there is an increase in the number of elderly people, which indicates the importance of research on the physiological mechanisms of aging. Gerontogenesis is an extremely complex multi–stage process, where the functional state of the human brain plays a leading role in the well-being and successful adaptation [5, 10].

It is known that neuroenergy exchange of the brain acts as a significant indicator affecting the preservation of neuropsychic activity in elderly age [15]. This parameter allows us to indirectly judge neuro-glio-capillary activity in the metabolism and, first of all, carbohydrate metabolism. The level of constant potential (DC-potential level) – as a slow-changing potential of the millivolt range reflects the degree of intensity of energy consumption, which is different at each age stage [3, 4]. It has been shown that the intensity of carbohydrate metabolism decreases with age [14]. However, there are scientific papers proving that in the conditions of northern latitudes, this process occurs somewhat differently [15, 16].

The presented research is aimed at identifying changes in the neuroenergy exchange of the brain in elderly women, taking into account external (climate) and internal (age) environmental factors.

The purpose of the study is to identify the features of the DC-potential level in various periods of old age.

Materials and research methods. Elderly residents of the Arkhangelsk region took part in a voluntary one-stage study. The sample consisted of 192 women aged 60-74 years, who were divided into 3 age groups: 1 – 60-64 YO, average age – 62.37±1.13 years (n=64); 2 – 65-69 YO, average age – 66.63±1.51 years (n=63); 3 – 70-74 YO, average age – 73.95±2.57 years (n=65). The groups formed differed statistically significantly in average age ($p<0.001$). The exclusion criteria for participation in the study were: acute cerebral circulatory disorders, dementia, being registered in a neuropsychiatric dispensary, traumatic brain injuries, acute, as well as chronic diseases during exacerbation.

Before starting the study, all participants were consulted by a neurologist. Motor tests (Romberg Test, Index Tests) and diagnostics of sensory organs were carried out. To exclude dementia in the anamnesis, the screening technique "MCFAS" (Montreal Cognitive Function Assessment Scale) was used, which allows for rapid screening of cognitive impairment. A cardiologist monitored blood pressure and performed electrocardiography. If there was any disease or symptom of the above conditions in the results of the examination and in the anamnesis

(extracts from the medical records of the examined women were analyzed), they were not included in the total sample.

The assessment of brain neuroenergy exchange was carried out using a 12-channel hardware-software diagnostic complex "Neuroenergometer-KM" NMF "Statokin" [3, 4]. The examination procedure was carried out in the morning individually. The subjects were at rest, in a sitting position with their eyes open, in an isolated room without visual and auditory stimuli. DC-potential level registration was performed monopolarly from 12 leads (Fpz- frontal central lead, Fd- right frontal lead, Fs- left frontal lead, Cz- central lead, Cd- right central lead, Cs - left central lead, Pz- central parietal lead, Pd- right parietal lead, Ps- left parietal lead, Oz- occipital abduction, Td- right temporal abduction, Ts- left temporal abduction), esTableished in accordance with the international scheme 10-20. The References electrode was located on the wrist of the right hand. Registration of the DC-potential level was carried out 5-7 minutes after the electrodes were applied to the points of the head and lasted on average for 15 minutes.

Statistical processing of the obtained data was carried out using the SPSS 27.0 for Windows application software package. The normality of the distribution was assessed using the Shapiro–Wilk criterion. The Kraskel-Wallis criterion was used to identify differences between the compared groups. The critical significance level was assumed at $p<0.017$. For the formation of centile Tables, 10, 25, 50, 75 and 90 percentiles in each group were calculated.

Results and discussion. When analyzing the results obtained, it was revealed that statistically significant differences between the groups of 60-64 years and 65-69 years were found in the following leads: Oz ($p=0.016$), Td ($p=0.002$). Significant differences were found between groups 65-69 years old and 70-74 years old in all studied leads: Fpz ($p=0.011$), Fd ($p<0.001$), Fs ($p<0.001$), Cz ($p<0.001$), Cd ($p<0.001$), Cs ($p=0.001$), Pz ($p<0.001$), Pd ($p<0.001$), Ps ($p<0.001$), Oz ($p<0.001$), Td ($p<0.001$), Ts ($p=0.004$), Sum ($p<0.001$). In turn, significant differences were found between the groups of 60-64 and 70-74 years in the leads Fd ($p=0.007$), Fs ($p=0.005$), Cz ($p=0.010$), Cd ($p=0.001$), Pz ($p=0.003$), Ps ($p=0.018$), Sum ($p<0.001$).

Tables 1-3 show the percentile distribution of the DC-potential level of the main indicators from monopolar leads in women of the studied age groups, namely 60-64 years, 65-69 years, 70-74 years. During the analysis of the data obtained, it was found that with increasing age in all the studied groups, there was a fluctuation in the median values of the DC-potential level of the brain.

To make the presentation clearer, an analysis of the dynamics of total DC-potential level indicators (Sum), as well as the values of temporal leads and leads along the sagittal line of the brain in women of the studied groups was carried out (Fig.1). The choice of leads was determined by their informativeness and frequency of analysis in studies when assessing changes in neuroenergy exchange in various age groups [2, 11].

When analyzing the total values of the DC-potential level (Sum) of the brain of the examined, it was found that the median values of the DC-potential level of 65-69-year-old women decreased by 12.77% compared to the group of 60-64-year-old women, and then increased by 26.79% in the 70-74-year-old group. Probably, this may indicate the presence of specific age dynamics with fluctuations in brain neuroenergy exchange in different age segments.

When analyzing the median values for the main leads of the sagittal line (Fpz, Cz, Pz, Oz), the same trend was observed. Thus, in the frontal central lead (Fpz), central (Cz), parietal central (Pz), and occipital (Oz) leads, the median values of the DC-potential level of the brain in 65-69-year-old women compared to the 60-64-year-old group decreased by 5,86 %, 17,27%, 10,75%, 24,93%, and increased by 41.68 %, 18,31%, 28,07%, 5,35% in the group of 70-74 years, respectively.

Median values in the right (Td) and left (Ts) temporal leads of 65-69 women decreased by 37.31% and 11.31% compared to the 60-64 year group, and then increased by 32.11% and 13.73% in the 70-74 year group.

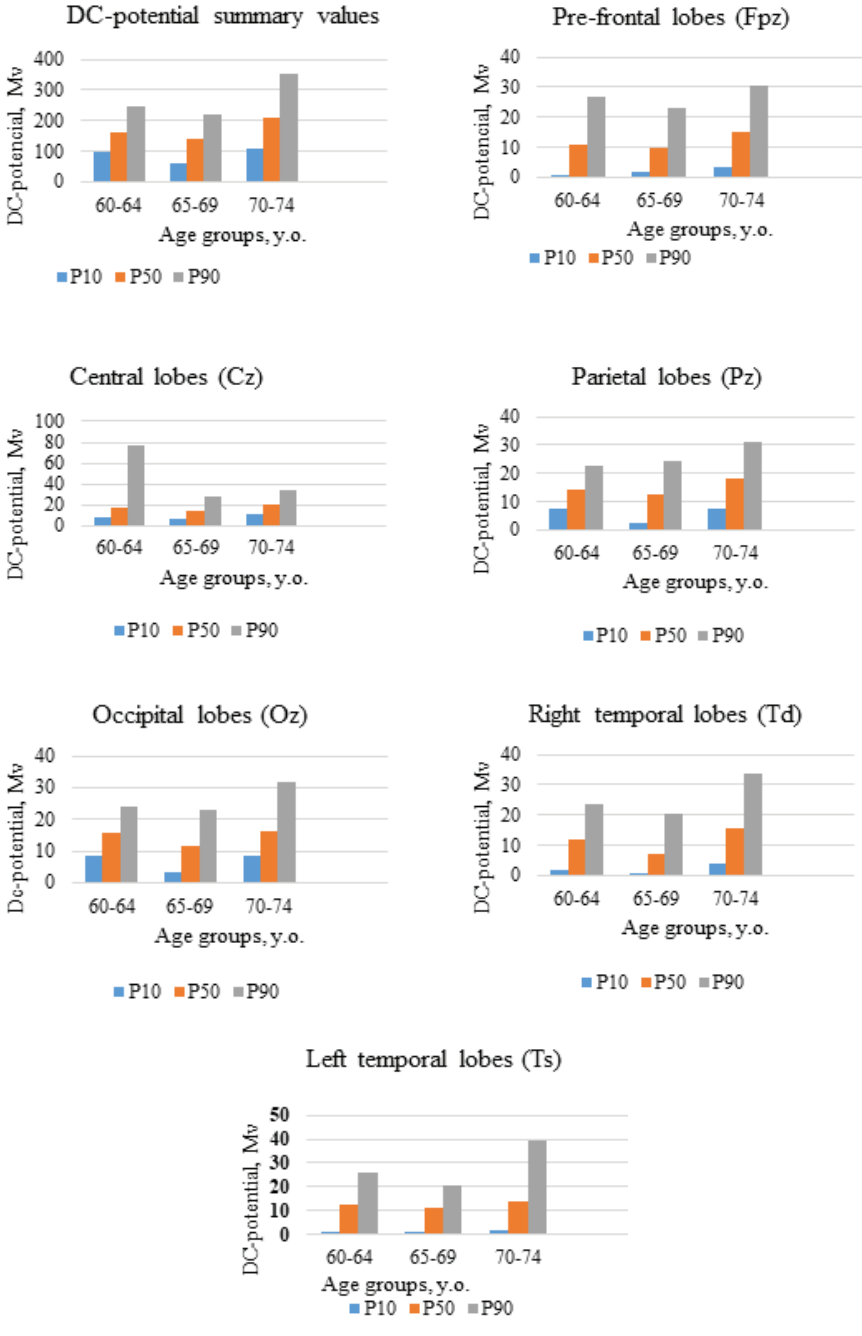
According to the study of Klimenko L.L., Deeva A.I., Fokina V.F., the metabolism of the brain decreases with age [1]. But in old age, there may be a multidirectional change between glucose metabolism and acid-base balance, indicating oxidative stress [17]. Many researchers explain this by an increase in acidity in the brain tissue caused by degenerative processes (a decrease in blood flow and cerebral pH balance) [9, 12].

It is generally believed that neuroenergometabolism is extremely sensitive to stress factors and in many studies is an indicator of the level of adaptation to stress [5, 6, 18]. In our study, in the elderly (60-64 years), high rates of DC-potential level of the brain are observed. Probably, this can be explained by a complex polymorphic combination of external (change of social role, completion of working age and retirement, etc.) and internal (growth of psycho-emotional load, hormonal changes in the postmenopausal period, physiological changes in the body) stress factors in the life of an elderly woman [13].

Then, at the age of 65-69, there is a gradual development of mental and phys-

Percentile distribution of constant potential level in the examined women

Leads	Percentiles		
	10	50	90
60–64 (Мв)			
Fd	-1.11	8.02	23.43
Fpz	0.15	10.58	26.91
Fs	0.46	8.98	22.54
Cd	5.41	14.73	24.49
Cz	7.71	17.37	76.64
Cs	5.22	15.47	24.12
Pd	3.96	15.11	25.02
Pz	7.50	14.32	22.39
Ps	5.43	14.68	26.80
Oz	8.58	15.66	23.87
Td	1.56	11.74	23.71
Ts	0.89	12.38	25.76
Sum	95.33	161.10	245.79
65–69 (Мв)			
Fd	-2.06	8.40	16.73
Fpz	2.07	9.96	23.18
Fs	0.88	6.17	21.76
Cd	0.90	14.02	25.17
Cz	5.99	14.37	27.23
Cs	4.26	14.54	23.99
Pd	2.41	11.30	22.96
Pz	2.70	12.78	24.59
Ps	4.06	12.65	24.08
Oz	3.52	11.76	23.06
Td	0.79	7.36	20.47
Ts	1.54	10.97	20.72
Sum	60.33	140.52	220.02
70–74 (Мв)			
Fd	1.99	12.66	28.58
Fpz	3.54	14.99	30.24
Fs	3.33	12.99	30.31
Cd	9.25	19.56	34.11
Cz	10.92	20.55	34.09
Cs	8.45	18.40	34.94
Pd	7.68	17.33	32.95
Pz	7.76	18.34	30.87
Ps	7.87	19.46	32.02
Oz	8.70	16.49	31.76
Td	3.97	15.51	33.61
Ts	1.88	14.08	39.53
Sum	107.07	207.26	352.87



Indicators of DC-potential level of the brain in women in the studied age groups: 60-64 years, 65-69 years, 70-74 years

iological compensatory mechanisms, which leads to a relative normalization of neuroenergy exchange of the brain. According to the results of our study, the stabilization of DC-potential level occurs precisely in the period of 65-69 years.

The next increase in the DC-potential level of the brain begins to be traced at the age of 70-74 years. At the same time, an increase in DC-potential level can act as an unfavorable sign of age-related degenerative changes in brain tissue [12]. Probably, it is at this age that the decline of physiological compensatory processes begins to occur.

Thus, changes in the DC-potential level in old age are a reflection of the polymorphism of external and internal factors that affect the functional state of the brain of an elderly woman.

Conclusion. In the studied groups of elderly women, there is a change in the median values of the DC-potential level, demonstrating pronounced fluctuations in the distribution of brain energy consumption in the aging process. Studies of the age dynamics of energy metabolism allow us to reveal the mechanisms of functional activity of the brain in old age, the understanding of which can increase the objectivity of functional diagnostics, and, ultimately, will contribute to the timely diagnosis and prevention of neurodegenerative changes, which will delay the period of decline of compensatory mechanisms of the nervous system of an elderly person.

It is important to note that the presented age percentile Tables were calculated based on a study of a sample of elderly women living in the Arctic zone of the Russian Federation. To increase the effectiveness of the diagnostic potential of the study, it is important to create standard centile Tables for men and expand the coverage of the sample by studying older people in other regions of Russia.

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S.I. Vdovenko

COMPARATIVE ANALYSIS OF EXTERNAL RESPIRATION SYSTEM OF THE NORTHERNERS IN THE AGE ASPECT

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This study aimed at the specific performance of respiration system based on the ontogeny. Four hundred and fifty-two male residents of Magadan aged 15-74 participated in a comprehensive age-associated survey that involved 4 groups: adolescents, early adults, workable men of mature age and the elderly. The lungs volumetric and velocity characteristics were analyzed using computer spirometry. Most indicators of external respiration proved to be significantly age specific. The maximum values were observed in the early adulthood followed by a fall in men of older age groups. The revealed changes indicated lowered reserve capabilities of the respiration performance with increasing duration of residence under the North conditions and suggested reduced adaptabilities of the body owing to the chronic adverse effects of natural and climatic environmental factors.

Keywords: North, adaptation, respiration system, men.

Introduction. Severe ecological and climatic factors of Russia's North-East are provided by not a long-term low atmospheric temperatures only, but a combination of abiotic environmental factors (the weather extremes, humidity and wind conditions, shifting daily and seasonal light periods, the influence of heliophysical effects, etc.). At the same time, this territory (Magadan Region, Chukotka, and Yakutia) receives the most dramatic climate changes [8]. Among all the body physiological systems, the external respiration is the first to face the outer environment and it experiences constant stress, due to continuous contact with natural extremes [9]. The increasing age results in pronounced changes in the breathing system, thereby aggravating the stress at various levels, from respiratory muscles to the conductive and convective zone of the lungs [2, 6, 12, 13]. Since the body experiences increased metabolic needs under the cold conditions, the optimal performance of the respiration system is the key to adequate oxygen supply and is crucial because of hypoxic changes in lungs resulting from a fall in the tissue respiration with increasing age [7]. Following on from the above, we see it is relevant to study changes in the respiration system functioning in men of different age groups – permanent residents of Magadan city.

Materials and Methods. Four hundred and fifty-two male residents of Magadan city, Caucasian by origin, participated in the survey. All subjects were divided into four groups based on their ages: adolescents, n = 85 (mean age 16.2±0.06 yrs, body height 179±0.75 cm, body mass 66.5±1.27 kg), young adults, n = 235 (19.2±0.5 yrs, 178.9±0.7 cm, 66.4±1.2 kg), mature men, n = 89 (37.1±0.59 yrs, 180.3±0.68 cm, 84.1±0.9 kg), and elderly men, n = 43 (65.6±1.09 years, 174.1±1.16 cm, 86.1±2.18 kg). The external respiration (or external breathing) function (EBF) of men was assessed by the standard and well-proven method of indexing volumetric pressure and pneumatic flow on a medical Diamant-C spirograph. All basic characteristics of the EBF were automatically compared with the proper values which are the values calculated for the population of residents of the Central part of Russia [5] We studied 21 indicators: vital and forced lung capacity (VC and FVC, l), forced expiratory volume in the first second (FEV_1, l), peak expiratory flow

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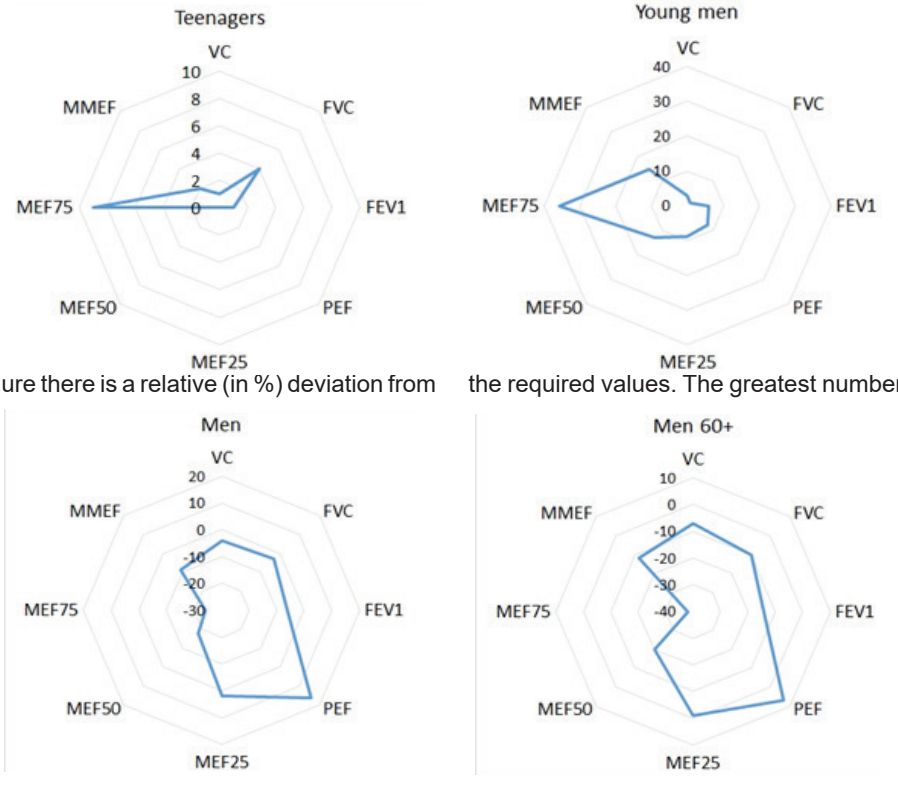
Indicators of external breathing function in males of different ages (M±m)

Indicators	Examined Groups				The level of significance of the differences					
	Adolescents (1)	Young adults (2)	Mature men (3)	Men over 60 (4)	1-2	1-3	1-4	2-3	2-4	3-4
Tvc (s)	1.95±0.07	1.88±0.04	2.31±0.09	2.1±0.12	p=0.39	**p<0.05**	p=0.29	**p<0.001**	p=0.09	p=0.17
VC (l)	4.97±0.07	5.03±0.04	5.1±0.07	3.8±0.08	p=0.46	p=0.2	**p<0.001**	p=0.47	**p<0.001**	**p<0.001**
VC (%)	101±1.69	103±0.75	96±1.01	93±1.99	p=0.29	**p<0.05**	**p<0.05**	**p<0.001**	**p<0.001**	p=0.19
Tfvc (s)	1.92±0.08	1.42±0.03	3.15±0.1	3.2±0.21	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	p=0.83
FVC (l)	4.93±0.06	4.84±0.05	5.03±0.08	3.6±0.13	p=0.26	p=0.33	**p<0.001**	p=0.07	**p<0.001**	**p<0.001**
FVC (%)	104±1.44	101±0.81	97±1.24	90±2.38	p=0.08	**p<0.001**	**p<0.001**	**p<0.01**	**p<0.001**	**p<0.05**
FEV_1 (l)	4.2±0.07	4.43±0.04	4.03±0.07	2.8±0.11	**p<0.01**	p=0.01	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
FEV_1 (%)	101±1.6	106±0.73	94±1.34	86±2.55	**p<0.01**	**p<0.01**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.01**
Tpef (s)	0.16±0.01	0.17±0.01	0.12±0.01	0.1±0.01	p=0.49	**p<0.01**	**p<0.001**	**p<0.001**	**p<0.001**	p=0.17
PEF (l/s)	8.87±0.18	9.68±0.1	11.13±0.18	8.4±0.32	**p<0.001**	**p<0.001**	p=0.21	**p<0.001**	**p<0.001**	**p<0.001**
PEF (%)	100±2.05	108±0.97	116±1.8	107±3.18	**p<0.001**	**p<0.001**	p=0.07	**p<0.01**	p=0.77	**p<0.05**
$MEF_{25\%}$ (l/s)	7.91±0.19	8.73±0.1	8.97±0.22	7.2±0.33	**p<0.001**	**p<0.001**	p=0.07	p=0.33	**p<0.001**	**p<0.001**
$MEF_{25\%}$ (%)	100±2.37	109±1.32	102±2.35	99±3.88	**p<0.01**	p=0.55	p=0.83	**p<0.05**	**p<0.05**	p=0.51
$MEF_{50\%}$ (l/s)	5.52±0.16	6.38±0.09	4.94±0.15	3.7±0.3	**p<0.001**	**p<0.01**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
$MEF_{50\%}$ (%)	100±2.94	113±1.54	82±2.37	80±4.94	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	p=0.72
$MEF_{75\%}$ (l/s)	3.03±0.1	3.78±0.06	2.1±0.08	1.2±0.1	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
$MEF_{75\%}$ (%)	109±3.69	136±2.3	76±2.7	62±5.57	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.05**
$MMEF_{25-75\%}$ (l/s)	5.5±0.14	6.24±0.08	5.34±0.14	4±0.23	**p<0.001**	p=0.43	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
$MMEF_{25-75\%}$ (%)	102±2.54	115±1.29	91±2.22	88±4.14	**p<0.001**	**p<0.01**	**p<0.01**	**p<0.001**	**p<0.001**	p=0.53
FEV1/VC, %	84±1.04	88±0.53	78±0.83	71±1.55	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
FEV1/FVC, %	85±1.07	92±0.45	80±0.77	78±1.77	**p<0.001**	**p<0.001**	**p<0.01**	**p<0.001**	**p<0.001**	p=0.31

(PEF, l/s), time of achieving the VC, FVC, PEF (s), maximal expiratory flow values at 25%, 50%, and 75% of FVC ($MEF_{25\%}$, $MEF_{50\%}$, $MEF_{75\%}$, l/s), mean maximal expiratory flow ($MMEF_{25-75\%}$, l/s), as well as two indices of bronchial obstruction, Gensler and Tiffeneau which are FEV_1/VC, FEV_1/FVC. The data obtained were processed using an applied statistical analysis package. The processing results are presented as an average value (M) and an arithmetic mean error (±m). The statistical significance of the differences was determined with the Scheffe criterion. The critical significance level (p) in the research was assumed to be 0.05; 0.01; 0.001. The research was carried out in accordance with the principles of the Helsinki Declaration, the research protocol was approved by the local bioethics commission of the Scientific Research Center "Arktika" FEB RAS. Prior to the breathing tests, all participants were given a detailed explanation of all the upcoming studies and provided written informed consent for voluntary participation.

Results and Discussion. The Table shows age dynamics of the respiration system variables in the range from adolescents to the elderly men and in the figure there is a relative (in %) deviation from the required values. The greatest number



Subjective positive and negative dynamics in indicators of external breathing, %

of differences existed between young adults and men of workable age and the elderly, and the least between men of the two older age groups. For all the examined groups, significant differences were found in terms of the forced exhalation indices in the first second, patency of small bronchioles and the Tiffeneau bronchial obstruction index. If to consider some indicators of external respiration, we can see similar trends for the time of normal and forced exhalation: the minimum values in both cases were typical for young adults, and the maximum values for men of workable and older ages. The indicator of the lung vital capacity which, due to its reproducibility [4]. is an informative physiological indicator for assessing the lung tissue condition, in real (l), and relative (%) values, proved to be significantly lower in older men as compared to other age groups. The same pattern was found for the forced lung capacity: adolescents and young adults exhibited the highest values and no significant intergroup differences. These were generally consistent with the data of L.B. Kim (2010) who reported age-associated reduction in VC. In our case, however, this occurs in a wider age period and somewhat later, not from 30 to 50, but from 35 to 65 years [6].

Interestingly, all the numerous expiratory volume flow values of bronchopulmonary indicators showed significant intergroup dynamics. The amount of forced exhalation in the first second is the most important indicator, since it is first to indicate possible obstructive pulmonary patency disorders, and normally it should be at least 0.8 of the vital lung capacity [17]. The FEV_1 values significantly raised up to 106% in young adults, then dropped to 94% and 86% in men of the middle and older age groups, respectively. The time to reach the peak expiratory flow also shortened from young adults to the elderly men. The initial part of the expiratory curve (25-33% of lung volume) depends more on the applied muscular effort, rather than the mechanical properties of the lung tissue [10]. In our studies, the peak expiratory flow (PEF), as the initial component of this curve, reached its highest values in absolute and relative values in men of workable age. In this case, it can be assumed that it is the greatest development of expiratory muscles in men of workable age that contributes to achieving the maximum PEF value in this group. We could see a similar pattern of changes with age in the patency of large, medium and small bronchi since the young adults demonstrated highest values compared to adolescents; then the indices gradually decreased to the group of the elderly. It is noticeable that in adolescence, the values of bronchial patency mainly corresponded to age standards whereas young male adults experienced dilation of the airways, and the elderly men developed a significant bronchial constriction. High subjective Tvc and Tfvc values in these groups indicated increased resistance to expiratory flow. Reduced pulmonary function with increasing age was also reported by other authors [14, 15]. It is caused by changes in both the lung tissue and in the respiratory muscles, thereby affecting the lung function.

The $MEF_{50\%}$ and $MEF_{75\%}$ indicators, with their isolated picture of a decrease, can be an early sign of bronchial obstruction [11]. At the same time, the smaller the pulmonary structures, the more dramatically the intergroup bronchial patency came down. The patency index of small (distal) bronchioles tended to be most variable with the range of deviations up to 74%, with a maximum shown by young adult men and a minimum in older men. Normally $MEF_{75\%}$ reflects the opening of small bronchioles, contributing to an increase in residual volume and growth in the amount of warm air in the pulmonary ways after exhalation [3]; thus the discovered fact of a significant fall in this indicator values with increasing age serves as a message of concern. J.F. Morris et al. (1975) reported a negative correlation existed between the patency index of bronchioles of this type and age [16]. In addition to the well-known fact of an age-related decrease in vagal nerve tone, I.V. Averyanova (2023) observed the similar picture for northern men who reduced the activity of the parasympathetic link of the ANS, which shifted the sympathetic-vagal balance to a relative condition of sympathetic activity [1]. In this aspect, the esTableished change in bronchial patency cannot be explained in terms of a shift in the ANS balance since a 20-40% narrowing of the bronchi lumen clearly contradicts the idea of the influence of age-associated sympathicotonia. It is obvious that the causal relationships of such pulmonary dynamics lie in the complex intersystem mechanisms of adaptation. This provides the priority and will be given emphasis in our further research. The intergroup dynamics of bronchial obstruction indices (FEV_1/VC, FEV_1/FVC) had a similar picture of a significant increase up to maximum levels which could be seen from the group of adolescents to young adults with a further gradual decrease to the elderly.

Conclusion. This study showed pronounced intergroup dynamics in the bronchopulmonary performance in Northerners of workable and older ages owing to the violation in the patency of the bronchi of various diameters as risks of developing bronchoobstructive disorders and weakened adaptabilities of the body. Along with constant adverse effects of natural and climatic environmental factors, these changes indicate age-related tension in the lung functioning which is increasingly stressed in small bronchioles and can cause restriction of access of the oxygen-enriched air mixture to the distal parts of the lungs where the main part of gas exchange occurs in the acinus's perfused alveoli. Such a picture may be a consequence of overstrain in the pulmonary function (after reaching maximum in early adulthood) which develops misalignment and weakening of regulatory mechanisms. Social relevance of the condition requires further detailed research.

