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POLYMORPHISM RS1127327 OF THE MICRORNA-146A TARGET GENE CCDC6 ASSOCIATED WITH A REDUCED RISK OF SEVERE HEMORRHAGIC FEVER WITH RENAL SYNDROME IN PATIENTS FROM THE VOLGA-URAL REGION OF RUSSIA

The association analysis of polymorphic variants common for miRNA-146a, miRNA-218, miRNA-410, miRNA-503 target genes was performed in patients with hemorrhagic fever infected with PUUV. It has been revealed that the genotype rs1127327*AA of the CCDC6 gene is associated with a reduced risk of severe disease form. Further studies of the network of genes that are targets of various miRNAs are needed to elucidate the molecular mechanisms that can influence the onset and development of HFRS.

Keywords: miRNA, target genes, hemorrhagic fever with renal syndrome.

Introduction. Orthohantaviruses are RNA viruses that belong to the most widespread zoonotic viruses transmitted by rodents (10). These viruses are the etiological agents of two clinical forms of human disease: hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus cardiopulmonary syndrome in America. Between 150,000 and 200,000 cases of orthochantavirus caused disease are reported worldwide each year, with most cases of hemorrhagic fever occurring in Asia, mostly in China (7). In the Russian Federation, HFRS occupies the leading place among all natural focal human diseases. In the Russian Far East, the annual incidence of HFRS is caused by two orthochantaviruses: Hantaan (genetic variants of Far East and Amur) and Seoul (6). Puumal virus (PUUV) is the main hantavirus causing hemorrhagic fever with renal syndrome in Europe. The number of patients diagnosed with HFRS in Europe is increasing and amounts to more than 3,000 cases per year (10). The Volga Federal District accounts for almost 90% of all cases of HFRS registered in the Russian Federation. The Republic of Bashkortostan, the largest source of HFRS in the Volga Federal District, has particularly high rates (6). Despite numerous attempts to study the disease, the pathogenesis of viral hemorrhagic fevers remains largely unknown. The course and outcome of the disease are thought to depend on the viral load, the genetic profile of patients, and the immune response (7). Active research is underway to address gaps in knowledge about the pathogenesis of HFRS. There are still no test systems for predicting the course of the disease with high accuracy, sensitivity and specificity. Promising markers in this respect could be microRNAs, which are endogenously expressed RNA molecules 18-22 nucleotides long that inhibit gene expression at the post-transcriptional level by binding to the 3′-translated mRNA target region and play an essential role in various biological processes, including cell cycle, apoptosis, cell proliferation and differentiation. Although the role of microRNAs in various viral infections has been extensively studied in recent years, there are only a few publications examining the role of circulating RNAs and microRNAs in Hantaan virus infection. A number of microRNAs (miR-146a, miR-410, miR-218, miR-503) have been identified that may be involved in the pathogenesis of HFRS (4,8,9,11). It is known that alteration of microRNA interaction with binding site resulting from single nucleotide substitution can modify expression of target genes involved in the initiation and development of various diseases (1), therefore, scientists put emphasis on identification of target genes for each microRNA.

The aim of the study is to analyze polymorphic variants in target genes, which are common for microRNA-146a, microRNA-218, microRNA-410, microRNA-503, which play a role in pathogenesis of HFRS, to find markers of HFRS risk.

Material and methods. Eighty-six individuals with moderate and eighty-eight patients with severe forms of HFRS and 115 healthy individuals were included in the study. All patients were hospitalized in infectious diseases hospitals in Ufa from 2018 to 2021 and gave voluntary informed consent to participate in the study. The diagnosis of HFRS was based on clinical findings (fever>38°C, acute kidney damage, thrombocytopenia) and was confirmed serologically. Patient blood samples were collected during hospitalization (mainly during the oliguric period).

According to the anamnestic data collected, none of the patients had received antiviral treatment before blood collection. All patients with HFRS were infected with PUUV. DNA from patients with HFRS was isolated by phenol-chloroform extraction. MicroRNA targets were determined using the mirdsnp database (http://mirdsnp.ccr.buffalo.edu/search.php#). In the first step we analyzed all possible targets for each microRNA separately - microRNA-146a, microRNA-218, microRNA-410 and microRNA-503 and found that polymorphic variants of the CCDC6 gene were "overlapping" targets for all of the above microRNAs. The polymorphic loci common to all microRNA targets selected for the study were genotyped by Taq-man allelic discrimination on a CFX96 Touch™ Real-Time PCR Detection System instrument. The results allelic discrimination were analyzed using the CFX96 Touch™ Real-Time PCR Detection System software. Pairwise comparison of genotype and allele frequencies in the patient and healthy person groups was performed using the χ2 criterion (P) for 2x2 contingency tables with Yates correction/

Results and discussion. We analyzed rs1127327, rs3802695, rs10821594, rs11540401, rs16914105 polymorphisms in the CCDC6 gene. The distribution of genotype frequencies for all polymorphic loci corresponded to Hardy-Weinberg equilibrium (p > 0.05). The clinical characteristics of the patients included in the study are shown in Table 1.

A comparison of allele and genotype frequencies between a sample of severe HFRS patients and a control group of healthy individuals revealed that the AA genotype of the polymorphic locus rs1127327 of the *CCDC6* gene was associated with a reduced risk of severe disease (OR=0.25; CI95%=0.07-0.9; p=0. 03), whereas the CC genotype demonstrated only a slight decrease in the frequency of occurrence in the patient group compared to controls and was not a risk marker for the development of HFRS (p>0.05, Table 2). Analysis of the distribution of polymorphic variants rs3802695, rs10821594, rs11540401, rs16914105 in the *CCDC6* gene in patients with HFRS and control individuals showed no statistically significant results (p>0.05). The *CCDC6* gene, which is the target of all microRNAs studied, including microRNA-146a, is located on the long arm of chromosome 10 (10q21) and contains 9 exons that encode a 3 KB transcript showing an open reading frame of 475 amino acids. The *CCDC6* gene promoter, located 259 bp upstream of the ATG site, controls its expression in various human tissues.

CCDC6 protein is a ubiquitously expressed proapoptotic protein. *CCDC6* is phosphorylated at T434 by ATM kinase, which stabilizes the protein in the nucleus in response to DNA damage. Loss of the *CCDC6* region recognized by ATM kinase or complete deficiency of the protein determines an increase in cell survival, allows DNA synthesis and promotes the transition to mitosis after exposure to genotoxic stress (2). Currently, the effect of the rs1127327 polymorphic variant on miR-146a expression has not been described, but it is known that, for example, the G/C polymorphism (rs2910164) in the pre-miR-146a sequence reduces pre and mature miR-146a in the presence of the C allele by 1.9 and 1.8 times, respectively, compared to the G allele. The C allele was also shown to prevent nuclear factor binding to pre-miR-146a, and decreased miR-146a resulted in less effective inhibition of target genes involved in the Toll-like receptor complex and cytokine signaling pathway (*TRAF6, IRAK1*) and *CCDC6* (3).

It is well known that miR-146a is involved in innate immunity and inflammatory responses in viral infection.

Table1

Clinical manifestations of the oliguric period of HFRS depending on the severity of the disease

Symptoms	Disease form				Total	
	Moderate		Severe			
	N	%	N	%	N	%
Oligoanuria	84	97.7	88	100	74	84
Weakness	86	100	88	100	88	100
Lower back pain	84	97.6	88	100	86	97.7
Abdominal pain	57	66.3	80	90.9	67	75.7
Nausea, vomiting	52	60.4	87	98.9	67	76.1
Petechial rash	36	41.9	73	83	52	59.3
Hemorrhagic enanthema	39	45.3	71	80.7	53	59.1
Bleeding at injection sites	17	19.7	67	76.1	39	44.3
Hemorrhages in the sclerae	6	6.9	15	17	9	10.2
Nosebleed	4	4.7	21	23.9	11	12.5
Microhematuria	86	100	88	100	88	100
Macrohematuria	7	8.1	22	25	12	13.6
Proteinuria	86	100	88	100	88	100

Table2

Distribution of allele and genotype frequencies of polymorphic locus rs1127327 of the CCDC6 gene in the group of HFRS patients and controls

Genotype, allele	Patients		Control		χ2	P-value	OR	95% CI
	n	pi	n	pi				
AA	3	3.4	14	12	4.99	0.025	3.9	1.09-14.1
AC	43	48.9	44	38	2.29	0.13	0.65	0.37-1.1
CC	42	47.7	57	50	0.06	0.79	1.07	0.6-1.8
A	49	27.8	72	31.3	0.57	0.45	0.84	0.55-1.3
C	127	72.2	158	68.7	0.57	0.45	1.18	0.76-1.8

Note. OR is the odds ratio, 95% CI is the lower and upper bounds of the 95% confidence interval for OR, p-value is the significance level of the criterion.

However, little is known about the effect of miR-146a on PUUV virus-induced infection and the molecular mechanisms by which this effect occurs. Previously, researchers demonstrated that live Hantaan virus can induce the expression of miR-146a, NFkBp65 and downstream proinflammatory cytokines. According to the literature, the miR-146a promoter has two binding sites to NF-kB, so it is suggested that NF-kB-dependent expression of miR-146a may be a regulator of innate immune responses (8). In a study by Qing-Zhou Chen et al. scientists concluded that NF-kB-dependent induction of miR-146a is also found in Hantavirus infection because HTNV NP/GP proteins promoted miR-146a and NF-kB promoter activity (8).

It is also known that miR-146a suppresses IFN-b expression. Interferons can provide paramount protection against viral infections in vertebrates, and activated NF-kBp65 can directly determine early IFNb production after viral infection. miR-146a has been shown to regulate type I IFN through negative feedback via NF-kB. High doses of Hantaan virus were also known to suppress interferon secretion, and virus ANDV- and virus SNV-encoded proteins had the potential ability to inhibit IFN-b induction and signal transduction (13). Tula hantavirus (TULV), ANDV, and New York hantavirus-1 (NY-1V) Gn proteins, but not PHV, suppress IFN-b production by inhibiting phosphorylation of IRF3 via TBK1 kinase early in viral infection (5), which also promotes HTNV replication.

The effect of Pumala virus on IFN secretion has not been studied, but it can be assumed that the described mechanism is universal, as many viruses can promote viral replication and proliferation by inhibiting IFN secretion in host cells (8).

Human miR-146 occurs in two different forms: miR-146a, localized on chromosome 5q33, and miR-146b, located on chromosome 10q24. Because the mature forms differ by only 2 nucleotides, many of the predicted target genes are common to both microRNAs, but each also has specific targets unique to the particular microRNA. The two related miR-146s are regulated differently, with miR-146a (but not miR-146b) being strongly induced by lipopolysaccharide. It has been suggested that miR-146 plays a role in Toll-like receptor and cytokine signaling and thus in the immune response, and there is evidence that miR-146a is regulated by NF-kappa B (12).

Conclusion. This study shows that the AA genotype of the polymorphic locus rs1127327 of the CCDC6 gene, which is a common target of non-xc microRNAs, is associated with a decreased risk of HFRS in patients from Bashkortostan (OR=0.25; CI95%=0.07-0.9; p=0.03). Nevertheless, further studies of the network of genes that are targets of different microRNAs are needed to elucidate the molecular mechanisms that may influence the occurrence and development of HFRS.

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POLYMORPHISMS RS738409 AND RS2294918 OF THE *PNPLA3* GENE IN THE YAKUT POPULATION

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The article presents the frequency of polymorphic variants of the PNPLA3 gene (rs2294918 and rs738409) in Yakuts (n=150) living in the Republic of Sakha (Yakutia) (RS (Y)).

Genotyping of PNPLA3 (rs738409 and rs2294918) was performed by PCR – RFLP. Single nucleotide polymorphism rs738409 (I148M) of the PNPLA3 gene in the Yakut population is characterized by a high frequency of the risk G allele (72%). From the data of the 1000 Genomes project, it follows that the G allele (148M) is found with a high frequency in the populations of Latin American countries (Peruvians - 71.8%, Mexicans - 55.5%, Colombians - 41%). Analysis of the distribution of the genotype frequency of the rs2294918 polymorphism showed that the G allele is found with a high frequency in all populations in the world. So in the studied sample of Yakuts, it was - 89.3%; in African populations it averages 91.3%; in the populations of Central and South America (Colombians, Mexicans, Peruvians and Puerto Ricans) on average - 78.8%, in the populations of East Asians (Chinese, Japanese and Vietnamese) on average - 81.8%; Europeans (Finns, British, Iberians, Tuscans and Utah residents of northern and Western European descent) on average - 62.9%; South Asians (Indians and Pakistanis) have an average of 77.2%.

In the studied sample of Yakuts, two diplotypes [GG] [GG] and [CG] [GG] are more common. These diplotypes carry the mutant allele G (rs738409) and do not carry the A allele (rs2294918), which has a weakening effect on 148M, which in turn promotes the accumulation of triglycerides in hepatocytes. Perhaps in the Yakuts, the accumulation of fat in the liver in the past did not lead to NAFLD, since the accumulated fat was quickly converted into energy to generate heat. In modern realities, this diplotype has its detrimental effect by increasing the frequency of metabolic diseases, including non-alcoholic fatty liver disease (NAFLD).

The data obtained on the frequencies of the markers rs738409 and rs2294918 of the *PNPLA3* gene can be used in the diagnosis of susceptibility to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to study the genetic mechanisms of human adaptation to cold, as well as the formation of risk groups for these diseases.

Keywords: gene, polymorphism, NAFLD, *PNPLA3*, liver.

Yakutia is the coldest region of Russia, whose territory is located in the permafrost zone. Preservation of heat in the body has been relevant for almost the entire history of mankind, especially in the northern regions of the planet. The body of indigenous people has adapted to living in harsh climatic conditions [1]. But in the modern world, people live in warm houses all year round, dress in warm clothes and are exposed to minimal effects of cold on the body. In addition to changing the effect of temperature on the body of the indigenous population, with the development of agriculture and road communications, the diet has also changed. Just a few generations ago, the basis of the diet was mainly protein and lipid products (meat, fish, dairy products), in modern conditions, the basis of the diet is carbohydrate products (potatoes, pasta and flour products, rice, buckwheat, etc.). Until recently, among the indigenous population, traditional high-fat foods were considered beneficial for the body and keeping warm, but at the moment this food has become the main source of various metabolic diseases, including type 2 diabetes mellitus, atherosclerosis, non-alcoholic fatty liver disease (NAFLD) and others [2].

NAFLD is characterized by changes in liver tissue due to excessive deposition of fat droplets in hepatocytes. If before industrialization and the use of modern approaches to maintaining heat in the body, under the influence of cold, this accumulated fat was converted into energy to generate heat, then at the moment it leads to various pathological changes in the liver.

Many foreign and domestic researchers indicate that the rs738409 polymorphism of the *PNPLA3* gene is the main determinant of liver fat and affects the development and progression of NAFLD [3,4]. Variant G (rs738409) of the *PNPLA3* gene leads to the accumulation of triglycerides in hepatocytes. The rs2294918 polymorphism of the *PNPLA3* gene reduces the expression of the PNPLA3 protein, reducing the effect of variant G (rs738409) on the predisposition to steatosis and liver damage [5].

The PNPLA3 protein belongs to the family of patatin-like phospholipases. It has hydrolase activity against triglycerides, catalyzes the conversion of lysophosphatidic acid to phosphatidic. A mutation in the gene results in the replacement of isoleucine with methionine at position 148 of the amino acid sequence, which leads to the loss of these functions and the accumulation of triglycerides and retinol palmitate in the liver. [6].

We previously found a high frequency of the G allele (rs738409) of the *PNPLA3* gene in the Yakut population (73%) [7]. The adaptation mechanisms listed above, such as the accumulation of fat in the liver, probably left their mark on the Yakut gene pool, in particular, in the genes that have an effect on metabolism. In this regard, the purpose of our study was to study the distribution of frequencies of alleles, genotypes, haplotypes and diplotypes of polymorphic variants of the PNPLA3 gene (rs2294918 and rs738409) in Yakuts.

Materials and research methods. Genotyping of polymorphisms rs2294918 and rs738409 of the PNPLA3 gene was carried out in the Laboratory of Hereditary Pathology of the Department of Molecular Genetics of the Yakut Scientific Center for Complex Medical Problems (YSC CMP). DNA samples from 150 healthy volunteers from the biomaterial collection of the YSC CMP were used for the study using the USU "Genome of Yakutia" (reg. No. USU_507512). All participants in the study were ethnically Yakuts and lived on the territory of the Republic of Sakha (Yakutia). For comparison, the data of

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the 1000 Genomes project [8] were used. The study was conducted with the written consent of the participants. The study protocol was approved by the local committee on biomedical ethics at the YSC CMP.

Isolation of DNA from peripheral blood lymphocytes was carried out using a commercial kit for the isolation of nucleic acids from whole venous blood produced by OOO Excell Biotech (Yakutsk, Russia). Primer selection was performed using the National Center for Biotechnology Information (NCBI) primer design tool, Primer-BLAST. The study site sequence for the primer selection matrix and primer specificity check were taken from the UCSC Genome Browser database (GRCh38/hg38). The primers were synthesized by Lumiprobe RUS Ltd, Moscow. The reaction mixture for PCR contained: primer forward and reverse, 10 pmol/μl (1 μl); Dream Taq PCR master mix -12.5 μl; deionized water 9.5 μl and DNA in the amount of 100 μg/ml - 1 μl. The total volume of the reaction mixture for amplification was 25 μl. The mixture for RFLP with a volume of 20 μl consisted of: amplificate - 7 μl, deionized water - 10.9 μl, restriction buffer - 2 μl and for polymorphism rs738409 restriction endunuclease BstF5 I (2 u), and for polymorphism rs2294918 - Ama87I (2 u).

Detection of PCR and RFLP products was carried out using horizontal electrophoresis in a 4% agarose gel plate with the addition of ethidium bromide, a specific intercalating fluorescent DNA (RNA) dye, using a standard tris-acetate buffer at a field voltage of ~ 20 V/cm for 30 minutes. The correspondence of genotype distributions to the expected values under Hardy-Weinberg equilibrium and the comparison of the frequencies of allelic variants/genotypes were performed using the χ2 test (chi-square). The frequency of haplotypes was determined using the EM algorithm. Linkage disequilibrium (LD) between SNP pairs was calculated using Lewontin's proposed D' coefficient and Pearson's r2 coefficient. Linkage disequilibrium blocks were determined using the "Solid spine LD" algorithm (D'>0.75).

Haploview software (v4.2) was used to evaluate *PNPLA3* haplotypes and frequencies based on genotyping data and to test the association between alleles and haplotypes of the *PNPLA3* gene [9].

Results and discussions. The PNPLA3 gene in the Yakut population according to the rs738409 polymorphism is characterized by a high frequency of the risky allele G (72%). From the data of the 1000 Genomes project [8], it follows that the G allele is found with a high frequency in the populations of Central and South America (Peruvians - 71.8%, Mexicans - 55.5%, Colombians - 41%). Europeans have an average G allele frequency of 22.6%. Among Asians, the high frequency of the G allele is in the Japanese (41.8%). The owners of the lowest frequency of the G allele are Africans, on average 11.8%. In the population sample of Yakuts for rs738409 due to the shift of genotypes towards the homozygous genotype GG, a deviation from the Hardy-Weinberg equilibrium was revealed, which may be evidence of the accumulation of this genotype as an adaptive mechanism to a cold climate (Table 1).

An analysis of the frequency distribution of the rs2294918 polymorphism genotypes according to the 1000 Genomes project [8] showed that the G allele occurs with a high frequency in all populations in the world. Thus, in the studied sample of Yakuts, it amounted to 89.3%; in African populations, it averages 91.3%; in the populations of Central and South America (Colombians, Mexicans, Peruvians and Puerto Ricans) on average - 78.8%, in the populations of East Asians (Chinese, Japanese and Vietnamese) on average - 81.8%; Europeans (Finns, British, Iberians, Tuscans and residents of Utah of northern and Western European origin) on average - 62.9%; South Asians (Indians and Pakistanis) have an average of 77.2%. According to the polymorphism rs2294918 of the PNPLA3 gene, which suppresses the negative effect of rs738409, the protective allele A in Yakuts was only 10.7%. According to the 1000 Genomes project [8], the protective allele A (rs2294918) is more common in Europeans than in other populations (32.3%). In the populations of the Negroid population from Barbados (ACB), Puerto Ricans (PUR) and the Telugu Indian population from England (ITU), the frequencies of the risk allele G rs738409 and the protective allele A rs2294918 are close in value (13.13%; 32.31% and 25.23 % respec-

Table1

The frequency of allele variants and missense mutations of the PNPLA3 gene in the Yakut population and in the populations of the 1000 genomes project

Population	Sub-population	SNP	Mutation	MAF	Ho	He	p
1	2	3	4	5	6	7	8
Россия	YKT (n=150)	rs738409	G (148M)	**0.720 (G)**	0.293	0.403	0.0019
		rs2294918	A (434K)	0.107 (A)	0.173	0.191	0.4386
Африка	AFR (n=661)	rs738409	G (148M)	0.118 (G)	0.188	0.208	0.0244
		rs2294918	A (434K)	0.104 (A)	0.174	0.186	0.1581
	ACB (n=96)	rs738409	G (148M)	0.13 (G)	0.219	0.227	0.9781
		rs2294918	A (434K)	0.13 (A)	0.219	0.227	0.9781
	ASW (n=61)	rs738409	G (148M)	0.172 (G)	0.213	0.285	0.1216
		rs2294918	A (434K)	0.115 (A)	0.164	0.203	0.3196
	ESN (n=99)	rs738409	G (148M)	0.126 (G)	0.192	0.221	0.3542
		rs2294918	A (434K)	0.056 (A)	0.111	0.105	1.0
	GWD (n=113)	rs738409	G (148M)	0.106 (G)	0.177	0.19	0.7074
		rs2294918	A (434K)	0.124 (A)	0.195	0.217	0.4458
	LWK (n=99)	rs738409	G (148M)	0.086 (G)	0.131	0.157	0.2819
		rs2294918	A (434K)	0.106 (A)	0.212	0.19	0.6110
	MSL (n=85)	rs738409	G (148M)	0.112 (G)	0.176	0.199	0.5317
		rs2294918	A (434K)	0.100 (A)	0.153	0.18	0.3655
	YRI (n=108)	rs738409	G (148M)	0.116 (G)	0.213	0.205	1.0
		rs2294918	A (434K)	0.097 (A)	0.157	0.176	0.5046

End of table 1

1	2	3	4	5	6	7	8
American	AMR (n=347)	rs738409	G (148M)	0.484 (G)	0.478	0.499	0.4795
		rs2294918	A (434K)	0.212 (A)	0.360	0.334	0.1942
	CLM (n=94)	rs738409	G (148M)	0.41 (G)	0.564	0.484	0.1772
		rs2294918	A (434K)	0.229 (A)	0.457	0.353	0.0037
	MXL (n=64)	rs738409	G (148M)	**0.555 (G)**	0.422	0.494	0.3260
		rs2294918	A (434K)	0.172 (A)	0.312	0.285	0.8301
	PEL (n=85)	rs738409	G (148M)	**0.718 (G)**	0.376	0.405	0.6473
		rs2294918	A (434K)	0.100 (A)	0.153	0.180	0.3655
	PUR (n=104)	rs738409	G (148M)	0.317 (G)	0.519	0.433	0.0742
		rs2294918	A (434K)	0.312 (A)	0.471	0.43	0.482
East Asian	EAS (n=504)	rs738409	G (148M)	0.350 (G)	0.419	0.455	0.0855
		rs2294918	A (434K)	0.182 (A)	0.284	0.297	0.3711
	CDX (n=93)	rs738409	G (148M)	0.231 (G)	0.333	0.355	0.6981
		rs2294918	A (434K)	0.21 (A)	0.312	0.331	0.7308
	CHB (n=103)	rs738409	G (148M)	0.383 (G)	0.456	0.473	0.8413
		rs2294918	A (434K)	0.141 (A)	0.282	0.242	0.2011
	CHS (n=105)	rs738409	G (148M)	0.39 (G)	0.438	0.476	0.3900
		rs2294918	A (434K)	0.238 (A)	0.343	0.363	0.238
	JPT (n=104)	rs738409	G (148M)	**0.418 (G)**	0.394	0.487	0.0736
		rs2294918	A (434K)	0.087 (A)	0.135	0.158	0.3183
	KHV (n=99)	rs738409	G (148M)	0.308 (G)	0.475	0.426	0.3992
		rs2294918	A (434K)	0.237 (A)	0.354	0.362	0.9730
Europian	EUR (n=503)	rs738409	G (148M)	0.226 (G)	0.344	0.349	0.7937
		rs2294918	A (434K)	**0.371 (A)**	0.479	0.467	0.6294
	CEU (n=99)	rs738409	G (148M)	0.217 (G)	0.354	0.340	0.9869
		rs2294918	A (434K)	0.323 (A)	0.438	0.438	0.8946
	FIN (n=99)	rs738409	G (148M)	0.172 (G)	0.303	0.284	0.8459
		rs2294918	A (434K)	0.369 (A)	0.495	0.466	0.7196
	GBR (n=99)	rs738409	G (148M)	0.253 (G)	0.374	0.378	1.0000
		rs2294918	A (434K)	0.346 (A)	0.473	0.453	0.8988
	IBS (n=107)	rs738409	G (148M)	0.257 (G)	0.364	0.382	0.7739
		rs2294918	A (434K)	**0.407 (A)**	0.551	0.483	0.2177
	TSI (n=107)	rs738409	G (148M)	0.229 (G)	0.327	0.353	0.5769
		rs2294918	A (434K)	**0.402 (A)**	0.449	0.481	0.5878
South Asian	SAS (n=489)	rs738409	G (148M)	0.246 (G)	0.354	0.371	0.3412
		rs2294918	A (434K)	0.228 (A)	0.350	0.352	0.9561
	BEB (n=86)	rs738409	G (148M)	0.244 (G)	0.419	0.369	0.3697
		rs2294918	A (434K)	0.198 (A)	0.349	0.317	0.6170
	GIH (n=103)	rs738409	G (148M)	0.311 (G)	0.388	0.428	0.4391
		rs2294918	A (434K)	0.209 (A)	0.32	0.33	0.9265
	ITU (n=102)	rs738409	G (148M)	0.221 (G)	0.324	0.344	0.6985
		rs2294918	A (434K)	0.225 (A)	0.373	0.349	0.7539
	PJL (n=96)	rs738409	G (148M)	0.198 (G)	0.271	0.317	0.2419
		rs2294918	A (434K)	0.297 (A)	0.406	0.417	0.9327
	STU (n=102)	rs738409	G (148M)	0.255 (G)	0.373	0.38	0.9960
		rs2294918	A (434K)	0.211 (A)	0.304	0.333	0.5155

Notes: MAF - is the frequency of the minor allele; Ho - observed heterozygosity; He is the expected heterozygosity; high frequencies of the minor allele are indicated in bold; YKT - Yakuts from Yakutia, Russia; AFR - Africans; ACB – African Carribian in Barbados; ASW - African Ancestry in Southwest US; ESN - Esan in Nigeria; GWD - Gambians in Western Division, The Gambia; LWK - Luhya in Webue, Kenya; MSL - Mende in Sierra-Leone; YRI - Yoruba in Ibadan, Nigeria; AMR - American; CLM - Colombian in Medellin, Colombia; MXL – Mexican Ancestry in Los Angeles, California; PEL - Peruvians in Lima, Peru; PUR - Puerto Rican in Puerto Rico; EAS - East Asian; CDX - Chinese Dai in Xishuangbanna, China; CHB - Han Chinese in Beijing, China; CHS - Southern Han Chinese, China; JPT - Japanese in Tokyo, Japan; KHV - Kinh in Ho Chi Minh City, Vietnam; EUR - European; CEU - Utah residents with Northern and Western European ancestry; FIN - Finnish in Finland; GBR – British in England and Scotland; IBS - Iberian population in Spain; TSI - Toscani in Italy; SAS - South Asian; BEB - Bengali in Bangladesh, India; GIH - Gujarati Indian in Houstan, Texas; ITU - Indian Telugu in the UK; PJL - Punjabi in Lahore, Pakistan; STU - Sri Lankan Tamil in The UK

tively). At the same time, in the populations of East Asia and America, the frequency of the risky allele G (rs738409) is significantly higher than the frequency of the protective allele A (rs2294918), while in the populations of Western Europe, a higher frequency of the protective allele A (rs2294918) is observed.

A weak linkage disequilibrium (LD) was observed between the two SNPs (D' = 0.096; r 2 = 0.003 in Yakuts. In other samples, strong linkage D' = 1, r 2 = 0.015 in Africans, D' = 0.98, r 2 = 0.242 in Americans, D' = 1, r 2 = 0.12 in East Asians, D' = 1, r 2 = 0.172 in Europeans, and D' = 1, r 2 = 0.097 in South Asians.

Analysis of the frequency distribution of genotypes in the studied sample of Yakuts showed the predominance of carriage of the GG genotype (57.3%). Genotypes AA and AG carrying the protective A allele are more common in European populations (13.1% and 47.9%, respectively).

The distribution of PNPLA3 gene haplotype frequencies for two SNPs (rs738409, rs2294918) based on all detected variants is presented in Table 2.

We identified two major haplotypes whose frequency was >0.1. One of the most common haplotypes carries the G variant (148M), the other carries the C variant (148I) and both carry the same G variant (434E). In other words, the more common two haplotypes carry the G (434E) allele, while the protective A (434K) allele does not occur in the major haplotypes found. The protective allele A (434K) is carried by both rare haplotypes. Haplotype G-A (148M-434K) was found only in Yakuts and Mexicans (6.9% and 1.1%, respectively).

The distribution of diplotype frequencies for two SNPs (rs738409-rs2294918) of the PNPLA3 gene showed 8 diplotypes out of nine possible variants. In Yakuts, two diplotypes [GG][GG] and [CG][GG] are more common. Both diplotypes carry the G allele (rs738409) (45.3% and 28%) and do not carry the protective A allele (rs2294918). The same distribution of diplotype frequencies was found in Peruvians (52.9% and 24.7%), Mexicans (32.8 and 23.4%) and Japanese (22.1 and 32.7%). Diplotypes carrying the protective allele A (rs2294918) occur at a low frequency (Table 3). Diplotypes [GG][AA] and [CG][AA] are absent in all 25 population samples, except for the diplotype [GG][AA] found in Yakuts (1.3%). In the Yoruba tribe, among the seven discovered diplotypes, [CC][GG] is more common (63.9%). This diplotype does not carry the pathological G allele (rs738409) and does not carry the protective A allele (rs2294918).

NAFLD is a multifactorial disease, timely developed patient management tactics will avoid the formation of complicated forms of the disease. The rs738409 polymorphism of the PNPLA3 gene is a major determinant of liver fat and predisposes to the full spectrum of liver damage in NAFLD. Many researchers have concluded that the G allele (rs738409) can increase the development of non-alcoholic fatty liver disease, while increasing serum ALT levels [2,5,6]. In their study, Donati, Motta, Pingitore, et al. (2016) found that carriers of the A (rs2294918) allele had lower levels of PNPLA3 protein in the liver ($P < 0.05$), thus this allele prevents the negative effects of the allele G (rs738409) [5].

Thus, in all samples of African origin, among the detected diplotypes, [CC][GG] is more common, which does not carry the pathological G allele (rs738409) and does not carry the protective A allele (rs2294918). An interesting fact is the absence of [GG][AA] and [CG][AA] diplotypes in all the 25 world samples studied, except for the Yakuts, in which we found the [GG][AA] diplotype with a frequency of occurrence of 1.3%. This diplotype may be found in the Yakut population due to the high prevalence of carriers of the homozygous GG variant (rs738409).

In our sample of Yakuts, two diplotypes [GG][GG] and [CG][GG] are more common. These diplotypes carry the mutant G allele (rs738409) and do not carry the A allele (rs2294918), which has a weakening effect on 148M, which in turn contributes to the accumulation of

Table2

The frequency of haplotypes I148M - E434K in the Yakut population and in the populations of the 1000 genomes project

Haplotypes	Protein	Haplotype frequency					
		YKT (n=150)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-G	148M-434E	**0.651**	0.118	**0.482**	0.350	0.226	0.246
C-G	148I-434E	0.243	**0.778**	0.306	**0.468**	**0.404**	**0.526**
G-A	148M-434K	0.069	0	0	0	0	0
C-A	148I-434K	0.037	0.104	0.210	0.182	0.371	0.228

Table3

Distribution of diplotypes by two SNP markers of the PNPLA3 gene in the Yakut population and in the populations of the 1000 genomes project

Genotype / SNP		Diplotype	Diplotype frequency					
rs738409	rs2294918		YKT (n=150)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
GG	GG	[GG][GG]	**0.453**	0.024	0.242	0.141	0.054	0.070
CG	GG	[CG][GG]	0.280	0.162	**0.282**	**0.317**	0.155	0.249
GG	AG	[GG][AG]	0.107	0.000	0.003	0.000	0.000	0.000
CG	AG	[CG][AG]	0.013	0.026	0.196	0.101	0.189	0.104
GG	AA	[GG][AA]	0.013	0.000	0.000	0.000	0.000	0.000
CC	AA	[CC][AA]	0.007	0.017	0.032	0.040	0.131	0.053
CC	AG	[CC][AG]	0.053	0.148	0.161	0.183	**0.290**	0.245
CC	GG	[CC][GG]	0.073	**0.623**	0.084	0.218	0.181	**0.278**
CG	AA	[CG][AA]	0.000	0.000	0.000	0.000	0.000	0.000

triglycerides in hepatocytes. The liver is responsible for the production of digestive bile, filtration of blood and processing of raw materials coming from food into the necessary chemical elements for the work of other organs. In his article Simcox J. and co-authors (2017) demonstrated in mice exposed to cold that acylcarnitines produced by the liver are necessary to maintain thermogenesis [10]. It is possible that in the Yakuts, the accumulation of fat in the liver in the past did not lead to NAFLD, as the accumulated fat was quickly converted into energy for heat generation. In modern realities, this diplotype has its detrimental effect by increasing the incidence of metabolic diseases, including NAFLD.

Conclusion. Thus, the high frequency of diplotypes [GG][GG] and [CG][GG] in Yakuts (45.3% and 25%, respectively) carrying mutant alleles G (rs738409) and not carrying allele A (rs2294918) which has a weakening effect on 148M indicates that these diplotypes in the past, they were probably adaptively favorable for the Yakuts. A normally functioning protein of the PNPLA3 gene regulates the activity of triglyceride hydrolase and acyltransferase of phosphatidic acid. Therefore, it can be assumed that the high frequency of the mutant allele G polymorphism rs738409, as well as the low frequency of the protective polymorphism rs2294918 of the PNPLA3 gene in Yakuts may be one of the reasons for the violation of the mechanism of lipid metabolism and lead to various liver diseases. The obtained data on the frequencies of markers rs738409 and rs2294918 of the PNPLA3 gene can be used in the diagnosis of susceptibility to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) for the prevention of these diseases, as well as in the study of the genetic mechanisms of human adaptation to cold.

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INDIVIDUAL DIFFERENCES IN THE NUMBER OF MITOCHONDRIAL DNA COPIES: THE EFFECT OF SOCIO-DEMOGRAPHIC FACTORS

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According to the published data, the number of copies of mitochondrial DNA (mtDNA copy-number) reflects the efficiency of mitochondria functioning and, hence, the amount of cell-produced energy (in the form of ATP), which is an important indicator of the normal functioning of an organism. Differences in mtDNA copy-number are caused by a complex effect of various environmental factors including chemical, biological or physiological stress, age, and embryonic development. However, to date it remains unknown, which factors and at what age have the most significant impact on mtDNA copy-number and cause greater allostatic load. Therefore, the present study aimed to assess the involvement of various socio-demographic parameters in manifesting mtDNA copy-number in healthy individuals aged 18-25 years (N=1065). The analysis of the relative mtDNA copy-number was carried out by quantitative real-time PCR. As a result of multiple linear regression analysis including socio-demographic factors as predictors of the relative mtDNA copy-number, the optimal model was obtained (r2 = 0.03; F = 10.83; P <0.05), where age (β = -0.02; P <0.01) and childhood maltreatment (β = 0.05; P = 0.05) were the most statistically significant predictors. The data obtained confirm the role of mitochondria as key components in the physiological response to stress in humans and also indicate that the processes of gradual reduction in the energy efficiency of mitochondria begin even at the age of 18-25 years.

Keywords: mitochondrial DNA, mitochondria, environmental factors, mitochondrial theory of aging, allostatic load.

Introduction. Mitochondria represent intracellular organelles present in almost all eukaryotic cells, whose main function is to produce biochemical energy in the form of adenosine triphosphate (ATP) [1]. Moreover, mitochondria play an important role in the regulation of iron and calcium homeostasis, hormone synthesis, apoptosis, and n maintain the redox balance [18]. Mitochondria differ from all other animal organelles by the presence of their own DNA (mitochondrial DNA, mtDNA), which encodes 37 genes in humans: 2 ribosomal RNA genes, 22 transport RNA genes, 13 protein-encoding genes [4]. According to the published data, mtDNA copy-number reflects the efficiency of mitochondria functioning and, hence, the amount of energy produced by cells (ATP), which is an important indicator of the normal functioning of an organism [9]. Molecular epidemiological studies have demonstrated that mtDNA copy-number in leukocytes might increase the risk of developing cancer, diabetes, cardiovascular diseases, aging-associated diseases, and mental disorders such as depression [11]. The mtDNA copy-number in the human body is strictly regulated during cell differentiation; moreover, the cells requirement for ATP positively correlates with mtDNA copy-number [8]. In addition, a number of studies demonstrating that environmental factors can influence mtDNA copy-number exist. Together with an environmental stress related to the environmental pollution, mtDNA copy-number can also be affected by psychoemotional stress associated with psychological environment, which affected individual especially in early childhood [13]. Moreover, health state of an organism and individual lifestyle represent the important factors that directly affect the optimal functioning of mitochondria, including mtDNA copy-number [19]. However, to date the certain factors and the age of the most significant effect on the changes in mtDNA copy-number, which cause a greater allostatic load remain unknown. In turn, the identification of such environmental predictors of the mtDNA copy-number will allow us to better understand the nature of several socially significant diseases. Therefore, the present study aimed to assess the involvement of various socio-demographic parameters in individual variance in mtDNA copy-number in healthy individuals even in early adulthood.

Materials and methods. The study included 1065 individuals (79.25% women, aged 18–25 years), who were students at the Universities of the Republic of Bashkortostan and the Udmurt Republic. The examined sample consisted of Russians – 357, Tatars – 340, Udmurts – 234, individuals of mixed ethnicity – 134. Participation in the study was voluntary, informed consent was obtained from all the participants. The design of the study was approved by the Ethics Committee of the IBG UFRC RAS. Information on the studied socio-demographic parameters was obtained via questionnaires, including 16 different indicators.

A quantitative analysis of the mtDNA copy number was carried out using real-time PCR on the CFX96 DNA Analyzer (BioRad, USA) according to the Wang et al. (2018) [16]. Each experimental sample was analyzed in triplicate. For further analysis, the average value of the Ct threshold cycle for the ND1 and HGB genes was used. A relative mtDNA copy number was estimated by the formula 2- ΔΔCt, where ΔΔCt = (Ct mtDNA (sample) – Ct ntDNA (calibrator)) - (Ct HGB

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(sample) – Ct HGB (calibrator)). Pooled DNA of several healthy individuals (calibrator) was used as a control sample and was identical in each run of the analyzer. Statistical analysis was carried out using a series of multiple linear regressions with an inclusion of examined socio-demographic parameters as the independent variables, followed by a backward stepwise exclusion of the least significant predictor until the most significant model was obtained. During the backward stepwise selection of variables, the Akaike information criterion, the coefficient of determination (r2) and the statistical significance level (p-value) were used to obtain the optimal model (according to the number of variables). Statistical analysis and data visualization was carried out under R v.4.1.2. The level of statistical significance was assumed to be 0.05.

Results and discussion. The mean values and a list of the studied socio-demographic indicators are shown in Table.

As a result of multiple regression analysis including 16 various socio-demographic factors as predictors of relative copy-number of mtDNA we obtained the optimal model ($R2 = 0.03$; $F = 10.83$; $P < 0.05$) including age ($\beta = -0.02$; $P < 0.01$) and maltreatment in childhood ($\beta = 0.05$; $P = 0.05$) (Table 2). According to the constructed model, relative copy-number of mtDNA was increased in individuals, who experienced maltreatment in childhood, whereas a negative association was reported with age (Fig. 1).

According to the published data, early adverse events may cause irreversible changes in a number of biochemical and molecular-genetic parameters [21], including changes in the number of mtDNA copy-number [14]. One of the potential systems, which can modulate these modifications, is the endocrine system, which functioning is mediated by an activation of the hypothalamic-pituitary-adrenal axis in individuals experienced childhood abuse [7]. Stress is known to induce the synthesis of glucocorticoids, which trigger molecular mechanisms [12] resulting in the changed mitochondrial density and functioning via modified expression of mitochondrial and nuclear genes [17]. Moreover, glucocorticoids can regulate the functioning of mitochondria by activating glucocorticoid receptors on mitochondrial membranes, thus regulating their membrane potential and triggering intracellular signaling pathways that significantly affect biogenesis and functional activity of mitochondria [12, 17].]. In addition, stressful life events occurring at an early age, which also include childhood maltreatment, are known to increase oxidative stress, which, in turn, causes mitochondrial damage [15]. To date, specific mechanisms responsible for regulating the mtDNA copy-number remain unknown, however, a hypothesis on the relation between the initiation of mtDNA replication and mitochondrial dysfunction caused by the effect of hypothalamic-pituitary system hormones was suggested [5]. The experiments with model animals demonstrated that mtDNA copy-number was increased by 210% in the group of stress- or corticosterone-exposed mice compared to the control group [3]. Therefore, the mtDNA copy-number seems to reflect the functional changes occurred in mitochondria, which affect the energy production by cells. Assuming the abovementioned data, stress significantly impacts the organism's state, primarily, homeostasis of cells, organs and tissues, resulting in enhanced demand for energy, which synthesis depends on mitochondria.

Table1

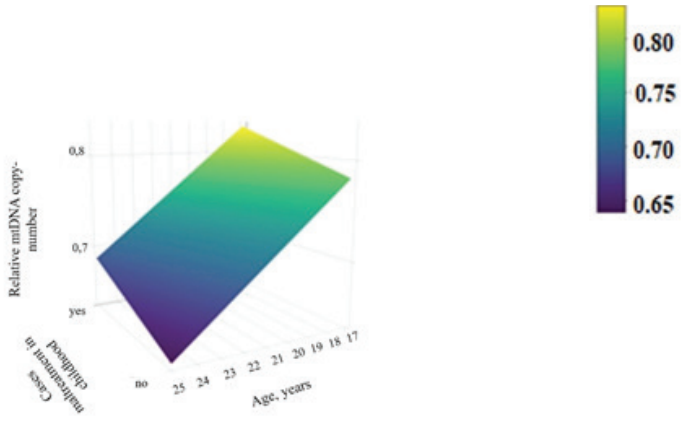
Studied socio-demographic parameters

Parameter	N (%)	Parameter	N (%)
Sex		Childhood maltreatment	
Men	221 (20.75)	yes	104 (9.78)
Women	844 (79.25)	no	961 (90.22)
Ethnicity		Bilingual rearing	
Russians	357 (33.52)	yes	591 (55.49)
Tatars	340 (31.92)	no	474 (44.51)
Udmurts	234 (21.97)		
Mixed	134 (12.59)		
Place of residence		Chronic disorders	
Urban	609 (57.14)	yes	344 (32.26)
Rural	456 (42.86)	no	721 (67.74)
Birth order		Smoking	
1	646 (60.65)	yes	95 (8.88)
2	327 (30.69)	previously	91 (8.57)
>3	92 (8.66)	non-smoking	879 (82.55)
Sibship size		Maternal care	
1	216 (20.29)	high	772 (72.49)
2	564 (53.00)	low	293 (27.51)
>3	285 (26.71)		
Premature birth		Maternal protection	
no	964 (90.53)	high	590 (55.44)
yes	101 (9.47)	low	475 (44.56)
Income level		Paternal care	
Under intermediate	113 (10.57)	high	564 (52.95)
Intermediate	878 (82.45)	low	501 (47.05)
Above intermediate	74 (6.98)		
Rearing in a full family		Paternal protection	
yes	892 (83.72)	high	500 (46.91)
no	173 (16.28)	low	565 (53.09)

Table2

The predictors of mtDNA copy-number variance included in the model

Predictor	β	Standard error	t-criterion	p
Intercept	1.09	0.10	11.46	<0.01
Childhood maltreatment	0.05	0.02	1.96	0.05
Age	-0.02	< 0.01	-3.92	<0.01



Relation between a relative mtDNA copy-number and childhood maltreatment

The second important result obtained in the present study is a negative association between individual age mtDNA copy-number, which is consistent with the mitochondrial theory of aging. According to this theory, the accumulation of damages within mtDNA replication (mtDNA has a lower replication accuracy and repair efficiency compared to nuclear DNA) results in impaired processes of oxidative phosphorylation and ATP synthesis [10]. In turn, these disturbances are accompanied by enhanced levels of reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxyl radical. ROS can cause oxidative damage to proteins, lipids, nucleic acids, redox enzymes, as well as cell membranes and organelles, including mitochondria, also promoting diminished ATP synthesis [20]. Moreover, ROS can cause new impairments in mtDNA, resulting to greater increase in ROS level in the organism. The mitochondrial theory of aging is confirmed by literature data indicating an increased heteroplasmy and a decreased mtDNA copy-number with age [6, 18], as well as by the results of the present.

Conclusion. Therefore, within the present study, the effect of a number of socio-demographic parameters on inter-individual variance in mtDNA copy-number was examined in healthy individuals aged 18-25 years. Among 16 parameters, statistically significant findings were shown for such variables as childhood maltreatment and age, confirming the role of mitochondria as key components in the physiological response to stress in humans. Previously, a decreased mtDNA copy-number was considered to start at ~50 years [18]; however, within the present study it was primarily shown that a negative relation between age and mtDNA copy-number was statistically significant even at the student age, hence, the processes of gradual decrease in the energy efficiency of mitochondria begin even at this age. Several studies describing the changes in the mtDNA copy-number accompanying the clinical symptoms of depression [11] and post-traumatic stress disorder [2] have been published, which indicates the role of mitochondrial dysfunction in the pathophysiological mechanisms of mental illness. A relation of the mtDNA copy-number and the psychoemotional state of a person has been also confirmed by the present study, thus, individual mtDNA copy-number varied depending on the presence of negative childhood experiences; however, the causal relationships have to be studied. Therefore, the results obtained by our group open up new opportunities for further research in gerontology and psychiatry.

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THE USE OF REAL-TIME PCR FOR THE DIAGNOSIS OF Z GENE MUTATION PI IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY

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The aim of this study is to develop a method for diagnosing PiZ mutation associated with alpha-1 antitrypsin deficiency using real-time PCR technology.

The number of patients and the control group was 503 and 81 individuals, respectively.

A simple method is proposed for detecting one of the most frequent mutations of the Pi gene PiZ associated with alpha-1 antitrypsin deficiency. Priority exclusion of the PiZ mutation as the most significant one may allow to speed up diagnosis and make it more accessible to practical healthcare.

Keywords: SERPINA1; alpha-1-antitrypsin deficiency, real-time PCR.

Introduction. The aim of this study is to develop a method for diagnosing frequent mutations associated with alpha-1 antitrypsin deficiency using real-time PCR technology.

Alpha-1 antitrypsin deficiency is a hereditary disease associated with a number of mutations in the Pi protease inhibitor gene. The gene controlling the structure of AAT - SERPINA1 is located on the long arm of chromosome 14 (14q31-32.2), contains 7 exons (four coding (2-4 and 5) and three non-coding (1a, 1b, 1c), for which more than 200 [5] allelic variants are known, inherited by autosomal codominant type (OMIM 107400).

The designation of alleles of the Pi gene is carried out by letters of the Latin alphabet from A to Z, depending on the position of the product in the gel during isoelectric focusing. The most common variants of alleles are PiM alleles, in which the concentration of AAT in the blood serum is within normal values (90-200 mg/dl or 16.5-36.8 μmol/L according to the method we used). Alleles associated with insufficient protein levels are registered much less frequently and in some cases are characterized, in addition to deficiency, by a decrease in the functional activity of AAT, such as the Z allele, which is the most significant in clinical practice [4]. It is known that 95% of patients with AATD have the PiZZ genotype [2].

Alpha-1 antitrypsin deficiency is a widespread, but to this day rarely diagnosed disease [6]. Diagnosis is often delayed for several years and there may be many undiagnosed individuals with AATD in the population [9]. Since PiZ is the most common pathological allele in most populations, depending on the spectrum of mutations in a particular population, it makes sense to start molecular diagnostics with it. The proposed method of genotyping can help speed up and make the diagnosis of AATD more accessible.

One of the most popular and widespread methods of molecular diagnostics is Real-Time PCR, which has a number of advantages over the classical method with the detection of PCR products by gel electrophoresis and in some cases, for example, over Luminex technology used for multiplex genotyping [8]:

- Reducing the risk of contamination and, accordingly, obtaining unreliable results. The method does not require working directly with the PCR product;
- Acceleration of the experiment as a result of the exclusion of gel electrophoresis, the method of restriction fragment length polymorphism (RFLP) and additional steps associated with the use of separate detection systems;
- The possibility of full automation of the test from DNA extraction to interpretation of the result;
- More accessible reagents and equipment for real-time PCR. The actions against the ongoing SARS-CoV-19 coronavirus pandemic and the use of RT-PCR as the main method of early diagnosis has contributed to a significant expansion of the global fleet of real-time PCR equipment. Laboratories working mainly on this technology are widespread in practical healthcare.

We propose a method for verifying the PiZ mutation using real-time PCR technology. The priority exclusion of the PiZ mutation as the most significant one can speed up the diagnosis of alpha-1 antitrypsin deficiency and make it more accessible for practical healthcare.

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Materials and methods. During the experimental part of the work, DNA samples were taken from 503 pediatric patients with lung and/or liver lesions characteristic of AATD [3]. Of these, 200 patients with liver damage and a group of patients (303 people) with respiratory tract diseases, which, in addition to those characteristic of AATD with chronic non-specific lung diseases, included patients with bronchial asthma and cystic fibrosis. A control group consisting of 81 practically healthy children was included in the study. Experimental samples were recruited on the basis of the FSAU "NMRC of Children's Health" of the Ministry of Health of the Russian Federation (NCD), Moscow and the GAU RS(Ya) "Republican Hospital No. 1-National Center of Medicine", Yakutsk.

Informed consent was obtained from the legal representatives of all patients and the comparison group included in the study.

DNA samples in the sample of patients were obtained from venous blood, and in children of the control group, DNA was obtained from an average portion of morning urine. DNA isolation was performed on spin columns with a sorbent on a silica gel matrix Blood genomicPrep Mini Spin Kit [Cytiva Life Sciences, USA] according to the manufacturer's protocol. In Yakutsk, DNA was isolated by standard phenol-chloroform extraction. The quality of DNA extraction was checked by micro-volume spectrophotometry, using a Nanodrop spectrophotometer [ThermoFisher Scientific, USA] or BioSpec Nano [Shimadzu, Japan].

A real-time DNA amplifier CFX96 [Bio-Rad labs, USA] was used to perform PCR. Real-time PCR was performed using Taqman technology [1].

The following primers and probes were used:

Straight

5'-GCTTCCTGGGAGGTGTC-CACG-3'

Reverse

5'-TTCCCATGAAGGGG-GAGACTTGG-3'

Probes

Wild Type

5'-FAM-CCAGCAGCTTCAGTC-CCTTTCTCGTC-RTQ1-3'

Mutant

5'-R6G-CCAGCAGCTTCAGTC-CCTTTCTTGTC-BHQ2-3'

The online tool Primer-BLAST [NCBI, USA] was used to develop oligonucleotide sequences.

The amplification protocol was as follows:

Initial denaturation	95 °C	15 мин	
Denaturation	95 °C	15 с	40 циклов
Annealing of primers	70 °C	1 мин	
Registration of fluorescence			

PCR was performed in a reaction mixture containing 2.5 µl of buffer "C" (pH 8.8) for Taq polymerase ThermoStar, 1.5 mmol of each dNTP, 10 pmol of each primer, 0.25 pmol of each probe, 1.5 units of Taq ThermoStar polymerase [Silex, Russia] and 0.3-1.0 µg of genomic DNA in a total volume of 25 µl. As reaction vessels, polypropylene tubes of the Eppendorf type with a capacity of 200 µl. with an optical lid or standard 96-well microplates with a capacity of 200 µl. sealed with an optically transparent film were used.

With a normal allele, fluorescence was recorded only from the FAM probe (Fig. 1 a), with a homozygote for the mutant allele only from R6G (Fig. 1 c), and in the case of a heterozygous state, both probes were recorded (Fig. 1 b).

In each series of PCR, negative and positive control samples were used, confirmed by Sanger sequencing on the basis of the V.A. Engelhardt Institute of Molecular Biology, Moscow. The first sample homozygous for the PiZ allele identified in this study was used as a positive control.

Results and their discussion. A total of 7 patients heterozygous for the mutant PiZ allele (PiMZ genotype) and 5 patients with the homozygous PiZZ genotype were identified. The detected mutation cases were verified using PCR-RFLP.

The use of a widely available real-time PCR method with priority exclusion of frequent mutations can speed up the diagnosis [7].

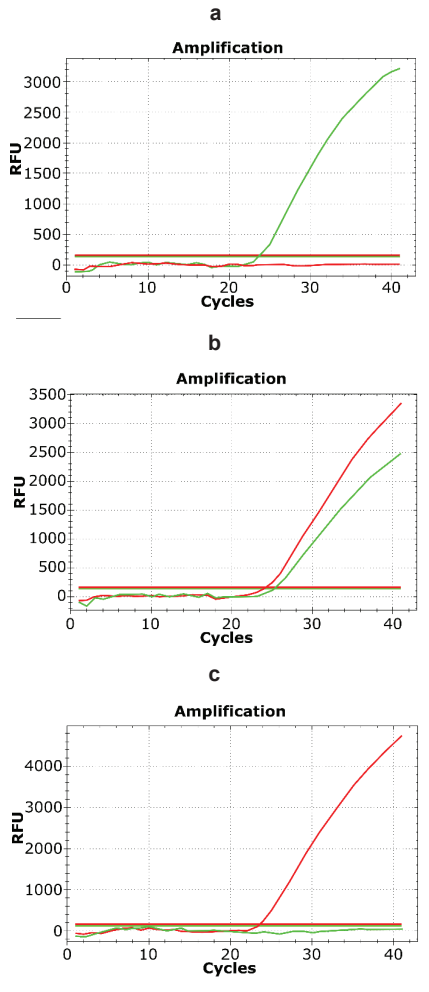
The algorithm of laboratory diagnostics of AATD using real-time PCR to exclude frequent mutations may look like this:

1. Clinical justification of the need to exclude AATD;

2. Determination of serum AAT level. If a reduced or threshold level of AAT is detected, the transition to stage 3;

3. Exclusion of frequent mutations for a given population, for example PiZ, by real-time PCR. The identification of a frequent mutation at this stage provides information that allows to complete the diagnostic search. In case of exclusion of frequent mutations – transition to stage 4;

4. Search for rare mutations by sequencing coding exons of the Pi gene. It can be produced in a higher-level institution (for example, a research institute).



Fluorescence curves in real–time PCR: a – normal allele, b – heterozygote by mutant allele, c - homozygote by mutant allele

Due to the high variability [10] of serum AAT levels in various mutations and genotypes, inflammatory reactions, molecular genetic diagnostics is recommended not only for low or threshold AAT levels, but also for patients who have a concentration of AAT that falls into the "gray zone".

Timely detection of mutations associated with alpha-1 antitrypsin deficiency is the key to optimal patient management, which significantly improves the quality of life and its expected duration.

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INFLUENCE OF WATER INFUSION OF THE HERB PULMONARIA OBSCURA DUM. ON THE BIOELECTRIC ACTIVITY OF THE BRAIN IN WAG/RIJ FEMALE RATS

The article presents the results of a study of the bioelectrical activity of the neocortex under conditions of oral administration of an aqueous extract of the herb Lungwort (*Pulmonaria obscura* Dum.) to female rats of the WAG/Rij line. During the experiment, the animals at the same time were orally administered an aqueous infusion of the herb at the rate of 1,5 g per 200 ml of water. The results of the study showed a statistically significant ($p<0,05$) decrease in the power of the theta rhythm (6,95±0,72%) and high-frequency beta rhythm (1,83±0,56%) by the end of the first week of the experiment in the anterior areas of the brain, the delta rhythm (64,25±4,95%) and theta rhythm (21,28±5,43%) also significantly ($p<0,05$) decrease in the posterior lobe of the brain. Thus, changes in the theta rhythm and high frequency beta rhythm in the frontal lobe of the neocortex of female rats may be associated with a decrease in excitability, anxiety, and fear. The data of our work demonstrated the stimulating effect of *Pulmonaria obscura* Dum. on the brain of female rats of the WAG/Rij line, manifested by activity on the electroencephalogram.

Keywords: absence epilepsy, Pulmonaria obscura Dum, electroencephalogram, rats of the WAG/Rij line, herbal medicine.

Introduction. Medicinal plants and herbal preparations of plant origin, despite the weaker pharmacological activity, in some cases, for example, in chronic diseases, can be much more effective than their synthetic or chemical counterparts. The advantage of preparations from medicinal plants, in comparison with synthetic agents, is that they act in a complex way, they are easier to tolerate and are tolerant for the metabolic system of the human body, the overall therapeutic effect of exposure consists of the sum of multiple actions of all substances of the plant both on individual organs and on the functional systems of the body as a whole [1, 5].

Plants of the genus *Pulmonaria* include about 70 species, they are widespread in many regions of Russia, have a good raw material base and are used in folk medicine for the treatment of diseases of the upper respiratory tract, gastrointestinal tract, and hematopoietic system [1, 15, 17, 22, 26]. Lungworts are mainly used in folk medicine, they are practically not used in official medicine, due to the insufficiently studied chemical composition. According to the literature, the pharmacological activity of some species of lungwort (*Pulmonaria officinalis* L., *Pulmonaria obscura* Dum., *Pulmonaria mollis* Wulf ex Hornem) has been established - anti-inflammatory, enveloping, emollient, expectorant, analgesic, wound healing, antiseptic, having a positive effect on the urinary system, processes hematopoiesis, regulation of the activity of the endocrine glands, a number of authors point to the use of lungwort infusions in the treatment of nervous diseases [3, 11, 16, 21, 23].

Of particular interest is the use of medicinal plants in epilepsy, since this neurological disease is one of the most common in the world. Epilepsy is complicated by the fact that it can begin at any age, however, approximately 70% of debuts occur in childhood and adolescence. Various synthetic drugs are used to treat epilepsy, however, despite the severity of the therapeutic effect, they have serious side effects [29]. Therefore, an urgent task is to study the possibility of using herbal remedies in the treatment of this neurological disease, since they can be used for a long time, be effective and safe [28].

In the literature available to us, we have not seen scientific works devoted to the influence of plants of the genus lungwort on electroencephalographic indicators of the functional state of the brain in epilepsy. In this regard, the aim of the work was to study the bioelectrical activity of the brain of rats with a genetic predisposition to absence epilepsy under conditions of oral administration of an

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aqueous infusion of the herb *Pulmonaria obscura* Dum.

Materials and research methods. The experiments were carried out on sexually mature female WAG/Rij rats (n=10, m=115-135 g) at the age of six months. The genetic line of WAG/Rij rats is a model of human absence epilepsy [28]. The females were kept in the vivarium of the Department of Physiology and General Biology of the Bashkir State University, where a constant temperature (20-22 °C) and humidity were maintained. The experimental part of the work was carried out in accordance with the international principles of the Helsinki Declaration on the Humane Treatment of Animals (2000).

The experimental group of female rats was orally administered 1 ml of an aqueous infusion of *Pulmonaria obscura* Dum. prepared at the rate of 1.5 g of crushed dry lungwort herb per 200 ml of water daily for 21 days. The electrical activity of the brain was recorded at the end of the first, second, and third weeks of the experiment at the same time from the frontal and parietal regions of the rat neocortex using needle electrodes on a Neuron-Spectrum-1 electroencephalograph (Russia).

The obtained data were processed using the STATISTICA v.12 software package (Stat Soft Inc., USA) using the nonparametric Mann-Whitney U test. Differences were considered statistically significant at p<0,05.

Research results and discussion. Since electroencephalography is a method of recording electrical potentials, it is characterized by such a concept as frequency. EEG activity, which is a wave of approximately the same constant frequency, is called a rhythm. The following main EEG rhythms are distinguished: delta rhythm (0,5-3 Hz), theta rhythm (4-6 Hz), alpha rhythm (8-13 Hz), low-frequency beta rhythm (13-18 Hz) and high-frequency beta rhythm (18-32 Hz) [10]. Highly informative in epilepsy are alpha, beta and theta rhythms. Sinusoidal activity in the range of these rhythms is a characteristic feature of seizures occurring during epilepsy [2, 14, 21].