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SCIENTIFIC REVIEWS

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MODERN METHODS OF EXPERIMENTAL EVALUATION OF BIOMECHANICAL PROPERTIES

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The review presents a description of methods and results of various experimental studies of corneal biomechanical properties: the technique of tensile testing, the indentation method, and atomic force microscopy. Corneas of experimental animals and humans (in particular, donor eyes and material obtained as a result of keratoplasty) are considered as "sources" of samples. Selective evaluation of individual corneal structures using classical mechanical tensile tests is limited to a certain extent due to the rather small thickness of these structures and, as a consequence, difficulties in fixing the specimen. In real practice, it remains promising to use indentation and AFM, which are more adapted for such studies, on the one hand, eliminating the need for mechanical fixation of the specimen, and on the other hand, providing the possibility of studying various areas and surfaces of the latter.

Keywords: cornea, biomechanical properties, methods of experimental evaluation.

The encyclopaedic interpretation defines biomechanics as "a section of biophysics that studies mechanical properties of biological tissues, individual structures and organs on the basis of models and methods". From the point of view of the tasks to be solved, biomechanical research can be divided into fundamental and applied. In the first case it is a question of determining various indices characterising mechanical properties of tissues, and in the second case - in addition to that, about clinical significance of these properties in terms of potential influence on pathogenesis, methods of diagnostics and treatment of various diseases.

The cornea, being a part of the outer fibrous membrane of the eye, in addition to conducting and refracting light rays, provides the function of maintaining a certain shape of the eyeball, primarily related to biomechanical properties. Besides, it is the cornea that is the zone of "application" of the most widespread in clinical practice aplanation methods of intraocular pressure measurement and the determined indices can also depend on the "biomechanics" of the cornea. Thus, in relation to the cornea, the applied direction of biomechanical research is connected with solving the problems of diagnostics and monitoring of glaucoma, as well as pathological changes in its thickness and shape induced by diseases and surgical interventions [2-3, 5, 14, 15, 22, 26-27, 32, 37, 44].

Methods for assessing the "biomechanics" of the cornea are divided into clinical and experimental methods. Clinical or lifetime (i.e. in vivo) methods are based on the analysis of changes in the corneal shape as a result of some effect, for example, using a McLakov tonometer of different masses or an air jet (elastometry and bidirectional corneal pneumoaplanation, respectively). Experimental methods are based on mechanical tests of isolated corneal specimens (i.e., ex vivo) obtained from experimental animals, from human donor eyes, and as a result of any corneal surgery [74].

To characterise the biomechanical features of a material, such an index as Young's modulus (modulus of elasticity), which characterises the material's resis-

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tance to tension/compression (i.e. stiffness), is used. In this case, the basis of biomechanical tests is the assessment of induced and expressed in varying degrees of deformation of the sample. In modelling experiments, mechanical stretching of specimens up to the moment of rupture, indentation method, and atomic force microscopy are used [4, 8, 15, 52]. The choice of the method of mechanical testing depends significantly on the metric characteristics (in particular, the area and volume) of the samples, which are largely related to the technique of obtaining the latter.

The aim of this review is to analyses modern experimental methods for studying the biomechanical properties of the cornea.

Methods based on tensile stretching of samples. The most common method is uniaxial stretching of biomaterial samples prepared as membranes, films, strips [7, 12, 47, 49]. Corneal fragments in the form of strips can be obtained from its different layers and in different directions [50]. It should be noted that the so-called sample preparation of corneal samples is associated with certain difficulties in terms of achieving a uniform thickness/width of the strip throughout the sample, as well as the use of small sample sizes to reduce the influence of heterogeneity of biomechanical properties of the material on the final results of the study.

During the experiment a strip of material is fixed from both ends in special holders. When fixing the specimens in the holders, it is necessary to ensure simultaneous sTable fixation without damage that may cause the specimen to rupture in the area of the holders [49]. In some cases, holders designed specifically for a particular specimen are used, and in some cases, fixation of the specimen in the holder with adhesive is used.

Before stretching, the specimen is usually preloaded to the minimum detecTable force and the initial length of the specimen is set. In some cases, preload/unload cycles with a small tensile amplitude are used [25]. Pre-cycling of the specimen allows to obtain more reproducible results of mechanical properties measurements. The necessary number of pre-treatment cycles is selected based on the best match of stress-strain diagrams in subsequent cycles.

The specimen is stretched by moving one of the holders at a given speed with the help of both special installations [10, 49] and universal mechanical testing systems [48]. During testing, the movement of the holder and the tensile force are recorded, usually using special load cells. Tensile testing is carried out until the specimen is ruptured. The obtained dependences of relative elongation (ratio of elongation to the initial length of the specimen, in %) on stress (ratio of force to the initial cross-sectional area of the specimen, in kPa or MPa) are used to determine the modulus of elasticity (Young's modulus in tension), elongation at break (maximum elongation) and stress at break (maximum stress). The modulus of elasticity is determined by the slope of the linear stress-strain relationship. The modulus of elasticity characterises the stiffness of the material: the greater the slope of the linear section, the higher the modulus of elasticity and the stiffer the material is. The maximum elongation and stress characterise the strength and resistance to rupture of the material.

The biomechanical properties of the cornea of human and porcine eyes were compared by uniaxial stretching on an Instron device [9] [9]. Similar results were obtained for the modulus of elasticity (value for human and pig corneas 42.814 ± 11.674 and 39.261 ± 11.039 MPa, respectively), which allowed us to conclude that porcine corneas can be used as a substitute for human corneas in various experimental studies according to this criterion.

In keratoconus, a higher strain value (0.45 ± 0.05 N) at lower load (8.2 ± 1.5 N) was observed compared to the data of the control group (0.35 ± 0.03 N at a load of 17.9 ± 0.9 N), as well as a decrease in Young's modulus (156 ± 35 and 376 ± 38 MPa, respectively) [10]. Similar data were obtained in another study [36]. At the same time, when comparing the stiffness of conditionally normal corneal samples (donor eyes) and corneal samples with keratoconus, no significant difference was found [24].

It should be noted that the classical principle of uniaxial stretching (i.e., force application in one direction) does not exclude the possibility that the anisotropy of corneal biomechanical properties due to a certain orientation of stromal fibrils may influence the final result.

A variation of mechanical stretching is the impact on the specimen with the help of liquid (English "inflation test") with the subsequent registration of the dependence of the specimen deviation from the initial position on the level of hydrostatic pressure. The method is more complicated in terms of fixation of the specimen and registration of deformation and requires a strong and hermetic fixation of a disc-shaped corneal specimen around the perimeter. The cornea, thus, as a membrane divides two adjacent chambers, one of which is injected with liquid (physiological solution) to create hydrostatic pressure, simultaneously registering the degree of corneal deviation from the initial position depending on the level of fluid pressure. The deviation is registered using a video camera or more complex methods (laser sensors, special marker objects on the corneal surface). The calculation of the elastic modulus requires special models describing the mechanical behaviour of the membranes.

In a selective study of different layers of rabbit and human cornea by liquid pressure stretching, it was concluded that the stroma was less stretchable than the descemet membrane regardless of species [32]. Another study evaluated the "biomechanics" of animal (cows, pigs, rats) and human descemet membrane in comparison with the anterior capsule of the lens [17]. In human samples, the biomechanical properties of the descemet membrane and the lens capsule were similar in contrast to animal samples, in which the membrane appeared to be stiffer than the lens capsule.

Indentation method. Mechanical testing by means of micro- and nanoindentation is actively used to assess the stiffness of various polymeric materials and metals, and in recent years the method has been actively applied to biological materials, including soft tissues [31, 41, 42]. In the latter case, the characteristic values of deformation using this method are only tens to hundreds of micrometres, so the term "microindentation" is more reasonable. Measurements by the indentation method are carried out both on specialised instruments [31] and with the help of universal measuring systems [21]. The requirements to the sample in such experiments are minimal and include certain surface flatness, sufficient thickness for indentation (hundreds of micrometres) and the possibility of sTable fixation on the surface. When measuring in air, sandpaper is glued to the substrate to prevent sliding and lateral movement of the lower part of the sample on the surface of the substrate. When measuring in liquid, the sample is usually glued to the substrate.

In the process of indentation, the indenter is dipped into the sample surface in a controlled manner. The contact part of the indenter can be made in the form of a cylinder, cone, pyramid, but for the examination of soft samples in order to prevent damage, a sphere of micrometre or millimetre dimensions is more often used. The indenter is made of rigid material (metal, ruby) in order to prevent its deformation during indentation. The

indenter is structurally connected with a strain gauge measuring the force acting on the indenter, as well as with motors for moving the indenter relative to the sample. Vertical movement occurs during indentation, while lateral movement can be used for indentation at different points of the specimen, i.e. for mapping mechanical properties [21, 40].

As a rule, the investigation is started when the contact part of the device is located at a certain height above or in direct contact with the specimen, and indentation is carried out to a given depth or load. In the latter case, the indentation process is carried out at a constant speed of indenter movement until the moment of fixation of the set force by the strain gauge, after which the indenter starts the reverse movement. As a result, the dependence of the force (F) on the penetration depth (δ) is determined, and contact mechanics models are used to obtain the value of Young's modulus (Young's modulus at indentation). For example, for a spherical indenter, the force-indentation relationship is approximated by the following equation corresponding to the Hertz model [41]:

$$F = \frac{4}{3} f(\delta) \frac{E}{1-\nu^2} \delta^{\frac{3}{2}} \sqrt{R},$$

where E is the Young's modulus, v is the Poisson's ratio of the sample (assumed to be 0.5 for most biological samples), R is the indenter radius. For specimens whose thickness is comparable to the indentation depth, a correction for thickness is required in the form of the function f(δ) calculated for this case and known from the literature [18, 24].

The current development of the microindentation method is associated with the use of more complex models that describe, in addition to elastic, viscoelastic and nonlinear behavior of the sample [43]. To do this, a phase is added to the testing process that includes assessing force relaxation or creep by holding the indenter at a constant depth or at a constant force level, respectively.

Using nanoindentation, the biomechanical properties of 17 corneas with keratoconus and 10 conditionally healthy corneas unsuiTable for transplantation were assessed. Nanoindentation was carried out at a depth of 25 μm at a force application rate of 300 μN/min. As a result, a lower elastic modulus was found in keratoconus (23.2 ± 15.0 and 48.7 ± 20.5 kPa) [33].

In another experimental study, the method was used to evaluate changes in the “biomechanics” of the rabbit cornea as a result of corneal crosslinking: after removal of the central zone of the epithelium, the cornea was treated with the photosensitizer riboflavin and UV radiation was applied for 30 minutes at a power of 3 mW/cm2. As a result, a significant increase in corneal stiffness was noted: an increase in Young's modulus by 78.4-87.4%, ultimate stress by 69.7-106.0% and a decrease in ultimate strain by 0.57-78.4% within 8 months observations [53]. In a similar study, after cross-linking, for topographic assessment of changes in the “biomechanics” of the rabbit cornea, 5 indentation zones were identified at a distance of up to 1.5; 1.5 - 3.0; 3.0 - 4.5; 4.5 - 6.0 and 6.0 - 7.5 mm from the central zone of the sample. An increase in the elastic modulus was noted, more pronounced in the central zone [51].

Atomic force microscopy. An atomic force microscope (AFM) is a type of scanning probe microscope that has been widely used in the field of biological research [6]. The AFM imaging process is based on scanning the surface with a special probe called a cantilever. The cantilever is an elastic beam (cantilever) of micrometer dimensions, which at one end is fixed to a special base, and at the free end it is a pointed needle in the form of a pyramid, cone or microsphere interacting with the sample. The tip radius of standard cantilevers ranges from 1 to 100 nm, whereas a microsphere can have a radius of several micrometers. Cantilevers are made of silicon or silicon nitride, usually the beam has a rectangular shape with a length of 100-300, a thickness of 1-10 and a width of 10-50 microns. For optimal light reflection, the top side of the beam is additionally coated with a thin layer of metal (aluminum or gold), which is necessary for the operation of the optical system for recording the cantilever bend, which includes a laser beam directed at the beam and a photodetector consisting of several sections to detect the position of the reflected beam.

AFM operation is based on the force interaction between the cantilever tip and the sample surface. The force acting on the probe from the surface is controlled using the optical system for recording the cantilever bend described above. The signal from the photodetector, usually measured in units of voltage or current, is further converted by calibration into a cantilever deflection signal in nanometers and a force measured in pico- or nanoNewtons. Images are obtained through a process of line-by-line relative movement of the cantilever and the sample under study, called scanning. Individual lines (surface profiles) are added to an array and form the final image. To carry out the scanning process, a piezomotor (scanner) is used, most often made in the form of a tube made of piezoelectric material with electrodes applied to it. When voltage is applied, the piezo tube bends, contracts, or stretches, moving the cantilever relative to the sample with subnanometer precision.

The main mode intended for measuring the physical properties of a sample in AFM is the mode of recording force curves. This mode is very close to testing using nanoindentation. Force curves reflect the dependence of the bending value of the cantilever (the force of interaction between the probe and the surface) on the vertical displacement of the scanner as the cantilever approaches and moves away from the sample, that is, during indentation. However, in addition to indentation itself, local force interactions between the probe and the surface (attractive forces, adhesion) also occur. The process of taking force curves is also called force spectroscopy.

The force acting on the cantilever is calculated in accordance with Hooke's law:

F = kd, where k is the cantilever stiffness coefficient, and d is its vertical deviation from the equilibrium position.

Cantilever stiffness values are provided by the manufacturer within a certain range, including permissible deviations during production, and depend on their geometric parameters and the material from which they are made. To clarify the rigidity values, it is calibrated using the thermal noise method against the background of recording thermal vibrations of the cantilever, the resonance parameters of which depend on the rigidity.

The force curves are further processed using the Hertzian model (in the case of a microsphere as a probe) or other models of contact mechanics. The Young's modulus obtained using AFM may differ from the Young's modulus obtained using indentation methods. When using AFM, the characteristic indentation depths are tens to hundreds of nanometers, which corresponds to the surface layer of the sample. Surface tension (surface energy) can play a large role if present. Biomechanics studies are usually carried out by immersing samples in a layer of liquid (physiological buffer solution), or less often, on completely dried samples. In the first case, a certain influence of capillary forces on the results of mechanical measurements is possible. Drying samples, despite improving the quality of morphological assessment, can lead to a signifi-

cant change in the mechanical properties of biological samples, mainly in the form of an increase in stiffness.

In a number of cases, the AFM method was applied to the study of tissue sections, in particular, those obtained on a cryotome [45, 46]. In this case, the samples are usually not subjected to the stage of chemical fixation; they are quickly frozen in a special medium, after which sections with a thickness of about 10 μm are obtained, transferred to slides, and examined by AFM in liquid.

The AFM method makes it possible to map mechanical properties with high spatial resolution - using a sharp probe on soft tissue of the order of hundreds of nanometers. The disadvantages of the method include the "attachment" of the measured properties to the surface of the sample, and to study the properties of the internal layers it is necessary to perform sections.

It should be noted that AFM significantly expands the possibilities of assessing the "biomechanics" of various layers of the cornea, the objective difficulties of which are primarily associated with the small thickness of the samples. The main directions of research are related to the selective assessment of Young's modulus of different layers of the cornea in normal conditions and after cross-linking in keratoconus, possible changes in the indicator with intraoperative use of dyes, as well as comparison of the biomechanical properties of Descemet's membrane and the lens capsule.

Differences in the elastic modulus of the anterior basement membrane of the epithelium, Bowman's membrane and Descemet's membrane have been revealed [16, 20, 35, 36]. The results obtained in these studies can be presented in the form of the following main provisions:

• Young's modulus of the anterior corneal stroma (281 ± 214 kPa) is significantly higher than the posterior one (89.5 ± 46.1 kPa);

• the Young's modulus of the Bowman membrane is almost twice as high as that of the Descemet membrane (109.8 ± 13.2 and 50 ± 17.8 kPa, respectively);

• the least rigid structure of the cornea is the basement membrane of the epithelium (Young's modulus - 7.5 ± 4.2 kPa).

In a series of comparative studies, rabbit cornea was used as an experimental model for AFM [50]. The average values of elastic modulus for all layers of the cornea (epithelium, anterior and posterior stroma, Descemet's membrane and endothelium) were significantly lower compared to similar indicators for the human cornea. The revealed pattern must be taken into account when using the cornea of rabbits as an experimental model when studying various pathological processes of the cornea and developing modifications of keratoplasty. In an experiment on isolated pig eyes, AFM revealed a statistically significant increase in the average Young's modulus (i.e., an increase in stiffness) in the crosslinking zone [28].

Conclusion. Introduction of the method of bidirectional pneumoaplanation of the cornea into clinical practice has significantly expanded the possibilities of lifetime study of the biomechanics of the eye. At the same time, despite the zone of application of mechanical influence of pnevoaplanation methods (cornea!) and terminological presence of corneal component in the determined indices (corneal hysteresis, corneal resistance factor), taking into account the anatomical integrity of the fibrous membrane, the question of potential influence of biomechanical properties of the sclera on these indices remains open. Besides, the methodology does not allow estimating biomechanical features of different corneal layers, in particular, when studying the mechanism of ectatic corneal diseases and developing modern methods of selective keratoplasty.

As experimental methods of selective corneal biomechanical testing we should consider the technique of sample stretching, indentation method, and AFM, and as sources of samples - corneas of experimental animals and humans (in particular, donor eyes and material obtained as a result of keratoplasty). Selective evaluation of individual corneal structures (e.g., border membranes) using classical mechanical tensile tests is limited to a certain extent due to the rather small thickness of these structures and, as a consequence, difficulties in fixation of the specimen. In real practice, it remains promising to use more adapted for such studies indentation and AFM, on the one hand eliminating the need for mechanical fixation of the sample, and on the other - providing the possibility of studying different areas and surfaces of the latter.

Absolute values of Young's modulus as the main index characterising biomechanical properties of corneal specimens obtained in different experimental studies can significantly differ due to a number of reasons: technology of specimen obtaining and preparation, metric characteristics of the specimen and research algorithm. On this basis, it is relevant to conduct comparative studies involving the determination of relative indicators.

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THE ROLE OF BLOOD TRANSPORT PROTEINS IN ADAPTATION REACTIONS TO EXTREMELY UNCOMFORTable CONDITIONS OF THE NORTH AND THE ARCTIC

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The purpose of this review is to integrate data on the role of blood transport proteins in adaptation reactions to extremely uncomforTable conditions of the North and Arctic of the Russian Federation. Regulation of shifts in homeostasis in humans under unfavorable Arctic conditions is carried out, among other things, by increasing the production of haptoglobin and transferrin, which perform antioxidant and immunomodulatory functions. An increase in the concentration of immunoglobulins in the blood ensures the efficiency of utilization of metabolic products, components of cellular destruction and damage. In the unfavorable conditions of the North and the Arctic, a shift and disruption of adaptive changes in lipid metabolism occurs.

Keywords: haptoglobin; transferrin; immunoglobulins; LDL; HDL; adverse conditions of the North and the Arctic; adaptation.

Introduction. The risk of adaptation failure is caused by stress and depletion of the body's functional reserves when exposed to adverse factors. Based on changes in the parameters of the hepatobiliary, immune, antioxidant and lipid transport systems that provide adaptive and compensatory adjustments, an assessment of the state of adaptability is carried out and the risks of disruption of physiological adaptation mechanisms are determined [39].

The influence on the human body of a complex of unfavorable factors in the northern and arctic territories is accompanied by a restructuring of the internal environment of the body and is manifested by changes in the physiological parameters of the blood system. A shift in the parameters of the blood system towards lower or higher values relative to the regional normal limits is a criterion for the risk of failure of adaptation, which in turn is caused by the tension of the immune, metabolic and endocrine regulatory mechanisms [9].

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It has been esTableished that residents of the North experience a predominantly decrease in albumin concentration and a change in the content of other protein fractions, including α2-macroglobulin, ceruplasmin, transferrin, and immunoglobulins [8,41].

The purpose of this review is to integrate data on the role of blood transport proteins in adaptation reactions to uncomforTable and extremely uncomforTable conditions of the North and Arctic of the Russian Federation.

The role of transferrin, haptoglobin, immunoglobulins and lipid transport complexes in adaptation reactions to the conditions of the North and the Arctic. In conditions of high latitudes, the development of hypoxia is due to oxygen deficiency and rarefaction of the air. With the development of a hypoxic state, hypoxia-induced factors (HIFs) are activated. Subsequently, in response to the low oxygen content in the blood, the activation of HIFs increases the transcription of various genes that ensure adaptation to hypoxia at the cellular and systemic levels [23,32].

HIF-1 controls an increase in erythropoietin levels, erythropoietic activity and hemoglobin synthesis. HIF-1 has been shown to regulate the expression of genes involved in iron metabolism: haptoglobin, transferrin, transferrin receptor (TfR). In addition, HIF 1 is involved in the regulation of metabolism and cellular metabolism. Thus, the regulation of HIFs target genes is aimed at ensuring optimal oxygen delivery, regulating metabolism and maintaining cell survival in hypoxic conditions [24,35].

Activation of erythropoiesis in the inhabitants of the North and the Arctic, including due to the effect of low temperatures on the body. During adaptation to cold, along with the intensification of erythropoiesis, an increase in oxygen consumption indicates a metabolic restructuring with the preferred use of lipid oxidation as an energy substrate. Activation of lipid metabolism causes an increase in the oxygen demand of tissues [32].

With an increase in the intensity of erythropoiesis in the conditions of the North and the Arctic, there is a need for binding and transport of free iron by transferrin and heme iron by haptoglobin. An increase in the intensity of erythropoiesis in the inhabitants of the European North and the Arctic is evidenced by an increase in the concentration of transferrin, a membrane and free receptor for transferrin [9,30,37].

The main function of transferrin is the transport of iron and ensuring the effectiveness of erythropoiesis by maintaining the survival, proliferation, and differentiation of erythroid cells [27]. An increase in blood concentrations of transferrin and receptors for this transport protein is associated with an increase in erythrocyte aggregation, with a 1.5-1.7 times higher frequency of cell aggregation in Arctic residents [26].

Intensification of erythropoiesis, an increase in transferrin levels occurs both in residents of high latitudes and highlands. When adapting to low oxygen levels in high-altitude, high-latitude conditions, activation of HIF-1 and an increase in transferrin content is a mechanism of physiological compensation for a decrease in the availability of Fe and O_2. However,

upregulation of transferrin promotes increased thrombosis and platelet aggregation. In residents of the Himalayan highlands, high levels of transferrin in the blood cause hypercoagulation, increasing the level of thrombin and factor XIIa while reducing antithrombin activity [22]. Increased thrombus formation at elevated transferrin concentrations is associated with the severity of COVID-19 disease and the need to sequester released iron when cells are damaged by the viral particle [7].

The increase in transferrin content in the blood is due, among other things, to its role in maintaining immunological reactivity. Transferrin supports cell proliferation by providing immunocompetent cells with the necessary amount of iron. Lymphocytes affected by antigen or mitogen express IL-2 receptors (CD25) and trigger the expression of transferrin receptor (CD71) in a certain cell cycle, which is a sign of lymphocyte activation and proliferation [9].

The main function of haptoglobin is to ensure the binding of free hemoglobin during the destruction of red blood cells in the circulation. The need for hemoglobin binding in the conditions of the North and the Arctic is due to an increase in damage to circulating erythrocytes as a result of activation of lipid peroxidation (POL) of erythrocyte membranes, depletion of antioxidant protection, and a decrease in the energy supply of erythrocytes [14,15,32].

In conditions of hypoxia, activation of lipid peroxidation processes is accompanied by disorganization and damage to the erythrocyte membrane. The integrity of the erythrocyte membrane is a membrane barrier that preserves the intracellular placement of hemoglobin. The destruction of erythrocytes in the bloodstream (intravascular hemolysis) under hypoxia is accompanied by the release of erythrocyte ATP and hemoglobin in the bloodstream. Free hemoglobin undergoes oxidative degradation to heme or irreversibly binds to haptoglobin [12,16].

The entry of haptoglobin into the intravascular space to neutralize free hemoglobin and the rate of excretion of the formed haptoglobin–hemoglobin (Hp–Hb) complex upon binding to the CD163 receptor of macrophages for subsequent heme cleavage depends on the structure and size of molecules of haptoglobin phenotypes: Hp 1-1; Hp 2-1; Hp 2-2. Thus, the size and molecular weight of Hp 1-1 is much smaller, which determines greater mobility when entering the bloodstream. Hp 1-1–Hb complexes are more efficiently absorbed and removed than Hp 2-2–Hb complexes. Thus, Hp 1-1 has great antioxidant and anti-inflammatory properties [36].

Variation in the frequency of haptoglobin types may determine the susceptibility of population groups to certain diseases. For the European population, Hp 2-1 is most common, 2-2 is less common, and Hp 1-1 is the lowest. The Hp1 allele has been studied most fully in the Russian population, which is characterized by a large frequency variation with a latitude variability of 0.17-0.51. Thus, low Hp1 frequencies are typical for the population of the circumpolar zone and the territory of the European North [3].

However, there is inconsistency in the data on the association of diseases with the type of haptoglobin. The relationship between the incidence of stroke in people with diabetes and the type of haptoglobin is ambiguous [20,25]. The study by Eriksson M.I. did not esTableish an association of haptoglobin type with small vessel disease of the brain (SVD), which is contrasted with data on the association of Hp1 type with SVD in type 1 diabetes mellitus [19]. The content of haptoglobin increases in colorectal cancer and gastric cancer [13,18]. It should be noted that for statistically significant results of the relationship of diseases with the type of haptoglobin, it is necessary to take into account that patients are most often burdened with several diseases [36].

During intravascular destruction of red blood cells, the formation of the Hp-Hb complex is aimed at preventing oxidative stress. Compared with systemic circulation, binding of free hemoglobin in the central nervous system occurs to a lesser extent, due to low production of haptoglobin by oligodendrocytes and astrocytes, as well as minimal CD163-mediated clearance of the formed Hp-Hb complexes by microglia. Increased levels of haptoglobin, Hp-Hb in the brain cause faster absorption of iron by the brain parenchyma and macrophages with a decrease in the neuroinflammation cascade [45].

Damage-related proteins (DAMPs), including haptoglobin, capable of initiating an effector immune response, are being considered in order to combat the development of cancer and autoimmune, neurodegenerative diseases. Haptoglobin has been shown to play an important role in the activation of dendritic cells, their expression of specific markers and Th1-associated proinflammatory cytokines. When stimulated by haptoglobin, the migration of dendritic cells to the lymph nodes and interaction with CD4+ and CD8+ lymphocytes leads to the activation of their effector functions [21].

In the process of adaptation to the conditions of the North and the Arctic, prolonged stress on the regulation of immune homeostasis leads to a change in the reactivity of the immune system, causing the risk of disruption of adaptive rearrangements and determining the tendency to transition acute inflammatory processes into chronic ones [9].

To assess the effect of adverse factors, including climatogeographic ones, on immunological reactivity, it is informative to determine the state of cellular and humoral immunity by determining the content of subpopulations of lymphocytes (CD), serum immunoglobulins (IgA, IgM, IgG, IgE), circulating immune complexes (CIC) and cytokines [39].

Clarifying the general patterns of changes in human immunological reactivity in the conditions of the North and the Arctic, determining the reserve and compensatory capabilities of immune homeostasis in specific conditions or in connection with certain factors, makes it possible to identify the risks of disruption of adaptive restructuring with the selection of the most optimal strategies to prevent the transition to a state of pre-disease, chronization of pathological processes and oncogenesis [33].

Thus, in Arctic conditions, when determining the subpopulations of CD10+ and CD71+ lymphocytes, an assessment of the adaptability of the immune system is carried out. In addition, it has been esTableished that increased cell-mediated cytotoxicity of lymphocytes in people living in the Arctic territory is associated with a reduction in the reserve capabilities of the regulation of the immune system with the risk of the formation of functional deficiency of T-lymphocytes, disimmunoglobulinemia, deficiency of phagocytic protection, causing the early development of environmentally dependent immunodeficiency's, tendency to chronic diseases [33,34].

The cell-mediated cytotoxic activity of CD8+, CD16+ lymphocytes are a reserve mechanism of immune defense in case of deficiency of mature CD3+ T-lymphocytes in the extremely unfavorable conditions of the North and the Arctic. However, the increased cytotoxic activity of lymphocytes causes an increase in the content of tissue damage products and cell destruction in the circulation. After the cytolysis reaction by lymphocytes, an increase in the number of antigenic determinants in combination with immunoglobulins indirectly indicates the presence of non-metabolized cell residues [28,42].

Residents of the North and the Arctic

may have different variants of an immune imbalance in the content of immunoglobulins in the blood. Negative shifts on the part of the immune system in adapting to the adverse climatic conditions of the North are a decrease in the blood content of T-lymphocytes (CD3+) and the concentration of IgA. With a deficiency of lymphocytes with a molecule of the associated signal transduction complex – CD3+, there is a decrease in the activity of the humoral response of IgG and IgA or a predominant predominance of IgM content. A decrease in IgA levels, along with high IgM concentrations, occurs when humoral immune defense factors are stressed, including in conditions of contrasting photoperiodic of the Northern and Arctic territories [9].

It has been shown that the depressing effect on humoral immunity also occurs in conditions of hypoxia in the highlands. Thus, in children and young men living near the middle Elbrus mountains (1850 m above sea level), a decrease in IgA and IgM levels was recorded with a return to baseline levels with long-term adaptation. A study of the main immunity indicators of permanent residents of the mountainous regions of the Tien Shan and Eastern Pamirs (2100-2600 m above sea level) revealed a decrease in the synthesis of IgA, IgM and IgG [4,40].

The functional activity of lymphocytes, including antibody-forming cells, is due to their metabolic program and energy supply. In hypoxia, the metabolism and functions of immunocompetent cells are inhibited. When HIF is activated under hypoxic conditions, the energetic reprogramming of B lymphocytes for glycolytic metabolism manifests itself in a deterioration in the production of high-affinity IgG [29,46].

An increase in the concentration of immunoglobulins in the inhabitants of the North and the Arctic suggests their protective and adaptive effect. Under unfavorable climate conditions, the spectrum of antigenic structures significantly increases and expands, causing the activation of antibody production. An increase in the synthesis of immunoglobulins is aimed at maintaining homeostasis of the body in changing conditions of the external and internal environment, providing directed transport of the substance or substrate that caused their formation and immune complexes to places of disposal and clearance [9,42].

In order to provide energy for adaptive and compensatory reactions, metabolic processes are rearranged with activation of lipid metabolism. The assessment of biochemical parameters of lipid metabolism (total cholesterol, triglyceride levels, LDL, HDL, atherogenicity coefficient) complements information about the adaptive capabilities of the body based on the analysis of the metabolic component of the functional reserves of the body. For people living in unfavorable conditions of the North and the Arctic, a change in the lipid transport system is characterized by the formation of dyslipedemia with an increase in the level of total cholesterol, triglyceride levels, LDL and a decrease in HDL. The occurrence of energy imbalance and disruption of metabolic homeostasis when exposed to unfavorable factors on the human body is a manifestation of disadaptation. The indigenous inhabitants of the North, who adhere to a traditional way of life and type of diet, have the most favorable lipid metabolism profiles. Strengthening protein-lipid metabolism and minimizing carbohydrate metabolism contributes to a high degree of adaptation to extreme climatic and geographical factors [5,6,7,17].

Shifts in lipid metabolism indicators reflect the mobilization of energy resources in response to the complex action of adverse factors. When mobilizing the body's reserves, a decrease in HDL levels causes insufficient compensation for dyslipidemia [44]. Thus, residents of the North and the Arctic are characterized by a high risk of developing disorders in lipid metabolism, manifested by a decrease in the anti-atherogenic protection of the body.

The decrease in HDL levels is due to the dysfunction of lipid transport particles, which occurs during the reorganization of lipid components and changes in the proteome during modification or substitution of the main apolipoprotein A-I (ApoA-I). Thus, an increase in the blood content of acute phase proteins (serum amyloid A, haptoglobin, ceruplasmin, fibrinogen, α1-antitrypsin), components of the complement system (C3, C4A, C4B, C9) leads to a competitive substitution of ApoA-I in HDL.

In conditions of high latitudes, human adaptation to adverse conditions is an extremely complex process that requires the restructuring of the body not only to a complex of climatic and geographical factors, but also to the influence of industrial working conditions. Changes in lipid metabolism indicators are informative under various unfavorable working conditions. It was found that workers of a machine–building enterprise with an increased level of vibration and noise have increased levels of atherogenic lipids (total cholesterol, LDL) and decreased levels of antiatherogenic HDL, which is associated with stress of the functional state of the body. At an oil refinery, workers exposed to the chemical factor showed an increase in concentrations of total cholesterol, LDL with a lower level of HDL. When exposed to electromagnetic fields of industrial frequency, employees were found to have an increase in the level of total cholesterol, LDL, and atherogenic index [11,31,43].

The changes and information content of hematological, biochemical, immunological parameters are shown when the body is exposed to various unfavorable factors, including climatic and geographical factors [1,2,8,10,38,41,47].

Conclusion. So, the effect of the complex of unfavorable climatic conditions of the northern and Arctic territories causes a sufficiently high voltage regulation of metabolic processes, creating a significant need for transportation with the accumulation of metabolic products in the blood, endogenous metabolites [9].

Insufficient utilization and excretion of various waste products from the body is an unfavorable factor. The need for binding and transport for subsequent clearance is due to the accumulation of non-utilized components of cellular damage, destruction with excessive cytotoxic activity of lymphocytes with an increase in blood concentrations of circulating immune complexes.

The change in the content of the components of the blood proteome is aimed at maintaining the optimal functional state of the body under specific conditions. The level of blood proteins must be considered in conjunction with immunological parameters to analyze the direction of changes in metabolism, homeostasis and determine the risk of adaptation failure.

In unfavorable, extremely unfavorable conditions of the North and the Arctic, there are risks of disruption of adaptation against the background of impaired effectiveness of clearance and utilization mechanisms through phagocytosis. Under these conditions, the need for transport proteins increases, ensuring effective binding, transport and utilization of various waste products, including transferrin, haptoglobin, immunoglobulins and HDL.

Thus, the determination of blood protein content is informative in assessing the adaptive capabilities of the body. A change in the proteome displays information about changes in the human body under the influence of adverse factors, including climatogeographic factors. The relationship of blood transport proteins is important for characterizing the state of the body and evaluating the intersystem,

intersystem relationship in the adaptation process.

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POINT OF VIEW

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TYPE 2 THYROID ALLOSTASIS IN THE RESIDENTS OF YAKUTIA

Type 2 thyroid allostasis is a dynamic stress response to changes in thyroid homeostasis that may occur in response to chronic exposure to cold. It is believed that, under these conditions, type 2 allostatic reactions can increase the basal metabolic rate to maintain priority thermogenic mechanisms in the body. For the first time, this work assesses the allostatic response of the thyroid gland among residents of the central region Yakutia with the most extreme climate (from -47°C to -11°C) using a mathematical model called SPINA. The SPINA model reflects the total activity of peripheral deiodinase enzymes (SPINA-GD), as well as the secretory capacity of the thyroid (SPINA-GT). The results showed that the SPINA-GT parameter was within normal limits for all individuals in the study. However, the SPINA-GD parameter was also within normal limits in 30% of those examined, with an increased SPINA-GD value found in 70% of the individuals examined. It was revealed that individuals with elevated SPINA-GD had higher free triiodothyronine (fT3) levels (6.79±0.62 pmol/L) and lower free thyroxine (fT4) levels (13.82±1.51 pmol/L) than those with normal SPINA-GD (fT3=5.96±0.48 pmol/L; fT4=15.37±0.98 pmol/L; p<0.001). This indicates an increased rate of T4 deiodination to T3 in 70% of the most individuals, and the reason for this is likely due to type 2 thyroid allostasis in response to cold stress. Using the SPINA parameters for the first time allows us to identify changes in hypothalamus-pituitary-thyroid axis homeostasis during the winter-spring season among 70% of surveyed residents of Eastern Siberia.

Keywords: type 2 thyroid allostasis, SPINA-GT, SPINA-GD, free triiodothyronine (fT3), free thyroxine (fT4), Yakutia.

Introduction. Allostasis, or the allostatic response, is a dynamic stress response that helps maintain stability by adjusting the functioning of homeostatic systems [14]. This response can occur in stressful and life-threatening situations [24; 30], where changes in hormone, neurotransmitter, and biochemical signaling levels, as well as organ and tissue regulation, may be observed [25]. In 2012, researchers proposed the concept of allostasis to explain the adaptive response of the thyroid in certain stressful situations [6]. Two types of allostatic responses have since been identified [30]. Type 1 thyroid allostasis occurs when the body detects a change in environmental or physiological conditions (diet, hunger, strenuous exercise, life-threatening illness, and depression) and predicts that energy intake will be insufficient to meet energy needs, and, active thyroid hormones are selectively suppressed, resulting in suppression of whole body metabolism [12; 30]. Type 2 thyroid allostasis occurs when the body detects a change in environmental or physiological conditions (pregnancy, obesity, endurance training, and adaptation to cold climates) and predicts that the change in energy needs can be met by increasing caloric intake and from existing energy stores in white adipose tissue, and then circulating free triiodothyronine (fT3) levels will increase, increasing whole body energy expenditure [12; 30].

In humans, changes in thyroid hormone homeostasis were first described in starving obese patients in the 1970s, where a decrease in blood concentrations of triiodothyronine (T3) was found after several days of fasting, which gave rise to the concept of "low T3 syndrome" [28]. Later, a decrease in T3 concentrations has been described in various calorie-restricted diets [15; 28; 29], and in eating disorders, such as anorexia nervosa [9; 16]. Through a compilation, a large number of other studies have also discovered factors where thyroid allostasis could occur. These include physical exertion, serious illnesses, depression, pregnancy, obesity, and adaptation to cold climates [14; 30].

It is believed that people who live in cold climates have certain adaptation mechanisms. In particular, thyroid hormones have been noted as important components of adaptation to cold stress [3; 19], as they play a significant role in regulating the main metabolic processes and generating heat (nonshivering and shivering thermogenesis) [20; 22; 23]. Previously, higher basal metabolic rates were documented among the indigenous peoples of Siberia, the Yakuts, Evenks and Buryats, compared to predicted values obtained from European populations [4; 5; 8; 27; 32]. Among the Yakuts, seasonal variations in the basal metabolic rate have been observed. Young men and women under 50 years of age showed an increase in their metabolism in winter, whereas older people showed a moderate decline [19]. At the same time, young men showed a positive correlation between their basal metabolic rate and fT3 levels [19]. Signs of "polar T3 syndrome", characterized by a decrease in fT3 and free thyroxine (fT4) levels, were found in children and adolescents from the Arctic regions [18] and in adults from central regions of Yakutia in the winter season [1; 19; 21]. This suggests that changes in thyroid hormone homeostasis during winter in Yakut residents are a result of allostatic response to cold stress.

Currently, there are no esTableished methods for assessing and differentiating the allostatic reactions of the thyroid gland. However, Dietrich and colleagues [2] have proposed using mathematical calculations based on the structural parameters of thyroid homeostasis (SPINA) to differentiate between these reactions. The parameter SPINA-GD measures the total activity of peripheral deiodinases, which catalyzes the conversion of thyroxine (T4) into T3 [31]. The parameter SPINA-GT represents the theoretical secretory capacity of the thyroid gland, or the maximum amount of T4 it can produce under stimulated conditions [31].

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Therefore, the aim of the present study is to evaluate the homeostasis thyroid hormone using SPINA parameters in the context of allostatic response to chronic exposure to cold.

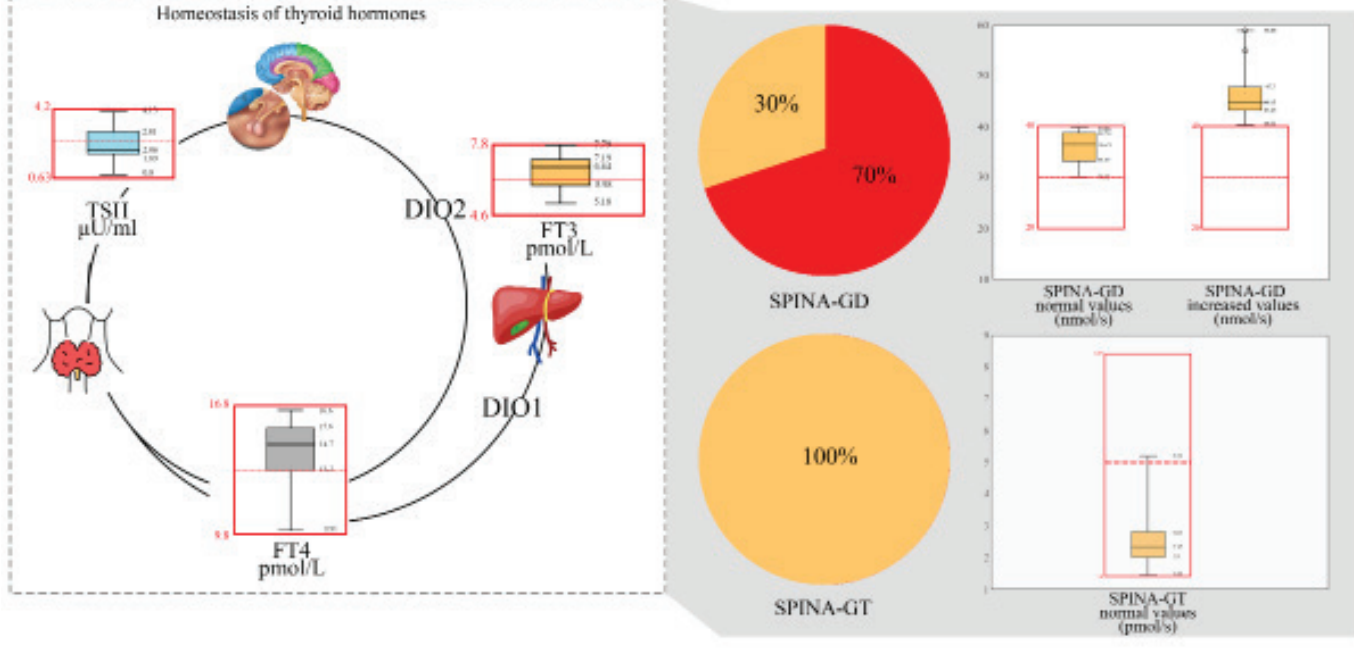
Materials and methods. *Subjects.* The research sample comprised of 92 individuals (with an average age of 19.91±1.88 years) who presented no health concerns at the time of the study. They independently completed a questionnaire which asked about their gender, ethnic background, age, the presence of chronic diseases and experience of taking antidepressants. All participants gave written informed consent for participation in the study. Study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center of Complex Medical Problems, Siberian Branch of the Russian Academy Scientific of Medical Sciences, Yakutsk, Russia (Yakutsk, Protocol No. 16, and 13 December 2014).

Anthropometric parameters, enzyme immunoassay and temperature parameters. Blood samples from the men we studied were carried out from December to May in 2014-2015. Venous blood for the study was collected in the morning after 8 hours of fasting from all participants. For each day of blood collection, the average ambient temperature (°C) was determined using archived data on weather reports (https://www.timeanddate.com). Anthropometric parameters (body weight in kilograms, height in centimeters) were measured in all participants using standardized methods. Body mass index (BMI) was calculated by dividing body mass by the square of height. The sample was divided into three groups according to BMI categories [10]: underweight (≤18.49 kg/m^2), normal weight (18.5–24.99 kg/m^2), and overweight/obese (≥25 kg/m^2). The levels of thyroid-stimulating hormone (TSH, μU/ml), fT3 (pmol/L) and fT4 (pmol/L) in blood serum were determined by time-resolved immunofluorescence analysis using the "DELFIA hTSH Ultra", "DELFIA Free Thyroxine", "DELFIA Free Triiodothyronine" (Perkin-Elmer Inc., USA). The concentrations of the three hormones in the samples were measured at a wavelength of 450 nm using a VICTOR X5 Multilabel Plate Reader (Perkin Elmer Inc., USA). The References values according to the kit recommendations were TSH 0.63-4.2 μU/ml, fT3 4.6-7.8 pmol/L, fT4 9.8-16.8 pmol/L.

SPINA parameters. Parameters for assessing thyroid homeostasis were calculated using the program SPINA Thyr (SPINA Thyr, RRID:SCR_014352, doi 10.5281/zenodo.3596049) [2; 6]. This program calculates the structural parameters of thyroid homeostasis based on the equilibrium concentrations of hormones TSH, T3 (total or free) and T4 (total or free) [2; 6]. The results of the evaluation studies and the algorithms underlying the mathematical theory have been published in several papers [6; 7; 26; 30]. The References values according to the recommendations of the SPINA Thyr program were SPINA-GT - 1.4-8.7 pmol/s, SPINA-GD - 20-40 nmol/s. TSH levels were within normal ranges (2.20±0.83 μU/mL) in the entire group of individuals. However, in one individual, we found elevated levels of fT3 (7.96 pmol/L) and fT4 (17.2 pmol/L). Elevated fT4 levels were also found in five other individuals (17-18.8 pmol/L). Elevated levels of fT4 were also found in five other individuals (17-18.8 pmol/L). In order to calculate parameters for assessing thyroid homeostasis, we normalized the sample by BMI and levels of fT3 and fT4. We excluded individuals who were underweight or overweight, as well as those with elevated of fT3 and/or fT4 levels (n=27) and excluded those selected during the warmer season (>0°C) (n=4). As a result, we calculated SPINA parameters for 61 healthy male with normal BMIs and normal TSH and fT3/fT4 levels.

Statistical analysis. The results were analyzed using a computer program for statistical data processing Statistica 13.5 (TIBCO Software Inc., USA). Quantitative results are presented as mean ± standard deviation. To compare the two groups, the nonparametric Mann-Whitney U test for small samples was used, *p* values ≤0.05 were considered statistically significant.

Results. *Parameters of thyroid homeostasis - SPINA in residents of Yakutia.* The results of calculating the parameters of SPINA homeostasis showed that, in all examined individuals, the parameter SPINA-GT was within normal limits and averaged 2.61±0.76 pmol/s. Elevated levels of SPINA-GD were found in 43



Homeostasis of thyroid hormones and parameters SPINA-GD and SPINA-GT

Comparative analysis of hormone levels of the pituitary-thyroid axis between groups according to SPINA-GD values

Hormones	Normal SPINA-GD values	Increased SPINA-GD values	*p*
TSH, μU/ml	2.15±0.92	2.34±0.81	0.676
FT3, pmol/L	5.96±0.48	6.79±0.62	<0.001
FT4, pmol/L	15.37±0.98	13.82±1.51	<0.001

individuals (70%; 45.7±4.1 nmol/s), and in the remaining 18 individuals (30%), SPINA-GD was within the normal range (35.94±2.90 nmol/s). There was a statistically significant difference in SPINA-GD values between individuals with normal SPINA-GD and those with elevated SPINA-GD ($p<0.001$) (Figure).

To detect changes in thyroid hormone levels, we calculated median, percentile (Q25; Q75) values, minimum and maximum values for the hormones TSH, fT3, and fT4. We compared these values with the median and minimum/maximum values of the References intervals. As a result, we found that the median fT3 value (6.58 pmol/L) and the median fT4 value (14.6 pmol/L) were both increasing from the median References intervals (6.2 and 13.3, respectively). The median TSH value was decreasing from the median of the References interval (2.05 vs 2.42, respectively) (Figure).

Comparative analysis of pituitary-thyroid axis hormone levels between groups based on SPINA-GD values. A comparative analysis was performed on the pituitary-thyroid hormone levels in individuals with normal and elevated SPINA-GD scores (Table). The analysis showed that those with elevated scores SPINA-GD had higher fT3 levels and lower fT4 levels, indicating an increased rate of T4 deiodination into T3. In contrast, those with normal scores SPINA-GD had a slower rate. The results indicate a change in thyroid hormone homeostasis in 70% of individuals examined living in extreme cold conditions in central Yakutia.

Discussion. *The SPINA-GD parameter as a marker of type 2 thyroid allostasis.* The present study was the first to evaluate thyroid hormone homeostasis in the context of chronic cold exposure using SPINA parameters among residents of the coldest region of Siberia. A total of 61 individuals were included in the study. Our findings showed that the median values of fT3 and fT4 increased compared to the median levels within the References interval. However, the median TSH values decreased compared to the median levels within the References interval (Figure). All participants had normal SPINA-GT levels, while 43 individuals (70%) had elevated SPINA-GD, which is associated with an increased rate of T4 deiodination to T3 ($p<0.01$). Similar to the characteristic phenotypic changes described by Chatzitomaris et al., who described changes associated with type 2 thyroid allostasis [30]

Since the sample was collected during the winter-spring period (from December to April), at ambient temperatures ranging from -47°C to -11°C, normalized by weight (excluding underweight and overweight individuals), sex (all males), age (18-27 years old), ethnicity (only Yakuts), and level of health (no acute or chronic diseases), the main cause of type 2 thyroid allostasis in 70% of studied residents of Yakutia is likely due to a general stressor - cold. The pronounced allostatic reaction in response to cold in our sample is probably associated with young age (average age 19.91±1.88 years); we assume that in other age groups this reaction may not be as pronounced. Several authors have suggested a similar allo-thyroid response type 2 may occur in response to cold exposure [12; 30], but this has only been previously confirmed in animals [30]. In this study, for the first time, evidence of type 2 thyroid allostasis has been found in people living in the extremely cold climate of central Yakutia.

Negative and positive aspects of thyroid allostasis. Currently, it is difficult to determine the health effects of thyroid allostasis, as there are few studies available. However, based on the classical view of allostasis, it is believed that short-term allostatic responses have a protective effect, but longer-term allostatic responses ("allostatic overload") can lead to pathological conditions and be life-threatening [14; 30]. This is why maintaining a balance between homeostasis and allostasis is essential for good health.

Chatzitomaris et al. [30] suggest that the direct negative impact of allostasis can only occur with "allostatic overload" in the terminal stages of thyroid diseases, such as thyroid storm and myxedema coma. An indirect negative effect of the allostatic reaction may occur in the diagnosis of thyroid diseases, which may pose some difficulties in making an accurate diagnosis and may cause problems or complications during treatment. Since high basal levels of fT3 and fT4 can be supported by mechanisms of type 2 allostatic reaction, this can cause difficulties in identifying hypothyroidism conditions (not detected/detection at a late stage).

On the other hand, allostatic responses are, first and foremost, a protective mechanism of the body against changes in the external environment or physiological states, helping the body to adapt to these changes [11]. Type 2 thyroid allostasis has been previously observed in pregnant women and those with obesity, and it has been interpreted as an adaptation mechanism characterized by an increased secretion of T4 from the thyroid gland and an increased deiodination [30]. We suggest that, in current conditions of physical inactivity, increased consumption of fast carbohydrates, and high levels of energy intake and basal metabolism, type 2 thyroid allostasis under cold stress may help to reduce the risk of obesity-related complications (cardiovascular disease and type 2 diabetes).

Conclusions. For the first time in this work, using the SPINA parameters, it has been possible to identify changes in the homeostasis of the hypothalamic-pituitary-thyroid axis in response to chronic cold stress in more than 70% of the examined residents of Yakutia.

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RATIO OF NEUTROPHILS TO LYMPHOCYTES AND APOPTOSIS OF LYMPHOCYTES IN PATIENTS WITH HBV AND HCV DEPENDING ON THE STAGE OF LIVER FIBROSIS

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A common complication of HBV and HCV is liver cirrhosis, which is based on chronic systemic inflammation associated with immune dysfunction that affects the progression of the disease. **The purpose of the study.** Determination of NLR and lymphocyte apoptosis index as a marker of the degree of inflammation and systemic immuno-inflammatory response in various degrees of liver fibrosis in patients with viral hepatitis.

Materials and methods. 107 patients underwent the study, of which 53 patients were diagnosed with HBV and 54 with HCV. The blood levels of leukocytes, neutrophils, and lymphocytes were studied in the studied patients and the neutrophil/lymphocyte ratio (NEU/LYM) was determined. In order to verify structural changes in the liver, ultrasound elastometric examination was performed on a 2D – Supersonic Aixplorer SWE device (France) for all persons with es-Tableished viral hepatitis. The examination of patients was carried out according to the Cut–off scale, and liver fibrosis was determined by the METAVIR scale. A group of 10 practically healthy individuals was selected as a comparison group. The values of the indicators were expressed in kPa, the value of the indicator 7.1 kPa corresponded to F2, 9.2 kPa – F3, F4≥13.5 kPa. Verification of HBV and HCV was carried out by PCR on the device “Rotor Qene Q” (Germany).

The results obtained showed an increase in the absolute number of lymphocytes with a decrease in the NLR indicator against the background of a decrease in the apoptosis marker of CB95+ lymphocytes with varying degrees of liver fibrosis. A decrease in this marker reflects the damaging effect of hepatotropic viruses, which is indirectly confirmed by the detected leukocytosis.

Keywords: viral hepatitis, liver cirrhosis, systemic inflammation, neutrophil to lymphocyte ratio, prognostic marker.

Introduction. Hepatitis B and C virus (HBV and HCV) infection remains a global problem that seriously threatens human health and is the main cause of terminal liver diseases, including cirrhosis of the liver (CL) and hepatocellular carcinoma [11]. According to WHO estimates, in 2019, there were 290 million people infected with HBV and HCV worldwide, and about 1.5 million people were newly infected every year [17].

Cirrhosis of the liver is a complex chronic disease that causes hepatocyte fibrosis and the development of portal hypertension and synthetic liver dysfunction [7.10].

One of the consequences of cirrhosis of the liver (CL) is a dysfunction of the immune system, which affects both innate and adaptive responses and is associated with systemic inflammation and immunodeficiency. In patients with advanced CL, chronic inflammation occurs as a result of activation of immune system cells by bacterial infection, followed by endotoxemia and increased production of inflammatory cytokines [14].

The persistence of systemic inflammation is associated with the progression of the disease, the appearance of complications and an unfavorable prognosis [6].

Despite the fact that inflammation plays an important prognostic role in patients with structural changes in the liver, clinical verification of the inflammatory status is somewhat difficult, mainly due to the lack of routine cytokine assessment outside research institutions [9].

Simple and accessible markers for assessing the severity and stage of inflammatory status would be of great value to practitioners. Recently, there has been increased interest in affordable and reliable biomarkers that not only contribute to the early diagnosis of the disease, but also determine its severity, reflect the dynamics of the pathological process and facilitate differential diagnosis. In addition to the traditional pro–inflammatory markers - erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin and fecal calprotectin also belong to them [16]. In their study, Moreau and co-authors [13] showed that the number of leukocytes and CRP levels progressively varied depending on the degree of CL, with the highest values observed in patients with grade III CL who had an unfavorable prognosis. Thus, the authors suggested that CRP levels and the number of leukocytes can be used as markers of inflammation and an unfavorable prognosis in patients with liver damage [9]. The ratio of lymphocytes to monocytes has been proposed as another surrogate marker of inflammation, which is a promising predictor of decompensation and mortality in patients with CL of viral HBV etiology [8,19].

Currently, a number of indicators have been proposed that allow us to judge the severity of inflammatory changes in the body. One of these methods can be the ratio of neutrophils to lymphocytes (NLR), a convenient and easy-to-use parameter that reflects the imbalance between various components of the immune system and can be easily implemented in everyday clinical practice. This indicator is a marker of systemic inflammation and emphasizes the connection between two immune pathways: the number of neutrophils indicates ongoing (or progressive) inflammation, whereas the number of lymphocytes reflects the activity of immunoregulatory pathways [12, 18].

To calculate NLR, the absolute number of neutrophils must be divided by the absolute number of peripheral blood lymphocytes [3]. An analysis of the literature in recent years has shown that NLR is used as an indicator of inflammation and is an accurate prognostic indicator of decompensated CL: with an increase in NLR, the prognosis and survival of patients deteriorates [5,15,20].

The purpose of the study. Determination of NLR and lymphocyte apoptosis index as a marker of the degree of inflammation and systemic immuno-inflammatory response in various degrees of liver fibrosis in patients with viral hepatitis.

Materials and methods. From 2020 to 2023, 107 patients were examined on an outpatient basis at the Central Research Laboratory(CRL) of the A. Aliyev Institute of Advanced Medical Education and the Medikus Clinic Medical Center in Baku, of which 53 patients were diagnosed with HBV and 54 with HCV. Clinical diagnosis of patients: Chronic viral hepatitis B/C. Cirrhosis of the liver, compensated/subcompensated stage (class A/B). The decompensated stage of cirrhosis (class C) was not included in this study, due to the very low immune status of patients at this stage and the difficulty of verifying the data obtained. The surveyed, aged 18 years and older, were from both Baku and the regions of the Republic The average age of hepatitis B patients: men - 37.7 ± 0.6 years, women - 38.7 ± 0.8 years; hepatitis C patients: men - 44.7 ± 0.6 years, women - 42.7 ± 0.6 years. As a control group, 10 practically healthy individuals of both sexes were examined, with an average age of 34.6 ±0.9 years. The inclusion criteria were patients with confirmed viral hepatitis – HBV and HCV.

At the same time, F0 corresponded to the absence of fibrosis, F1 – underdeveloped fibrosis, F2 – moderate fibrosis, F3 – severe fibrosis, F4 – cirrhosis.