The study of the background EEG from both lobes of the neocortex of the control group of female rats (before the introduction of the herbal decoction) revealed the theta rhythm to be predominant; by the end of the first week of the experiment, the delta rhythm became the dominant rhythm. On the 14th day of taking the herb *Pulmonaria obscura* Dum. in females, a pronounced transition of the theta rhythm to the delta rhythm was noted, and on the 3rd week of the experiment, the theta rhythm prevailed on the EEG (Fig. 1).

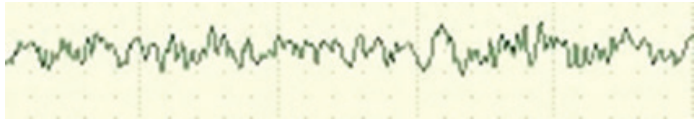
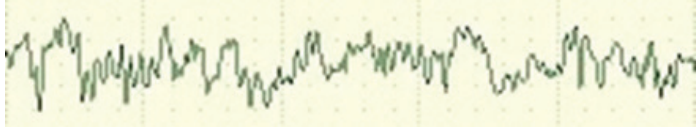
Days of definition	EEG of females
Control group (before applying *Pulmonaria obscura* Dum.)	
7th day	
14th day	
21st day	

Fig. 1. Dominant rhythms during EEG recording in female WAG/Rij rats before and after taking an aqueous infusion of the herb Pulmonaria obscura Dum.
Scale: 10 μV/mm. Development: 25 mm/s.

The study of the bioelectrical activity of the brain from the frontal region showed a significant decrease in the average power of theta rhythm (6,95±0,72%) and high frequency beta rhythm by the end of the first week of the experiment (1,83±0,56%). We associate the obtained results with a possible decrease in excitability, anxiety, and fear [9, 19, 29]. By the 21st day of the experiment, we revealed a generalized increase in the spectral power of theta- (19,20±3,75%) and beta-rhythm of high frequencies (3,23±0,46%), as well as a decrease in the delta rhythm (66 ,48±3,55%) compared with the data obtained on the 7th day of the introduction of the herb infusion. The positive effect of the water infusion of lungwort observed by us from the second week of administration is possibly associated with an increase in the theta rhythm, since the generation of theta rhythm is caused by the hippocampus, and its mossy cells regulate the course of epileptic seizures [27] (Table).

Changes in the frequency power function of electrical activity from the parietal region of the cerebral cortex have specific features. So, on the 7th day of the introduction of lungwort infusion (in comparison with the control group), we found a significant decrease in the power of the high-frequency beta rhythm in females (1,97±0,37% and 3,75±0,49%, respectively) and a statistically significant increase in the delta rhythm (76,74±3,11%). And by the 21st day of oral administration of lungwort, we found a significant increase in the beta rhythm of high frequencies (3,68±0,63%), which indicates an increase in the level of brain activation [8, 24]. In addition, by the end of the experiment, the delta rhythm (64,25±4,95%) and theta rhythm (21,28±5,43%) were statistically significantly reduced compared to the data obtained on the 7th day of the study. Most likely, the revealed results testify to the effective action of *Pulmonaria obscura* Dum. due to the high content of saponins, flavonoids and rosmarinic acid in it. Our data are consistent with the data obtained by Budantsev A.L. and Lesiovskaya E.E. (2012) [4], Polukhina T.S. and Nurgalieva G. B. (2017) [20] (Table).

After analyzing the background EEG recording, we were able to determine the presence of visual phenomena "Epileptiform activity" (Fig. 2) and complexes "acute wave - slow wave" (Fig. 3), which are signs of the presence of absences in the experimental animal model. During the experiment, a decrease in the number of these phenomena is noted, which confirms the positive effect of the use of an aqueous infusion of the herb *Pulmonaria obscura* Dum.

The results of the statistical evaluation of the spectral characteristics of the electroencephalogram from the neocortex of female WAG/Rij rats before and after 7. 14. 21 days of taking an aqueous infusion of lungwort obscure

Experiment day	The share of the neocortex	Delta rhythm.%	Theta rhythm.%	Alpha rhythm.%	Low-frequency beta rhythm.%	High-frequency beta rhythm.%
Control group (determination before application of *Pulmonaria obscura* Dum.)	Frontal	72.75±4.12[1]	13.03±2.89[2]	6.98±0.80	3.63±0.29	3.33±0.27[5]
	Parietal	67.08±4.43[7]	17.33±3.16	7.53±0.59	4.10±0.35	3.75±0.49[10]
7th day	Frontal	76.55±2.00	6.95±0.72[2.3]	6.88±1.27	3.50±0.71	1.83±0.56[5.6]
	Parietal	76.74±3.11[7.8]	11.71±2.81[9]	6.74±1.79	2.78±0.78	1.97±0.37[10.11.12]
14th day	Frontal	74.63±5.11	10.03±3.05[4]	7.68±1.81	4.35±1.24	3.13±0.78
	Parietal	70.00±5.66	14.25±3.74	8.25±1.82	4.00±0.64	3.30±0.50[11]
21st day	Frontal	66.48±3.55[1]	19.20±3.75[3.4]	7.38±1.67	3.50±0.52	3.23±0.46[6]
	Parietal	64.25±4.95[8]	21.28±5.43[9]	6.88±1.03	3.73±0.14	3.68±0.63[12]

Note: 1 - statistically significant differences ($p < 0.05$) on the 7th and 21st days of the study; 2 - the values are reliable ($p < 0.05$) when comparing the control group and on the 7th day of the experiment; 3 - statistically significant differences ($p < 0.05$) on the 7th and 21st days; 4 - reliable values ($p < 0.05$) on the 14th and 21st days; 5 - statistically significant differences ($p < 0.05$) of the control group and on the 7th day of the experiment; 6 - the values are reliable ($p < 0.05$) on the 7th and 21st days; 7 - statistically significant differences ($p < 0.05$) of the control group and on the 7th day of the experiment; 8 - the values are reliable ($p < 0.05$) on the 7th and 21st days; 9 - the values are reliable ($p < 0.05$) on the 7th and 21st days; 10 - the values are reliable ($p < 0.05$) when comparing the rhythm frequencies of females in the control group and on the 7th day of the introduction of lungwort; 11 - statistically significant differences ($p < 0.05$) on the 7th and 14th days; 12 - the values are reliable ($p < 0.05$) on the 7th and 21st days of the study.

Earlier studies of the antiepileptic effect of plant materials showed that intragastric administration of total extracts from Mongolian astragalus (Astragalus mongholicus Bunge) at a dose of 1250 mg/kg revealed a significant effect on the EEG of rats: the intensity of the theta rhythm (stress rhythm) decreased - the effect manifested itself as in the sensorimotor in the cortex and in the hippocampus, it was detected in 30-45 minutes, reaching a maximum in 60-90 minutes after administration. Restoration of the initial bioelectrical activity was observed 120–180 min after administration [7]. Comparing the results obtained by Zhalsray Aldarmaa on the study of Mongolian Astragalus with our data, we can conclude that both Mongolian Astragalus and Lungwort have a positive effect on the central nervous system, due to changes in the theta-rhythm power indicators.

In another experiment, two groups of subjects were involved: the first group took a standardized (pharmacopoeial) alcoholic extract of Rhodiola rosea (*Rhodiolae rosea* L.), the second - a tincture of (*Schizandra chinensis* (Turcz.) Baill.) in standard dosages (30 drops per 100 ml of water). After a single dose of Rhodiola rosea extract, the majority of the subjects changed (decreased compared to the initial values) in the average values of delta, beta and gamma rhythms in both hemispheres. Schisandra chinensis tincture intake did not lead to statistically significant changes in EEG rhythms; the most significant changes occurred in the theta rhythm [12]. Thus, we came to the conclusion that long-term use of *Pulmonaria obscura* Dum. has a better effect than *Schizandra chinensis* (Turcz.) Baill., but less effective than a single application of *Rhodiolae rosea* L.

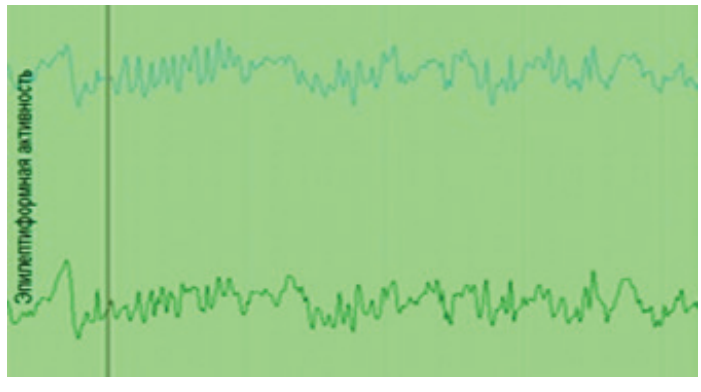


Fig. 2. Epileptiform activity. Scale: 30 μV/mm. Reamer 30 mm/s

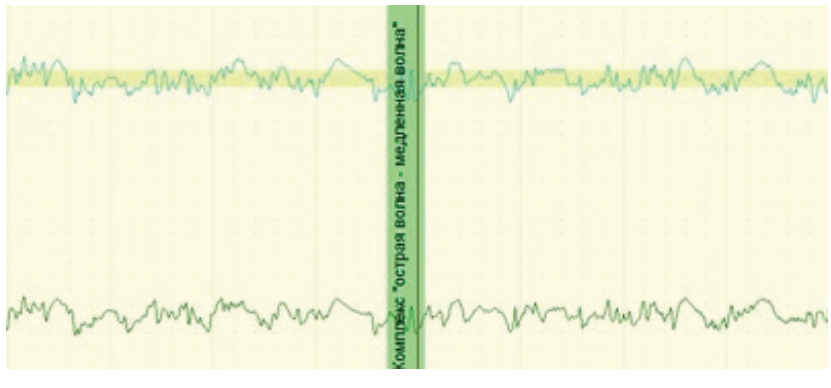


Fig. 3. Complex "acute wave - slow wave" on the electroencephalogram. Scale: 30 μV/mm. Reamer 30 mm/

Conclusion. Thus, as a result of the study, for the first time data were obtained from an electroencephalographic study of the brain of female WAG/Rij rats with oral administration of an aqueous infusion of *Pulmonaria obscura* Dum. Experimental data showed that the course of taking the water infusion of Pulmonaria obscura Dum. at a dose of 1,5 g per 200 ml of water and for a duration of

three weeks, it has a beneficial effect on the electroencephalogram of the brain of rats prone to absence epilepsy [6]. The study lasted 21 days, since the effect of phytopreparations, as a rule, manifests itself by the 3rd week of their use [25]. We assume that *Pulmonaria obscura* Dum. has a positive effect on the state of the functional activity of the brain of rats with absence epilepsy due to the content of a complex of biologically active substances (anthocyanins, flavonoids, saponins, ascorbic, rosmarinic acids, various macro- and microelements) [4, 20]. Further research in this area should be continued to substantiate the possibility of using lungwort herb in the complex therapy of patients with epilepsy.

Restrictions. During the experiment, the result of recording the interictal (interictal) background EEG was evaluated, on which it is possible to determine the beginning, end, and duration of the ictal (attack) sections of the EEG. In addition, by examining the inerictal areas, we can indicate the location of the affected areas [13, 18]. In our study, interictal activity on the baseline EEG plays a key role, as we study absence epilepsy, which is characterized by acute wave-slow wave complexes that typically last 3 to 5 seconds. In this study, the ictal areas of the electroencephalogram were rare. We attribute this to the fact that the EEG recording was not long enough (about 120 minutes).

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DIAGNOSTIC AND TREATMENT METHODS

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RESULTS OF THE STUDY OF COGNITIVE FUNCTIONS IN PATIENTS WITH BRAIN INJURY

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УДК 616-06:616.89-008.46

In the Amur Regional Psychoneurological Dispensary of the Amur Medical Academy, a controlled, open, randomized study was conducted to study cognitive functions in 20 patients with a history of traumatic brain injury (men aged 36 to 58 years, the main group). The control group consisted of 20 practically healthy volunteers. Cognitive functions were assessed using the Montreal Cognitive Assessment (MoCA-test), the Schulte Table method, and the 10-word test. The results of the study showed that in patients in the late period of traumatic brain injury, the presence of cognitive disorders is recorded in 100% of cases. Mild and moderate cognitive impairment in patients with traumatic brain injury up to 6 years is expressed by a 3-fold decrease in work efficiency relative to healthy volunteers, mental stability, short-term and long-term memory. It was concluded that it is necessary to conduct a mandatory neuropsychological examination in patients with craniocerebral injury in the long-term period in order to timely and pathogenetically substantiated pharmacological correction of post-traumatic cognitive dysfunction.

Keywords: cognitive impairment, traumatic brain injury, remote period, work efficiency, degree of development, mental stability, memory, attention, patients.

The problem of cognitive impairment in patients with traumatic brain injury remains a priority today, taking into account the statistical increase in the number of traumatic brain injuries in modern society and the sufficient development of neurorehabilitation methods to compensate for motor deficits, which leads to a less pronounced decrease in the quality of life of patients. than the presence of a defect in cognitive functions [1, 4, 16]. The works of domestic researchers show that the severity and qualitative characteristics of the consequences of various craniocerebral injuries directly depend on the severity and mechanism of injury: in 20% of cases, the consequences of a craniocerebral injury lead to disability, in 45% - to a decrease in working capacity, and only 25% patients return to their previous work [3, 6, 7, 12]. At the same time, it should be noted that in the last decade, most scientists unanimously leave the prevailing positions behind cognitive impairments that form in the late period of mild and moderate traumatic brain injury [2]. This is due to the late diagnosis of cognitive disorders, since patients with traumatic brain injury, as a rule, are represented by a contingent of young people with a high potential for compensatory abilities [9]. For a long time, this category of patients is able to almost fully perform certain work, compensating for the lack of attention and concentration by additional checking of the results of work, and memory loss - by using auxiliary techniques in the form of written recording of the necessary information or repeated verbal repetition [4]. However, the use of auxiliary techniques is an additional load on the functional reserve of the central nervous system, which leads to increased fatigue, and, ultimately, to a decrease in mental performance. That is why, during the initial visit to the doctor in the late period of mild and moderate craniocerebral injury, patients present with complaints that fall into the asthenic range (decreased performance, fatigue, decreased concentration and memory, etc.), which should focus the doctor to conduct a neuropsychological examination to assess cognitive functions, since even minimal dysfunction and mild cognitive impairment can transform into post-traumatic dementia. Moderate cognitive impairment is a decrease in cognitive abilities that goes beyond the age-related educational gender norm, which is reflected in the patient's complaints and may be noticeable to others, however, the presence of moderate cognitive impairment does not lead to significant difficulties in everyday life and is not accompanied by a change in social, household and professional activities, with the exception of the most complex activities [5]. The presence of moderate cognitive impairment in patients with a history of traumatic brain injury is an urgent problem in psychoneurology and predetermines the need for early diagnosis and adequate pathogenetically substantiated therapy in order to correct neuropsychological symptoms and maintain the habitual lifestyle of patients for the longest possible time [13].

The aim of the study was to study cognitive functions in patients in the late period of traumatic brain injury.

Material and methods. A prospective controlled open randomized study was

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conducted in accordance with the Rules of Good Clinical Practice of the Eurasian Union, approved by the decision of the Eurasian Economic Commission (No. registration of pharmaceutical products intended for humans (ICH-GCP - International Conference on Harmonization of Technical Requirements for Human Use) and with the permission of the Local Ethical Committee of the Amur State Medical Academy of the Ministry of Health of Russia.

On the basis of the Amur Regional Psychoneurological Dispensary (Blagoveshchensk), 20 patients aged 36 to 58 years with a history of traumatic brain injury were under observation.

Criteria for inclusion of patients in the study: age over 18 years; cognitive dysfunctions established on the basis of complaints and neuropsychological examination in patients with a history of documented traumatic brain injury of varying severity (S06 according to ICD-10); age-appropriate indicators of the activity of the cardiovascular, respiratory and urinary systems; written voluntary informed consent.

Criteria for exclusion from the study: refusal to sign informed consent; acute infections, including hepatitis B and C, HIV; severe concomitant diseases of internal organs; inability to perform tasks included in the neuropsychological examination (psycho-emotional state of patients).

The number of patients included in the study, depending on the severity of a history of traumatic brain injury and the duration of the disease, is shown in Fig. 1, 2. At admission, all patients complained of decreased performance, fatigue, general weakness, impaired memory and concentration, and recurrent headaches. Standard therapy was prescribed in accordance with the Clinical Guidelines for the Management of Patients with Organic, Including Symptomatic, Mental Disorders in Adults (2016): pathogenetic therapy with the inclusion of dehydration, detoxification, normalizing brain hemodynamics and metabolism of drugs; symptomatic therapy aimed at eliminating the existing productive psychopathological symptoms.

The control group consisted of 20 practically healthy volunteers who, in parallel with the patients of the main group, performed tasks included in the minimum neuropsychological examination to assess cognitive functions. The choice of methods for assessing cognitive functions was based on the studies we performed and described earlier [8, 10, 14, 15].

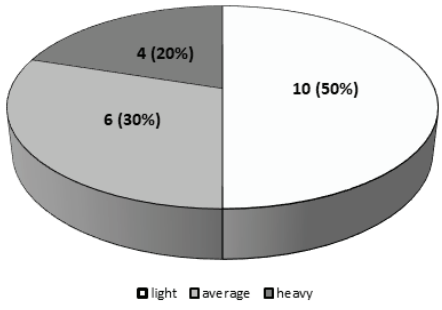

Fig. 1. The number of patients included in the study, depending on the severity of traumatic brain injury in history (%)

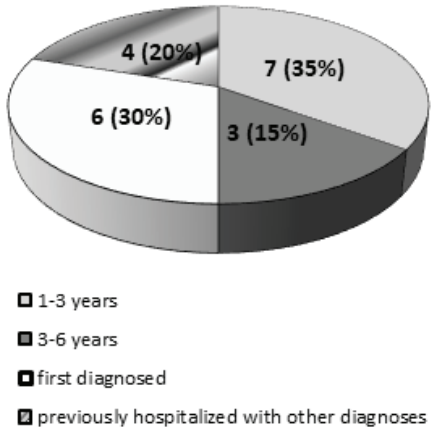

Fig. 2. Number of patients included in the study, depending on the duration of the disease (%)

Before treatment and on the 11th day of therapy, a neuropsychological examination of patients was performed with an analysis of cognitive impairment according to The Montreal Cognitive Assessment (MoCA-test), which was developed as a means of rapid assessment of moderate cognitive impairment. detection (screening) and assessment of the severity of cognitive impairment, allows you to assess visual-constructive / performing skills, memory, attention, speech, the ability to name and abstract, delayed reproduction and orientation.The time for the MoCA test is ± 10 minutes. The maximum score for performance of all tasks is 30; ≥26 points is within the normal range; ≤25 points indicates the presence of cognitive impairment [5].

Diagnostics of the properties of switching and distribution of attention, tempo and sensorimotor reactions was carried out according to the method of "Schulte's Table". Schulte's technique allows you to explore voluntary attention. Schulte tables are tables with randomly arranged numbers, 5 × 5 elements in size. The subject was presented with the first table, voicing the instruction: "This table contains numbers from 1 to 25. Show and name all the numbers in order." Simultaneously with the start of the task, a stopwatch was turned on. Subsequent tables were presented without any instructions. A total of 5 tables were shown. When processing the results, the following indicators were evaluated: work efficiency, degree of workability, mental stability.

The assessment of mnestic disorders was carried out using the test "10 words". The technique allows to evaluate such memory processes as memorization, preservation and reproduction, was first proposed by A.R. Luria. The test was carried out in a quiet environment, without additional sources of noise. The subjects were asked to memorize 10 monosyllabic words that did not have associative links among themselves (for example: umbrella, whale, ruble, mustache, pain, mole, lie, cube, rum, hedgehog). The instruction was read out: “Now we will check your memory. I will tell you the words, you will listen to them, and then repeat as many words as you can, in any order. Then a series of words were read. At the end of the reading, the words memorized by the subjects were recorded in the protocol. Then the instruction was read again: “Now I will sound the words to you again, then you must repeat all the words that you remember.” After fixing the data in the protocol, the experiment was repeated without instructions. The material was presented 5 times. Before the next readings, the instruction was not repeated. At each stage of the study, a protocol was filled out, which indicated the number of words reproduced, the words duplicated during reproduction and superfluous were noted. After the end of the repetition of words, the subject was told that the same words should be repeated after 30 minutes. The results were recorded in the protocol. Based on the results, a memory curve was built. Miller's rule was used to estimate the amount of memory. The number of words reproduced in the first series is the volume of auditory short-term memory. The norm is the volume equal to 7 ± 2 words (information units). The volume of short-term memory was assessed by the number of correctly reproduced words after the first presentation.

Statistical processing of the obtained results was carried out using the program Statistica. Data are presented as median (Me) and 95% confidence interval (CI). To check the normality of the distribution, the Shapiro–Wilk W test and the Kolmogorov–Smirnov test with the Lilliefors correction were used for data that do not follow a normal distribution. Signif-

icance of differences was assessed using the Mann–Whitney test (for unrelated groups) and the Wilcoxon test (for related groups). Differences were considered significant at $p < 0.05$.

Results and discussion. The results of the study showed that in patients with a history of traumatic brain injury, when assessing cognitive disorders on the MoCA scale, both at the beginning of the observation and by the 11th day of standard therapy, none of the patients (0%) scored the corresponding normal range of 26 - 30 points, which differed from similar indicators in healthy volunteers who effortlessly completed the tasks included in screening testing, gaining more than 26 points (Fig. 3). Patients with post-traumatic CI experienced the greatest difficulties in passing the MoCA test in tasks for memorizing and reproducing information, including delayed, concentration, and abstract thinking.

Considering that the time to complete the tasks of the "Schulte Tables" test is normally 40-50 seconds, it should be noted that in patients with a history of traumatic brain injury (main group), the average time spent on one table and indicated by the indicator of work efficiency, in The 1st day of observation was 3.1 times higher than the similar parameter in healthy volunteers, by the 11th day of observation - 3.2 times (Table 1, Fig. 4). However, it should be noted that the value of the index of the degree of workability in the main group throughout the entire observation (days 1 and 11) was less than one, which indicates a good degree of workability, in contrast to healthy volunteers, whose workability was 1.00 (1st day) and 1.02 (11th day) conventional units, which requires additional research and appropriate justification. At the same time, the fact of a sufficiently high ability of healthy volunteers to concentrate on any activity for a long time is obvious already in this observation, since the indicator of mental stability was below one, which could not be registered in patients with cognitive impairment due to traumatic brain injury - the amount of time spent to work with the fifth (last) table exceeded the efficiency of work and testified to the impossibility of the subjects to concentrate on a specific search task for a long time.

According to Miller's rule, the number of words reproduced in the first series and characterizing the volume of auditory short-term memory should normally be 7 ± 2 words, which was clearly demonstrated by healthy volunteers both at the beginning of the observation and after 10 days (Fig. 5). In turn, patients with a history of traumatic brain injury on the 1st day reproduced on average 3 words, which corresponds to moderate disorders of short-term memory, on the 11th day - 4 words, which corresponds to mild disorders of short-term memory. It is necessary to note the positive dynamics of the "memorization curve" from presentation to presentation in the main group during standard therapy, however, by 4-5 presentations, all 10 words (normal) were not reproduced by any patient (0%).

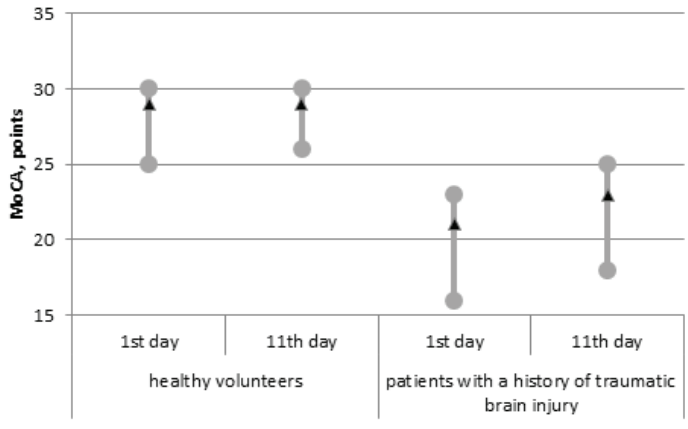

Fig. 3. Dynamics of indicators on the MoCA scale in healthy volunteers and patients with a history of traumatic brain injury

Indicators of neuropsychological status in healthy volunteers and patients with a history of traumatic brain injury

Parameters	Healthy volunteers			Patients with a history of traumatic brain injury		
	Me_1 (95% ДИ)	Me_2 (95% ДИ)	p*	Me_1 (95% ДИ)	Me_2 (95% ДИ)	p*
MoCA, points	29 (25 – 30)	29 (26 – 30)	0.001	21 (16 –23)	23 (18 – 25)	0.059
$Schulte_1$, seconds	46 (39 – 54)	44 (40 – 49)	0.008	136 (122 – 140)	136 (120 – 143)	0.829
$Schulte_2$, seconds	45 (38 – 52)	44 (38 – 49)	0.001	140 (128 – 149)	130 (109 – 141)	0.733
$Schulte_3$, seconds	48 (40 – 51)	42 (39 – 46)	0.011	144 (122 – 140)	138 (118 – 154)	0.007
$Schulte_4$, seconds	45 (41 – 51)	42 (38 – 48)	0.005	145 (116 – 151)	145 (122 – 159)	0.511
$Schulte_5$, seconds	44 (39 – 50)	43 (40 – 51)	0.003	144 (124 – 149)	139 (110 – 148)	0.051
Efficiency, seconds	45.6 (39.4–51.6)	43.0 (39.0–48.6)	0.001	141.8 (122.4–145.8)	137.6 (115.8–149.0)	0.009
Degree of workability	1.00 (0.98–1.05)	1.02 (1.01–1.03)	0.382	0.96 (0.96 – 1.00)	0.99 (0.96–1.04)	0.368
Mental stability	0.96 (0.96–0.99)	1.00 (1.02–1.05)	0.063	1.02 (1.01–1.02)	1.01 (0.99–1.03)	0.082
test 10 $words_1$	7 (6 – 10)	8 (7 – 10)	0.374	3 (1 – 5)	4 (2 – 6)	0.789
test 10 $words_2$	8 (6 – 10)	9 (8 – 10)	0.051	3 (2 – 5)	4 (3 – 6)	0.158
test 10 $words_3$	9 (7 – 10)	9 (8 – 10)	0.001	4 (3 – 6)	5 (4 – 8)	0.011
test 10 $words_4$	9 (8 – 10)	10 (9 – 10)	0.018	4 (3 – 5)	6 (4 – 8)	0.369
test 10 $words_5$	9 (8 – 10)	10 (9 – 10)	0.009	5 (4 – 8)	8 (6 – 9)	0.072

Note: * Wilcoxon test; Me_1 and Me_2 are the median values at the beginning of the observation and on the 11th day, respectively; test 10 $words_{1, 2, 3, 4, 5}$ - test "10 words" after the 1st, 2nd, 3rd, 4th and 5th presentation, respectively.

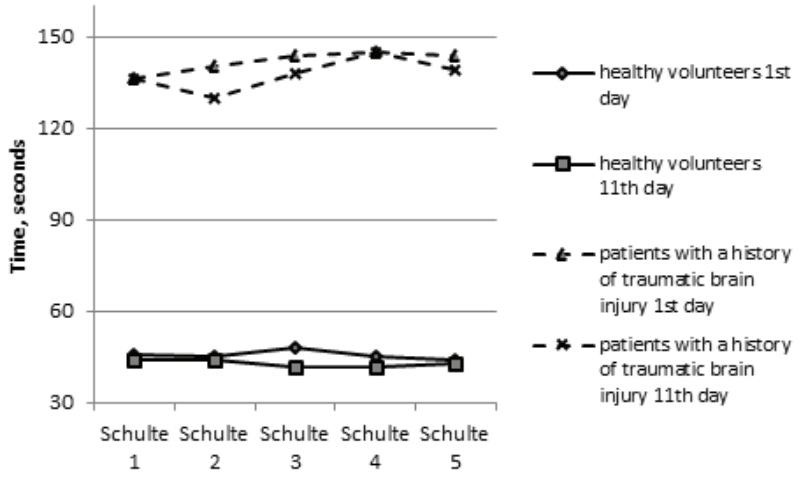

Fig. 4. Dynamics of the parameters of the "Schulte Tables" test in healthy volunteers and patients with a history of traumatic brain injury

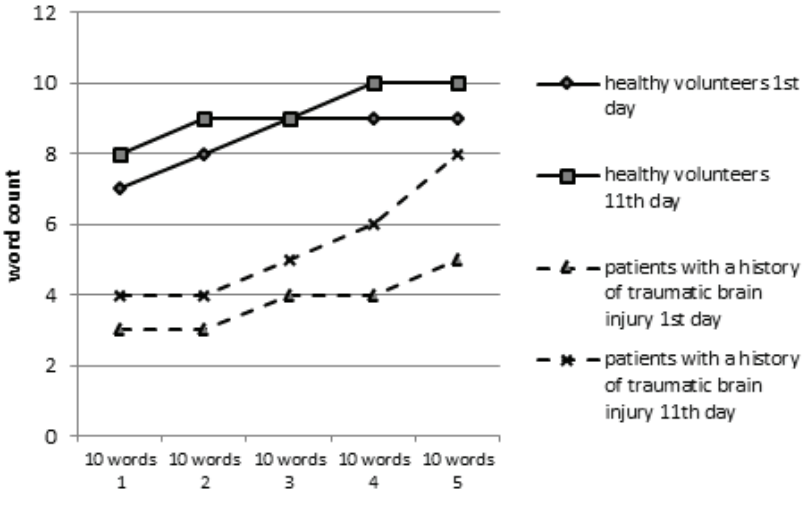

Fig. 5. Dynamics of the "10 words" test indicators in healthy volunteers and patients with a history of traumatic brain injury

Thus, the results of the study allow us to state the formation of CI in patients with TBI in the long-term period, which predetermines the need for a mandatory neuropsychological examination, regardless of the severity of the TBI, in order to timely and pathogenetically substantiated pharmacological correction of post-traumatic cognitive dysfunction.

Conclusions

1. The presence of cognitive disorders registered using the Montreal Cognitive Function Assessment Scale (MoCA-test) was confirmed in 100% of patients in the late period of traumatic brain injury with an injury duration of up to 6 years.

2. In the long-term period of traumatic brain injury in patients, a decrease in work efficiency by 3 times relative to healthy volunteers, mental stability, short-term and long-term memory volume is recorded, which corresponds to mild and moderate cognitive impairment.

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T.Ya. Jalilov

RESULTS OF THE USE OF A MODIFIED CORRECTIVE MANEUVER OF ARC ROTATION IN THE SURGICAL TREATMENT OF SEVERE SCOLIOSIS

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The aim of the study was to study the effectiveness of the method of correction of severe scoliosis with the help of a modified cantilever maneuver without osteotomies or discectomies.

Materials and methods. The correction of progressive severe scoliosis was evaluated radiologically and clinically.The technique was performed in 24 patients with an average degree of deformation of 82.780±19.890 (minimum 570, maximum 1200) according to Cobb. Of these, 2 are male and 22 are female. The age of the patients was 12-32 years. The long-term results of the 2.5-year period are presented. In all patients, the etiological factor is idiopathic scoliosis.

All patients underwent pre-and postoperative X-rays in standard positions. The Cobb angle of the frontal arc of the deformation was measured and the mobility of the deformation was calculated, which was the difference in the magnitude of the main arcs in the functional images. Surgical placement was performed by posterior access in all patients. The transpedicular screws were applied without the use of an O-arc, using the "hands-free" technique. Neuromonitoring and the wake-up test were not used.

Results. The degree of the main bend is 82.780±19.890 (min. 570, max. 1200). Bending graphs and the average value 21,580±14,460 (26.10%±13.69%; minimum 2.00, maximum 40.10) are determined to measure the mobility of the curvature arc. On the other hand, the average postoperative correction of the main bends 50,080±13,230 (60.49%±14.14%; minimum 33.50, maximum 82.30).

Conclusions. The technique of arc rotation developed by us in order to correct severe rigid scoliosis makes it possible to significantly achieve correction and avoid postoperative complications associated with osteotomies and discectomies performed with the "classic" version of surgical treatment.

Keywords: scoliosis, treatment, modified maneuver.

Introduction. Today, despite the extensive development of technology and medicine, the treatment of severe scoliosis remains a challenge before surgery.

Surgical correction of this type of scoliosis is considered a risky procedure. Hirurgic correction of scoliosis at an angle of 50°-55° can be carried out by corrective maneuvers of derotation, compression- distraction or by variable replacement of the rod.[2]

Surgeons often use special long-head screws of spondylolisthesis in all vertebrae, this helps with the adaptation of the rod in acute-angle deformities. In many cases, in order to treat persistent deformities above 550, posterior osteotomy such as PSO, VCR and Ponte is required. However, these procedures entail high neurological insufficiency and risks of bleeding, according to some authors, complications can reach 80% not only during surgery, but also 6 months after surgery.[1]

There are many sources in the literature describing the difficulties of vertebral osteotomy and the risks of complications. Despite the risks of neurological complications, in 2017 Prataly et al. gave a report on the high clinical effect of vertebral resections, but at the same time they noted a high (60%) complication rate.[6] Trobisch et al. Pedicular osteotomy (PSO) was performed on 22 patients without neuromonitoring and an average blood loss of 2302 ml was reported. Neurological disorders were noted in two patients.[10]

Two-step correction is used in cases of curvature of more than 70 ° according to Cobb, while anterior discectomies are performed, followed by gallovytyazhenie for 2-3 weeks and posterior fusion.[4,6]

The Cantilever maneuver was first described by Chang in 2003, but the author himself noted the time of the first operation in 1998.[3]

The aim of the study is to study the effectiveness of the method of correction of severe scoliosis with the help of a modified cantilever maneuver without osteotomies or discectomies.

Materials and methods. Correction of progressive severe scoliosis was evaluated radiologically and clinically.

The technique was performed in 24 patients with an average degree of deformation of 82.780±19.890 (minimum 570, maximum 1200) according to Cobb. Of these, 2 are male and 22 are female. The age of the patients was 12-32 years. The long-term results of the 2.5-year period are presented. Idiopathic scoliosis is an etiological factor in all patients. The study was approved by the Ethical Council of the AMU (Minutes of the Expert Council No. 15 dated 16.10.2020 Chairman -Candidate of Medical Sciences, Associate Professor R.O. Baylarov - Vice-Rector for Scientific Work of the AMU)

All patients underwent pre- and postoperative X-rays in standard positions. The Cobb angle of the frontal arc of deformation was measured and the mobility of deformation was calculated, which was the difference in the magnitude of the main arcs in functional images. 3D CT and NMRI examinations of the spine were performed. Densitometry was per-

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formed to determine bone density, including echocardiography of the heart.

Surgical placement was performed by posterior access in all patients. Transpedicular screws were applied without the use of an O-arc, using the "hands-free" technique. Neuromonitoring and the wake-up test were not used.

As safety measures during such screws, the channel of the vertebral arch leg was carefully mechanically checked, in case of suspected damage to the wall of the screw channel, they refused to use the screw at this level or used screws of smaller diameters.

Hirrurgic technique. Posterior chirrugic access to the spine was performed under neuroleptoanalgesia. The patient is brought into the pronation position, lying on parallel cylindrical supports. Starting from the cervical region, the surgical area and the lower extremities are treated with an antiseptic solution and covered with a sterile insulator. The skin incision was made according to the projection of the spinous processes of the C7-S1 vertebrae. (fig.1).

Subperiosteal dissection of the paravertebral muscles is carried out from the spinous to the transverse processes. Three semi-axial transpedicular screws are implanted starting from the cranial neutral vertebra in the concave part of the deformity. On the concave and convex parts of the deformation, the spondylolisthesis screws are placed at all possible levels. The rod is bent by repeating the bending of the arc of curvature and is mounted in three cranial screws located on the cranial part of the concave area. The assistant corrects the deformation by applying force in opposite directions; one hand of the assistant is located in the convex part of the rib, the other hand is in the iliac crest of the patient.

The surgeon inserts the rod into the caudal screws, carefully watching the cranial screws to avoid their spontaneous exit. The rod is rotated around its axis by special holders, the proposed arc rotation maneuver is performed and the rod is fixed in the slots of the caudal screws as a result. A light derotation maneuver is performed. The limit of the implementation of the derotation maneuver is the feeling of increasing resistance to the surgeon's hands. Next, we place the rod on a convex area in the same shape and connect it with screws. We carefully carry out the derotation as far as possible. If a large derotation is carried out, a spontaneous exit of the screws may occur. The rod of the concave part is removed, its bending in the frontal plane decreases, it is mounted back into the screws and

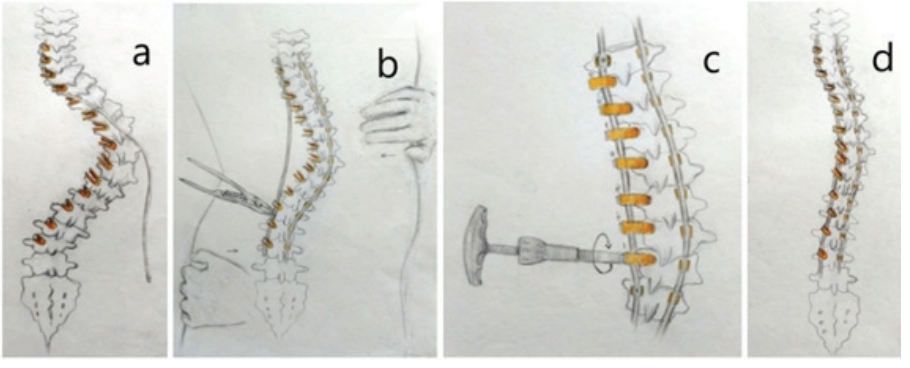

Fig. 1. Arc rotation is a cantilever technique (a) Mount the screws from the cranial neutral vertebra to the caudal neutral vertebra using long-headed spondylolisthesis screws on the concave side, connect the rod with three screws of the cranial neutral vertebrae, the rod will have the position as shown in the figure, (b) a passive correction was performed by the assistant and the rod was inserted into the caudal screws by the operator, (c) the screws are superimposed in the convex side of the curvature arc and the rod is also placed in a similar position. Further, the rod is removed from the concave part and re-placed in its place after straightening with the rod flexor (d) as a result of straightening and derotation of the rod in the convex region, the rod has reached the spondylolisthesis screw in the concave region.

derotirovaetsya. At the same time, there is a decrease in resistance to the derotation maneuver and it is done with ease. The same is done on the convex side of the arc of curvature, while not forgetting about the risk of dislocation of the screws. The assistant can still correct by applying pressure with his hands in order to avoid dislocation during derotation. One or two transverse connectors are placed between the rods and the fusion of the auto-fluid is carried out. The wound is stitched in layers, the wound is bandaged. The results of the treatment were evaluated by SPSS statistical analysis. The probability index is 0.05.

Results. The degree of the main bend is 82.780±19.890 (min.570, max. 1200). Bending graphs and average value 21,580±14,460 (26.10%±13.69%; minimum 2.00, maximum 40.10) are determined to measure the mobility of the curvature arc. This means that all patients were with rigid deformities (t:2.01; p>0.05). On the other hand, the average postoperative correction of the main bends 50,080±13,230 (60.49%±14.14%; minimum 33.50, maximum 82.30) with static confidence (t:14.85 ; p<0.01). (Table).

Operations were performed without neuromonitoring, neurological disorders of patients were not observed. One of the patients had postoperative decompensation of the trunk, which was corrected by additional fixation of the L4 vertebra. Complications related to surgical infection, secondary displacement of screws, blood loss and mortality were not observed.

Clinical example: A 19-year-old male patient was admitted to the clinic with severe and rigid right-sided thoracic idiopathic scoliosis (1230 Cobb), with decompensation of the trunk. The main arc was rigid with a mobility of 2°. The patient underwent preoperative studies and was offered surgery to correct the spine with

Indicative static data

	Average Value	Limits
Age	19.04±5.62	12-32
Cobb angle	82.78±19.89	57-120
Arc mobility (degree)	21.58±14.46	2-40.1
T	2.01	
P	>0.05	
Correction (degree)	50.08±13.23	33-82
T	14.85	-
P	<0.01	-
%FLEX,**	26.10±13.69	-
%COR,***	60.49±14.14	-
T	-15.42	-
P	<0.01	-

a transpedicular system with posterior fusion. The operation was performed using a corrective maneuver of arc Rotation. Postoperative radiographic images show that the deformity was corrected by 57.70 % and this is 47 % of the correction. The patient was very pleased with the result (Figure 2).

Clinical example: A 14-year-old patient came to our clinic with rigid right-sided idiopathic thoracic scoliosis (1100 Cobb). The main bend was rigid with mobility 11.40. The patient underwent preoperative studies and was offered a spinal correction operation with a transpedicular system with posterior fusion. The operation was performed using a corrective maneuver of arc Rotation. Postoperative radiographic images show that the deformation was corrected to 74.70 and this is 68° correction. After 9 months, the patient was admitted to the clinic for the purpose of subsequent surgery for additional correction during which we reduced the bending of the rods in the frontal plane by placing 2 more screws on the concave side of the curvature. Additionally, we have achieved 100 corrections and this is 77.2%. The patient is satisfied with the result (Figure 3).

Discussion. Thus, the operative correction of scoliotic deformities using polyaxial transpedicular systems is carried out by a derotation maneuver, 3-mesh technique, direct derotation of the vertebral body, segmental derotation and cantilever maneuvers.[4]

First of all, the classic cantilever maneuver provides for bending the rods using a rod flexor on the convex side, with the screws and the rod already installed. We think that this will not be effective enough in deformations of 900-1200. Obviously, the traditional cantilever maneu-

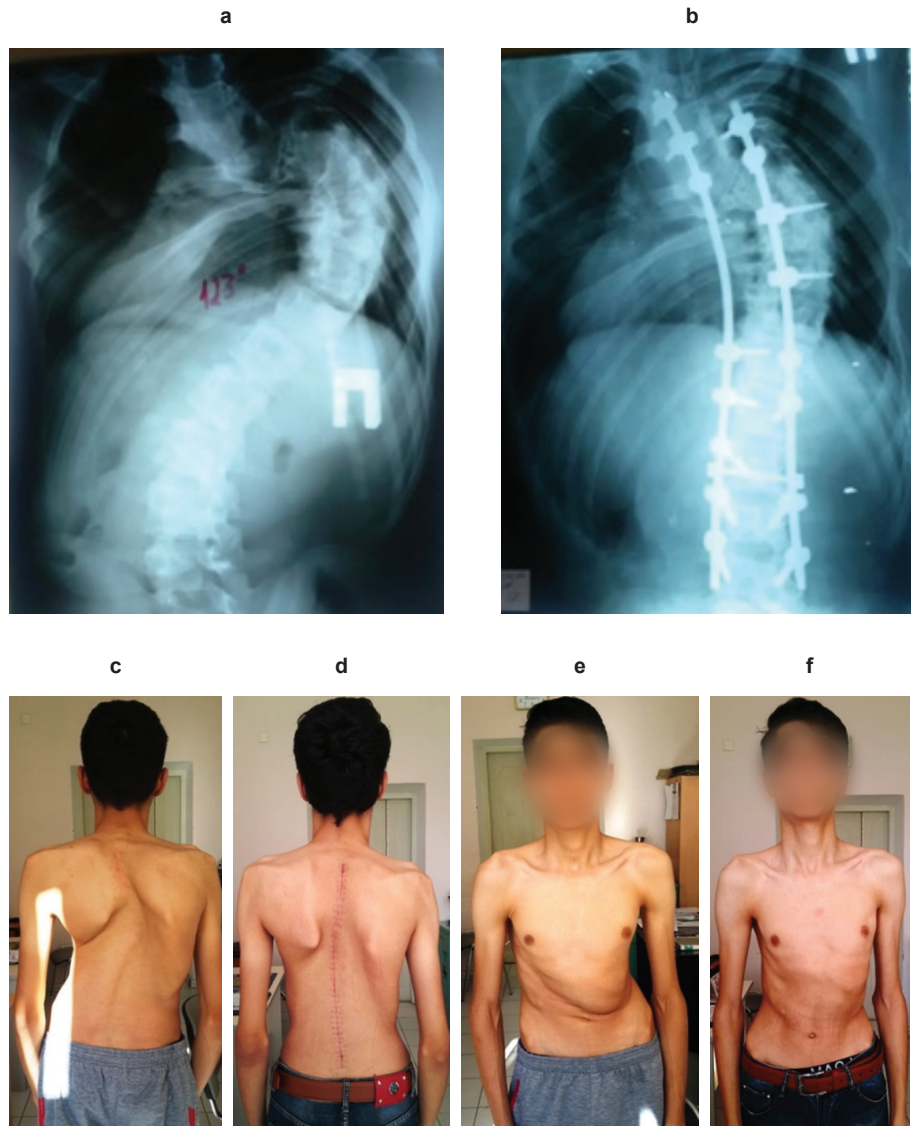

Fig. 2. Radiographs of the spine and photographs of the patient before and after surgery. A) An X-ray of the patient's spine before surgery, B) an X-ray after surgery C) a photo of the back before surgery, D) a photo of the back 6 months after surgery, E) a photo of the torso in front before surgery, F) a photo of the torso in front after surgery

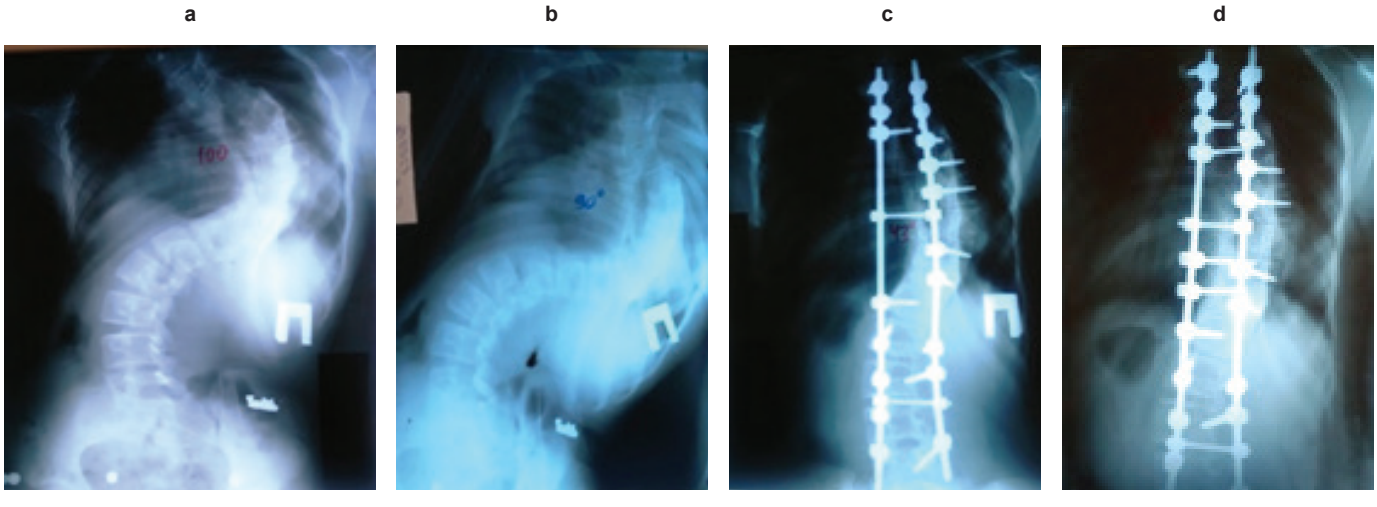

Fig. 3. Radiographs of the patient's spine before and after surgery a) X-ray of the patient before the operation, b) X-ray of the patient before the operation in the functional position, c) X-ray of the patient after the operation d) X-ray of the patient after the second operation of additional correction.

ver in cases of rigid scoliosis will make heavy operations necessary, such as anterior discectomies or pedicular osteotomies.

We gave the modified maneuver the name "Arc Rotation". The first movement corrects the deformation in the frontal plane, which begins with 3 screws on the cranial arc of deformation and helps to obtain a primary correction by turning the rod in the frontal plane. Further stages of correction consisted of classical corrective maneuvers. The correction of the main arc of curvature was 82.780±19.890 (min.570, maximum 1200). The deformities of the patients were rigid, the correction of bends in the bending graphs (26.10%±13.69%) was not statistically significant (p> 0.05). The average value of the correction of the main bending 60.49%±14.14 with a static value (p<0.01). At this time, interest indicators of postoperative correction was higher than the correction of the curves in the graphs of the curves with a static value (p> 0.01).

It is possible to obtain sufficient radiological and cosmetic correction performing this maneuver on their respective convex and concave sections of the scoliotic arch.

In the traditional methodology, the correction of severe scoliosis requires vertebral osteotomy Ponte, pedicular osteotomy (PSO) or removal of the vertebral body, which leads to increased bleeding, surgery time and risks of neurological complications. According to Saifi, transient neurological complications can reach 13.8%, persistent neurological complications can reach 6.3%, with 50-70% correction during spinal column resection.[8] According to our studies, similar correction indicators were obtained in us, but we did not observe neurological complications in our patients. We attribute this to the loss of the need for vertebral osteotomies during the proposed arc rotation maneuver.

According to Shankoil, in order to reduce the risk of dislocation in a classic cantilever maneuver, several spondylolisthesis screws with oblong heads should be applied.[9]

We tried to show it as a separate maneuver and demonstrate its strength without osteotomy. It is not difficult to place the rod when stretching the spine to obtain a passive correction. But this requires the help of two people - one must pull the patient from the armpits, and the other pull from the legs. We carried out a passive correction using the strength of one assistant who pressed with muscular force (ribs and pelvic area) on the frontal surface.

The traction method is used in cases of severe scoliosis. Halotraction is used in various methods of exposure both in the case of vertebral osteotomy and after anterior thoracotomy. The disadvantage of the technique is the long period of hospitalization.

In 2018, Qiao et al. proposed a 3-stage surgical correction in the treatment of severe scoliosis. [7]

1. Stage-1: Smith-Petersen posterior vertebral osteotomy.

2. Stage-2: in the second phase, stretching over the shoulder area and hips with prolonged heavy loads.

3. Stage-3: posterior correction and fixation in the third stage.

63 patients participated in the study. The average frontal Cobb angle of the main bend was 118.70 before surgery, the postoperative degree of correction averaged 57.3° (55%). According to Qiao, displacement of 17 screws was observed in 12 patients in the first phase of surgery, which were corrected during the last phase of surgery. Pleural injury in 2 patients. Pleural discharge was noted in one of two patients whose pleura was opened and closed thoracic drainage was applied. One of the patients had a short-term postoperative neurological disorder. Total complications were 19.0% after the first operation and 4.8% after the last operation. Two patients suffered from brachial plexus paralysis and one patient had femoral nerve paralysis. After conservative treatment, nerve functions were restored. Two patients had short-term hematuria. One of the patients had gastrointestinal symptoms, and these symptoms were mitigated after lowering the load applied for traction. Two patients had deep vein thrombosis (DVT), one of the patients had a venous filter applied. Complications related to stretching were 11.1%. [7]

We did not observe any spontaneous displacement (pull-out) of the screws with the modified Arc Rotation technique. Pleural complication was not noted with the proposed technique due to the absence of the need for thoracoplasty. Postoperative neurological insufficiency was not noted.

There is a lot of information in the literature about the complexity of vertebral osteotomies and the risks of complications, including the risks of neurological hemorrhagic nature. Modi HN and the authors developed and made a report on the results of posterior polysegiental vertebral osteotomy (PMVO) for the correction of severe idiopathic and neuromuscular scoliosis. The average indicator of the number of osteotomy levels is 4.2±0.8 (norms 3-5). The average Cobb angle before surgery was 99.20±29.60, after surgery this indicator decreased to 44.70±12.30. Correction of frontal deformation was 54.3% according to the authors. The average rate of blood loss and operation time, respectively, 3015 ± 1213 ml and 6.01 ± 1.09 hours. Three of the patients had respiratory complications, two of the patients had hemothorax, and one had lung atelectasis. Two of the patients had complications associated with implants; 1 screw fracture. Long periods of bed rest imposed psychological stress on patients. [5].

Conclusions. The technique of arc rotation developed by us in order to correct severe rigid scoliosis makes it possible to significantly achieve correction and avoid postoperative complications associated with osteotomies and discectomies performed with the "classic" version of surgical treatment.

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BEHCET'S DISEASE IN RUSSIA: DIAGNOSTIC AND TREATMENT EXPERIENCE OF CLINICS IN ST. PETERSBURG AND YAKUTIA

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Behcet's disease (BD) is a rare systemic vasculitis. It is rare in Russia, and the data on epidemiology are very limited. The study included 42 patients (M=19 (45.2%), W=23(54.8%)), with 26/42 (63.4%) having onset in childhood. Asians were 12/42 (28.6%), Europeans 30/42 (71.4%). Among the clinical features, the following organs and systems were affected in BB patients: oral ulcers (92.8%), genital ulcers (50%), eye lesions (42.9%), and skin lesions (45.2%). Laboratory tests showed increased non-specific inflammatory markers. The frequency of HLAB51-positivity was 50% and HLAB27-positivity 40%. Therapy: systemic corticosteroids (71.4%), colchicine (42.9%), TNF-a inhibitors (26.2%). Remission was recorded in 5/24 (20.8%) patients. Physicians in the Russian Federation are still insufficiently informed about this disease, which requires an expansion of the list of educational materials and programs for physicians of different specialties, taking into account the multiorgan nature of the lesion.

Keywords: Behcet's disease, vasculitis, golimumab, etanercept, ulcers.

Introduction: Behçet's Disease (BB, M35.2) is a systemic vasculitis of unknown etiology characterized by vascular lesions of different caliber and localization, with predominant clinical manifestations including recurrent oral and genital ulcers, uveitis, joints, gastrointestinal tract and central nervous system [2,3]. BD has a very wide geographic distribution with predominance in Asian and Middle Eastern countries; previously, BD was called the disease of the Great Silk Road, which connected China, India, Middle Eastern countries, including Turkey. The highest prevalence was reported in northern China and Iran (100 per 100,000) and Turkey (80-370.0 per 100,000). In Western Europe, IB is much less common with a prevalence of 0.1 per 100,000 in Sweden, 7.1 per 100,000 in France, and 15.9 per 100,000 in Southern Italy[2,21].An epidemiological study conducted in Paris showed that the prevalence of BD in persons of North African or Asian origin was significantly higher than in populations of European origin. Similar changes have been noted in Germany[2,21]. The disease occurs at almost any age, with a predominant debut in young adults, with a higher incidence in males. The delay in accurate diagnosis is at least three years, even in countries endemic for BD.

The etiology and pathogenesis of BD, like most systemic immune diseases, are currently not fully understood. It is assumed that immunological, genetic and infectious factors play a role in the onset of this disease. Both viral and bacterial infections, in particular streptococcus and herpes simplex viruses, have been described as trigger factors [23]. The HLA-B51 antigen, a member of the HLA-B5 gene family, is identified as a genetic marker of predisposition. HLA-B51-positive patients exhibit neutrophil hyperfunction. Cytokine production by T-lymphocytes in patients with IBD is biased toward type 1 (Th1) T-helpers, especially in the acute stage[23]. IL-1β, IL-6, and TNF-α play an important role in the induction of the immune response in IBD and, therefore, represent potential therapeutic targets for the disease. IL-1 and IL-6, together with IL-21 and IL-23, are involved in T-cell activation and TNF-α in the induction of autoimmunity[14]. As mentioned above, vasculitis in BD affects almost all types and sizes of vessels. Venous lesions are more common than arterial lesions. Vein involvement leads to both superficial thrombophlebitis and deep vein thrombosis[16]. The mechanisms of thrombosis in BD are still unclear. It is supposed that endothelial

dysfunction and neutrophil infiltration of the vascular wall are the key factors in the thrombotic process [27].Neutrophils can enhance chemotaxis and effector response with formation of reactive oxygen species, phagocytosis, formation of neutrophil extracellular traps and secretion of cytokines, capable to cause Th1-mediated immune response. Moreover, reactive oxygen species produced by neutrophils contribute to endothelial dysfunction and, through modification of fibrinogen structure, to thrombosis development. [25].

In the 1990s, the International Study Group (ISG) criteria were introduced, which are most commonly used in real medical practice and reflect the clinical picture [2,27]. Since 2014, an updated version of these criteria, International Criteria for Behçet's Disease (ICBD), was issued, where the pathergy test was not a mandatory but useful method [2,3]. In 2016, the Consensus classification criteria for paediatric Behçet's disease was developed, in which the paternity test was not included at all[20]. A comparison of diagnostic criteria is presented in Table 1 for clarity. The BDCAF (Behçet Disease Current Activity Form) index is also useful for practicing physicians to assess the overall activity of BD [3].

Objective: to describe clinical, laboratory, instrumental characteristics and outcomes of IBD in patients from different regions of the Russian Federation.

Materials and Methods: Included data from case histories of patients from 2014-2021 who were examined in the Third Pediatric and Ophthalmologic Departments of the SPbSPMU Clinic, the Rheumatology Department of the Yakutsk Republican Clinical Hospital and the Cardiorheumatology Department of the Pediatric Center of the Republican Hospital №1-National Center of Medicine, Yakutia, in a continuous, multicenter retrospective cohort study. We evaluated epidemiology, family history, clinical and laboratory features, treatment options and outcomes. Diagnosis was made according to the 2016 Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort (PEDBD). [20].

Results: In our study, we included data on 42 patients of different ages, sex, and racial backgrounds. The sex distribution was approximately equal, with a predominance of European origin. Childhood debut occurred in 63.4% of patients, but in one patient a reliable age of debut could not be established. A burdened family history of immunopathological diseases was described in 2 patients: maternal psoriasis (n=1), Crohn's disease (n=1). Maternal relatives of two patients had recurrent oral and genital ulcers, but the diagnosis of Behcet's disease was not established.

Clinical manifestations: Among the clinical manifestations, recurrent oral aphthas/ulcers were reported in the vast majority of patients (n=39, 92.8%), while genital ulcers were reported in half of patients (n=21, 50%). Oral mucosal ulcers were the most frequent debut manifestation of BD (n=29/40, 72.5%), which was the reason for referral to specialists. Eye lesions (anterior, posterior uveitis, iridocyclitis) (n=18/42, 42.9%), joint syndrome (arthritis or prolonged arthralgia) (n=24/42, 57.1%) were quite common, involvement of the nervous system (n=9/42, 21.4%) and gastrointestinal tract (n=15/42, 35.7%) were much less common, fever syndrome was recorded in 5 patients (11.9%). The fact of thrombus formation in the right ventricular cavity in one patient, as well as pulmonary embolism in a patient with hereditary thrombophilia (mutation in the RAI -4G/4G gene) is interesting. We also noted that Crohn's disease was diagnosed in 4 patients. Pathergy test was performed in 6 patients and was positive in half of them.

Laboratory changes: moderate inflammatory activity was laboratory noted: elevated CRP in 12/42 (28.6%) patients, with maximum numbers up to 65 mm/h, and CRP in 11/42 (26.2%), but it was impossible to estimate maximum values due to different laboratory reference values and methods of determination. Specific immunological tests were not examined in all cases: HLA-B51 was detected in 6/12 (50%) of the examined patients, and HLA-B27 antigen in 2/5 (40%). HLA A1, 25; B7,35 were detected in one.

Systemic glucocorticosteroids (71.4%) were the main mode of treatment for Behçet's disease. Non-biologic disease-modifying antirheumatic drugs were also used (n=29/42, 38.7%), in particular methotrexate, mycophenolic acid, azathioprine, colchicine, cyclophosphamide. Colchicine, was used in 18 patients (42.9%). In addition, therapy with genetically engineered immunobiological drugs (GIBP) of different groups was used. TNF-alpha blockers (etanercept, adalimumab, golimumab, infliximab) were used in 11 patients (26.2%), interleukin-1 inhibitor (canakinumab) in one, interleukin-6 inhibitor (tocilizumab) in two, and the Janus-kinase blocker tofacitinib was used in one patient. Due to lack of information, only 24 patients could be evaluated for long-term follow-up, of whom only 5 were able to achieve remission and no exac-

Table1

Diagnostic criteria for BB [2,3,35,20]

International StudyGroup (ISG), 1990		International Criteria for Behçet's Disease (ICBD), 2014		Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD, 2016	
Main symptom	Recurrent oral ulcers	Aphthous stomatitis	2	Oral mucosal lesions	1
Additional signs	Recurrent genital ulcers	Genital ulcers	2		
		Eye lesion	2	Genital lesions	1
	Skin lesion	Skin lesion	1	Eye lesion	1
		Nervous system lesions	1	Nervous system lesions	1
	Positive paternity test	Vascular lesion	1	Sign of vasculitis	1
		Positive paternity test	1*		
Oral ulcers + 2 additional signs		A score of ≥4 is required. * counts only when the test is performed, not required		Three of six points are required	

erbations were recorded. Among those who were prescribed GIBP, three patients had to be switched to another drug because of insufficient efficacy and control of the disease. Detailed demographic characteristics of the patients included in the study are shown in Table 2.

Discussion: A study by Isabelle Koné-Paut et al. analyzed 86 cases of BD from Turkey, France, Iran, and Saudi Arabia. Researchers noted sex differences in the clinical presentation of BD in children. Although gender did not affect the occurrence of BD, male patients had a more malignant course because they were found to have an increased risk of necrotizing folliculitis, eye disease, and vascular complications, including arterial aneurysms and deep vein thrombosis. In girls, the course of the disease was more benign, with isolated mucosal lesions and arthritis [22]. Probably, testosterone has a role in the pathogenesis of a more malignant course of IB in male patients, since it not only affects the function of neutrophils, but also changes the expression levels of IL-10, TLR4, IL23R, CCR1, ERAP1 on mononuclear cells and neutrophils [34]. In a study including 3,382 patients with IB between October 1986 and December 2005 at the Behçet Department of Ankara University Medical School and the private clinic of Atmac, 110 children (3.3%) were found to have the disease in childhood. All patients were residents of Turkey, and the boy/girl ratio was 1.7:1. The age of manifestation was 1 to 16 years (mean: 11.63 ± 3.46) and the age of diagnosis was 6 to 16 years. (mean: 14.15 ± 2.13), indicating a delay in diagnosis of 2 to 3 years [9]. Depending on the presence of primary and secondary symptoms, several types of BD are distinguished (Table 3):

The initial manifestations of BD are most often recurrent oral ulcers and genital ulcers. Skin lesions are represented by papulopustular rashes and erythema nodosum and are quite common [9]. Among our patients, oral and genital ulcers were the most frequent symptoms, while cutaneous manifestations were less common. The most frequent abdominal complaints are abdominal pain, diarrhea, nausea, weight loss and bloating, which leads patients with BD to a gastroenterologist. According to the literature, the gastrointestinal (GI) tract is affected in 15%-50% of patients based on complaints and symptoms, and in 0.7%-30% based on instrumental findings, with GI involvement being more common in children [35, 13, 18]. A distinctive feature of gastrointestinal syndrome in BD is involvement of any gastrointestinal region,

Table2

Characteristics of patients with Behcet's disease

Parameter	Result n (%)
Demographics	
Gender, M/W, n (%)	19 (45.2) / 23 (54.7)
Debut of disease in childhood, n (%)	26/41 (63.4)
Asian/European, n (%)	12 (28.6) /30 (71.4)
Clinical manifestations	
Oral ulcers, n (%)	39 (92.8)
Genital ulcers, n (%)	21(50)
Fever, n (%)	5 (11.9)
Eye damage (uveitis), n(%)	18 (42.9)
Skin lesions (erythema nodosum, panniculitis), n (%)	19 (45.2)
Pathergy test, n (%), n (%)	3/6 (50)
Central nervous system lesions, n (%)	9 (21.4)
Gastrointestinal tract lesions, n (%)	15 (35.7)
Arthralgia/arthritis, n (%)	24 (57.1)
Thrombovaculitis (venous thrombosis), n (%)	6 (14.3)
Laboratory characteristics	
Erythrocyte sedimentation rate, Me (25%-75%)	26 (21-65)
Erythrocyte sedimentation rate acceleration, n (%)	12 (28.6)
Increased C-reactive protein (> 5 mg/L), n (%)	11 (26.2)
Anemia, n (%)	8 (19)
Rheumatoid factor seropositivity, n (%)	2/11 (18.2)
Presence of HLA-B27 antigen, n (%)	2/5 (40)
Presence of HLA-B51 antigen, n (%)	6/12 (50)
Therapy	
Systemic corticosteroids, n (%)	30 (71.4)
Methotrexate, n (%)	4 (9.5)
Mycophenolic acid, n (%)	1 (2.3)
Azathiaprine, n (%)	11 (26.2)
Colchicine, n (%)	18 (42.9)
Cyclophosphamide, n (%)	4 (9.5)
TNF-a inhibitors, n (%): Etanercept, n (%) Adalimumab, n (%) Golimumab, n (%) Infliximab, n (%)	16 (38.1) 1 (2.3) 7 (16.7) 4 (9.5) 4 (9.5)
Kanakinumab, n (%)	1 (2.3)
Tocilizumab, n (%)	2 (4.7)
Tofacitinib, n (%)	1 (2.3)
Outcomes	
Remission, n (%)	5/24 (20.8)
GIBT change, n (%)	3/11 (27.3)
Associated pathology, n (%): Crohn's disease. Bronchial asthma	 4 (9.5) 1 (2.3)

Abbreviations: TNF-a - tumor necrosis factor-a.

diffuse involvement occurs in no more than 15% of patients, more often there is local ulceration with localization in the small and large intestine [35]. The most difficult task is differential diagnosis of BD and inflammatory bowel disease (IBD). In our cohort, 15/42 (35.7%) had gastrointestinal involvement, with Crohn's disease diagnosed in 4 patients.

The following "red flags" noted on endoscopic examination of the intestine (fibrocolonoscopy) are assumed to be characteristic of BD: large (over 1 cm), round or irregularly shaped ulcers, with a perforated appearance, usually located in the deep layers; longitudinal ulcers are rare; less than six round and focal ulcers [35].

As for the much threatened complication of some rheumatologic diseases, macrophage activation syndrome (CAM), it is not such a characteristic clinical feature for BD. An Italian review of CAM in rheumatologic pathology describes one case associated with Epstein-Barr virus[10, 24]. Studies in patients with BD have traditionally shown signs of significant activation of monocytes and macrophages, as well as increased numbers and activation of circulating T cells and natural killer cells [35].

Only 12 (28.6%) patients were positive for the HLA-B51 antigen and 2/5 (40%) for the HLA-B27 antigen. Determination of HLA-B51 may be useful when a familial case of IBD is suspected. According to the literature, patients with simultaneous HLA-B27 and HLA-B51 positivity had a less severe course of uveitis (less retinal involvement, fewer complications, and fewer surgical techniques) and a more favorable long-term visual prognosis than HLA-B51-associated uveitis-Behçet's [30, 7, 5].

The following scope of examinations for suspected BD is suggested (Table 4).

A special form of hypersensitivity test for BD is the patergia test (phenomenon), which is a delayed skin reaction to a needle puncture in the dermis of the forearm. The reaction is considered positive if a papule or pustule forms at the puncture site 48 hours later. Only erythema is considered negative [6].

Interestingly, in the face of new challenges associated with COVID-19, a British study showed that patients with Behcet's syndrome were not at increased risk for worse outcomes. But at the same time, it is noted that 32.2% of patients with IB had an exacerbation of at least one symptom against a new coronavirus infection [26,12].Specific data indicating that patients with BD regardless of therapy were more susceptible to SARS-CoV-2 or the more severe forms of COVID-19 are not available. In general, the course of COVID-19 did not differ from the general population, and the severity of COVID-19 infection was predominantly mild [12,15].

In the context of modern ideas about personalized medicine, as well as the importance of psychological and social adaptation of patients, it seems important to form communities where volunteers, medics and patients learn about life with chronic diseases in close connection. Such global communities have been created for patients with bronchial asthma, diabetes, and other diseases. Interestingly, in the United States there is already a similar special community for patients of the American Behçet's Disease Association - ABDA [17].However, in the Russian Federation, currently, there is no such community. When establishing the diagnosis of Behcet's disease, differential diagnosis with other diseases is an urgent issue. The main points of differential diagnosis are presented in Table 5.

Differential diagnosis of inflammatory changes in the eye is important for practicing ophthalmologists for timely diagnosis of Behcet's disease. Peculiarities of eye lesions in BD and other diseases are presented in Table 5.

Conclusion: Behcet's disease requires study and attention from doctors and researchers. Physicians in the Russian Federation are still insufficiently informed

Table3

Types of Behcet's disease [31]

Complete BD type	Incomplete BD type	Probable
Presence of 4 major symptoms: 1. Recurrent aphthae/ulcers of the mouth 2. Genital ulcers 3. Eye involvement (anterior/ posterior uveitis, retinal vasculitis, etc.) 4. Skin involvement (erythema nodosum, pseudofolliculitis, etc.)	• Presence of 3 main symptoms, or • Presence of 2 primary and 2 secondary symptoms, or • Presence of recurrent ocular inflammation combined with one or more major symptoms.	• Presence of only 2 primary signs, or • Presence of 1 major and 2 minor signs.

Table4

Laboratory and instrumental diagnosis of BD

Laboratory data	Instrumental data
General blood count: increased sedimentation rate, mild anemia, neutrophilic leukocytosis (in the active stage of the disease).	Radiography of affected joints (to detect joint lesions) and overview radiography of the lungs (to detect pulmonary vascular lesions)
Biochemical blood tests: increase in C-reactive protein, alpha-trypsin, evaluation of blood electrolytes, liver tests, transaminases, and lipid spectrum.	Retinal fluorescence angiography (yellow spot edema or ischemia)
Immunological blood test: increased levels of circulating immune complexes, increased rheumatoid factor.	Abdominal ultrasound (to detect organic lesions of the gastrointestinal organs)
HLA typing: detection of HLA-B51	ECG (for the detection of cardiac lesions)
General urinalysis: moderate proteinuria, moderate hematuria.	EchoCG (to detect valve and myocardial damage)
	FGDS (to detect ulcerative and vascular lesions of gastrointestinal mucosa)
	Positive pathergy phenomenon

Abbreviations: GI - gastrointestinal tract, sedimentation rate – erythrocyte sedimentation rate, USG - ultrasound examination, FGDS - fibrogastroduodenoscopy, ECG - electrocardiography, EchoCG - echocardiography

Table5

Differential diagnosis of Behcet's disease [8,11]

The symptom	BD	JIA, systemic variant of debut	Periarteritis nodosa	SLE	Non-specific aortoarteritis Takayasu	Sarcoidosis	Crohn's disease
Oral/genital ulcers	+	-	-	+	-	+ (sarcoid ulcers)	+
Vasculitis	all vascular calibers	-	Necrotizing vasculitis, Aneurysms, stenoses, or occlusions of arteries	Microcirculatory blood vessels	Various vascular lesions (predominantly large caliber)	-/+	-/+
Rash	Papulopustular rash and erythema nodosum	Erythematous rash	ulcerative defects and lesser	butterfly erythema, heliotrope rash		erythema nodosum	erythema nodosum
Reference points	HLA B51, paternity test, all types of vascular lesions	Arthritis accompanied by prolonged fever	Specific histologic picture	ANF, multiorgan lesions, DNA antibodies	Differential BP in the extremities, vascular ultrasound findings, hypotrophy of the extremities, major vascular lesions	Intrathoracic lymph node study, bronchoscopy, spirography, histological study	Endoscopic findings, increased fecal calprotectin levels

Abbreviations: BP - blood pressure, ANF - antinuclear factor BD - Behcet's disease, SLE - systemic lupus erythematosus, JIA - juvenile idiopathic arthritis

Table6

Differential diagnosis of ocular lesions in IB [19, 28, 29, 32, 33, 1,4]

The symptom	BD	JIA	Sarcoidosis	HLA-B27-associated uveitis	Nephritis (TINU)-syndrome
Age of debut	More often in middle-aged people	More often in children	More often in children	More often in older individuals	More often in children and adolescents
Eye damage	Bilateral	Bilateral	Bilateral	Unilateral	Bilateral
Intraocular pressure	Normal or low at first, then increased	Increased	Increased	Normal or low	Increased
Extraocular manifestations	Oral ulceration, skin lesions, vasculitis	Fever, rash, hepatosplenomegaly, lymphadenopathy, serositi	Arthritis and skin lesions	Spondyloarthritis	Fever, weight loss, abdominal and flank pain, and arthralgia (related to renal dysfunction)
Complications	Cataracts, increased intraocular pressure, macular edema or maculopathy, and optic atrophy	Bacillary keratopathy, cataracts, posterior synechiae, glaucoma, maculopathy, hypotonia, and amblyopia	Keratopathy, cataracts, and glaucoma	Pupillary occlusion, cataracts, glaucoma, corneal dystrophy	Optic disc edema, multifocal chorioiditis, decreased visual acuity

Abbreviations: BB - Behcet's disease, JIA - juvenile idiopathic arthritis

about this disease, which requires expanding the list of educational materials and programs for physicians of different specialties, given the multiorgan nature of the lesion.

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HEALTHY LIFESTYLE. PREVENTION

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ETIOLOGICAL AND PATHOGENETIC CHARACTERISTICS, TREATMENT AND PREVENTION OF INFLAMMATORY PERIODONTAL DISEASES

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Nowadays there is a high prevalence of periodontal diseases among the population, which has a negative impact on the functional state of organs and tissues of the oral cavity, as well as, as a chronic focus of oral infections, can provoke the development of focal-related diseases in the organism. At the same time, despite a wide study, the problems of etiological factors, pathogenetic mechanisms of development, integrated treatment and prevention of periodontal diseases remain unresolved. In this regard, the priority task of dentistry, and medicine in general, is to continue research aimed at expanding theoretical knowledge about etiopathogenesis, improving therapeutic and preventive measures and comprehensive rehabilitation of patients with nflammatory and destructive diseases, which is of current importance. The initial stage of complex treatment of inflammatory periodontal diseases is etiotropic therapeutic measures to eliminate factors contributing to maintenance of inflammatory processes in periodontal, related to hygienic education, professional hygiene, closed curettage and oral cavity sanitization. At the same time, one of the main principles of integrated treatment is drug therapy with antiseptics, anti-inflammatory drugs, vitamins, enzymes, immunomodulators.

According to symptoms, as a rule, surgical and orthopedic methods of treatment are carried out. Rational organization and planning of methods of integrated medical and social rehabilitation of patients with inflammatory diseases of periodontal tissues is of important clinical and practical importance. The high prevalence of inflammatory periodontal diseases among the population and the unresolved problems of their etiopathogenetic factors, integrated treatment, prevention and rehabilitation need further interdisciplinary studies which will improve medical and preventive care taking into account the socio-economic aspects of morbidity. In addition, the main etiological and pathogenetic mechanisms for the development of periodontitis require further research in order to expand their theoretical ideas, which will contribute to the improvement of curative and preventive measures and improve the quality of life of patients.

Keywords: etiology, pathogenesis, chronic periodontitis, diagnostics, comprehensive treatment, prevention, medical and social rehabilitation.

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Introduction. Periodontal diseases are an urgent problem of medicine and dentistry, which is associated with the high rate of population frequency. Inflammatory periodontal diseases as chronic foci of infection contribute to the formation and development of various general diseases [23, 38]. At the same time, inflammatory-destructive processes of periodontal tissues often create prerequisites for tooth loss, the development of dysfunction of the jugular system, pathological processes of the gastrointestinal tract, in addition, rheumatoid polyarthritis, endocarditis, nephritis, hepatitis, etc. [1, 21]. In this regard, our research aim studying the pathological processes of periodontal tissues is of important scientific, theoretical and practical importance for medicine and dentistry.

Our studies established the main etiological and pathogenetic mechanisms for the development of periodontitis, but at the same time, it requires further study to expand the theoretical ideas that will improve medical and preventive measures.

Etiological characteristics of periodontal diseases of inflammatory and destructive nature. The high frequency of periodontal diseases among the population determines the importance of studying periodontal diseases, which is associated with the need to improve treatment, prevention and comprehensive medical and social rehabilitation [21]. At the same time, there is a loss of 4 to 9 teeth as a result of the complications of periodontal diseases by the age of 35 [1, 4]. Periodontal diseases have a wide range of clinical manifestations, which include various forms of gingivitis (inflammation of the gum without loss of jugular attachment) and periodontitis (loss of periodontal tissues as a result of inflammation). Thus, gingivitis usually goes into periodontitis with the immune decrease, the presence of risk factors and inflammatory mediators, as well as with an increase of periodontal pathogenic bacteria [5]. In this case, a true pathological periodontal pocket arises, which is a reservoir for opportunistic pathogenic bacteria that support periodontitis and can contribute to the progression of the disease [6]. The quantitative and qualitative changes in periodontopathogenic microflora are influenced to a certain extent by poor oral hygiene [6, 25] Gingival recession in the presence of a pathological periodontal pocket with advanced untreated periodontitis migrates to the apical side [29, 35].

The periodontal diseases development is directly influenced by the microflora of the pathological periodontal pocket [4]. The studies have proven the negative

effect of soft plaque microorganisms on the course of inflammatory processes in periodontal tissues with their pronounced destruction [2, 3, 4]. At the same time, the characteristics of virulence of microorganisms in the pathogenesis of periodontitis are established and presented, which are confirmed by experimental studies [2, 3, 33]. Recently, numerous studies of Russian and foreign researchers have found more than 700 types of microorganisms in the oral cavity [32]. At the same time, about 15 species of periodontopathogenic microorganisms that have highly adhesive and toxic properties are of particular importance in the development of periodontitis [7, 28]. There are a wide range of bacterial strains, where in addition to flotating forms, there are microorganisms capable of creating associations for joint growing with the formation of a biofilm in the periodontal pocket. At the same time, these biofilms determine the dynamic equilibrium of bacteria that are protected from chemical and physical antimicrobial effects. In this regard, modern etiological factors of periodontitis characterize the presence of cluster microorganisms with the acquisition of completely new properties for them, which they did not possess before the formation of composite groups, where they become resistant strains insensitive or poorly sensitive to treatment [7].

Currently, there is information about the main causes of periodontal pathogenic microorganisms increase in the development of fast-progressing periodontitis [32]. At the same time, the main causes of aggressive forms of periodontitis are Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis and Prevotella intermedia. These microorganisms isolate their vital products that destroy the collagen fibers of periodontal tissues, which determines their aggressiveness in the development of fast-progressing periodontitis [7, 15, 28]. Meanwhile, the studies found out that there are significant differences in quantitative and qualitative indicators of microflora in patients with generalized and localized forms of aggressive periodontitis. Thus, Actinobacillus actinomycetemcomitans is often detected in aggressive forms of localized periodontitis compared to generalized periodontitis. In addition, there is some evidence characterizing the involvement of herpes viruses, including cytomegaloviruses in the etiopathogenesis of localized juvenile periodontitis. The analysis of etiological factors of rapidly progressing periodontitis allows us to assert the need of the regulatory role of the immune system in the development of pathological conditions of periodontal tissues as modern scientific ideas. Meanwhile, most children, as a rule, have non-aggressive microflora and only in some cases it may include microorganisms with a high level of virulence that actively damage bone tissue and the periodontal ligament [1, 2, 3, 4]. With a low level of local and general immunity, a pronounced destructive process extends to various structures of periodontal tissues, where certain differences in the depth of damage in people of the same age are revealed. This clinical situation characterizes the periodic course of chronic periodontitis, which includes independent subsidence and acute exacerbation of the disease with the same level of hygienic state of the oral cavity in various patients [2, 3, 23].

We should note that in the structure of inflammatory periodontal diseases, a significant predominance of chronic periodontitis is determined, which can lead to the loss of externally intact teeth, as well as a violation of the function of the entire dentition system. This is to a certain extent due to numerous local and general etiological factors for the development of inflammatory periodontal diseases. Among local etiological factors, calculus, which can appear as supra-gingival and sub-gestational localizations, is not of little importance. In general, it consists of organic and inorganic components that appear in the imbalance of oral fluid function and in the presence of an inflammatory process of the marginal gum [31]. At the same time, the inflammation of the marginal gum and the formation of a subgingival calculus support the inflammatory process and contribute to further damage of the periodontal tissues, where the calculus is directly associated with the vital activity of periodontal pathogenic microorganisms [33].

It is important to emphasize that some etiological factors for the development of chronic periodontitis are functional traumatic periodontal overload due to a change in occlusive load on various groups of teeth. Meanwhile, a traumatic occlusion disorder generally has a localized focus associated with tooth row defects happen due to dental caries complications and periodontal diseases, dysocclusions, increased tooth erasability, tooth position abnormalities, etc., creating injury nodes. [21, 38]. In the event of dental row defects, functional overload of periodontal tissues causes the teeth to tilt towards its defect in the type of dental alveolar elongation, which contributes to the violation of biomechanics and the occlusive ratio of teeth. In this case, pathological changes of periodontal tissues occur in pressure zones and depend on the direction of the traumatic factor. In addition, relational points of polyfactory origin associated with alien carious cavities and root caries, poorly installed fiilings, crowding of teeth, orthodontic devices, crowns, clammers and saddle parts of prostheses, etc. contribute to a violation of the functional activity of periodontal tissues. Meanwhile, such congenital malformations of organs and tissues of the oral cavity as the small vestibule of the oral cavity, the strands of the transitional fold and the mucous membrane in the gum area also cause the development of localized periodontitis, where their elimination forms the basis of successful treatment [6, 25].

It should be emphasized that the structure of etiological factors of periodontitis development is dominated by endogenous factors that are associated with the presence of various general diseases [5]. Among the above general diseases, endocrine diseases are the most important for the development of inflammatory periodontal diseases, especially diabetes mellitus (the frequency of periodontal tissue damage is 70-90%), as well as neuro-somatic diseases that are associated with metabolic disorders. In addition, the inflammatory-destructive process of periodontal tissues is most often accompanied by diseases of the organs of the hematopoietic system, hypovitaminosis, various infectious diseases and pathologies of the gastrointestinal tract. At the same time, there is evidence that such comorbid conditions as diseases of the cardiovascular and respiratory systems, as well as overweight and obesity have a negative effect on the functional state of periodontal tissues with the subsequent development of chronic periodontitis [17, 31].

It is important to mention that the researches contain information about the role and values of the central nervous system in the development of the pathological process of periodontal tissues of inflammatory nature, which is associated with impaired regional circulation, associated with neurovegetative and neurohormonal mechanisms. In addition, the relationship between the development of periodontitis with the disorder of intrauterine fetal development was revealed, which creates the prerequisites for the formation and development of periodontal disease of inflammatory and dystrophic nature. Meanwhile, factors such as heredity, gender, age, socio-economic situation, etc. play a certain role in the development and course of inflammatory periodontal diseases. [17]

Thus, the main etiological factors for the development of the chronic inflammatory process of periodontal tissues are the interaction of periodontal pathogenic microflora with the immunobiological reactivity of the body, which largely depend on local, general risk factors and determine the clinical course of periodontal diseases. In this regard, it is necessary to take these factors into account when conducting comprehensive therapy for inflammatory periodontal diseases, which will have a positive effect in increasing the effectiveness of the medical and preventive measures.

Pathogenetic mechanisms of formation and development of pathological processes of periodontal tissues. Nowadays the synergistic interaction of microorganisms included in the periodontal pocket biofilm community, primarily the main representatives of periodontal pathogenic microflora, is of paramount importance against the background of a decrease in nonspecific antimicrobial protection of the macroorganisms in the development of inflammatory periodontal diseases [11, 14]. At the same time, the main predisposing factors for the development of oral dysbiosis are the use of antibiotics, changes in the state of local immunity, disorders of hormonal status, stress effects on the body and various allergic reactions [7, 15]. In addition, a non-specific response to microbial invasion is an important pathogenetic mechanism for the development of marginal gum inflammation. Meanwhile, the inflammatory process is aggravated by an unsatisfactory hygienic state of the oral cavity, where significant thickening of the soft plaque is determined. Meanwhile, the presence of a significant number of dental deposits and the presence of periodontal pathogenic microorganisms determine the intensity of the inflammatory-destructive process of periodontal tissues [1, 4].

We should also say that there is a microcirculation disfunction in periodontitis, which contributes to a decrease in the level of oxygen consumption by the periodontal tissues, followed by a change in the bone density of the alveolar process of the upper and lower jaws. At the same time, the loss of antagonist teeth leads to a decrease in the functional activity of periodontal tissues, which contributes to impaired microcirculation and oxygen starvation of periodontal tissues. Meanwhile, prolonged occlusive trauma with mechanical overload contribute to impaired blood supply to periodontal tissues with the formation of vascular thrombosis, swelling and destruction of collagen fibers. Osteoporosis develops, leading to bone resorption of the alveolar process of the upper and lower jaws [21, 23]. Among the local risk factors, the pathological ratio of teeth, carious cavities in the cervical region of the teeth, the presence of orthodontic devices, poor-quality restorations with filling materials, made with disorders of the technological features of the crown clamper and saddle-shaped parts of orthopedic structures, as well as congenital malformations associated with the presence of mucosal strands in the gum and transitional fold, small oral cavity preversion are of particular clinical significance [5]. These local factors contribute to the occurrence of the inflammatory process of the marginal gum, accompanied by a dysfunction of the microvasculature, followed by the development of chronic localized or generalized periodontitis [29].

Currently, the main pathogenetic theories of the occurrence of a chronic inflammatory process of periodontal tissues are environmental and key periodontopathogenic theories that cause the transition of microorganisms from a state of symbiosis to dysbiosis, leading to the activation of the opportunistic periodontal pocket microflora, where some bacteria in small concentrations interact with the inflammatory processes of periodontal tissues and thereby support chronic inflammation. Meanwhile, the formed microbial community captures and holds a niche for habitat for a long time [14, 31]. At the same time, the appearance of zones with insufficient oxygen access and a large number of tissue decay products contributes to an active shift towards anaerobic species that have the greatest pathogenicity and virulence [11, 14, 17].

The researches contain information on a wide range of mechanisms of genetic variation of microorganisms, manifested in biofilms, which are aimed at creating an effective defense against the immune system of the macro-organism and antimicrobial drugs [16]. Such genetic changes in microorganisms cause their ability to persist and acquire resistance to a wide range of antibiotics. In addition, metabolic products (ammonia, indole, hydrogen sulfide) are released during the vital activity of microbial cells, which have a toxic effect on periodontal tissues. At the same time, bacterial enzymes (gingipains, cysteine proteinases, etc.) have a direct effect on the inflammatory-destructive processes of periodontal tissues with the formation of a pathological periodontal pocket [4]. At the same time, the inflammatory process contributes to insufficient oxygen access to periodontal tissues, where favorable conditions for the growth of periodontal pathogenic microorganisms and maturation of the bacterial biofilm are created in tissue decay products [8]. This pathogenetic mechanism of chronic periodontitis contributes to quantitative and qualitative changes in the structure of microorganisms, where there is an active shift in the composition of the microbiome in favor of anaerobic species, characterized by pronounced aggressiveness [7, 14, 28, 33].

Recent studies have established the presence of a critical level of microorganisms, at which the intensity of the inflammatory process in periodontal tissues increases. At the same time, the main periodontopathogens characterized by the most virulent and aggressive properties are Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia. In addition, a direct relationship between the degree of microflora balance disturbance and the severity of periodontitis was determined [7, 14, 15, 32].

It should be emphasized that the reseaches contain information on limiting the intensity of the inflammatory process in the pathological periodontal pocket due to the extraction of inflammatory mediators related to cytokines and chemokines, which, when bound to specific receptors, change the survival rate of targeted cells, where the concentration of mediators in the inflammatory focus becomes sufficiently high for local exposure [23, 38]. The intensity of the periodontal tissue inflammatory process is influenced by the synthesis of IL-1β and TNF-α, which increase the adhesion of neutrophils and monocytes to endothelial cells and enhance the synthesis of small inflammatory mediators (prostaglandins E2 and F2α, matrix metalloproteinases) by fibroblasts and macrophages, while causing neutrophil degranulation with the activation of osteoclasts.

In the last period, the researches present information on different interpretations of IL-4 activity by the authors. At the same time, one of the options considered that IL-4 increases the production of anti-inflammatory cytokines, which contributes to the stabilization of the focus of progressive destruction. Meanwhile, another interpretation characterizes that this cytokine exhibits anti-inflammatory properties with stimulation of antimicrobial immunity, and on the other hand is responsible for immune-mediated destruction of periodontal tissues. In this regard, IL-4 in the pathogenesis of inflammatory-destructive processes of periodontal tissues belongs to the group of leading pro-inflammatory cytokines [4, 5, 23, 38].

A special place is occupied by the disbalance between optimal cytokine concentrations and small inflammatory mediators in the development of a chronic inflammatory process in periodontitis. In addition, disturbances in the relationship between nuclear factor kB activator receptor ligand (RANKL) and osteoprotegerin, destructive forms of eicosanoids and anti-inflammatory lipid mediators, as well as matrix metalloproteinases and their tissue inhibitors, which directly affect the severity of the inflammatory process in periodontitis, are important.

Also, the local inflammatory-destructive process of periodontal tissues, accompanied by the formation of a pathological periodontal pocket, usually contributes to the entry of microbial cells, toxins and antigens into the bloodstream, thereby initiating the appearance and activation of an autoimmune reaction [9, 24]. This situation contributes to the involvement of systemically activated immune cells in the focus of periodontal tissue inflammation, which provide a longer local inflammatory response [12, 14].

It is important to emphasize that continuous microbial invasion and tissue response to it in chronic inflammatory periodontal diseases depends to a certain extent on free radical oxidation, which is normally a way to neutralize a foreign agent [14]. Meanwhile, reactive oxygen species create the necessary conditions for neutrophils to form extracellular traps that have antimicrobial properties. At the same time, the main targets for the damaging effect of reactive oxygen species are membrane phospholipids, proteins, nucleic acids. Meanwhile, a high content of free radicals of neutral extracellular traps leads to damage to the vessels of the capillary channel and contributes to impaired blood circulation in the periodontal tissues. Thus, it indicates a significant pathogenetic role of neutrophils in the development and progression of periodontitis [27, 34, 37].

Today the direct relationship of generic diseases with the resistance of periodontal tissues to the pathogenic influence of the microbial community has been proved [19, 27]. The structure of systemic diseases that have a negative impact on the clinical course of periodontal diseases includes diseases of the gastrointestinal tract, cardiovascular, nervous, endocrine and genitourinary systems, as well as autoimmune diseases, pregnancy and menopause, psychoemotional overexertion, etc. [18, 22]. Moreover, in patients with diabetes mellitus, the severity of chronic periodontitis significantly increases, where constant control of blood sugar level can reduce the aggressiveness of the inflammatory-destructive process in periodontal tissues [19, 21, 27].

The presence of a deficiency of vitamins of group "A," "B," "C" and "E" contributes to the emergence and progression of inflammatory periodontal diseases. At the same time, there is evidence that the vitamin "D" receptor gene is one of the genetic markers of periodontitis. The negative effect of smoking on microcirculation in periodontal tissues has also been proven, since toxic substances contained in inhaled smoke initially contribute to vasodilation with a sharp increase in blood flow, and after 30 minutes vasoconstriction occurs with a decrease in blood flow [6. 21. 27].

All above characterizes the presence of a wide range of pathogenetic mechanisms for the formation and development of inflammatory periodontal diseases, which must be taken into account when carrying out complex medical and preventive measures. At the same time, all pathogenetic mechanisms of the development of inflammatory-destructive processes of periodontal tissues have not been fully studied, which determines the further research work mproving the pathogenetic therapy of periodontal diseases.

The basic principles of improving the prevention of periodontal diseases at the current stage. Nowadays one of the important tasks is to improve the medical care and prevent dental diseases [4, 5]. Taking into account the wide range of etiological factors and pathogenetic mechanisms of the development of inflammatory periodontal diseases and their individual characteristics of the course in each specific case, the treatment of chronic generalized periodontitis should be complex and personalized [3, 21, 23, 38]. Rational preparation of a plan and organization of medical and preventive measures is carried out in close cooperation of a periodontologist and a patient, where the main measures include systemic and local therapeutic, if necessary orthopedic, surgical and orthodontic treatment, physiotherapeutic methods with professional oral hygiene, increased immunobiological reactivity of the body, as well as mandatory dispensary observation [18, 20, 30].

It should be noted that in the complex treatment of chronic periodontitis, destruction of the microbial biofilm is of key importance, including its instrumental removal, followed by alignment and detoxification of the root surface, which should be carried out simultaneously or within 24 hours in order to prevent bacterial recolonization [30]. In addition, teaching and educating patients on oral hygiene and monitoring it with the correct selection of hygienic products, which are very important for achieving good treatment results and extending the remission phase, is of important practical importance in etiopathogenetic therapy [13, 26].

It is necessary to pay attention to the elimination of local risk factors that contribute to the development of periodontitisn in the integrated treatment of chronic periodontitis. It is recommended to perform surgical correction of the structure of soft tissues of the oral vestibule, in addition, splinting of movable teeth, selective grinding, elimination of supracontacts of the teeth of the upper and lower jaws. In this case, the general treatment provides for the use of antibacterial preparations in combination with antifungal, as well as probiotic and prebiotic agents, anti-inflammatory and immunomodulatory preparations. In the meantime, agents that control the inflammatory response of the body are applied systemically and locally, the action of which will restore the balance between pro-inflammatory and anti-inflammatory mediators. This group of drugs includes non-steroidal anti-inflammatory medications, antagonists of pro-inflammatory cytokines, recombinant anti-inflammatory cytokines, bisphosphonates, antibiotics in subantimicrobial doses, probiotics and prebiotics, as well as platelet growth factor [18, 20]. Such a general complex treatment should be used in the treatment of patients with susceptibility to periodontitis and often repeated exacerbations with insufficient effectiveness of conventional treatment [26, 30]. General treatment is usually combined with occupational oral hygiene and local antibacterial therapy, taking into account the clinical picture and the presence of systemic aggravating factors [13].

Thus, the initial stage of the integrated treatment of inflammatory periodontal diseases is etiotropic therapeutic measures aimed at eliminating factors that contribute to the maintenance of inflammatory processes in periodontal disease associated with hygienic education and upbringing, removal of supra and subgingival dental deposits, closed curettage and oral sanitation. The next stage of complex treatment is drug therapy using antiseptics, anti-inflammatory drugs, vitamins, enzymes, immunomodulators. Further, according to the indications, surgical and orthopedic methods of treatment are carried out. In addition, it is necessary to rationally organize and plan methods of comprehensive medical and social re-

habilitation of patients with inflammatory diseases of periodontal tissues.

Conclusion. The high prevalence of inflammatory periodontal diseases among the population and the unresolved problems of their etiopathogenetic factors, integrated treatment, prevention and rehabilitation dictate the need for further interdisciplinary research improving medical and preventive care taking into account the socio-economic aspects of morbidity.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

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THE IMPACT OF THE INTRODUCTION OF THE INTERNAL EVALUATION SYSTEM ON THE PERFORMANCE OF THE MEDICAL ORGANIZATION

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The requirements of Russian legislation for quality control and safety of medical care include the creation of internal performance appraisal system (PAS) of medical personnel involved in the provision of medical services. The effectiveness of such a system can be determined by changes in the performance of a medical organization.

The aim of the work: to study the results of the implementation of internal performance appraisal system of medical personnel on the performance indicators of a medical organization.

Materials and methods. This paper presents an analysis of the performance indicators of a medical organization after the introduction of internal PAS of employee of medical structural units in a state medical organization. The system was developed in the course of previous studies, and its feature was the combined use of personnel performance evaluation and the level of development of his competencies. The data were collected by anonymous questionnaire using medical information system, statistical, sociological, analytical and expert methods were used, comparative and content analysis of a number of indicators of the work of a medical organization, personnel and patients before and after the implementation of internal PAS.

Results. The implementation of the internal PAS of medical personnel on the performance showed a statistically significant ($p < 0,05$) positive dynamics of the performance indicators of the medical organization and patient satisfaction indicators.

Conclusion. The use of an internal PAS is an important factor for improving the performance of a medical organization, improving the quality of medical care and patient satisfaction.

Keywords: performance appraisal, satisfaction, heads, competence, management, medical organization, effectiveness.

Introduction. Quality control and safety of medical care in medical organizations is one of the priority tasks facing Russian healthcare. Ensuring this type of activity should be carried out by complying with a number of regulatory requirements, including the creation of PAS of medical personnel involved in the provision of medical services [8; 9]. Currently, the Russian healthcare system has not developed unified methodological approaches that allow objectively and systematically assess the impact of the activities of specific medical heads and workers on the work of medical organizations.

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The aim of the work: to study the results of the implementation of internal PAS of the activities of personnel of medical structural units on changes in hospital performance indicators.

The objectives of the study: analysis of the studied performance indicators of medical organization and personnel, including the satisfaction of personnel and patients of medical organization before and after the implementation of an internal PAS of medical personnel to identify statistically significant changes.

Materials and methods. The basis of the study was the State budgetary healthcare institution "Chelyabinsk Regional Children's Clinical Hospital". Three groups of indicators were selected by the expert method to analyze the impact of the new internal PAS on the performance indicators of medical organization:

Group of indicators No. 1. "Hospital performance indicators" (Table No. 1). The data were obtained using medical information system and analyzed in comparison before and after the introduction of a new assessment system the performance of medical heads (2020 to 2018).

Group of indicators No. 2. "Satisfaction of hospital personnel with the evaluation of their work". The number of employees who consider subjective the evaluating methods of personnel performance. The number of employees who have a need for an objective evaluation of activity. The number of employees who disagree with the management style and methods. The study of the opinion of personnel was carried out using an electronic questionnaire (Google form) by the method of double anonymous questioning. Responses were taken into account to calculate the indicators: "Agree" and "Partially agree". Initial survey (January, 2019, n = 273) was carried out when the performance of heads was evaluated by the traditional method: according to the indicators described in effective contracts.

A new system of internal PAS of medical personnel was developed and implemented, the peculiarity of which was that in addition to evaluating the effectiveness of work, an assessment of the severity of competencies was carried out [5]. Procedure of performance appraisal consisted of comparing the planned indicators and the actual results of the work. To assess competencies, an organizational model of competencies has been developed, where each competence and the degree of its development are described by precise definitions and numbers(indicators). Procedure of performance appraisal consisted in determining the degree of competence development on a 4-point scale. At the first stage, employee independently assessed his activities for 1 year. At the second stage, performance appraisal of the effectiveness and the degree of competence development was carried

Performance indicators of a medical organization before and after the introduction of a system for evaluating the activities of personnel of medical structural units

№ п/п	Indicator	2018 (n = 16328)		2020 (n = 17291)		Difference in data
		abs., n	relates., % [95% CI]	abs., n	relates., % [95% CI]	
1	Total hospital mortality, people.	71	0.43% [0.34; 0.54]	46	0.27% [0.20; 0.35]	- 0.16% $\chi^2_{(1)}$ = 6.90 p=0.009
2	Number of defects in outpatient records	1883	11.53% [11.05; 12.03]	1325	7.66% [7.27; 8.07]	-3.87% $\chi^2_{(1)}$=145.7 p<0.001
3	Number of defects in medical records	1786	10.94% [10.47; 11.42]	1586	9.17% [8.75; 9.61]	-1.77% $\chi^2_{(1)}$=14.64 p<0.001

out by his direct supervisor. The repeated survey (November, 2019, n = 259) was conducted after the introduction of internal PAS.

Group of indicators No. 3. "Patient satisfaction with commercial medical services and willingness to recommend a hospital." The study of patients' opinions was carried out using an electronic questionnaire (Google form) by double anonymous questionnaire (n = 60). To calculate this indicator, the answer "Yes" to the questionnaire question was taken into account: "Would you recommend our hospital to provide paid medical services to relatives and friends?"

During the statistical analysis of the survey results, absolute and relative values (in %) were calculated. Relative values were provided with a 95% binomial confidence interval (95% CI) calculated by the Jeffries method (Bayesian apriority interval). The significance of differences in independent samples was assessed by the Pearson *chi*-square criterion and in partially overlapping samples of respondents – by the presence or absence of transgression of the calculated 95.0% CI ($p > 0.05$ or $p < 0.05$, respectively). The calculations were performed using MS Excel 2016 and the Epitools package [12].

The results of the study. Data analysis showed that, after the implementation of PAS of medical employees, positive statistically significant changes occurred in the studied indicators:

1. Improvement of hospital results: reduction in the number of defects when filling out medical documentation and reduction in total hospital mortality (Table No. 1).

2. Increasing the satisfaction of hospital personnel with the evaluation of their work by reducing the number of employees who consider evaluation methods subjective (25,7% [20,74; 31,06] to 40,2%, [34,32; 46,21], $p \leq 0.05$) and by reducing the number of employees who disagree with the management style and methods of their immediate supervisors (11,7% [8,31; 15,94] to 35.5% [29,88; 41,48], $p < 0.05$).

3. Increased patient satisfaction with commercial medical services and their willingness to recommend a hospital (83,3% [72,45; 91,10] to 53,3%, [40,80; 65,55], $p < 0.05$).

Discussion. The mechanism of influence of the evaluation of the activity of a particular employee on its effectiveness is the personalization and use of numbers when setting tasks. This helps to increase the accuracy and objectification when monitoring the results of work, which leads to stimulation of self-control, increased internal motivation and increased employee responsibility for the result of work. Such a work environment is formed, among other things, if there is an objective and fair evaluation of the employee's activity [6]. An objective evaluation of the labor activity of healthcare workers makes it possible to understand not only the effectiveness and potential, but also contributes to the development of labor motivation and satisfaction with the work performed [1;11]. More than 60,0% of employees in public medical organizations and about 50,0% of employees of private clinics agree with the need to use such an evaluation [6]. To increase the competitiveness of medical institutions, it is important to create and develop key competencies of personnel [2; 4; 7; 10]. The indicator showing the attitude of employees to the performance of their work and its results is the indicator of satisfaction of employees of medical organizations with the evaluation of their activities, which can be evaluated in relation to patient satisfaction with the quality of medical services [3].

Conclusions: After the implementation of internal PAS of personnel of medical structural units based on performance indicators and the degree of competence development, statistically significant trends were noted in all groups of the studied indicators: improvement of hospital results (reduction in the number of defects when filling out medical documentation, reduction in total hospital mortality), increase in personnel satisfaction with the evaluation of their work, growth in patient satisfaction with medical services. Thus, the use of internal PAS of medical personnel activities based on performance indicators and the expression of competencies is an important factor contributing to improving the quality of medical care by improving hospital performance, patient and personnel satisfaction.

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MEDICAL AND DEMOGRAPHIC SITUATION AND INCIDENCE OF THE POPULATION OF THE AMUR REGION

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УДК 614.2

Summary. The situation with the COVID-19 pandemic has to some extent changed the structure of morbidity and mortality in the Russian Federation and its regions.

Aim of the study. Based on an analysis of the medical and demographic situation in the Amur Region, the Far Eastern Federal District and the Russian Federation in the context of the COVID-19 pandemic, recommendations are given for making managerial decisions at the municipal, regional and federal levels.

Materials and methods of research: statistical, analytical. The materials of official state statistics of the Ministry of Health of the Russian Federation and Rosstat were used.

Results and discussion. The mortality rates of the population of the Amur Region, the Far Eastern Federal District and the Russian Federation for the years of analysis (2016-2020) have been studied. It was revealed that in the Amur region. the indicators are higher for all the years of analysis, in 2020 they amounted to 16.2‰, in the Far Eastern Federal District - 13.9‰, in the Russian Federation - 14.6‰. The difference in mortality rates in the administrative entities of the Amur Region (2020) is 2.3 times. The mortality rate of the population of the Amur Region from COVID-19 (in 2020) was 0.84‰00, for the urban population it is higher - 0.93‰00, than for the rural population - 0.67‰00. The first detected incidence of the population in the Amur Region, the Far Eastern Federal District and in the Russian Federation (2020) was studied. It has been established that in the Amur Region the figures are higher - 80294.8 per 100 thousand of the population than in the Far Eastern Federal District (74596.5), in the Russian Federation (75840.1). In the Amur Region, there are higher rates of primary morbidity with diseases of the digestive system. Very high rates were noted in Tynda and Zeya, which determines the need for an in-depth study of the causes of this incidence in the region. The frequency of detected COVID-19 in the Amur Region was 3141.3 per 100 thousand of the population (3.9% of the total number of primary incidence), in the Far Eastern Federal District - 3394.9‰00 (4.55%), in the Russian Federation - 3384.5‰00 (4.46%). The primary incidence of the entire population of the Amur Region has decreased over the years of analysis (2016-2020). Higher rates of newly diagnosed morbidity were noted in children (0-14 years old) and adolescents (15-17 years old) than in the general population, which requires strengthening preventive work with this age group of the population.

Conclusion. The identified features of the medical and demographic situation in the Amur Region should be taken into account by the heads of governments at the municipal regional and federal levels in order to develop management decisions. Taking into account the COVID-19 pandemic and with a focus on the health of the future.

Keywords: medical and demographic situation, mortality, newly diagnosed morbidity, age groups, administrative units.

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Improvement of the medical and demographic situation in the country and public health indicators ultimately leads to economic growth in any territory [8, 4]. Decreasing the mortality of the population, increasing the birth rate and healthy life expectancy are among the key goals of the national project "Demography" [3]. Achieving the goals and strategic objectives outlined by the National Healthcare Project is possible only with the use of all available reserves - both at the level of managing the health care system as a whole and at the level of the region [7]. The territorial and climatic and geographical features of the Russian Federation

determine the inequality in the availability of medical care to the population [5, 11]. The high mortality rate in the Amur Region [9] is a cause for concern.

In March 2020, the World Health Organization declared a pandemic of a new coronavirus infection COVID-19 [9]. In the Russian Federation, COVID-19 began to be registered from January 2020 [12, 13]. The situation with the COVID-19 pandemic has imposed changes in the structure of morbidity and mortality in the Russian Federation and its regions, which has determined the need to develop management decisions at the regional level [1,6].

Purpose of the study. Based on an analysis of the medical and demographic situation in the Amur Region, the Far Eastern Federal District and the Russian Federation in the context of the COVID-19 pandemic, recommendations are given for making managerial decisions at the municipal, regional and federal levels.

Materials and methods of research: statistical, analytical. The materials of the official state statistics of the Ministry of Health of the Russian Federation and Rosstat "The natural movement of the population of the Russian Federation for 2020 (statistical bulletin)", Amurstat https://amurstat.gks.ru/storage/media-bank/tfUgKfcx/07_1_64.htm, the collection "Morbidity of the entire population" were used Russia, FGBI "TsNIIOIZ" of the Ministry of Health of Russia, 2021.

Results and discussion. The population of the Amur Region in 2020 amounted to 790 thousand people, including urban - 67.8% and rural 32.2%. Over the years of analysis (2016-2020), the total population of the Amur Region decreased by 1.9%. The urban population of the Amur Region during the analysis period decreased by 1.7%, the rural population decreased by 2.8%.

Over the years of analysis (2016-2020), the birth rate in the Amur Region decreased from 13.2 to 9.4 per 1000 population. The highest birth rates in administrative entities in the Amur Region (2020) were noted in Konstantinovsky, Tambovsky, Ivanovsky districts, in the city. Raychikhinsk, in Blagoveshchensk, etc.

It should be noted that the higher mortality rates of the population of the Amur Region than in the Far Eastern Federal District and in the Russian Federation for all years of analysis (2016-2020). In 2016, the indicator was 13.7 per 1000 population, in 2020 it increased to 16.2‰. In the Far Eastern Federal District in 2020, the indicator was 13.9‰, in the Russian Federation - 14.6‰. The difference in mortality rates by administrative units in the Amur Region (2020) is 2.3 times. The highest rate was noted in the Shimanovsky district - 26.8 per 1000 population, the lowest in the Blagoveshchensk district - 11.8‰ [10]. The death rate of the population of the Amur Region from COVID-19 in 2020 amounted to 84.3 per 100 thousand population, for the urban population the figure is higher - 92.7 000 than for the rural population - 66.8 000.

The incidence of the population of the Amur region with a diagnosis established for the first time, in dynamics for 2016-2020 [2]

age group	Year				
	2016	2017	2018	2019	2020
0-14 years old	199399.0	203693.0	199013.3	201424.4	166656.9
15-17 years old	155805.6	147957.0	165467.1	161662.3	147023.4
Over working age	50625.1	49642.6	51523.2	50391.3	58377.5
Adult	52408.2	52791.1	53270.0	51989.2	55952.2
Total	83919.0	84699.1	85011.3	84510.2	80294.8

In the course of the study, an analysis of the incidence with a diagnosis established for the first time was carried out by disease classes in the Amur Region, the Far Eastern Federal District and in the Russian Federation (2020) [1,5]. In the Amur Region, the figure is higher - 80294.8 per 100 thousand of the population, in the Far Eastern Federal District - 74596.5‰00, in the Russian Federation - 75840.1‰00. In the first place in the structure of primary morbidity in the Amur Region is the class of respiratory diseases (47.2%); in second place are injuries, poisonings and some other consequences of external causes (10.2%); subsequent places were occupied by the following classes: diseases of the digestive system (10.2%); diseases of the skin and subcutaneous tissue (4.4%), etc.

In the Amur Region, the primary incidence rates of diseases of the digestive system are significantly higher - 8172.1‰00 than in the Far Eastern Federal District - 3496.8‰00 and in the Russian Federation - 2627.0‰00, which requires an in-depth analysis of the causes of this pathology in the region. The frequency of detected COVID-19 (in 2020) in the Amur Region was 3141.3 per 100 thousand population (3.9% of the total number of primary incidence), in the Far Eastern Federal District - 3394.9‰00 (4.55%), RF – 3384.5‰00 (4.46%).

In the Amur Region, the primary incidence of respiratory diseases was (2020) 37,935.4 per 100,000 population. The highest rates were noted in the city of Zeya - 58318.8‰00, the city of Raychikhinsk (56358.6), the city of Blagoveshchensk (54275.4) and others. In the class of diseases, injuries, poisoning and some other consequences of external causes in general in the region, the indicator was 8180.1 per 100 thousand of the population, the highest values were in the city of Zeya (11090.3), in Skovorodinsky (10410.1), in Shimanovsky districts (9792.8), etc. In the class of organ diseases digestion in the region as a whole, the indicator was 8172.1 per 100 thousand of the population, very high rates were noted in the city of Tynda (50465.7), the city of Zeya (42573.1), in other administrative districts the indicators are lower, in the city of Blagoveshchensk (6193.1), in the Seryshevsky district (2628.5), etc. This determines the need for a special study of the causes of this incidence in the city. Tynda and Zeya.

The table shows the indicators of primary morbidity of the entire population of the Amur Region in dynamics for 2016-2020. by age groups of the population. The primary incidence of the entire population of the Amur Region has decreased over the years of analysis, a decrease was noted in the age groups of 0-14 and 15-17 years, while the rates increased in the adult population and people older than working age.

We noted higher rates of newly diagnosed morbidity (2020) in children (0-14 years old) - 166656.9 per 100 thousand of the corresponding population and adolescents (15-17 years old) - 147023.4‰00, than the total population - 80294.8‰00, which requires strengthening preventive work with this contingent.

Discussion. Conclusion. A high mortality rate was noted in the Amur Region and an increase in the indicator from 13.7‰ (2016) to 16.2‰ (2020), (RF - 14.6‰), which indicates the need for an in-depth analysis of the medical and demographic situation in the region.

An analysis of the primary morbidity of the population of the Amur Region revealed administrative districts with extremely high incidence rates of diseases of the digestive system, which determines the need for an in-depth analysis

of the causes of this pathology. High rates of morbidity in children and adolescents have been determined. It is necessary to strengthen federal, regional, republican programs of preventive work with the population, primarily with children and adolescents, the introduction of new organizational technologies and forms of work.

Conclusions. The identified features of the medical and demographic situation in the Amur Region should be taken into account by the heads of governments at the municipal regional and federal levels in order to develop management decisions. taking into account the COVID-19 pandemic and with a focus on the health of the future generation.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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THE INFLUENCE OF VESSEL POLYPEPTIDE COMPLEX ON THE VIABILITY OF RATS UNDER COLD STRESS

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The study of the mechanisms of preserving human viability in deep hypothermia, as well as the resilience of elderly people with hypothermia, is an urgent problem of physiology and medicine. The aim of the work is to study the effectiveness of the use of the vessels polypeptide complex (VPC) to stimulate the functions of the respiratory and cardiovascular systems in violation of life stability in the model of experimental hypothermia. Wistar's line rats were divided into an experimental group (injection of VPC) and a control group (injection of saline solution). VPC was administered intraperitoneal to rats at a dosage of 15.6 mg/kg of animal body weight 1 hour before the animals were immersed in a bath with cold water. The breath rate, heart rate, rectal temperature, esophageal temperature, and the degree of saturation of arterial hemoglobin with oxygen were evaluated. The heart rate in the rectal temperature range of 30-16 ° C was significantly higher after the use of VPC in comparison with the control. The breath rate began to decrease at a rectal temperature of 27.7 ± 0.3 oC during the cooling process in rats, which obtained VPC. A decrease in breath rate in the control group was observed, starting with a higher rectal temperature - 30.4 ± 0.4 oC . The threshold for stopping breathing after the use of VPS was 11.6 ± 0.3 oC for rectal temperature and 14.1 ± 0.3 oC for esophageal temperature. In the control, these indicators were equal, respectively, 16.0 ± 0.3 oC and 19.1 ± 0.3 oC, which is 4-5 oC higher. The cooling time of rats to respiratory arrest increased by 2 times after the use of VPC in comparison with the control. It can be assumed that VPC slows down the process of cold respiratory depression and cardiac activity. The obtained results indicate the ability of the VPC to maintain the functions of the respiratory and cardiovascular systems for a long time in case of a violation of life stability in the model of experimental hypothermia. This indicates the prospects for further investigation of the VPC geroprotective properties and its ability to increase the cold resistance of the body in hypothermia.

Keywords: resilience, cold stress, breathing, vessel polypeptide complex, geroprotection.

Introduction. Prolonged exposure to cold can lead to hypothermia, when thermoregulatory mechanisms fail to maintain normal body temperature. At a body temperature below 35 ºC, the most important functions of the body are disturbed. Especially dangerous is deep hypothermia, when breathing stops and the heart stops, which leads to the risk of death. However, moderate hypothermia is used in medicine in the treatment of patients with brain and heart lesions [4, 11]. It is known that the regulation of body temperature is disturbed in the elderly, which reduces their vitality (resilience). One of the external factors leading to a decrease in vitality is stress caused by hypothermia. In the elderly, the risk of hypothermia is especially high, since people in this group often suffer from chronic diseases and have reduced immunity. To maintain the functional activity of the body in people over 60 years of age under the influence of adverse factors of the internal or external environment, it is important to mobilize the resources of individual viability [2].

The mechanisms leading to cell death under various damaging effects are similar. These are excessive generation of oxygen free radicals, activation of lipid peroxidation, release of glutamate, disruption of the cell membrane potential, and an increase in the intracellular concentration of calcium ions [1, 6, 11]. Along with this, hibernating animals are an example of natural adaptations to a significant decrease in body temperature, which is observed during hibernation, while their cellular structures are not damaged [12]. The development of methods for increasing cold resistance, maintaining breathing and heart function at low body temperatures will allow a person to return to life even after a cardiac arrest during deep cooling.

The polypeptide complex of calf vessels (VPC) has angioprotective properties, normalizes lipid peroxidation, restores the density of microvessels in the cerebral cortex of old animals, and reduces the area of necrosis in a model of acute myocardial infarction in rats [5]. It has been established that VPC has an antiarrhythmic effect, softens the effect of catecholamines on the walls of blood vessels under extreme conditions [7]. The purpose of the work is to study the effectiveness of the use of VPC to stimulate the functions of the respiratory and cardiovascular systems in violation of vitality in the model of experimental hypothermia.

Material and methods. The experiments were performed on 13 white male Wistar rats weighing 300-320 g. I.P. Pavlov Academy of Sciences, supported by the program of bioresource collections of the Federal Agency of Scientific Organizations of Russia. Animals were anesthetized with urethane (125 mg/100 g of body weight, intraperitoneally), local anesthesia was applied (novocaine, 2%). The rats were kept under standard vivarium conditions with natural light and free access to water and food. The studies were carried out in accordance with the

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European Convention for the Protection of Animals Used for Scientific Purposes.

Cooling was carried out in a water bath at a temperature of 9-10 ºC. The animals were fixed on the platform so that the upper back and head were above the water surface. Using copper-constantan thermocouples, the temperature in the rectum at a depth of 4.5 cm (Tr) and in the esophagus (Tes) was recorded. The thermocouple in the esophagus actually measured the temperature of the heart. A sensor for recording the breath rate (BR) was fixed around the chest of the rat. Heart rate (HR) was determined from the electrocardiogram in the second lead. The degree of oxygen saturation of hemoglobin in arterial blood (SpO2) was determined using a veterinary pulse oximeter BP-12C (Biocare), the sensor was attached to the front paw. Rats of the experimental group (n=5) 1 hour before immersion in cold water were injected intraperitoneally with VPC at a dosage of 15.6 mg/kg of animal body weight. The control group of rats (n=8) was similarly injected with 1 ml of saline. The data were recorded using an external E14-140-M module (L-Card, Russia) and the PowerGraph program. The reliability of the results obtained was assessed using Student's t-test using the Statistica 6.0 software package. Experimental data are presented as mean ± error of mean (M ± m). Differences were considered significant at $p<0.05$.

Research and discussion. Before immersion in cold water, the rectal temperature in rats was 35.8±0.3°C, the temperature in the esophagus was 36.4±0.2°C, HR was 441±8 beats/min, BR was 118±6 cycles/min, SpO2 was 98±1%. The cooling time of the control animals to stop breathing was 60±7 min, which corresponded to the previously obtained data [1]. In animals that received VPC, this time increased by 2 times to 125±9 min. The curves reflecting the dependence of the temperature in the esophagus on the rectal temperature during cooling did not differ in the control and experimental groups (Fig. 1). The rate of decrease in Tr and Tes in the first 30 min of cooling did not differ significantly in control (Tr 0.32±0.02 °C/min, Tes 0.28±0.02 °C/min) and experimental rats (Tr 0.35±0.01 °C/min, Tes 0.30±0.02 °C/min). min). During the next 30 minutes, both indicators decreased to 0.1±0.001 °C/min in the control group and to 0.12±0.01 °C/min in the experimental group (p≥0.05). In the experimental group, cooling to respiratory arrest continued, and in the next 60 minutes the rate of decrease in Tr and Tes was 0.07±0.01 °C/min.

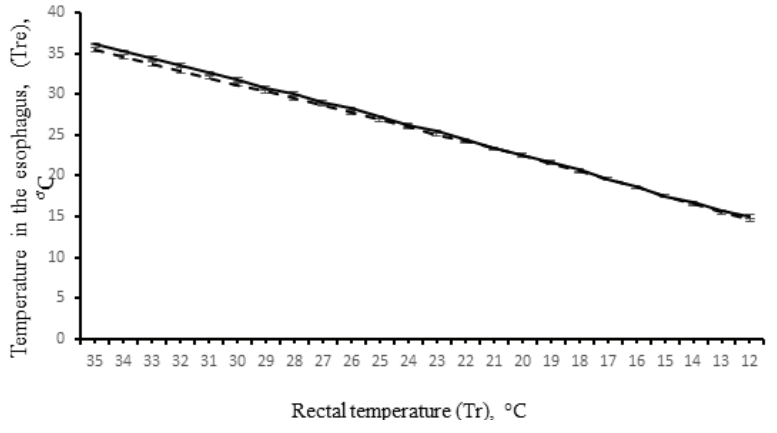

Fig. 1. Temperature dynamic in the esophagus (Tes) depending on the rectal temperature (Tr) when rats are cooled in water: dotted line - control, solid line - the use of VPC

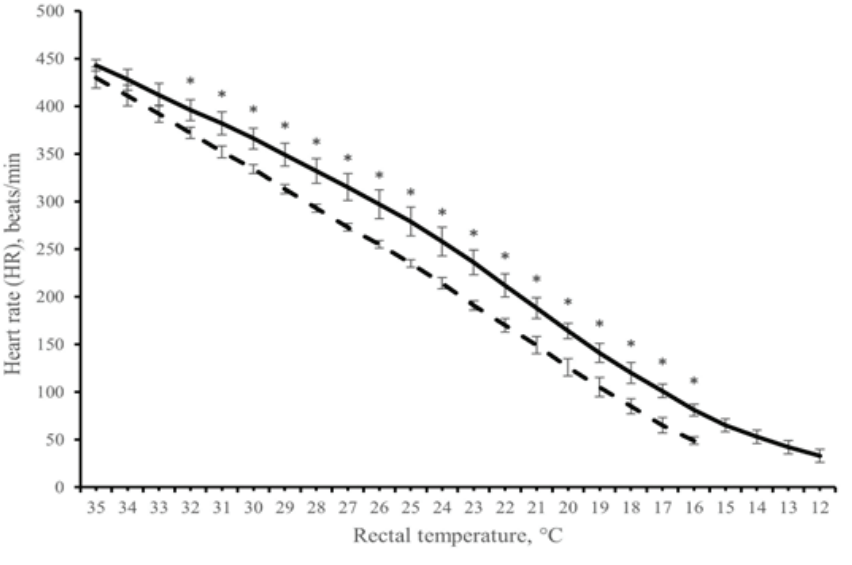

Fig. 2. The effect of VPC on the heart rate (HR) depending on the rectal temperature (Tr) when cooling rats in water: dotted line - control, solid line - the use of PCR.
* - $p < 0.05$ - compared to the corresponding indicator in the control.