107 patients underwent the study, of which 53 patients were diagnosed with HBV and 54 with HCV. The blood levels of leukocytes, neutrophils, and lymphocytes were studied in the studied patients and the neutrophil/lymphocyte ratio (NEU/LYM) was determined. In order to verify structural changes in the liver, ultrasound elastometric examination was performed on a 2D – Supersonic Aixplorer SWE device (France) for all persons with esTableished viral hepatitis. The examination of patients was carried out according to the Cut–off scale, and liver fibrosis was determined by the METAVIR scale. The stages of fibrosis were estimated from F0 to F4. At the same time, F0 corresponded to the absence of fibrosis, F1 – underdeveloped fibrosis, F2 – moderate fibrosis, F3 – severe fibrosis, F4 – cirrhosis. The values of the indicators were expressed in kPa, the value of the indicator 7.1 kPa corresponded to F2, 9.2 kPa – F3, F4≥13.5 kPa. Verification of HBV and HCV was carried out by PCR on the device "Rotor Qene Q" (Germany).

According to the results of a comprehensive examination, all patients were divided into comparison groups according to the stage of liver fibrosis: HBV -fibrosis stage – F0-1-14 patients, F- 2-14, F-3-14 and F-4-11 patients; HCV-fibrosis stage – F0-1 -10, F-2-15, F-3-15 and F-4-14 patients. A group of 10 practically healthy individuals was selected as a comparison group.

The syndrome of systemic inflammatory response was not esTableished in the study groups. During the examination, the following criteria were taken into account: body temperature >38 ° C or <36 ° C, respiratory rate >20 per minute, heart rate >90 beats. in min. and the

leukocyte level is >12 thousand/μl or < 4 thousand/μl.

The number of lymphocytes with the marker of their apoptosis CD95⁺ was determined in peripheral blood. The procedure for phenotyping lymphocytes with the CD95⁺ marker was carried out according to the attached instructions. Smear microscopy was performed on a Lumam luminescent microscope at a magnification of 5x100. A panel of monoclonal antibodies from Sorbent LLC (Moscow) was used for CD95⁺ immunophenotyping. In practical healthy individuals, the expression of the CD95⁺ marker on blood lymphocytes averaged 51.7±2.0%.

Statistical processing of the obtained data was carried out using the analytical program Microsoft Excel–2010. The Student's t–criterion and the Mann–Whitney criterion (U) were calculated. The correlation analysis was carried out according to Pearson's double criterion.

The results of the study and their discussion. The analysis of laboratory data depending on the stage of liver fibrosis in patients with HBV and HCV revealed some significant differences in the indicators of clinical blood analysis (Fig).

In the groups of patients with HBV and HCV, the number of circulating leukocytes was mainly lower compared to the group of healthy individuals (6.9±03x10⁹/l) (Fig), except for patients with HBV at stage F0-1, however, these differences were statistically unreliable. There was no fundamental difference in the studied indicator between the different stages of fibrosis, except for a statistically significant increase in leukocytes in patients with HCV (5.6±0.2) compared with HBV (5.0±0.1) at stage F4. In patients with HBV and HCV with progressive fibrosis, a decrease in the number of leukocytes was revealed.

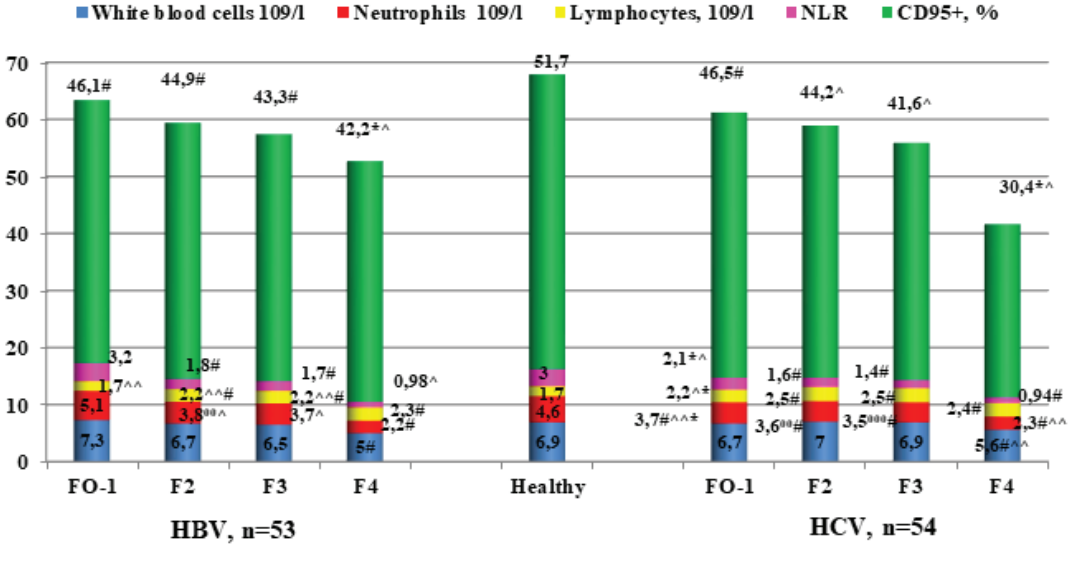
The absolute number of neutrophils in peripheral blood in patients with viral hepatitis was lower than in healthy individuals (with the exception of HBV patients at the stage of fibrosis F0-1–5.1±03x10⁹/l versus 4.6±03x10⁹/l). There were no statistically significant differences between the groups of patients with HBV and HCV in terms of neutrophil levels. At the same time, a decrease in neutrophils was determined depending on the severity of fibrosis. A statistically sTable relationship was determined in HBV patients between the stages of fibrosis F2 - F4 (p<0.001), F3 - F4 (p<0.001).

The study revealed an increase in the absolute number of peripheral blood lymphocytes in comparison with the group of healthy individuals (1.7±01x10⁹/l), as well as their high level in HCV patients in relation to patients with HBV. Comparison of these lymphocyte levels between groups using the Mann-Whitney criterion revealed a statistically significant increase in the absolute number of lymphocytes in HCV patients at stages F0-1, F2 and F3 relative to patients with HBV. The detected lymphocytosis in both etiological variants of chronic hepatitis is quite expected, because many viral infections are accompanied by an increase in the number of lymphocytes [4]. In our study, an increase in the number of lymphocytes with the progression of fibrosis was determined. Lymphocyte levels were inversely correlated with neutrophil levels in HBV patients (F0-1, r=-0.37; F2- r= -0.72; F3- r= -0.74; F4-r= -0.3) and in HCV patients (F0-1r= -0.4; F2- r=-0.72; F3- r= -0.74; F4- r=-0.25).

As the results of our studies show, in patients with HBV and HCV, there is a decrease in the absolute number of neutrophils and an increase in the absolute number of lymphocytes, and, accordingly, a decrease in NLR. The results obtained are consistent with the data of I.V. Mannova, who esTableished inverse correlations between these hematological parameters [4].

According to Table 1, the NLR index in the groups of patients with HBV and HCV was statistically significantly reduced relative to healthy individuals, and its decrease was determined depending on the stage of fibrosis. In the two studied groups of patients, a statistically significant decrease was determined at the stage of fibrosis F2, F3 and F4 (p<0.001). In patients with HBV with CL, there was a decrease in the NLR index by 3.1 times (p<0.001), and in patients with HCV - by 3.2 times (p<0.001).

It is known from the literature that the persistence of HBV and HCV increases the proliferative potential of lymphocytes and reduces the level of apoptosis of these cells [2]. Among the numerous protective antiviral mechanisms, one of the key places belongs to apoptosis, which helps to prevent viral replication and persistence [1]. Apoptosis is a universal biological mechanism. In viral hepatitis, apoptosis can lead to excessive death of not only hepatocytes, but also other cell populations. This mechanism reflects either a systemic immuno-inflammatory response to infection or extrahepatic persistence of the virus [1].



The indicators of the general blood test and the marker of CD95+ lymphocyte apoptosis in patients with HBV and HCV, depending on the stage of fibrosis (M±m)

In this regard, in our study, the study of the marker of apoptosis ($CD95^+$) of peripheral blood lymphocytes in patients with HBV and HCV at various stages of fibrosis was of particular interest. In patients with HBV and HCV and in healthy individuals, the number of peripheral blood lymphocytes in a state of apoptosis with the $CD95^+$ marker was determined immediately after isolation. It was found that $CD95^+$ levels were elevated in patients with HBV and HCV compared to controls. There was no statistically significant difference between the groups of patients with HBV and HCV. A decrease in the $CD95^+$ marker was determined in two groups of patients, depending on the severity of fibrosis. At stage F4, the $CD95^+$ level in HBV patients was 42.2±0.9%, and in HCV - 30.4±2.6%, which was 1.4 times higher ($p<0.05$).

At the same time, the lowest levels of the $CD95^+$ marker were observed at the F4 fibrosis stage, that is, with the progression of the fibrosis stage, a decrease in the $CD95^+$ marker was recorded. Correlations were found in HBV patients between the level of lymphocytes and $CD95^+$ markers (F0-1r=0.6; F2-r=0.71; F3-r=0.51; F4-r=0.2) and in HCV patients (F0-1r=-0.6; F2-r=-0.2; F3-r=-0.41; F4-r=-0.35). A correlation was also determined between elastometry indices and $CD95^+$ apoptosis markers in HBV patients (F0-1r=-0.2; at F4- r= -0.23) and in HCV patients (at stage F0-1r= -0.34; at F4-r= -0.21).

Thus, our study revealed some laboratory patterns, the nature and degree of previously described hematological and immunological changes in patients with $CD95^+$ with varying degrees of liver fibrosis were clarified.

Conclusions:

1. In patients with HBV and HCV with varying degrees of liver fibrosis and without systemic inflammatory response syndrome, a decrease in the absolute number of neutrophils, an increase in the absolute number of lymphocytes, a decrease in the NLR index against the background of a decrease in the level of the $CD95^+$ lymphocyte marker was revealed.

2. In patients with HBV and HCV, there is a decrease in the programmed death of peripheral blood lymphocytes, which may reflect the damaging effect of hepatotropic viruses, indirectly confirmed by lymphocytosis in patients with HBV and HCV.

3. Given the simplicity and accessibility of the NLR determination method, it can be recommended for use in everyday clinical practice as one of the diagnostic markers for assessing the course and predicting complications of liver cirrhosis in patients with HBV and HCV.

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DATING THE TIME TO THE MOST RECENT COMMON ANCESTOR OF THE SAKHA (YAKUTS) WITH Y CHROMOSOMAL HAPLOGROUP N3A2-M1982: NEW ETHNOGENETIC RECONSTRUCTIONS

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Time to the most recent common ancestor (TMRCA) of Sakha men with haplogroup N3a2-M1982 of the Y chromosome was evaluated by 23 STR markers using the mutation rate constant of Y-STR loci that we had previously calculated. The obtained TMRCA values indicate a period of ~1300-1400 years ago (VI-VII centuries AD), associated with the primary expansion of the population. Based on genetic data and analysis of texts from ancient Chinese chronicles, a hypothesis has been put forward about the connection of the ancestral Sakha population with the Yuzhe people, who supplied mammoth ivory to China

Keywords: TMRCA, STR, Y-chromosome, Yakuts, haplotypes

Introduction. The most striking feature of gene pool of the Yakut ethnos is the dominance of men with the rare haplogroup N3a2-M1982 of the Y chromosome (>80%) due to the founder effect. When using a panel of 17 STR loci, carriers of three STR haplotypes - Ht1, Ht2 and Ht3 - stand out among them [20, 43]. Haplotype Ht1, otherwise called the “Tygyn Darkhan/Elley lineage”, has higher frequencies in the Yakut population. The carriers of this lineage are the majority of men - 33% of Central, 40% of Northern and 13% of Vilyui Yakuts [20, 21, 43]. Ht2 conventionally called the “Omogoy lineage” takes a second place, distributed to a greater extent in central Yakutia (30%), to a lesser extent in Vilyui (8%) [20, 43], among the Northern Yakuts it is found with a frequency of 3% [19]. Haplotype Ht3 is more typical for the Vilyui Yakuts (20%), in central and northern Yakutia its frequencies are 4% and 5%, respectively [20, 43].

Determining the TMRCA (time to the most recent common ancestor) for men with haplogroup N3a2-M1982 is of great interest for ethnogenetic reconstructions, because it is associated with the beginning of the formation of the Yakut gene pool characteristics, distinguishing it from other ethnic groups. The period during which all the observed diversity of N3 haplotypes of the Yakuts arose, calculated in the study of B. Pakendorf, based on the mutation rate of 9 STR markers and was initially estimated at ~880±440 years ago [34]. Much larger TMRCA values were proposed by V.N. Kharkov using 7 STR markers ~4.45 ± 1.96 thousand years ago [17] and S.A. Fedorova using 6 STR markers ~1540 ± 580 years ago [19, 27] . It should be noted that such strong differences in the ages of “Yakut” N3 haplotypes in the early studies of geneticists were determined mainly by the use of different sets of STR markers and different mutation rate constants in STR loci. Average STR mutation rate in the Y chromosome in the study of B. Pakendorf was taken to be ~0.003 mutations per locus per generation (according to Kayser et al., 2000 [29]), and in the studies of V.N. Kharkov and S.A. .Fedorova ~0.00069 (according to Zhivotovsky et al., 2004 [42]).

The value of Y chromosomal STR mutation rate constant, in turn, depends on the length of a male generation, which in early studies was taken to be 25 years [17, 19, 27, 42]. Meanwhile, the size of the intergenerational interval can vary greatly due to differences in marriage traditions and demographic parameters among different peoples. Therefore, the value of this indicator for the Yakut population was clarified based on the genealogical data of 712 families, reconstructed from revision tales from 1768, 1795, 1816, 1858, and church registers for the period from 1768 to 1918, and materials from the 1917 census [9]. The length of a male generation among the Yakuts turned out to be on average 35.7 years, which is much higher than the average general population values previously used in genetic studies when calculating the time of genetic divergence of the Y chromosome [9].

To estimate the mutation rate of at Y-STR loci in the Yakut population more accurately, we also used a rare approach based on constructing a phylogenetic tree of the N3a2-M1982 Y chromosome relying on the massively parallel sequencing data, which has become more accessible in the last decade [2]. The mutation rate of 23 STR markers of the Y chromosome was calibrated using radiocarbon dating of an ancient sample with the “Yakut” N3a2-M1982 haplogroup, found in the lower reaches of the Yana River in the Arctic zone of Yakutia. A bone specimen of this medieval male Yana Young, ~800 years old, was found by local residents during the mining of the Yana Mammoth Cemetery [46]. Our adjusted estimate of the STR mutation rate constant for 23 marker STR haplotypes of Yakuts turned out to be equal to 0.0024 mutations per locus per generation [2], which is much different from the values of this indicator used in earlier publications [17, 19, 34].

The purpose of this study was to clarify the time to the most recent common ancestor for the “Yakut” N3a2-M1982 haplotypes using recalculated mutation rate constant for 23 marker Y-STR loci and to reconstruct the genetic history of the Sakha people using updated data.

Materials and methods. To calculate TMRCA, 51 samples of men with hap-

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logroup N3a2-M1982, residents of Yakutia, were selected from previously published works. Of these, 29 samples had data on 23 STR markers: [25] – 16, [37] – 5, [26] – 4, [39] – 2, [49] – 1, [3] – 1. In 22 samples from [45], 21 STR loci from the PowerPlex Y23 panel were genotyped; they lack data for loci with relatively low mutation rates DYS549 and DYS643.

The age of the most recent common ancestor *T* was calculated using the ASD (average squared distance) method, or determining the average root-mean-square distance [25, 30] using the formula:

$$T = \frac{1}{L\bar{\mu}} \sum_{k=1}^{L} \frac{1}{N_k} \sum_{i=1}^{N_k} [A_k(i) - A_k(0)]^2,$$

where $L = 23$ is the number of STR loci in the sample of haplotypes;

$\bar{\mu}$ is mutation rate constant per locus, averaged over all STR loci;

N_k is number of samples in which alleles at STR locus k are known;

$A_k(i)$ is value of the STR allele of locus k in sample i;

$A_k(0)$ is value of the ancestral allele of STR locus k.

The mutation rate constant for 23-marker PowerPlex Y23 haplotypes, calibrated in [2] using radiocarbon dating of a sample of the ancient man Yana Young, ~800 years before present, is equal to 0.0024 mutations per locus per generation. The average interval of one male generation, previously calculated basing on an analysis of the genealogical data of the Yakuts of the 18th-19th centuries, was taken to be 35.7 years [9]. A description of the method for calculating the uncertainty of the TMRCA estimate is given in the Appendix.

The age of the recent common ancestor was also estimated by constructing a phylogenetic network of the generated sample of haplotypes (n=51) using the ρ-statistics method. TMRCA calculation is built into the program for constructing phylogenetic networks using the median-joining algorithm [28] Network v.10.2.0.0. The weight for all STR loci was set to 10, with the parameter ε = 0.

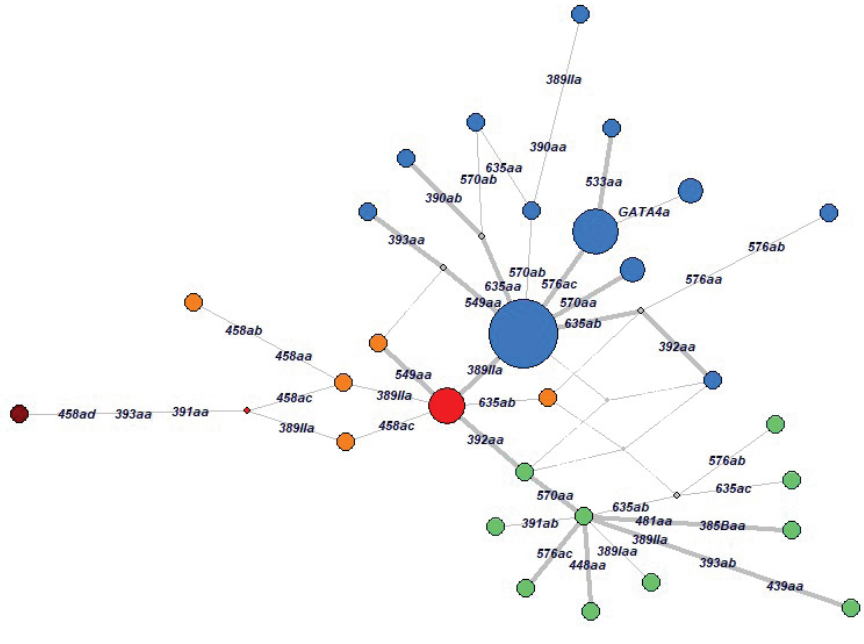
Results and Discussion. Time to the most recent common ancestor of men in the studied sample, calculated by the ASD method, is 1380 ± 460 years BP or before 1950 (Note: 1950 is chosen for the "present time" date in the sciences that using radiocarbon dating. The donors of the DNA samples used to calculate the TMRCA were born in the second half of the twentieth century, so a small correction for recalculation to 1950 can be neglected).

Ancestral haplotype selected as an average 23-marker variant, in the format of recording loci DYS19, DYS385a, DYS385b, DYS389I, DYS389B, DYS390, DYS391, DYS392, DYS393, DYS437, DYS438, DYS448, DYS456, DYS458, DYS481, DYS533, DYS549, DYS570, DYS576, DYS635, DYS643, GATA H4 matches the Ht3 haplotype and looks like this:

14-11-13-14-17-23-11-16-14-14-11-10-19-14-16-20-11-12-19-16-22-12-12.

Figure shows the median network built using 51 samples of haplogroup N3a2-M1982. Three samples of N-F23218 Buryats from Hulun Buir (China, [41]) were added as outliers to determine the root of the phylogenetic tree. The TMRCA estimate based on the median network using the ρ-statistics method was 1260 ± 460 BC. (Note: The lower TMRCA value using this method compared to ASD is due to the fact that Network does not account for back mutations at the DYS389II locus in the two samples, HGDP00945 and HGDP00969).

According to the phylogenetic network (Figure) structure and TMRCA calculations (Table 1), during the period of the primary increase in population size ~ 1300-1400 years ago from the MRCA lineage (Ht3) more widespread in Vilyui, a lineage had occurred leading to the Ht2 haplotype, characteristic to the Central Yakuts. The secondary increase in population size began much later, ~900 years ago, apparently due to another influx of migrants from the southern regions [2, 3, 21]. At the same time, further splitting of Ht3 occurred into a lineage leading to Ht1. Thus, in VI-VII centuries AD in the ancestral population there were obviously men with haplotypes Ht3 and Ht2, while the dominant modern haplotype Ht1 ("Elley's lineage") arose much later, in the ~11th century, and its divergence began during a period of sharp increase in population size starting from ~14th century [3, 21]. The territorial distribution of evolutionarily more ancient haplotypes Ht3 and Ht2 may indicate the initial settlement of the Vilyuy region and then central Yakutia by the ancestors of the Yakuts, which corresponds to the concept of the famous Yakut historian and ethnographer G.V. Ksenofontov [12, 13]. However, archaeological findings in recent years indicate that pastoral groups appeared on the Olekma River in Southern Yakutia in the 3rd-4th centuries [4], therefore, the settlement of the Lena-Amga interfluve could also occur through Olekma. Resolving this issue requires additional archaeological researches and phylogeographic studies of haplotype frequencies distributions in modern and ancient populations. Dating ~1300-1400 years BP does not contradict archaeological materials, according to which groups of southern pastoralists appeared on the territory of Yakutia in the



Phylogenetic median network of 23-marker STR haplotypes of men (n=51) with haplogroup N3a2-M1982. The ancestral haplotype is highlighted in red, Ht1 and its derivatives in blue, Ht2 and its derivatives in green, Ht3 derivatives in orange, and the 17-marker STR haplotype of the Buryats from Hulun Buir (China) in brown. The branches of the phylogenetic tree of haplogroup N3a2-M1982 reconstructed on complete sequencing data of 23 male samples in [2], are highlighted in bold.

3rd-4th centuries AD [4], because indicates the most probable time of appearance of the most recent common N3a2 ancestor at the period of primary expansion of the Sakha people.

The obtained TMRCA values of the most recent common N3a2-M1982 ancestor in comparison with data of other authors are shown in Table 1. Taking into account the confidence intervals, the TMRCA estimates in this paper are consistent with the results of studies [3, 19, 26, 27, 34] and the YFull group [48]. In general, it should be noted that TMRCA values calculated in recent years from samples of haplotypes with a large number of STR loci and expanded fully sequenced samples almost all indicate a time interval of ~1300-1400 years BP. A slight overestimation of TMRCA in [26, 33] is partly explained by the use of other Y-SNP mutation rate constants – $0.74 \cdot 10^{-9}$ and $0.76 \cdot 10^{-9}$, instead of $0.82 \cdot 10^{-9}$ per site per year in [3] and YFull calculations [48].

The age we calculated for the most recent common ancestor of the Yakuts based on the N3a2 chromosome data corresponds to the periods of the First and Second Turkic Khaganates, the nomadic states of the Orkhon Turks (or Kok-Turks), which existed in 552 - 744 AD. The main policy of the Turks at that time was to conquer the zone of the Eurasian steppes and control the routes of the Great Silk Road [18]. To north of territories of the Kok-Turks, numerous Tele tribes roamed. In translation of a fragment of the "Xin Tangshu" (1060) text made by Iakinf Bichurin, it is noted that "They [Tele] were considered subjects of the Tukyue House. The people of Tukyues were heroic with their forces in the deserts of the north" [6], i.e. it is implied that Kok-Turks hired the Tele to represent their interests in the north. The text of the later Chinese historical encyclopedia "Wenxian Tongkao" (1273-1317) records that "When the Tujue state conducted punitive campaigns to the east and west, [it] always used their [Tele] services to curb the northern steppe" [14]. (The mentioned texts of Chinese chronicles are publicly available on the sites https://chinesenotes.com/xintangshu/xintangshu217a.html, https://ctext.org/wiki.pl?if=gb&chapter=681264&remap=gb, their modern translation shows that it was really about bribery or hiring). The northernmost of the Tele tribes were the Kurykans. B.B. Dashibalov supposed that "...through the Kurykan the Turks carried out extortions from the taiga population of Eastern Siberia, the Kurykans were suppliers of furs, livestock, and iron" [8].

It is curious that a bone sample of a medieval man Yana Young, ~800 years old, a carrier of the "Yakut" N3a2-M1982 haplogroup, was found by local residents during the mining of the Yana mammoth cemetery. Analysis of SNP mutations on the Y chromosome showed that the Yana Young lineage is located on the branch of Ht1, which is dominant among the male lineages of modern Sakhas, but evolutionarily arose earlier than the "Elley lineage" [2, 3, 46]. More recent mutations (M1988 and Y25011) are absent in the ancient Yana Young sample [2, 3]. The Yana Young man Y-chromosome lineage has not been preserved in the modern population. The mitochondrial DNA of this medieval man belongs to the branch of haplogroup D4o2 [47], which is often found today among the Central Yakuts [27], the age of this branch according to YFull MTree is ~1350 years (95% CI 3800-325 years). In PC analysis of SNP data, the Yana Young sample is located into the cluster of modern Yakuts [32]. Genome-wide analysis using the ADMIXTURE algorithm (K=7) also showed the genetic proximity of the Yana Young person to modern Yakuts [44]. Thus, the results of genome-wide studies showed that the ancient man Yana Young, found in a mammoth cemetery, was not genetically different from modern Yakuts. Accordingly, it can be assumed that the Sakha have long been suppliers of mammoth ivory to China and medieval Muslim countries [1, 7, 23]. The world's main reserves of fossil mammoth ivory are located in Yakutia; the total resources are es-

Table 1

Summary data of Y chromosomal haplogroup N3a2-M1982 TMRCA

TMRCA, years	Genetic markers	n	Age estimation method	Ref.
1380 ± 460	23 STRs	51	ASD	This study
1260 ± 460	23 STRs	51	ρ-statistics	This study
1300 ± 500	17 STRs	237	ASD	[3]
880 ± 440	9 STRs	162	ρ-statistics	[34]
4450 ± 1960	7 STRs	97	ASD	[17]
1540 ± 580	6 STRs	215	ASD	[19, 27]
1270 ± 250	SNPs in combBED region (8.5 Mbp)	23	Y-SNP mutations counting	[3]
1350 95 % CI 900-1800	SNPs in combBED region (8.5 Mbp)	17	Y-SNP mutations counting	[48]
1737 95 % CI 919-2609	SNPs in 6.2 Mbp region	4	Y-SNP mutations counting	[33]
1589 95 % CI 821-2580	SNPs in 9.8 Mbp region	4	Y-SNP mutations counting	[26]

Table 2

Information from the Chinese chronicles of the Tang Dynasty about the countries that supplied the khutu horn (gǔduō骨咄)

Source	Year of publishing	juàn	Country of gǔduō 骨咄 origin	Notes
Tongdian	801	200	Юйчжэ	
Tanhuiyao	961	98	Юйчжэ	written gǔtǔ 骨吐
Taiping Huanyuji	976-983	198	Юйчжэ	
Taiping Huanyuji	976-983	199	Кыргызы	
Cefu Yuangui	1005-1013	961		no information about 骨咄
Xin Tangshu	1060	217b	Кыргызы	
Xin Tangshu	1060	39	Мохэ	written 骨骨出

timated from 34,000 up to 450,000 tons [16]. In this regard, it was interesting to trace Referencess to mammoth ivory and the countries from which it was supplied, in ancient manuscripts.

The extensive historiography about medieval European unicorn legends mentions a bone of unknown origin called a "khutu horn" [31]. In the Middle Ages, "khutu horn" (وتخ, khutū, khutuw, chutww, etc.) was highly valued among the Turkic peoples, in the Muslim East and in China [22, 35], because it was rare and was used in the manufacture of prestigious items - knife handles, sheaths, caskets, belt linings, etc. It was believed to has the ability to detect and neutralize poisons. Due to the high price, the "khutu horn" became an attribute of diplomatic gifts between the rulers of Central Asia [38]. In the ideas of the medieval Turks, reflected by Mahmud Kashgari in "Divan lugat at-Turk" (1074), "khutu horn" is a bone (horn, whisker) of a sea fish or a tree root brought from China [15, 30, 31]. Following this narrative, the great polymath Biruni inquired its origins ambassadors from the Khitan Liao Empire (circa 1027). The ambassadors replied, "This is the frontal bone of a bull; the same is said in the books, but with the addition that this bull is found in the land of the Khirkhiz" (Yenisei Kyrgyz) [1]. Obviously, the ambassadors referred to Chinese written publications of that time. The word "khutu" itself, being Siberian in origin, came to Muslims through the Chinese characters gǔduō 骨咄 (pronounced in Russian transcription as "kuto"). The use of hieroglyphs gǔduō to denote this ornamental material has been noted since the Chinese Tang Dynasty (VII-X centuries). Table 2 provides information about the countries that supply gǔduō.

Sung scholars began compiling the collection "Xin Tangshu" in 1044, that is, after Biruni's meeting with the Khitan ambassadors. However, the text about the country of the Kyrgyz, which mentions the khutu beast, was known earlier. From the surviving documents, the same entry is contained in the Taiping Huanyuji encyclopedia, compiled in 976-983, which also reproduces an older text about the country of Yuzhe, as a supplier of the bone. Thus, the information from Taiping Huanyuji occupies an intermediate position in ideas about the origin of gǔduō in the 10th century. In the later encyclopedia "Tsefu Yuangui" (1005-1013), the mention of gǔduō is already excluded from the description of the country of Yuzhe. It should be noted here that trade and other ties of the Yenisei Kyrgyz began to expand after the defeat of the ancient Uyghurs in 840. The strategically advantageous geographical location of the Kyrgyz territory at the junction of the steppe and the Siberian taiga allowed them to intercept from the Kurykans access to northern riches, including mammoth ivory. Judging by the data of Chinese chronicles, starting from the 10th century, the Kyrgyz played a role of key intermediaries in the supply of mammoth raw materials, in particular ivory, and before that date the source of bone was the country of Yuzhe (Table 2).

The earliest information about gǔduō is contained in the "Tongdian" encyclopedia (801). This message is in the "Taiping Huanyuji" encyclopedia translated by N.V. Küner looks like this: "The state of Yujia is located east of the state of Ju, 15 days' drive. This country is vast and densely populated. The customs are the same with Bayegu. Few cows and horses, many sables and gutu" [14]. The same thing is written in "Tang Huiyao" (961), but khutu is designated somewhat differently (gǔtǔ 骨吐) [14]. A message about the country of Yuzhe is included in the "Tongdian" encyclopedia from an unknown road guide of the mid-7th century, the original of which has not survived [10].

The countdown of the days of travel from China to the northern countries of Yuzhe, Ju, Damo, Gushi began from the lands of the Bayirku, one of the Tele tribes. According to the monuments of the Darasun culture, the country of Bayirku was located in the southern part of Transbaikalia and northern Mongolia and called Bayegu [11]. The Ju country of reindeer herders was located northeast of the Bayegu country, and Yuzhe was located 15 days' journey east of the Ju country [14]. But in determining the distance from the Bayegu country to the Ju country, sources differ: "Tong Dian" and "Tang Huiyao" give 6 days of travel (500 li), and "Taiping Huanyuji" - 50 days of travel. North in Chinese sources is shifted to the northwest [5], due to the orientation towards sunrise in the summer. Taking this into account, the country of the Ju reindeer herders, according to the "Taiping Huanyuji", was located somewhere in the lower reaches of the Olekma and correlates with the ancestors of the Evenks, and the country of Yuzhe is in Central Yakutia and is possibly associated with the ancestors of the Sakha.

Conclusion. Thus, the obtained TMRCA dating for the "Yakut" N3a2-M1982 haplotypes of ~1300-1400 years allows us to take a new insight at the information from the Tang chronicles of the 7th-10th centuries about the Yuzhe people. The Yuzhe people were engaged in breeding horses and cattle, had similar customs with one of the Tele Bayirku tribe, and there was a lot of diāoshǔ (sable) and gǔduō (mammoth ivory) on their land. Extraction of tusks from mammoth cemeteries could have been a traditional trade for the ancestors of the Yakuts since the 7th century AD. A small clan or tribe in which the most recent common ancestor of the Yakut branch N3a2-M1982 was born may have belonged not to the Baikal Kurykans, but to the people called "Yuzhe" in Chinese ancient chronicles.

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The authors declare that they have no conflict of interest.

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Appendix

Contribution of covariance to the error of TMRCA estimation using the ASD method. STR mutations are assumed to occur randomly according to a Poisson distribution. For simplicity, let's consider the case of single-marker haplotypes, i.e. one STR locus. In the stepwise mutational model (SMM) the contribution of covariance to the total variance of the TMRCA estimate using the average squared distance (ASD) method is described by the formula:

$$D_{cov} = \mu\bar{t} + 2\mu^2\bar{t^2}, \quad (1)$$

where μ – is the mutation rate constant; $\bar{t}$ – is the average age of shared branches for all pairs of the studied sample of STR haplotypes, i.e. average time interval from the most recent

common ancestor of the entire sample to the common ancestor of a randomly selected pair of haplotypes; $\bar{t}^2$ - is the average squared age of shared branches for all pairs of the studied sample of STR haplotypes.

As a rule, the value of $\bar{t}$ is significantly less than the estimated age of the most recent common ancestor T, and the quadratic term in formula (1) can be neglected. For this case

$$D_{cov} \cong \mu\bar{t} = \frac{2\mu}{N(N-1)}\sum_i \sum_{i<j}(T - T(i,j)), \quad (2)$$

T(i,j) – is age of the common ancestor of a pair of haplotypes i and j, *N* is sample size. Summation is performed over all pairs of haplotypes, there are $N(N-1)/2$ pairs in total.

Let us introduce a notation for the average age of the common ancestor of a randomly selected pair of STR haplotypes:

$$T^* = \frac{2}{N(N-1)}\sum_i \sum_{i<j} T(i,j). \quad (3)$$

Estimator for the age of a pair of hplotypes for the ASD method [24, 40] is

$$T_{ij} = \frac{(A(i)-A(j))^2}{2\mu}, \quad (4)$$

where *A(i), A(j)* – are allele values of STR haplotypes *i* and *j*, respectively. Then

$$T^* = \frac{1}{\mu N(N-1)}\sum_i \sum_{i<j}(A(i) - A(j))^2 =$$

$$= \frac{1}{\mu N(N-1)}\sum_i \sum_{i<j}[(A(i) - \bar{A}) - (A(j) - \bar{A})]^2,$$

where $\bar{A} = \frac{1}{N}\sum_i A(i)$ is average STR allele value for the sample. Taking into account its properties,

$$T^* = \frac{1}{\mu N}\sum_i (A(i) - \bar{A})^2. \quad (5)$$

Substituting the resulting expression into formula (2), we finally obtain:

$$D_{cov} = \mu(T - T^*) = \frac{1}{N}\sum_i (A(i) - A(0))^2 - \\ - \frac{1}{N}\sum_i (A(i) - \bar{A})^2, \quad (6)$$

where *A*(0) – is an ancestral allele value.

Total relative error of the TMRCA estimation by the ASD method is calculated as:

$$\frac{\sigma}{\mu T} = \sqrt{\frac{1+2\mu T}{N\mu T} + \frac{T-T^*}{\mu T^2}}. \quad (7)$$

CLINICAL CASE

U.V. Semenova, A.I. Borisov, T.N. Alexandrova, I.I. Mulina, V.N. Yadrikhinskaya

CLINICAL CASE OF THE DEVELOPMENT OF SWEET'S SYNDROME IN A PATIENT WITH MYELODYSPLASTIC SYNDROME

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Sweet's syndrome is a rare type of dermatoses, which characterized by a recurrent course, painful bright red papules, inflammatory plaques, fever and neutrophilic leukocytosis. The article demonstrates a clinical case of Sweet's syndrome associated with hypomethylating agents in patient with myelodysplastic syndrome. The diagnosis was verified based on clinical features which included purplish-red colored skin plaques with ulcerative-necrotic defects right after azacitidine and decitabine therapy; profound therapeutic effect from steroids, plasmapheresis, ineffectiveness of antibiotics, antifungal drugs; increasing the level of neutrophils. The concurrent severe course of the diseases was complicated by extensive necrotic skin lesions of the lower extremities, which required surgical intervention. The recurrent course of Sweet's syndrome and the ineffectiveness of maintenance doses of prednisolone required a consideration of changing treatment approach of myelodysplastic syndrome with the discontinuation of hypomethylating agents.

Therapeutic tactics for patients with a rare disease, Sweet's syndrome, should be selected individually, taking into account the form of the disease and concomitant pathology.

Keywords: Myelodysplastic syndrome, skin vasculitis, Sweet's syndrome, acute neutrophilic dermatosis.

Introduction. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal blood disorders characterized by cytopenia, signs of dysmyelopoiesis and a high risk of transformation into acute myeloid leukemia. Clinical manifestations of MDS are nonspecific and are most often caused by quantitative and qualitative changes in complete blood count (cytopenic syndrome, infectious complications). In 10% of cases, MDS starts with autoimmune and inflammatory manifestations, among which the most common are anemia, thrombocytopenia, and less often polyserositis, arthritis and skin vasculitis [2]. At the same time, the results of previous studies have proven a significantly higher risk of developing MDS and acute myeloid leukemia in people with autoimmune diseases [6].

Montoro J. et al. showed that autoimmune disorders, detected in 48% of patients with MDS, significantly worsen overall survival (69% compared with 88% in patients without autoimmune diseases), and also increase the incidence of infectious complications and mortality rates (71,0% compared with 47,2%, p = 0,0056) [3, 4].

In some patients with MDS, the autoimmune process manifests with vasculitis, the prevalence of which varies from 5 to 60% according to data of different investigators [3, 13]. At the same time, small vessels involvement (leukocytoclastic vasculitis) is most often observed, which is a serious clinical problem that complicates the verification of diagnosis and treatment of MDS. Histologically, this type of vasculitis is characterized by inflammation of small vessels, in which the inflammatory infiltrate is represented by neutrophils. One of the rare forms of cutaneous vasculitis associated with neutrophilia is Sweet's syndrome, characterized by a relapsing course, painful bright red papules and inflammatory plaques, fever and neutrophilic leukocytosis [8].

According to data of literature, the development of Sweet's syndrome is described in 10% of patients with MDS and acute myeloid leukemia. A potential trigger for the development of dermatosis can be both the disease itself and the ongoing anticancer therapy. To date, a number of clinical observations have been published proving the relationship between the onset of Sweet's syndrome and the hypomethylating agent 5-azacytidine [5, 10, 11, 14]. The results of these works have demonstrated the effectiveness of immunosuppressive therapy in relieving the clinical feature of neutrophilic dermatosis, however, long-term use of glucocorticosteroids in patients with hematologic malignancies is associated with an increased risk of infections, which explains the relevance of this problem [10].

The aim of the study: to describe a clinical case of Sweet's syndrome that developed during therapy with hypomethylating agents in patient with myelodysplastic syndrome.

Clinical case. Patient N., 51 years old, first contacted a hematologist in July 2022 with complaints of anemic syndrome – weakness, dizziness, fatigue, shortness of breath on exertion. During examination complete blood count revealed cytopenia of three blood lineages (erythrocytes 2.48 x 10^{12}/l, hemoglobin 82 g/l, leukocytes 2,02 x 10^{9}/l, platelets 104x10^{9}/l). Bone marrow examination demonstrated hypercellular smear with an increase in the number of blast cells up to 11,5%, as well as signs of dysgranulo-, erythro-, and megakaryocytopoiesis characteristic of MDS. An immunophenotypic study revealed myeloid lineage of blast cells (6%) with expression of CD13, CD33, CD177+, lines of nonspecific markers HLD-DR4+, CD38+, CD34+. Based on the results of trephine biopsy of the bone marrow, a histological signs of hypercellular bone marrow with secondary hyperplasia and dysplasia of granulocytopoiesis; MDS with excess blasts 2 was revealed. Thus, the diagnosis was verified as MDS refractory anemia with excess blasts - 2, a high-risk group according to IPSS (5,5).

According to the Federal clinical guide-

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lines for the treatment of patients with MDS, from 09.06.2022 to 10.06.2022, the first course of chemotherapy with low doses of cytarabine was carried out. There were no complications after treatment; bone marrow biopsy showed a reduction of blast cells to 4,6%.

Next, treatment protocol was changed to hypomethylating agent 5-azacytidine 75 mg/2 days 1–7. The first cycle with standard doses was carried out from 2.11.2022 to 8.11.2022 and was complicated by prolonged myelotoxic agranulocytosis with infectious complications, febrile fever, as well as the development of extensive ulcerative-necrotic lesions of the skin of the lower extremities. Thus, on the 1st of December 2022, at the 23rd day of azacitidine therapy completion, the appearance of an area of painful skin thickening on the right leg, accompanied by an increase in the level of neutrophils, was noted (Fig. 1.1, Fig. 2). According to ultrasound examination, local thickening of tissue up to 1.9 cm was noted in the lower third leg along the inner surface. Taking into account the presence of febrile fever in the post-cytostatic period, antibacterial and antifungal therapy was prescribed. In dynamics, there was an increase of area of skin lesions in lower extremities with necrosis of the skin and adjacent tissues, progressive pain that is not relieved by taking non-steroidal anti-inflammatory drugs. Since 5th of December 2022, worsening of pain in the right leg and expansion of involved tissue have been noted. A differential diagnosis was carried out between erysipelas, mucormycosis, thrombophlebitis of the veins of the lower extremity, taking into account data from instrumental studies indicating infiltration of soft tissues, echo signs of moderate phlebitis of the main trunk of the great saphenous vein at the level of the right lower third leg. Repeated microbiological examinations of the affected skin area did not reveal pathological growth. According to the results of histological examination, necrotic masses were obtained twice, which did not allow verification of the diagnosis. Local therapy was carried out in volume - heparin ointment, compression bandaging of the lower extremities and venotonic therapy.

On December 13, 2022 with prolonged febrile fever, progressive necrotic lesions of the right lower limb (Fig. 1.2), patient was admitted to the intensive care unit (ICU) of the surgical hospital, where for the first time diagnosis of cutaneous vasculitis in the stage of incomplete drug remission was verified. Taking into account the lack of effect from massive antibacterial and antifungal therapy, we suspected the immunoinflammatory nature of the skin changes. In this regard, pulse therapy with methylprednisolone and discrete plasmapheresis sessions were initiated, achieving a rapid clinical response with normalization of temperature. Surgical debridement with necrectomy was performed within the involved area of skin (Fig. 1.3).

Taking into account the development of life-threatening complications, it was decided to abstain from chemotherapy, but in March 2023, progression of the underlying disease was registered with an increase of blast cells in bone marrow up to 7,4% and increased need for blood transfusions, which was an indication for the resumption of specific therapy. The 2nd course of 5-azacytidine therapy was complicated by the appearance of similar pustular skin lesioms in the inguinal area and in the middle third of the right forearm with febrile fever, which regressed after the administration of prednisolone at a dose of 90 mg/day. Subsequently, 2 more courses of therapy with 5-azacytidine were carried out with low doses of prednisolone 15–30 mg/day. Considering the recurrent course of dermatosis with acute fever, neutrophilia (Fig. 2), the therapeutic effect of immunosuppressive therapy with prednisolone, Sweet's syndrome, or acute febrile neutrophilic dermatosis, was suspected in this case. This diagnosis was confirmed based on anamnesis of the disease (the appearance of rashes after a course of chemotherapy, a profound therapeutic effect from glucocorticosteroids, plasmapheresis, lack of effect from treatment with antibiotics, antifungal drugs); clinical presentation (presence of merging plaques of purplish-red color, forming ulcerative-necrotic defects); laboratory findings (increase of neutrophil levels at same time with the appearance of plaques, progressive anemia and thrombocytopenia in a complete blood count).

Since July 2023, taking into account recurrent ulcerative necrotic skin lesions associated with the administration of azacitidine, therapy was changed to decitabine 20 mg/m2 for days 1–5. However, the post-course period was also complicated by prolonged febrile fever, the appearance of ulcerative formations on the dorsum of both hands with severe pain, requiring opioid analgesics. Pathogenetic therapy with prednisolone 90 mg/day, combined antimicrobial therapy, and discrete plasmapheresis sessions were performed with improvement. Despite the relief of the life-threatening condition, it was decided to refrain from specific therapy in the future. Blood transfusion and symptomatic therapy are recommended. Currently, the patient's condition is satisfactory, and dynamic observation continues.

Discussion. The presented clinical case demonstrates the complexity of management of patients with a competing course of a rare disease, Sweet's syndrome, and MDS. Firstly, treatment of hemoblastosis requires strict adherence to the doses and intervals of administration of chemotherapy drugs. The development of life-threatening complications,

Fig 1.1 Fig 1.2 Fig 1.3

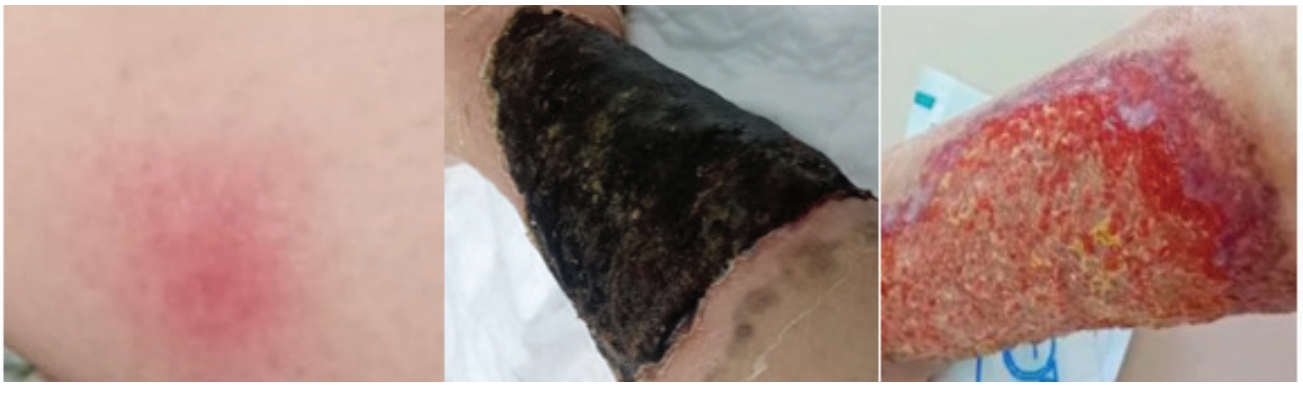

Fig. 1. Dynamics of skin lesions in patient (december 2022 – february 2023)

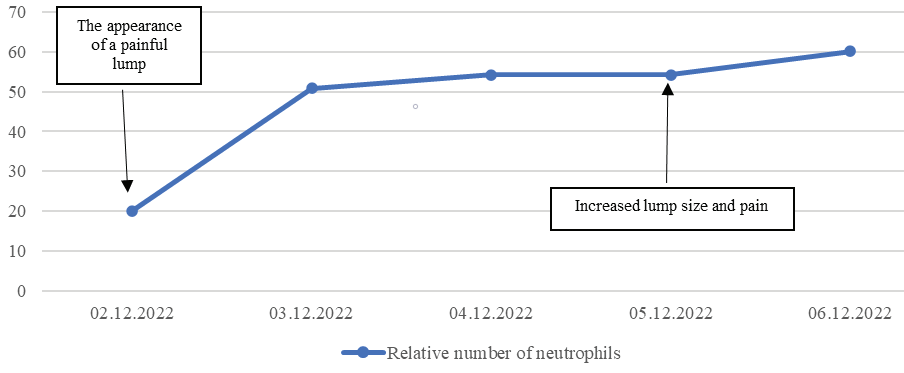

Fig. 2. Dynamics of neutrophils level

Diagnostic criteria of classic form of Sweet's syndrome

	Major criteria	Minor criteria
Diagnostic criteria	Sudden appearance of painful, erythematous skin nodules or plaques.	Fever 380C or more
		Association with hematologic or visceral malignancy, inflammatory disease or pregnancy, or previous upper respiratory tract infection
	Histological signs of a dense neutrophilic infiltrate without signs of leukocytoclastic vasculitis	Pronounced response to treatment with corticosteroids
		Abnormal laboratory tests (3 of 4): ESR > 20 mm/h, high CRP, leukocytes > 8000, neutrophils > 70%

which required intensive care unit administration, led to discontinuations of courses, which may worsen a prognosis of the disease in patient with high-risk group. Secondly, accurate verification of diagnosis in this cohort of patients is often difficult due to the atypical course of the disease caused by secondary immunodeficiency and persistent thrombocytopenia, that limits surgical interventions and biopsy of the affected area.

In this patient, the undulating course of dermatosis, clearly associated with chemotherapy and characterized by the appearance of painful erythematous pseudovesicular plaques, fever and neutrophilia, allowed us to make a diagnosis of Sweet's syndrome, which is an inflammatory dermatoses. The prevalence of the disease is 1–9 cases per 1 million population. In the Russian Federation, single clinical cases are described [1]. According to the literature, the disease is more commonly seen in women aged 30 to 60 years. Depending on the cause of the development of this syndrome, three clinical forms are distinguished: classic, cancer- and drug-related. Taking into account the manifestation of acute febrile neutrophilic dermatosis after courses of hypomethylating drugs (5-azacytidine and decitabine), the described case most likely corresponds to the drug-related form. It is described that most commonly drug-related form is associated with the administration of granulocyte colony-stimulating factor (G-CSF), which also occurred in this clinical case. In addition, some immunosuppressive agents, such as azathioprine, have also been described as triggers for the development of Sweet's syndrome, which is based on a type IV hypersensitivity reaction that manifests within 1–4 weeks of taking an immunosuppressive drug [8,9].

The most likely theory of pathogenesis explaining the connection of Sweet's syndrome with malignant neoplasms is the overproduction of pro-inflammatory cytokines and growth factors (G-CSF and GM-CSF). Excessive production of G-CSF stimulates the proliferation of granulocyte lineage cells, which leads to an increase in the level of neutrophils [8]. In case of initial neutropenia caused by hematopoietic depression, the differential diagnosis of this condition can be difficult. However, figure 2 shows an increase in the level of neutrophils by 3 times, accompanied by the appearance of characteristic skin elements and fever. It should be noted that, according to the literature, leukocytosis is not always observed. Especially in patients with Sweet's syndrome of paraneoplastic origin, anemia, thrombocytopenia, and neutropenia may instead be observed [8].

5-azacytidine is characterized by immunoregulatory properties, which are due to its ability to suppress the secretion of proinflammatory cytokines and increase the number of CD4+CD25+/forkhead-box-p3+ T-regulatory cells. Previous clinical case described that the anti-inflammatory properties of 5-azacytidine make it possible in some cases to relieve neutrophilic dermatosis, however, in some cases, the development of Sweet's syndrome in patients with MDS may be considered as an adverse effect of 5-azacytidine therapy [5, 7, 10].

Dermatological manifestations of Sweet's syndrome were characterized by appearance at the site of skin damages: microtraumas, including drug injection sites, biopsies, radiation therapy areas, insect bites [1, 5]. Thus, one of the episodes of the appearance of skin plaques in this clinical case was mediated by multiple attempts at venipuncture.

The diagnosis of Sweet's syndrome is verified based on diagnostic criteria proposed by S. Su and C. Liu in 1986, later modified in 1994 by P. van den Driesch (Table) [12]. In this clinical case, the patient had 1 major and 4 minor criteria, and a biopsy of skin elements was not performed due to the high risk of progression of ulcerative-necrotic lesions and the development of hemorrhagic complications in the presence of critical thrombocytopenia. In our opinion, the available data were sufficient to verify this rare clinical condition and change the patient's management tactics.

Conclusion: Description of clinical case of rare diseases is necessary to increase the awareness of doctors of various specialties and expand the range of differential diagnosis of pathological conditions with a similar clinical feature. Therapeutic tactics for patients with a rare disease, Sweet's syndrome, should be selected individually, taking into account the form of the disease, concomitant and competing pathology.

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ULLRICH CONGENITAL MUSCULAR DYSTROPHY: CLINICAL CASE STUDY

Introduction. Ullrich congenital muscular dystrophy (Ullrich CMD, OMIM #254090) is the most severe form of skeletal muscle collagenopathy associated with three genes (*COL6A1, COL6A2, COL6A3*).

The purpose of the report was to present our own observation of clinical cases with Ullrich congenital muscular dystrophy in two unrelated Yakut families.

Materials and methods. A clinical and genealogical examination, electroneuromyography, muscle MRI, muscle biopsy, and molecular genetic research using the massively parallel sequencing method were carried out.

Results. The cause of the disease in the first family was two mutations in a compound heterozygous state: c.1561C>T and c.2329T>C in the *COL6A2* gene; in the second family, the c.2329T>C mutation in the *COL6A2* gene in a homozygous state. The clinical picture of the disease was manifested by muscle weakness and hypotonia, hypermobility of the interphalangeal joints, contractures of the elbow, ankle and knee joints, delayed motor development, spinal deformity, and skin changes. The type of inheritance in families is autosomal recessive.

Conclusions. Despite the rarity of the disease, neurologists and geneticists, when identifying symptoms of myopathy, delayed motor development, and the presence of hypermobility in the distal joints, contrasting with retractions of the proximal and axial joints, must be alert to Ullrich CMD. Next-generation sequencing techniques make it easier to diagnose the disease.

Keywords: congenital muscular dystrophy, Ullrich's disease, *COL6A2*, Yakut family, clinical case.

Introduction. Congenital Ullrich muscular dystrophy (Ullrich CMD, OMIM #254090) is the most severe form of collagenopathy. It was first described by Ullrich in 1930 and is associated with a deficiency of type VI collagen. Type VI collagen is a protein heterotrimer of the extracellular matrix, essential for the functioning of skeletal muscle and skin, present in the stroma of internal organs, and also forms a microfibrillar network closely associated with the basement membrane in most tissues of the body. It consists of three peptide chains, each of which is encoded by a separate gene: *COL6A1* and *COL6A2* (locus 21q22.3) and the *COL6A3* gene (locus 2q37). Mutations of these three genes lead to the development of myopathies - from the more severe form of Ullrich CMD to the milder in children form of Bethlem CMD in adults (OMIM 158810). The prevalence of Ullrich CMD is 0.13 per 100,000 population, Bethlem CMD is 0.5 per 100,000 population. In Russia there are isolated descriptions of clinical cases. The classic clinical picture includes muscle hypotonia and weakness, marked hypermobility in the distal joints, contrasting with retractions of the proximal and axial joints.

Materials and methods. Medical-genetic center of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine named after Nikolaev M.E. observed three patients from two unrelated yakut families with undifferentiated form of congenital muscular dystrophy. To diagnose these cases, clinical and genealogical examination, electroneuromyography (Neurosoft device, Ivanovo), and molecular genetic research using the massively parallel sequencing (MPS) method were carried out at the medical genetic center "Genotek" (Moscow). Validation of the results was carried out using the direct Sanger sequencing method on an automatic sequencer ABI 3500 (USA) in the research laboratory “Molecular medicine and human genetics” of the Medical Institute of the North-Eastern Federal University named after. M.K. Ammosova". The primer sequence is shown in Table 1.

The study was approved by the local committee on biomedical ethics of the NEFU named after. M.K. Ammosov" (Extract from protocol No. 22 dated February 26, 2020): carried out without violations of ethical and legal standards. All study participants signed voluntary consent.

Results and discussion. *Family 1*. Child S. born in 2009, boy, Yakut ethnic group. Only child. Parents deny consanguineous marriage. First case in the family.

From the medical history: a child from the first normal pregnancy, term birth. He screamed immediately, birth weight 2900 g, height 52 cm, Apgar score 8/9 points. Prolonged physiological jaundice was observed. Psychomotor development with delay: began to hold his head from 6 months, sit from 8-9 months, phrase speech from 2 years, intelligence was in accordance to the age, began to walk from 2 years, fell often, from 3 years he stopped walking independently. From 6 months annually underwent examination and treatment in the psychoneurological department and rehabilitation center with suspected neuromuscular disease due to the presence of signs of myodystrophy. In 2012, a child aged 3 years was sent to the Medical Genetic Center (MGC) of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine named after Nikolaev M.E. to clarify the diagnosis. At the time of examination, the child had severe muscle weakness, weight loss, and a myopathic “duck-like” gait. Can't run or jump. He holds his head satisfactorily in a sitting position, but cannot lift his head from a lying position. Sits steadily and stands up with support.

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Table 1

Sequence of primers for validation of mutations in the *COL6A2* gene using direct Sanger sequencing

Mutation	Forward (5′→ 3′)	Reverse (5′→ 3′)
c2329T>C (p.Cys777Arg)	GCG-GTG-GTC-ATC-ACG-GAC	ATC-CTG-GGC-TGC-ACA-TTC-ATC
c.1561C>T (p.Arg521Ter)	CTC-TGC-TCA-CAG-CCA-GAAC	GAC-CTA-TCC-TTC-ACT-GAG-TC

The shape of the head is hydrocephalic, high forehead, pronounced vascular pattern on the forehead. Laboratory and instrumental diagnostics were carried out. General and biochemical blood tests were without abnormalities. The level of creatinine phosphokinase is normal. A molecular genetic study did not detect deletions of exons 7 and 8 of the SMN1 gene.