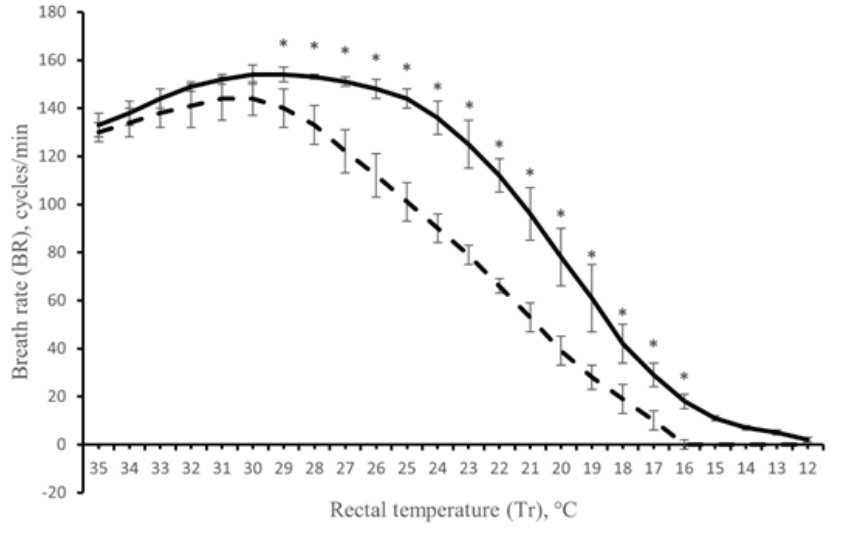

Fig. 3. The effect of VPC on the respiratory rate (BR) depending on the change in rectal temperature (Tr) when cooling rats in water: dotted line - control, solid line - the use of VPC.
* - $p < 0.05$- compared to the corresponding indicator in the control

The rate of decrease in HR in the control in the first 30 min of cooling was 9.8±3.4 beats/min, in the next 30 min it was 2.9±0.4 beats/min. In experimental rats, in the first 30 min, the rate of decrease HR was 9.5±2.2 (p≥0.05), in the next 30 min - 2.7±0.5 beats/min, which also did not differ from the control (p≥0.05), and in the last 60 min - 0.7 ±0.03 beats/min. It was noted that the HR at Tr 31-16 ºC in the experimental animals was significantly higher than in the control (Fig. 2).

In rats that were injected with VPC, the BR did not decrease to Tr 27.7±0.3ºC. At the same time, in control rats, a decrease in BR was observed, starting from Tr 30.4±0.4ºC (Fig. 3). The decrease in BR in the control and in the experimental group occurred at the same rate: in the first 30 min of cooling, 3.1±0.5 cycles/min, in the next 30 min, 2.7±0.4 cycles/min. In the experimental group of rats, within 60 minutes before stopping breathing, the BR decreased very slowly - 0.2±0.02 cycles/min.

Respiratory arrest in control animals was observed at Tp 16.0±0.3 ºC, Tes 19.1±0.3 °C, HR - 20±3 beats/min. In the experimental group of rats, respiration stopped at lower temperatures: Tr - 11.6±0.3 ºC, Tes - 14.1±0.3 °C, HR - 25±4 beats/min (p<0.05). Thus, after the application of VPC, the temperature threshold for respiratory arrest decreased by approximately 4-5ºC. In the experimental group of rats, during the last 60 min of cooling to respiratory arrest, the rate of decrease in heart rate and respiratory rate decreased corresponding to a significant slowdown in the cooling process. At this stage of the experiment, the HR decreased gradually from 70 to 26 beats/min. The BR was low, at first at the level of 11 - 8 cycles/min, and approximately 30 minutes before the respiratory arrest, the respiratory rate decreased to 5 - 3 cycles/min, then breathing stopped. In contrast, in the control, as noted above, respiratory arrest occurred at higher values of Tr and Tes, and the decrease in BR and HR before respiratory arrest occurred quickly. The level of blood oxygen saturation in all rats was kept at the level of SpO2 85-96% to Tr 18-19°C. Then, in control animals, this indicator decreased, in accordance with the decrease in respiration. In animals treated with VPC, with the rare breathing, SpO2 was at the level of 90-92%.

The data obtained complement the previously identified protective effect of VPC on the indicators of the functional activity of the cardiovascular system in models of age-associated pathology [7]. The mechanism of the protective effect of VPC on the cells of the organs of the cardiovascular and respiratory systems in violation of vitality during experimental hypothermia may be due to the tripeptide KED that is part of it [3]. This tripeptide can penetrate into the cytoplasm and nucleus of vascular endotheliocytes and specifically interact with the CACC nucleotides sequence in DNA, regulating the expression of the gene encoding the Ki67 proliferatropic protein [9]. By the same mechanism, or by interacting with the nucleosome (the complex of DNA and histone proteins) [8], the KED peptide can regulate gene expression and protein synthesis of apoptosis (p53), proliferation (VEGF), and adhesion (E-selectin) of endotheliocytes during development. cold stress of cells, pathology of the cardiovascular system and aging [10]. It is likely that by using VPC, which slows down the development of pathological damage in cells during hypothermia, it is possible to slow down the cessation of breathing and increase the time reserve for therapeutic measures, when saving people with deep hypothermia, as well as when hypothermia occurs in people of older age groups.

Conclusion. The results obtained indicate the ability of VPC to maintain the functions of the respiratory and cardiovascular systems for a long time in case of violation of viability in the model of experimental hypothermia. These data expand the possibilities for further research into the geroprotective properties of VPC and its ability to increase the body's resistance to hypothermia.

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GROUPING OF DISTRICTS OF THE REPUBLIC OF SAKHA (YAKUTIA) BY MEDICAL AND DEMOGRAPHIC INDICATORS OF CHILDREN AND ADOLESCENTS HEALTH CARE

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The Republic of Sakha (Yakutia) is an example of a region with a low population density and underdeveloped transport infrastructure, which affects the availability of full-fledged and high-quality medical care. Specialized medical care is provided mainly in the capital of the republic, Yakutsk. The article presents a variant of the grouping of the Republic Sakha (Yakutia) districts according to medical and demographic indicators of children and adolescents health. It is shown that unfavorable indicators are observed in most of arctic districts. In these conditions, it becomes obvious that modern technologies must be widely used to ensure the availability and quality of medical care in settlements with a small population and low transport accessibility.

Keywords: children, adolescents, medical and demographic indicators, medical care, accessibility, quality, Yakutia.

Introduction. The constituent entities of the Russian Federation differ significantly in many parameters, including climate and geographic, socio-economic, ethnic structure, population settlement patterns, development of transport infrastructure, etc. The Republic Sakha (Yakutia) is an example of a region with a large territory, low density and ethnic heterogeneity of the population. The territory of Yakutia is divided into 36 administrative-territorial units (34 municipal districts and 2 urban districts). The healthcare system in the republic is extremely centralized, and specialized medical care is provided mainly in Yakutsk city. Transport distance from the center and low population density are the main factors that influence on availability and quality of medical care. In these conditions, it becomes obvious that it is necessary to consider the peculiarities of some territories of the republic in order to plan and organize effective medical care for the population.

One of the modern methods that allows grouping regions/districts with similar indicators is cluster analysis. This technique is successfully used in such industries as economics, ecology, healthcare [1, 4, 5, 8].

Earlier, in the Republic Sakha (Yakutia), several variations for zoning of Yakutia territory were developed and implemented, with considering of medical and demographic indicators [5, 6]. These works were carried out in the early 2000s. At present, in the conditions of the 3-level healthcare system of the Republic Sakha (Yakutia), it is necessary to clarify the directions for applying forces to achieve target indicators of efficiency for targeted projects at both the regional and federal levels. In this regard, the purpose of the study was to group the municipalities of the Republic Sakha (Yakutia) according to the degree of well-being of children's health indicators in order to determine the directions for optimizing of medical care organizing technologies.

Materials and methods: Based on the conjunctural reports of the medical organizations of the Republic Sakha (Yakutia), the average values of indicators for a 5-year period (2016-2020) were calculated [3]. This approach is justified by the fact that the use of average values over a 5-year period will make it possible to smooth out fluctuations in the levels of the series. The city of republican significance Yakutsk was excluded from the analysis as the main center for providing specialized assistance to the child population.

The analysis includes the following indicators:

- characterizing the health status of children and adolescents: the morbidity of children per 1000, the morbidity of adolescents per 1000, infant mortality (0–12 months) per 1000 live births, child mortality per 10,000 child population (0–17 years).

-characterizing the resource provision of health care per 10,000 inhabitants: the number of doctors, nursing staff, the number of round-the-clock hospital beds, the capacity of outpatient clinics.

Statistical analysis of the data was performed using the IBM SPSS STATISTICS 22 package. The division of municipalities into groups with different levels of morbidity and mortality was carried out using cluster analysis by the K-means method. Spearman's rank correlation analysis was used to analyze the relationship between the studied variables. When comparing clusters, nonparametric Kruskal-Wallis analysis of variance was used. The critical value of the level of sta-

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tistical significance of differences (p) was taken equal to 5%.

Results. The analysis of indicators reveals the presence of significant differences between the municipalities of the republic. Thus, the proportion of children and adolescents in the age structure of municipalities population varied from 23% (in Neryungrinsky) to 37% (in Momsky). Infant mortality rates ranged from 1 to 18 per 1000 live births, infant mortality - from 3.9 to 15 per 10000 child population, child morbidity - from 789 to 3133 per 1000 child population (Table 1). Correlation analysis found that children morbidity positively correlated with adolescents morbidity (r=0.64, p<0.001), child mortality with the children morbid-

Table1

Grouping of municipalities according to the degree of well-being of children's health indicators

District	Medico-social zone	Infant mortality per 1000*	Child mortality per 1000*	Morbidity in children per 1000*	Morbidity in adolescents per 1000*
1 cluster n=15					
Abyisky	Arctic	5.1	11.9	2170.5	1370.3
Momsky,	Arctic	7.4	9.4	2143.9	1250.5
Eveno-Bytantaysky	Arctic	3.4	6.6	1849.6	1511.5
Lensky	Industrial	6.7	6.1	2378.4	1446.1
Neryungrinsky	Industrial	4.5	8.0	2412.3	1577.1
Oymyakonsky	Industrial	17.9	12.0	2505.9	1440.1
Mirninsky	Industrial	4.1	4.8	2138.8	1505.9
Amginsky	Agricultural	14.2	13.9	2448.1	1422.5
Vilyuisky	Agricultural	5.1	7.0	1935.4	1541.1
Gorny	Agricultural	0.8	4.4	2292.6	1550.2
Namsky	Agricultural	4.0	6.3	2093.7	1783.0
Suntarsky	Agricultural	8.0	6.5	2160.4	1321.3
Ust-Aldansky	Agricultural	7.0	5.5	1903.8	1344.5
Churapchinsky	Agricultural	1.5	3.9	1774.8	1520.0
Khangalassky	Смешанная	4.4	4.6	2343.9	1587.7
2 cluster n=11					
Allaikhovsky	Arctic	5.0	12.3	2902.7	1888.1
Bulunsky	Arctic	9.8	8.0	2583.1	1788.4
Nizhnekolymsky	Arctic	2.9	7.6	3133.4	2251.9
Oleneksky	Arctic	6.4	15.1	2922.5	1494.3
Srednekolymsky	Arctic	3.6	6.7	2929.5	1733.8
Ust-Yansky	Arctic	12.0	5.8	2812.4	1784.1
Aldansky	Industrial	3.9	5.0	2757.5	1718.8
Tattinsky	Agricultural	4.7	7.7	2491.1	1769.2
Kobyaisky	Mixed	3.1	4.2	2650.5	1643.9
Olekminsky	Mixed	9.6	9.1	2577.5	1906.3
Ust-Maysky	Mixed	11.7	7.5	2816.9	2128.7
3 cluster n=8					
Anabarsky	Arctic	2.6	4.9	1334.8	1216.8
Verkhoyansky	Arctic	3.6	5.1	789.2	1015.4
Zhigansky	Arctic	7.6	5.6	1619.0	1147.6
Verkhnekolymsky	Arctic	3.9	4.1	1256.2	1948.3
Verkhnevilyuisky	Agricultural	7.0	10.3	1137.9	1049.8
Nyurbinsky	Agricultural	6.5	4.5	1614.5	950.6
Megino-Kangalassky	Agricultural	4.3	12.6	1669.1	1549.1
Tomponsky	Mixed	4.8	4.8	1707.7	1073.9

Note: *— average values of indicators for a 5-year period (2016-2020)

ity (r=0.37, p=0.032), children morbidity with the number of nursing staff (r=0.35, p=0.043) and the capacity of outpatient clinics (r=0.34, p=0.047). No statistically significant correlation was found between the share of the child population and children morbidity.

High morbidity rates may be a reflection of the availability of medical care. In this regard, the formation of clusters was carried out according to the average values for a 5-year period of infant mortality per 1000 live births, the morbidity of children and adolescents per 1000 of the population. Infant mortality was included as an integral indicator of the level of the health care system. During the analysis, three clusters were formed with a sufficient number of observations (Table 1). Cluster 1 included 15 municipalities, cluster 2 - 15 municipalities, cluster 3 - 8 municipalities.

Considering the medical and social zones according to the classification of M.A. Tyrylgin and the list of territories classified as the Arctic zone in accordance with the Decree of the President of the Russian Federation dated May 13, 2019 No. 220 "On Amendments to the Decree of the President of the Russian Federation dated May 2, 2014 No. 296 "On the land territories of the Arctic zone of the Russian Federation", then the territory of the republic can be conditionally divided into 5 zones [6, 7]: Yakutsk is a city of republican significance (urban districts of Yakutsk and Zhatay); Arctic zone - Abyisky, Allaikhovsky, Anabarsky, Bulunsky, Zhigansky, Momsky, Nizhnekolymsky, Oleneksky, Srednekolymsky, Ust-Yansky, Eveno-Bytantaysky, Verkhoyansky, Upper Kolymsky; Industrial zone - Aldansky, Lensky, Mirninsky, Neryungrinsky, Oymyakonsky; Agricultural zone - Amginsky, Verkhnevilyuisky, Vilyuisky, Gorny, Megino-Kangalassky, Namsky, Nyurbinsky, Suntarsky, Tattinsky, Ust-Aldansky, Churapchinsky; Mixed zone - Kobyaisky, Olekminsky, Tomponsky, Ust-Maysky, Khangalassky.

With considering of these two approaches, an analysis of the results of clustering was carried out (Table 2). The most prosperous in terms of the totality of indicators of mortality and morbidity in children is the 3rd cluster, it includes 8 districts. Of these, 4 are arctic, 3 are agricultural, and 1 is a region of mixed economy. Cluster 1 occupied an intermediate position between clusters 2 and 3. It was characterized by relatively high rates of mortality and morbidity in children. It includes 15 districts, including 3 arctic, 4 industrial, 7 agricultural, 1 area of mixed economy. The most unfavorable situation in relation to the quality of children's health was observed in the municipalities assigned to the 2nd cluster. This cluster has the highest rates of mortality and morbidity in children. Of the 11 municipalities of this cluster, 6 are regions of the Arctic zone, 1 is industrial, 1 is agricultural, 3 are mixed (Table 1). However, this group is characterized by high rates of staffing and beds, which reflects the low population density in most of these areas. Thus, the clusters with unfavorable indicators (1 and 2) of children's health over the past 5 years (2016-2020) included 9 out of 13 Arctic districts of the RS (Y).

When comparing clusters by the level of healthcare development, it was found that cluster 1 was statistically significantly different from clusters 2 and 3 in terms of the number of round-the-clock beds per 10,000 population.

Conclusion. The performed analysis showed that there are significant differences between the municipalities of the Republic of Sakha (Yakutia) in terms of children's health. Unfavorable indicators are observed in most of Arctic districts, where sufficiently high rates of staffing, beds and outpatient clinics do not provide the necessary availability and quality of medical care due to the remoteness of some settlements from regional centers. For areas with very low population density and limited transport accessibility, it is necessary to search for and use organizational technologies that increase the availability of medical care for the population. In these conditions, one of the leading is the organization of regular on-site medical examinations of the population with the widespread use of instrumental and laboratory methods of research at the 1st stage, the organization of one-day hospitals, the using of new information technologies: remote audio advisory centers, telemedicine technologies and others. Along with this, planned measures are needed to improve the medical literacy of the population.

The work was carried out within the framework of the research topic of the Federal State Budgetary Scientific Institution "YSC CMP" "Physical development and health status of the child population in the conditions of the Far North (on the example of Yakutia)" (state registration number: 1021062411641-9-3.2.3), within the framework of the state assignment of the Ministry of Science and Education of the Russian Federation (FSRG-2020-0016).

Table2

Mean scores (with 95% CI) by cluster*

Indicator	1 cluster n=15	2 cluster n=11	3 cluster n=8	p
Infant mortality per 1000 live births	6,3 (3,8-8,8)	6,6 (4,3-9,0)	5,1 (3,6-6,6)	0,791
Child mortality per 10,000 child population	7,4 (5,7-9,1)	8,1 (5,9-10,2)	6,5 (3,8-9,1)	0,282
Children morbidity per 1000 population	2170,1 (2043,7-2296,6)	2779,7 (2651,3-2908,2)	1391,1 (1121,6-1660,7)	<0,001
Adolescents morbidity per 1000 population	1478,1 (1405,8-1550,5)	1828,0 (1685,0-1970,9)	1243,9 (960,6-1527,0)	<0,001
Provision with doctors per 1000 population	34,6 (32,2-37,1)	38,9 (32,3-45,5)	36,4 (30,4-42,9)	0,350
Provision of nursing staff per 1000 population	108,3 (96,3-120,2)	121,2 (110,3-132,0)	106,9 (92,7-121,2)	0,126
Number of round-the-clock beds per 10,000 population	73,8 (65,1-82,5)	92,2 (80,6-103,8)	87,8 (79,9-95,2)	0,011
Capacity of outpatient clinics per 1000 population	320,0 (233,9-406,0)	448,4 (332,5-564,3)	386,6 (241,6-531,4)	0,050

Note: *— average values of indicators for a 5-year period (2016-2020); p - achieved level of significance of differences (Kruskal-Wallis test).

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THE CONTRIBUTION OF VIRUSES TO THE STRUCTURE OF ACUTE RESPIRATORY DISEASES IN THE POPULATION OF YAKUTSK IN 2019-2020

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The aim of the study was to identify the viral etiology of acute respiratory diseases in patients hospitalized to the infectious hospitals in Yakutsk. **Methods:** nasal and pharyngeal swabs were obtained from the examined patients. The presence of the genetic material of the respiratory viruses was determined by real-time PCR. **Results:** During the study, 178 patients admitted to the infectious hospitals in Yakutsk from November 2019 to April 2020 were selected according to the inclusion criteria. 99/178 (55.6%) samples were positive for at least one of the studied viruses, 79/178 (44.4%) samples were negative. Respiratory syncytial virus; rhinoviruses; metapneumovirus; parainfluenza viruses of types 1, 2, 3 and 4; coronaviruses NL-63, 229E, HKU-1 and OC-43; adenoviruses groups B, C and E; bokavirus, as well as influenza A and influenza B viruses were identified. The results of the study are necessary to improve and optimize diagnostic tactics, for control and prevention of respiratory viral infections.

Keywords: human viruses, acute respiratory viral infections, influenza, respiratory syncytial virus, rhinovirus, bronchiolitis, fever.

Introduction. Acute respiratory viral infections (ARVI) occupy a leading place in infectious pathology, accounting for about 90% in the structure of infectious diseases, which is associated with high contagiousness and rapid spread of infections by airborne transmission, while the most susceptible to infection is the child population and the elderly [14,15]. In addition, cases of severe course of the disease are more often observed in young children, the risk of complications and deaths is higher[10]. The diverse etiological structure of ARVI is characterized by heterogeneity and variability of pathogens not only in time, but also in space [2,5]. In the distribution of ARVI diseases among the population, the territory of his residence is of great importance. The presence of territorial differences in the circulation of pathogens and the incidence of respiratory diseases (in particular, pneumonia, chronic bronchitis, bronchial asthma, etc.) have been studied by various authors. It has been shown that the severity of these diseases is due to the climatic and socio-demographic features of the habitat [1].

Materials and methods. The study was organized on the basis of infectious

diseases hospitals in Yakutsk. The study was approved by the Committee on Biomedical Ethics at FITZ FTM (Protocol No. 4-2019).

The study included hospitalized patients of all age groups in the acute stage of respiratory disease (no later than 7 days after the onset of symptoms).

Taking samples. In all patients participating in the study, sterile probe swabs were taken from the nose and throat and placed in a test tube with a transport medium. Test tubes with samples were stored in a Dewar vessel with liquid nitrogen before the study.

Real-time polymerase chain reaction. All the samples obtained were used to identify the genetic material of the influenza virus and other respiratory viruses (respiratory syncytial virus; rhinoviruses; metapneumovirus; parainfluenza viruses of types 1, 2, 3 and 4; seasonal coronaviruses(NL-63, 229E, HKU-1 and OC-43); adenoviruses of groups B, C and E; bokavirus) using polymerase chain reaction (PCR) in real time using kits of reagents "Amplification of influenza virus A/B-FL", " Influenza A/H1-swine-FZ virus Amplification", "Influenza A-type-FZ virus amplification", "ARVI-screen-FL b Amplification" (InterLabService, Russia) in accordance with the manufacturer's instructions.

Statistical analysis. Statistical analysis was pperformed using Statistics 10.0 software. The reliability of differences between groups was evaluated using the Chi-square criterion.

Results and discussion. Selection of patients in accordance with the criteria for inclusion in the study.

During the study, doctors of infectious diseases hospitals in Yakutsk for the period from November 2019 to March 2020 selected 178 patients who met the criteria for inclusion of patients in the study. Each patient received written informed consent to participate in the study, after which samples of clinical material were taken. A total of 123/178 (69.1%) children aged 0-17 years and 55/178 (30.9%) adults aged 18-70 years were included in the study. At the same time, in children 56/123 (45.5%) samples were obtained from boys and 67/123 (54.5%) samples were obtained from girls; in adults, 20/55 (36.4%) samples were obtained from men and 35/55 (63.6%) samples were obtained from women. Among the children included in the study, 36.5% (65/178) were aged 0 - 2 years. The smallest number of samples were obtained from children aged 15-17 years (10 samples, which was 5.6% (10/178) of all samples received from children) and from elderly people aged over 65 years (5 samples, which was 9.1% (5/55) of samples received from adult patients), which was associated with a low level of hospital admissions of patients of these age groups. The gender and age structure of the sample is shown in Figure 1.

Detection of the genetic material of the influenza virus and other respiratory viruses by PCR in real time. 99/178 (55.6%) samples were positive for at least one of the studied viruses, 79/178 (44.4%) samples were negative. These data are consistent with previous studies in Pittsburgh (59.7%), in Vitoria in southeastern Brazil (54.3%), in Huzhou in China (57.7%), while in our earlier study in Novosibirsk, the detection rate of respiratory viruses was significantly higher (72,3%) [10,7-9,18]. Such differences in the level of virus detection may be related to differences in the design of studies (in particular, the age structure of the included patients), different geographical territories, climatic conditions, population density [6,7]. The level of virus detection in children was significantly higher (64.2%) than in adults (36.4%), which is probably due to the peculiarities of the immune status in children and their higher susceptibility to viruses than in adults [16,13]. The detection of the influenza virus was 8.4% (15/178). Influenza B virus infection was detected in only two of all analyzed cases (13.3% of all positive flu samples). Among the influenza A virus, A (H1N1) pdm09 prevailed, which was detected in 80% (12/15) of all influenza cases. Influenza A (H3N2) virus was detected in 6.7% (1/15) of cases. Thus, in studies conducted in China, the detection rate of the virus among hospitalized children with ARVI was 8.9% in Beijing and Shanghai [19], and according to estimates presented in a systematic review of 100 studies, the influenza virus accounted for 5% of hospitalizations with acute lower respiratory tract infection [17]. These data are consistent with our results, although direct comparison is impractical due to differences in the structure of the study and differences in influenza activity in different seasons, in different regions and population groups [6]. Among other respiratory viruses, the most common were bokavirus - 17.4% (31/178), parainfluenza viruses - 14.6% (26/178), rhinovirus - 10.6% (19/178), seasonal coronaviruses (NL-63, 229E, HKU-1, OC-43) - 6.7% (12/178) and adenovirus - 6.2% (11/178). The remaining respiratory viruses were detected in less than 5% of cases. Viral co-infection was observed in 20/123 (16.2%) children, 1/55 (1.8%) cases of co-infection were detected among adults (Figure 2). According to the results of previous studies, the level of co-infection in children can reach 30% [9,16], which is associated with the immaturity of the immune system and, consequently, greater susceptibility to infections [8].

Age and sex differences in the level of detection of influenza virus and other respiratory viruses. When comparing the level of virus detection in different age groups, it was shown that the proportion of influenza virus increased with age with the highest frequency of occurrence in the adult population (80%). The remaining respiratory viruses were significantly more common in children than in adults. At the same time, bokavirus was found only among children, and the detection rate among children was significantly higher in the age group of 0 - 2 years compared with children older than 3

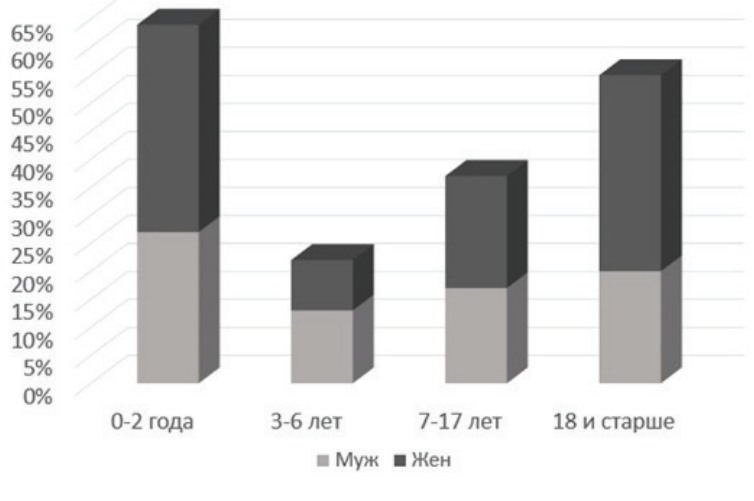

Fig. 1. Age and sex composition of the sample of patients included in the study

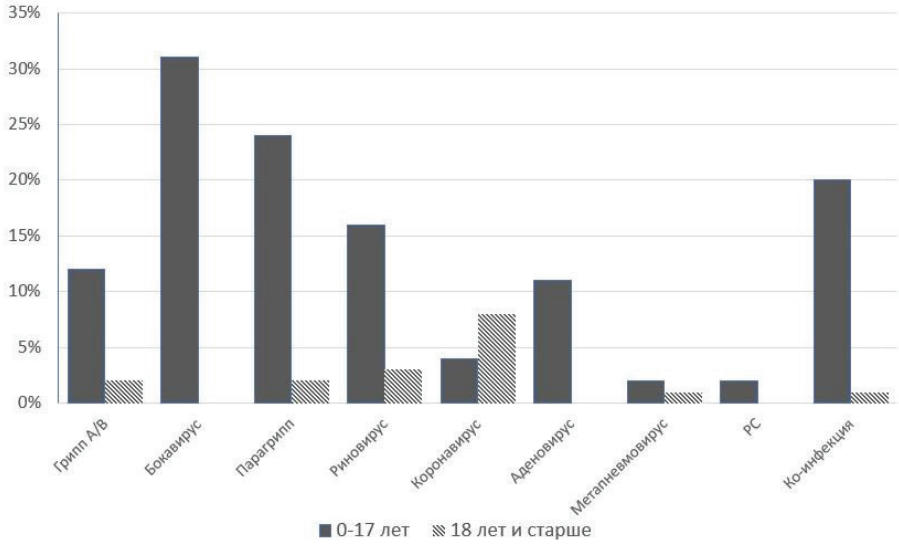

Fig. 2. The level of detection of respiratory viruses in patients as a percentage of the total number of examined patients in each group

years (67.7% and 32.3%, respectively, -2 = 27.79 and -2 = 48.03). For other respiratory viruses, no significant differences were found in different age groups. There were no sexual differences in the frequency of occurrence. In the study conducted by A.A. Sominina et al., there were also no sex differences in the frequency of occurrence of respiratory viruses [3].

The influence of bad habits and background diseases on the level of detection of influenza viruses and other respiratory viruses. Among 99 patients in whom influenza viruses and other acute respiratory infections were detected by PCR, 73 patients have never smoked, 2 patients have smoked before and 24 patients are currently smoking (for patients under the age of 14, the smoking habit of one of the parents was taken into account). At the same time, the detection rate of influenza virus and other respiratory viruses in smoking patients was 13.7 times higher than in non-smokers. Among the patients included in the study, concomitant chronic pathology was observed in 21 (11.8% of the total number of examined) people in the following age groups: 0-17 years - in 5 patients, 18 years and older - in 16 patients. Of the chronic pathology, neuromuscular disease was noted in 5 people, cardiovascular diseases in 3 people, chronic obstructive pulmonary disease and bronchial asthma - 1 patient each, other background diseases were noted in 10 people. When comparing the frequency of detection of respiratory viruses and influenza virus in the presence of background pathology and without it, no significant differences were found. Similar data were obtained earlier by A.A. Sominina et al. [3].

Etiology of diseases in patients admitted to the intensive care unit. A total of 5 patients aged 0 to 14 years (2.8% of the total number included in the study) were hospitalized in the intensive care unit (ICU) during the follow–up, of which 2 (40%) patients were children of the age group 0 - 2 years. Not a single patient over the age of 15 required hospitalization in the ICU. In 4 patients hospitalized in the ICU, any respiratory virus (bokavirus, type 1 parainfluenza virus) was detected, the influenza virus was not detected in this group.

Clinical diagnoses at discharge from the hospital. The most frequent (44.7%) diagnosis upon discharge to the hospital was "Pneumonia without specifying the causative agent", of which 61.8% had a viral infection. Bokavirus was detected in 27.6% of the examined, parainfluenza virus and rhinovirus - in 23.7% and 9.2% of patients with this diagnosis, respectively.

"Acute upper respiratory tract infection" was the second most common diagnosis at discharge - 22.3%. Among these patients, the viral etiology of the disease was confirmed in 39.4% of cases, seasonal coronavirus (NL-63, 229E, OC-43, HCU-1) was detected most often in this group of patients - 33.3%.

15.8% of patients were hospitalized with a diagnosis of Acute bronchitis, of which 81.5% of patients had respiratory viruses, and the most frequently detected were bokavirus and rhinovirus - in 25.9% and 22.2%, respectively.

Conclusion. Early and rapid detection of respiratory viruses by molecular methods is important for the prevention and control of emerging viral diseases [4]. The study demonstrates the contribution of viral infections to the structure of acute respiratory pathology of the upper and lower respiratory tract in hospitalized patients in Yakutsk. The results of the study are necessary to improve and optimize diagnostic and therapeutic tactics, control and prevention of respiratory viral infections.

In addition, knowledge of the viral etiology of respiratory infections is also important for differentiating bacterial and viral infections [11], since the use of antibiotics in viral infections does not improve clinical results, but exacerbates problems associated with antimicrobial resistance. Informing doctors about making decisions about the rational administration of antibiotics, taking into account the viral etiology, not only improves the clinical outcomes of the disease, but will also contribute to reducing antibiotic resistance [12].

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TOPICAL ISSUE

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PREDICTORS OF THE DEVELOPMENT OF HYPERTENSION IN YOUNG PEOPLE WITH HIGH NORMAL BLOOD PRESSURE

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Aim: to identify predictors of the development of arterial hypertension (AH) in young people with high normal blood pressure (HNP) based on the study of risk factors, hemodynamic parameters, structural and functional parameters of target organs. 155 patients under 45 years of age were included, mean age 35.1±3.2 years. Taking into account the indicators of office and ambulatory blood pressure (BP), the distribution into groups of HNP (68 patients) and AH (87 patients) was carried out. Conducted general clinical, laboratory, functional examination. Daily BP monitoring was performed for 24 hours using the BpLAB device (LLC Petr Telegin) with the integrated Vasotens® system, which makes it possible to evaluate central BP along with BP in the brachial artery. A complex of factors that increase the risk of developing hypertension in young people with HNP has been identified. Among them are hemodynamic, a number of risk factors (increased very low density lipoprotein cholesterol, triglycerides, total cholesterol, low density lipoprotein cholesterol, smoking experience, body mass index and waist circumference, age), intima-media thickness of brachiocephalic vessels, LA dimensions.

Keywords: arterial hypertension, high normal blood pressure, developmental predictors, young age.

Introduction. Numerous studies demonstrate that high normal blood pressure (HNP) is an independent risk factor (RF) for the development of cardiovascular disease (CVD). Patients with HNP have a higher risk of developing arterial hypertension (AH) than patients with optimal blood pressure (BP) [4]. The data obtained in the epidemiological study Framingham Heart Study revealed the formation of hypertension in HNP and normotensive profile in 54.2% and 23.6% in men and in 60.6% and 36.2% (respectively in HNP and normal blood pressure) in women . Thus, the risk of AH in baseline HNP increased by 2.25 times ($p<0.0001$) in men and by 1.89 times in the female population ($p<0.0001$) [8]. According to Y. Ishikawa et al. in a prospective cohort study conducted in Japan, it was shown that after 11 years, 26.1% of persons with prehypertension developed AH, the risk of developing AH in persons with VNP was 3.57 times higher than in persons with normotension [5].

The combination of several RFs contributes to the earlier progression of VNP to AH. Thus, the results of an American study involving more than 30,000 patients showed that in individuals with VNP and three RFs, the appearance of stable AH was noted for 4 years [1]. In a Korean cohort study that included patients with a normotensive status and prehypertension, the main predictors of the transformation of HNP into AH were: hypercholesterolemia, hyperglycemia, hyperuricemia, smoking, age, and an early family history of hypertension [7]. In another study, ethnicity, older age, higher body mass index (BMI), and the presence of diabetes or chronic kidney disease were independently and positively associated with the development of hypertension [11]. It should be noted that the studies included either adolescents or patients of older age groups; there are no data on predictors of hypertension in patients under 45 years of age. In addition, a complex of factors possibly associated with the development of AH has not been previously studied: hemodynamic, behavioral, structural and functional.

The aim of the study was to identify predictors of the development of arterial hypertension in young people with high normal blood pressure based on the study of risk factors, hemodynamic parameters, structural and functional parameters of target organs.

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Material and methods. On the basis of the consultative polyclinic department No. 2 of the Diagnostic Center of the Altai Territory and the therapeutic department of the National Healthcare Clinical Hospital at the Barnaul station in 2015–2020. 155 patients were examined. The inclusion criteria for the study were: age from 20 to 45 years; the presence in patients of the criteria for hypertension or VNP according to the anamnesis and measurements of office blood pressure; informed consent of the patient; lack of regular intake of antihypertensive drugs. The average age of the subjects was 35.1±3.2 years. Taking into account the indicators of office and ambulatory blood pressure, the distribution into groups of VNP and AH was carried out. Depending on the indicators of office BP, patients were divided into groups according to the level of office and daily BP according to the current classification (ESC 2018): the second with hypertension (with blood pressure of 140/90 mm Hg or more). In 4 patients who met the criteria for VNP according to the level of office BP, a masked form of AH was detected and these patients were assigned to the AH group. Thus, the number of patients with HNP was 68 people (mean age 33.1±7.5 years), the group with AH consisted of 87 people (mean age 36.4±6.6 years).

During medical appointments, patients were assessed body mass index (BMI), waist circumference, office assessment of blood pressure, heart rate. The levels of glucose in blood serum samples, total blood cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), uric acid, creatinine were determined with the calculation of glomerular filtration rate (GFR) according to the formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), daily albuminuria. Daily blood pressure monitoring was carried out for 24 hours using the BpLAB device (LLC Petr Telegin) with the integrated Vasotens® system, which allows to evaluate central blood pressure along with blood pressure on the brachial artery: mean systolic and diastolic blood pressure (SBP and DBP) average daily, in daytime and nighttime, mean pulse BP, degree of nocturnal decrease in SBP and DBP, amplification index and augmentation index. Echocardiography was performed using the EnVisorC device from Philips (Holland) with a 3.5 MHz transducer according to the standard technique. Ultrasound examination of brachiocephalic vessels (BCV) was performed using an EnVisor C ultrasonic device from Philips (Holland) with a linear scanner for surface studies. During this examination, the thickness of the intima-media complex (ITM) of the carotid arteries in the areas of carotid bifurcations and in the area of the common carotid arteries was determined.

Statistical calculations were carried out in the RStudio program (version 1.2.5001 – © 2009-2019 RStudio, Inc., USA, URL https://www.rstudio.com/) in R language (version 3.6.1, URL https:// www .R-project.org/). Empirical distributions of data were tested for agreement with the law of normal distribution according to the Shapiro-Wilk test. The nonparametric Mann-Whitney U-test was used to compare scores between groups. For statistical testing of hypotheses about the equality of the numerical characteristics of sample distributions in the compared groups, the unpaired Mann-Whitney U-test was used, the distribution bias was calculated with the construction of a 95% confidence interval for the bias. The identification of AH predictors was carried out by building logistic regression models. Statistical hypotheses were tested at a critical significance level p = 0.05, i.e. the difference was considered statistically significant if p < 0.05.

Predictors of the development of arterial hypertension

Predictor	OR [95% ДИ]	p
Гемодинамические факторы		
Systolic blood pressure on the aorta at night	2.06 [1.38; 4.47]	0.010
Systolic blood pressure on the aorta daily allowance	1.55 [1.23; 2.31]	0.004
Systolic blood pressure on the aorta afternoon	1.4 [1.17; 1.83]	0.002
Pulse blood pressure on the aorta	1.11 [1.02; 1.26]	0.046
Systolic blood pressure	1.49 [1.18; 2.32]	0.014
Diastolic blood pressure	1.34 [1.13; 1.76]	0.006
Systolic blood pressure on the brachial artery at night	1.2 [1.11; 1.32]	<0.001
Systolic blood pressure on the brachial artery afternoon	1.16 [1.09; 1.26]	<0.001
Diastolic blood pressure on the brachial artery at night	1.15 [1.07; 1.26]	0.001
Risk factors		
Very low lipoprotein cholesterol	4.24 [1.63; 12.27]	0.005
triglycerides	2.02 [1.24; 3.46]	0.007
Total blood cholesterol	1.9 [1.35; 2.77]	<0.001
Low-density lipoprotein cholesterol	1.82 [1.2; 2.84]	0.007
Smoking history	1.34 [1.11; 1.77]	0.011
Body mass index	1.1 [1.03; 1.18]	0.007
Waist circumference	1.05 [1.02; 1.08]	0.003
Age	1.09 [1.03; 1.15]	0.002
Structural indicators of target organs		
Left ventricular myocardial mass index	3.25 [1.36; 8.69]	0.012
Left atrium	9.41 [3.37; 29.74]	<0.001
Intima media thickness	11.35 [1.58; 107.42]	0.023

Note: The results of the calculations are shown in the tables as indicators of the odds ratio (OR) of adverse events (AH) in individuals with VNP to increase the indicators by 1 unit of measurement. The table also shows estimates of the significance level p, which is calculated in the program through standardized statistics z for the coefficients of the model.

Results and discussion. By constructing single-factor logistic regression models, individual predictors of hypertension were identified (Table 1). Among the hemodynamic variables, the increase of which by 1 mm Hg. was associated with an increase in the chances of hypertension, indicators of daily monitoring of central blood pressure: SBP at night (by 2.06 [1.38; 4.47] times) and daytime hours (by 1.4 [1.17; 1.83] times), average daily (by 1.55 [1.23; 2.31] times) and pulse central pressure (by 1.11 [1.02; 1.26] times). An increase in office SBP (by 1.49 [1.18; 2.32] times) and DBP (by 1.34 [1.13; 1.76] times) and BP monitoring indicators on the brachial artery was associated with the risk of hypertension: SBP at night (by 1.2 [1.11; 1.32] times), SBP in the daytime (by 1.16 [1.09; 1.26] times), DBP at night (by 1.15 [1.26] times). 07; 1.26] times).

Risk factors were identified, the increase of which was associated with the risk of AH: increased VLDL cholesterol (OR 4.24 [1.63; 12.27]), triglycerides (OR 2.02 [1.24; 3.46]), total cholesterol (OR 1.9 [1.35; 2.77]), LDL cholesterol (OR 1.82 [1.2; 2.84]), smoking history (OR 1.34 [1.11; 1.77]), body mass index (OR 1.1 [1.03; 1.18]) and waist circumference (OR 1.05 [1.02; 1.08]), age (OR 1.09 [1.03; 1.15]). The most significant predictors of the development of AH in individuals with VNAD were: IMT of brachiocephalic vessels (OR 11.35 [1.58; 107.42]), left atrial size (OR 9.41 [3.37; 29.74]) and LVH (OR 3.25 [1.36; 8.69]

By constructing a multivariate logistic regression model, significant predictors of AH were identified that act multiplicatively: LA diameter (p = 0.006), an increase in LA diameter by 1 cm is associated with an increase in the chances of AH by 6.43 [1.84; 26.43] times; total cholesterol (p = 0.014), an increase in the indicator by 1 mmol/l is associated with an increase in the chances of AH by 1.75 [1.14; 2.81] times.

The identification of risk factors for the progression of hypertension in a population of young patients with VNP is more informative than a simple comparison of hypertensive and normotensive groups, because it may actually reflect which risk factors need to be identified and managed. The heterogeneity of the hemodynamic picture at a young age determines a different prognostic scenario. Of particular interest is associated with young patients, since the role of an isolated increase in blood pressure in this category of individuals is currently being discussed. Some studies have shown that isolated systolic hypertension (ISAH) in young people is a "false phenomenon" [3], while others, on the contrary, have concluded that it is associated with increased cardiovascular risk [10]. The results of our study showed that an increase in both office SBP and DBP has approximately the same predictor significance. In addition, 24-hour brachial BP monitoring does not have a significant advantage over office measurements in assessing the odds ratio of developing AH in individuals with VNP. The value of central BP as a significant predictor of new onset hypertension after 4 years of follow-up was previously determined in a study of 7840 subjects with normal BP (mean age 51 years) (P<0.001) [12]. Our results also identify central BP as a significant tool for predicting the risk of hypertension.

Obviously, the development of hypertension is due not only to the hemodynamic profile, but also to the multifactorial nature of the increase in blood pressure. When studying risk factors, we identified predictors of the development of hypertension in young people with VNP: dyslipidemia, smoking, obesity, and age. Attention is drawn to the association of the development of AH with the indices of the lipid spectrum and the thickness of the intima-media of the brachiocephalic vessels. This relationship is based on several pathogenetic mechanisms: endothelial dysfunction, oxidative stress and vascular inflammation, activation of the renin-angiotensin system [6].

It is noteworthy that the diameter of the left atrium was a predictor of the development of AH not only in univariate, but also in multivariate analysis. Atrial dilatation occurs when an increase in filling pressure leads to stretching of the walls of the chamber of the heart. The role of an increase in the structural and volume parameters of LA in the development of CVD, in particular atrial fibrillation and heart failure, including diastolic, is known. In a previous meta-analysis of 20 echocardiographic studies, it was shown that in individuals with VNP, in comparison with individuals with normal blood pressure, an increase in the diameter of the left atrium is determined [2]. Our study demonstrated data supporting an association of increased AH risk with left ventricular myocardial mass index in young patients with VNP. These data are consistent with a previous study by Chinese authors, which included 10,547 patients with hypertension, prehypertension, and normotensives, and showed that the prevalence of left ventricular hypertrophy was statistically different between the three groups (p<0.001); SBP, DBP, and mean SBP were independent risk factors for structural changes in the left heart [9].

Conclusion. A complex of factors that increase the risk of developing hypertension in young people with VNP has been identified. Among them are hemodynamic (SBP and DBP, determined by monitoring the central and brachial, office measurement), clinical (VLDL cholesterol, total cholesterol, LDL cholesterol, smoking experience, body mass index and waist circumference, age). The thickness of the intima-media of the brachiocephalic vessels, the size of the left atrium and LVH were significant predictors of the development of AH in individuals with VNP. The multivariate model shows the predictor value of the diameter of the left atrium and total cholesterol.

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DEPENDENCE OF IMMUNE REACTIONS ON THE STAGE OF ONCOLOGICAL DISEASE

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Summary. 612 people with oncological diseases of various localization were examined. It has been established that immune responses in malignant neoplasms differ depending on the stage of the disease. At the initial stages (I-II), a cytokine reaction develops, antibody formation with the participation of IgE against the background of inhibition of phagocytic activity, which is associated with the reorientation of the phagocyte to exocytosis. At III-IV stages of cancer, the activity of cytokine and reagin reactions increases in parallel with autosensitization. This period of the disease is characterized by an increase in the phagocytic activity of neutrophils.

Keywords: immunity, oncology, cytokines, deficiency, natural killers, phagocytosis, autoantibodies, IgE.

The main protective role in the body in the fight against a tumor belongs to the immune system, a violation of its functioning leads to the failure of antitumor protection. Therefore, understanding the features of the immune response in the tumor process underlies the development of effective immunotherapy. The difficulty lies in the fact that the mechanisms that provide antitumor immunity are no different from those in anti-infective immunity, allergies, and autosensitization. It seems that it is the mixing, the formation of antigenic stress during the immune response to a tumor, the presence of a large number of qualitatively different autoantigens, the addition of a reagin defense mechanism and autoimmune damage that cause the ineffectiveness of immune responses in malignant neoplasms [33]. It is known that an immune response is formed to tumor cells both by cellular and humoral pathways, which is confirmed by their infiltration by lymphocytes, macrophages, dendritic cells, etc. [34]. At the same time, the formation of a specific tolerance of the immune system to a tumor in many people is beyond doubt [19, 31]. The specificity of tumor tolerance is also proved by the fact that cancer patients show a normal immune response to any other foreign antigens, infection, or transplant [7, 11, 26]. However, the positive effect of tumor regression upon vaccination with various tumor-specific vaccines is negligible and does not exceed 2.5% [28].

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Aim: to determine the characteristics of immune responses depending on the stage of oncological disease.

Materials and methods. 612 people with cancer of various localization who applied to the medical company "Biokor" (Arkhangelsk) were examined, 103 of them with stomach cancer, 105 with colon cancer, 112 with rectal cancer, 163 with breast cancer, 129 with cancer uterus. Cytogram and phagocytic activity of neutrophilic granulocytes were studied in smears of peripheral venous blood stained according to Romanovsky-Giemsa. Expression of markers of T-helper cells and natural killer cells was determined on lymphocytes by indirect immunoperoxidase reaction and flow cytometry (Epics XL, USA). In blood serum, the content of cytokines IL-6, TNFα (Bender MedSystems, Austria), anti-dsDNA, anti-RNP, IgE was determined by enzyme immunoassay using Multiscan MC (Finland) and Evolis (USA) analyzers. The results of the study were processed using the Statistica 6 software package (StatSoft, USA). To test the statistical hypothesis of the difference in values, the Shapiro-Wilk test was used. Significance of differences $p < 0.017$. Correlation analysis of the parameters was performed taking into account Spearman's rank correlation. The critical level of significance in testing statistical hypotheses was $p < 0.05$.

Results and discussion. Malignant neoplasms can form systemic immune responses; in all cases of accidental detection, not yet treated, and regardless of the location and type of tumor, patients quite often have an increase in the concentration of TNFα and IL-6, as well as autoantibodies to dsDNA and IgE (Table 1).

Attention is drawn to the most frequent increase in blood levels of interleukins and autoantibodies to double-stranded DNA in neoplasms of the large intestine and rectum. What this means is difficult to say now, but perhaps this is a reflection of the characteristics or advantages of immunocompetent intestinal tissue. Gut associated lymphoid tissue (GALT) is known to be one of the largest organs in the immune system, contains more than 1012 cells and produces the largest amount of cytokines and secretory IgA and IgE. In addition to diffusely located immunocompetent cells, phagocytes, T- and B-lymphocytes, plasma cells, the immune tissue of the intestine is represented by organized lymphoid structures in the form of an appendix, mesenteric lymph nodes and Peyer's patches. Peyer's patches are lymphoid follicles, the epithelium of which is represented mainly by M-cells, forming a cavity, called a package, in contact with lymphoid tissue. The bags contain polymorphonuclear leukocytes, macrophages, T- and B-lymphocytes, and plasma cells. Particularly rich in immunocompetent cells is the lamina propria mucosa, which consists of connective tissue located between the muscular layer of the mucosa and the epithelium. The lamina propria contains macrophages, mast cells, lymphocytes and plasma cells, as well as granulocytes, including eosinophils. Among the epithelium of lamina propria are intraepithelial lymphocytes. Statistically significant positive relationships were established between the concentrations of cytokines, autoantibodies, and reagins ($r = 0.75$, $p < 0.001$), from which it follows only that cell transformation and damage causes the appearance of autoantibodies, which requires an increase in the immune response from eosinophils and obese cells.

The ineffectiveness of the mechanisms of antitumor protection of innate immunity can be due to several reasons. Before decay, the tumor actually contains nothing foreign, it is not noticed by natural killers and phagocytes [13, 14, 24]. In any case, in malignant neoplasms,

Table1

The frequency of registration of signs of a systemic immune response in patients

Diagnosis	Increased blood levels, %			
	TNFα > 20 pg/ml	IL-6 > 20 pg/ml	Anti-dsDNA> 50 IU/ml	IgE> 100 ME/ml
Stomach cancer	31.57	26.32	55.26	44.74
Colon cancer	**47.37**	**57.89**	**73.68**	63.16
Rectal cancer	**81.82**	**68.18**	**77.27**	59.09
Mammary cancer	31.43	22.86	37.14	25.71
Uterine cancer	36.36	27.27	45.45	54.55

a deficiency of phagocytic protection (<50% active) on the part of neutrophilic granulocytes was recorded almost always (93.95%), except for a few cases (Table 2). It seems that everything begins with a lack of phagocytosis. However, the deficiency of phagocytic protection cannot be used as a risk criterion due to the wide distribution (up to 33%) of this defect among practically healthy people at the time of examination [1, 2]. In more than half of the cases, low levels of natural killers (CD3-CD16+CD56+; NK) and T-helpers were recorded in the peripheral blood (Table 2).

Thus, in malignant neoplasms, a high frequency of a deficiency in phagocyte activity, the content of natural killers and T-helpers in the blood, as well as elevated levels of IL-6, TNFα, with activation of the reagin defense mechanism and an increase in the concentration of autoantibodies, is recorded. Phagocytes, especially macrophages, damage the tumor cell by antibody-dependent cytolysis and subsequent utilization of cell debris. The decrease in the importance of phagocytic protection during tumor transformation may be due to a deficiency in phagocytic activity, inhibition of chemotaxis factors or phagocyte secretion products. The activity of natural killers ensures the body's natural resistance to a tumor, protects against metastasis, and participates in the formation of an adaptive level of IFNγ. IL-6 is known to be the most sensitive marker of tissue damage. Fever, leukocytosis, the content of acute phase proteins, increased vascular permeability are comparable with the release of IL-6 [27, 30]. An increase in the expression of the IL-6 gene by cells occurs under the influence of IL-1β, tryptase, histamine, or upon direct stimulation by mast cells [8]. IL-6 induces the transcription of acute phase protein genes and enhances the production of cortisol, which inhibits the expression of proinflammatory cytokine genes [18, 21]. An increase in the content of activated T-lymphocytes by increasing the energy resource of the cell against the background of elevated concentrations of IL-6 is explained by its stimulating effect on glycogen production, lipolysis and fat oxidation, and ATP synthesis. According to our studies, an increase in the content of IL-6 in the blood is associated with the activation of lymphocyte recirculation and with an increase in the concentration of T-lymphocytes with the transferrin receptor [3]; this is understandable, because IL-6 is the main inducer of the key regulator of iron levels – hepcidin.

The question of the possible role of the protective action of reagins has not been studied. The reaginic reaction is the fastest and appears almost instantly. Due to the release of a large number of chemoattractants, eosinophils, neutrophils, macrophages, and lymphocytes are attracted, which prolongs the reaction of antibody-dependent cytotoxicity. IgE are involved in antigen presentation; in addition, they can directly participate in the maturation of dendritic cells and activate the specific proliferation of T-lymphocytes [4]. Binding of reagins to receptors on basophils and eosinophils contributes to the release of large amounts of histamine and IL-4, IL-5, IL-13 [22]. It seems that an increase in the activity of antibody-dependent reactions is an informative criterion for prolonging the course of almost any pathological process and has a prognostic value. It can be considered that an increase in the content of IgE in the blood of patients with malignant neoplasms enhances various protective reactions, including hemodynamic reactions, and can be used in a complex of diagnostic signs.

An unfavorable prognosis for the course of the disease is associated with tumor metastasis. There is evidence that an unfavorable course is associated with an increase in the content of activated CD3+CD4+CD25+, CD3-CD4+CD25+, and CD4+CD25+Foxp3+ T cells in the peripheral blood [10, 12, 29, 32]. Perhaps these associations arise, but do they reflect the further development of the immune response to the tumor? The opinion that activated cells in the immune response to a tumor have nothing to do with tumor cytotoxicity reactions is rather doubtful. On the contrary, activated cells are able to block cytotoxic T cells [23, 26]. After all, the immune response, accompanied by lymphoproliferation, significantly exceeds the level that is necessary for an adequate immune response. And not all activated lymphocytes will be included in the number of cells for subsequent differentiation; most of them undergo apoptosis. But the main question in this situation is the question of the specific weight of suppressors in the composition of differentiated T cells. Does the degree of activating and suppressing activity remain proportional in this case as well? If this proportionality is preserved, as in an adequate immune response, then the inductor cells responsible for the activation of differentiation themselves become the target of the suppressor action. In this case, the degree of suppressor activity increases in proportion to the number of activated cells. Cytotoxic T-lymphocytes

Table2

The frequency of registration of defects in immune defense in patients, %

Diagnosis	Active phagocytes < 50 %	NK content in blood < 0,25×109cell/l	CD3+CD4+ content in blood < 0,40×109 cell/l
Stomach cancer	59.22	56.31	65.52
Colon cancer	51.43	55.34	61.05
Rectal cancer	61.61	60.71	74.29
Mammary cancer	57.03	52.15	51.53
Uterine cancer	54.21	61.24	55.81

(CD3+CD8+) of immune donors cause lysis of tumor cells under in vitro conditions, and spontaneous tumor disintegration under in vivo conditions in the experiment. At the same time, CD3+CD8+ retain their specific activity in cell culture for up to 6-12 months. However, it is interesting that even with the most unfavorable outcome, the CD3+CD8+ content always remains very high, often significantly exceeding the concentration of CD3+CD4+ [5, 6, 25].

We found that, regardless of localization, in stages III-IV of cancer, the frequency of registration of deficiency of actively phagocytic neutrophils is lower (average 38.54±0.43%) compared with stages I-II - 59.68±0.56% ($p < 0.001$) and higher frequency of detection of elevated IgE concentrations (respectively 79.33±1.29% in stages III-IV and 65.38±0.92% in stages I-II, $p < 0.01$). The assessment of the significance of this reaction is probably ambiguous; maybe this is a signal that an alternative risky defense mechanism is being used, or maybe this is a sign of using the last reserve to fight the tumor. But, at least, there is every reason to believe that such a reaction is necessary and useful for enhanced clearance of tumor decay products from the body. The relationship between the content of serum IgE and pro-inflammatory cytokines in the blood is quite constant in adults. It is usually positive and stronger in various pathological processes associated with inflammation and destruction. The relationship between the content of pro-inflammatory cytokines and autoantibodies is largely stable and strong.

Deficiency of phagocytic protection at the level of blood neutrophils active in phagocytosis <50% among all those examined with malignant neoplasms is detected on average in 49.48±1.62%. At stages III and IV of the disease, the concentrations of cytotoxic lymphocytes, % of active phagocytes, and the concentration of autoantibodies are significantly higher than at the initial stages of the disease (Table 3).

In inflammatory processes, the facts of an increase in the content of autoantibodies to a wide range of cytokines and nuclear proteins are known [9, 20, 35]. As can be seen from the presented data, the frequency of registration of elevated concentrations of autoantibodies to double-stranded DNA and the ribonucleotide complex is noticeably higher in III and IV stages of the disease. The average concentrations of anti dsDNA were not high and, depending on the stage of the disease, ranged from 41.87 ± 0.38 - 57.29 ± 0.42 IU / ml at stages I-II and 48.15 ± 0.31 - 86, 29±0.34 IU/ml at III and IV stages. Thus, autosensitization during tumor decay is confirmed not only by an increase in the frequency of registration of elevated levels of autoantibodies, but also by an increase in their concentrations.

Table3

The frequency of registration of elevated concentrations in the blood of CD8+, active phagocytes and autoantibodies in patients, %

Cancer, localization, stage	CD8+ > 0,4×109 cell/l	Active phagocytes > 65 %	Anti-dsDNA> 50 IU/ml	Anti-RNP >1,0 IU/ml
Stomach cancer I-II stage (n=41)	43.90	31.71	29.26	36.58
Stomach cancer III-IV stage (n=62)	**90.32**	**88.71**	**90.32**	**93.55**
Colon cancer I-II stage (n=48)	47.92	43.75	39.58	35.42
Colon cancer III-IV stage (n=57)	**89.47**	**85.96**	**82.46**	**71.93**

Conclusion. Deficiency in the content of actively phagocytic neutrophilic granulocytes in malignant neoplasms is a known fact. An increase in the activity of phagocytes in an unfavorable course of the disease with metastases and tumor decay requires an explanation. Neutrophil granulocytes perform an important effector function in the immune response. Neutrophils, through the generation of cytokines, chemokines, expression of receptors, etc., modulate cell functions, regulating the formation of the immune response, as well as the development of apoptosis. The literature today is rapidly replenished with facts about the regulatory role of neutrophils. Neutrophilic granulocytes secrete various proteolytic enzymes, reactive oxygen species, as well as acid hydrolases, cathepsins and collagenases that destroy cells and intercellular structures. The literature contains numerous data on the function of vesicular structures in inflammation, angiogenesis, and oncopathology [15, 16]. It is known that neutrophils differentiate into phagocytes and cells with predominantly secretory functions. Functionally, different neutrophilic granulocytes differ in the set of membrane receptor structures. The low phagocytic ability of neutrophilic leukocytes coincides with low extracellular activity and high superoxide-anion-forming ability (NST-test), which is most often detected in chronic inflammatory processes.It seems that in malignant neoplasms, neutrophilic granulocytes are oriented towards extracellular activity, and therefore a sharp decrease in the percentage of active phagocytes and a high frequency of its deficiency are recorded. Activation of the reagin defense mechanism during this period is probably necessary to stimulate the migration, chemotaxis of neutrophils and their phagocytic capacity. A feature of reagins is their ability to bind conformational epitopes, while other immunoglobulins recognize linear protein epitopes [17]. This ensures the formation of an antibody-dependent cytotoxicity reaction even at a very low antigen concentration. The activity of the reagin reaction is significantly enhanced by the activation of cells that express the high-affinity IgE receptor (FcεRI) on their surface - eosinophils, basophils and mast cells. These cells have a wide range of secreted cytokines, vasomotor amines and other biologically active substances, thus modulating the intensity of the immune response, leading to a more severe reaction of antibody-dependent cytotoxicity. The concentration of IgE and inflammatory mediators affects the severity of the protective reaction. At the same time, too hyperreaction of antibody-dependent cytotoxicity can cause the formation of a pathological process associated with damage to the body's own tissues.

High concentrations of autoantibodies damage through activation of the complement system and are associated with very extensive damage [7]. In turn, cell damage causes, through Toll-like receptors, the launch of a cascade of reactions leading to the synthesis of inflammatory mediators - chemokines, adhesion molecules, acute phase proteins, cytokines, etc. The production of cytokines - interleukins, neurotransmitters, vasomotor amines, neuropeptides and hormones that provide migration, cooperation, proliferation, differentiation and suppression of the activity of cells involved in the reactions of preventive and pathological inflammation. A local increase in the concentration of cytokines is necessary to cope with the local problems that have arisen; an increase in the content of cytokines in the blood indicates the need for systemic regulation. Damage to the cellular structure induces the release of

the most significant concentrations of cytokines and the expansion of their spectrum of activity.

So, immune responses in malignant neoplasms differ depending on the stage of the disease. At the initial stages of the disease, a cytokine reaction develops, antibody formation with the participation of IgE against the background of inhibition of phagocytic activity, which is associated with the reorientation of the phagocyte to exocytosis. With the disintegration of the tumor and metastasis, the activity of cytokine and reagin reactions increases in parallel with autosensitization. During this period of the disease, the activity of phagocytes increases. The main question in this situation is to find out what provides the deficiency of phagocytic protection during the period of tumor formation? Elucidation of this problem will provide new knowledge about the pathogenesis of malignant neoplasms.

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CORONAVIRUS INFECTION IN CHILDREN: EPIDEMIOLOGICAL AND CLINICAL FEATURES

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Aim: To study epidemiological and clinical features of COVID-19 in children who were admitted to a hospital.

Materials and Methods. The study was conducted within April 1st and July 31st 2020. Overall 176 children aged from 0 to 17 with confirmed COVID-19 were included. These patients were divided on three clinical groups: first - patients with asymptomatic form – 49 (27.84%), second – children with mild form – 84 (47.73%), third – patients with moderate form of COVID-19 – 43 (24.43%). COVID-19 was diagnosed by PCR. Statistical analysis of the data was performed using the Statistica 10.0 package. Pearson's χ^2 was used to compare two independent groups. The criterion level $p < 0.05$ was considered statistically significant.

Study Results. COVID-19 was found more often in age groups 4-7 and 12-17, mainly in boys. Most of the children had close contact with people diagnosed with COVID-19. The average incubation period was 3.0 [1.0; 7.0] days, the average time from first symptoms to the hospitalization was 3.0 [1.0; 4.0] days. Fever, cough, weakness, runny nose, sore throat were the most common symptoms.

Conclusion. The largest number of cases of COVID-19 was registered amongst senior schoolchildren, mainly in boys. The minimal tourist activity and low level of flu vaccination were found in children with COVID-19. The widest range of clinical symptoms was more common for children with moderate form of the disease.

Keywords: coronavirus infection, COVID-19, SARS-CoV-2, children, clinic, epidemiology.

Introduction. The appearance of a new coronovirus infection (2019-nCoV) has attracted worldwide attention and WHO has declared COVID-19 as an extraordinary public health situation with international importance [7]. The fact of transmission of SARS-CoV-2 from one person to another at home and in a hospital, when moving from city to city or country to country has been confirmed as the epidemic was spreading [14]. Children form the specific group and can be potentially dangerous for infection spread, because of close family contacts and susceptibility to cross infection [14].

Some investigations reported that clinical symptoms of COVID-19 in children are less expressed and similar to ones in adults [8,11,12]. Children are infected much rarely than adults [9,17] and it explains less data about epidemiological and clinical features of COVID-19 in pediatrics.

Study Objective: To study epidemiological and clinical features of COVID-19 in children who were admitted to a hospital.

Materials and Methods. Overall 176 children aged from 0 to 17 with confirmed COVID-19 were included. These children were admitted to the first on the territory of Zabajkalskij kraj monohospital opened for patients with new coronavirus infection (COVID-19) - City Clinical Hospital № 1 in Chita.

Inclusion criteria:

- children ages from 0 to 17;
- informed consent to participate in the study signed by child's parents or by patients aged 15 and older;
- laboratory confirmation of COVID-19.

Exclusion criteria:

- absence of informed consent to participate in the study signed by child's parents or by patients aged 15 and older;
- absence of COVID-19 laboratory confirmation.

According to the guidelines "Features of clinical symptoms and management of the disease caused by new coronavirus infection (COVID-10) in children" (Version 2, 03.07.2020) [3] all patients were divided on three groups depending on the disease severity: first - patients with asymptomatic form – 49 (27.84%) [2], second – children with mild form – 84 (47.73%), third – patients with moderate form of COVID-19 – 43 (24.43%).

The median age of the patients with SARS-CoV-2 was 8,0 [4,0; 8,0] years old, there were more boys [n=98 (55,68%)] than girls [n=78 (44,32%), p=0,034].

According to the guidelines "Features of clinical symptoms and management of the disease caused by new coronavirus infection (COVID-10) in children" (Version 2, 03.07.2020) [3] the diagnosis of COVID-19 was based on the complex of clinical and epidemiological, laboratory and radiological data. The clinical examination was composed of anamnesis taking, physical examination and dynamic observation during the hospitalization. COVID-19 confirmation was carried out by isolating SARS-CoV-2 RNA in material collected from the oropharynx and nose by using PCR test systems registered in the Russian Federation, according to the manufacturer's instructions.

The study was approved by Local Ethical Committee of Chita State Medical Academy (protocol №101, 15.04.2020). All participants or their legal representatives signed the informed consent.

Statistical analysis of the data was performed using the Statistica 10.0 package. Pearson's χ^2 was used to compare two independent groups. The criterion level $p < 0.05$ was considered statistically significant. Descriptive statistics are presented as a median (Me) indicating the 25th and 75th percentiles.

Results and discussion. In figure 1 the age and gender composition of participants is shown. There was a prevalence of teenagers (59 participants – 33.52%) and children aged 4 to 7 (42 participants – 23.86%) amongst those who were admitted to a hospital with COVID-19. There also were 38 junior school children (21.59%), 20 children aged younger 1 year (11.36%) and 17 toddlers (aged 1 to 3; 9.67%). However, M.A. Shackmaeva et all. have noticed that there was a prevalence of children aged younger 1 year

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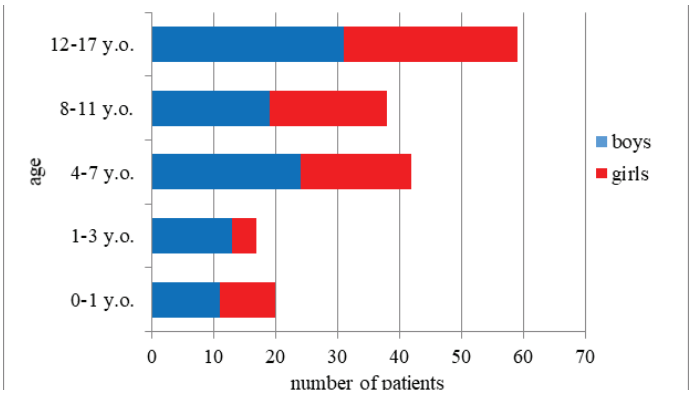
(56.5%) with COVID-19 and the infection was registered less frequently amongst children aged 1 to 3 (17.4%), 3 to 7 and 7-14 (10.1% both) and 14 to 17 (20.3%) [4]. The study of Y. Dong showed average age of patients as 7 [2; 7; 13]. According to the study of S.A. Evseeva et all. there were 53.6% of children aged older 7 [1].

Regarding the gender there was shown a prevalence of boys (55.68% of boys and 44,32% of girls, p=0,034) that matches with the results of other authors [7]. The boys aged 0 to 1 and 1 to 3 more often had asymptomatic form of 2019-nCoV (p<0,05), while teenage boys 12 to 17 were 3.4 and 2.6 times more likely to have mild form of the disease (p<0,05).

More than 80% of the children had confirmed contact with people with identified COVID-19 infection. Only two children amongst 176 ones admitted to the hospital had travelled abroad two weeks before the symptoms of the disease appeared. 39 patients (22.16%) could say the exact date of the contact with people with identified or suspected COVID-19. 27 patients (15.34%) have not had any epidemiological features that is 3% more of published data [15]. According to published data family cases of contacts were73,3% [10]. In another study there were registered 89% cases of family transmission of the disease and 33% cases were the result of contacts in epidemic zone.

The average incubation period was three days [1,0; 7,0], the average period from first symptoms appearance till the admission to the hospital was three days [1,0; 4,0]. V. De Sanctis [6] showed the longer incubation period for teenagers that was 6.5 days [2,0; 10].

There were vaccinated against the flu only 29 (16.48%) of children and there were 147 (83.52%) unvaccinated children (p<0,001).



Gender and age of children with COVID-19, abs.

98 children (55.68%) had the acute beginning of the COVID-19 with fever. The comprehensive analysis showed that 51 participant (28.98%) had fever lower than 38°C and 47 children (26.70%) were registered with fever higher than 38°C. This data matches with the results of Tung Ho CL. et al. who found that the fever was frequent symptom (53.9%) amongst included patients [16]. Chinese researchers also concluded that the fever is one of the main symptoms while a child is admitted to a hospital [13].

The disease was also characterized by the presence of catarrhal symptoms such as cough (66 patients, 37.50%), running nose (28 children, 15.91%), sore throat (26 patients, 14.77%), difficulty in nasal breathing (18 participants, 10,23%), weakness (45 children, 25.57%), fatigue (11 participants, 6.25%), loss of appetite (8 patients, 4.55%), headache (5 children, 2.84%) and drowsiness (2 participants, 1.14%).

In general, the clinical symptoms of 2019-nCoV amongst the children admitted to a hospital have not differed from the symptoms showed in other similar studies [1,5,6].

Anosmia/hyposmia was registered in 16 children (7.95%) in the beginning of the disease that again matches with the results of other studies [4].

The symptoms from digestive system (stomach pain, diarrhea, nausea) and myalgia were seen equally often (6.25%). Taste problems (2.27%), joint pain (1.70%) and dizziness (1.14%) were rare symptoms.

The physical examination found paleness in 21 children (11.93%), hyperemia of the oropharynx in 112 patients (63.64%), and difficulty in nasal breathing in 22 participants (12.5%). The auscultation showed the shortening of percussion sound in 4 children (2.27%), hard breathing in 38 patients (21.59%) and weakened breathing in 3 cases (1.70%).

The analysis of epidemiological and clinical data in children with mild and moderate COVID-19 was done on the next step.

Table1

Epidemiological characteristic of COVID-19 in children

Epidemiological characteristics	Children with COVID-19							
	Group 1 (n=49)		Group 2 (n=84)		Group 3 (n=43)		In all (n=176)	
	abs.	%	abs.	%	abs.	%	abs.	%
Contact with people with identified COVID-19 infection	44	89.80	69	82.14	36	83.73	149	84.66
Exact contact date	15	30.61[1]	13	15.48	11	25.58	39	22.16
Travelling abroad two weeks before	1	2.04	0	0	1	2.33	2	1.14
Did not have any certain epidemiological features	5	10.20	15	17.86	7	16.28	27	15.34
Vaccination against flu	4	8.16	13	15.48	12	27.91	29	16.48
The average incubation period	4.0 [1.0; 8.0]		2.5 [2.0; 7.0]		2.0 [1.0; 5.0]		3.0 [1.0; 7.0]	
The average period from first symptoms appearance till the admission to the hospital	1.0 [1.0; 4.0]		3.0 [1.5; 4.0]		3.0 [2.0; 6.0]		3.0 [1.0; 4.0]	

Notes: n – number of cases; p1 – statistical significance of differences (p<0,05) between groups 1 and 2; p2 – statistical significance of differences between groups 1 and 3; p3 – statistical significance of differences between groups 2 and 3 (Pearson's χ^2).

Table2

Clinical characteristic of COVID-19 in children

Symptom \ Groups of patients		Group 1 (n=49)		Group 2 (n=84)		Group 3 (n=43)		In all (n=176)	
		abs	%	abs	%	abs	%	abs	%
Fever		-	-	63	75	35	81.4	98	55.68
Cough		-	-	36	42.86	30[3]	69.77	66	37.50
Weakness		-	-	22	26.19	23[3]	53.49	45	25.57
Running nose		-	-	20	23.81	8	18.60	28	15.91
Sore throat		-	-	19	22.62	7	16.28	26	14.77
Difficulty in nasal breathing		-	-	12	14.29	6	13.95	18	10.23
Anosmia/hyposmia		-	-	8	9.52	8	18.60	16	9.09
Fatigue		-	-	3	3.57	8[3]	18.60	11	6.25
Myalgia		-	-	4	4.76	7[3]	16.28	11	6.25
Loss of appetite		-	-	3	3.57	5	11.63	8	4.55
Diarrhea		-	-	3	3.57	1	2.33	4	2.27
Headache		-	-	2	2.38	3	6.98	5	2.84
Drowsiness		-	-	2	2.38	-	-	2	1.14
Stomach pain		-	-	1	1.19	4[3]	9.30	5	2.84
Dysgeusia		-	-	1	1.19	3	6.98	4	2.27
Joint pain		-	-	1	1.19	2	4.65	3	1.70
Nausea		-	-	1	1.19	1	2.33	2	1.14
Dyspnea		-	-	0	0	1	2.33	1	0.57
Dizziness		-	-	0	0	2[3]	4.65	2	1.14
Algidity		-	-	0	0	1	2.33	1	0.57
PHYSICAL EXAMINATION									
Skin	pale	3	6.12	6	7.14	12[2.3]	27.91	21	11.93
	pale pink	44	89.80	78	92.86	31[2.3]	72.09	153	86.93
	marble	2	4.08	0	0	0	0	2	1.14
Oropharynx	clean	49[1]	100	1	1.19	14[2.3]	32.56	64	36.36
	hyperemia	0[1]	0	83	98.81	29[2.3]	67.44	112	63.64
Nasal breathing	free	49[1.2]	100	69	82.14	36	83.72	154	87.5
	difficult	0[1.2]	0	15	17.86	7	16.28	22	12.5
Percussion of lungs	pulmonary	49	100	84	100	39[2.3]	90.70	172	97.73
	dullness	0	0	0	0	4[2.3]	9.30	4	2.27
Auscultation of lungs	vesicular	49[1.2]	100	75	89.29	11[3]	25.58	135	76.70
	hard	0[1.2]	0	9	10.71	29[3]	67.44	38	21.59
	diminished	0	0	0	0	3[3]	6.98	3	1.71

Notes: n – number of cases; p1 – statistical significance of differences ($p<0,05$) between groups 1 and 2; p2 – statistical significance of differences between groups 1 and 3; p3 – statistical significance of differences between groups 2 and 3 (Pearson's χ^2).

89.80% of children with an asymptomatic form were in close contact with people with confirmed SARS-CoV-2, the same showed 82.14% patients in the second group and 83.73% participants in the third group (respectively, p = 0.234, p = 0.389, p = 0.825). The patients with an asymptomatic form of 2019-nCoV were twice as likely to provide the exact date of their contact with the patients with confirmed or suspected cases of COVID-19 as the patients with mild form of the disease (p=0,039). Despite the fact that there was noted a tendency to shortening of incubation period along with worsening of COVID-19 statistically significant difference between studied groups was not found (p>0,05). The average period from the first clinical symptoms to the hospital admission was not correlated to the disease severity (p>0,05).

The fever was found as often amongst children of the second group as amongst those of the third group (75,00%, 79,07%; p=0,610). The patients with moderate form of COVID-19 coughed 1.6 times more frequently than the ones with the mild form (respectively, 69,77%, 42,86%; p=0,005). Half of the participants of the third group (53,49%) had the weakness comparing to the children of the second group, who were found with this symptom twice less (26,19%, p=0,003). Running

nose (p=0,504), sore throat (p=0,403) and difficulty in nasal breathing (p=0,960) appeared as often in children with mild form of COVID-19 as in children with moderate form.

Fatigue (18,6% against 3,57%) and myalgia (16,28% against 4,76%) were presented more often in patients of the third group comparing to the second one (respectively, p=0,005 and p=0,029). Such symptoms as stomach ache and dizziness mainly appeared in single cases amongst participants with moderate form of COVID-19 (respectively, p=0,027 and p=0,047). The rate of other clinical symptoms has not differed between the groups (p>0,05).

In children of the third group paleness (p=0,002) and hyperemia of the oropharynx (p<0,001) were seen more often. The shortening of percussion sound and weakened breathing were presented only in children with moderate form of the disease (respectively, p=0,005 and p=0,015).

Conclusion. The main way of the transmission of SARS-COV-2 was close contact with the people with confirmed or suspected COVID-19 infection. Only two patients had travelled abroad two weeks before the first symptoms of the disease appeared. Amongst all patients with 2019-nCoV only 16.48% were vaccinated against flu. COVID-19 infection was mainly found in senior school age children with the male gender prevalence and was characterized by asymptomatic form. Most of the cases of SARS-COV-2 in children began with fever, were followed by cough and different catarrhal symptoms. Weakness, fatigue, myalgia, stomach ache and dizziness were noted for the moderate form of COVID-19.

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RESULTS OF THE SURVEY OF PATIENTS WHO UNDERWENT COVID-19

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Sources indicate that being infected with COVID-19 leaves patients with undesirable symptoms that form a new disease – post-covid syndrome. We examined the health status of 155 people who suffered a coronavirus infection. Informed consent to the study was obtained from all participants. They were interviewed, asked to fill out a series of questionnaires to assess symptoms and quality of life, and underwent a medical examination.

Our results showed that after 8 months, people who have had COVID-19 complain about the symptoms of post-covid syndrome. At the same time, the most common clinical manifestations were sleep disorders (50.9%), hypertension (47.7%), weakness (33.5%), dizziness (32.9%), shortness of breath (27.7%), headaches (24.5%), gastrointestinal disorders (diarrhea, abdominal pain) (18.7%). Our statistical analysis showed a significant dependence of increased blood pressure (1.7 times higher) with the degree of lung damage.

Keywords: COVID-19, SARS-CoV-2, post-covid syndrome, long-term clinical manifestations.

Introduction. A new coronavirus infection caused by the SARS-CoV-2 virus was first detected in China in December 2019, in Wuhan. On March 11, 2020, the World Health Organization (WHO) declared a global emergency and announced a pandemic. More than two years have passed since the beginning of the pandemic, over the past period of time, the medical community has studied clinical manifestations and developed specific treatment regimens. The incubation period, manifestations, various forms of the disease in different age groups and possible complications are also known. However, there are very few studies researching the development of post-covid symptoms and their duration.

Sources indicate that people who have had a coronavirus infection often have undesirable symptoms (weakness, sleep disturbance, cough, headaches, dizziness, etc.), which are combined into a new disease – post-covid syndrome [12]. Post-covid syndrome is an officially recognized disease that has its own code in the International Classification of Diseases of the 10th revision (U09.9). Based on the data of many independent studies, it has been established that the symptoms of post-covid syndrome can be observed for a long time [4;6;9;10]. The data indicates a variable duration of residual symptoms - from a week and up to six months, however, we have not encountered articles describing symptoms with a longer time period (6<). The amount of research investigating the relationship between the severity of COVID-19 and the frequency of clinical manifestations in the post-covid period was especially lacking.

For a comprehensive and systematic identification of the symptoms, we used clinical databases and questionnaires of people who had a coronavirus infection 8 months after discharge from the hospital. This approach makes it possible to identify not only respiratory symptoms, but also nervous, digestive and cardiovascular ones. These results will help in treatment planning, rehabilitation, and the development of interdisciplinary strategic care to reduce chronic health loss among COVID-19 survivors.

Epidemiology: The SARS-CoV-2 virus differs from other respiratory infections by its rather high virulence and mortality. According to the COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) on February 10, 2022, an outbreak of coronavirus disease caused by SARS-CoV-2 led to the death of more than 5,777,230 people and infected more than 403,224,427 worldwide. In Russia, 330,609 people died from this disease, 13,128,679 were infected.

As for the epidemiology of post-covid syndrome, there is no statistically reliable data because of insufficient research of the topic. But there is a noticeable amount of long-term clinical manifestations with repeated hospitalization. So, according to the UK website, more than 1.1 million people who have had a coronavirus infection have come with symptoms that persist after four weeks from the moment of recovery. At the same time, 670 thousand patients reported that these symptoms negatively affected their quality of life, and 196 thousand people reported that their daily life became severely limited. Moreover, 13% of individuals continued to experience these symptoms for 3 months. Thus, a significant number of people who have had a coronavirus infection experience manifestations of the post-covid syndrome for many months, which leads to chronic loss of health.

Materials and methods. We studied the health status of 155 people who had a coronavirus infection and were discharged from the hospital in the period from August to September 2020. Informed consent to the study was obtained from all participants of the study (according to the protocol of the Ethics Committee of the YSC CMP No. 52 dated March 24, 2021, decision 1). Clinical indicators of the disease, such as the degree of lung damage assessed by computed tomography, were taken from a medical record statement.

All participants were personally interviewed, they filled out a series of questionnaires to assess symptoms and quality of life, underwent a medical examination, and passed blood tests for biochemical and immunological research. The general characteristics of the examined patients are presented in Table 1.

Statistical processing of research results was carried out using the Microsoft Excel application software package and the IBM SPSS Statistics 24 statistical program. The relationship between the degree of lung damage and the risk of developing post-covid syndrome was assessed by the odds ratio (OR) with a 95% confidence interval (95% CI). When comparing the groups, the differences were considered statistically significant at $p < 0.05$.

Results. According to the data obtained, the most common late (8 months after recovery) clinical manifestations of COVID-19 were: sleep disturbance (50.9%), hypertension (47.7%), weakness (33.5%), dizziness (32.9%), shortness of breath (27.7%), headaches (24.5%), gastrointestinal disorders (18.7%). We examined the frequency of clinical manifestations depending on the degree of lung damage during the course of the disease. The analysis of clinical manifestations depending on the degree of lung damage showed reliable values only with: increased blood pressure (Table 2). In the study group of COVID-19

Table1

General characteristics of the examined patients who have had a coronavirus infection

Indicator:	Values:
Number of examined	155
Age, years (median):	53.00 (41.50-61.50)
Men / Women	59/102
BMI	28.03 (24.14-31.74)
Disease severity (CT degree):	Абс.число (%)
1	81 (52.2)
2	43 (27.7)
3	25 (16.1)
4	6 (4.0)
Subjective symptoms:	
Sleep disturbance	79 (50.9)
Increased blood pressure	74 (47.7)
Weakness	52 (33.5)
Dizziness	51 (32.9)
Shortness of breath	43 (27.7)
Headaches	38 (24.5)
Gastrointestinal disorders (diarrhea, abdominal pain)	29 (18.7)

Table2

Subjective symptoms of the examined patients who have had a coronavirus infection, depending on the degree of lung damage

	Sleep disturbance+	Sleep disturbance-	χ^2	p	OR (95 CI)
CT1-2 n=124	63	61	0.006	0.936	0.968 (0.440-2.128)
CT3-4 n=31	16	15			
	Increased blood pressure+	**Increased blood pressure-**	χ^2	p	OR (95 CI)
CT1-2 n=124	52	72	8.374	0.004	0.295 (0.125-0.693)
CT3-4 n=31	22	9			
	Weakness +	**Weakness-**	χ^2	p	OR (95 CI)
CT1-2 n=124	42	82	0.028	0.865	1.075 (0.464-2.491)
CT3-4 n=31	10	21			
	Dizziness+	**Dizziness-**	χ^2	p	OR (95 CI)
CT1-2 n=124	43	81	0.785	0.377	1.490 (0.614-3.617)
CT3-4 n=31	8	23			
	Shortness of breath+	**Shortness of breath-**	χ^2	p	OR (95 CI)
CT1-2 n=124	34	90	0.032	0.858	0.923 (0.386-2.204)
CT3-4 n=31	9	22			
	Headaches+	**Headaches-**	χ^2	p	OR (95 CI)
CT1-2 n=124	27	97	2.502	0.113	0.506 (0.216-1.184)
CT3-4 n=31	11	20			
	Gastrointestinal disorders+	**Gastrointestinal disorders-**	χ^2	p	OR (95 CI)
CT1-2 n=124	21	103	1.275	0.258	0.586 (0.231-1.487)
CT3-4 n=31	8	23			

patients with more severe lung damage, the frequency of clinical manifestations of high blood pressure was 1.7 times higher, compared with those who had an infection with less severe lung damage.

Discussion. Since the first case of COVID-19 was registered two years ago, articles on the long-term clinical consequences of this disease are just beginning to appear. Due to the huge number of cases and the severity of the disease, many people experience long-term effects of COVID-19. Researchers indicate various durations of residual symptoms: a month [3], three months [1;4], six months [5;13], works describing symptoms with a longer duration (6<) have not been found.

The SARS-COV-2 virus damages lung cells in the lower respiratory tract (small bronchi and alveoli), provoking a strong inflammatory reaction. Lung CT is the main method of diagnosing the severity of the disease. Many researchers note the dependence of the severity and duration of symptoms of coronavirus infection with the degree of lung damage in the course of the disease [11;15;7].

Our results indicate that even after 8 months, people who have had COVID-19 complain about the symptoms of post-covid syndrome. At the same time, the most common clinical manifestations were sleep disorders (50.9%), hypertension (47.7%), weakness (33.5%), dizziness (32.9%), shortness of breath (27.7%), headaches (24.5%), gastrointestinal disorders (diarrhea, abdominal pain) (18.7%). Our statistical analysis showed a significant dependence of increased blood pressure (1.7 times higher) with the degree of lung damage. Dizziness, muscle weakness and sleep disorders were quite common, but we did not notice statistically significant differences depending on the degree of lung damage (Table 2).

According to Silvagno, an increase in blood pressure in COVID-19 is associated with the way the virus enters the human body. The SARS-CoV-2 virus enters the cell through interaction with the ACE2 protein (angiotensin converting enzyme 2). SARS-CoV-2 blocks ACE2 by internalizing it. The loss of ACE2 receptor activity leads to a rapid drop in the production of angiotensin-1–7 (Ang 1-7), and consequently the accumulation of angiotensin II (Ang II). Imbalance between angiotensin II (hyperactivity) and angiotensin 1,7 (deficiency) may play a role in the occurrence of an acute increase in blood pressure [2;8;14].

In people who have had a coronavirus infection, there is a significant increase in blood pressure, depending on the degree of lung damage. Perhaps this is due to the fact that high blood pressure is, according to many authors, a concomitant risk factor for complications of COVID-19.

Thus, statistically significant differences between the degree of lung damage and an increase in blood pressure were found in persons who had a coronavirus infection 8 months after discharge from the hospital.

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POST-COVID STATE OF EXTERNAL RESPIRATORY FUNCTION IN HOSPITALIZED AND OUTPATIENT PATIENTS

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A one-time medical and biological examination of the health status of 161 residents of Yakutsk aged 20 to 72 years who recovered from COVID-19 3-12 months ago during the first wave of the pandemic was carried out. Changes in lung function were detected in 29.5% of 139 patients who underwent spirometry. Among them, 7.2% of the surveyed revealed extremely severe changes. The appearance of symptoms and disturbances in the function of external respiration in the post-covid period did not have significant differences in hospitalized and outpatients, and were not associated with the post-covid period, the severity of lung damage in the acute period of the disease, smoking, and the presence of chronic diseases of the respiratory system. The obstructive and restrictive type of disorder was more often observed in women treated on an outpatient basis, which indicates a protracted recovery that requires the same rehabilitation measures that are carried out for hospitalized patients in order to eliminate multiple organ post-COVID complications.

Keywords: COVID-19, pneumonia, spirometry, external respiration.

Material and research methods. The study involved a total of 161 people who had been ill for 3-12 months. ago with a new coronovirus infection - COVID-19 at the age of 20 to 72 years. Of these, women - 101 (62.7%), men - 60 (37.3%). The average age of all examined was Me=51.1 years (41.5; 61.5), men – Me=50.9 years (40.0; 61.7), women – Me=53.7 years (42.0; 61.5).

According to the protocol of computed tomography (CT) from the anamnesis in the acute period of the disease, the subjects were divided according to the severity of lung damage into 5 groups: CT0 (zero) - no signs of viral pneumonia; CT1 (mild) - the presence of a ground-glass compaction zone, involvement of less than 25% of the lung volume; CT2 (moderate) - damage to the lungs from 25 to 50%; CT3 (severe) - damage to the lungs from 50 to 75%; CT4 (critical) - lung damage more than 75% (Table 2). According to the post-COVID period, they are divided into 4 groups: up to 3, up to 6, up to 9, up to 12 months ago (Table 1).

The study used a questionnaire that included questions about the presence of chronic diseases, complaints after suffering from COVID-19, and a questionnaire on the Hospital Anxiety and Depression Scale (HADS). The biomedical study included an appointment with a cardiologist, neurologist, rheumatologist, therapist, determination of hematological, biochemical and immunological parameters, ECG, anthropometry, spirometry. Spirometry was performed in 139 participants of the study using the diagnostic system "Valenta": 88 women (63.3%), the average age was Me - 50.9 (42.0; 61.0) and 51 men (36.7%), the average age - Me - 50.0 (40.0; 61.0). 22 participants were excluded due to contraindications and rejection of the study.

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Table1

Groups according to the degree of lung damage (CT), abs. number / %

Groups	The severity of lung injury					Total
	CT0	CT 1	CT 2	CT 3	CT 4	
Men	7/13.7	15/29.4	12/23.5	15/29.4	2/3.9	51/100
Women	13/14.6	39/43.8	27/30.3	7/7.9	3/3.6	89/100

Note. Pearson chi-squared =11.908, df=4, p=0.018.

The function of external respiration was assessed in terms of VC, FVC, FEV1, Tiffno index (TI).

VC (vital capacity) - the maximum amount of air that can be exhaled after a maximum breath. FVC (forced vital capacity) is the volume of air that can be exhaled after a maximum inhalation at the maximum possible rate. FEV1 (forced expiratory volume in the first second) - the volume of air that the subject can exhale in the first second of maximum forced exhalation. Tiffno index - the ratio of FEV1 to VC, expressed in%. IT decreases with obstructive syndrome. The study was approved by the local committee on biomedical ethics at the Federal State Budgetary Scientific Institution YSC CMP No. 52 dated March 24, 2021 and was conducted subject to the voluntary informed consent of the participants.

Statistical processing was performed using the IBM SPSS Statistic 23 software package. The normality of the distribution of quantitative indicators was determined using the Kolmogorov-Smirnov test. The descriptive analysis values are presented as the median (Me) and the 25th and 75th quartiles (Q1-Q3) when the distribution is not normal. Nominal data are presented as absolute values and percentages, and their comparison in contingency tables was carried out using Pearson's chi-square. Correlation analysis was performed according to the method of Pearson and Spearman, where r is the correlation coefficient, p is the significance of the result. When testing statistical hypotheses, the critical level of significance (p) was taken at p<0.05.

Introduction. As time goes on, it becomes clear that one of the major problems associated with the SARS-CoV-2 pandemic is its long-term consequences. Recent studies have shown that those who have recovered from COVID-19 may experience certain symptoms that persist from 2 months to a year [7,12,14]. Symptoms persisting for more than 3 months are described as "post-COVID syndrome" [3]. In addition to problems of general well-being (fatigue, decreased performance, etc.), symptoms associated with the development of pathology of the respiratory and cardiovascular systems, gastrointestinal tract, and other organs appear, neurological, psychoemotional symptoms appear [21], i.e. . the novel coronavirus SARS-COV-2 is responsible for multiple organ syndrome [19].

At the same time, information often began to appear that post-COVID symptoms appear not only in patients with a severe course of the disease, but in people who have recovered from COVID-19 of mild and moderate severity [18,9]. The main severe manifestation of SARS-COV-2 infection is respiratory distress syndrome, the frequent development of extensive bilateral interstitial damage to the lung tissue, accompanied by thrombovasculitis of the microvasculature [22], which in turn is associated with a very high expression of the ACE2 protein receptor (angiotensin-converting enzyme-2) in the lung tissue, through which the SARS-CoV-2 virus penetrates into the cells of the alveolar epithelium, and replicates in the cytoplasm of cells [15]. In the future, continuing respiratory failure causes the development of hypoxia. In addition, damage to the alveolar epithelium and endothelium of the pulmonary vessels can cause the growth of fibroblasts, which is a factor in the formation of lung tissue fibrosis during the recovery period. Especially in men, smokers and the elderly [8].

Table2

Groups of men and women by post-COVID period, abs. number / %

Groups	Post-covid period, months				Total
	3	6	9	12	
Men	5/9.8	18/35.3	18/35.3	10/19.6	51/100
Women	9/10.2	40/45.5	28/31.8	11/12.5	88/100

Long-term hypoxia negatively affects the central nervous system and can cause anxiety and depressive disorders [2], increased fatigue, decreased performance, brain encephalopathy, stroke, muscle weakness, neuropathy (damage to the peripheral nerves of the extremities) with the development of motor paresis and paralysis, movement disorders, shortness of breath [23].

In this regard, in the absence of specific post-COVID symptoms and certain periods of their manifestation, which complicate diagnosis and treatment, the study of the long-term effects of COVID-19 on the respiratory system, regardless of the severity of the disease, is necessary to prevent severe complications and rehabilitate patients to maintain quality of life.

The aim of the study was a comparative assessment of symptoms and lung function after COVID-19 in hospitalized and non-hospitalized patients living in Yakutsk. Results and discussion. Earlier, in our published work, it was shown that the degree of lung damage (CT) in the acute period of COVID-19 disease was directly dependent on factors such as age (r=0.307; p<0.000), gender (r=-0.238; p<0.002), BMI (r=0.286; p<0.000) [5]. In addition, there was a dependence on the presence of arterial hypertension (r=0.373; p<0.000) and comorbidity (r=0.292; p<0.000).

The relationship between the severity of lung damage by the new SARS-CoV-2 coronavirus and gender is shown in Table 2. Among the subjects who underwent spirometry, mild and moderate lung tissue damage (CT1 and CT2) is more than 2 times more common in women, and vice versa, the incidence severe lung damage from 50 to 75% (CT3) was 2 times more common in men. There were only 6 people (3.7%) examined with CT4: 3 men and 3 women, since the survival rate of patients with critical lung disease (more than 75%) is extremely low.

Of the total number of those examined (n=161), 21 people had chronic respiratory diseases, which amounted to 13.46%. In them, 4 people (2.56%) suffer from bronchial asthma and 17 people (10.8%) suffer from chronic bronchitis. At the time of the examination, 13 people (8.33%) had chronic bronchitis in remission, and a prolonged exacerbation of bronchitis was observed in 4 people (2.56%). Pathology of the respiratory organs in the surveyed takes the 3rd place after diseases of the cardiovascular system (59.6%) and endocrine diseases (30.5%). Table 3 gives the frequency of pathologies in hospitalized and outpatient patients.

Frequent post-covid symptoms were sleep disturbance (48.2%), fatigue (43%), hair loss (33.1%), decreased performance (32.7%), shortness of breath (28.2%), weakness (26.6%) and sweating (25.5%). Symptoms such as shortness of breath, heaviness in the chest, a lump in the throat were indicated by 12.2%, 10.3% and 8.9%, respectively. Table 3 shows the prevalence of post-COVID symptoms in the hospitalized and outpatient groups. Post-covid symptoms were not only in patients with severe lung disease (hospitalized patients), but also in those who had mild to moderate COVID-19 and were treated on an outpatient basis (Table 4). There were 82 hospitalized patients (50.9%), outpatients - 79 (49.1%). One study showed that among hospitalized patients, the prevalence of ongoing symptoms ranged from 32.6% to 87%. [7].

In another study, among non-hospitalized patients, 37% complained of fatigue, 30% of cognitive impairment [11]. In a study including 433 non-hospitalized patients, 9.6 months after infection with SARS-CoV-2, signs of subclinical multiorgan damage associated with pulmonary, cardiac, thrombotic and renal functions were revealed. There were no signs of structural brain damage, neurocognitive impairments, or deterioration in the quality of life [17].

According to spirometry among the study participants, violations of the function of external respiration were revealed. Decreased value of VC, FVC, OVF1 was observed both in hospitalized and outpatients, and more often in women (Table 5).

The Tiffno index (FEV1 / VC, %) as a sensitive index of the presence or absence of deterioration in airway patency showed that cases of low values were detected in 24 people (17.3%): in 8 men, mostly hospitalized and 16 women, of which 7 were treated on an outpatient basis (Table 4). There were no significant differences in the frequency of ventilatory dysfunction between hospitalized and outpatients (p=0.248). It should be noted that men treated on an outpatient basis had fewer violations of respiratory function than women. Our data do not contradict the literature. X-ray studies of those who recovered after 3 months revealed pulmonary anomalies in 71% and functional disorders in 25%, despite the fact that only less than 10% had severe pneumonia, i.e. lung function abnormalities did not depend on the severity of the disease [16]. Lung function impairment among COVID-19 survivors 1 year after discharge is widespread, and persistent impairment of lung function has been

Table3

Frequency of pathologies among study participants, %

		1 group	2 group	Total	X^2 Pearson	df	p
Diseases respiratory system	Да	13/15.9	8/10.1	21/13.0	1.920	3	0.589
	Нет	69/84.1	71/89.9	140/87.0			
Diseases of the cardiovascular system	Да	53/64.6	32/40.5	85/52.8	15.106	1	**0.000**
	Нет	29/35.4	47/54.7.7	76/47.2			
Type II diabetes	Да	13/15.9	7/8.9	20/12.4	2.078	1	0.149
	Нет	69/84.1	72/91.1	141/87.6			
Obesity	Да	16/19.5	14/17.7	30/18.6	0.358	1	0.549
	Нет	66/80.5	65/82.3	131/81.4			
Anxiety	Да	18/22.2	20/25.7	38/	0.253	1	0.615
	Нет	63/77.8	58/74.4	121			
Depression	Да	22/26.8	17/21.5	39/24.2	0.620	1	0.431
	Нет	6073.2	62/78.5	122/75.8			

Note: 1 - hospitalised; 2-outpatients

Table4

Occurrence of post-convulsive symptoms in patients, units/%

gender	Groups	Symptoms				
		1	2	3	4	5
Men	hospitalized	12/61.9	14/73.7	12/66.7	5/100	9/64.3
	ambulatoryses	8/38.1	5/26.3	6/33.3	0/0.0	5/35.7
Women	hospitalized	27/46.6	12/38.7	21/42	6/42.8	13/43.3
	ambulatoryses	31/53.4	19/61.3	29/58	8/57.2	17/56.7

Note: 1-sleep disturbance, 2-decreased performance, 3-fatigue, 4 - labored breathing, 5 - shortness of breath.

Table5

The frequency of reduced values of spirometry, units/%

gender	Groups	VC, <80%	FVC, <80%	FEV1, <80%	FEV1/VC, <70%
Men	hospitalized	20/60.6	17/63.0	9/81.8	7/87.5
	ambulatoryses	13/39.4	10/37.0	2/18.2	1/12.5
Women	hospitalized	32/45.7	25/41.0	17/56.7	9/56.3
	ambulatoryses	38/54.3	36/59.0	13/43.3	7/43.7

Note: Pearson's chi-square=4.128, df=3, p=0.248.

Table6

The frequency of the decrease in respiratory function indicators at different time intervals, units /%

Indicators Functions of external respiration	Post-covid period, months				Total
	3	6	9	12	
VC, <80%	10/9.8	41/40.2	33/32.4	18/17.6	102/100
FVC, <80%	11/12.5	34/38.6	30/34.1	13/14.8	88/100
FEV1, <80%	4/8.7	23/50.0	12/26.1	7/15.2	46/100
FEV1/VC %,<70%	2/8.3	11/45.8	6/25.0	5/20.8	24/100

found in about 40% of survivors. The authors suggest that lung damage may be associated with pulmonary fibrosis [13].

The frequency of decrease in indicators of the function of external respiration was not associated with the post-COVID period (Table 6).

The decrease in the Tiffno index is mild, moderate and significant. Table 5 shows the incidence of severity of airway disorders according to the Tiffno coefficient in hospitalized and outpatient patients. There was a significant difference in the frequency of the decrease in this index among men: there was no moderate or significant decrease in IT in those treated on an outpatient basis.

The obstructive type of violation of the respiratory function (decrease in FEV1 and Tiffno index), due to the deterioration of the airway patency at any level, was in 20 people (14.4%), the restrictive type of violation of the respiratory function (decrease in FEV1, VC, FVC), due to a decrease in the functional tissue of the lungs, 37 people (26.6%) had Mixed type of violation of respiratory function, when all the listed indicators are lowered, was detected in 14 people (10.1%). In the group of men treated on an outpatient basis, obstructive and mixed disorders of respiratory function were not detected. Among persons with respiratory problems, non-smokers were 3.7-5.7% more (Table 8).

Thus, women treated on an outpatient basis had a moderate and significant decrease in airway patency. Also among women there are all types of violations of respiratory function. This is probably due to the fact that recovery in women is slow, and outpatients did not receive proper treatment and rehabilitation. It should be noted that CT of the lungs in dynamics is necessary for accurate diagnosis of violations of respiratory function.

Indications for obstruction were more common in patients with diseases of the endocrine and cardiovascular systems. In the group with a significant decrease in airway patency, only one person had a history of respiratory system pathology - chronic bronchitis with prolonged exacerbation, five had endocrine pathology (obesity, diabetes, hypothyroidism, goiter), two had coronary artery disease, hypertension, one had anxiety, the other - depression.

The lowest percentage of VC was found in patients with clinically pronounced depression. There is a significant decrease in the median VC in people with depression. This is also evidenced by a direct correlation between VC impairment and depression (r=0.257; p<0.002).

Table7

The severity of pulmonary ventilation disorders according to the Tiffno coefficient, units /%

gender	Groups hospitalized	FEV1/VC, (according to R.F. Kliment et al.)				Total
		1	2	3	4	
Men	ambulatoryses	19/63.3	5/16.7	3/10.0	3/10.0	30/100
	hospitalized	19/95.0	1/5.0	0/0.0	0/0.0	20/100
Women	ambulatoryses	28/71.8	8/20.5	0/0.0	3/7.7	39/100
	hospitalized	38/80.9	4/8.5	3/6.4	2/4.3	47/100

Pearson's chi-square =9.215, df=3, p=0.027. 1 - norm (M.: 84.2-109.6%, F-78.2 -113.3%); 2 - slight decrease (M<71.5%, W<73.1%); 3 - moderate decrease (M<65.1%, W<66.7%); 4 - significant decrease (M<52.4%, W<54%).

Table8

Types of violations of respiratory function in men and women, units /%

Type of violation of respiratory function, unit/%	Men			Women			Smoking	
	1	2	Total	1	2	Total	Yes	Not
obstructive	5/9.8	0/0.0	5/9.8	8/9.1	7/8.0	15/17.1	3/15	17/85
restrictive	7/13.7	2/1.4	9/15.1	16/18.2	12/13.6	28/31.8	8/21.6	29/78.4
Mixed	2/1.4	0/0.0	2/1.4	7/8.0	5/5.7	12/13.7	3/21.4	11/78.6

Note: 1 - hospitalised; 2-outpatients.

In our earlier published work, data on the frequency of anxiety and depressive disorders in study participants (161 people) are presented. More than 24% of the examined patients had anxiety and depressive disorders, regardless of the post-COVID period and the severity of lung damage. [6].

Frequent symptoms such as sleep disturbance, fatigue, decreased performance, especially in women, confirm the literature data that long-term neuropsychiatric disorders are an important part of the multisystem post-COVID syndrome [4] and the role of hypoxia in the mechanism of development of these symptoms is obvious, along with other factors, such as inflammatory pathogenesis (encephalopathy, myocarditis, pneumonitis); the immunological mechanism of development (consequences of the release of cytokines, activation of humoral and cellular immunity, the formation of circulating immune complexes) and impaired blood rheology (thromboembolic complications) [1,20]. Chaolin Huang et al's analysis of the 6-month follow-up of COVID-19 showed that the risk of anxiety or depression as an important psychological complication and impairment of lung diffusivity in patients treated in hospitals was higher in patients with more severe disease [10]. However, we did not find a significant difference in the incidence of these ailments between groups of inpatients and outpatients.

In the rehabilitation of patients with impaired lung function, especially for those with depressive disorder, osteopathy, massage, acupuncture, hirudotherapy, infusion therapy, the introduction of nootropic drugs, absorbable therapy, detoxification, the use of multivitamins and mineral complexes, the appointment of biostimulants will be useful for recovery [1].

Conclusion. In this study, we found that the post-COVID period in hospitalized and outpatient COVID-19 patients, the onset of symptoms and respiratory dysfunction had no significant differences and was not associated with the post-COVID period, the severity of lung damage in the acute period of the disease, smoking and with chronic diseases of the respiratory system. The obstructive and restrictive type of disorder is more common in women treated on an outpatient basis, which indicates a protracted recovery of the female body from post-COVID complications and requires the same rehabilitation measures that are now being carried out for patients treated for COVID-19 in hospitals.

Further long-term studies of long-term lung dysfunction associated with SARS-CoV-2 infection are needed to understand the underlying mechanisms and the con-

sequences of long-term lung dysfunction on other organs and body systems.

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ARCTIC MEDICINE

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DYNAMICS OF DEMOGRAPHIC INDICATORS AND FEATURES OF MORTALITY IN THE ARCTIC ZONE OF THE REPUBLIC OF SAKHA (YAKUTIA) FOR THE PERIOD 2000-2019

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The article presents the dynamics of the main medical and demographic indicators and features of mortality in the Arctic zone of the Republic of Sakha (Yakutia). For the period 2000-2019 there is a tendency to reduce overall mortality, including from diseases of the circulatory system and external causes, against the background of continuing birth rates. The mortality rate from external causes was 1.9 times higher than the average for the Russian Federation, and 1.6 times higher than the average for the Republic of Sakha (Yakutia). The infant mortality rate in the Arctic zone was also higher than the average for the republic and the Russian Federation as a whole. High rates of infant mortality and mortality from external causes in the Arctic zone testify to the unfavorable socio-economic situation in the region.

Keywords: Arctic, Yakutia, demography, birth rate, mortality, external causes of death.

Introduction. In accordance with the Decree of the President of the Russian Federation dated 02.05.2014 N 296 "On the land territories of the Arctic zone of the Russian Federation" (as amended on 05.03.2020), the territories of 9 subjects of the Russian Federation, including the Republic of Sakha (Yakutia), are fully or partially assigned to the Arctic zone of the Russian Federation [11]. The features of this territory are extreme, uncomfortable natural and climatic conditions for human living and work, low population density, remoteness from industrial, administrative, business, educational and cultural centers, vulnerable life support of the population and ecosystems. The availability of reserves of various minerals makes this region a strategic resource base of the country.

The population of the Arctic zone of the Russian Federation is about 2,5 million people. This territory is home to 82.5 thousand representatives of the minor indigenous peoples of the North [8]. Human health in the Arctic is dependent on a multitude of factors, including the adaptation of the body to extreme environmental conditions, social and living conditions, ecology, lifestyle and nutrition, availability of medical care and medication.

Medical and demographic processes reflect the level of socio-economic development of society and characterize the quality of life of the population. The novel coronavirus infection pandemic has changed the characteristics of the medical and demographic situation due to excessive mortality. Thus, only in the first year of the spread of infection, the total mortality in the Russian Federation increased from 12.3 to 14.6 per 100 thousand population [12]. In the current situation, it is necessary to distinguish between changes caused by the consequences of coronavirus infection and long-term trends in the medical and demographic situation that characterize general patterns. In this regard, the purpose of the study was to assess the dynamics of the main medical and demographic indicators and features of mortality in the Arctic zone of the Republic of Sakha (Yakutia) for the period 2000-2019, for characterize the general direction of the situation.

Materials and methods. For the analysis, information from the Federal State Statistics Service and the Territorial Department of the Federal State Statistics Service for the Republic of Sakha (Yakutia) for the period of 2000-2019 was used [4, 10, 12]. The 20-year period was divided into 10-year intervals and the average values of the indicators were calculated.

Spearman's rank correlation coefficient (IBM SPSS STATISTICS, version 22) was used to assess the strength of the relationship between the indicators.

The limitation of the study is the use of crude mortality rates due to the lack of available data on age-specific mortality rates in the territorial administrative units of the Republic of Sakha (Yakutia).

Results and discussion. The Republic of Sakha (Yakutia) is a subject of the Russian Federation with an area of 3.1 million square km, located in the northeast of the Asian continent. The population of the republic as of 01.01.2020 is 971 thousand people [10]. The population density is 0.32 people/sq. km. The territory of the Republic is divided into 36 administrative-territorial units (34 municipal districts/ulus and 2 urban districts). According to the National Population Census (NPS) of 2010, the main ethnic groups are Yakuts (45.5%), Russians (41.2%), Ukrainians (3.6%), Evenks (1.9%), Evens (1.2%) [4].

In accordance with the Decree of the President of the Russian Federation "On the land Territories of the Arctic Zone of the Russian Federation" (as amended by Decrees of the President of the Russian Federation dated 27.06.2017 No. 287, dated 13.05.2019 No. 220, dated 05.03.2020 No. 164), the territories of the following 13 municipalities of the Republic of Sakha (Yakutia) are assigned to the Arctic zone of the Russian Federation [11]. These are territories with a very low population density. As of January 1, 2020, 67,652 people lived in these areas. During the period 2000-2019, the popu-

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lation in this region decreased by 22%. The population of the Arctic territory of Yakutia is mainly represented by indigenous ethnic groups. The share of minor indigenous peoples of the North (MIPN) averages 32%, considering the share of the population of the Yakut nationality, it should be assumed that in this zone mainly lives the indigenous population of Yakutia. Only in the Verkhnekolymsky district the share of Yakuts and MIPN is less than 50%. The most significant population decline over a 20-year period occurred in areas with a smaller proportion of the indigenous population. The age structure of the population also had significant differences. In most districts, the average age of the population was higher than in the republic in whole.

The analysis of the gender and age structure of the population of the Arctic zone of the Republic as of 01.01.2020 showed that the ratio of men (33491) and women (34161) was comparable. The age structure had a disproportion, up to 45-49 years the number of men exceeded the number of women. Especially pronounced differences were observed at the ages of 25-29 years (the number of men is 1.5 times more than women) and 30-34 years (1.2 times, respectively). At the age of 70 and older, there were 2 times less men than women.

Numerous studies have shown that adaptation to the unfavorable factors of the North causes tension in the regulatory systems of the human body and can lead to early depletion of functional reserves [2, 5, 7, 13, 23]. Along with this, in a short period of time, the lifestyle and diet of the population of the North have changed, new stress factors have appeared [6, 17]. This changed the structure of morbidity and mortality, increasing the proportion of chronic non-communicable diseases, with a decrease in infectious morbidity [14, 20]. The combined influence of these factors is reflected in higher rates of morbidity and mortality of the population, low life expectancy of the population of the northern regions [15, 16, 18, 22]. In the Republic of Sakha (Yakutia) for the period of 1992-2019, the incidence of diseases of the circulatory system per 10,000 population increased from 90 to 328; diseases of the endocrine system, eating disorders and metabolic disorders, respectively, increased from 56 to 131 [3, 9].

The analysis of the dynamics of mortality indicators showed that for the period from 2000 to 2019, there was a decrease in mortality in the Russian Federation, these trends were also noted and the republic in whole and in the Arctic zone (Table 1). The average rate of decline in the Arctic zone was -0.7%. The indicators of total mortality in the Arctic zone in each 10-year period were higher than in the Republic of Sakha (Yakutia) as a whole, with comparable birth rates. Over the last 10-year period (2010-2019), the average mortality rates ranged from 8.6-13.2 per 1000 population. The highest mortality rates were observed in areas with a larger proportion of the elder population, the correlation coefficient between the average age of the population and mortality was 0.73 ($p<0,001$).

Birth rates in the Arctic zone were comparable to the average for the republic in whole. The average growth rate of the indicator in the Arctic zone over a 20-year period was 0.03%. The variability of indicators was noted, for example, in 2010-2019. in the Verkhnekolymsky district, the birth rate averaged 11.8 per 1000, while in the Oleneksky district the average was 23.3. Birth rate positively correlated with the proportion of the minor indigenous peoples in the districts ($r=0,71$, $p<0,001$).

The Republic of Sakha (Yakutia) is one of the subjects of the Russian Federation with a continuing natural increase in population. Over 20 years, there is an increase in the indicator of natural population growth. The period of 2011-2014 was the period of the highest rates of natural growth for both the Russian Federation as a whole and the Republic. In the Arctic zone, natural growth rates with similar trends were slightly lower than in the republic in whole.

The infant mortality rate is one of the indicators of socio-economic well-being of society. Over a 20-year period, the mortality rate of children under 1 years old has significantly decreased both in the Russian Federation as a whole and in the Republic of Sakha (Yakutia), in-

Table1

Demographic indicators of the Arctic zone of the Republic of Sakha (Yakutia) [4] [10]

Territory	Total mortality per 1000 population*		Birth rate per 1000 population*	
	2000-2009	2010-2019	2000-2009	2010-2019
Abyysky district	13.4 (12.1-14.8)	14.4 (12.5-16.2)	12.2 (11.2-13.2)	11.3 (9.6-13.0)
Allaikhovsky district	14.4 (12.7-16.0)	17.0 (14.7-19.3)	13.0 (11.4-14.6)	13.2 (11.1-15.4)
Anabarsky district	19.1 (17.4-20.8)	20.0 (18.4-21.5)	10.9 (9.6-12.2)	8.6 (7.5-9.7)
Bulunsky district	13.8 (12.8-14.8)	14.1 (12.5-15.7)	10.6 (10.1-11.1)	9.0 (7.6-10.3)
Verkhnekolymsky district	11.3 (9.9-12.6)	11.8 (10.3-13.2)	13.1 (11.7-14.4)	13.1 (11.7-14.5)
Verkhoyansky district	15.5 (14.6-16.5)	17.5 (15.6-19.4)	12.7 (12.1-13.2)	11.4 (10.5-12.3)
Zhigansky Evenki National district	16.8 (14.6-19.1)	21.2 (19.1-23.3)	11.9 (10.8-13.0)	11.2 (10.1-12.4)
Momsky district	18.6 (17.3-19.9)	19.9 (17.3-22.5)	13.0 (11.2-14.8)	9.7 (8.4-11.1)
Nizhnekolymsky district	14.1 (12.3-15.9)	15.7 (13.9-17.4)	12.6 (10.8-14.5)	12.5 (10.9-14.0)
Oleneksky Evenki National district	17.5 (16.3-18.6)	23.3 (22.3-24.3)	11.9 (10.4-13.5)	10.9 (9.1-12.7)
Srednekolymsky district	15.2 (13.6-16.7)	17.8 (16.1-19.5)	11.0 (10.2-11.9)	12.0 (11.0-13.0)
Ust-Yansky district	10.9 (9.8-11.9)	16.0 (13.9-18.2)	11.1 (10.0-12.2)	12.6 (11.2-13.9)
Even-Bytantaysky National district	18.4 (15.8-21.0)	19.9 (17.7-22.1)	12.8 (11.7-13.9)	10.3 (8.5-12.2)
The whole Arctic zone of the Republic Sakha (Yakutia)	15.3 (14.8-15.8)	17.6 (16.2-19.0)	12.1 (11.5-12.6)	11.2 (10.3-12.1)
The whole Republic of Sakha (Yakutia)	15.0 (14.3-15.7)	16.2 (14.9-17.4)	10.0 (9.8-10.2)	8.6 (9.1-13.0)
Russian Federation (whole)	10.4 (9.6-11.2)	12.4 (11.5-13.2)	15.4 (14.8-15.9)	13.0 (12.6 -13.4)

Note: * - average values of indicators for 10-year periods are calculated (95%CI).

cluding its Arctic zone [10, 12]. It should be noted that there are significant differences between the indicators of municipalities. In the last 10-year period, the average infant mortality rate ranged from 3.4 to 14.2 per 1,000 live births. In general, in all periods, the infant mortality rate in the Arctic zone was higher than in the whole RS (Ya) and the Russian Federation. Similar trends are observed among the population of the Arctic territories of other countries [16].

The analysis of mortality by the most common causes of death for 2015-2019 was carried out (Table 2). Over a 5-year period, a reduction in mortality rates from diseases of the circulatory system and external causes both in the Republic and in the Russian Federation were noted. Along with this, both in the Republic and in the Arctic zone there is an increase in mortality from neoplasms. Mortality rates from diseases of the circulatory system (DCS), neoplasms and external causes in the Arctic zone were slightly higher than in the Republic as a whole. At the same time, it is necessary to consider the differences in the age structures of the population. The most significant differences are noted in mortality rates from external causes. In the Arctic regions of the Republic, the average mortality rate for the analyzed period is 1.9 times higher than the average for the Russian Federation, and 1.6 times higher for the Republic of Sakha (Yakutia).

If we consider the structure of total mortality (2015-2019), then a significantly higher proportion of mortality from external causes in the Arctic zone is noteworthy than in the Russian Federation and the RS (Ya) as a whole. On average, in all Arctic regions, the share of external causes in the structure of mortality from all causes is 19.6%. There are significant fluctuations in the indicator ranging from 11.1 to 28.8%. In the Anabar and Even-Bytantay districts, mortality from external causes accounts for about 30% of all causes of death.

Analysis of the main causes of death from external causes showed that, on average, over the period 2015-2019, mortality from all types of transport injuries (V01-V99) in the Arctic zone of the RS (Ya) was lower than in the republic and the Russian Federation as a whole. Mortality from accidental alcohol poisoning (X45) increased from 0.9 to 12.1 per 100,000 population and was higher than in the RS (Ya) and the Russian Federation in whole in 2018-2019.

In dynamics over a 5-year period, there has been a decrease in the suicide rate both in the country as a whole and

Table2

Mortality rates by major classes of causes of death per 100,000 population [10]

Territory	2015	2016	2017	2018	2019	Average 2015-2019
Diseases of the circulatory system (ICD-10, I00-I99)						
Abyysky district	389.3	662.3	470.5	450.2	429.0	480.3
Allaikhovsky district	553.9	296.3	662.5	590	444.0	509.3
Anabarsky district	293.3	317.5	339.6	279.2	220.7	290.1
Bulunsky district	465.1	500.9	430.1	335.7	344.1	415.2
Verkhnekolymsky district	699.8	705.2	623.2	758.7	422.3	641.8
Verkhoyansky district	471.6	395.5	413.4	382.5	315.4	395.7
Zhigansky Evenki National district	705.6	329.6	401.9	309.5	530.8	455.5
Momsky district	478.7	461.3	611.8	372.9	377.5	460.4
Nizhnekolymsky district	726.3	457.0	439.0	396.3	491.2	502.0
Oleneksky Evenki National district	427.7	225.2	396.0	438.0	309.7	359.3
Srednekolymsky district	345.8	531.6	373.0	361.8	474.4	417.3
Ust-Yansky district	579.9	553.9	518.3	397.1	456.0	501.0
Even-Bytantaysky National district	286.9	287.8	393.3	602.8	282.1	370.6
The whole Arctic zone of the RS (Ya)	494.1	440.3	467.1	436.5	392.1	446.0
The whole Republic of Sakha (Yakutia)	386.7	368.7	364.2	354.0	357.1	366.1
Russian Federation (whole)	635.3	616.4	587.6	583.1	573.2	599.1
Neoplasms (ICD-10, C00-D48)						
Abyysky district	121.7	245.3	297.2	25.0	126.2	163.1
Allaikhovsky district	184.6	37.0	147.2	184.4	111.0	132.8
Anabarsky district	88.0	86.6	113.2	195.4	137.9	124.2
Bulunsky district	83.5	59.6	131.4	155.9	83.1	102.7
Verkhnekolymsky district	116.6	164.6	119.8	220.3	248.4	173.9
Verkhoyansky district	104.8	140.6	149.5	177.9	180.2	150.6
Zhigansky Evenki National district	164.6	141.2	141.8	238.1	289.5	195.0
Momsky district	215.4	169.9	171.3	124.3	125.8	161.3
Nizhnekolymsky district	158.9	228.5	254.2	209.8	140.4	198.4
Oleneksky Evenki National district	125.8	50.1	148.5	219.0	214.4	151.6
Srednekolymsky district	172.9	172.8	159.9	214.4	162.6	176.5
Ust-Yansky district	207.1	166.2	98.1	141.8	199.5	162.5
Even-Bytantaysky National district	107.6	107.9	107.3	177.3	176.3	135.3
The whole Arctic zone of the RS (Ya)	142.4	136.2	156.9	175.7	168.9	156.0
The whole Republic of Sakha (Yakutia)	130.1	134.6	136.5	139.8	140.1	136.2
Russian Federation (whole)	205.1	204.3	200.6	203.0	203.5	203.3
External causes (ICD-10, V01-Y98)						
Abyysky district	267.6	294.3	247.6	125.1	126.2	212.2
Allaikhovsky district	110.8	222.2	294.4	110.6	222.0	192.0
Anabarsky district	381.3	259.7	113.2	167.5	193.1	223.0
Bulunsky district	190.8	83.5	143.4	143.9	154.3	143.2
Verkhnekolymsky district	233.3	141.0	119.8	146.8	49.7	138.1
Verkhoyansky district	296.9	228.5	211.1	266.8	108.1	222.3
Zhigansky Evenki National district	376.3	141.2	236.4	142.9	265.4	232.4
Momsky district	71.8	242.8	195.8	149.1	75.5	147.0
Nizhnekolymsky district	181.6	228.5	231.1	186.5	117.0	188.9
Oleneksky Evenki National district	251.6	225.2	297	267.6	214.4	251.2
Srednekolymsky district	159.6	292.4	213.2	214.4	216.9	219.3
Ust-Yansky district	220.9	193.9	280.2	127.6	142.5	193.0
Even-Bytantaysky National district	358.7	323.7	286.0	177.3	211.6	271.5
The whole Arctic zone of the RS (Ya)	238.6	221.3	220.7	171.2	161.3	202.6
The whole Republic of Sakha (Yakutia)	145.3	135.4	122.6	122.6	109.4	127.1
Russian Federation (whole)	121.3	95.3	114.2	104.0	98.5	106.7

Table3

Mortality rates for the main external causes of death per 100.000 population [10]

Territory	2015	2016	2017	2018	2019	Average 2015-2019
1	2	3	4	5	6	7
Transport accidents (V01-V99)						
Abyysky district	24.3	0	0	0	0	4.9
Allaikhovsky district	0	0	0	0	0	0
Anabarsky district	0	0	0	0	0	0
Bulunsky district	0	11.9	0	12	0	4.8
Verkhnekolymsky district	0	23.5	0	24.5	0	9.6
Verkhoyansky district	8.7	8.8	0	8.9	18	8.9
Zhigansky Evenki National district	47	0	47.3	0	0	18.9
Momsky district	0	24.3	0	0	0	4.9
Nizhnekolymsky district	0	45.7	0	0	0	9.1
Oleneksky Evenki National district	25.2	0	24.8	0	0	10
Srednekolymsky district	0	0	13.3	0	0	2.7
Ust-Yansky district	13.8	13.8	28	28.4	0	16.8
Even-Bytantaysky National district	35.9	0	0	0	0	7.2
The whole Arctic zone of the RS (Ya)	11.9	9.8	8.7	5.7	1.4	7.5
The whole Republic of Sakha (Yakutia)	13	11.1	12.4	12.1	8.7	11.5
Russian Federation (whole)	17	15	14	13	12	14.2
Accidental poisoning by and exposure to alcohol (X45)						
Abyysky district	0	0	0	0	25.2	5
Allaikhovsky district	0	0	0	0	37	7.4
Anabarsky district	0	0	0	0	0	0
Bulunsky district	11.9	0	11.9	24.0	23.7	14.3
Verkhnekolymsky district	0	0	0	0	0	0
Verkhoyansky district	0	17.6	0	0	9	5.3
Zhigansky Evenki National district	0	0	0	23.8	24.1	9.6
Momsky district	0	0	0	0	0	0
Nizhnekolymsky district	0	0	0	0	0	0
Oleneksky Evenki National district	0	0	49.5	48.7	23.8	24.4
Srednekolymsky district	0	0	0	0	0	0
Ust-Yansky district	0	27.7	0	28.4	14.2	14.1
Even-Bytantaysky National district	0	0	0	70.9	0	14.2
The whole Arctic zone of the RS (Ya)	0.9	3.5	4.7	15.1	12.1	7.3
The whole Republic of Sakha (Yakutia)	4.8	9.3	11.1	10.1	10.3	9.1
Russian Federation (whole)	10.0	10.0	8.0	4.0	4.0	7.2
Intentional self-harm (X60-X84)						
Abyysky district	24.3	147.2	24.8	25	0	44.3
Allaikhovsky district	36.9	37	73.6	0	37	36.9
Anabarsky district	264	115.4	0	55.8	55.2	98.1
Bulunsky district	35.8	35.8	23.9	24	0	23.9
Verkhnekolymsky district	46.7	23.5	0	24.5	0	18.9
Verkhoyansky district	52.4	43.9	52.8	80.1	45.1	54.9
Zhigansky Evenki National district	23.5	23.5	47.3	23.8	72.4	38.1
Momsky district	23.9	97.1	48.9	24.9	0	39
Nizhnekolymsky district	22.7	22.9	23.1	0	0	13.7
Oleneksky Evenki National district	0	0	99.0	48.7	0	29.5
Srednekolymsky district	79.8	93	106.6	93.8	108.4	96.3
Ust-Yansky district	55.2	41.5	28	14.2	42.7	36.3

in the republic. At the same time, suicide mortality in the Arctic zone is significantly higher than in the Republic of Sakha (Yakutia) and the Russian Federation as a whole. On average, over a 5-year period, suicide mortality was 3.3 times higher than in the Russian Federation and 1.7 times higher than in the republic in whole. The main causes of death in this class are suicide and homicide. According to the sources, the suicide rate in the Arctic communities of other countries is also high [19, 21]. High death rates from homicides are associated with alcohol consumption. According to the Analytical reviews of the NSC of Narcology of the Ministry of Health of the Russian Federation, the number of patients with alcohol dependence syndrome (alcoholism), including alcoholic psychoses, registered by narcological institutions in the period 2015-2019 was 1,631 per 100,000 population in the Republic of Sakha (Yakutia) (RF-990 per 100,000 population) [1]. During the same time, the Arctic zone of the Republic experienced similar indicators - 2,237 per 100,000 population.