In March 2014 (at 5 years old), the patient was hospitalized in the second department of psychoneurology of the Research Institute of Pediatrics and Pediatric Surgery (Moscow, Russia) in order to clarify the diagnosis. The results of laboratory and instrumental studies: general and biochemical blood tests were unchanged. According to electrocardiography (ECG), migration of the supraventricular pacemaker was recorded against the background of minor tachycardia, moderate arrhythmia, incomplete blockade of the right bundle branch, increased electrical activity of the right ventricle, and disruption of the repolarization process in the myocardium of the posterior wall of the left ventricle. Muscle MRI was performed: severe diffuse damage to the thigh muscles with the presence of a "tiger stripe" effect in the anterior group; pronounced diffuse damage to the muscles of the leg with the greatest interest in the posterior group. MRI conclusion: the MRI pattern may be consistent with collagenopathy. Based on clinical history and instrumental studies, the patient was given a clinical diagnosis of congenital muscular dystrophy, collagenopathy.

In 2017 (at 8 years), upon examination of the patient, generalized muscle weakness, wasting of all muscles, contractures of the elbow, knee, and ankle joints were revealed, contrasting with distal hypermobility; hyperkeratosis was noted on the skin. Full exome sequencing was carried out: two previously described mutations in the compound heterozygous state were identified in the *COL6A2* gene on chromosome 21: c.1561C>T (p.Arg521Ter) in exon 19 (rs773686174) and c.2329T>C (p.Cys777Arg) in exon 26 exon (rs267606747) [7, 8]. Validation of the results of exome sequencing con-

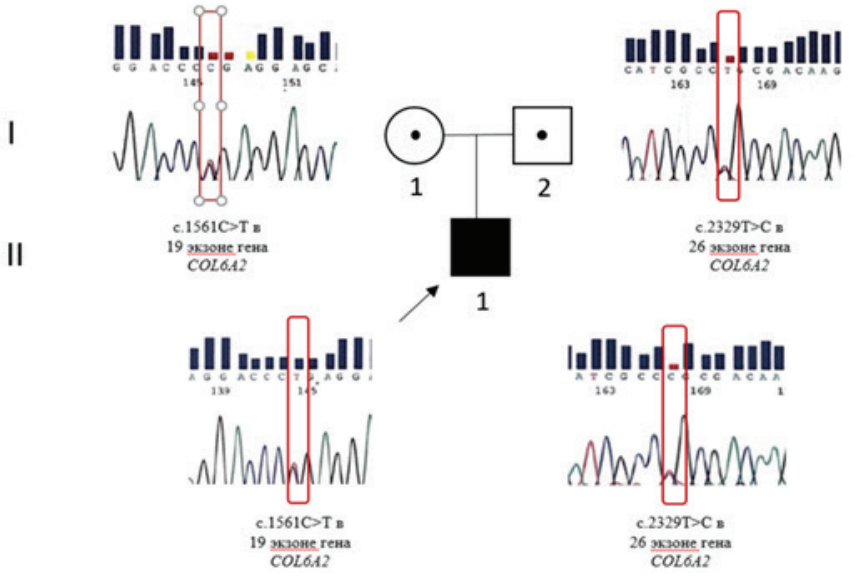

Fig. 1. A fragment of the family tree 1 is presented with the results of Sanger sequencing. I-1 mother of the proband: healthy, heterozygous carrier of the c.1561C>T mutation in exon 19 of the *COL6A2* gene; I-2 father of the proband (marked by arrow): healthy, heterozygous carrier of the c.2329T>C mutation in exon 26 of the *COL6A2* gene; II-1 proband: patient with Ullrich CMD, two mutations were found in the compound heterozygous state: c.1561C>T in exon 19 and c.2329T>C in exon 26 of the *COL6A2* gene.

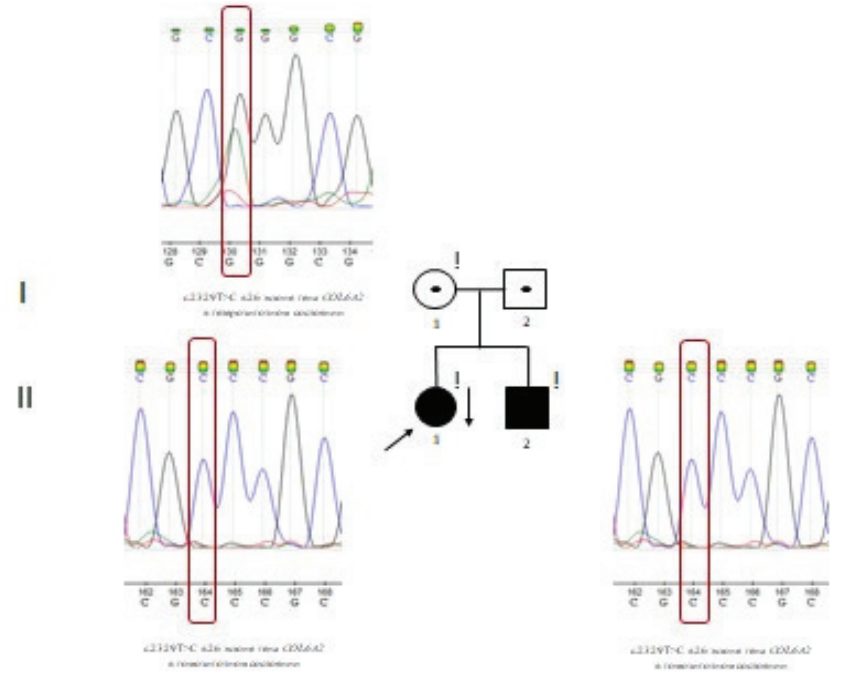

Fig. 2. The pedigree of the family 2 is presented. II-1 – proband (marked by arrow), patient with Ulrich CMD; II-2 sibling of the proband, patient with Ulrich CMD; I-1 mother of the proband, healthy, heterozygous carrier of the c.2329T>C mutation in exon 26 of the *COL6A2* gene; I-2 the proband's father is healthy (not examined), a heterozygous carrier of the mutation is assumed.

firmed the presence of a mutation in the proband; the mother was diagnosed with the c.1561C>T mutation in exon 19 of the *COL6A2* gene in a heterozygous state; the father has the c.2329T>C mutation in exon 26 of the *COL6A2* gene, also in a heterozygous state (Fig. 1). Thus, based on clinical and anamnestic data and molecular genetic analysis, the patient was given a final diagnosis of Ullrich congenital myodystrophy (OMIM #254090).

Family 2. Proband E. born in 2007, girl, Yakut ethnic group. She was observed at the medical genetic center from an early age for floppy child syndrome. The family pedigree is shown in Fig. 2.

A child from the first pregnancy, which occurred in the second half on the background of exacerbation of chronic pyelonephritis. Body weight at birth was 2880 g, height 50 cm. She screamed immediately. Psychomotor development with delay. At 7 months of age, she was consulted by a geneticist regarding floppy baby syndrome. Direct DNA diagnostics of Werdnig-Hoffmann spinal amyotrophy was carried out: no deletion of exons 7 and 8 of the SMN1 gene was detected. Repeated consultation at the age of 1 year 10 months, there were complaints of drooling and weakness. At the age of 4 years, an examination in the neuropsychiatric department revealed elevated LDH and CPK results, she was consulted by a neurogeneticist, and signs of myodystrophy were identified. The progression of the disease was noted in the form of an increase in muscle weakness, she could not sit or run on her own, she began to often stumble and fall, she stopped climbing stairs on her own, and there was a decrease in body weight. Needle EMG was not performed for technical reasons. According to stimulation electroneuromyography, a decrease in motor responses was detected.

In 2012, at 5 years old she was at the Federal State Budgetary Institution Moscow Research Institute of Pediatrics and Pediatric Surgery in the Department of Psychoneurology and Epileptology No. 1 with a diagnosis of Bethlem congenital muscular dystrophy. An MRI of the muscles was performed - a study of the muscles of the thigh and lower leg revealed dystrophic changes in the muscle's characteristic of collagenopathy. The results of a muscle biopsy revealed signs of muscular dystrophy; immunohistochemical analysis revealed the absence of collagen.

In 2018, at 11 years old, the girl was again consulted by a geneticist. At the age of 10 years, the progression of the disease was noted - she stopped

Table 2

Clinical and genetic characteristics of patients

Family	Patient	Gene, mutation	Gender	Age at which independent walking begins	Contractures	Changes in the skin	Spinal deformity	Echo-KG	CPK level (norm 38-174 U/l), LDH (norm 0-247 U/l)
I	S	*COL6A2*, c.2329T>C and c.1561C>T in compound heterozygous state	male	started walking at the age of 2	yes	hyperkeratosis	yes	Congenital heart defect: VSD	Normal CPK / Normal LDH
II	P	*COL6A2*, c.2329T>C in homozygous state	male	started walking at the age of 1 year 3 months	yes	keloid scar at the site of wound healing after muscle biopsy	yes	Signs of cardiomyopathy	CPK level is normal, LDH is increased: 253.6 U/l
	E	*COL6A2*, c.2329T>C in homozygous state	female	started walking at the age of 1 year 2 months	yes	"goose bumps", focal rounded hypertrichosis on the back, keloid scar at the site of wound healing after muscle biopsy	Yes	AV insufficiency grade 1-2. Front wall seal MV. Slight expansion of the aircraft trunk. Additional trabecula in the LV cavity	CPK level increased: 232 U/l / Normal LDH

VSD – ventricular septal defect; AV – aortic valve; MV – mitral valve; PA – pulmonary artery; CPK – creatinine phosphokinase; LDH – lactate dehydrogenase; AR – autosomal recessive type of inheritance, LV - left ventricle

walking and standing, kyphoscoliosis worsened, she began to eat and dress with outside help, and a tendency to constipation appeared. The physique is asthenic. Moves in a wheelchair. The skin is dark, «goose pimples», focal rounded hypertrichosis on the back, a keloid scar at the site of wound healing after muscle biopsy. Subcutaneous fatty tissue is underdeveloped. Severe hypotrophy of all muscle groups. Contracture of the elbow, knee, ankle joints, hypermobility of the interphalangeal joints. The face is symmetrical, no microanomalies of development were identified. The torso is proportional, the chest is deformed and flat. Severe kyphoscoliosis, flat back, "wing-shaped" shoulder blades. Neurological status: there are no abnormalities in the cranial nerves. Moderate tetraparesis. Muscle tone in the limbs is low. Hypotrophy of all muscles. Tendon reflexes from the limbs are low, D=S. There are no pathological or meningeal signs. Sensitivity is not impaired. Coordinator tests are performed satisfactorily. There are no pathological signs. Contractures of the wrist, ankle, knee, elbow joints. He can't walk on his own, he can't stand it. Speech is normal.

Results of instrumental studies. An X-ray of the thoracic spine revealed right-sided thoracolumbar kyphoscoliosis of the 2nd degree, an anomaly of the lumbosacral spine. According to the ECG, it is a variant of the age norm. According to spirometry, there is a severe disorder of the restrictive type. Obstructive type disorder of moderate severity. The patient is unable to perform forced breathing maneuvers. The child underwent molecular genetic diagnostics using the MPS method using Clinical Exome kits (Illumina Inc., USA). As a result of exome sequencing, the previously described mutation c.2329T>C (p.Cys777Arg) in exon 26 of the *COL6A2* gene was identified in a homozygous state (rs267606747), the same mutation was found in the mother in a heterozygous state, the father of the patients from DNA diagnostics refused (Fig. 2). The patient died suddenly at home from respiratory problems in 2018 at the age of 11 years.

Patient P., born in 2011, boy, Yakut ethnic group, sibling of proband E. From the anamnesis: a child from the second pregnancy, which proceeded well. Second birth, urgent. He screamed right away. Body weight at birth 4100 g, length 56 cm, Apgar 7/8 b. Early development with delay: holds head from 3 months, sits from 11 months, walks from 1 year 3 months. At 1 year 1 month. There were complaints about the lack of independent walking.

The phenotype is generally similar to his sister. The physique is asthenic. On the skin side - a keloid scar at the site of wound healing after taking a biopsy. Neurological status: no features from the cranial nerves. Moderate tetraparesis. Muscle tone in the limbs is low. Severe hypotrophy of all muscle groups. Tendon reflexes from the limbs are low, D=S. Contractures of the elbow, knee, ankle joints, hypermobility of the interphalangeal joints. Frequent falls. The gait is changed, he walks on tiptoes with support slowly. A laboratory and instrumental examination were carried out. X-ray of the thoracic spine in 2017 revealed a slightly pronounced kyphotic deformity of the thoracic spine. Needle EMG was not performed for technical reasons. Spirometry from 2018: severe ventilation impairment of mixed type. The cause was the same mutation as sister's one.

Table 2 presents the clinical and genetic characteristics of our patients with congenital Ullrich myodystrophy. When comparing probands from the two presented unrelated Yakut families, it can be noted that in a patient from the first family with a mutation in the compound heterozygous state, muscle weakness was more pronounced, the onset of walking was later than in patients from the second family, from the age of two; however, the levels of CPK and LDH were normal. In general, the clinical manifestations of the disease in our patients are the same as those described in the literature and reflect lesions associated with collagen VI deficiency.

Conclusion. Thus, in the presented families, the cause of the disease was mutations in the *COL6A2* gene of chromosome 21. In the first family, the cause was two mutations in the compound heterozygous state (c.1561C>T и c.2329T>C), and in the second family, mutation c.2329T >C in the homozygous state. Despite the rarity of Ulrich's CMD, neurologists and geneticists need to be alert to this pathology.

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SPINOCEREBELLAR ATAXIA TYPE 1 WITH CERVICAL DYSTONIA: CLINICAL POLYMORPHISM OR A COMBINATION OF TWO DISEASES? (CLINICAL CASES)

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Autosomal dominant spinocerebellar ataxias (AD SCA) can present with a wide variety of non-cerebellar symptoms, including movement disorders. In fact, movement disorders are common in many different subtypes of SCA, and they may be present, dominant, or even an isolated feature of the disease. In this article we describe 9 clinical cases of spinocerebellar ataxia type 1, the clinical picture of which includes cervical dystonia with laterocollis. In all cases, a mutation in the ATXN1 gene was detected.

Keywords: cerebellar ataxia; movement disorders; spinocerebellar ataxia; cervical dystonia.

Introduction. Spinocerebellar ataxias with an autosomal dominant pattern of inheritance are a heterogeneous group of hereditary progressive neurodegenerative diseases characterized by progressive cerebellar ataxia, dysarthria and a number of other variable neurological symptoms: pyramidal or extrapyramidal symptoms, ophthalmoplegia, cognitive dysfunction and peripheral neuropathy. Currently, more than 40 autosomal dominant spinocerebellar ataxias have been identified. AD SCA is a disease with a late onset, usually after 30-40 years, less often in childhood or in old age [1, 2]. Based on the fact that these diseases are disabling and affect mainly people of working age, the problem of research on SCA blood pressure is important in the healthcare and social care system [1]. The most common 6 types of progressive AD SCA are: 1, 2, 3, 6, 7, 17 and dentatorubro-pallidoluis atrophy (DRPA). In the Russian Federation, spinocerebellar ataxia type 1 (SCA1) has a high prevalence [4].

According to literary studies, the main neurodegenerative syndromes accompanied by muscular dystonia with an autosomal dominant type of inheritance are spinocerebellar ataxia type 3, Machado-Joseph disease, dentatorubro-pallidoluis atrophy, and Huntington's disease [1, 4, 7, 8].

Machado-Joseph disease in the modern classification is characterized as spinocerebellar ataxia type 3 (SCA3). The gene that causes this disease is located on chromosome 14 at the 14q24.3-q32 locus. The main clinical feature of SCA 3 is progressive ataxia due to dysfunction of the cerebellum and brainstem. Ataxia, however, never occurs in isolation. Numerous other clinical problems reflect progressive dysfunction of the brainstem, oculomotor system, pyramidal and extrapyramidal tracts, lower motor neurons, and peripheral nerves. The age of onset varies widely; Symptoms have been reported in individuals aged 5 to 70 years. This variability reflects differences in repeat size, with larger repeats on average leading to earlier disease development. Dystonia in the hands is often an extrapyramidal symptom; athetosis and parkinsonism are less common. A specific manifestation of the disease is the presence of the "bulging eyes" symptom, that is, the development of external ophthalmoplegia, which is observed in 30-50% of patients. When making a diagnosis, family history is important. DNA diagnostics helps to accurately determine the disease [4, 8].

Dentatorubropallidoluis atrophy is an autosomal dominant spinocerebellar ataxia caused by a CAG repeat expansion in the *ATN1* gene, which is located on chromosome 12p13 [2]. Pathological CAG repeats reach 48 or more repeats, and the age of onset and clinical severity of the disease correlates with the length of the CAG repeat. The symptoms of dentatorubro-pallidoluis atrophy are extremely polymorphic. The disease can begin between the 1st and 6th decades of life and manifests itself in the form of horseathetosis, ataxia, dementia, myoclonus, epileptic seizures, and less commonly, dystonia [2, 3]. An important role in diagnosis is played by DNA analysis and neuroimaging methods, which make it possible to identify atrophic changes in the tectum of the brain [4]. It is worth carrying out a differential diagnosis with Huntington's disease, which occurs in the juvenile Westphal variant, observed in 5-10% of cases. The core of the clinic is muscle rigidity; in adolescents, dystonia, myoclonus, athetosis, and convulsions may occur; hyperkinesis in the form of chorea may be absent or manifest only in the oromandibular muscles. Characterized by changes in behavior, memory loss, and criticism. An accurate diagnosis is esTableished after a molecular genetic study [4, 8].

In the available literature, we did not find clinical descriptions of SCA type 1 in combination with cervical dystonia. The presented clinical cases will help neurologists in their practical activities when making a diagnosis in such cases and developing a personalized approach to their management.

Material and research methods. Written informed consent for the study was obtained from all patients. The severity of ataxia was assessed using the Scale for Ataxia Assessment and Rating (SARA).

Research materials. Patients included in the registry of the YSC CMP for SCA type 1 (n=9)

Inclusion criteria:

1. The age of patients is over 18 years;
2. A molecular diagnosis confirmed in patients with a mutation in the *ATXN1* gene;

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3. Clinical picture with symptoms of cerebellar ataxia and muscular dystonia;
4. Voluntary informed consent for inclusion in the study.

Exclusion criteria:

1. Absence of a molecular diagnosis with a mutation in the *ATXN1* gene;
2. Absence of symptoms of muscular dystonia in the clinical picture of cerebellar ataxia;
3. Age less than 18 years;
4. Refusal of the patient to participate in a scientific study.

Research methods

1. Clinical method for identifying the onset and course of ataxia, the addition of symptoms of muscular dystonia;
2. Genealogical method to identify the type of inheritance;
3. Scale for Ataxia Assessment and Rating (SARA);
4. Statistical research method. Statistical processing was carried out using the IBM SPSS Statistics 27 application package using standard methods of variation statistics: medians (Me), quartiles (Q1; Q3) were calculated.

Table 1 shows the median age of onset in the studied patients and the manifestations of their clinical syndromes of the disease. The data from the Table corresponds to the indicators of other scientific studies on SCA1 [1, 2, 3].

Table 1

Clinical characteristics of the examined group of patients with spinocerebellar ataxia type 1

Indicator	Median age M(Q1;Q3)
Age of disease onset (years)	53(44;59)
Duration of disease (years)	14(9;19)
Age of onset of cerebellar syndrome (years)	32(24;42)
Age of onset of dystonic syndrome (years)	45(32;52)
SARA scale (points)	20(16;25)
Number N of repetitions	30(27;30)
Number of pathological repetitions	48(42;50)

Table 2

Symptoms of cerebellar and dystonic syndrome

Symptoms of cerebellar syndrome	Number of patients N	Symptoms of dystonia in patients with cerebellar syndrome	Number of patients N
Ataxia of the limbs and trunk, slow saccades, scanned speech, dysarthria, dysphagia	9	Laterocollis Laterocollis with corrective gesture Laterocollis with dystonic head tremor	4 1 3

From Table 2 it follows that all patients had clinical manifestations of both cerebellar syndrome and dystonic syndrome. At the same time, dystonic syndrome manifested itself only as a focal form of muscular dystonia – cervical dystonia with laterocollis. In one patient it was accompanied by a corrective gesture, in three patients it was accompanied by dystonic head tremor.

Table 3

Manifestations of dystonic syndrome in the parent and siblings

Пациент	Number of sick sibs in the family	Manifestations of dystonia syndrome in parents and siblings	Gender	Type of inheritance	Place of birth of parent\place of residence	Number of CAG repeats	Botulinum therapy
1	0	Нет	Ж	ADT of inheritance through the mother	Namsky district\ Amginsky district	28/48	no
2	0	Нет	Ж	ADT of inheritance through the father	Abyisky district/ Abyisky district	30/52	no
3	3	Нет	М	ADT of inheritance through the mother	Abyi district. Yakutsk	27/43	Yes (with good effect)
4	4	Нет	Ж	ADT of inheritance through the mother	Ust-Aldansky district / Ust-Aldansky district	Unknown, because the result was lost by the patient	no
5	0	Нет	Ж	ADT of inheritance through the father	Lensky district/ Namsky district	25/42	Yes (with reduction of dystonic tremor)
6	1	Yes, his sister has SCA type 1	М	ADT of inheritance through the father	Tattinsky district / Tattinsky district	30/53	no
7	1	Yes, her brother has SCA type 1	Ж	ADT of inheritance through the father	Tattinsky district / Tattinsky district	30/53	no
8	2	Нет	Ж	ADT of inheritance through the mother	Tattinsky district / Tattinsky district	29/40	no
8	0	Нет	Ж	ADT of inheritance through the mother	Abyisky district / Yakutsk	28/43	Yes (no significant effect)

Table 3 shows the results of the genealogical research method, which show the manifestations of dystonic syndrome in parents and siblings of patients with SCA type 1. Patients 6 and 7 are siblings. However, the father did not experience symptoms of cervical dystonia, who died at the age of 59 years. It is worth noting that in patient No. 7, cervical dystonia was diagnosed before the symptoms of ataxia. In the remaining patients, no hereditary form of SCA type 1 with dystonia was observed in relatives. According to genealogical inheritance, the mutation in the *ATXN1* gene was transmitted through the maternal line in 5 cases. On the paternal side in 4 cases. There were more natives from the Abyisky and Tattinsky districts, which are geographically located at a distance of 1800 km from each other. Abyisky ulus is located in the tundra arctic zone, and Tattinsky in the central zone of the Republic of Sakha (Yakutia). Botulinum therapy was performed in 3 patients, with a positive effect in 2 cases. The rest were not carried out due to the severity of the condition and the patients' disagreement with the procedure.

Conclusion. Thus, the study showed that in hereditary SCA type 1, manifestations of muscular dystonia may occur in the form of its focal form - cervical dystonia. Is this a manifestation of clinical polymorphism or is it a combination of two neurodegenerative diseases, when the olivopontocerebellar neurodegenerative process is a trigger for the development of further neurodegeneration in a certain area of the extrapyramidal system? The answer to this question can be provided by further molecular genetic studies, namely whole-genome sequencing. Considering the positive effect of botulinum therapy for cervical dystonia in practical medicine, this treatment method may become promising in the management of patients with SCA type 1 and improve their quality of life.

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A CLINICAL CASE OF THE EFFECTIVE USE OF VALVE BRONCHOBLOCATION IN THE COMPLEX TREATMENT OF A PATIENT WITH CASEOUS PNEUMONIA WITH MULTIDRUG RESISTANCE OF THE PATHOGEN TUBERCULOSIS

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Valvular bronchoblocation is a minimally invasive non–drug method of treating pulmonary tuberculosis and its complications. The method is based on the creation of therapeutic hypoventilation in the affected area of the lung while maintaining the drainage function of the bronchus by installing an endobronchial valve in its lumen. The article describes a case of effective application of the valvular bronchoblocation method in an acute progressive form of tuberculosis - caseous pneumonia, in a patient with multidrug-resistant tuberculosis pathogen (MDR MBT).

Keywords: tuberculosis, method of treatment, valvular bronchoblocation, effectiveness of treatment, multidrug resistance, causative agent of tuberculosis.

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Introduction: One of the main obstacles to achieving success in eliminating tuberculosis is multidrug-resistant tuberculosis (MDR-TB) [4]. Valvular bronchoblocation (CBB) is a minimally invasive non–drug method used in the complex treatment of pulmonary tuberculosis and its complications. The method is based on the creation of therapeutic hypoventilation in the affected area of the lung while maintaining the drainage function of the bronchus by installing an endobronchial valve (EC) into its lumen. The EC is designed in such a way that with

intense exhalation and coughing, air and bronchial contents exit through it from the blocked area of the lung, and when inhaled, atmospheric air does not enter there, this leads to local collapse of the lung, sometimes up to atelectasis. The valve is installed during fibrobronchoscopy under general or local anesthesia [5].

Also in recent years, the installation of endobronchial valves has been used to accelerate the repair processes in patients with destructive tuberculosis with multiple and broad drug resistance (MDR and XDR) [2]. The possibilities of conservative treatment in such patients are often exhausted, and surgical treatment is possible only in 15% of them due to concomitant diseases and/or the prevalence of the process [3]. Currently, there are already many reports on the effectiveness of using the valvular bronchoblocation method, among the first were publications on the treatment of decay cavities in the infiltrative form of tuberculosis, including drug–resistant mycobacterium tuberculosis (MBT) [1].

Here is an example of successful treatment of a patient with an acute progressive form of pulmonary tuberculosis - caseous pneumonia in the phase multidrug-resistant MBT inseminations with the use of CBB during the intensive phase of chemotherapy in inpatient settings.

A clinical example. Patient A. Age: 30 years old, mechanic-car mechanic.

Anamnesis of the disease: He became acutely ill, had an increase in body temperature to 38.5 ° C, was treated independently. Before the disease, FLH did not pass for 2 years. I went to the polyclinic and as a FLG (+) was sent for a computed tomography (CT) of the chest organs (OGK). Conclusion dated 02/21/2022: Infiltrative-destructive-focal changes in the upper lobe of the right lung, infiltrative-focal changes in S4,5,6,9,10 of the right lung and in S1-2, 4,5,6 of the left lung.

Anamnesis of life: Born in ulus. Secondary education, worked as a mechanic. He is married and has 2 children. Bad habits: smokes half a pack a day; drinks alcohol, has been registered with a narcologist since 2020. Drug use: denies. Previous diseases: acute respiratory viral infections. The presence of hepatitis, venereal, oncological diseases in oneself and relatives: denies. Chronic diseases: gastritis. Allergic history: not available for food, not available for medicines. Blood transfusion: denies. Frostbite at the age of 12 of the right hand.

Epidemiological history: he was not ill with a new coronavirus infection (NCVI). I have not received vaccinations against covid-19, influenza. Over the past 14 days, he has denied contact with infectious patients. I have not traveled outside the RS. According to him, he has not been in contact with tuberculosis patients.

He was admitted for inpatient treatment on 03/05/2022. with a diagnosis of Caseous pneumonia of the upper lobe of the right lung with insemination. MBT (+), MDR MBT was taken for the following drugs: isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, levofloxacin, cyclocerin, ethionamide, ofloxacin (H,R, S,E,Z, Lfx,Cs,Eto,Ofx).

Concomitant diseases: Chronic bronchitis. Amputation stumps of the fingers of the right upper and lower extremities n/a frostbite n/a Peptic ulcer of the stomach. the ulcer of the prepiloric department is associated with HP+ in the scarring stage. Duodenogastric reflux. Duodenite.

Upon admission, he complained of coughing with foamy sputum, an increase in body temperature to 39.5 °, weakness, chest pain, weight loss of 10 kg per month, poor appetite.

According to the examination, anemia was noted in the general blood test (hemoglobin – 99 g/ l), lymphocytopenia – 9%, ESR – 36 mm per hour. In a biochemical blood test, an increase in CRP to 216 mg / l.

Microscopic examination of sputum on MBT is positive. MDR to H,R,S,E,Z,Lfx-,Cs,Eto,Ofx from 03/9/12 by seeding on dense nutrient media.

He was treated in the department of multidrug-resistant tuberculosis. In the hospital, he received chemotherapy for intensive phase IV of the standard regimen – 240 doses (5 drugs); bedaquiline (Bq) – 400 mg per day, linezolid (Lzd), - 600 mg 1 time per day intravenously, moxifloxacin (Mfx) - 400 mg, 1 time per day orally, amikacin (Am).– 930 mg 1 time per day, orally, delamanide (Dlm) – 100 mg 2 times a day.

Due to the prevalence of the process and resistance to 9 anti-tuberculosis drugs, the patient was selected for valvular bronchoblocation (CBB) at a medical commission with the participation of the attending physician, the head of the department and an endoscopist. CBB was

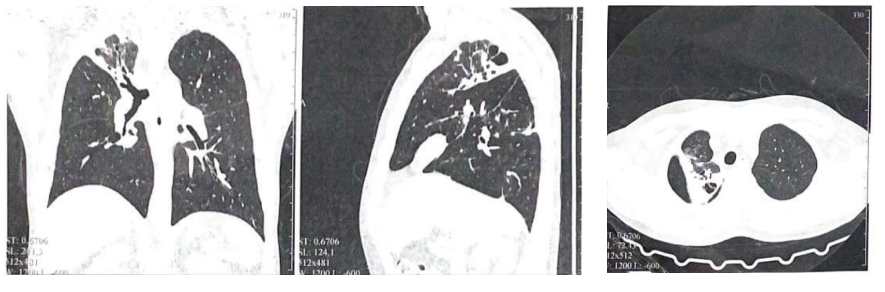

Fig. 1. Computed tomography of the chest organs from 11.09.22. to the installation of CBB

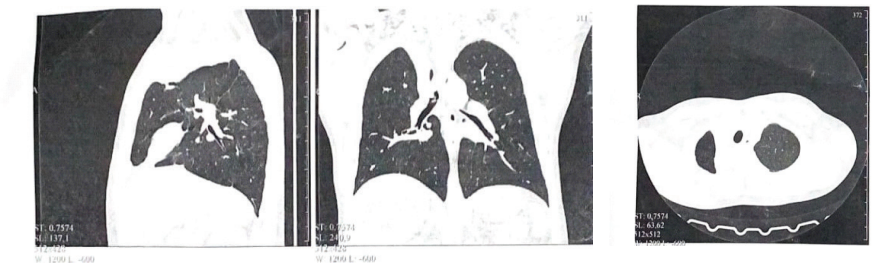

Fig. 2. Computed tomography of the chest organs from 10/31/12 after the installation of CBB

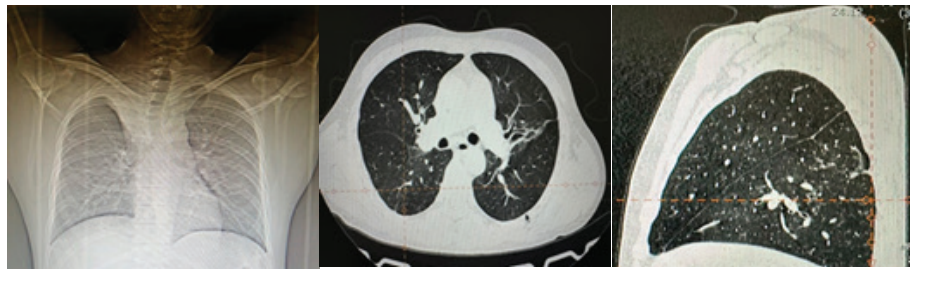

Fig. 3. Computed tomography of the chest organs from 04/15.24

performed on 11.10.2022 under combined endotracheal anesthesia, FB15 V(3) device; tracheoscope No.14.

From the protocol: intubation with tracheoscope No. 14. The mucous membrane of the trachea is hyperemic. Karina is sharp and mobile. The bronchial mucosa is hyperemic. There is a viscous mucosa of sputum in the lower parts. Sanitation, aspiration. Into the lumen of the right upper lobe bronchus (PVDB) KBB No. 11 is installed, the fixation is good, the KBB is functioning. The mouths of the remaining bronchi can be traced to 4-5 orders of magnitude in the lumen of mucous sputum, aspiration.

Conclusion: KBB PVDB. Recommended: Antitussive drugs, R-control.

Objective examination: Heart rate 70 in 1 min. BDD 16 in 1 min. Blood pressure 120/70 mmHg. t° 37.5°.Objectively: general condition: moderate severity, Consciousness: clear Position of the patient: active, Peripheral lymph nodes: enlarged, Skin: clean, moist, normal color. Auscultation breathing: carried out in all fields to the right of the wheezing from the KBB. Heart tones: muted, rhythmic. Tongue: moist, clean. Abdomen: not enlarged, soft, painless, Liver: not enlarged, elastic, consistency Spleen: not enlarged. Peripheral edema: no, Urination: free, painless, Stools: daily, every other day, decorated.

Prior to the esTableishment of the CBB, in the protocol of the OGK CT examination dated 11.09.22. (photo 1) it was revealed that the upper lobe of the right lung is reduced in volume. In S1, S2, and partially S3 of the right lung, a compaction of the lung tissue with cavities (up to 2.1x2.6 cm in size) and bronchial lumen in the structure is revealed. Foci of low and medium intensity can be traced in the adjacent lung tissue. In S3, S4, S5 of the right lung, there is a compaction of lung tissue with bronchial lumen in the structure. In S5, S6, S10 of the right lung, S6, S9 of the left lung, foci of medium intensity up to 0.5 cm in size are determined. Bronchi are visualized to a sub-segmental level, the lumen of the segmental bronchi is not changed.

In the upper mediastinum, the lymph node of the retrocaval space is up to 1.0 cm in size, the tracheobronchial space is up to 0.9 cm in size. There is no free fluid in the pleural cavity.

In the protocol of the OGK CT examination dated 31.10.22. (photo 2) the positive dynamics of the process has been revealed. In dynamics, there is a complete resorption of areas of inflammatory pulmonary tissue compaction by the type of frosted glass, without clear contours in S4,8,9 of the right lung. The upper lobe of the right lung is reduced in volume, atelectatized, and KBB is traced at the level of PVDB. In S3, S4, S5 of the left lung, there is a decrease in the volume and compaction of lung tissue with lumen of expanded bronchi in the structure, due to fibrous changes. In S5, S6, S10 of the right lung, S6 of the left lung, scattered foci of various sizes of medium intensity are detected against the background. In dynamics, in S6 of the right lung, foci decreased in number, in S10 of the right lung, a small thin-walled cavity decreased in size to 0.5x0.3 cm. Bronchi are visualized to a subsegmental level, the walls of segmental bronchi are compacted.

The roots are structural. The mediastinum is slightly shifted to the right, the trachea is also slightly curved to the right. In the mediastinum there is a lymph node of retrocaval space up to 0.6 cm in size, tracheobronchial space up to 0.8 cm in size. There is no free fluid in the pleural cavity.

Since June 2022, he has had 13 negative sputum culture results on MBT. Since 11/29/12, he has been abacillated, the patient has been removed from the bacillarity register. The patient was discharged from the hospital on 11/30/12, transferred to the continuation phase up to 310 doses on an outpatient basis. Terizidone (Trd) was prescribed – 500 mg per day, sparfloxacin (Sfx) – 200 mg per day, aminosalicylic acid (Pas) – 800 mg per day, up to 310 doses. Extract from the minutes of the meeting of the medical commission No. 234 MDR dated 05/16/2023 Diagnosis: A16.0 Cirrhotic tuberculosis of the right lung. KBB PVDB dated 10.11.22 A18.3 Intestinal tuberculosis in the subsiding stage I MBT(-) MDR HRSEZLfxCsEtoOfx from 03/9/12

In the protocol of the OGK CT examination dated 04/15.24. (photo 3) in dynamics, the upper lobe of the right lung is reduced in volume, atelectatized, and the valvular bronchoblocker remains in the PVDB. S3, S4, S5 of the left lung are reduced in volume due to fibrous changes with expanded bronchial lumen in the structure. In conclusion, atelectasis of the upper lobe of the right lung, the condition after CBB of the right upper lobe bronchus. Formation of fibroatelectasis in S3, S4,S5 of the left lung. Foci in S5, S6, S10 of the right lung. Positive dynamics.

At this time, the patient is being monitored in the III group of dispensary supervision, the patient has no adherence to treatment, did not visit a phthisiologist regularly, deblocking was scheduled for the end of April 2024.

Conclusion. It should be noted the high efficiency of this method in the complex treatment of the patient. Based on the presented clinical observation, it can be concluded that in cases where the patient has multidrug resistance of Mycobacterium tuberculosis and a widespread tuberculous process in the lungs, in our example caseous pneumonia, it is advisable to use valvular bronchoblocation. The method of temporary occlusion of the bronchi of CBB allows to achieve closure of the decay cavities, sanitation of the pleural cavity and in many cases to avoid surgical intervention.

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CLINICAL CASE OF WILLEBRAND DISEASE COMBINED WITH CROHN'S DISEASE IN AN ADOLESCENT SAKHA

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The article presents an interesting clinical case of Willebrand's disease in combination with Crohn's disease and congenital heart disease in a 17-year-old Sakha teenager. Such clinical cases are rare in the public literature, since the combination of these diseases is practically not found. The onset of Crohn's disease at the age of 16 significantly affected the development and severity of clinical manifestations. Therapy with a genetically engineered biological drug and substitution therapy made it possible to achieve clinical and laboratory remission.

Keywords: Willebrand,s disease, Von Willebrand,s factor, homeostasis, Crohn,s disease, congenital heart disease.

Introduction. Von Willebrand disease (WD) is an inherited disease that occurs with quantitative or functional von Willebrand factor deficiency. Willebrand factor is a glycoprotein involved in hemostasis, synthesized in endothelial cells and megakaryocytes. After transcription and translation, it binds to form dimers and then the von Willebrand factor propetide is cleaved and secreted into the vessel lumen. Willebrand factor functions as a factor VIII carrier and aids in platelet adhesion and binding to endothelial components after vascular injury. Any qualitative deficiency leads to bleeding and this syndrome is called von Willebrand disease [7,8,11].

Hereditary phenotypic forms of von Willebrand disease are: Type 1: Autosomal – dominant disease caused by partial quantitative deficiency of von Willebrand factor; type 2: Autosomal – dominant disease caused by several qualitative defects of the Willebrand factor. It has four subtypes – 2A – AD (AR), 2B – AD, 2N – AD, 2M – AD. Of there, the most common is 2A; type 3: Autosomal recessive disease caused by a complete defect of the von Willebrand factor, where the levels of the factor are not detected, and is manifested by a severe bleeding disorder [4, 9].

The incidence of von Willebrand disease is 1% in the population, the prevalence is 1 – 2 people per 10,000 population, while the severe course of the disease is observed in 125 patients per 1 million people [3, 10].

Diagnosis of BV is complex and often requires evaluation with bleeding assessment tools, family history, and in – depth laboratory testing. Bleeding symptoms do not always correspond to levels of von Willebrand factor or factor VIII activity, and may also vary depending on type, age and sex, which complicates both diagnosis and treatment [6].

The tendency to bleed is usually proportional to the degree of Willebrand factor deficiency, since Willebrand factor is a carrier of factor VIII in circulating blood [5]. Thus, in BV, the goal of treatment is to correct the double defect of hemostasis – impaired internal coagulation due to low levels of factor VIII.

Crohn's disease is a chronic inflammatory bowel disease, with predominant damage to the ileum and colon, any part of the gastrointestinal tract can also be affected. It is characterized by the formation of granulomas in the affected area of the intestine, later it captures the deep layers, affecting the entire thickness – transmural lesion. The disease is complicated by systemic organ damage [1, 2].

The combination of von Willebrand disease and Crohn's disease is rare in the literature, and since both diseases affect the hemostasis system in different directions, the management of patients should be carried out by a multidisciplinary team of doctors [1].

The purpose of the study: to describe a clinical case of the course of von Willebrand disease, Crohn's disease and congenital heart disease in a 17 – year – old teenager.

Anamnesis: a child from 8 years old is registered with a hematologist with a diagnosis of von Willebrand disease. 1 type. At the onset of the disease, heavy nasal bleeding was noted, followed by severe anemia (hemoglobin level up to 40 g/l). The diagnosis was first made in March 2014, based on medical history, typical clinical manifestations, characteristic laboratory data (activated partial prothrombin time (APTT) – 51 seconds, Willebrand factor – 1%, VIII and IX clotting factors – 100%). Replacement therapy was prescribed: 500 IU of coagulation factor VIII; 1200 IU von Willebrand factor in the prophylaxis regimen 2 times a week. At the age of 12 in 2018 an episode of severe iron deficiency anemia (hemoglobin 40 g/l) was detected, stopped by the administration of perenteral iron intravenously by drip. At 16 years old in 2022 again profuse nasal bleeding, decreased appetite, paraclinically – hemoglobin 43 g/l. He was hospitalized at the place of residence, received EMOLT replacement therapy (erythrocyte mass depleted of leukocytes and platelets) with a positive clinical and laboratory effect.

To determine the cause of anemic syndrome and to correct therapy for von Willebrand disease in august 2023, was sent to the oncohematological department of the Pediatric Center of National Center of Medicine named after M.E. Nikolaev.

Complaints upon admission: according to the mother, they noticed dark feces, dizziness, tremors of the hands. The child did not receive replacement therapy for the underlying disease due to complex venous access.

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On examination: moderate condition due to anemic and asthenic syndromes. Height – 161cm, weight – 55.4 kg. Respiratory rate – 20 per minute. Saturation – 99%. Heart rate – 77 per minute. BP – 120/65. Appetite is broken. Sleep is calm. The consciousness is clear. The physique is correct. The throat is not hyperemic. The mucous membranes of the mouth and pharynx are clean, pale in color. Nasal breathing is free. Osteoarticular system without features. Lymph nodes are not enlarged. The chest is of regular shape. Percussion – clear pulmonary sound is all fields. Vesicular breathing, no wheezing. Heart tones are clear, rhythmic. The abdomen is soft, painless. Liver and spleen were not enlarged. Urination is free, painless. No peripheral edema.

He was examined by otolaryngologist and pediatric surgeon to exclude acute surgical pathology.

Paraclinically:

Complete blood count from 22.09.2023: Hb-60g/l; RBC-2,4x10^{12}/l; PLT-250x10^{9}/l; WBC-16.8x10^{9}/l; lymphocytes – 12%; monocytes – 0.4x10^{9}/l; stab neutrophils-8%, eosinophils-3%, ESR to Panchenkov-20mm/h. Conclusion: decreased hemoglobin, erythrocytes, lymphocytosis, leukocytosis, neutrophil shift of the leukocyte formula, increased ESR.

Clotting time – 13min, Activated Partial Prothrombin Time – 51sec.

Biochemistry analysis of the blood from 22.11.2023: ALT-10U/L; AST-8.9U/L; C-reactive protein-114.9mg/L; total protein-65.8g/L; urea-4.00mmol/L, glucose-5.75mmol/L; creatinine-49.4mmol/L. Conclusion: creatinine, C-reactive protein increased.

Abdominal ultrasound from 26.09.2023: Liver not enlarged. Intrahepatic bile ducts are not dilated. Vascular pattern preserved. Hepatic veins are not dilated.

Echocardiography from 28.09.2023: Congenital heart disease. Perimembranous ventricular septal defect. Open oval window-0,24cm. Additional trabecula in the left ventricular cavity.

Computed tomography from 06.10.2023: Focal and infiltrative changes in the lung parenchyma were not detected.

Colonoscopy from 22.09.2023: The lumen of the cecum is narrowed by 1/3 due to edema of the bauginium shutter, the mucous membrane of the bauginium shutter is sharply edematous and hyperemic, with multiple ulcers up to 2.0cm, with fresh undercut edges, the crater is covered with fibrin. The mouth of the flap is spasmed, not passable. The rest of the examined areas of the colonic mucosa are undistinguished. Intestinal mucosa fragments were taken for histological examination. Microscopic description: foci of lymphoid infiltration with single lymphoid follicles were found in the material of the small intestine mucosa. Conclusion: Terminal ileitis. Crohn's disease. Active stage with ulcers and strictures.

Based in complaints, medical history, clinical symptoms and laboratory and instrumental data, the patient was given the main clinical diagnosis: von Willebrand disease. Type1. Concomitant diagnosis: Crohn's disease. Active stage with ulcers and strictures. Congenital heart disease.

Perimembranous ventricular septal defect. Open oval window. Additional trabecula in the left ventricular cavity. Anemia of mixed genesis, severe. Iron deficiency and vitamin V12 – deficiency anemia. Clinically, the combination of these diseases is manifested by a pronounced asthenic syndrome.

Treatment was prescribed: replacement therapy – clotting factor VIII – 500IU, Willebrand factor – 1200IU, intravenous drip pulse therapy with methylprednisolone succinate – 500mg in sodium chloride solution. Against the background of therapy, clinical and laboratory positive dynamics is noted. Additional examination in the federal center is recommended.

In January 2024 the patient was examined at the National Medical Center for Childrens Health of the Ministry of Health of the Russian Federation. Clinical diagnosis: Hereditary deficiency of factor VIII, von Willebrand disease. Type1. Crohn's disease 1b. Ileite and colitis (L3). Stenotic form (B20), no growth retardation (GO). Congenital heart disease. Ventricular septal defect – 0.27cm. Perimembranous ventricular septal defect. Open oval window – 0.24cm. Additional trabecula in the left ventricular cavity. Bilateral deafness. Iron deficiency anemia. Vitamin V12 – deficient anemia. High – grade myopia.

Therapy with Adalimumab (Humira) 40mg 1 every 2 weeks (every 2 weeks) was initiated continuously. As replacement therapy, the patient was recommended to continue replacement therapy: Coagulation factor VIII 500IU+Willebrand factor (Gemate) at a dose of 1200IU 3 times a week.

Over time, improvement – in the complete blood count of 26.01.2024: Hb – 124g/L; RBC – 5.35x10^{12}/L; PLT – 343x10^{9}/L; WBC – 6.21x10^{9}/L; LYMF – 1.46%; monocytes – 7.4x10^{9}/L; stab neutrophils – 3%; segmented neutrophils – 62%; eosinophils – 0.04%; determination of ESR by Panchenkov – 9mm/h.

Treatment follows clinical guidelines for two major diseases (Crohn's disease and hereditary deficiency of clotting factor VIII and von Willebrand disease). Combination therapy with Adalimumab and blood coagulation factor VIII+von Willebrand factor (Gemate) improved the patient's condition and normalized peripheral blood counts.

Conclusion. This clinical case of a child with von Willebrand disease is aggravated by the onset of Crohn's disease at the age of 16, which was clinically manifested by the development of severe hypochromic anemia against the background of ulcers of the large intestine. Against the background of therapy of Crohns disease with a genetically engineered biological drug and replacement therapy of Willebrand disease, the child has a persistent clinical and laboratory remission. The management of this child requires a multidisciplinary team: pediatrician, hematologist, gastroenterologist, cardiologist

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INTRADURAL LIPOMA IN A NEWBORN

Intradural lipoma (spinal cord lipoma) is a rare benign tumor in the spinal cord consisting of white fatty tissue. The article presents a clinical case of intradural lipoma in a newborn.

Keywords: newborn, intradural lipoma, spinal cord, tethered spinal cord syndrome, skin appendage, surgical treatment.

Introduction. Intradural lipoma is a rare benign tumor of white fatty tissue inside the spinal cord. This formation of dysembryogenetic genesis is located in the lumbar-sacral region, originating from the conus of the spinal cord. The clinical picture of intradural lipoma includes: rudimentary appendages (tail), hypertrichosis, subcutaneous formation in the lumbar region of a soft-elastic consistency. Intradural lipomas limit the mobility of the spinal cord, which is called tethered spinal cord syndrome [5;6].

Tethered spinal cord syndrome (TSCS) is a complex of pathological symptoms that is caused by tension of the spinal cord due to fixation of its caudal part [1]. Received widespread publicity in 1976, neurologist Hoffman published observations of typical symptoms in 31 patients. In children, the true incidence is unknown. According to some data, 0.8-1.4 cases per 1000 live births [9;11]. Risk factors include folic acid deficiency in the first trimester of pregnancy. TSCS is manifested by impaired sensitivity and motor function of the lower extremities, dysfunction of the pelvic organs, and skin symptoms in the lumbar region [8]. Surgical treatment consists of eliminating fixation factors: removal of pathological tissue (lipomas, dermal sinus), excision of the pathologically altered filament terminale. The earlier the surgery is performed, the lower the patient's risk of developing severe neurological deficits in the future.

Clinical case. Below is a clinical case of a newborn with a congenital malformation of the musculoskeletal system and tethered spinal cord syndrome at the State Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine named after M.E. Nikolaev, Perinatal Center.

The child was born to a 26-year-old woman from the first pregnancy, which occurred in the 1st trimester цшер grade 1 anemia (she took Maltofer), and in the 2nd trimester with shortness of breath. She was observed by a cardiologist with cardiac arrhythmias - frequent single extrasystole with episodes of bigeminy, trigeminy, quadrigeminy. Rare single supraventricular extrasystole, no treatment was carried out. Taking into account the Rh negative blood type - blood group AB(IV) Rh(-), Rh immunization was carried out at 30 weeks. Prenatal ultrasound diagnostics carried out within the screening period without any special features. The boy was born from the first spontaneous labor at 39.1 weeks in a cephalic presentation, after medical preparation of the birth canal with mifepristone. The condition of the child at birth is satisfactory, the Apgar score is 8/10 points. Physical parameters correspond to gestational age: birth weight 3300 g, body length 54 cm, head circumference 34 cm, chest circumference 33 cm. Among the features of the course of labor is a long anhydrous period of 12 hours, the waters are light. From the first hours of life, the child is breastfed. During the initial examination on the mother's abdomen in the delivery room, special attention was drawn to a soft tissue formation (dimensions 1.5x1.5 cm) in the sacral region, from the top of which a "tail" up to 2.0 cm long extends.

From the medical history of the child's mother it is known: she has been registered with the antenatal clinic since the early stages of pregnancy, and has regular visits. Denies bad habits, injuries, surgeries, blood transfusions. Gynecological diseases - ovarian cyst, cystectomy in 2022. Common diseases - chicken pox, rubella, acute respiratory infections, chronic bronchitis. The epidemiological history is calm. In a registered marriage, the husband is 25 years old, healthy, not burdened by heredity.

At the age of 3 days of life, a newborn boy was transferred from the neonatal department to the pathology department of newborns and premature infants for further examination and treatment with a diagnosis of: Q 79.9 Congenital malfor-

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mation of the musculoskeletal system, unspecified.

At the time of examination at the Department of Pathology of Newborns and Premature Children, the boy's weight was 2980g (weight loss 9%). The condition is moderate according to the disease. On examination he is active, has an emotional cry, and opens his eyes. The physique is proportional. Breastfed. Muscle tone is physiological, reflexes are evoked, d = s. In particular, support reflexes, automatic walking, plantar reflex are symmetrical, physiological. The head is round in shape. Large fontanelle 1.0x1.0 cm. The seams are tight. Skin with icterus zone 3-4 according to Kramer, elements of toxic erythema throughout the body. According to bilitest 50/40 units. Continuous phototherapy was prescribed. The umbilical remnant is in a bracket, the periumbilical area is without signs of inflammation. Auscultatory breathing is puerile, there are no wheezes. BH 56 per minute. Heart sounds are clear and rhythmic. Heart rate 140 per minute. The abdomen is soft and accessible to palpation. The liver and spleen are not enlarged. Urinates on his own in his diaper. There was no stool during the examination. External genitalia according to the male type, testicles in the scrotum. No dysfunction of the pelvic organs was noted during the observation period.

Locally in the sacral region there is a soft tissue formation measuring 1.5x1.5 cm, from the top of which there is a "tail" up to 2.0 cm long (Fig. 1).

The newborn was consulted by specialists in the Perinatal Center of the "Republican Hospital No. 1-National Center of Medicine named after M.E. Nikolaev" of the Ministry of Health of the Republic of Sakha (Yakutia) in Yakutsk.

The child was examined by a surgeon (1st day of life): formation of the sacral region. An MRI examination was prescribed to exclude a connection with the spinal canal, with a subsequent decision on surgical treatment. Surgeon (10th day of life): stigmas of dysembryogenesis, skin growth in the coccygeal region. - Planned excision of the formation under local anesthesia is recommended.

Consulted by a neurosurgeon: intradural lipoma at level S 4.5. Fixed spinal cord. Skin formation in the gluteal region on the right. It is recommended that MRI of the lumbar spine and sacral spine be performed once a year.

Paraclinically: In the general blood test on the 4th day, moderate reticulocytosis is noted, other indicators for the entire observation period are within the age norm. In a biochemical blood test,

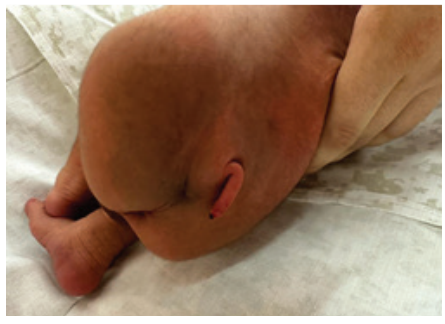

Fig. 1. Third day of life

hyperbilirubinemia is noted from the 4th day of life due to the indirect fraction of bilirubin. Indicators of the acid-base state of the blood are within the References values. The general urine analysis was unremarkable.

Ultrasound examination of the brain, abdominal organs, cervical spine - without pathologies. According to ultrasound, the thymus gland shows a moderate increase due to its width. Echocardiography is unremarkable. Electrocardiogram - sinus rhythm with heart rate 155 per minute. Electrical axis of the heart sharply to the right. Block of the posterior branch of the bundle branch. Violation of intraventricular conduction. The potentials of the right ventricle are increased.

Conclusion of magnetic resonance imaging of the lumbosacral spine and spinal cord: at level S 4.5, an intradural lipoma measuring 5x6x11 mm is determined. The spinal cord is fixed to the lipoma. In the soft tissues of the gluteal region on the right, a soft tissue structure measuring 18x4 mm is detected on the skin.

Surgical intervention was performed on the 11th day of life (Fig. 2): in the department of pediatric surgery, under local anesthesia with novocaine 0.5% - 0.2 ml, the skin appendage of the coccygeal region was cut off with an electric knife, with the application of 1 suture. After 10 days, the suture is removed, the postoperative area is without any features.

Histology of the skin appendage: skin with underlying fibro-fatty tissue.

The child was discharged on the 14th day (Fig. 3). With a weight of 3608g. Condition is satisfactory, breastfeeding. The skin is subicteric, with regression. Postoperative area without inflammation.

Based on clinical and laboratory manifestations and magnetic resonance imaging data, the main clinical diagnosis was made: Q 06.8 Tethered spinal cord syndrome: intradural lipoma at the level of S4, S5. Fixed spinal cord. Congenital cutaneous appendage of the coccygeal region. Associated: P59.0 Neonatal jaundice of newborns.

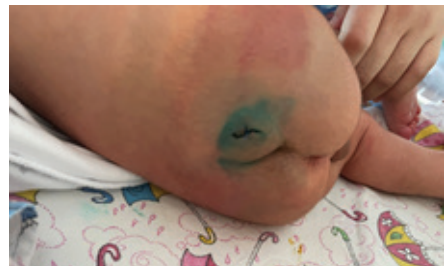

Fig. 2. 3rd day after surgical removal of the skin appendage

Conclusion: Carrying out prenatal ultrasound diagnostics with an expert-class device would make it possible to suspect this pathology in utero, and refer the pregnant woman for additional examination - MRI of the fetus, as well as psychologically prepare the mother for childbirth with such a pathology in the child. This clinical case draws the attention of neonatal and pediatric doctors to the presence of a syndrome such as tethered spinal cord syndrome. Manifested by skin symptoms in the lumbar region; impaired pain and tactile sensitivity of the lower extremities; violation of pelvic functions, which can occur at any age [8]. In this patient, the skin appendage of the sacral region, which did not communicate with the spinal cord canal, was surgically removed.

Spinal lipomas are often part of a complex of congenital anomalies; therefore, additional neuroimaging of the brain and spinal cord is required to exclude craniospinal dysraphism.

Outpatient follow-up for intradural lipomas after surgical treatment: observation by a neurologist, pediatrician, urologist, orthopedist, ophthalmologist. MRI control three months after surgery. If there are no signs of relapse of spinal cord tethering, MRI is indicated annually for up to three years.

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POSITIVE CONTRIBUTION OF TIMELY DIAGNOSIS AND CORRECTION OF ADRENAL DYSFUNCTION REQUIRING EXTRACORPOREAL MEMBRANE OXYGENATION IN PATIENTS WITH SEVERE PNEUMONIA IN THE EARLY POSTPARTUM PERIOD

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Introduction. The main diagnoses leading to the use of ECMO in pregnant women and the postpartum period are acute respiratory failure (62.7%). Adrenal dysfunction due to critical illness (CAD) often determines the severity of the patient's condition and the outcome of their illness.

Aim. Timely detection and adequate correction of CAD in women in labor using ECMO.

Materials and methods. A patient after delivery with community-acquired severe bilateral polysegmental pneumonia who required the use of ECMO. Results. Against the background of combined treatment with norepinephrine and hydrocortisone, early stabilization of hemodynamics and septic complications was achieved.

Conclusions. CAD is characterized by vascular insufficiency requiring the use of vasopressors. Timely and adequate correction of adrenal dysfunction during the development of a critical condition makes it possible to reduce the severity of the intensive care patient's condition and improve the outcome.

Keywords: critical illness, hydrocortisone, cortisol, extracorporeal membrane oxygenation, adrenal glands, adrenocorticotropic hormone, hypothyroidism, thyroxine.