In the Arctic zone of the RS (Ya), high rates of homicide deaths persist. The differences in indicators reach 5.5 times with the Russian Federation and 2 times with the RS (I) as a whole.

Conclusion. High rates of mortality from external causes and infant mortality in the Arctic zone indicate an unfavorable socio-economic situation in the region. A significant increase in mortality rates from accidental alcohol poisoning in the Arctic zone of the Republic requires stricter control over the quality of alcoholic beverages sold.

Only the close attention of the state can affect the development of the Arctic as a whole, including the development of the healthcare system, education, agriculture, culture and transport infrastructure. The development and implementation of regional research programs in the field of public health, ensuring the availability and quality of medical services, the construction of cultural and wellness centers, the promotion of a healthy lifestyle, increasing the employment of the local population at the objects of industrial development of the Arctic, the preservation of traditional crafts through the development of reindeer husbandry, fish farming, etc. can improve the demographic situation and the quality of life in the Arctic.

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Окончание табл. 3

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Even-Bytantaysky National district	107.6	0	143.0	35.5	105.8	78.4
The whole Arctic zone of the RS (Ya)	59.4	52.4	51.6	34.6	35.9	46.8
The whole Republic of Sakha (Yakutia)	34.7	30.2	27.7	23.9	22.9	27.9
Russian Federation (whole)	17.0	16.0	14.0	12.0	12.0	14.2
Assault (X85-Y09)						
Abyysky district	48.7	73.6	49.5	25.0	50.5	49.5
Allaikhovsky district	0	37.0	36.8	73.7	37.0	36.9
Anabarsky district	29.3	0	28.3	0	27.6	17
Bulunsky district	23.9	0	23.9	24	47.5	23.9
Verkhnekolymsky district	46.7	47	47.9	0	24.8	33.3
Verkhoyansky district	52.4	52.7	17.6	17.8	18.0	31.7
Zhigansky Evenki National district	47.0	47.1	47.3	23.8	48.3	42.7
Momsky district	0	72.8	48.9	0	0	24.3
Nizhnekolymsky district	45.4	0	46.2	0	23.4	23
Oleneksky Evenki National district	75.5	50.1	74.3	97.3	71.5	73.7
Srednekolymsky district	0	39.9	13.3	0	27.1	16.1
Ust-Yansky district	13.8	55.4	56	28.4	28.5	36.4
Even-Bytantaysky National district	0	71.9	71.5	35.5	0	35.8
The whole Arctic zone of the RS (Ya)	29.4	42.1	43.2	25.0	31.1	34.2
The whole Republic of Sakha (Yakutia)	20.7	20.1	18.2	14.3	13.4	17.3
Russian Federation (whole)	8.0	7.0	6.0	5.0	5.0	6.2

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THE STATE OF GENERAL AND LOCAL IMMUNITY IN CHILDREN OF THE MURMANSK REGION

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The aim of the work is to analyze the changes in the characteristics of general and local immune responses in children of different age groups. It has been established that in all age groups there is a high prevalence of insufficiency of local and general immune defense, manifested in a decrease in the activity of phagocytosis, the sorption capacity of the epithelium, an increase in CEC levels and a decrease in the amount of sIgA. In all groups, increased levels of pathogenic and conditionally pathogenic microflora are observed.

Keywords: adaptation, children, local immunity, immunodeficiency.

Introduction. Extreme climatic conditions of the Far North (sudden pressure change, photoperiod disturbances, low temperatures, tense ion-magnetic environment) have a negative impact on the mechanisms of immunity. Children are especially sensitive to environmental conditions. A frequent manifestation of a decrease in immune resources is an increase in the level of activated T-cells in the blood and a decrease or complete absence of inactivated, reserve T-cells. Signs such as eosinophilia and increased immunoglobulin levels are often present, which is associated with a high risk of allergy. These imbalances coincide with the high incidence of infectious diseases and parasitic infections among the children of the North [3,5]. Their formation takes place against the background of a high level of IgA deficiency and an increased content of circulating lymphocytes. In the north, neutopenias associated with the migration of neutrophils into tissues, due to tissue hypoxia, or for other reasons, are common in humans. A decrease in neutrophils can be considered a sign of tension in the mechanisms of maintaining the constancy of the internal environment [1,2]. Children living in the northern regions have a slower pace of immunity formation. In extreme conditions of high latitudes, most of the body's protective reserve is spent on combating adverse conditions and maintaining homeostasis, which significantly slows down the age-related development of the immune system in children [3,5,10]. A detailed consideration of this problem will expand knowledge about age development in the north. Observation of tendencies in the processes of adaptation of the body to adverse climatic conditions is important for diagnosing and preventing the development of immunodeficiency conditions among residents of the north.

Materials and methods. A survey of 125 children aged 3 to 16 living in Lovozero, Murmansk region, was carried out. All studies were performed in compliance with the ethical standards set forth in the Declaration of Helsinki and the Directives of the European Community (8/609EC). For the study, a conclusion was received from the ethical committee of the Federal State Budgetary Institution Fitzchia of the Ural Branch of the Russian Academy of Sciences (Protocol No. 1 dated 01/20/2020). In the examined, the determination of hematological and immunological parameters of peripheral blood was carried out; analysis of microflora in throat swabs. The analysis of the survey results was carried out according to the scheme of age periodization of human development, adopted at the International Symposium (1965), in three age groups: 3-7 years old - the period of the first childhood; 8-12 years - the period of the second childhood; 13-16 years old - adolescence. Blood smears were fixed with a solution of eosin-methylene blue according to May-Grunwald, and stained according to the Romanovsky-Giemsa method. In smears stained according to Romanovsky-Giemsa, the phagocytic activity of neutrophils was determined, counting up to one hundred cells at a magnification of 10 × 100. In smears from the pharyngeal tonsils stained by Gram, a study of the cellular composition and microflora was carried out, with the definition of Str.viridans, Bac.fusiformis, C.pyogenes, Streptococcus pneumoniae, Candida, Staphylococcus aureus and yeast-like fungi. To determine the activity of the mucosal epithelium, the sorption capacity of epitheliocytes in relation to microflora was studied on the basis of the average number of microbial bodies per cell.

When determining the deficiency of neutrophilic granulocytes (neutropenia) and their elevated values (neutrophilia), the values in the range were considered normal - from 2.17 to 5.53 × 109 cells / l for the younger group, from 2.8 to 5.07 53 × 109 cells / l for the middle one, from 2.79 to 4.9 × 109 cells / l for the older one. When determining elevated (monocytosis) and decreased values of monocytes (monocytopenia), the following normal values were used - from 0.17 to 0.85 × 109 cells / l for the youngest, from 0.15 to 0.73 × 109 cells / l for the middle one, from 0 ,14 to 0.69 × 109 cells / l for the older one. Increased (lymphocytosis) and decreased (lymphopenia) content of lymphocytes was determined according to the norm - from 2.21 to 5.1 × 109 cells / l for the younger group, from 1.74 to 3.92 × 109 cells / l for the middle group, from 1, 52 to 3.45 × 109 cells / l for the older one. The content of eosinophils was considered elevated (eosinophilia) with values exceeding the limits from 0.04 to 0.60 × 109 cells / l in the younger group, from 0.04 to 0.51 × 109 cells / l in the middle group, from 0.03 to 0.41 ×109 cells/l in the older group [6].

When determining conditionally pathogenic microflora (Streptococcus viridans, Corynebacteria pyogenes, Bacillus phusiformis), the content of < 2 lg 10*/g of microorganisms in the smear was considered the norm.

Statistical processing was carried out using the program "Statistica". Since

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the values of the variables in this paper do not obey the laws of normal distribution, the data are presented in the form of medians with 25 and 75 quartiles. The significance of the differences was determined using the nonparametric statistical Mann-Whitney U-test. The critical significance level is p= 0.05.

Results and discussions. It was established that neutropenia is often recorded in children in all studied age groups (respectively, in the younger - 50%, in the middle - 65%, and in the older age group - 49%), significant differences in the level of neutropenia by age were not established. The low content of neutrophilic granulocytes in the peripheral blood is associated with a high incidence of deficiency of mature segmented nuclei. Against this background, a shift to the left is recorded with an increase in the level of stab neutrophils in the peripheral blood (Table 1). Neutropenia is significantly common among residents of the northern regions and is often observed in the early stages of the development of ARVI [1]. Neutrophilia is 2 times more likely to be detected in young children - in 14% of those examined and 7% in children aged 8-12 years and adolescents. Neutrophilic leukocytosis with a shift to the left is probably associated with the need to replenish the circulating pool by activating the release of cells from the depot. Starting from the age of 8, increased levels of monocytes, lymphocytes and eosinophils in peripheral blood are more often recorded in children. In younger children, lymphopenia is more often detected - in 21% of children, in older age groups its frequency remains at the same level (respectively, in children 8-12 years old - in 9% and children 13-16 years old, also in 9% of cases) (Table 1).

Assessing the content of lymphocyte phenotypes, it was found that most of the indicators are within the physiological norm. In children aged 13-16 years, the average content of CD4+ lymphocytes is below the norm and amounted to 0.32 (0.21-0.52) × 109 cells / l (Table 2), which may be associated with the presence of chronic inflammatory processes and a decrease in cellular immune defense in adolescence [4,7]. The average content of CD16+ is above the norm in all age groups (in the younger - 0.53 (0.31-1.26), in the middle - 0.69 (0.51-0.92), in the older - 0.57 (0 ,4-0.97)×109 cells/l), which is often a sign of the initial stage of infectious diseases [7,8]. The average level of CD23+ in children of younger and middle age groups is higher compared to the examined older children (respectively 0.93(0.25-1.02), 0.62(0.45-0.74) and 0.43 (0.3-0.68)×109 cells/l). This is probably due to a greater propensity for allergic reactions at a younger age [4,8]. For children of all age groups, a decrease in the level of activation of immunocompetent cells is characteristic. The average content of CD71+ is below normal in all age groups (in the younger - 0.4(0.16-0.6), in the middle - 0.35(0.27-0.64), in the older - 0.43(0. .27-0.7) × 109 cells / l). The content of CD25+ lymphocytes is also quite low in all examined groups (in the younger group - (0.47 (0.2-0.81)) in the middle group - (0.66 (0.46-0.98)), in the older group - (0.66 (0.46-0.98) × 109 cells / l), because the expression of this phenotype is initiated by an increase in CD71 [4,7].

Table1

Peripheral blood parameters in different age groups

	Age group		
	Junior age group (3-7 years old)	Middle age group (8-12 years old)	Senior age group (13-16 years old)
Neutrophils, ×10⁹ cells	2.35(1.53-2.98)	2.50(1.82-3.22)	2.87(2.02-4.01)
Neutrophilosis, %	14±2.66	7±0.48	5±0.52
Neutropenia, %	50±0.25	65±1.46	49±1.62
Stab neutrophils, above normal ×10⁹ cells	0.25(0.15-0.4)	0.25(0.13-0.38)	0.30(0.2-0.45)
stab neutrophils below normal, %	21±3.26	25±0.91	26±1.18
Segmented neutrophils, ×10⁹ cells	1.96(1.36-2.55)	2.24(1.57-2.94)	2.57(1.84-3.62)
segmented neutrophils above normal, %	14±2.66	5±0.40	2±0.33
segmented neutrophils below normal, %	64±5.68	69±1.5	53±1.68
Monocytes, ×10⁹ cells	0.42(0.3-0.48)	0.35(0.24-0.51)	0.45(0.17-0.54)
Monocytosis, %	-	9±0.54	12±0.80
Monocytopenia, %	-	11±0.6	5±0.52
Lymphocytes, ×10⁹ cells	3.04(2.5-3.47)	2.69(2.05-3.28)	2.48(1.87-3.3)
Lymphocytosis, %	-	13±0.65	21±1.06
Lymphopenia, %	21±3.26	9±0.54	9±0.69
Eosinophils, ×10⁹ cells	0.14(0.7-0.2)	0.09(0.06-0.27)	0.10(0.05-0.19)
Eosinophilia, %	-	2±0.26	2±0.32

Table2

Ratio of lymphocyte phenotypes in different age groups, Me(Q1-Q3)

Lymphocyte phenotypes, ×10⁹ kl/l	Me(Q1-Q3)			Validity of differences
	Age group			
	Junior age group (3-7 years old)	Middle age group (8-12 years old)	Senior age group (13-16 years old)	
CD3	0.69(0.3-1.86)	0.85(0.55-1.06)	0.7(0.44- 0.98)	
CD4	0.47(0.27-0.51)	0.42(0.4-0.61)	0.32(0.21-0.52)	
CD8	0.35(0.33-0.53)	0.38(0.25-0.57)	0.39(0.25-0.6)	
CD16	0.53(0.31-1.26)	0.69(0.51-0.92)	0.57(0.4-0.97)	**p_{2-3}= 0.021**
CD23	0.93(0.25-1.02)	0.62(0.45-0.74)	0.43(0.3-0.68)	**p_{2-3}= 0.038**
CD10	0.36(0.24-0.66)	0.38(0.32-0.54)	0.30(0.27-0.68)	**p_{2-3}= 0.038**
CD25	0.47 (0.2-0.81)	0.66(0.46-0.98)	0.66(0.46-0.98)	**p_{2-3}=0.008**
HLADR	0.66(0.31-93)	0.71(0.42-0.99)	0.59(0.37-0.74)	**p_{2-3}= 0.021**
CD71	0.4(0.16-0.6)	0.35(0.27-0.64)	0.43(0.27-0.7)	
CD95	0.6(0.36-1.14)	0.65(0.53-0.94)	0.61(0.44-0.96)	

Table3

Indicators of local immunity in throat swabs, Me (Q1-Q3)

Показатель	Age group			Validity of differences
	Junior age group (3-7 years old)	Middle age group (8-12 years old)	Senior age group (13-16 years old)	
% active phagocytes, %	60(57-68)	57.5(52-62)	55(51-57)	**p_{1-3}=0.004**
Frequency of phagocytic defense deficiency, %	86±6.6	100±1.81	98±2.29	
Sorption activity of the epithelium, microbes /cell	50(50-100)	50(10-50)	10(10-50)	
Frequency of epithelial sorption activity deficit, microbes /cell	71±5.99	80±1.62	91±2.21	
CIC, g/l	2.5(2-2.5)	2(1.5-2.5)	2.5(1.5-3)	
Frequency of registration of elevated CICs, %	64±5.68	42±1.17	50±1.7	
sIgA, g/l	0.8(0.8-1)	0.8(0.6-0.8)	0.6(0.6-0.8)	**p_{1-2}=0.048** **p_{1-3}=0.003**
Frequency of sIgA deficiency, %	100±7.11	100±1.69	100±2.15	

Table4

Indicators of microflora in throat swabs, lg 10 * / g

	Age group			Validity of differences
	Junior age group (3-7 years old)	Middle age group (8-12 years old)	Senior age group (13-16 years old)	
Str. Viridans	4 (3-5)	3(3-5)	3(3-5)	
Increased content Str. Viridans, %	78±6.23	87±1.69	86±2.15	
Corynebact pyogenes	3(2-3)	2(2-3)	3(2-3)	
Increased content *Corynebact pyogenes,* %	50±5.02	13±0.65	25±1.16	
Bacillus phusiformis	2.5(1-3)	3(2-4)	2(2-3)	p_{1-2}=0.014
Increased content *Bacillus phusiformis*, %	14±2.66	36±1.08	19±1.01	
Staphylococcus aureus, %	-	24±0.89	7±0.61	
Str. Pneumoniae, %	14±2.66	11±0.6	25±1.16	
Candida, %	-	13±0.65	2±0.33	
Yeast-like fungi, %	14±2.66	2±0.25	2±0.33	

Deficiencies in sIgA, phagocytic defense, and sorption capacity of the epithelium, which are detected with equal frequency in all studied groups, testify to stress in the immune system (Table 3).

Concentrations of circulating immune complexes (CIC) exceeding the norm (more than 2 g/l) are recorded in children of the younger age group more often (in 64% of the examined), in children 8-12 years old and 13-16 years old, this figure is lower and amount to 42%, respectively. and 50%. High concentrations of CEC may indicate an inflammatory response to the infectious process and insufficiency of phagocytosis, which is evidence of a reduction in the reserve capacity of immune regulation (Table 3).

An increase in the concentration of opportunistic microflora can be a provoking factor in the development of an inflammatory reaction against the background of a deficiency in the sorption activity of the epithelium, phagocytosis, and high levels of CEC.

The frequency of registration of elevated levels of pathogenic microflora increases in children older than 8 years. In children of the younger age group, no Staphylococcus aureus and Candida were found in throat swabs, but yeast-like fungi were detected 7 times more often (36%) compared with the results in other age groups (Table 4).

Thus, it was found that children of all age groups are characterized by a decrease in the reserve capacity of local immune defense, which manifests itself in a rather high frequency of registration of a deficiency in the sorption activity of the epithelium of the mucous membrane of the throat, phagocytic reactions and sIgA against the background of increased concentrations of CEC. The immune status of children is characterized by an increase in the content of neutrophils with age, mainly due to an increase in the circulation of mature segmented cells. At the same time, there were no significant differences in the level of neutropenia in the studied groups. Starting from the age of 8, eosinophilia is more often recorded, which is probably associated with a higher level of infection with pathogenic microflora. Decreased CD3 observed in all ages indicates complicated respiratory and other infections. During the period of puberty (starting from the age of 13), when the lymphoid organs undergo a decrease, the predominance of humoral immunity over cellular immunity begins, the level of CD4 decreases, which can also be a sign of a secondary immunodeficiency state.

Conclusion. The study found that children of all age groups have imbalances in local immunity. Starting from the age of 8, eosinophilia is more often recorded, which is probably associated with a higher level of infection with pathogenic (St. aureus, Klebsiella pneumoniae) and opportunistic microflora (Candida).

Determination of the content of lymphocytes in the blood showed that in the older group, the largest percentage of the examined have a reduced number of T-helpers and mature T-lymphocytes, compared with younger children.

Increased values of cytotoxic lymphocytes are also more often recorded in the older group. This increase can be associated with both allergic reactions and infectious processes in the body. An increase in the number of natural killers is more often detected in the middle group, which may be associated with long-term chronic inflammatory diseases.

In the system of local immunity, there is a tendency to reduce the content of the CEC; an increase in the infection of children with opportunistic and pathogenic microorganisms was established, which negatively affects the level of phagocytosis and the content of secretory immunoglobulin A.

Thus, in children living in the Far North, the age-related formation of the immune system is inhibited against the background of a deficiency of phagocytic protection, the synthesis of local antibodies, and infection with pathogenic microflora. One of the reasons for the development of phagocytic defense deficiency may be a high level of neutropenia, recorded in all age groups at a fairly high level, and high concentrations of circulating immune complexes. The insufficiency of local defense reactions initiating all other stages of the immune response is associated with the fact that by older age there is no normal level of immune defense.

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CERVICAL CANCER IN THE STATE ENTITIES OF THE RUSSIAN ARCTIC ZONE: A COMPARATIVE ANALYSIS OF INCIDENCE AND MORTALITY IN THE PERIOD FROM 2016 TO 2020

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On the basis of age-standardized and calculated per 100,000 population cervical cancer (CC) incidence and mortality rates, an analysis of the prevailing over 5 years, from 2016 to 2020, is presented. CC data analysis was conducted among nine state entities of Russia, whose territories are wholly or partially located in the Arctic. The calculations carried out using the Friedman's and Wilcoxon's tests, as well as the T-test showed that in these territories there is an unfavorable situation in relation to CC. In most state entities, the CC incidence and its dynamics, as well as the dynamics of CC mortality over five years from 2016 to 2020 show worse results than in Russia as a whole. The most vulnerable to cervical cancer at the present time is the population of Krasnoyarski Krai, Nenetski and Chukotski Autonomous Okrugs. Therefore, these territories especially require the use of new and strengthening of existing measures aimed at the CC prevention, early detection and improvement of treatment.

Keywords: health disparities, human papillomavirus, ethnic groups, indigenous population, North.

Cervical cancer (CC) has still been remaining one of the most common cancer sites among malignant neoplasms (MN) in spite of a screening and an immunization against the human papillomavirus (HPV), as well as the development and implementation of new treatment ways in the health care system. The latest available data reflecting the global cancer statistics - 2020 from the International Agency for Research on Cancer (IARC) of the World Health Organization [1] showed that CC has occupied the top positions in terms of the incidence and mortality amongst all cancer sites. According to its age-standardized incidence rates (ASIRs) CC has ranked, in descending order, to the 5th place in the world including both sexes (13.3 cases per 100,000 populations) and following breast, prostate, lung and colorectal cancers. In the case of women CC has ranked the 4th in the world following breast cancer, colorectal cancer and lung cancer. In terms of the age-standardized mortality rate (ASMR) CC has ranked the 7th (7.3 cases per 100,000 population) worldwide including both sexes following lung, breast, colorectal, liver, stomach, and prostate cancers; and the 3rd place in the case of women following breast and lung cancer [2].

According to the IARC too in Russia in 2020 CC was almost in the same positions – the 6th place (14.1 cases per 100,000 populations) in ASIR including both sexes following breast cancer, prostate cancer, colorectal cancer, lung, and corpus uteri cancer, and the 4th in women following breast cancer, cancer of the corpus uteri and colorectal cancer. In ASMR the CC ranked to 7th place (6.1 cases per 100,000 populations) including both sexes following lung, breast, colorectal, prostate, stomach, and pancreatic cancers, and tied for 3rd place with lung cancer in women following breast cancer and colorectal cancer [2].

The CC incidence (CCI) in Russia in 2020 continues to significantly exceed the level set by the WHO in its global strategy to accelerate the elimination of CC as a public health problem for the period 2020-2030 with the aim to achieve and maintain the CCI at a level of less than 4 cases per 100,000 thousand women per year [3].

Russia is a country with a large population - according to the World Bank in 2020 its population was 144.104 million people. Such a population allowed Russia to take the 9th place among all countries of the world in order to theirs citizens' number [4]. Among the state territorial entities of the upper level (SEs) of the Russian Federation there is a significant variability in population's density, number, ethnic groups, income, educational level and other demographic and social indicators [5]. Therefore, CC disparities among the population in different territories are expected and, moreover, confirmed in studies [6].

Studies on health disparities in different territories make possible to show the residence area of the population, which are in first needs to be organized activities to prevent, early detect and increase effectiveness for certain diseases treatment.

In the Investment Portal of the Arctic Zone of the Russian Federation (AZRF) of the Ministry for the Development of the Russian Far East and Arctic there is the statement saying the AZRF forms a fifth of the federal budget revenues [7]. Also the Document entitled "Foundations of the Russian Federation State Policy in the Arctic for the Period up to 2035", approved by Decree of the President of the Russian Federation No.164 dated March 5, 2020, has the statement saying the prosperity and well-being of people living in the Arctic is one of the main interests of Russia [8].

The current study is devoted to the CCI and CCM status evaluation, which has developed over a period of five years, from 2016 to 2020, among the SEs of the Russian Federation, the settlements of which are fully or partially attributed to the Russian Arctic such as the Arkhangelskaya Oblast (AO), the Murmanskaya Oblast (MO), the republics Karelia (RKa), Komi (RKo) and Sakha (Yakutia) (RSYa), the Krasnoyarski Krai (KK), the Chukotski Autonomous Okrug (ChAO), the Yamalo-Nenetski Autonomous Okrug (YaNAO) and the Nenetski Autonomous Okrug (NAO). The period 2016 – 2020 was chosen because of these 5-years data are available as close as possible to the

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time of this study. Difference analyses of the CCI and CCM as well as changes in the CCI and CCM rates in 2020 compare to 2016 among the SEs and Russia as whole with spotting of SEs with the most CC burden were made.

Materials and methods. For a comparative analysis of the CCI and the CCM, the age-standardized CCI and CCM rates per 100,000 populations (CC ASIRs and CC ASMRs, respectively) were used. These statistical indicators are presented in the books of the Moscow Research Oncological Institute named after P.A.Herzen - a branch of the Federal State Budgetary Institution "National Medical Research Center of Radiology" of the Ministry of Health of Russia, which were published from 2017 to 2022 on the Website for medical and pharmaceutical workers "ONCOLOGY.ru" [9]. In the study the indicators of all nine SEs the settlements of which are fully or partially attributed to the Russian Arctic such as the AO, the ChAO, the YaNAO, the NAO, the MO, the RK, the RKo, the KK, the RSYa as well as all-Russian indicators were included.

Retrospective time period is from 2016 to 2020. Cancer site is cervix; code is C53, according to the international classification of diseases (ICD, International Classification of Disease, ICD, 10th revision, version 2010).

Because the preliminary used the Kolmogorov-Smirnov's test showed that the distribution of mean values of the annual CC ASIRs and ASMRs in all nine selected SEs and in Russia as a whole in the mentioned above time period does not correspond to the normal one ($0.999 \geq p \geq 0.481$ and $1.000 \geq p \geq 0.606$, respectively), for finding differences in the CCI and the CCM across multiple indicators and between them Friedman's two-way rank test and Wilcoxon's signed rank test, respectively, were used.

Since included in the study the CC ASIRs and ASMRs in each year are presented in the above-mentioned books as an mean with its error then to find CC incidence and mortality differences between 2020 and 2016, T –test was used.

Differences have been considered significant at $p<0.05$. If $0.05 \leq p \leq 0.1$ differences have been considered to have a tendency to exist.

Results. The annual CC ASIRs and ASMRs in the period 2016-2020 in all nine SEs of the Russian Arctic and in Russia as a whole are shown in Table 1.

Friedman's test revealed the heterogeneity of the annual CC ASIRs in 2016-2020 in the total observation group in which all nine SEs and Russia as a whole were included ($p=0.010$). The ranking of the annual CC ASIRs of all nine SEs and Russia as a whole in this time period is shown in Figure 1. By continuing to carry out Friedman's test and by excluding one by one indicators of the SEs with minimum ranks from the group, it was found that the maximum CCI, estimated by the annual CC ASIRs in this time period were observed in four SEs - in the NAO, the RSYa, the KK and the AO. In these SEs we had seen the homogeneity of the CC ASIRs ($p=0.323$). The Wilcoxon's test, which is presented in Table 2, showed that the CCI in the NAO, which was assigned the maximum rank in accordance with Friedman's test, tended to exceed that one of three SEs - the MO, the ChAO and the YaNAO; the CCI in the RSYa, which take the 2nd place according to Friedman's test, was significantly higher than ones in four SEs - the MO, the RKa, the ChAO and the YaNAO; the CCI in the KK (the 3rd place) was higher than that in three SEs - significantly higher as compared with in the MO and had a tendency to be higher as compared with one in the ChAO and in the YaNAO; the CCI in the AO (the 4th place) were as close as possible to the CCI in the KK and the RSYa (please, see p values) and exceeded those of two SEs - significantly as opposed to in the MO and had a tendency to exceed that in the ChAO.

Also, using the Wilcoxon's test, it was revealed that the CCI in 2016-2020 in most SEs of the Russian Arctic (55.5% or in five out of nine), such as the AO, the MO, the KK, the RSYa and the NAO, significantly exceeded or had a tendency to exceed the all-Russian level. Only in the ChAO the CCI was lower than the all-Russian one.

In 2020 compared to 2016 estimated by its ASIRs the CCI did not increase in any SEs. On the contrary, in the RKa, the RKo, the RSYa and YaNAO, as well as in Russia as a whole, the CCI has significantly decreased (in all listed cases, $p<0.05$). However, again, in most SEs of the Russian Arctic (55.5% or five out of nine SEs), such as the AO, the MO, the KK, the NAO and the ChAO, in 2020 compared to 2016, neither a CCI significant decrease nor tendency toward it were observed.

Friedman's test of the CC ASMRs in the general observation group in the period 2016-2020 revealed only a tendency to heterogeneity ($p=0.070$). The ranking results can also be seen in Figure 1. As well as in the case of the CCI we continued carry out Friedman's test and excluded the SEs with minimum ranks from the general observation group and it was found that the CC ASMRs in most SEs, with the exception of the YaNAO and Russia as a whole, the CCM in this period of time did not differ in accordance to our chosen significance for p.

The presented in Table 2 results of Wilcoxon's test showed that the CC ASMRs in 2016-2020 in the ChAO assigned the maximum average rank in accordance to Friedman's analysis had a tendency to exceed those ones in the AO and significantly exceeded in the RSYa. Comparing the CC ASMRs in the followed the ChAO the NAO with the ranks of other SEs and Russia as a whole did not reveal either the required significance or a tendency towards differences. However, the CC ASMRs in the NAO had a minimal probability of having differences with the ChAO's and the KK's CC ASMRs (please, see p values). The CC ASMRs in the KK, which shared the second place with the NAO in terms of the average rank, had a tendency to exceed those ones in the AO and significantly exceeded those in the RKa. The CC ASMRs in the RKo, the average rank of which was in a third place (according to Friedman's test), had a tendency to exceed those in the AO (which took 7th place), and at the same time, it's the CC ASMRs were closer to those in the MO (4th place) and the RSYa (5th place) than to the ranks of the ChAO, the NAO and the KK (please see p values). The CC ASMRs in the remaining SEs such as the MO, the RSYa, the RKa and the AO did not have significant pairwise differences with each other when calculating the Wilcoxon's test. Therefore, finally, we believe that the maximum CCM estimated by the CC ASMRs in 2016-2020 were noted in the ChAO, the NAO and the KK. The excess over the all-Russian CCM was noted in three SEs of the Russian Arctic – the ChAO, the KK, and in the RKo (Table 2).

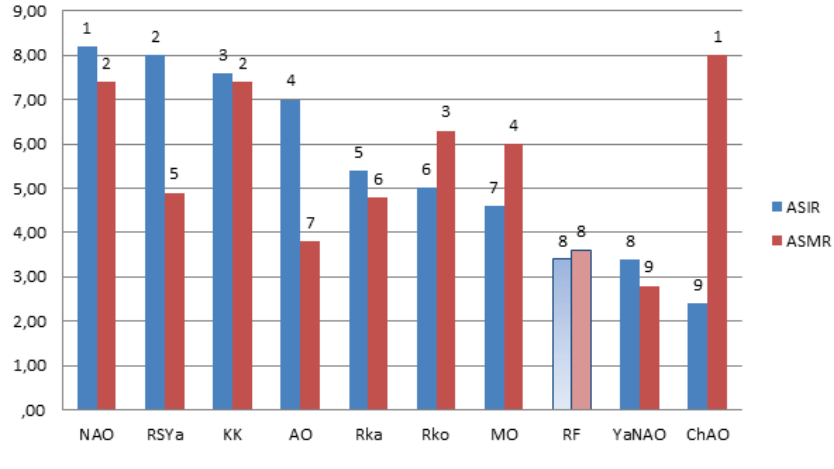
As well as the CCI the CCM, estimated by CC ASMRs, in 2020 in contrast with 2016 did not increase in any of SEs. The CCM in Russia as a whole, in the MO and the RSYa significantly decreased ($p<0.05$), while CCM in the AO had a tendency to decrease ($0.05 \leq p \leq 0.1$). Despite the fact that in this time period in the NAO the CC ASMR decreased by more than 3 times, the difference did not reach either the required significance or a trend towards its presence, as in other SEs, such as the RKa, the RKo, the KK, the ChAO and the YaNAO. That is, in six out of nine SEs (66%), or, if we exclude the NAO from the calculations (because as mentioned above p did not reach the required significance or a trend towards its pres-

Table1

Annual values of CC ASIRs and ASMRs in the SEs of AZRF and in RF in 2016-2020

SE	CC ASIR M (95% CI)				
	2016	2017	2018	2019	2020
RF	15.45 (15.33-15.57)	15.76 (15.64-15.88)	15.80 (15.68-15.92)	15.38 (15.26-15.50)	13.67 (13.55-13.79)
AO	18.32 (16.76-19.88)	17.78 (16.27-19.29)	23.69 (21.91-25.47)	28.85 (26.77-30.93)	15.16 (13.76-16.56)
MO	16.26 (14.63-17.89)	17.73 (15.79-19.67)	20.76 (18.90-22.62)	17.00 (15.26-18.74)	13.57 (12.03-15.11)
RKa	22.58 (20.16-25.00)	19.94 (17.75-22.13)	20.06 (17.92-22.20)	14.64 (12.92-16.36)	13.26 (11.46-15.06)
RKo	17.13 (15.48-18.78)	23.50 (21.54-25.46)	16.77 (15.05-18.49)	17.75 (16.06-19.44)	12.10 (10.68-13.52)
KK	18.90 (17.95-19.85)	21.06 (20.07-22.05)	21.49 (20.50-22.48)	21.03 (20.03-22.03)	19.71 (18.75-20.67)
ChAO	21.30 (13.98-28.62)	13.11 (7.43-18.79)	9.01 (4.02-14.00)	11.28 (5.87-16.69)	11.76 (4.84-18.68)
RSYa	22.85 (20.99-24.71)	20.20 (18.45-21.95)	21.57 (19.76-23.38)	18.38 (16.70-20.06)	16.43 (14.86-18.00)
YaNAO	20.39 (17.90-22.88)	15.96 (13.47-18.45)	12.53 (10.67-14.39)	12.69 (10.86-14.52)	12.21 (10.33-14.09)
NAO	8.01 (2.39-13.63)	29.37 (19.11-39.63)	31.38 (22.15-40.61)	32.50 (22.53-42.47)	25.15(13.42-36.88)
SE	CC ASMR M (95% CI)				
	2016	2017	2018	2019	2020
RF	5.26 (5.19-5.33)	5.18 (5.11-5.25)	5.07 (5.00-5.14)	5.01 (4.94-5.08)	4.84 (4.77-4.91)
AO	7.22 (6.28-8.16)	4.05 (3.39-4.71)	3.81 (3.14-4.48)	5.08 (4.27-5.89)	4.94 (4.20-5.68)
MO	6.83 (5.76-7.90)	7.09 (5.98-8.20)	5.21 (4.34-6.08)	7.35 (6.22-8.48)	3.84 (3.00-4.68)
RKa	5.06 (4.04-6.08)	5.60 (4.56-6.64)	5.56 (4.49-6.63)	4.90 (3.98-5.82)	5.60 (4.56-6.64)
RKo	6.84 (5.84-7.84)	4.89 (4.04-5.74)	5.59 (4.71-6.47)	6.01 (5.05-6.97)	5.35 (4.48-6.22)
KK	6.61 (6.07-7.15)	6.80 (6.25-7.35)	6.40 (5.87-6.93)	6.21 (5.69-6.73)	6.06 (5.53-6.59)
ChAO	19.07 (11.52-26.62)	19.07 (11.52-26.62)	4.78 (1.51-8.05)	5.51 (1.77-9.25)	6.07 (1.95-10.19)
RSYa	6.84 (5.81-7.87)	6.84 (5.81-7.87)	4.61 (3.80-5.42)	5.49 (4.60-6.38)	4.15 (3.38-4.92)
YaNAO	5.64 (4.31-6.97)	4.13 (3.03-5.23)	4.43 (2.94-5.92)	4.03 (2.67-5.39)	5.22 (4.02-6.42)
NAO	0.00 (0.00-0.00)	18.98 (10.37-27.59)	6.53 (2.07-10.99)	9.53 (4.20-14.86)	5.39 (1.72-9.06)

Note: M – mean value, CI - confidence interval. Please, see the explanation of abbreviations in Tables 1-3 and Fig.1 in the text.



Average ranks of the annual CC ASIRs and ASMRs in the SEs of AZRF in 2016-2020

ence), in five out of nine SEs (55.5%) the CCM has not changed, despite the fact that mortality in Russia as a whole has decreased.

Thus, the maximum CCI, estimated by the ASIRs, in the period from 2016 to 2020 among the SEs, the settlements of which belong to the Russian Arctic, was observed in the NAO, the RSYa, the KK and the AO. The excess over the all-Russian level of CCI was noted in the AO, the MO, the KK, the RSYa and the NAO. Despite the decrease in the all-Russian CCI in 2020 as opposed to 2016, neither CCI significant decrease nor a trend towards its presence was recorded in the AO, the MO, the KK, the NAO and the ChAO. The maximum CCM estimated

Table2

The p-values for pairwise differences in the ranks of the CC ASIRs/ASMRs between the SEs of AZRF and Russia as a whole in 2016-2020

	AO	MO	RKa	RKo	KK	ChAO	RSYa	YaNAO	NAO
RF	0.043**/ 0.893	0.080*/ 0.138	0.225/ 0.225	0.138/ 0.080*	0.043**/ 0.043**	0.345/ 0.080*	0.043**/ 0.345	0.686/ 0.223	0.080*/ 0.345
AO	N/A	0.043*/ 0.225	0.686/ 0.686	0.220/ 0.080*	0.893/ 0.080*	0.080*/ 0.080*	0.893/ 0.345	0.138/ 0.686	0.345/ 0.345
MO	0.043**/ 0.225	N/A	0.893/ 0.345	0.893/ 0.893	0.043**/ 0.686	0.225/ 0.225	0.043**/ 0.345	0.225/ 0.225	0.080*/ 0.345
RKa	0.686/ 0.686	0.893/ 0.345	N/A	0.686/ 0.500	0.225/ 0.043**	0.043**/ 0.225	0.043**/ 0.686	0.043**/ 0.138	0.345/ 0.500
RKo	0.220/ 0.080*	0.893/ 0.893	0.686/ 0.500	N/A	0.138/ 0.138	0.138/ 0.345	0.138/ 0.715	0.225/ 0.043**	0.138/ 0.345
KK	0.893/ 0.080*	0.043**/ 0.686	0.225/ 0.043**	0.138/ 0.138	N/A	0.078*/ 0.500	0.686/ 0.225	0.080*/ 0.043**	0.345/ 0.686
ChAO	0.080*/ 0.080*	0.225/ 0.225	0.043**/ 0.225	0.138/ 0.345	0.078*/ 0.500	N/A	0.043**/ 0.043**	0.138/ 0.043**	0.080*/ 0.893
RSYa	0.893/ 0.345	0.043**/ 0.345	0.043**/ 0.686	0.138/ 0.715	0.686/ 0.225	0.043*/ 0.043**	N/A	0.043*/ 0.138	0.500/ 0.345
YaNAO	0.138/ 0.686	0.225/ 0.225	0.043**/ 0.138	0.225/ 0.043**	0.080*/ 0.043**	0.138/ 0.043**	0.043**/ 0.138	N/A	0.080*/ 0.345
HAO	0.345/ 0.345	0.080*/ 0.345	0.345/ 0.500	0.138/ 0.345	0.345/ 0.686	0.080*/ 0.893	0.500/ 0.345	0.080*/ 0.345	N/A

Note. *- differences have been considered to have a tendency to exist, **- differences have been considered significant, N/A- not applicable.

by CC ASMRs, in the period from 2016 to 2020 was in the ChAO, the NAO and the KK, and their CCM also exceeded the all-Russian one. In the RKa, the RKo, the KK, the ChAO, the YaNAO and the NAO in 2020 as opposed to 2016 the CCM had not changed despite a decreasing the all-Russian one.

In each SE a parameter estimated by the CC ASIRs and ASMRs indicating an unfavorable situation in relation to CC there is. However, it is necessary to identify the most vulnerable SEs, which in first needs to be organized activities to prevent, early detect and increase effectiveness of CC treatment. Therefore, a summary table was compiled (Table 3), in which we present the summarized results of this study. In accordance with the results, the most unfavorable situation in relation to CC in the period 2016-2020 based on the annual CC ASIRs and ASMRs were developed in the KK, the NAO and the ChAO.

This is partially confirmed by a study based on the analysis of CCI in the same SEs group but including a longer time period - from 2011 to 2019 (9 years). An unfavorable situation regarding to CC was revealed in the same territories [10].

Stand to take into consideration that all three SEs such as the KK, the NAO and the ChAO in which the most unfavorable situation in relation to CC was revealed are located in the eastern part of the Arctic zone of Russia. Also, the territories of two of these three SEs – the NAO and the ChAO belong to the Russian Arctic completely and are characterized by ethnic diversity.

Conclusion. Based on the CC ASIRs and ASMRs in 2016-2020 in SEs, the settlements of which are fully or partially assigned to the Russian Arctic, and on all-Russian ones it can be argued that they all have an unfavorable situation with regard to CC. Therefore, in these SEs it is necessary to apply new and strengthen existing activities aimed at prevention, early detection and increasing the effectiveness of treatment. In most SEs the CCI and its changes, as well as the CCM changes, over five years from 2016 to 2020 a worse situation than in all Russia has showed. The most CC burden the populations of the KK, the NAO and the ChAO at the present time have.

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Table3

The sum of the calculated CCI and the CCM indicators ranks in SEs of AZRF in 2016-2020

Indicator	AO	MO	RKa	RKo	KK	ChAO	RSYa	YaNAO	NAO
Max CCI	1				1		1		1
The change in CCI in 2020 compare to 2016			-1	-1			-1	-1	
Max CCM					1	1			1
The change in CCM in 2020 compare to 2016	-0.5	-1					-1		
The sum	**0.5**	**-1**	**-1**	**-1**	**2**	**1**	**-1**	**-1**	**2**

Note. 1 - the presence of the indicator, 0.5 – the tendency towards the presence of the indicator. In the lines "The change in ..." negative values correspond to a decrease in the CCI or CCM.

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DOI 10.25789/YMJ.2022.78.23

УДК 612.123:612.592.1

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A VERIFIED CASE OF THE PRESENCE OF ACTIVE BROWN ADIPOSE TISSUE IN AN INDIGENOUS INHABITANT OF THE ARCTIC REGION OF YAKUTIA

A case of verification of active brown adipose tissue in a 40-year-old patient, a professional hunter resident of the Arctic ulus of Yakutia, is described. Real brown adipose tissue was found in samples of adipose tissue from the paranephral fiber. Adipose tissue samples showed high immunoreactivity to the activity marker of this tissue - mitochondrial protein UCP1.

Keywords: brown adipose tissue, cold, histology, immunohistochemistry, UCP1.

Introduction. Yakutia is one of the largest regions of the Russian Federation with a predominance of extremely low temperatures throughout the year. More than 40% of the territory of our republic is located beyond the Arctic Circle and belongs to the Arctic zone.

The extreme conditions of the Arctic have an impact on the adaptive potential, affect the functional state of the human body and its working capacity, the level of health and the duration of active life.

The exploration and development of the Arctic is one of the priorities of Russia's state policy. The life support and economic potential of the country are essentially determined by the health of the population. Research aimed at ensuring the health of the Arctic population is becoming especially relevant in modern conditions.

The first description of brown adipose tissue dates back to 1551, when Gessner described this tissue in a book on anatomy as "nec pinguitudo nec caro", which means "neither fat nor flesh" [1]. However, as a thermogenic organ necessary for mammalian thermoregulation, it was recognized only less than half a century ago [2]. During the second half of the XX century and the beginning of the XXI, it was believed that it is present only in newborns and disappears after a year [2,3]. Although some indirect data had previously led several authors to assume its presence [1,4-9], and only with the advent of positron emission tomography with 18-fluorodeoxyglucose (PET-FDG), a functional imaging method evaluating areas of increased metabolic activity, began to be used more often in the observation of certain types of cancer, brown adipose tissue was It was found in at least one subgroup of the adult human population [2,10-14]. This discovery aroused great interest among researchers in this field and the hypothesis that the presence or absence of brown adipose tissue may be the cause of such common metabolic diseases as obesity and type 2 diabetes, as well as probably a potential therapeutic target, since excess energy is spent through non-contractile thermogenesis.

However, despite the presence of many indirect signs of activation of brown adipose tissue in adult residents of regions with extremely cold climates, up to now the fact has not been confirmed by histomorphological verification of brown adipose tissue.

In this article we describe a case of a verified fact of the presence of metabolically active brown adipose tissue in an indigenous inhabitant of the Arctic ulus of Yakutia.

Material and methods of research. Histological studies were carried out on the basis of the pathoanatomical Department of t Republican Hospital № 1 of the National Medical Center and the Faculty of Human and Animal Anatomy of the Polytechnic University del Marche (Ancona, Italy). The work was carried out within the framework of international cooperation between the Yakutsk Scientific Center for Complex Medical Problems (Yakutsk) and the Polytechnic University of del Marche (Ancona, Italy).

The patient received samples of adipose tissue from paranephral tissue taken from the area surrounding the renal artery after nephrectomy for urolithiasis.

Patient R., male, 40 years old, height 168 cm, slim build, was born and lives in Srednekolymsky ulus (Arctic zone of Yakutia), professional hunter-cadre officer, nationality Evenk. He spent a significant part of his working time outdoors and was exposed to significant exposure to cold.

Ethics Committee. The study was approved by the local Committee on Biomedical Ethics of the Yakut Scientific Center of Complex Medical Problems(Protocol No. 46 of May 24, 2018).

Histology. The collected samples were fixed by immersion in 4% paraformaldehyde in 0.1 M phosphate buffer (FB), pH 7.4. After thorough washing in FB, the samples were dehydrated in a graduated series of ethanol, purified in xylene and waxed. Serial paraffin sections with a thickness of 3-4 microns were obtained from each sample. The samples were stained with hematoxylin and eosin to assess morphology. All studies were carried

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out on a Nikon Eclipse 800 light microscope (Nikon, Tokyo, Japan).

Immunohistochemistry. Immunoreactivity on the mitochondrial protein UCP1 was studied as minima. The slices were incubated in 3% H2O2 solution (in dH2O; 5 min) to block endogenous peroxidase, then washed in phosphate buffered saline solution (PBS) and incubated in 2% blocking solution (in PBS; 20 min).

Histochemical reactions were performed using a set of Vectastain ABC (Vector Laboratories) and SigmaFast 3,3'-diaminobenzidine (Sigma-Aldrich) as a substrate. Further, the sections were stained with hematoxylin, dehydrated and installed in Eukitt (Fluka, Deisenhofen, Germany). To assess the specificity of antibodies in each case, negative control data were obtained by excluding the primary antibody.

Morphometry. Sections stained with UCP1 were used to count adipocytes (~5000 adipocytes in each sample). The number of adipocytes was calculated using the Lucia Image software (version 4.82, Nikon Instruments, Florence, Italy). The results are presented as a percentage of UCP1-immunoreactive multilocular adipocytes from the total number of counted adipocytes.

Results and discussion. The material presents fragments of paranephral fiber taken from the area surrounding the renal artery. Among white adipocytes with a univacuolic structure and an eccentric nucleus, there are extensive fields of smaller cells with a multivacuolic structure, a central location of the nucleus and pronounced vascularization – brown adipocytes (Fig. 1).

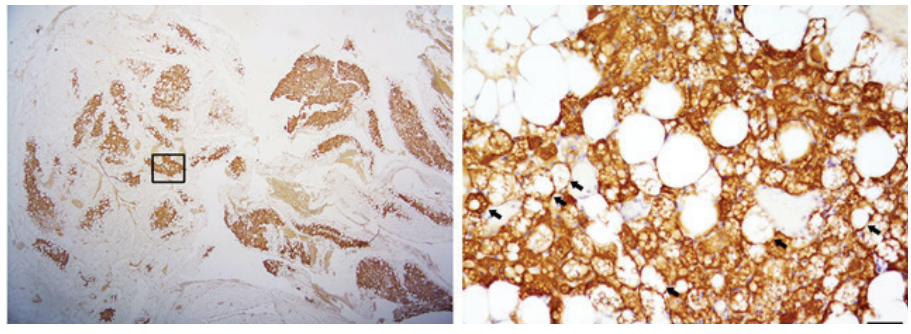
Microscopic examination shows characteristic of brown adipose tissue, compared with white adipose tissue, a typical histological picture of brown adipose tissue was revealed.

Immunohistochemical examination on UCP 1 showed that the percentage of multilocular and paucilocular adipocytes was 54.9% (Fig. 1). All UCP1-positive multilocular adipocytes of this patient were particularly intensely immunoreactive compared to those examined in biopsies obtained during necropsy.

However, the presence of abundant single-ocular immunoreactive UCP1 cells in all the studied visceral deposits confirms the idea that the visceral adipose tissue of adult men is endowed with the ability to transdifferentiate adipocytes. In particular, the almost exclusive presence of monoclonal immunoreactive UCP1 cells in the perirenal fat of the studied especially supports such plasticity. Typical climatic conditions of the Arctic can explain the high content of multilocular adipocytes in the examined.

In conclusion, it should be noted that this report is the first evidence of the presence of brown adipose tissue confirmed by the UCP1 marker in adults living in the Arctic region. It should be noted that a significant abundance of multilocular cells, their population expressing UCP1, and more intense immunoreactivity in persons exposed to cold support cold-induced browning of visceral fat in adults, which may later become the basis for specific therapy of obesity and related metabolic disorders.

a b



Immunohistochemical analysis (UCP1) of the adrenal fat of a patient who underwent nephrectomy for urolithiasis. Magnification, left figure 600 microns and right figure 40 microns

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SCIENTIFIC REVIEWS AND LECTURES

S.E. Avetisov, S.N. Illarioshkyn, Z.V. Surnina, A.N. Moskalenko, S. Georgiev

POSSIBILITIES OF NEUROIMAGING MARKERS IN THE DIAGNOSIS OF PARKINSON'S DISEASE

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УДК 616.43, 616-06

The review summarizes the results of studies on the application of the principle of neuroimaging for the early diagnosis of Parkinson's disease (PD). The term "neuroimaging" combines various methods of directly or indirectly displaying the structure, functions and biochemical characteristics of the components of the nervous system. Indication of specific defects in brain structures has become possible thanks to such methods as positron emission tomography, single photon emission computed tomography, transcranial sonography in B-mode, MRI of the brain in SWI mode, and neuromelanin-sensitive MRI (NM-MRI). The ocular component of neuroimaging in PD may be associated with the study of the structural and functional state of various neuroelements of the eye, in particular, with the assessment of the state of the corneal nerve fibers (CNF). The difficulties of conducting research in this area of neuroimaging may be associated not only with the reliable detection of CNF changes in PD, but also with the assessment of the specificity of these changes, taking into account their potential polyetiology.

Keywords: Parkinson's disease, neuroimaging, corneal nerve fibers.

Parkinson's disease (PD) is a chronic, steadily progressive neurodegenerative disease that occurs predominantly in older people. PD is the second most important and common neurodegenerative disease after Alzheimer's disease. The incidence among the population is on average 1 case per 1000 people, while there is a regular increase in PD cases with age. So, at the age of up to 65 years, the number of cases is 1-2%, while up to 80 years - already 4% of the population, while more than 300 thousand new cases of PD are registered annually [33].

The disease was originally described by James Parkinson in his 1817 Essay on Shaking Palsy, which outlined the main motor signs of the disease [27]. Currently, the diagnosis is based on clinical data, and there is no reliable method for the early detection of PD, except for genetic testing, which is limited to rare cases of monogenic forms of the disease. In the presence of severe clinical symptoms, the diagnosis of PD does not cause difficulties, however, it should be taken into account that a significant motor deficit appears only after the death of more than 50% of neurons in the substantia nigra of the brain [7,16]. In the early stages, the diagnosis causes certain difficulties, even with the correct application of the updated diagnostic criteria .

The clinical picture of PD is represented by the syndrome of parkinsonism, which includes hypokinesia, muscle rigidity, rest tremor, and postural disturbances [29]. Among the various diseases, the clinical picture of which is represented by the syndrome of parkinsonism, the most common, according to the data of pathomorphological and epidemiological studies, is PD [17]. Other diseases with a leading syndrome of parkinsonism include the so-called parkinsonism-plus diseases or atypical parkinsonism: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal degeneration, etc. All of the above diseases are the result of impaired function of the nigrostriatal system and belong to the group of diseases with degenerative forms of parkinsonism. In addition, non-degenerative forms are distinguished, for example, vascular, drug-induced, toxic, psychogenic parkinsonism, etc. The main distinguishing feature of this group of diseases is the preservation of the presynaptic nigrostiatic pathway [31]. The need for a differential diagnosis between non- and degenerative parkinsonism is due to the different course and prognosis of diseases, as well as approaches to therapy.

The etiology and pathogenesis of PD are still poorly understood, and early diagnosis of the disease is very difficult. As a rule, the genesis of the disease is idiopathic, but familial cases are often found in practice. According to a number of studies, the main pathomorphological findings in PD are Lewy bodies containing phosphorylated alpha-synuclein (p-α-syn), as well as the loss of dopaminergic neurons in the substantia nigra (SN), leading to difficulty in voluntary movements [11]. In addition to the central structures, p-α-syn deposits were also found in the peripheral nervous system: skin nerve fibers, laryngeal nerves, submandibular nerves, as well as in the minor salivary glands and ganglia of the digestive system [2,30,13,28]. In the conducted retrospective studies on a sufficient sample of patients (1376 patients with PD), changes in thin non-myelinated peripheral nerve fibers (TnNF) were detected in 53.4% of cases, while in large peripheral nerve fibers (LPNF) - in 16.3% of cases [13] . In addition, in PD, a decrease in the density of small intraepidermal nerve fibers and a deterioration in the innervation of the sweat glands and m. erector pili (hair lifting muscle). Based on the above, it was suggested that there is a single mechanism of changes in the central and peripheral nervous systems in PD, which confirms the presence of p-α-syn in the SN and biopathies of damaged peripheral nerve fibers of the skin. Thus, PD is currently considered to be a multisystem disease of the nervous system [2].

It should be noted that changes in the peripheral nervous system in PD may be a consequence of not only the underlying disease, but also the result of a neurodegenerative process caused by long-term

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therapy of the underlying disease with levodopa [20]. In one of the studies, to assess the degree of neurodegeneration of peripheral nerve fibers in PD without sensory impairment, confocal microscopy of material obtained by skin biopsy and stained with specific antibodies was used in 85 patients [21]. Patients were divided into the following groups: 1) receiving levodopa; 2) without levodopa therapy (37 and 48 cases, respectively). It was found that LPNF are damaged to a greater extent during levodopa therapy, and TnNV degeneration occurs to the same extent in both groups. It was also noted that pronounced changes in TnNV are already present in the early stages of the disease in most patients.

So far, reliable biomarkers have not yet been identified to reliably determine the presence of PD at the preclinical stage (i.e., before most of the dopaminergic neurons are lost). The study of the possibilities of early diagnosis and monitoring of the disease is carried out in several directions. One of the promising directions involves the use of the principle of neuroimaging. The term "neuroimaging" combines various methods of directly or indirectly displaying the structure, functions and biochemical characteristics of the components of the nervous system. Preliminary data indicate the promise of modern neuroimaging methods for the development of specific biomarkers for PD and other extrapyramidal diseases . Thus, the indication of specific defects in the brain structures became possible thanks to such methods as positron emission tomography (PET), single photon emission computed tomography (SPECT), transcranial sonography in B-mode (TCS), MR brain studies in SWI mode (magnetic susceptibility-weighted images), neuromelanin-sensitive MRI (NM-MRI), etc. [32].

Taking into account the fact that neurodegeneration of dopaminergic structures plays a key role in the pathogenesis of PD, leading to the development of neurotransmitter imbalance, PET and SPECT scanning, which allow assessing dopamine metabolism and the integrity of post- or presynaptic dopaminergic pathways, have firmly established themselves as effective methods for diagnosing degenerative parkinsonism. . These studies make it possible to visualize functional processes in the brain by detecting a radioactive ligand after it enters the systemic circulation and binds to a molecular target. It should be noted that in the updated criteria for diagnosing PD, among all the proposed neuroimaging markers, only the absence of a dopamine metabolism disorder according to SPECT data is an absolute exclusion criterion for the disease, and myocardial scintigraphy with metaiodobenzylguanidine is a confirming criterion [11,22]. However, despite the undoubted diagnostic advantages of PET and SPECT, these techniques have a number of limitations, in particular, the safety profile associated with contact with radioactive isotopes; high cost of research; the impossibility of unequivocal differentiation of PD from other forms of degenerative parkinsonism.

The TCS technique is based on obtaining a hyperechoic signal from the emergency in PD. The exact mechanism of hyperechoic SN is not entirely clear, it is believed that the hyperechoic signal occurs as a result of accumulation or increased iron content [4]. The results of TCS differ in PD and other forms of both degenerative and non-degenerative parkinsonism, which makes it possible to use the technique for differential diagnosis . TCS also has a number of disadvantages, such as the likelihood of various artifacts and the high dependence of the results obtained on the technical characteristics of the device and the qualifications of the doctor performing the scan. In addition, in some cases, hyperechogenicity of the CS can also occur in a healthy population [6].

MRI in standard modes does not allow to determine pathognomonic changes for PD and is applicable only to exclude other organic pathology that can cause secondary parkinsonism. With the widespread introduction of high-field tomographs into clinical practice, a detailed assessment of the structural characteristics of brain regions, primarily involved in the pathological process in PD, has become possible. Thus, the following potential biomarkers of PD have been proposed: the absence of visualization of nigrosomes and a decrease in the neuromelanin pigment in the SN. The term nigrosome refers to clusters of dopaminergic neurons in the compact part of the SN. When visualizing nigrosomes using a standard protocol that includes the SWI sequence (images weighted by magnetic susceptibility), in PD, a loss of dorsolateral nigral intensity is noted due to the pronounced involvement of nigrosomes in the neurodegenerative pathological process . NM-MRI (MRI with T1-weighted images) is used to visualize neuromelanin in the SN . In patients with PD, there is a decrease in the area and contrast ratio of T1-high-signal pigmentation of the NM in the SN [19].

The above methods have high sensitivity and specificity in the diagnosis of early stages of PD. However, it should be noted that when using MRI markers for the differential assessment of various variants of degenerative parkinsonism, conflicting results were obtained, and therefore the differential diagnostic value of structural MRI requires further study in prospective studies [18].

According to the literature, the ocular manifestations of PD include disturbances in color perception and pupillary reactions, an increase in the latent period during saccadic eye movements, a decrease in the thickness of the retinal nerve fiber layer, the presence of scotomas, as well as a decrease in tear film rupture time and corneal thickness [9,15,20]. Taking into account the fact that the neurodegenerative process in PD affects both the central and peripheral nervous systems, structural changes in the corneal nerve fibers are also considered as another promising biomarker [33]. Thus, the ocular component of neuroimaging in PD can be associated with the study of the structural and functional state of various eye neurons using visual evoked potentials (VEP), oculography to record saccadic eye movements, optical coherence tomography (OCT) of the retina and optic nerve, as well as confocal microscopy of corneal nerve fibers.

At the stage of hemiparkinsonism, an increase in the latency of a positive P100 response was noted, as well as a decrease in the maximum amplitude of late oscillations compared to the “uninvolved” hemisphere; as the disease progressed, the asymmetry of latencies and amplitudes practically disappeared [34]. The N75 and N145 components correlate with the severity of motor manifestations and duration of the disease [34]. Changes in VEP are explained by biochemical and electrophysiological changes in the retina, the neurons of which are rich in dopamine, which is confirmed by electroretinography data. At the same time, in another study of VEP on a reverse checkerboard pattern in patients with PD, no significant amplitude-temporal asymmetry of the components between the more and less affected sides was found during stimulation of the corresponding eye [35]. Also, no correlations were found between these indicators and the clinical manifestations of PD, with the exception of bradykinesia, and when analyzing the results of the study of VEP for a flash of light, there was no dependence of the indicators on the stage of the disease.

Saccadic eye movements are also considered as one of the potential markers reflecting age-related and pathological changes in the central nervous sys-

tem. Saccades are fast, jerky movements of the eyeballs, with the help of which the points of fixation of the gaze change. The presence of saccades is determined by the coordinated work of various parts of the brain, including stem structures, subcortical nuclei, and various parts of the cerebral cortex. In PD, there was an increase in the latent period, reaction time, and the proportion of multisaccades, which are mainly fixed when the gaze is directed towards the limbs with pronounced clinical signs of the disease [3].

Optical coherence tomography of the retina and optic nerve can be used as an additional diagnostic test in PD. Thus, one study revealed thinning of retinal ganglion cells, the inner plexiform and peripapillary layer of nerve fibers in this disease [10]. Another study reported a significant correlation between the presence of progressive supranuclear palsy and the thickness of the retinal nerve fiber layer, but no such changes were found in the control group and the group of patients with PD. The authors suggest using the technique as an additional study for the differential diagnosis of PD and progressive supranuclear palsy, but there is a need for further researches due to the small cohort of patients [25].

Taking into account the above data on the predominant change in thin non-myelinated peripheral nerve fibers and a decrease in the density of small intraepidermal nerve fibers in PD [31,13], it is promising to analyze potential changes in corneal nerve fibers (CNFs). The possibility of intravital visualization of CNF is due to the transparency of the cornea and the parallel location of the nerve plexus in relation to the surface of the cornea. It was noted that the highest concentration of peripheral unmyelinated thin nerve fibers is located in the subbasal corneal nerve plexus. At the same time, the cornea is the most innervated structure of the human body – the density of nociceptors reaches 7000 per square millimeter [12,26].

In a series of previous studies using confocal microscopy of the cornea, age-related features, as well as changes in CNF, were studied both in ocular and systemic diseases [3,5,8,14,23,24,30]. Age-related changes are manifested in a significant decrease in the density of CNF, while there is a sharp decrease in the number of central epithelial nerve terminals, as well as a significant increase in irregularly shaped nerve fibrils located under the basal layer of the cornea.These observations indicate the need for a clear standardization of comparison groups when conducting scientific research on induced by any reason changes in CNF. In the absence of such reasons, the structure of the corneal plexus remains unchanged for at least three years, while the specified time interval is limited to the intervalongoing research [23]. Changes in CNF can occur with ophthalmohypertension, wearing contact lenses, as a result of keratoectatic diseases, after keratorefractive interventions, phaco- and antiglaucoma surgery, and even panretinal laser photocoagulation of the retina [8,14,1]. A number of studies have shown the possibility of using the CNF state as a biomarker of pathological changes in the peripheral nervous system in systemic diseases (diabetes mellitus, Graves' disease) [1,5,24].

In a few studies, the results of which can be regarded as preliminary, the state of thin unmyelinated CNF in PD has been studied. In one of them, based on confocal microscopy using proprietary software, CNF changes were analyzed in 24 patients (48 eyes) with PD (the control group included 26 healthy volunteers) [30]. Simultaneously, a skin biopsy of the dorsal surface of both feet was performed, followed by a histological analysis of the state of the intraepidermal nerve fibers. In PD, there was a simultaneous decrease and increase in the density of CNF in different parts of the cornea, as well as heterogeneous CNF branching in severity, which, according to the authors, reflects the variable ability of CNF to regenerate at different stages of the disease. The degree of degenerative changes in CNF coincided with the data of the functional assessment of the parasympathetic nervous system, however, there was no correlation between the duration of levodopa therapy, the severity of the disease, and changes in the structure of CNF. At the same time, changes in intraepidermal nerve fibers, correlated with both the severity of the disease and the duration of levodopa therapy.

In another preliminary study on a small sample of observations, the state of CNF in PD was assessed using the author's quantitative indicators [3]. A significant decrease in the directivity anisotropy coefficient and an increase in the CNF directivity symmetry coefficient were established. Along with this, CNFs were pronouncedly tortuous, multidirectional, "clearly shaped", and an increased number of branches from the main nerve trunks was observed.

The results of the studies presented in this review indicate the prospects for further study of various methods for the early diagnosis of PD, which are based on the principle of neuroimaging. From the point of view of the supposed simplicity and accessibility, the direction associated with assessing the state of CNF in PD is of particular interest. The difficulties of conducting research in this area of neuroimaging may be associated not only with the reliable detection of CNF changes in PD, but also with the assessment of the specificity of these changes, taking into account their potential polyetiology.

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NEW CORONAVIRUS INFECTION COVID-19 AND WOMEN'S REPRODUCTIVE HEALTH. FACTS AND ASSUMPTIONS

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The review presents data on the possible ways in which the SARS-CoV-2 and COVID-19 virus affects the female reproductive system and the already recorded negative consequences. Recommendations on pregnancy planning and the specifics of using hormonal contraceptive methods, as well as approaches to specific prevention of a new coronavirus infection from the standpoint of safety and preserving the reproductive health of women during the COVID-19 pandemic are outlined.

Keywords: new coronavirus infection, SARS-CoV-2, COVID-19, women's reproductive health.

The pandemic of new coronavirus infection (NCI) COVID-19 caused by the SARS-CoV-2 virus continues to inflict damage of medical and demographic nature irrespective of geographic position, financial status and the development level of the health care systems in involved countries. Over a 2-year period of NCI pandemic four main waves of infectious process have been registered against the background of multiple mutations of SARS-CoV-2. According to the official data of the interactive web-based dashboards of the World Health Organization, hosted by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, on COVID-19 (accessed on 04.02.2022) the total number of infected people around the world reached more than 380 mln. people, the number of deaths from NCI is 5.7 mln.; more than 10 billiard doses of anti-covid vaccines manufactured by different companies have been administered. In the Russian Federation the number of confirmed cases of NCI exceeds 12 mln., the mortality rate is about 320 thousand people, more than 150 mln. doses of anti-covid vaccines have been administered [11].

According to the data of the Federal State Statistics Service the size of the standard population of the Russian Federation as of 1st August 2021 is 145.8 mln. people. The natural population decline (difference between the birth and death rate) is 421.9 thousand people, which is 59% more than for the same period in 2020. Thus, in 2021 the decrease in the population size of Russia was 2 times faster [10]. Of course, taking into account the dynamics of the demographic situation, and the NCI COVID-19 contributes to this, everyone's attention is focused on the clarification of potential influence of COVID-19 on the reproductive health (RH) of people, since the successful reproduction is required for any species to continue its existence. The status of the RH of the population is an important component of the social and demographic development. It influences to a great extent the level of the development of the society as a whole. RH care is defined as a set of methods, techniques, approaches and services that contribute to the RH and welfare by preventing and solving the problems of the reproductive sphere [10].

The question of the potential influence of the COVID-19 infectious agent on the human reproductive system currently remains open and is in the focus of the scientific interests. The understanding of the fact whether SARS-CoV-2 could damage the tissues of ovaries, endometrium, embryo at the early stage of its development is critical in the context of the safety of any type of human reproduction in the period of pandemic.

NCI and its potential influence on the female reproductive system. It is considered that potentially SARS-CoV-2 could negatively affect human reproductive system through its immediate influence on gonads, through damaging effect of the hyperthermia and systemic oxidative stress on the cells and tissues of the reproductive system, potential toxic effect of the medications, their high doses and long-term administration in the course of the NCI therapy [7, 31].

Nowadays the negative effect of the long-term fever as well as of the oxidative stress on the main parameters of the ejaculate, disturbance of the function and morphology of the sperm, damage of the membranes and DNA, induction of male sex- cells apoptosis is proved [29, 35]. However, the studies of the influence of hyperthermia and oxidative stress including the one associated with NCI COVID-19, on tissues and cells of the testes could not be found in the available publications.

The probability of immediate susceptibility of tissues and cells of the reproductive system to SARS-CoV-2 presents great interest. At present we know that this virus enters the target-cells with the help of the cellular receptor, angiotensine converting enzyme-2 (ACE-2), and transmembrane serine protease TMPRSS2 that promotes the virus binding with the receptor ACE2 activating the virus S-protein. The necessary condition

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for the access of the virus to the cell is the presence of both ACE2 and TMPRSS2 receptors on the cell [12]. The role of other receptors in entrance of SARS-CoV-2 into the cells are being discussed. For example, the role of the transmembrane glycoprotein basigin (CD147), that is part of immunoglobulin gene super family and has high expression on the surface of many cells. It is assumed that cells, tissues and organs with high expression of the above-named receptors are more susceptible to SARS-CoV-2 [15].

In the study by F.M. Reis et al. (2011), the expression of ACE2 was registered in primordial, primary, secondary and antral follicles, stroma and corpus luteum of the ovaries of women of the reproductive age [34].

Expression of basigin in the granulosa cells of the follicles of all the development stages, in the germinal epithelium, corpus luteum, female endometrium was confirmed in the studies of Anna M. Smedts et al. (2006), K.Li, R.A. Nowak (2020) [28].

Analysis of the manuscript by K. E. Stanley et al. (2020) testifies to the fact that SARS-CoV with little probability has a long-term effect on the human reproductive function due to the co-expression of ACE2 and TMPRSS2, as well as basigin in the cells of the antral follicles of the non-human primates and human cumulus [19]. European Society of Human Reproduction and Embryology (ESHRE) (2020) presented the information about the absence of receptors for SARS-CoV-2 in oocytes and embryos, therefore they are not susceptible to the influence of this virus. The shell of the oocyte provides high level of protection of the oocytes and embryos from the influence of SARS-CoV-2 [16]. Thus, the question whether SARS-CoV-2 virus affects the folliculogenesis, as well as the potential decrease in the quality of human oocytes remains debatable.

The expression of the ACE-2 and basigin (CD147) was observed in the human endometrium in epithelial and stromal cells throughout the menstrual cycle with predominant contraception in epithelial cells for ACE2 and in stromal ones – for CD147. It was noted that the expression of ACE-2 and basigin (CD147) in the endometrium changes in the course of the menstrual cycle – higher expression is observed in the secretory phase. Apparently, the expression level affects local homeostasis of the angiotensine-II and proliferative activity of the endometrium, could regulate its regeneration process. Thus, SARS-CoV-2 could potentially damage epithelial cells of the endometrium, influence the process of its cyclic remodeling, and consequently the embryo implantation [36].

NCI and menstrual disorders. NCI COVID-19 influences the parameters of female menstrual cycle. Findings of the study by K. Li et al. (2020) demonstrate that menstrual disorders (MD) are observed in 28% of women of the reproductive age after the NCI COVID-19. They are manifested in 25% changes in the volume of the menstrual blood loss and prolongation of the cycle - in 19% of cases [14]. According to the data of the study by Ya.A. Parphyonofoy et al. (2020) an increase in the frequency of MD (oligomenorrhea/amenorrhoea, abnormal uterine bleeding) are observed in 3-6 months after the NCI. It has direct dependence on the severity of NCI COVID-19 (p=0.002) [9]. Based on the results of the survey of 1,031 women aged 15-45 a statistically significant increase in the variability of the menstrual cycle is observed since the beginning of pandemic (p=0.010): changes in the regular pattern of the menstruation is noted in 46% of the surveyed women, deterioration of the pre-menstrual symptoms is observed in 53% of women; considerable increase in the volume of the blood loss during menstruation was revealed in 18%; 30% showed newly occurring dysmenorrhoea; 9% had menoschesis up to 60-120 days (they had regular cycle before), 45% of the surveyed women said that they had decrease in libido [30]. In another study based on the results of the survey of 263 women aged 26.3±6.9 years an increase in the parameters of anxiety during the COVID-19 pandemic accompanied by decrease in duration (p=0.003) and intensity of menstruation (p=0.002) as compared to the values before the breakout of NCI [22] was established. In the study by Melekhova M.A., Boglakova Yu.V. (2021) no statistically significant differences in the evaluation of duration, intensity of menstruation and intensity of menstrual pain were observed between 583 women who had and who did not suffer from COVID-19, interviewed with the help of the survey created by the authors and located in social media. Statistically significant shortening of the last menstruation was noted in women vaccinated from COVID-19 relative to those who were not vaccinated (5 (4-6) and 5 (5-6) days, respectively, p=0.043). But the values were still within the normal range of the duration of the menstruation [6].

It is well-known that psycho-emotional distress is an important reason of the development of functional MD, since the chronic activation of hypothalamo-pituitary-adrenal axis leads to suppression of the hypothalamus- hypophysis-ovaries axis. Nonovulation, oligomenorrhea and amenorrhoea, hyperplastic processes of endometrium, abnormal uterine bleedings, formation of the ovarian masses are those very gynecologic pathologies that are associated with MD, and in their turn may result in fertility disorders. In different countries on different continents statistically significantly similar data are obtained about high level of psycho-emotional tension in the period of NCI COVID-19 pandemic. For example, in Germany based on the results of the cross-section study that involved 15,704 residents of Germany aged ≥18 high prevalence of generalized anxiety (44.9%), depression (14.3%), psychological distress (65.2%) and fear connected with COVID-19 (59%) was revealed [25]. Online survey of 1,653 people from 63 countries showed that in more than 70% of respondents stress level exceeded the average level. Notably, 59% corresponded to the criteria of clinically significant anxiety, 39% informed about moderate depression symptoms [39].

Large-scale meta-analysis (2021) shows the following prevalence rate of psycho-emotional disorders among the population amid the COVID-19 pandemic (n=189159): depression – 15.97% (95% CI 13.24-19.13), anxiety - 15% (95% CI 12.29-18.54), insomnia – 23.87% (95% CI 15.74-34.48), posttraumatic stress disorder - 21.94% (95% CI 9.37-43.31), psychological distress – 13.29% (95% CI 8.80-19.57) [32]. A connection between the anxiety induced by COVID-19, stress, depressive symptoms and increased prevalence of MD is revealed [37]. T. Ding et al. (2020), based on the registered decrease in the level of Anti-Mullerian hormone (AMH), increase in the level of testosterone and lactotropin in 78 women of older reproductive age (median is 43.5) against the background of COVID-19 of various degree of severity relative to the healthy women of the similar age group, drew a conclusion about the probable negative effect of NCI on ovarian reserve and endocrine function of ovaries in patients with COVID-19 [13].

NCI and pregnancy. A lot of reports of different kind have been published about the specific features of the NCI COVID-19 course in pregnant women, obstetric and perinatal outcomes in this category of patients. The data mainly refers to the manifestations of the NCI in the 2nd and 3rd trimesters of the pregnancy. Part of the studies are indicative

of the absence of the severe course of COVID-19 in pregnant women as compared to non-pregnant ones [27, 33]. Others point to an increased risk of hospitalization to the intensive care units, necessary use of artificial pulmonary ventilation and lethal outcome in pregnant women. The presence of bronchial asthma, arterial hypertension, diabetes mellitus, excess body weight and obesity, kidney and liver diseases could be associated with the increased risk of severe course of COVID-19 in pregnant women [5, 18].

Pregnant women with manifested NCI COVID-19 of various degree of severity demonstrate high frequency of pre-term labor (14.3-25%), C-section (42%-72%) [1, 5, 18, 23], that undoubtedly subsequently bring about the risks of the disturbance of the reproductive health of a women. Active discussion of the possibility to use vertical transmission of SARS-CoV-2 is going on. In a number of studies the vertical transmission of virus has not been proved in the case of the negative SARS-CoV-2 RNA samples from the newborns analyzed with PCR (nasopharyngeal swab, amniotic fluid, umbilical cord blood and human milk) [21]. Other manuscripts speak for the probable vertical transmission of COVID-19 [5, 18]. Perinatal outcomes in pregnant women with COVID-19 are characterized by the development of the fetus distress (26.5-39%), infantile asphyxia (1.4%). Perinatal mortality rate is 0.35 – 2.2% [5,23].

The amount of papers devoted to the obstetric and perinatal outcomes or risk of early pregnancy loss in the case of NCI manifestation in the 1st trimester is limited, the evaluation periods during pandemic differ, the data are controversial. Besides, unfavorable outcomes of gestation in the 1st trimester are subsequently associated with the development of various diseases of female reproductive system, in particular with infertility and recurrent miscarriage [4]. S. Cosma et al. (2021) conducted the research during the first wave of COVID-10 pandemic. They stated that NCI CIVUD-19 if manifested in the 1st trimester of pregnancy proceeds in asymptotic or mild form. No cases of covid-associated pneumonia were registered. The conclusion has been drawn about the absence of the high risk of spontaneous miscarriage in the 1st trimester of gestation against the background of NCI COVID-19 and probable favorable disease progression at the beginning of the pregnancy [20]. In the study by Yu.V. Khaydukova et al. (2021) the pregnancy outcomes in 50 women with manifestation of NCI COVID-19 (1st and 2nd wave) in the 1st trimester of gestation have been analyzed retrospectively. Moderate to mild form of the NCI prevailed. There were no patients with extremely severe course of the disease. 16% of women underwent artificial abortion. In half of the cases it happened due to the diagnosed NCI and it was necessary to take medications that were counter-indicative in case of pregnancy. In 42% of cases inevitable miscarriage occurred. Moreover, according to the data of ultra-sound examination non-developing pregnancy was revealed in 81% of cases. The pregnancy prolonged and finished in delivery at term in 42% of cases. It was established that the severity of NCI/presence of pneumonia do not have statistically significant effect on the pregnancy outcome in the form of its prolongation or inevitable miscarriage. Even mild form of NCI in the 1st trimester of gestation is associated with high risk of unfavorable outcome [2].

In the study by F. Halici-Ozturk et al. (2021) SARS-CoV-2 RNA analysis of tissues of the spontaneous abortus from 21 pregnant women with confirmed NCI COVID-19 using the method of real-time reverse transcription polymerase chain reaction (RT-PCR) revealed negative results [26].

Today medical community does not recommend postponing pregnancy planning and childbirth to a post-covid period [29, 30]. In this regard against the background of pandemic both at the stage of pregnancy planning and during pregnancy, it is necessary to observe all the measures of non-specific, pharmacological and specific prophylaxis to prevent SARS-CoV-2 infection or development of the severe NCI COVID-19 [29, 30]. The only means of specific prophylaxis is vaccination. Taking into account high probability of SARS-CoV-2 infection during pregnancy and absence of the data about the adverse effect of anti-COVID-19 vaccines on male and female fertility, vaccination is recommended to men and women of reproductive age at the stage of childbirth planning [7].

R. Orvieto et al. (2021) did not reveal negative effect of anti- SARS-CoV-2 vaccine mRNA on the ovarian reserve in the nearest cycle following vaccination in the programs of assisted reproductive technologies (Art) [3]. N.V. Dolgushina et al. (2021), published preliminary data about the absence of negative effect of the Russian vaccine Gam-COVID-Vac on the ovarian reserve and level of antiphospholipid antibodies in women based on the assessment of the number of antral follicles, determination of the level of Anti-Mullerian, follicle-stimulating, thyroid-stimulating hormones, estradiol, antiphospholipid antibodies in blood serum before vaccination and 90 days after the administration of the 1st component of the vaccine [24]. Pregnancy planning is possible in 28 days after the administration of the 1st component of the vaccine, that is in the period when the protective immunity against SARS-CoV-2 is being developed [7].

In the study by A. Edelman et al. (2022), the connection between the anti-COVID-19 vaccine and changes in the cycle and duration of menstruations was evaluated in those who received vaccine (n=2403), relative to those who did not (n=1556). Anti-COVID-19 vaccine was associated with the less than 1 day changes in the duration of the cycle for both cycles of the vaccine administration relative to the cycles before vaccination (0.71 day fewer following the 1st dose, 98.75% (CI 0.47-0.94), 0.91 day fewer following the 2nd dose, 98.75% (CI 0.63-1.19). No notable changes relative to the three basic cycles were observed in non-vaccinated women [17].

It is recommended to start pregnancy planning in not less than three months after the COVID-19 and with necessary adequate preconception preparation. For patients who have had COVID-19 it is recommended to postpone the programs of ART until complete recovery. In this respect it is necessary to have individual approach in groups of infertile patients. All the patients of the ART programs who have had COVID-19 and have additional risk factors of thromboembolic complications (TEC), it is necessary to give preventive doses of low molecular heparin (LMH) prior to and throughout the ovarian stimulation [7].

NCI and contraception. During COVID-19 pandemic the issue of availability and safety of various methods of contraception, especially of hormone one, to prevent unwanted pregnancy and negative consequences of its interruption for RH of women remains topical. In 2020 at the beginning of the pandemic WHO supports the use of all the contraception methods without special limitations. Additional attention is paid to the absence of necessity to remove intra-uterine contraception systems including levonorgestrel releasing intrauterine system as well as implants in patients with NCI. If necessary it is possible to somewhat prolong the period of their usage in observance of a number of recommendations. For example, in addition to levonorgestrel releasing intrauterine system it is possible to use oral progestogen-containing con-

traceptives (PC) or barrier contraception. Considering NCI treatment patterns one should remember that the use of some antibiotics could decrease the efficiency of hormone contraceptives [38].

Russian guidelines (5th version) give reference to joint recommendations of the Spanish colleagues – a group of experts from Spanish medical scientific communities (Spanish Menopause Society, SMS; Sociedad Española de Ginecología y Obstetricia, SEGO; Sociedad Española de Trombosis), that are made for women in the period of menopausal transition using CHC. In case of mild NCI it is recommended to stop using CHC for the period of isolation and limited mobility. If hormonal contraception is required then it is possible to continue the use of CHC if there are no risk factors of TEC. Otherwise, to start using PC together with preventive doses of LMH. In case of NCI of moderate severity, if it is impossible to stop using hormonal contraception, it is also recommended to start using PC together with preventive doses of LMH. If the disease course is severe then CHC should be discontinued, LMH should be prescribed in accordance with the treatment protocols. It is recommended to resume taking CHC only after recovery and full mobilization [7].

It is advised to provide an opportunity of long-distance medical consultations (using various means of on-line communication without personal contact) with regards to contraception, its beginning and termination, and the choice of contraception methods [26, 41, 61].

Thus, to clarify the consequences of NCI for the female reproductive health it is necessary to conduct further research. It is reasonable in the period of pandemic to take measures aimed at prevention of negative effect of distress on the reproductive system. The strategy of maintaining reproductive health in the conditions of NCI and psycho-social distress should include certain approaches and methods that have positive influence on a woman's body as a whole and reproductive system in particular: compliance with work and rest schedule, sleep hygiene, healthy balanced diet, physical activity, meditation and yoga, psychological assistance, balanced psycho-correction and psychotherapy (on indications), reasonable (safe and efficient) contraception and pregnancy planning. Women of reproductive age who have had NCI, especially in severe form, should be included into the group of high risk in terms of development of disorders of the menstrual and reproductive functions, and should undergo a more profound follow-up care. It is necessary to ensure availability of medical consultation, including long-distance ones, on the use of various contraception methods during pandemic to prevent unwanted pregnancy. The usage of CHC is reasonable with due account of additional evaluation of risks with regard to manifestation of or previous NCI. It is not recommended to postpone the pregnancy planning and childbirth to a post-covid period. After the previous NCI the pregnancy should be planned in not less than three months against the background of adequate pre-conception preparation. Considering the absence of data on negative effect of anti-COVID-19 vaccines on female fertility, fetus at the early stage of gestation, pregnancy course and perinatal outcomes, vaccination is recommended including the stage of pregnancy planning (in compliance with the practice guidelines) as the low level of collective immunity (<70-80%) could be one of the reasons of high NCI incidence among the population.

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THE GENETICS OF MUCOPOLYSACCHARIDOSES

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This review aims to summarize scientific data on the contribution to the study of hereditary lysosomal disease - mucopolysaccharidoses. The article presents a review of the literature on the clinical picture and diagnosis of mucopolysaccharidosis in patients, the frequency of these diseases in the world is given. The available medical literature on the study of MPS was analyzed using the PubMed database, eLIBRARY.RU, Google Academia

Keywords: mucopolysaccharidosis.

Introduction. The first information about disorders of lysosomal accumulation appeared at the end of the 19th century, and Tay-Sachs disease was first described in 1881 and 1882. The disease was named after doctors Warren Thau and Bernard Sachs and French dermatologist Philippe Gauche. 50 years later, in 1932, Dutch physician John Pompei announced the type II glycogen disease that would later become his name. Pompe disease is the first hereditary disease to be identified as a lysosomal storage disorder. Lysosomes were discovered experimentally between 1949 and 1952, when the biochemist Christian de Dube and colleagues discovered that they were the organelles responsible for the intracellular degradation and reuse of macromolecules. This finding further elucidates the pathophysiological basis of lysosomal storage disorders. After the first clinical phenotype was identified in the 19th century, lysosomes were recognized in 1955/56, and since 1963 the biochemical defects underlying LSD have been proven and knowledge of LSD has increased. In the 1970s and 1990s, research focused on the mannose phosphate 6 receptor pathway, the sorting mechanism of lysosomal enzymes, the identification of the molecular basis of LSD, and the development of tools and strategies to investigate lysosomal biology. Attempts to treat these diseases with enzyme replacement therapy were first made in the 1990s. Currently, research is focused on the role of lysosomes as signaling platforms for the control of cellular

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metabolism and the development of new therapies.

Glucosaminoglycans are polysaccharides composed of hexosamine amino sugars, which are the carbohydrate portion of proteoglycans. In the body, glycosaminoglycans are covalently linked to the protein portion of the proteoglycan and do not exist in free form. In the past, mucopolysaccharides were called mucopolysaccharides because they were contained in the secretions of the mucosa (mucosa), giving them viscosity and lubricity. Together with GAG, proteoglycans are important components of the extracellular matrix and play an important role in intercellular interactions, the formation and maintenance of the shape of cells and organs, and the formation of the skeleton for tissue formation, in particular by interacting with collagen, elastin, fibronectin, laminin and other extracellular matrix proteins. . Since it is a polyanion, in addition to water, a large number of cations (Na +, K +, Ca2 +) can be attached, which are involved in the formation of tension in various tissues and can prevent the spread of pathogenic microorganisms. [2,18,22,27]

Currently, there are 6 types of glycosaminoglycans: chondroitin-4-sulfate (chondroitin sulfate A), chondroitin-6-sulfate (chondroitin sulfate C), dermatan sulfate, keratan sulfate, heparan sulfate and hyaluronic acid.

Excessive accumulation of glycosaminoglycans in organs and tissues causes damage and swelling of organs containing a large amount of extracellular matrix. In this case, lysosomes accumulate incompletely destroyed glycosaminoglycans and fragments of their oligosaccharides, which are excreted in the urine.

Mucopolysaccharidosis type I. Mucopolysaccharide disease (MPS) type I (ICD10: E 76.0) is a disease caused by a mutation in the IDUA gene that causes a deficiency or a significant decrease in the activity of the enzyme α-L-idronidase. Inhibition by enzyme mutations is a chronic progressive disease with disorders of various organs and systems, including the skeletal system, cardiovascular system, central nervous system, and ophthalmic system [28]. The incidence was wide: 1:10 million ~ 1:14 million in Harra syndrome, 1:30 million and 1:64 million in Chai and Morcio syndrome [26].

In 1919, the German pediatrician Gertrud Harler reported patients with characteristic skeletal disorders, mental retardation, and corneal clouding. This type of disease was later called "Pfaundler-Hurler syndrome". In connection with the appearance of the phenotype of the patient, similar to the gargoyle, in 1936 the British doctor R. Ellis suggested another name for the disease - "Gargoyle disease". In 1962, Dr. Scheie, an ophthalmologist, described a patient with corneal clouding with mild disease. This disease is called Scheye's syndrome, and for some time was considered a type of mucopolysaccharidosis. However, in 1971 it was discovered that Scheye's syndrome and Hurler's syndrome were the same cause of decreased activity of an enzyme called α-L-idronidase. Subsequently, several cases of an intermediate type have been reported. They were not classified as severe or mild and were classified as more severe Scheye syndrome. It has been found that MPS type I is caused by mutations in the same gene, but its clinical manifestations are very diverse [28].

Currently, 3 types of phenotypes have been reported: Hurler syndrome (MPS type IH - severe type), Scheye syndrome (MPS type - mild type) and Hurler-Scheye syndrome (MPS type I H/S - intermediate type). More than 90 mutations have been identified in the α-L-IDUA gene. In α-L-idronidase deficiency, dermatan sulfate and heparan sulfate accumulate in lysosomes, causing damage to various organs and systems [14, 15, 16]. With Hurler's syndrome, the first signs appear already in the 1st year of life. The main clinical symptoms are short stature, short neck, scaphocephaly, microcephaly, coarse facial features, full lips, wide nostrils, sunken nose bridge, eye hypertelorism, small sparse teeth (Hurler phenotype), hepatosplenomegaly, deafness, umbilical and inguinal hernia. Later, as the patient develops, deep dementia, stiffness in large and small joints, scoliosis, kyphosis, hearing and vision impairment, obstructive sleep apnea syndrome, heart failure, etc. develop. Due to the rapid progression of the disease, he may also die within 10 years of birth [26,28].

Scheye syndrome - with this form of joint stiffness manifesting at the end of the first decade of life and characterized by slow progression, growth and intelligence do not suffer. Facial features very gradually coarsen and change according to the type of gargoilism ("broad-short face"). Multiple dysostosis is mainly represented by stiffness of the joints of the hands, the formation of a "clawed paw", painful stiffness of the feet, hollow foot, valgus deformity of the knee joints. Carpal tunnel syndrome often develops, which, along with stiffness, leads to limited function of the upper extremities [26].

The intermediate form of MPS, IH/S (Hurler-Scheie syndrome), is characterized by normal and subnormal intelligence with progressive somatic pathology and multiple dysostosis. The disease manifests itself in childhood, at the age of 3-8 years. The course of the disease is progressive. Joint stiffness, sensorineural hearing loss, corneal clouding, airway obstruction, cardiovascular pathology in the form of valve damage, myocardial thickening, systemic and pulmonary hypertension, narrowing of the coronary arteries up to a heart attack. Micrognotia of facial shape and hydrocephalus.

Mucopolysaccharidosis type II. Mucopolysaccharide type II (Hunter's syndrome) (ICD10: E 76.1) is a serious progressive disease caused by a deficiency of the enzyme iduronate-2-sulfatase. The genetic form is X-linked recessive, so it mostly develops in males. However, there are isolated cases of Hunter syndrome in women due to mutations in the IDS gene on the maternal X chromosome and asymmetric inactivation of the paternal X chromosome [24].

The incidence of MPS type II in newborn boys ranges from 1:100,000 to 1:132,000 [25]. In 1980, Schaap and Bach studied the incidence of Hunter syndrome in boys in Israel, which was 34,000 per 1 newborn [16].

The IDS gene was mapped to the long arm of the X chromosome Xq28. Although the range of mutations found in Hunter syndrome is very wide. The phenotype is extremely heterogeneous and rather conditionally subdivided into severe and mild forms, representing in fact a continuum of clinical phenotypes differing in severity [16,24]

In severe form, it differs little from Hurler's syndrome, although it is characterized by a slower progression of somatic and neuropsychiatric symptoms and some features of the clinical phenotype (absence of corneal opacity, less severe mental retardation). The course of the disease is progressive. Manifestation of the disease at 3 years of age. Severe neurological symptoms (encephalopathy, decreased motor activity to immobility, cachexia, lack of response to the environment, severe mental retardation). At an early age, they suffer from frequent respiratory diseases. Corneal opacity is uncommon in MPS II, but patients may have severe retinal degeneration. The pathognomonic symptom of the disease is combined heart defects (mitral valve stenosis, severe diffuse insufficiency of the coronary circulation). Patients die at the age of 10–15 years from airway obstruction or heart failure. [6,24].

The mild form bears clinical resemblance to Scheye's syndrome and is characterized by normal or subnormal

intelligence with slowly progressive somatic pathology and slowly developing multiple dysostosis. [37]. The manifestation of the disease is 3–8 years, for benign forms at 10–15 years. As a rule, the patient's intelligence is not impaired. In some cases, there is also the possibility of mild mental retardation. Patients often live to age 30 or older [2,6,16,24].

Mucopolysaccharidosis type III. The Sanfilippo syndrome, a clinical manifestation of type III MPS, was first reported in 1963 by the American pediatrician Sylvestra Sanfilippo, a patient with behavioral disorders and reduced psycholinguistic development.

The incidence of MPS type III ranges from 1:58,000 to 1:100,000 in MPS IIIA and MPS IIIB [7].

Due to the deficiency of enzymes involved in the degradation of heparan sulfate, 4 subtypes are currently known. MPS IIIA, alpha-N-acetylglucosaminidase in MPS IIIB, acetyl-CoA-α-glucosaminide-N-acetyltransferase in MPS IIIC, and N-acetylglucosamine 6-sulfatase in MPS IIID. [19]. The disease is caused by mutations of four genes encoding these enzymes: lysosomal aN-acetylglucosaminidase (type IIIA MPS) - the gene is mapped to 17q25.3, acetyl-CoA-α-glucosaminide-N-acetyltransferase (type IIIB MPS - the gene is mapped to 17q21.2, lysosomal N-acetylglucosamine-6-sulfatase (MPS IIIC type - the gene is mapped to 8 p11.2-p11.1, sulfamidase (MPS IIID type) - the gene is mapped to 12q14.3. All enzymes are involved in the metabolism of heparan sulfate, the accumulation of which causes severe CNS disorders More than 200 mutations have been registered in these genes that lead to the development of various types of MPS III, and their number continues to grow [25].

The main clinical manifestations of type III MPS are progressive disorders of the central nervous system, dementia syndrome, severe behavioral disorders, chronic diarrhea. Symptoms include sensorineural deafness, joint contracture, and moderate facial roughness. In children, shortness of breath often occurs at an early age, but the symptoms gradually subside. This often occurs in the 2nd year of life. Patients with MPS III are more likely to have hepatomegaly than splenomegaly [7,19,25].

Mucopolysaccharidosis type IV. Mucopolysaccharidosis type IV (Morquio syndrome) was described in 1929 by pediatrician Morkio L. and British doctor Brailsford J.F. This disease is associated with a defect in N-acetylgalactosamine-6-sulphate sulfatase (MPS type IVA)-16q24.3 due to a mutation in the GALNS gene and a defect in β-galactosidase (MPS type IVB)-3p22.3 due to a mutation in the GLB1 gene . These enzymes are involved in the metabolism of keratan sulfate and chondroitin sulfate.

The incidence ranges from 76,000 to 1 in Northern Ireland and from 64 to 1 million newborns in Australia [11].

The genetic type is autosomal recessive inheritance. More than 220 mutations leading to the development of the disease have been registered in the GALNS gene [14].

The main clinical manifestations are short stature, keeled chest, skeletal deformity, increased mobility of small joints, etc. It is important to note that children with Morquio syndrome have normal intelligence [31, 100, 107, 160, 256]. Patients have visual and hearing impairments, hepatomegaly, and lesions of the respiratory and circulatory systems [11,22].

Type IV MPS disease has a progressive type of course. The onset age is 1–3.5 years, although the final diagnosis is delayed for many years (3–15 years) and is characterized by progressive valgus deformity of the knee joints, kyphosis, growth retardation against the background of a disproportionate shortening of the trunk and neck, and “duck gait” . The clinical picture is dominated by skeletal deformities in the form of spondyloepiphyseal dysplasia with secondary neurological complications. The main features of Morquio syndrome, which are not found in other types of MPS, are small joint hypermobility and wrist deformity. Hip subluxation and knee instability are common in patients with type IV MPS. The combination of dentate hypoplasia and ligamentous laxity can lead to instability of the atlas axis, which can subsequently lead to narrowing of the spinal canal and compression of the spinal cord [3,4].

Most patients have a classic disease phenotype, but some patients may have serious impairments in other systems, such as cardiopulmonary failure, even if they do not have typical outward symptoms [5].

The life expectancy of patients with type IV MPS can vary from 10 to 20 years, but there is also a certain percentage of patients who survive to an older age. In patients with Morquio syndrome, respiratory dysfunction is one of the main concerns. This may be caused by obstructive or restrictive processes. Destructive diseases can develop due to shortening or deformity of the chest and impaired mobility of the diaphragm. Obstructive sleep apnea syndrome (OSAS)

Table1

Pathology of the cardiovascular system

Sign	MPS I	MPS II	MPS III	MPS IV	MPS VI	MPS VII	MPS IX	MPS-PS
Age of manifestation of CCC pathology	6-24 months.	3-8 years; benign form 10-15 years	2-6 years	1-3.5 years	The first year of life	The first year of life	The first year of life	4 months
Pathology of the valve apparatus	+	+	+	+	+	+		+
Pathology of the mitral valve	+	+	+	+	+			+
Pathology of the aortic valve	+	+	+	+	+			+
Pathology of the tricuspid valve	+	+	+	+	+			+
Pathology of the pulmonary valve	+	+			+			+
Cardiomyopathy	+	+	+	+	+	+		+

Table2

Respiratory system injury

Type of MPC	Chronic bronchitis	Apnea	Pneumonia	Noisy breathing
MPS I	+	+	+	+
MPS II	+	+	+	+
MPS III	+	+	+	+
MPS IV		+		+
MPS VI	+	+	+	+
MPS VII	+	+		
MPS IX				
MPS-ПС	+	+	+	+

is one of the first signs of damage to the respiratory system. An abnormally high heart rate and arterial hypertension have been reported in adult patients. Respiratory disturbances characteristic of this type of MPS can lead to cardiovascular complications, such as pulmonary hypertension with subsequent development of cor pulmonale [3,4,5,11,22].

Mucopolisaccharidosis type VI. Patients with type VI MPS (Maroteau-Lami syndrome) were first reported in 1963 by Dr. Pierre Maroteau and Dr. Maurice Lamy (84). The incidence rate was 320,000 per birth [20].

The prevalence of type VI MPS in patients with different types of MPS ranges from 2% to 4% [88,89] in Scandinavia (Sweden, Norway, Denmark) to 8% (301) in the Netherlands. Selective screening in Brazil and northern Portugal has shown a higher risk of having children with Marotto-Lami syndrome. Patients with MPS VI in these countries were diagnosed in 18.5%, and in patients with various types of MPS, 16% were diagnosed [31].

The genetic form is autosomal recessive inheritance. This disease is caused by mutations in the ARSB gene. The gene is mapped on the long arm of chromosome 5 (5q13-5q14). It is known that there are more than 130 mutations in the ARSB gene, leading to the development of the disease. The absence or decrease in the activity of arylsulfatase B (N-acetylgalactosamine-4-sulfatase) leads to the deposition of dermatan sulfate in lysosomes. Chondroitin 4-sulfate is also a pathogenetic factor in the development of the disease [1].

Arylsulfatase B is an important enzyme involved in the structure of connective tissue. With a deficiency, lesions of the musculoskeletal system, cardiovascular system, and respiratory system develop. Studies by a group of scientists have shown that the accumulation of dermatan sulfate contributes to the development of pathological changes in the cardiovascular system and damage to the joints [4].

The clinical manifestations of the disease are heterogeneous, and their onset ranges from a few months to 10 years. The first symptoms are usually detected in the 1st year of life, but there are also cases when the disease progresses slowly [3]. In rapidly progressive Maroteau-Lami syndrome, patients experience significant growth retardation, and by 3–4 years of age, growth stops, reaching 120 cm [20]. Stiffness of large and small joints, respiratory failure, heart failure, etc. will gradually increase. Early rough facial features of the gargoylism type are observed, such as protruding frontal tubercles, sunken bridge of the nose, macroglossia, gingival hypertrophy, delayed teething. Hirsutism, chest deformity, contracture, scoliosis and kyphosis, hepatosplenomegaly, umbilical and inguinal hernia, noisy breathing, shortness of breath, rhinitis, sinusitis, and otitis media are common in most patients. In addition to progressive corneal opacity, damage to the optic nerves due to compression and hydrocephalus can also lead to visual impairment [5]. In the second year of life, he develops severe obstructive pulmonary disease and respiratory failure requiring tracheostomy. It should be noted that the intellectual development of the patient remains within the normal range. Stenosis or regurgitation of the heart valve requires arthroplasty, and complications requiring surgical intervention appear with age. Severe damage to the joints, especially the hip, requires arthroplasty. Median nerve decompression is necessary for toe deformity due to carpal tunnel syndrome. With severe spinal deformity, stenosis of the spinal canal in the cervical region also requires surgical correction [20].

The slowly progressive form of Maroteau-Lami syndrome is characterized by a slow onset of clinical symptoms. However, even if it progresses slowly after the second decade, orthopedic complications, valvular heart disease, and deterioration in lung function may develop [31].

Recently, intermediate types have begun to be described, since there are no clear descriptive criteria for determining the severity. For example, severe symptoms can develop within a single system to the point of requiring major surgical intervention [3].

Mucopolysaccharidosis type VII. Sly's syndrome is a rare disease among mucopolysaccharidoses. The defective GUSB gene responsible for the development of the clinical picture of Sly's syndrome is located on the long arm of the 7th chromosome (7q21.1-11). Not a single case has been registered in Russia, it occurs in less than 1 in 1,250,000 newborns. In fact, this disease develops in the womb, and most babies who develop it die before or shortly after birth. If it is not severe, then in the 1st year of life the same signs appear as in the Hurler syndrome.

Type of inheritance - autosomal recessive. The essence of the disease lies in the deficiency of an enzyme called β-glucuronidase, which decomposes mucopolysaccharides (glycosaminoglycans, GAGs). GAG degradation products accumulate in the tissues of many organs, leading to the development of pathology. In Sly's syndrome, edema and hyperplasia of many organs usually appear earlier and are more pronounced than in other types of mucopolysaccharidosis. First, hydrocephalus (cerebral edema), enlarged liver and spleen are detected.

Anomalies in the development of a fetus with Sly's syndrome can be detected with regular ultrasound examinations in the 2nd or 3rd trimester; in this case, prenatal diagnosis is additionally performed with amniocentesis and measurement of enzyme activity. However, because it is an extremely rare disease, the significance of the β-glucuronidase enzyme is rarely tested. The most severe cases of MPS VII are characterized by high water pregnancies or excessive accumulation of fluid in the tissues of the fetus, which can lead to the death of the baby before or shortly after birth. The symptoms and stages are varied due to the variety of mutations in the genes themselves. In mild cases of Sly syndrome, neonatal jaundice may occur. The mild form of MPS VII, like many other mucopolysaccharides, develops at the age of 1 year. These include coarse facial features and

a flat bridge of the nose, a large disproportionate head (megacephaly), umbilical and inguinal hernias, a very large abdomen due to abnormal enlargement of the liver and spleen, and delayed physical development (inability to roll from the abdomen to the back or maintain a sitting position). After 1 year, hypoplasia and multiple bone malformations become noticeable. Between the ages of 7 months and about 8 years, clouding of the cornea of the eye may occur. As the disease progresses, hearing loss, speech delay (not necessarily with intellectual impairment), recurrent upper respiratory tract infections, heart disease, and hirsutism (excessive growth of facial and body hair appear) [2, 13, 18, 23, 31].

Mucopolysaccharidosis type IX. Mucopolysaccharidosis type IX is caused by a deficiency in an enzyme called hyaluronidase 1 (Hyal-1), which breaks down hyaluronic acid (HA). MPS type IX is the rarest MPS, with only 4 patients reported to date. In 1996, the first MPS IX patients with periarticular soft tissue masses and nodular hyperplasia, short stature, and acetabular erosion were reported [46]. In 2011, Imundo and colleagues reported that 3 brothers from the Middle East developed juvenile idiopathic arthritis (JIA) [Imundo et al. 2011]. All reported patients with MPS IX had joint and bone problems. Other symptoms included short stature, cysts, frequent ear infections, and lupus (suppositories) [17].

Mucopolysaccharidosis-plus syndrome. MPS-PS is a new hereditary disease, identified and described in 2017 by a group of scientists from Yakutia and Japan, Turkey [Kondo et al., 2017; Dursun et al., 2017] molecular genetic cause of autosomal recessive disease mutation in the VPS33A gene (NM_022916.4: c.1492C> T, NP_075067.2: p.Arg498Trp), VPS33A gene (NM_022916.4: c.1492C> T, NP_075067.2: p.Arg498Trp, hereinafter referred to as p.R498W). The VPS33A gene is mapped and located on chromosome 12q24.31 and contains 13 exons. The mutation is located in exon 12, which codes for domain 2 of the VPS33A protein. To date, only p.R498W has been described as a mutation that leads to the development of this disease and the accumulation of heparan sulfate in the urine and plasma of patients. MPS-PS leads to multisystem damage to organs and systems with signs of lysosomal mucopolysaccharidosis accumulation disease. The frequency of the mutant allele among the Yakut population is 1:81 and 0: 1218 among the Turkish population. The predicted value of the incidence rate in the Republic of Sakha (Yakutia) is 1: 12000 newborns. The new disease was entered into the McCusick international database under the number OMIM # 617303 and was named mucopolysaccharidosis-plus syndrome (MPS-PS).

The clinical course of patients is similar to that of other types of MPS. A characteristic feature of MPS-PS is early manifestation of the disease and early infant mortality, multisystem organ damage - lungs, kidneys (secondary nephrotic syndrome, severe proteinuria 2–3 g / day, nephromegaly, the activity of enzymes involved in GAG metabolism was within normal limits) , heart (septal heart disease and severe course), central nervous system and damage to the hemopoietic system (severe anemia requiring blood transfusion, coagulopathy with hemorrhagic syndrome) [22,31].

Conclusion. Since mucopolysaccharide disease was first reported in 1917, thousands of cases have been reported worldwide. MPS are multisystemic diseases, most of them are characterized by phenotypic features, which makes it possible to suspect the diagnosis “at first sight” of a person of the type of “gargoylism”. A rather striking feature of MPS is multiple dysostosis. Of course, the idea of MPS is formed on the basis of a comparison of clinical and instrumental data, and the final diagnosis can only be verified using laboratory methods. Knowledge of the onset and characteristics of the various subtypes of MPS allows for early diagnosis, which is essential for maintaining organic function and improving quality of life.

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ISOLATED SPINAL CORD INJURY IN CHILDREN - SCIWORA SYNDROME

The relevance of the isolated injury of the spinal cord in children is due to the severity of damage, which often leads to unsatisfactory results of the therapy. Objective. Analyse and legend in the form of an overview of literature Scientific products. Materials and methods. Scientific publications to write a review of literature were obtained from the PabMed, eLIBRARY, CYBERLENINKA. Literature sources were searched for the following keywords: isolated spinal cord injury, SCIWORA syndrome, SCIWONA syndrome, SCIWORET syndrome. Results and discussion. SCIWORA syndrome diagnostic frequency among children who have been injured by the postcase is from 3% to 6% of cases. Initially, this syndrome is to meet fishing up to 8 years of age, boys predominate among the victims. Most often other parts of the spinal cord are affected cervical. Lead to the development of SCIWORA syndrome car accident. The main clinical symptoms of diseases are weakness in the limbs, the feeling of the passage of the "electric current" on the spine, various neurological disorders: from a minor deficit to the complete absence of motor and sensitive functions. The severity of neurological coupling will determine the scale of F. Frankel and the ASIA scale. The leading diagnostic method is the magnetic-reserved tomography. The patient's treatment with SCIWORA syndrome conducts conservative and operational methods, while the standard of therapy is currently not developed. The most important projection criteria during SCIWORA syndrome is the initial neurological status of patients after injury and results magnetic resonance tomography. Children with the lightest in neurologically delicacy are restored completely. Conclusion. SCIWORA syndrome problem keeping your apartment. The necessary developed uniform approaches and standards in the tactics of the treatment of children with this melting pathology.

Keywords: children, isolated spinal cord injury, SCIWORA syndrome, literature review.

Introduction. The isolated injury of the spinal cord in children is an actual problem of modern traumatology and neurosurgery [26, 31, 32]. The relevance is due to the severity of damage gained by children, which often leads to unsatisfactory results of the therapy [22, 37]. In the domestic medical literature devoted to the spinal-spinal injury in children, aspects of SCIWORA syndrome - isolated spinal cord injury without related damage to the bone structures of vertebrals and intervertebral discs are not fully reflected.

Objective. Analyze the main domestic and foreign publications dedicated to isolated spinal cord injuries in children - SCIWORA syndrome. The obtained information is recycled and submit in the form of a review of literature.

Material and methods. Scientific publications To write a review of literature on the topic "Isolated spinal cord injury in children - SCIWORA syndrome" were obtained from modern PubMed, eLIBRARY, CYBERLENINNKA databases. A total of 42 scientific articles were used, which reflect the most actual problems and aspects of the topic studied. Domestic literary sources used - 4 (9.53%), foreign - 38 (90.47%).

The search for literature sources was carried out according to the following keywords: isolated spinal cord injury in children, SCIWORA syndrome, SCIWONA syndrome, SCIWORET syndrome.

Results and discussion. One of the first authors who reported the damage to the spinal cord in children without X-ray confirmations from the vertebrae and the spine binder, was S. Lloyd, published on this topic in 1971 [16]. The decade later, at the beginning of the 80s of the last century, the american authors of D. Peng et al., presented the medical community to the publication, in which 20-year-old clinical experience was set forth on a scientific basis about 24 children without radiation (x-ray and computer-tomographic (CT)) symptoms characteristic of the injuries of the vertebrae. This state of the authors have been defined as «Spinal Cord Injury Without Radiographic Abnormality» (abbreviated: SCIWORA) [21].

With a wide introduction into the clinical practice of magnetic resonance tomography (MRI), when it became possible to diagnose even minor damage to the spinal cord, a new term was proposed – SCIWONA (Spinal Cord Injury Worth Neuroimaging Abnormality). This abbreviation describes the clinical situations of damage to the spinal cord in children and adolescents unchanged on the MRI grams of the spine and the spinal cord [42]. In cases where the damage to the spinal cord is diagnosed in the absence of reliable history data on injuries, the term SCIWORET is used (Spinal Cord Injury Worth Radiographic Evidence of Trauma) [10].

In English-speaking medical literature, when describing the isolated spinal cord injuries in children, the term "SCIWORA" was the greatest distribution. Pathological conditions, regarded as "SSIWONA" and "SCIWORET" in pediatric patients describe significantly less often [41]. Scientific publications in foreign literature dedicated to SCIWORA syndrome sufficiently, which cannot be said about articles in domestic sources [4]. Even in the regulatory medical activities of documents, in relation to the spinal-spinal inju-

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ry, there are no recommendations for the diagnosis and treatment of SCIWORA. So, A.K. Dulaev et al., Analyzed all the domestic regulatory documentation available by 2021, the practical guidelines and clinical recommendations approved by the Ministry of Health of the Russian Federation indicate that they do not consider the provision of medical care to patients with this syndrome [2].

It is now known that the incidence of SCIWORA among children with various types of spinal injuries ranges from 3% [13] to 38% [38] of cases. In children and adolescents who are hospitalized in neurosurgical departments, the frequency of diagnosing this condition is in a wider range: from 3% [1] to 64% [4] of clinical observations. Despite the fact that in modern medical literature, especially foreign, there are a sufficient number of publications about the SCIWORA syndrome, the frequency of its diagnosis depends, according to D. Pang et al. "from the awareness of doctors of the local medical community about this condition" [20].

Most often, SCIWORA syndrome is diagnosed in children under 8–9 years of age [18, 26]. At the same time, cases have been published in the literature when adolescents predominate in the group of studied patients with this syndrome [34]. The main injury mechanisms leading to this type of injury are situations in which hyperextension, hyperflexion, and spinal distraction occur almost simultaneously [17, 19, 22]. Typically, such sharp and high-amplitude movements of the head and torso of patients occur during traffic accidents, as well as during sports training or competitions in such sports as wrestling, gymnastics, acrobatics, equestrianism [20, 31, 40]. At the same time, the literature describes clinical cases of the development of the SCIWORA syndrome in children with falls from a height of about 50 cm [32]. According to J. Knox, 87% of pediatric patients with spinal cord injury are diagnosed with various concomitant injuries of the skull, chest, limbs, pelvis, and internal organs [15].

Preferential damage to the spinal cord than to the vertebral bodies in young children is primarily due to the anatomical and physiological features of the growing spine [26, 30]. These include greater elasticity and extensibility of the muscular-ligamentous-capsular apparatus of the children's spine than of the spinal cord [7, 27], hyperhydrophilicity of the intervertebral discs [22], less intense blood supply to the spinal cord than in adults [39], structural features of the vertebrae (age-related underdevelopment of the uncinate (lunate) processes and more horizontal orientation of the articular processes at the cervical level) [7, 23]. In the development of the SCIWORA syndrome, the physiological disproportion in the size of the head and body of young children [40], the weakness of their paravertebral muscles [24] is of great importance. Almost all authors studying SCIWORA agree that the cervical level of the spine is affected more often than the thoracic and lumbar ones [18, 28]. So, according to T. Carroll et al. in the structure of injuries, the cervical region accounts for up to 87% of injuries, thoracic - 9.5%, lumbar - 1.5%, both thoracic and lumbar levels - 2% [31]. With regard to injuries of the cervical spine in children of younger age groups (up to 8-9 years old), pathology is more often diagnosed at the level of the cranio-cervical junction, in adolescent patients - at the subaxial level [15, 20]. At the same time, scientific articles were published that provide data from cohort studies on the predominant diagnosis of SCIWORA syndrome at the thoracic level of the spinal canal [23, 37]. Thus, the Chinese authors Z. Zou et al. reported that among 140 children with this syndrome, in 77% of cases, the pathology was localized at the thoracic level [22].

Most of the authors in their publications present gender differences in patients with this pathology in a ratio of 2:1, with a predominance in boys and young men [26, 29]. Information has also been published in the literature that the incidence of SCIWORA syndrome is 2.5:1.0 in favor of females [22].

The leading clinical symptoms of the disease are transient weakness and paresthesia in the extremities, a feeling of “electric current passing” along the spine [3, 21, 32]. In children of younger age groups, parents often indicate weakness in the legs when walking [32]. Vertebrogenic pain syndrome and breathing difficulties of the type of "post-traumatic apnea" are not recorded in all victims [4]. During a clinical examination, patients are often diagnosed with hypertonicity of the extensor muscles of the spine [25], episodes of encopresis and enuresis [32].

Researchers involved in the SCIWORA problem diagnose various conditions in patients: from a slight neurological deficit (type D, according to the F. Frankel scale) to a complete absence of motor and sensory functions (type A, according to the F. Frankel scale) [5, 32, 37] . In addition to the F. Frankel scale, the American Spinal Injury Association (ASIA) scale is used in clinical practice to standardize the examination and make a neurological conclusion in patients with clinical manifestations of SCIWORA [1, 33].

Since the CT of the spine does not fully appreciate the state of the spinal cord, MRI is given a leading role in the diagnosis of SCIWORA [1, 26, 31]. It is this procedure that allows you to investigate the contents of the spine channel, and with no other method of neurovalization to determine the fact and nature of damage to the spinal cord, if any. In most cases, during the diagnosis of SCIWORA, both research methods - CT and MRI [14, 32] are used [14, 32]. Some researchers pre-conduct X-ray of the injured spine [5, 25, 37]. It is important to note that the MRI criteria for the damage to the spinal cord in children with a diagnosis of SCIWORA are often detected during testing research, while this diagnostic procedure performed immediately after injury may not fix the symptoms of pathology [28, 31]. Japanese authors J. Ouchida et al. particularly emphasize that "... a delayed MRI study may represent extremely important information on the state of the spinal cord after the acute injury of the spine." This conclusion by the authors was made on the basis of three series of MRI-visualization of the spine in 68 patients with a diagnosis of SCIWORA: at the time of entering the hospital after the injury is received, after 2 days and after 2 weeks from the moment of hospitalization [11].

Treatment of children with a diagnosis of SCIWORA is carried out both conservative and operational methods, while the generally recognized standard of therapy is currently not developed [26]. All patients are attributed to compliance with the strict bed regime with immobilization of the injured spine, most often cervical, orthopedic products [5, 14, 32, 37]. Physiotherapeutic procedures are also used in the therapy of the spinal-spindy injury [25, 32, 37]. Medical therapy is to prescribe to patients with drugs from the corticosteroid group [31]. So, S. Sharma et al. [6] and S.P. Mohanty et al. [10] using the intravenous administration of methylprednisolone for these purposes in the first 48 hours of finding patients in the hospital. The main indication for surgical treatment of patients with SCIWORA syndrome is the lack of positive dynamics during neurological symptoms or its progression [9]. Most often, the volume of surgical intervention is to decompression of the injured spinal cord department by means of laminectomy [14]. Chinese authors C. Qi et al. they consider the optimal period of operational intervention for the first 3 days, which have passed after injury. In their opinion, based on the experience of surpassing 57 patients with SCIWORA syndrome, the quantity of time on op-

erational intervention is postponed, the worse the forecast [36].

According to T. Carroll et al., who analyzed 31 scientific articles, which presented a generalized experience in the diagnosis and treatment of 433 children diagnosed with SCIWORA, spinal immobilization and steroid therapy were used in 62.84% and 33.88% of injured children, respectively. Surgical treatment was subjected to 3.28% of the victims [31].

In generally, the majority of patients with SCIWORA syndrome register a marked improvement in neurological status during therapy. The main reason for choosing conservative therapy in the treatment of this category of patients is the absence of damage to the vertebrae, requiring their reposition and stabilization [26]. The two most important predictors of prognosis during SCIWORA are baseline neurological status and MRI findings [8, 33]. In children with complete spinal cord injury, the outcome of the treatment is unfavorable in terms of regression of neurological symptoms. Pediatric patients with a mild initial neurological deficit have every chance of a full recovery [12].

In the long-term period, the prognosis for health and life in children who have had a moderate severity of clinical manifestations of the SCIWORA condition is, as a rule, favorable [31, 26]. At the same time, they may reacquire clinical symptoms similar to the original symptoms of SCIWORA. Eight such clinical observations, which developed on average 2 weeks after the discharge of patients from hospitals, are reported in their article by D. Pang et al. all children repeatedly injured their spine during traumatic sports (4 children) or as a result of car injuries (4 children) [20]. Turkish authors N. Yalcin et al. cite data that neuromuscular scoliosis developed in 4 children, on average 17 months after undergoing SCIWORA, requiring subsequent surgical correction [35].

Conclusion. Various aspects of the spinal cord injury in children continue to maintain their relevance. During the analysis of modern scientific publications on the problem of SCIWORA, data and new facts were established to expand the horizons of specialist doctors providing specialized medical care in this category of patients. Thus, the frequency of occurrence of this type of damage in children was found out, it is shown in which age category patients are most often traumatized, the main mechanisms of injury and spinal cord levels affecting most often. In the literary review, the anatomy-physiological features of the growing spine, which determine the preemptive defeat of the spinal cord in children in comparison with damage to the bodies of the vertebrae. The clinical symptoms of SCIWORA syndrome, the most informative methods of radiation visualization of injuries obtained by children are described in detail. Treatment of children with isolated injury to the patients's spinal cord is carried out both conservative and operational methods, while all researchers, articles of which are analyzed and are given in the present literary review, noted the absence of uniform, generally accepted algorithms used during the course of therapy. The forecast for the health and life of children undergoing symptoms of SCIWORA syndrome is usually favorable. Those patients who had an initial light neurological deficit have every chance of complete recovery.

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MACRO- AND MICROMORPHOLOGICAL CHARACTERISTICS OF PLACENTA IN PHYSIOLOGICAL PREGNANCY AND COVID-19 AT DIFFERENT STAGES OF PREGNANCY

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Our article presents the macro- and micromorphological characteristics of placenta during physiological pregnancy and COVID-19 according to domestic and foreign literature. A search was made for foreign and domestic scientific publications on the morphological assessment of the placentas of healthy pregnant women and women with a confirmed diagnosis of COVID-19 (positive PCR test for SARS-CoV-2 virus).