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Introduction. Respiratory distress syndrome (RDS), associated with lung damage from the H1N1 influenza virus-RDS, can develop rapid and almost total lung damage [2]. Due to the long-term restoration of gas exchange in the lungs with H1N1 - RDS, the risk of the need for veno-venous extracorporeal membrane oxygenation (VV ECMO) increases. The combination of primary viral and secondary inflammatory lesions of the lungs causes the development of a combination of viral-bacterial sepsis with multiple organ dysfunction (MOD), one of the components of which may be adrenal dysfunction caused by critical illness (CAD) [11]. CAD determines the severity of the patient's condition and the outcome of their disease [4, 6]. Timely and adequate correction of CAD often improves the outcome of the disease in intensive care patients [5, 6, 7]. However, the problem of adrenal dysfunction (AD) remains outside the scope of intensive care directions implemented by the treating team of the intensive care unit. The presented clinical observation illustrates for the first time the importance of timely detection and adequate correction of CAD in a postpartum woman with severe community-acquired pneumonia that required VV ECMO.

Results and discussion. Patient L., 37 years old, 28 weeks of pregnancy, on the 15th day of illness with a diagnosis of "Acute purulent right-sided otitis media" was hospitalized in the ENT department of the regional hospital. On the third day of hospitalization, during treatment, the severity of the condition worsened: cough with light sputum, shortness of breath, weakness. On examination, breathing is spontaneous, respiratory rate (RR) is 37 times per minute, O2

saturation in arterial blood is 60% with insufflation of humidified O2 10 l/min. According to laboratory data: acid-base balance of arterial blood: pH 7.39; partial pressure of carbon dioxide 30.7 mm. rt. Art.; partial pressure of O2 43 mm. rt. Art.; lactate 3.76 mmol/l; base excess -5 mm. rt. Art. Due to respiratory failure (RR>35 times per minute, respiratory index <90%, O2 partial pressure <60 mmHg), the patient was transferred to artificial pulmonary ventilation (ALV). Hemodynamics after transfer to mechanical ventilation were unsTable and were supported by norepinephrine 0.1 mcg/kg/min. Blood pressure (BP) 119/64 mmHg. Art. Chest X-ray shows signs of bilateral polysegmental pneumonia. Due to progressive intrauterine hypoxia of the fetus, an operation was performed: emergency laparotomy, cesarean section in the lower uterine segment. On the fourth day of hospitalization (19th day of illness), the patient's condition is extremely serious, sedation, mechanical ventilation is performed, meningeal symptoms and gross focal symptoms are not determined. Microbiological examination of sputum revealed Acinetobacter baumannii. swab from the oropharyngeal mucosa - the causative agent of the influenza virus - H1N1. Therapy provided: antibacterial, antiviral, sedative, proton pump blockers, diuretics, low molecular weight heparins, infusion therapy, Dostinex, immunoglobulin, paracetamol.

On the 5th day of hospitalization (20th day of illness), taking into account the progression of respiratory failure, the increase in hypoxemia with an increase in the O2 fraction to 100% and positive end-expiratory pressure up to 12 cm H2O, it was decided to initiate veno-venous extracorporeal oxygenation (VV ECMO) with subsequent transfer on the same day by air ambulance to the ECMO center (State Scientific Center of the Russian Federation - FMBC named after A.I. Burnazyan of the Federal Medical and Biological Agency).

Admission to the ECMO center. At the time of admission to the ECMO center (C0), the patient's condition was extremely severe; on the Acute Physiology and Chronic Health Evaluation II scale, the condition corresponded to 20 points, and on the Sequential Organ Failure Assessment (SOFA) scale, 12 points. A CT scan of the head revealed subarachnoid hemorrhage. Sedation, analgesia and muscle relaxation during the observation period were carried out: Dexdor, queatiapine, pregabolin, morphine 1% 1 ml, Arduan 4 mg. Temperature 37.1° C. The results of computed tomography of the chest, abdominal and pelvic organs show a bilateral infiltrative process in the lungs with subtotal damage to the parenchyma. According to laboratory data: hemoglobin 93 g/l, red blood cells 3.16 × 10 12/l, leukocytes 12.2 × 109/l, platelets 208 109/l, procalcitonin > 0.05. Ventilation: in Bi-Vent/APRV mode, with parameters: respiratory rate 19/min., positive end-expiratory pressure 12 cmH2O. Art., O2 fraction 40%, tidal volume 350-400 ml, peak pressure - 27 cm H2O, O2 saturation 99−100%. Parameters of VV ECMO: revolutions 2880 ml/min., volume 4.60 l/min., O2 fraction 4 l/min. Hemodynamics were unsTable; norepinephrine was infused at a dose of 0.27 mcg/kg/min. Blood pressure: 113/62 mmHg. ECG – sinus rhythm. Adrenal dysfunction (AD) was diagnosed. Based on clinical, laboratory and instrumental data, the condition was assessed as septic with the development of septic shock. The levels of cortisol and adrenocorticotropic hormone (ACTH) in the blood plasma were: cortisol (1837 nmol/l) and ACTH (3 pg/dl). In accordance with existing recommendations for the treatment of patients with septic shock, on the day of admission to the ECMO center, hydrocortisone was added to therapy at an initial dose of 300 mg (100 mg IV bolus, then 50 mg every 6 hours) [7].

Thus, the severity of the patient's condition was due to H1N1-RDS, which required VV ECMO, MOD (cerebral, respiratory, cardiovascular, renal, intestinal, and endocrine). On the next day of ECMO treatment, the patient was removed from sedation, and consciousness was restored. The duration of VV ECMO was 11 days. During this period, when assessing the severity of the condition by C11 (the day of weaning from ECMO), the SOFA score decreased to 4 points. The level of leukocytosis decreased to 11.2 109/l, c-reactive protein to - 59 mg/l. Procalcitonin and lactate levels returned to normal by the third day of ECMO.

Hemodynamics also stabilized on the 3rd day of ECMO. Positive dynamics in the patient's condition made it possible to begin reducing respiratory support at C6 of the ECMO procedure, and to complete the ECMO procedure itself on the 11th day. On C1 ECMO, hydrocortisone was administered at a dose of 200 mg/day. 50 mg, IV, bolus, 4 times a day. Against this background, the need for norepinephrine decreased by the second day of observation with its complete abolition by the third day, when the dose of hydrocortisone was 100 mg/day. On the 4th day of ECMO, the dose of hydrocortisone was 50 mg/day; on the 5th day, due to stabilization of hemodynamics, hydrocortisone was discontinued. At the same time, the level of sodium in the blood plasma was 152-144 mmol/l over the course of 4 days. During a dynamic assessment of cortisol levels, its concentration in plasma was at C1 – 1704 nmol/l, C3 – 641.00 nmol/l, C5 – 296 nmol/l, C7 – 347 nmol/l, C9 – 452 nmol/l and per day weaning from ECMO – 547 mmol/l. The ACTH level in the blood plasma was 2 ng/dL at C1, 1 ng/ml at C3, 10 ng/ml at C5, 28.1 ng/ml at C7, 29 ng/ml at C9, on the day of weaning from ECMO – 28 .9 ng/ml. On the eighteenth day from the moment of admission to the ECMO center, the patient was transferred to the department with subsequent discharge.

The presented clinical observation illustrates for the first time the use of hydrocortisone when using ECMO in the early postpartum period. In pregnant women and women in labor, the problem of endocrine dysfunction becomes even more complicated. The course of the disease in the patient under discussion demonstrates that there is an urgent need to continue research into a deeper understanding of the pathophysiology of infection during pregnancy. Pregnancy is often not only an initially immunodeficient state that can lead to the development of infection, but also changes the response of the endocrine system in a woman's body, including the hypothalamus-pituitary-adrenal system. This analysis suggests that in pregnant women in the critical illness (CI) there is a rapid depletion of the synthesis of endogenous cortisol and an increase in receptor resistance to it, which can be considered as a manifestation of CAD [9]. During septic shock in pregnancy, an overactive immune response leads to hyperinflammation, causing vasodilation and hypotension. Under these conditions, the anti-inflammatory properties of hydrocortisone are an attractive therapeutic option for the treatment of sepsis-mediated hypotension in parturient women. Fluctuations in the level of ACTH and total cortisol during the development of CI characterize the phases of a critical condition: the acute phase is most often determined by an increase in the level of ACTH and, as a consequence, an increase in the level of cortisol. Subacute phase - characterized by persistently high levels of total cortisol with low levels of ACTH. In the acute phase of CI, a significant increase in cortisol levels in the first stages is caused by ACTH and is characterized by a stress reaction [10]. In the case of the development of POD syndrome, the CI enters the subacute (up to 14-21 days), and then

into the chronic phase (more than 14-21 days) [3, 12]. In the subacute and chronic phases of CI, cortisol levels are often higher than References values against the background of suppressed ACTH levels [10]. It is likely that overproduction of cortisol in this case, through negative feedback, suppresses the synthesis and secretion of ACTH. We observed this laboratory picture in the patient on the day of admission to the ECMO center. However, it should be remembered that a high level of cortisol is not always an indicator of the safety of the hypothalamus-pituitary-adrenal-target tissue system, since glucocorticoid resistance cannot be excluded [8, 1].

Conclusion. Thus, our observation showed that with a long history of the disease leading to the development of CI and the use of ECMO; unsTable hemodynamics requiring the use of vasopressors, it is necessary to consider the adrenal gland (without focusing on the levels of ACTH and cortisol) and carry out replacement therapy with hydrocortisone. Considering the properties of hydrocortisone, it is necessary to reduce the initially recommended treatment regimen (300 mg/day - the first day, then 200 mg/day the next day) after reducing and completely eliminating norepinephrine, and also adjusting the dose of hydrocortisone requires monitoring the level of sodium in the blood plasma. The duration of hydrocortisone administration after norepinephrine withdrawal depends on the target blood pressure and sodium levels. In particular, the patient needed three days to compensate for adrenal function.

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A CLINICAL CASE OF HUNTINGTON'S DISEASE

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The article presents a clinical case of Huntington's with the aim of analyzing the causes of difficulties in making a diagnosis. The etiopathogenetic basis of the disease is given. It is noted that Huntington's disease is a disease caused by the expansion of tandem microsatellite repeats. It has been shown that as a result, a mutant huntingtin protein is synthesized, which plays an important role in the formation of the nervous system in the embryo.

A clinical case is described in a child diagnosed with Huntington's disease (Westphal form), confirmed by molecular genetic research: CAG repeats were detected in the first allele of the HTT gene. It is noted that during diagnosis, an important point is to determine the type of inheritance and determine the Sherman effect and anticipation.

Keywords: Huntington's disease, Huntingtin, Sherman effect, anticipation.

Introduction. The prevalence of neurodegenerative diseases is of great concern to scientists worldwide, and the study of the course and clinical prognosis is highly relevant.

Huntington's disease (HD) is a severe hereditary degenerative disease of the nervous system, which is characterized by a progressive course, inherited diseases of the nervous system, motor, cognitive and psychiatric disorders. The striking clinical manifestation of HD is extrapyramidal hyperkinesias. The disease is transmitted by autosomal dominant type of inheritance and is characterized by complete penetrance, antisense, and the effect of paternal transmission [3].

The disease is based on an increase in trinucleotide repeats of the CAG of the HTT gene, located on chromosome 4 in exon 1 (4p.16.3). The gene encodes a protein called gentingtin, which plays an important role in the formation of the nervous system in the embryo. Gentingtin is a large protein with a molecular mass of 348 kD and consists of several domains. It is believed that gentingtin provides cell signaling, supports vesicular transport, synaptic transmission, and is involved in the regulation of cellular autophagy and apoptosis, association and dissociation of intracellular proteins [1]. Gentingtin expression is predominant in the brain (neurons of striatum, pale globe, thalamus, cerebral cortex, glial cells). It is also expressed in testes, heart, liver and lungs [6]. In the cell, the protein is localized predominantly in the nucleus and cytoplasm surrounding the nucleus. However, gentingtin is considered a poorly studied protein and its functions are poorly described.

The gentingtin protein in the first exon normally contains up to 35 CAG repeats, each of which encodes glutamine as part of the protein. An increase in CAG repeats over 35 leads to an increase in the glutamine content of the polyglutamine portion of the protein. Abnormally elongated due to glutamine, gentingtin loses its normal properties, loses its quaternary structure, and forms intracellular amyloid-like inclusions due to polyglutamine aggregation. As a result, the altered protein penetrates into cell nuclei, initiating neurodegeneration. The mechanisms of neurodegeneration are oxidative stress, microglial activation, excitotoxicity (glutamine toxicity), mitochondrial dysfunction, apoptosis, disorders of morphology and physiology of neuronal transport systems, dysregulation of transcription, and dysfunction of proteins aggregating with mutant gentingtin [6].

As a result of neglected molecular genetic mechanisms, severe clinical manifestations develop, which are largely determined by the amount of glutamine residues of gentingtin and the quality of available compensatory mechanisms.

Materials and Methods. Clinical case

A child (boy), 13 years old, complains of speech, memory and concentration disorders (with a tendency to worsen), slowness, involuntary and irregular movements in various muscle groups (mainly in the hands), "rotational" body movements. Low motivation for learning, prolonged falling asleep, bruxism (rare) are also noted.

With the above complaints has been observed by a neurologist since 2021 after hospitalization in November 2021 in the neuropsychiatric department of OGKUZ IODKB (Irkutsk Regional Children's Clinical Hospital). He was examined by a geneticist. After hospitalization, the diagnosis was made: unspecified encephalopathy with cognitive impairment. Associated diagnosis: mild mental retardation without pronounced behavioral disorders; motor disorders; high degree myopia; complex myopathic astigmatism.

He was examined and treated in OGKUZH IOKPB No. 1 (Irkutsk Regional Clinical Psychiatric Hospital No. 1). Diagnosis: Mild mental retardation with persistent pronounced disorders

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of asthenic, passive-dependent types, with pronounced mental infantilism, pronounced emotional-volitional disorders on the background of residual organic insufficiency of the CNS (dysontogenetic, neurodegenerative genesis) with motor stereotypes.

For further observation he was sent for hospitalization to the Clinic of the Scientific Center for Family Health Problems and Human Reproduction.

Child from 3 pregnancies. The first pregnancy - a boy of 22 years old (healthy), the second pregnancy was a medical abortion. Pregnancy proceeded against the background of threatened termination of pregnancy. The labor was independent at the term of 40 weeks. Apgar score 7-8 points. Birth weight 3686 g, height 53 cm. Discharged from the maternity hospital with the diagnosis of perinatal lesion of the central nervous system (CNS) of mixed genesis. He was breastfed until the age of 1 year. Neuropsychiatric development was delayed. The genealogical anamnesis on the paternal side (father and grandfather) shows Huntington's disease.

Objective. At the time of examination, no disorders on the part of somatic organs were detected. There is a decrease in body weight (at height 156.3 cm, weight 40.2 kg, body mass index (BMI) 16.5 units), but according to WHOAnthroPlus body weight is normal.

The main severity of the disease is determined by neurological pathology. Olfaction is not impaired, he can see. Pupil reaction to light is alive, eyeball movement is in full volume, convergence is weakened. Eye slits D=S. Trigeminal points are painless. The face is symmetrical. Sensitivity on the face is preserved. Chewing muscles tense enough, chews slowly. Hearing is preserved. No nystagmus. The pharyngeal reflex is positive. Low standing of the wishbones of the soft palate. Head movements in full volume. Tongue along the center line, with a slight deviation to the left. Movement in full. Muscle tone is altered by extrapyramidal type in the muscles of the hands. Fine motor skills are insufficient. Muscle strength is sufficient. Tendon and periosteal reflexes from the hands are enlivened D=S, from the legs are enlivened D=S. No pathologic reflexes. Meningeal signs are negative. Dermographism is red, persistent. In Romberg's pose sTable. Coordination tests: paltsenosovaya, patellofemoral test performs slowly, does not miss. Palpation of paravertebral points and percussion of spinous processes are painless. Gait is not grossly disturbed. Walking on heels, toes, jumps. Dermographism is red, persistent, hyperhidrosis of palms and feet is noted. Sensory disorders are not revealed. The function of pelvic organs is controlled. Involuntary and unregulated movements in the hands are noted. He is oriented in place, time and identity. She reacts positively to the examination, enters into verbal contact, responds in one-word answers. There is a violation of sound pronunciation. Instructions are carried out after repetition. There is a decrease in intellectual functions.

Consulted by an endocrinologist: no endocrine system disorders were found. Ultrasound (ultrasound examination) of the thyroid gland and ultrasound of the adrenal glands without peculiarities.

An interference EMG (electromyogram) of the tibia muscles was performed: at rest, spontaneous activity of fibrillation potentials on the right side was recorded; after tonic tests, fibrillations and pseudomyotonic discharges were noted (Fig. 1).

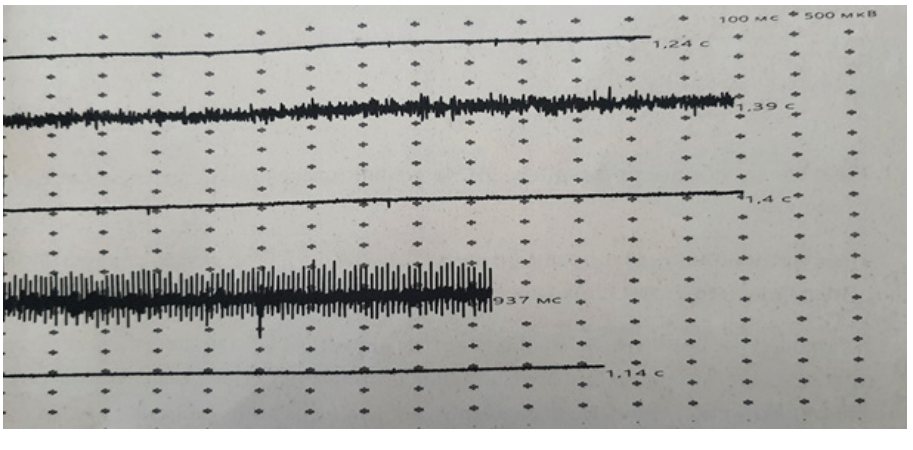
Introduction. The prevalence of neurodegenerative diseases is of great concern to scientists worldwide, and the study of the course and clinical prognosis is highly relevant.

Huntington's disease (HD) is a severe hereditary degenerative disease of the nervous system, which is characterized by a progressive course, inherited diseases of the nervous system, motor, cognitive and psychiatric disorders. The striking clinical manifestation of HD is extrapyramidal hyperkinesias. The disease is transmitted by autosomal dominant type of inheritance and is characterized by complete penetrance, antisense, and the effect of paternal transmission [3].

The disease is based on an increase in trinucleotide repeats of the CAG of the HTT gene, located on chromosome 4 in exon 1 (4p.16.3). The gene encodes a protein called gentingtin, which plays an important role in the formation of the nervous system in the embryo. Gentingtin is a large protein with a molecular mass of 348 kD and consists of several domains. It is believed that gentingtin provides cell signaling, supports vesicular transport, synaptic transmission, and is involved in the regulation of cellular autophagy and apoptosis, association and dissociation of intracellular proteins [1]. Gentingtin expression is predominant in the brain (neurons of striatum, pale globe, thalamus, cerebral cortex, glial cells). It is also expressed in testes, heart, liver and lungs [6]. In the cell, the protein is localized predominantly in the nucleus and cytoplasm surrounding the nucleus. However, gentingtin is considered a poorly studied protein and its functions are poorly described.

The gentingtin protein in the first exon normally contains up to 35 CAG repeats, each of which encodes glutamine as part of the protein. An increase in CAG repeats over 35 leads to an increase in the glutamine content of the polyglutamine portion of the protein. Abnormally elongated due to glutamine, gentingtin loses its normal properties, loses its quaternary structure, and forms intracellular amyloid-like inclusions due to polyglutamine aggregation. As a result, the altered protein penetrates into cell nuclei, initiating neurodegeneration. The mechanisms of neurodegeneration are oxidative stress, microglial activation, excitotoxicity (glutamine toxicity), mitochondrial dysfunction, apoptosis, disorders of morphology and physiology of neuronal transport systems, dysregulation of transcription, and dysfunction of proteins aggregating with mutant gentingtin [6].

As a result of neglected molecular genetic mechanisms, severe clinical manifestations develop, which are largely determined by the amount of glutamine residues of gentingtin and the quality of available compensatory mechanisms.



Electromyography of the child's lower leg muscles (fibrillations and pseudomyotonic discharges)

Materials and Methods. Clinical case. A child (boy), 13 years old, complains of speech, memory and concentration disorders (with a tendency to worsen), slowness, involuntary and irregular movements in various muscle groups (mainly in the hands), "rotational" body movements. Low motivation for learning, prolonged falling asleep, bruxism (rare) are also noted.

With the above complaints has been observed by a neurologist since 2021 after hospitalization in November 2021 in the neuropsychiatric department of OGKUZ IODKB (Irkutsk Regional Children's Clinical Hospital). He was examined by a geneticist. After hospitalization, the diagnosis was made: unspecified encephalopathy with cognitive impairment. Associated diagnosis: mild mental retardation without pronounced behavioral disorders; motor disorders; high degree myopia; complex myopathic astigmatism.

He was examined and treated in OGKUZH IOKPB No. 1 (Irkutsk Regional Clinical Psychiatric Hospital No. 1). Diagnosis: Mild mental retardation with persistent pronounced disorders of asthenic, passive-dependent types, with pronounced mental infantilism, pronounced emotional-volitional disorders on the background of residual organic insufficiency of the CNS (dysontogenetic, neurodegenerative genesis) with motor stereotypes.

For further observation he was sent for hospitalization to the Clinic of the Scientific Center for Family Health Problems and Human Reproduction.

Child from 3 pregnancies. The first pregnancy - a boy of 22 years old (healthy), the second pregnancy was a medical abortion. Pregnancy proceeded against the background of threatened termination of pregnancy. The labor was independent at the term of 40 weeks. Apgar score 7-8 points. Birth weight 3686 g, height 53 cm. Discharged from the maternity hospital with the diagnosis of perinatal lesion of the central nervous system (CNS) of mixed genesis. He was breastfed until the age of 1 year. Neuropsychiatric development was delayed. The genealogical anamnesis on the paternal side (father and grandfather) shows Huntington's disease.

Objective. At the time of examination, no disorders on the part of somatic organs were detected. There is a decrease in body weight (at height 156.3 cm, weight 40.2 kg, body mass index (BMI) 16.5 units), but according to WHOAnthroPlus body weight is normal.

The main severity of the disease is determined by neurological pathology. Olfaction is not impaired, he can see. Pupil reaction to light is alive, eyeball movement is in full volume, convergence is weakened. Eye slits D=S. Trigeminal points are painless. The face is symmetrical. Sensitivity on the face is preserved. Chewing muscles tense enough, chews slowly. Hearing is preserved. No nystagmus. The pharyngeal reflex is positive. Low standing of the wishbones of the soft palate. Head movements in full volume. Tongue along the center line, with a slight deviation to the left. Movement in full. Muscle tone is altered by extrapyramidal type in the muscles of the hands. Fine motor skills are insufficient. Muscle strength is sufficient. Tendon and periosteal reflexes from the hands are enlivened D=S, from the legs are enlivened D=S. No pathologic reflexes. Meningeal signs are negative. Dermographism is red, persistent. In Romberg's pose sTable. Coordination tests: paltsenosovaya, patellofemoral test performs slowly, does not miss. Palpation of paravertebral points and percussion of spinous processes are painless. Gait is not grossly disturbed. Walking on heels, toes, jumps. Dermographism is red, persistent, hyperhidrosis of palms and feet is noted. Sensory disorders are not revealed. The function of pelvic organs is controlled. Involuntary and unregulated movements in the hands are noted. He is oriented in place, time and identity. She reacts positively to the examination, enters into verbal contact, responds in one-word answers. There is a violation of sound pronunciation. Instructions are carried out after repetition. There is a decrease in intellectual functions.

Consulted by an endocrinologist: no endocrine system disorders were found. Ultrasound (ultrasound examination) of the thyroid gland and ultrasound of the adrenal glands without peculiarities.

An interference EMG (electromyogram) of the tibia muscles was performed: at rest, spontaneous activity of fibrillation potentials on the right side was recorded; after tonic tests, fibrillations and pseudomyotonic discharges were noted (Fig. 1)

EEG (electroencephalogram) shows moderate changes in bioelectrical activity, alpha rhythm is significantly disorganized, predominant in the right occipital region, frequency 9.6-11.4 Hz and amplitude up to 41 μV. No epileptiform activity was registered.

Magnetic resonance imaging (MRI) revealed an MRI picture of external, open, moderately pronounced hydrocephalus, diffuse signals from the heads of caudate nuclei and shell on both sides. Indirect signs of intracranial hypertension were detected.

The child has been counseled by a geneticist. Presumptive diagnosis of Huntington's disease, Westphal's form. Referred for genetic testing in the HTT gene.

A genetic examination for Huntington's disease revealed CAG repeats in the first allele of the HTT gene 77 (corresponding to a pronounced expansion) and 15 in the second allele (corresponding to the norm). The diagnosis of Huntington's disease, Westphal form, was confirmed. Treatment has been prescribed.

Discussion of results. The clinical manifestations of Huntington's disease are well and thoroughly described. Characteristic clinical symptoms, autosomal dominant type of inheritance and progressive course of the disease allow to assume with high accuracy that the patient has HD. The effect of paternal transmission, the Sherman effect (the possibility of increasing the number of repeats in each subsequent generation) and, as a consequence, anticipation (the effect of aggravation of clinical manifestations of the disease) are not unimportant additional features that allow to suspect HD. However, the "gold standard" of diagnosis verification is DNA diagnosis with determination of the number of CAG repeats in HTT gene alleles [2]. The diagnostic value is more than 36 copies of trinucleotide CAG repeats.

The important role of gentingtin in living organisms is emphasized by the fact that homologous proteins encoded by homologs of the HTT gene have been found in many animals, starting with protozoa. It is a large protein with a molecular mass of 348 kD, consisting of several domains. Its main functions are currently known. Gentingtin is required to maintain the clonal potential of neural stem cells during the process of neural induction (in the experiment HTT gene knockout mice died before the development of the nervous system); Gentingtin controls the interaction between neuroepithelial cells. Gentingtin participates in the formation of the protein framework by interacting with b-tubulin and binds to microtubules, localizes at the poles of the spindle during mitosis (controlling the orientation of the spindle), and regulates the processes of intracellular transport (by interacting with the dynein/dynactin complex). It is known that gentingtin is a regulator of transcription, affecting brain-derived neurotropic factor (BDNF) through regulation of the transcription factor REST/NRSF, which negatively affects the regulation of BDNF. The interneuronal function of genentigtin is important for the proper formation of

excitatory synapses of the cortex and striatum [7,8].

Formation of mutant gentigntin causes proteolysis and formation of toxic glutamine fragments of gentigntin that aggregate in the cell, transcription is impaired due to inhibition of histone acetyltransferase activity, chromatin condensation and BDNF (neurotrophin that stimulates and supports neuronal development), protein homeostasis and mitochondrial function are disturbed, ATP production is reduced, axonal transport, synaptic transmission and transport of organelles (mitochondria, autophagosomes and synaptic vesicles) are disturbed, synaptic plasticity is disturbed and excitotoxicity is formed, and neuroglia dysfunction occurs due to disruption of glutamate capture by astrocytes [5].

All this leads to severe neurological changes. In this clinical case, the detected 77 trinucleotide CAG repeats caused severe neurological changes at an early age. The first clinical manifestations could be seen immediately after birth, which was recorded as perinatal CNS lesions and delayed neuropsychiatric development. However, until the age of 10, neurodegenerative changes developed relatively slowly, the child attended a general education school and only in the 7th grade was transferred to a remedial school.

Despite the fact that the child was repeatedly examined, the diagnosis could be esTableished only by the age of 13 years. This is due to difficulties in determining the type of inheritance [4] due to the fact that the family lives without the father and has no information about the father's health status and the health status of relatives on the father's side. After repeated examinations by specialists, the mother still managed to recall some abnormalities in the neuropsychiatric condition of the father and grandfather on the father's side. It was noted that the grandfather's neuropsychiatric state was less disturbed than the child's father's. This made it possible to suspect the presence of tandem microsatellite repeat expansion disease and eventually make a diagnosis.

Conclusion. Timely diagnosis of Huntington's disease is an important aspect of patient care. Tandem microsatellite repeat expansion diseases are often difficult to diagnose, as are neurodegenerative diseases. The main tool to help esTableish the correct diagnosis is the determination of the type of inheritance. However, an obstacle in its determination is the difficulty in collecting (or inability to collect) genealogical anamnesis, which significantly increases the time of diagnosis of the disease. The fundamental signs that allow to suspect expansion diseases are the Sherman effect and anticipation, and it is these that should be paid attention to in the first place in the diagnosis. An important point in the diagnosis of hereditary pathology is the timely consultation of the patient by a geneticist and his examination in a specialized department of hereditary pathology.

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