In connection to the pandemic caused by a novel coronavirus infection, the study of the pregnancy and search for specific changes in women with a confirmed diagnosis of COVID-19 is of great interest among scientists around the world. Recent scientific publications focused mostly on nonspecific changes and signs of maternal and fetal vascular malperfusion. We reviewed publications, scientific articles, dissertations, literary reviews on E-library, Pubmed, Cyberleninka with access to the full text, whereas publications with paid access or abstract only were omitted.

Keywords: COVID-19, SARS-Cov-2, macroscopic changes, microscopic changes, placenta, umbilical cord, macrometry, morphological changes.

Despite the fact that pregnancy is a physiological process, its result is an adaptive mechanism [1]. Herewith changes in a woman's body should be maintained within the framework of average homeostasis and functional indicators, so-called "pregnancy norm" [6]. At the same time, during adaptive mechanisms, the body undergoes functional changes, taking into account hereditary, climatic-geographical, constitutional, age-related and other factors, which undoubtedly affect the course of pregnancy [8]. In the study of adaptive mechanisms, functional and morphological indicators, the placenta is a frequent object of research by anatomists, histologists, physiologists, and pathologists [3, 9]. The "mother-placenta-fetus" system during physiological pregnancy is in complex functional harmony. The placenta is an intermediate barrier organ (hemato-placental barrier) that develops during pregnancy, promotes the growth and development of fetus, structurally and functionally connecting the mother and fetus. Therefore, the placenta is an accurate record of the child's prenatal experience [5]. And without a doubt, the actualization of modern morphometric data on the placenta, on individual variability, age, ethnic characteristics and variability, taking into account the influence of external factors, is necessary in modern medicine. These data can be valuable scientifically and practically for establishing the norm of indicators and provide a personalized approach.

According to modern morphometric general data, placenta has a disk-like

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shape with a diameter of 15–20 cm and a thickness of 2.5–3.5 cm, and the mass reaches 500–600 g [2]. During physiological pregnancy, the umbilical cord is 50–55 cm long and 1–1.5 cm in diameter (up to 2–2.5 cm in the fetal region) [13]. During embryogenesis up to 12–16 weeks, the surface of the chorion is covered with villi, part of the villi adjacent to the basal plate forms the fetal part of placenta (villous chorion), and the villous and smooth chorion form placenta [9]. In turn, the maternal part of placenta, which faces the uterus wall, is rough, formed by the structures of the basal part of the decidua. The fetal part of placenta, which faces the fetus, is covered by the amniotic membrane [4]. During the normal course of pregnancy, starting from the 2nd trimester placenta is characterized by the predominance of intermediate undifferentiated and differentiated villi, and syncytiocapillary membranes appear subsequently. The proportion of intervillous space ranges from 25.5 to 33% depending on age, and the magnitude is quite stable throughout the reproductive period [7]. The proportion of elements of the chorionic plate varies from 5.0 to 8.0%; the proportion of elements of the maternal part of placenta is 1.8-5.2%; intervillous maternal fibrinoid - 1.8-5.4%; vascular bed of villi - 5.5-11.4%; their epithelium - 10.5-14.6%; peripheral trophoblastic elements - 5.3-6.0%; local pathohistological changes (calcifications, inflammatory infiltrates, areas of necrosis) - 3.8-7.5%. In the mature placenta, the terminal (30.2-43.5%), mature intermediate (28.0-32.0%) and stem (16-18% of the total) villi are predominant in relative quantity; mesenchymal villi are minimally represented (0.5–1.5%) [7].

The morphology of placenta depends on various factors, maternal diseases and environmental influence. Currently, one of the main trends in medical science is the study of the COVID-19 pandemic. A year after the recognition of the first outbreak, it spread throughout the world, grew into a global pandemic with more than 3.1 million deaths worldwide [24]. Even first publications related to COVID-19 confirmed the vertical transmission of the infection in a retrospective analysis of 10 newborns born from mothers with COVID-19 [27]. Over time, there are different information about the route of transmission of the infection and the detection of the virus in the tissues of the placenta. So, despite the available molecular and ultrastructural data on the SARS-CoV-2 virus in placental tissues of COVID-19 positive mothers, newborns were not infected [25]. And the teratogenic effect of COVID-19 infection in neonates has not been reported. Gajbhiye, Modi et al. (2020) noted that only 24 (8%) of 313 newborns born to mothers with COVID-19 had a positive PCR test for SARS-CoV-2 [15], which raises an important question about the problem possible transplacental viral transmission. Notably, maternal infection does not equate to placental infection. Similarly, evidence of viral infection of the placenta does not guarantee intrauterine vertical transmission to the fetus [19].

For these reasons, the study of the morphological features of placenta and umbilical cord in COVID-19 becomes necessary to determine and study the prenatal history of the fetus, the risks to the child and mother due to the disease.

In December 2021, authors from Slovakia Pavel Babal, Lucia Krivosikova et al. described a clinical case of fetal death in a pregnant woman with confirmed COVID-19 but no other noteworthy clinical or obstetric disorder, indicating that fetal death is a possible consequence of SARS-CoV-2 infection during pregnancy. On macroscopic examination, placenta corresponded to gestational age, the umbilical cord was varicose. Cross section of placenta showed numerous confluent grayish-white areas of infarction and dark red hemorrhagic lesions. The authors suggest that SARS-CoV-2 viral infection of the fetus was not the direct cause of death. Persistence of viral protein expression by trophoblasts results in extensive intercoupling fibrinoid deposition with successive placental infarction and ischemia which in turn leads to fetal death. This rare complication of pregnancy can occur regardless of the severity of the clinical course of COVID-19 in a pregnant woman [10].

A Swiss study (Thomas Menter, Kirsten Diana Mertz et al) describes cases of transplacental transmission of SARS-CoV-2 viral infection and the presence of viral RNA in both placenta and the umbilical cord. In an immunohistological study of a case of acute COVID-19, lymphohistiocytic villitis was found, which may be potentially associated with infection. The cellular composition of the inflammatory infiltrate was similar to cytomegalovirus placentitis or chronic villitis. The study also confirms pathological findings about maternal and fetal malperfusion, which may be associated with an altered coagulation state caused by SARS-CoV-2 infection, but this cannot be consistently proven due to confounding factors [18]. Another study by Lausanna University Hospital (David Baud, Gilbert Greub, et al.), 2020, in placental histology describes macrophage infiltrates and fibrin deposits, which the authors most likely attribute to direct viral infection. However, such intervillitis may be of a different etiology and therefore may not be associated with the presence of the SARS-CoV-2 virus [12]. Similar reports of the most frequently recurring features such as infarcts, fibrin deposits were in Zhang P., Salafia C. et al. (2020) and Hecht J.L., Quade B. et al. (2020) [26,16].

Another case study by French authors Alexandre J. Vivanti, Christelle Vaulop-Fellous et al. showed that, on microscopic examination, the placenta also showed signs of perivillitis, fibrin deposits with infarction and intervillitis. In this case, the neonate tested positive for PCR and required intensive care unit assistance for respiratory support [22]. Another publication (USA, June 2020, Rebecca N Baergen, Debra S Heller) reports placental histological changes. In a study of placentas from 20 women, there was a positive SARS-CoV-2 PCR test when routinely tested during pregnancy (32 to 40 weeks), 10 placentas showed evidence of possible fetal vascular malperfusion or fetal vascular thrombosis as a result of intramural fibrin deposition and stromal vascular karyorrhexis. However, there was no control group for comparison, which made it difficult to interpret the findings. The results were mostly of poor quality and may be related to other etiologies [11]. In a study by Elisheva D. Shanes, Leena B. Mitchal et al., May 2020, USA, placental results from 16 PCR-positive women were published. The placentas were from mothers between the ages of 16 and 40, with 11 maternal SARS-CoV-2 infections diagnosed around the time of birth and five diagnosed earlier in pregnancy. It has been reported that 12 out of 15 third trimester placentas show signs of maternal vascular malperfusion: abnormal and damaged maternal vessels, chorangiosis, or decidua arteriopathy [20]. These are quite statistically significant changes, for the reliability of the results, but the pathologists who conducted the examination were not blind to the mother's PCR-positive status. Since pathological changes have been shown in mothers with SARS-CoV-2 infection in most cases, and histological evidence of placental vascular malperfusion is somewhat subjective, these results must be interpreted with caution [23].

Studies by Brazilian scientists in 2021 show transplacental transmission of the SARS-CoV-2 virus only in some cases

(depending on the premorbid state of the pregnant woman), the virus was found in the amniotic fluid, umbilical cord, peripheral blood, but exclude reliable direct evidence of transplacental transmission of infection and specific morphological changes in placenta [17]. Also, pathognomic histological patterns in the placentas of mothers infected with SARS-CoV-2 have not been established, as shown in the review by Sharps M.C., Hayes D.J.L., et al. (2020) of 20 studies [21].

A 2020 study of Chinese scientists published at the beginning of 2021 (S. Chen, B. Huang et al.), in a retrospective analysis of 3 clinical cases of pregnant women with COVID-19 infection in the 3rd trimester of pregnancy, revealed that in the study group, placental changes are similar to manifestations as in women with normal pregnancy who are not infected (control group), and no serious adverse pregnancy outcomes were found. Pathological analysis shows that there are no morphological changes associated with viral infection in the placental tissue, and no vertical transmission of intrauterine infection from mother to fetus was found [14].

Conclusions. Our review shows a diverse range of outcomes in women infected with SARS-CoV-2. Care is being taken to treat pregnant women as a homogeneous group as outcomes may depend on the current status of the pregnant woman in light of the COVID-19 phenomenon. In acute COVID-19, marked lymphohistiocytic villitis may occur, which may be associated with infection of placenta with SARS-CoV-2. In addition, there are pathological findings of maternal and fetal malperfusion that may be related to the altered coagulative state caused by SARS-CoV-2 infection; however this cannot be consistently proven given the many confounding factors. In the literature, we did not find works related to the description of morphometric changes in the architectonics of the vessels of placenta and umbilical cord, and other histological changes in the tissue structures of the placenta, which could provide important information about the state of the fetus and perinatal outcomes in women with COVID-19.

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CHARACTERISTICS OF LOCAL ANESTHESIA METHODS AND AGENTS IN CLINICAL DENTISTRY

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The review examines the current aspects of improving the effectiveness and safety of local anesthesia in dentistry, since specialized care is the most common among the population due to the high prevalence of dental caries, its complications and periodontal diseases. At the same time, a significant proportion of clinical cases require anesthesia, where adequate anesthesia is achieved taking into account the psychoemotional state, comorbidity, age of patients, types of anesthetics and trigeminal nerve ramus block techniques. Currently, this problem has not been completely solved. Therefore, there are the researches increasing the anesthetic effect and safety of local anesthesia.

Keywords: local anesthesia, anesthetics, trigeminal nerve, anesthesia complications, premedication, efficiency and safety of anesthesia.

Nowadays, the priority state task is public health, which includes the preservation, strengthening the health of citizens, as well as increasing the medical care provided and its accessibility, training of qualified personnel. At the same time the preservation of the functional state of the organs and tissues of the oral cavity, as well as the maxillofacial region is one of the necessary indicators of the life quality of the population [14, 43]. In this regard, improving the quality and accessibility of therapeutic and preventive care to the population is a key area of health care development [28, 33].

Currently, dentistry is characterized by historical stages in the development of local anesthesia. In the middle of the last century, anesthesia of the maxillofacial region was carried out with the use of reusable syringes of the "Record" type. Meanwhile, in the 80s of the 20th century, disposable plastic syringes were used in dentistry. At the end of the century, the cartridge syringe technology of local anesthetic injection appeared in practical dentistry, which provided a significant improvement in the quality of anesthesia, due to the convenience and sterility of the solution [6, 41].

Today, we observe the development of medical science, clinical dentistry, including local anesthesia. In this connection the search of effective means and methods of anesthesia aid is carried out for the improvement of treatment and preventive care [17, 43]. High-quality anesthesia during dental interventions helps to reduce the psychoemotional state of patients, which ultimately has a positive impact on the results of treatment [3].

The dental pain-free medical manipulations largely depend on quality anesthesia, which is important for the patient in clinical practice. At the same time, up to 80% of patients need local anesthesia for their indications, which determines the importance of adequate anesthesia. In view of the above, clinical dentistry researches aimed at improving and safety of local anesthesia [25, 34]. Currently, the term "Personalized approach" is most widely used in the practical work of doctors, which is based on the knowledge of individual anatomical-topographic features of oral organs and tissues, as well as maxillofacial region [1, 2, 8, 23]. At the same time, the main factor of inadequate anesthesia in the maxillofacial region is a violation of the technological features of its performance, which requires a personalized approach that takes into account individual anatomical-topographic features of the jaws [7]. Meanwhile, insufficient efficiency of local anesthesia can be associated with variability in topography of trigeminal nerve ramus, which in some cases can be accompanied by traumatic needle damage of nerves, vessels, as well as masticatory muscles. Despite the study of the local anesthesia problems, it has not been yet solved. In this connection, researches improving the quality of local anesthesia are of great importance [3, 8, 18, 25].

Modern dentistry has the necessary level of effective and safe medications to perform adequate anesthesia in the maxillofacial region [3, 31, 35]. In addition, methods controlling psycho-emotional stress before a dental appointment are used to increase the effectiveness of anesthesia [17, 20, 40].

Today, a significant problem in clinical dentistry is the adequate preparation of the patient for medical intervention, since almost all patients experience fear. At the same time, patients with various concomitant somatic diseases require special attention, for whom dental treatment, as a rule, causes negative emotions, which leads to stress, disorganization of the functional systems of the body, changes in mental state [16, 22]. This situation at the stages of doctor's appointment dictates the need to monitor the patient's behavior, his motor skills, emotional and autonomic reactions. At the same time, it is necessary to conduct a thorough questioning, which allows to find out the peculiarities of subjective experiences and the patient's attitude towards medical interventions [3, 10].

It should be noted that various questionnaires and psychometric scales are widely used to determine the psychoemotional status of patients.

At the same time, the professional experience of a specialist plays an important role in the diagnosis and prevention of anxiety at dental appointments, which can allow a timely response to the possible prevention of the occurrence of various genesis of dental phobia [24, 26]. It should be emphasized that in certain clinical situations premedication methods are successfully used for adequate anesthesia in dental interventions [20, 24]. Premedication has several forms, which are characterized as nonspecific and

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specific forms. Nonspecific premedication is based on the use of substances that have mainly peripheral M-cholinolytic effect (atropine, scopolamine, methacin), that have sleeping and sedative effects (barbituric acid derivatives), non-barbiturates (noxiron, nembutal), ataractic agents - tranquilizers, neuroleptics and antihistamines [24]. Specific premedication involves the use of drugs that eliminate disorders in the body caused by the underlying disease, or reduce their severity. In this case, the most common simple and convenient method of premedication in outpatient dental practice is the use of pills, powders and solutions per os [20].

Three main groups of drugs are used in clinical practice: benzodiazepines, sedative-hypnotics, and antihistamines, which have a calming effect [12]. Chlordiazepoxide, diazepam, relanium, oxazepam, nitrozepam, medazepam, phenazepam, lorazepam, midazolam, dermicum, etc. are often used among benzodiazepine drugs. Drug action of benzodiazepines group, depending on their dose, is accompanied by inhibition of emotional and vegetative brain centers, which are located in limbic system [24, 37].

It is known that patients with pathological processes of organs and tissues of the oral cavity, as well as of the maxillofacial region are treated with painful symptoms of both local and general nature at dental appointments. Pharmacological methods (remedies, drugs, etc.) are used to relieve pain of the nervous system at different receptor, conductive, nuclear levels. This fact confirms that today medicinal analgesia in dentistry is the most widespread [4, 37]. In addition, pharmacological substances have multifaceted effects of the nervous system at different levels. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in dental practice. The pharmacological activity of these drugs is due to their anti-inflammatory, analgesic, antipyretic, and antiaggregant effects, which together have a positive effect in increasing the effectiveness of local anesthesia [13, 30].

Thus, the prevention of patient distress is important at the dental clinic. For example, nowadays, perfect computerized technology is used for local anesthesia, which provides guaranteed and stable success of anesthesia, full control over the procedure and reduction of patient's fear of injection [17]. Thus, the intensive development of innovative technologies in dentistry allowed the company "Milestone Scientific" (USA) to develop an automated computerized syringe "Wand" in 1997. One of the positive properties of the device is the absence of fear in patients before the injection, as it is not perceived as an ordinary syringe [17]. In addition, electronic injection systems "Sleeper One" and "Quicksleeper" (Dental Hi Tec) are used for local anesthesia, as well as "Amsa" and "P-Asa" block anesthesia. There is also a method of injecting the anesthetic into the tissues using high pressure (needle-free method). For example, in 2001, the new-generation needleless injector of the Injex system sized like a ballpoint pen and weighing 75 grams was developed by Rösch AG Medizintechnik (Germany) [19].

It should be noted that psychological correction is effective in severe forms of physical discomfort at dental appointments for patients with an acute syndrome [10, 15]. In addition, for the prevention of emotional stress and pain at high surgical and anesthetic risk, unmitigated fear, and when an allergic history prevents the administration of local anesthetics, suggestive therapy can be used. One method of dealing with emotional tension at the dental appointment is reflexive action on acupuncture points. This method is used as a means of adaptive management of the body and as a way to prevent the development of stress reactions by triggering more appropriate adaptation reactions, which together with adequate anesthesia increases the quality of medical interventions and their effectiveness [9]. Percutaneous electroneurostimulation (PENS) is successfully used to suppress nociceptive impulses at the level of spinal neurons during stimulation of acupuncture points HE-GU or ZU-SAN-LI. At the same time, the use of the CHENS method in practice reduces the need for analgesics in the postoperative period in some patients. In addition, a pronounced clinical effect can be obtained by electrostimulation (electrodentoanalgesia) of the auricular reflexogenic zones by changing the frequency and duration of stimulating impulses when the analgesic effect occurs during electrostimulation. For this purpose the apparatus "Analgedenta" is successfully used [19, 29].

Local anesthesia with a wide range of drugs is widely used in practical dentistry, which is the most convenient and safe way to control pain in dental practice [21, 42]. Thus, local anesthetics with different compositions and components are used to anesthetize tissues of the maxillofacial region, the improvement of which is the main link in the development of local anesthesia in dentistry [5, 25, 32, 38]. Lidocaine, mepivacaine and articaine preparations are the most widespread in practice [4, 39].

For the last period, a wide range of local anesthetic preparations has been presented in the Russian dental market, which facilitates the choice of means for carrying out interventions [5, 21, 36]. At the same time, there are a number of drugs for anesthesia, both Russian and foreign-made, which are generics - drugs that do not differ by their international nonproprietary name from the original drug, but differ by trade name and manufacturing technology, as well as by the composition of auxiliary substances. Manufacturers take measures to ensure the safety of drugs, use preservatives and stabilizers of the active substance, such as EDTA - a complexing agent that captures the metal ions (Al, Pb), leached from the glass. The presence of EDTA in anesthetics can cause headache, nausea, vomiting, local tissue irritation, kidney damage, cardiac arrhythmia, and allergic reactions [11, 22]. Often generic manufacturers do not offer a full range of forms and dosages, sometimes have different indications for use than for the original drugs. This situation needs to improve the knowledge of dentists on the pharmacokinetics and pharmacodynamics of local anesthetics [5, 27].

Thus, there are a wide range of methods and agents of local anesthesia in dentistry. Despite this, the problems of efficiency and safety of anesthesia in the maxillofacial region have not been completely solved. This situation determines the necessity of further studies increasing the efficiency and safety of local anesthesia and their implementation into the practical activity of doctors of medical preventive institutions of dental profile.

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IMMUNOMODULATORY PROPERTIES OF ANGIOGENIC FACTORS AND MYELOID SUPPRESSOR CELLS: A ROLE IN THE GESTATIONAL PROCESS

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The review presents data on the immunomodulatory role of angiogenic factors and myeloid suppressor cells. The mechanisms that play a key role in shaping the balance of proangiogenic and antiangiogenic factors, the role of endothelial growth factor (VEGF), placental growth factor (PlGF) and myeloid suppressor cells (MDSC, MS) in the development of gestational immunosuppression are shown. Data are presented on the molecular mechanisms of immunosuppression, the expression of check-point molecules that play a major role in the suppression of cellular immunity reactions. The role of tyrosine kinase receptors for proteins of the VEGF family - VEGF-1 (Flt-1), VEGFR-2 (KDR/Flk-1) in the regulation of immune responses has been characterized. Data are presented on the cross-regulatory interaction of angiogenic factors and myeloid suppressor cells and the immunomodulatory effect on cellular immunity responses. Disturbance of these mechanisms may be associated with the development of gestational complications, in particular preeclampsia. Based on the presented data, the possibility of evaluating VEGF and MS in pregnant women as prognostic biomarkers of preeclampsia is considered.

Keywords: vascular endothelial growth factor (VEGF), placental growth factor (PlGF), myeloid suppressor cells (MDSC), preeclampsia.

The process of formation of new vascular vessels plays an important role in many diseases and pathological conditions. the most intense neoangiogenesis occurs during embryonic development, pregnancy, and tissue repair [32].

Both activating and inhibiting angiogenic factors are involved in the regulation of angiogenesis [28]. Both during the tumor process and during pregnancy, a balance of proangiogenic and antiangiogenic factors is formed [9]. The formation of new organs is carried out due to two mechanisms - angiogenesis and vasculogenesis. Angiogenesis is the process of neovascularization from already inflammatory vessels, while vasculogenesis is the process of colon formation from cells - elevated angioblasts. During pregnancy, the processes of vasculogenesis and angiogenesis develop, including the key role of the growth of vascular endothelial inflammation (VEGF) [28].

Recent studies have expanded our understanding of the role of pro-angiogenic factors, in particular VEGF-A, in the regulation of immune responses. It is known that the cytotoxic activity of VEGF significantly increases the toxic activity of T cells, can increase the number of T cell regulators (Treg) and myeloid suppressor cells (MDSC), and also prevent the differentiation and activation of dendritic cells (DC) [10]. Basically, the VEGF family exerts its influence on T cell function through binding to type 2 receptors (VEGFR-2) [32], while the function of type 1 receptors (VEGFR-1) remains unclear. To identify a selective ligand for VEGFR-1 is placental growth factor (PlGF), also identified for a protein of the VEGF family, a study of the PlGF study to assess the role of VEGFR-1 signaling T-cells in the regulation of T-lymphocyte functions. At the same time, the revealed immunomodulatory properties make it possible to identify new manifestations of T-cell immunosuppression in conditions of neoangiogenesis [2].

Receptors for VEGF. Three types of tyrosine kinase receptors are known for the VEGF family - VEGF-1 (so-called Flt-1), VEGFR-2 (so-called KDR/Flk-1) and VEGFR-3 (Flt-4); and as a coreceptor of neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2) bundles [9]. Neuropilins exhibit an extracellular part, a transmembrane segment, and a short (about 40 amino acid residues) intracellular domain that require enzymatic activity [9]. Also, NRP-1 and NRP-2 form complexes that are included in the composition and form in a cooperative mode [28]. Neuropilins, acting as co-receptors, increased VEGF affinity for VEGFRs [34].

Thus, the VEGF family stimulates the cellular response of binding to receptors with tyrosine kinase activity on the cell surface, and the products are activated due to their transphosphorylation [28]. Each VEGF receptor has an extracellular portion consisting of 7 immunoglobulin-like regions; an intracellular portion containing a tyrosine kinase domain; and one transmembrane region. As a result of alternative splicing, receptors can be membrane-bound and free.

The VEGFR-2 receptor binds VEGF-A with high affinity and can also bind VEGF-C and VEGF-D [32]. It mediates the main properties of VEGF-A - acti-

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vation of angiogenesis and an increase in endothelial permeability; moreover, when bound to this receptor, the immunomodulatory activity of VEGF A is realized, which manifests itself in inhibition of the function of T-lymphocytes [34]. It is known that VEGFR-1 binds VEGF-A, VEGF-B, and PIGF, but its role in the implementation is insufficient (it is believed that it modulates VEGFR-2 signals) [28]. Another function of VEGFR-1 is solved as an "empty" receptor, isolating the VEGF protein from the VEGFR-2 receptor (which is especially important during angiogenesis during the development of the fetal volume). It has recently been shown that activation of VEGFR-1 upon binding to PlGF on immune cells can modulate the functions of the latter [8].

Immunomodulatory functions of VEGF family factors. The angiogenic role of all of the above factors is well known, and to a lesser extent, the immunomodulatory properties of VEGF-A and PIGF. In addition to stimulating neoangiogenesis, vascular endothelial growth factor has an immunosuppressive function, which manifests itself in the ability to suppress the functions of T-lymphocytes, differentiation and activation of dendritic cells (DCs), as well as stimulate an increase in the number of T-regulatory cells (Tregs) and myeloid suppressor cells (MDSCs) [33 34].

VEGF-VEGR interaction leads to activation of MAPK (mitogen-activated protein kinase, mitogen-activated protein kinase) and PI3K-Akt (PI3K–Akt signaling pathways, Akt signaling pathway) signaling pathways both in human CD4+ T cells and in endothelial cells [6]. It has been shown that activated T cells are characterized by increased expression of VEGFR-2 [34]. In addition to the direct immunomodulatory effects of VEGF A, it has been shown to have an indirect effect on T cells through combination with cyclooxygenase, activating FasL (Fas ligand). [34]. Apoptotic signaling occurs when the membrane form of FasL binds to Fas receptors that are expressed on the membrane of another cell.

It has been shown that VEGF-A, produced in the tumor microenvironment, enhances the expression of inhibitory check-point molecules, including PD-1 (Programmed cell death 1; CD279), CTLA-4 (cytotoxicT-lymphocyte-associated protein 4; CD152), TIM- 3 (T-cell immunoglobulin and mucin domain 3) and LAG-3 (Lymphocyte-activation gene 3), which are involved in the deletion of CD8+ T cells. Thus, VEGF A significantly reduces the cytotoxic activity of T cells [23].

An increase in VEGF production leads to the generation of Tregs, which have suppressor properties and can help reduce the number of effector T cells and suppress their proliferation [34]. Various types of Tregs are known to be involved in negative regulation of the immune response, including CD4+CD25+FOXP3+, CD8+CD25+FOXP3+, CD4+CD25+CD127 cells. At the same time, VEGFR 2 is selectively expressed by FOXP3high Tregs, which indicates the involvement of VEGFR-2 in the induction of the suppressor activity of regulatory cells [12].

Factors of the VEGF family suppress the maturation of dendritic cells, which are antigen-presenting cells and act as mediators between the innate and adaptive immune systems [14]. Immature DCs express relatively low levels of the surface MHC IMHC II (major histocompatibility complex) and costimulatory molecules such as CD80 and CD86 [34]. Mature DCs are characterized by an increased ability to process antigens [14]. Activated DCs differ from quiescent mature DCs in the expression of higher levels of MHC and co-stimulatory molecules and in the production of cytokines. In this case, maturation and activation can occur simultaneously [14]. Thus, factors that prevent differentiation, maturation, and activation of DCs can lead to the formation of tolerogenic DCs. According to research, VEGF A may be one such factor. Thus, it has been shown that an elevated level of VEGF A is associated with the presence of immature DC in the peripheral blood of cancer patients [34]. Probably, binding of VEGF to VEGFR blocks the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which leads to inhibition of DC maturation.

Vascular endothelial growth factor can recruit monocytes to the tumor and promote the generation of tumor-associated macrophages (MAOs), which are characterized by low antigen-presenting ability, reduced cytotoxic function and high production of IL-10, TGF-β and prostaglandins. Most MAOs are type 2 (M2) macrophages with tolerogenic activity, which promote tumor progression and metastasis [34].

The immunomodulatory properties of PlGF have been studied to a lesser extent. Nevertheless, this angiogenic factor, when bound to VEGFR1, has been shown to be able to suppress the differentiation of dendritic cells and induce a tolerogenic DC phenotype by inhibiting their Th1-stimulating activity [3, 24]. Our studies have shown that the activation of T-lymphocytes is accompanied by a pronounced increase in VEGFR1 expression. When PlGF binds to VEGFR1, T cell proliferation is inhibited, affecting both CD4 and CD8 T cells [2]. In addition, the addition of PlGF to T cells activated through the T cell receptor enhances the expression of VEGFR1 and VEGFR2 [8].

Myeloid suppressor cells. In recent years, new data have emerged that expand our understanding of the role of VEGF as an immunoregulatory factor. Thus, according to studies, VEGF is able to induce the generation of myeloid derived suppressor cells (MDSC) (MS), which have a pronounced suppressor activity [5, 29].

Myeloid suppressors are bone marrow cells of myeloid origin, which are formed from hematopoietic precursors, accumulate in the bone marrow and then enter the peripheral blood, lymph nodes, and other organs of the immune system [16]. Initially, MS represent a heterogeneous population of immature myeloid cells with a pronounced suppressor activity. Subsequently, MC accumulate in peripheral lymphoid organs and are able to differentiate into mature myeloid cells - macrophages, dendritic cells, granulocytes. Currently, 3 populations of MS have been characterized in humans: monocytic (M-MDSC), granulocytic (PMN-MDSC or G-MDSC), and early MS (e-MDSC) [6]. All types of MS are registered in the peripheral circulation: CD11b+CD14+HLA-DR−/loCD15− M-MDSC; CD11b+CD14−CD15+ PMN-MDSC and Lin− HLA-DR−CD33+ e-MDSC [13]. A number of authors consider MS as a key population of regulatory cells capable of controlling the immune response [29], including during the development of inflammation, trauma, autoimmune and oncological diseases, as well as during pregnancy [5, 18, 19, 26, 25].

The regulatory role of MS is due to the expression of a number of not only surface suppressor molecules - CD73, ADAM17, PD-L1, galectin-9 (Gal-9), but also intracellular markers such as arginase 1 (Arg 1), iNO-synthase (iNOS) , indolamine-2,3-dioxygenase (IDO) [15, 7]. Expression of a large number of suppressor molecules on MC, which bind to the corresponding receptors on cells, leads to suppression of the immune response and the formation of immunosuppression and death of T-lymphocytes. One of these mechanisms is the activation of inhibitory check-point molecules, in particular, the interaction of PD-L1 with the death receptor, PD-1 (Programmed Cell Death 1), which is present on all T cells [7]. The interaction of Gal-9 with the TIM-

3 receptor, which is expressed on the surface of CD4 and CD8 lymphocytes, leads to suppression of T-cell activity and MC generation [30].

Metabolic disorders and deficiency of arginine and tryptophan, due to increased production of Arg 1 and activation of IDO, can lead not only to the suppression of T-lymphocyte proliferation, but also to the suppression of macrophages and dendritic cells [22]. The ability of MC to produce suppressor cytokines (IL- 10, TGF-β1), which, together with the expression of a number of suppressor molecules, enhances their regulatory activity [19].

The presented data indicate the regulatory properties of VEGF and MC, which is manifested by the suppression of the functions of effector cells and the activation of lymphocytes with suppressor properties.

The role of VEGF and MS in the development of gestational complications. The processes of angio- and vasculogenesis and the formation of immunological tolerance are necessary conditions for successful placentation and the development of pregnancy. The development of late gestational complications is largely due to impaired endothelial function, which leads to the development of preeclampsia (PE). Preeclampsia is a multisystem pathological condition that develops after 20 weeks of pregnancy, is characterized by the appearance of symptoms of arterial hypertension, proteinuria, and still remains one of the five main causes of maternal death [1, 20].

The formation of the placenta during pregnancy and the accompanying changes affecting the mother's cardiovascular system are a highly regulated sequence of events. Normal maturation and development of placental tissue is necessary to provide the developing fetus with nutrients and oxygen. Violation of angiogenesis in the placenta determines incomplete remodeling of the uterine spiral arteries and, as a result, insufficient perfusion of the placenta and an imbalance in the production of angiogenic and antiangiogenic factors by trophoblast cells, which ultimately can lead to intrauterine growth retardation or PE [1, 4, 20]. Ischemia and hypoxia resulting from impaired trophoblast invasion lead to increased production of pro-inflammatory cytokines in the placenta. The state of hypoxia triggers a cascade of reactions, in which a group of transcription factors is activated: HIF 1 α and HIF 2 α (hypoxia-induced factors - 1-alpha, 2-alpha), which trigger the synthesis of angiogenesis stimulators, in particular, the VEGF factor [6, 4, 31].

Available data suggest that placental ischemia, which develops as a result of endothelial dysfunction with subsequent release of placental anti-angiogenic factors into the bloodstream, is of decisive importance in the development of PE. Currently, the possibility of using VEGF, PlGF, endoglin (sEng), and inhibin as biomarkers of timely prediction of the development of PE is being considered [1, 21]. The key molecules regulating early changes in placental vessels are VEGF A, PlGF, as well as Flt 1 (VEGFR-1) and KDR (VEGFR-2) receptors. Both VEGF and PlGF circulate at high concentrations during pregnancy, and their reduction can lead to poor vascularization and impaired vascular development during trophoblast invasion [6, 27]. It is known that the level of sFlt-1 increases in the blood of patients with PE [10]. According to experimental data, sFlt-1, obtained from chorionic villi in women with PE, induced an antiangiogenic state, which was leveled by the blockade of sFlt 1. When sFlt-1 was administered to pregnant rats, characteristic signs of PE appeared: hypertension, glomerular endotheliosis, and proteinuria [17]. Another anti-angiogenic factor secreted by the placenta that is elevated in women with PE is soluble endoglin (Eng). An increase in sEng concentration is observed in the blood sera of women with PE [6]. The exact role of these molecules during pregnancy and placentation is unclear, but it is suggested that Eng, via TGF-β, may play a role in the development of PE [6].

Thus, a significant decrease in the production of angiogenic factors - PlGF, VEGF, as well as an increase in the production of antiangiogenic factors - sEng and sFlt-1, are associated with the pathogenesis of PE [6]. Indeed, blocking VEGF by VEGF antagonists in cancer patients with monoclonal antibodies (bevacizumab, ranibizumab, and aflibercept) can lead to the development of a condition very similar to the development of PE - severe hypertension and proteinuria, as well as to an eclamptic pattern similar to leukoencephalopathy [17].

In recent years, data have appeared on the involvement of MS in the induction of physiological immunosuppression during pregnancy [18, 26]. However, data on the content of MS during pregnancy and their significance in the gestational process are presented by a few works. Thus, an increase in the number of MC in the peripheral blood in pregnant women compared with non-pregnant women and a decrease in MC in women with a threatened miscarriage were found [11]. An increase in the proportion of MS also occurs at the local level in the area of the fetoplacental complex. Placental MS shifts the T-cell response towards the Th2 type, suppressing the proliferation of the Th1 type. In this case, the overexpression of Arg1 and NOS2 (nitric oxide synthase), as well as the production of ROS (tyrosine kinase receptor) and IDO can serve as the mechanism of T cell suppression [15]. VEGF, the level of which also increases during pregnancy, can act as an inducer of MC generation [8].

Thus, the immunomodulatory activity of angiogenic factors and myeloid suppressor cells plays a significant role in the induction and maintenance of physiological tolerance to fetal antigens, and disturbance of their functions can be considered as a prognostic factor in the development of gestational complications.

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POINT OF VIEW

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NON-COGNITIVE DISORDERS IN PATIENTS WITH DEMENTIA HOSPITALIZED IN THE CENTRE OF NEURODEGENERATIVE DISEASES OF THE YAKUT SCIENTIFIC CENTRE FOR COMPLEX MEDICAL PROBLEMS FOR 2019 -2021

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A specific problem of the therapy of neurodegenerative disorders is mental symptoms, which significantly worsen the social adaptation of patients and further prognosis, require additional therapy with antipsychotics, often giving various side effects. For the period from 2019 to 2021, 51 clinical cases of various nosological forms of dementia were analyzed in the neurodegenerative center Yakut scientific center. Alzheimer's disease was most often diagnosed - 29 cases (56.8%), patients with frontotemporal dementia were most often admitted in second place - 9 people (17.6%), dementia with Levi's corpuscles (7.8%) and vascular dementia (7.8%) were most often diagnosed in third place. The average overall score on the Moca scale was 10.08+5.9 points, which corresponds to severe cognitive impairment. The difference in the age of manifestation in different ethnic groups of patients was established, as well as clinical and psychopathological features of patients with various nosological forms of dementia, taking into account ethnicity, as well as features of corrective therapy. Of the non-cognitive neuropsychic disorders, the symptom of agitation and aggression was most often detected.

Keywords: non-cognitive symptoms, dementia, Alzheimer's disease, frontotemporal dementia.

Introduction: One of the urgent problems of health care and social protection is to render qualitative medical and social help to patients with neurodegenerative diseases (NDD). It is known that neurodegenerative diseases are age-dependent and affect people of older age group. In 2019, the Center for Neurodegenerative Diseases at YSC CMP began its activities to provide specialized medical care to patients with NDD. The Center is the main link in the proposed improved organizational model of specialized care for patients with NDD and represents a single block of specialized care, including psychiatric care, where all stages of medical care are interconnected [1]. A separate problem in NDD therapy is mental disorders, which significantly worsen patients' social adaptation and further prognosis and require additional therapy with antipsychotics, often with various side effects.

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Behavioral and psychiatric symptoms of dementia (BPSD) include a heterogeneous group of non-cognitive manifestations: behavioral disorders and agitation, anxiety, irritability, depression, apathy, disinhibition, delusions, hallucinations, sleep and appetite disorders [5]. Ninety to 97% of patients with dementia have at least one PPSD, with apathy, depression, irritability, agitation, and restlessness being observed more frequently [6]. In 70% of patients with dementia, agitation is the most severe symptom [4]. The causes of behavioral and psychiatric symptoms are usually manifold and include biological, psychological, social, and environmental factors. To correct non-cognitive symptoms in patients with dementia, it is extremely important to characterize the social and physical environment that causes or aggravates behavioral and mental symptoms [3].

Materials and methods: the material of the study were clinical cases of patients hospitalized in the Center for Neurodegenerative Diseases between 2019 and 2021 years. The Montreal cognitive assessment scale was used to analyze the structure and degree of cognitive impairment. Statistical processing of the study results was performed using Statistica 6.0 software. Spearman rank correlation analysis, Mann-Whitney coefficient and Kolmogorov-Smirnov were used in the analysis. Differences were considered statistically significant at $p<0.05$

Results and Discussion: A total of 51 clinical cases of dementia in patients hospitalized in the Department of Neurodegenerative Disorders of YSC CMP from 2019 to 2021 were analyzed. The mean age at the time of the first hospitalization with this syndrome was 73.21+7.37 years. There were 39 women (76.5%) and only 12 men (23.5%). Mostly urban residents were hospitalized - 40 people (78.4%). The number of rural residents among the patients was small - only 11 people (21.5%). By nationality representatives of the yakut ethnic group (39 persons (76.5%)), the russian group (10 persons (19.6%)), other ethnic groups (2 persons) (Ukrainian, Korean) were mostly admitted for inpatient examination and treatment. Moreover, this trend persisted among urban patients as well. Thirteen people (24.5%) had secondary school education, 17 people (33.3%) had specialized secondary education, and 21 people (41.2%) had higher education. Only 9 persons were previously engaged in low-skilled labor, the rest worked as specialists, with school teachers being the most common occupation (17.6% or 9 persons). There were 25 married at the time of hospitalization (49%), 19 widows/widowers (37.2%), and only 7 single persons (13.7%).

Most often Alzheimer's disease was diagnosed - 29 cases, which accounted for more than half of all dementia cases (56.8%), in the second place we had 9 patients with frontotemporal dementia (17.6%), in the third place most often dementia with Levi's corpuscles (7.8%) and vascular dementia (7.8%) were diagnosed. The total duration of the disease averaged 2.3 + 1.3 years. According to

the degree of severity, moderate (cognitive disorders were already pronounced, criticism was reduced or absent, but the patient still retained self-care skills) and severe (severe cognitive disorders, loss of self-care skills, need for constant supervision and care) were diagnosed most frequently, which was 37.2% each. Mild degree of dementia was diagnosed (initial memory and attention disorders, the presence of full and partial criticism) less frequently and was identified in 13 people (25.4%). Cognitive impairments were assessed in almost all patients using the Moca scale. The mean total score was 10.08+5.9, corresponding to severe cognitive impairment. No significant differences in the overall score by gender were found, with an average score of 11.4 for males and 10.1 for females.

A correlation analysis revealed statistically significant correlations between the degree of dementia severity and the overall Moca score (r = - 0.544). Indeed, as the degree of dementia became more severe, the Moca score decreased. A statistically significant direct correlation was also found between the degree of aggression expression and morbid ideas. Indeed, the more aggressive the behavior, the more frequent the occurrence of painful ideas in the structure of the mental status.

When comparing patients of the yakut ethnic group and the russian group, no significant differences in the clinical picture were revealed. The only thing that was found was a statistically significant difference between the age of manifestation of dementia. Thus, the age of manifestation in the yakut group was 74.7+6.6, while in the russian group it was 68.4+8.1 ($p<0.05$). This difference was probably due to the large difference in the number of patients in these two groups.

Patients without pronounced behavioral and psychopathological symptoms were most often admitted to the department, since the department is not designed to treat patients with severe psychiatric disorders. But due to the fact that dementia is quite often accompanied by mental disorders, especially at a moderate and severe degree, patients were quite often diagnosed with some or other moderate mental disorders. Aggressive behavior was observed in 12 patients, which was approximately 23.5%, i.e., approximately ¼ of the patients. Aggression was mostly verbal, and was more frequently detected in patients with frontal temporal lobe degeneration. Aggressive behavior in patients was fairly well controlled by the use of the atypical antipsychotic quetiapine and the minor neuroleptic sulpiride. Anxiety states were also observed quite frequently in patients with dementia and accounted for 23.5%. Hallucinatory experiences were much less frequently observed in patients and were diagnosed only in five clinical cases and mainly in patients with dementia with Levy corpuscles, in which hallucinatory symptoms are pathognomic A characteristic feature of hallucinations in dementias is extracranial projection and predominantly lesions of the visual analyzer. Delusions (most often unsystematized, unstable, and polymorphic) were diagnosed in 5 (9.8%) patients and in all cases were accompanied by marked aggression. We would like to note that the delusions were mainly formed on the basis of memory disorders, and were extremely unstable, of domestic content, directed toward caring relatives. Self-care skills were preserved only in 11 (21.5%) patients, while severe disorders were observed in 10 (19.6%) cases, in all other cases partial preservation of primitive self-care skills was observed, when complex ones were already lost. Such impairments were characteristic of dementia of moderate severity. Only 8 (15,6%) out of 51 patients had previously applied or were already registered in the psychiatric hospital due to some or other mental disorders and consequently received psychotropic medications. It should be noted that only two patients from our sample underwent inpatient treatment in the psychiatric hospital after diagnosis, i.e. their psychiatric symptoms were so severe that they required urgent hospitalization in the psychiatric hospital. One patient was subsequently deprived of legal capacity. In general, it is possible to note low frequency of various productive psychopathological disorders in the patients. At the analysis of emotional-volitional disorders, it appeared that the majority of patients had some disorders, while the remaining patients (43.1%) had no expressed disorders. The most frequently diagnosed was a dullishly complacent mood (23.5%), which accompanied a severe degree of dementia and was indicative of a loss of critical faculties. In the second place, apathy, passivity, with no apparent decrease in mood was most frequently observed, which was detected in 9 cases (17.6%). We would like to note that in our study moderate or severe depressive states were practically not encountered, probably this feature is related to the fact that depression is characteristic mainly at the very beginning or in the prodrome of dementia disorders and to some extent reflects the preservation of critical faculties. Since severe and moderate depressive disorders were not detected, accordingly, suicidal tendencies in dementia patients were also not established during examinations. In general, it can be noted that many authors also note rare suicidal behavior in this category of patients, especially in moderate and severe dementia. Early onset of loss of criticism, apathy, indifference, and emotional dullness on the background of rapidly progressing cognitive disorders are protective factors against suicidal behavior. The established risk factors for suicidal behavior in dementia are: depressive disorders, relatively young age (age of onset of the disease up to 65 years), concomitant somatoneurological pathology, lack of positive dynamics from the ongoing therapy, loss of autonomy and social isolation [2].

Practically all patients with one or another mental symptoms received therapy with modern psychotropic drugs. To relieve aggressive behavior and productive symptoms, we used the drug quetiapine in doses ranging from 25 to 100 mg and sulpiride in doses ranging from 50 to 150 mg/s. For the correction of disorders of the emotional sphere, the most frequently used drugs were Grandaxin, Fevarin, Spitomine, and Velaxin, which also corresponds to modern standards of therapy of mental disorders. It also can be noted when prescribing nootropics, choline donators, some patients had worsening of behavior in the form of aggression, appearance of hallucinations, mainly in patients with Alzheimer's disease of average, severe degree of severity, which regressed after discontinuation of the drug.

Conclusions: 1. Patients who lived inYakutsk were most often admitted, and most of the patients belonged to the yakut ethnic group. It is likely that such a pronounced difference in the ethnic composition of patients with dementia is due to the fact that many elderly people who are not from the yakut ethnic group move to other regions of the Russian Federation for permanent residence, while patients of yakut nationality in most cases remain resident in the Republic.

2. No differences were found in the clinical picture of dementias between the yakut and russian groups. The only difference that was found was the difference in the dementia manifestation. Thus, the age of dementia manifestation in the yakut group was 74.7+6.6, and in the russian group was 68.4+8.1 ($p<0.05$), but due to the small number of patients in the russian sample, this difference found in our study requires further testing on larger patient samples.

3. Among psychiatric disorders, aggressive (agitated) behavior was the most common, occurring in 23.5% of all patients. Of all patients, only 15.6% (8 people) were at the time of hospitalization or were subsequently taken for outpatient observation in the psychiatric hospital of the Republic of Sakha (Yakutia) and regularly received medication correction of mental disorders.

4. No clinically significant depression was detected among the patients, which was due to the fact that most patients were admitted with a moderate to severe degree of dementia.

5. In case of early manifestations of cognitive disorders at the outpatient level, it is necessary to refer to the department of YSC CMP , in order to make an early diagnosis, to select appropriate therapy to suspend the progression of these diseases, to prolong patients' independence. If marked psychotic and behavioral disorders are detected, refer for treatment to psychiatrist at the regional psychiatric hospital of the Republic of Sakha (Yakutia).

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A CASE FROM PRACTICE

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BOTULINUM THERAPY FOR WRITING SPASM

The article presents a clinical case of a writing spasm, examines the clinical features of this disease at the present stage, and also provides modern methods of treatment that facilitate the patient's condition and quality of life.

Keywords: dystonia, hyperkinesis, botulinum therapy, botulinum toxin type A, focal dystonia, writing spasm, dyskinesia.

Introduction. Writing spasm is a type of focal dystonia characterized by a violation of the motor skills of the leading hand, in view of which the act of writing and small movements of the brush are greatly hindered or become impossible. It was first described by Bernardino Ramazzini in 1713 and was called the "scribal disease" manifested by pronounced fatigue of the hand when writing.

This disease affects not only those who write long and fast, it can also occur in musicians, machinists, programmers. It occurs equally in both men and women. The main characteristic of the writing spasm is the gradual development, often patients do not notice the appearance of the first symptoms, the disease initially manifests itself with slight changes in handwriting, a feeling of awkwardness when performing small movements of the brush, symptoms disappear after the termination of writing, changing position or shaking the hand. Then gradually the handwriting becomes rough, the movements become sharp and difficult to control, a pronounced kinetic tremor appears, and twisting of the brush can also be observed. Patients use corrective gestures, thereby reducing hyperkinesis. And they can also feel relief when changing the position of the hand when writing, using pens of certain shapes or changing the angle of inclination [7].

When this disease occurs, many factors precede it. First of all, it should be noted the nature of the work - as previously mentioned, musicians, programmers and professions related to writing mostly suffer. The monotony of actions against the background of emotional tension has a special effect. There are also a number of other reasons–features of the shoulder muscles, scoliosis, mental injuries, personal characteristics [3].

According to the Govers classification, writing spasm is divided into 4 types: convulsive – characterized by hypertonicity in the muscles of the hand, a feeling of heaviness and awkwardness of the hand. Paretic - sharp weakness in the muscles of the hand when writing. Tremor – tremor in the working hand. Neural – accompanied by pain during work [3].

It is noteworthy that with palpation, the muscles of the hands of normal consistency are painless. Patients are completely free to perform other motor acts. Further, these properties are gradually lost and other motor functions that require a high level of coordination of movements begin to suffer.

Diagnostics. In addition to a thorough neurological examination, it is necessary to test the letter - the quality of the handwriting, the speed of writing, the presence of corrective gestures are evaluated. You should also consult a psychiatrist

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to exclude mental disorders, borderline character traits. ENMG assessment of the regulation of muscle tone of the forearm. MRI of the brain to exclude organic intracranial pathology (encephalitis, brain tumors) [4].

Differential diagnosis is carried out between muscle diseases (myotonia, myopathy), ulnar nerve damage, carpal tunnel syndrome, vertebrogenic pathology (radicular syndrome, intervertebral hernia). They also differentiate between primary and secondary dyskinesia. Primary dyskinesia means professional neurosis thus the collection of anamnesis should include clarification of the nature of the work. And under secondary – a possible debut of torsion dystonia, that is, a hereditary history should be taken into account [3].

Treatment. The drugs of choice are muscle relaxants, benzodiazepine derivatives, adrenoblockers. But often, due to the lack of a quick effect, patients independently interrupt taking medications, and also stop due to side effects. The fastest and most promising method of treatment to provide real help to patients with writing spasm are injections of botulinum toxin type A, which relaxes the muscles leads to a decrease in dyskinesia [6].

Here is a description of a clinical observation of a patient with successful treatment of a writing spasm with botulinum therapy type A in the clinic of the YSC CMP.

Female, 58 years old. She turned to the neurological department of the YANC KMP with complaints of trembling, handwriting changes, tightening of the muscles of the right hand when writing and performing small movements.

Anamnesis of the disease: 4 years ago, after physical exertion, I noticed a restriction of movement in my right arm, pain in the right shoulder area. After 2 years, the trembling in the right hand began to bother me when writing, the handwriting changed a lot. At first, the patient controlled the tremor by a certain hand position when writing, regular massage and shaking the brush when writing. Gradually, the trembling began to bother when performing certain actions, such as typing in a phone, controlling a computer mouse, holding devices (forks, knives). According to the appointment of a neurologist, I took muscle relaxants, but I did not notice any effect. The occurrence of the above symptoms is associated with work (working as a teacher), as well as with a stressful load at work.

In neurological status: Tone in the hands according to the type of gear wheel with multidirectional actions. Muscle strength in the extremities - 4.5 points. Reflexes from the hands with biceps D = S are alive, from the triceps are reduced, carporadial are reduced, the finger test is performed with the intention of more on the right. Kinetic tremor of the right upper limb, manifested when writing, eating. Otherwise, no pathological changes were detected.

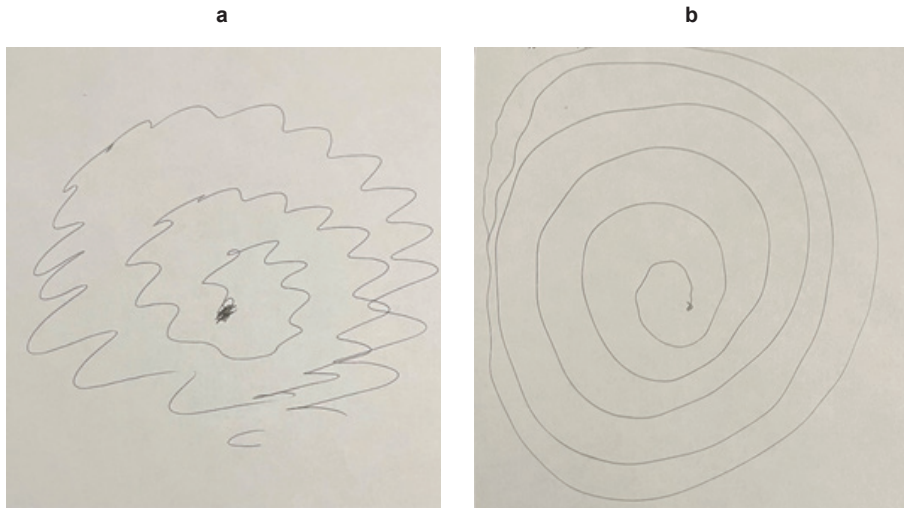

Fig. 1. Drawing the "Archimedes spiral" before the treatment: a - with the right hand, b - with the left

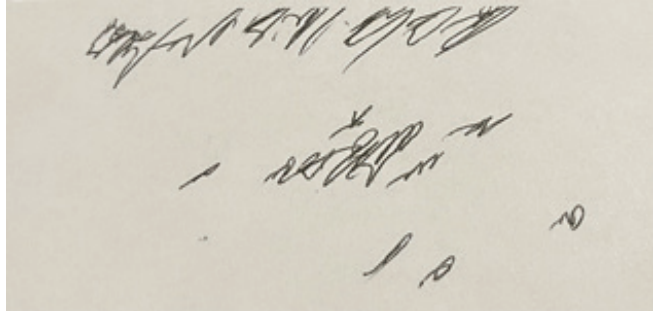

Fig. 2. The patient's handwriting

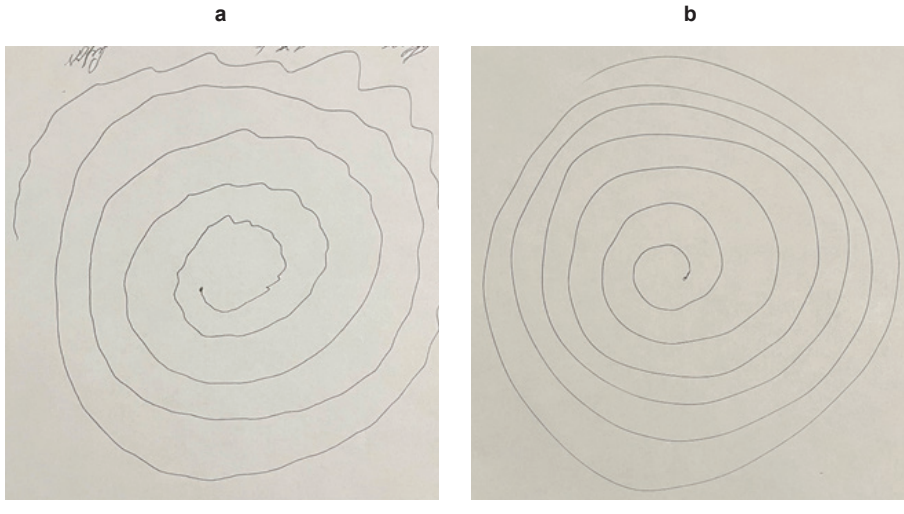

Fig. 3. The result of the test of drawing the "Archimedes spiral" after the treatment: a - with the right hand; b - with the left

MRI of the brain Conclusion: - few foci of the large hemispheres, most likely, of a vasogenic-glycemic nature; - unexpressed uneven swelling of the mucous membrane of the maxillary sinuses, cells of the lattice labyrinth without exudation, single cysts of the right maxillary sinus. There are no arteriovenous malformations, aneurysmal dilation, pathological stenotic narrowing of the intra-

cranial arteries. - decreased blood flow along the transverse and sigmoid sinuses, the initial sections of the internal jugular vein on the left against the background of hypoplasia. Психиатр при осмотре патологический изменений не выявил.

The patient was prescribed Sirdalud 4 mg per day, Anaprilin 60 mg per day, and botulinum therapy is also recommended.

Botulinum therapy was performed in the spastic muscles of the right forearm with botulinum toxin type A at a dose of 90 units.

Repeated results of letter testing are presented. The test was performed 7 days after botulinum therapy.

The test results clearly show that botulinum injections had a significant positive effect on the quality of writing. Also, the patient herself notes that the feeling of spasm and pain in the muscles of the right upper limb has significantly decreased. It became better to hold devices when eating, write texts in a mobile device.

Conclusion. Thus, on the example of the described clinical case, it should be assumed that botulinum therapy in the treatment of writing spasm has a significant and rapid positive effect and can be considered as a promising method of treatment for this pathology.

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A CLINICAL CASE OF ANCA-ASSOCIATED SYSTEMIC VASCULITIS IN A NINE-YEAR-OLD SAKHA CHILD

ANCA-associated vasculitis (AAV) is a group of diseases characterized by chronic immune inflammation of the small vessel wall, a polymorphic clinical picture with frequent involvement of the lungs and kidneys and the presence of circulating autoantibodies to neutrophil cytoplasm (ANCA). The article presents a clinical case of ANCA-associated systemic vasculitis with lung and kidney involvement.

Keywords: ANCA, vasculitis, inflammation, lung, kidney, child.

Introduction. Systemic vasculitis is a group of acute and chronic vasculitis, the most important pathomorphological features of which are considered to be inflammatory and necrotic lesions of the vascular wall [7]. ANCA-associated vasculitis is a systemic necrotizing vasculitis associated with antibodies to neutrophil cytoplasm (ANCA). ANCA vasculitis is represented by two major variants - granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

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The annual incidence is 20 cases per 1 million population worldwide [12]. In Europe and the United States, the prevalence of AAV is 1-2 cases per 100,000 population [2,4].

A definite association with the carrier of Staphylococcus aureus (HB - in aggravation), medications (EGPA), genetic factors has been established: The presence of HLA-DPB1*0401 (with which an increased risk of granulomatous disease in Europe is associated), polymorphism of genes encoding proteinase 3 (PR3) and its major inhibitor α1 - antitrypsin (SERPIN A1), which predisposes to hyperproduction of antibodies to proteinase-3[5]. Necrotizing inflammation of small and medium caliber vessels causes severity and multi-organ lesions in AAV.

The disease is characterized by high mortality due to damage of vital organs. Against the background of adequate immunosuppressive anti-rheumatic therapy in adults, the 5-year survival rate, according to some authors, is 70-75% [10,1].

Involvement of the kidneys in the pathological process is typical for all ANCA vasculitides. Clinically, renal damage manifests itself as a rapidly progressing nephritic syndrome [10,1]. ANCA-vasculitis belongs to renal diseases with the least favorable prognosis due to severe rapidly progressive drug-induced glomerular damage in the form of focal necrotizing inflammation of the glomerular capillaries, as well as rapidly progressive fibroplastic changes [11,9,1].

In children, the relevance of the problem is due to the high frequency of glomerulonephritis development [3,6,12]. Glomerulonephritis in AAV in children is a frequent and major manifestation, proceeding severely with a high risk of acute kidney damage with the outcome in terminal renal failure [6].

In this pathology, only timely clinical and morphological, immunological diagnosis and subsequent adequate therapy are the main factors of disease prognosis [1].

Clinical example: Girl A. born in 2012, a child of 1 pregnancy. On-time delivery, operative. Birth weight 3750, length 51 cm. Breast-feeding until the age of 1 year. She was growing and developing according to her age. Rare colds were registered.

Debut of the disease at the age of 4 years in May 2016, the child had a rash on the face, with the accession of a purulent infection. A district pediatrician diagnosed her with streptoderma. Treatment was prescribed: externally - levomikol ointment, lycopid in a dose of 1mg per day for 10 days.

Since 14.05.2016, the temperature rose to 38.0-38.5C°, cough, outpatient treatment was prescribed by the district pediatrician: bromhexin, nebulizer therapy with berodual 10 drops 2 times a day for 10 days, Sumamed in an age dosage. Since 30.06.2016 there was improvement: cough less often, temperature normalized. Since 29.07.2016 cough intensified, temperature increased to 39C°, pain and limitation of movement in knee and ankle joints appeared. Paraclinically: accelerated erythrocyte sedimentation rate (ESR) up to 60 m/hour (normal: 2-8 mm/hour). Chest X-ray of the chest organs dated 3.08.2016: Left-sided polysegmental pneumonia.

The patient was hospitalized by emergency indications on 8.08.2016 to the pulmonology department of RC RC RC №1-NCM in a serious condition with phenomena of respiratory failure of degree 2: respiratory rate up to 70 per min, fever up to 39.0ºC, pronounced signs of intoxication and arthritic syndrome.

Paraclinically: sedimentation rate 98 mm/hour (the norm: 2-5 mm/hour), neutrophil leukocytosis -12.3x109/l (the norm: 5-9.5 200x109/l), iron deficiency

anemia - blood hemoglobin 103 g/l (the norm: 105-145 g/l).

Computed tomography of the chest organs of 8.08.2016: multiple polymorphic foci with indistinct contours, with a tendency to fusion and formation of infiltrates, mainly in the lower and middle parts of the lungs. Focal infiltrative changes in both lungs, probably bilateral polysegmental bronchopneumonia.

Abdominal ultrasound - diffuse changes of both kidney parenchyma with thickened sinuses.

The patient was prescribed ceftriaxone, fluconazole, caspofungin, pentaglobin with insignificant positive dynamics.

Dynamics of chest CT scan data:

- 15.08.2016: partial resorption of foci in the lungs and restoration of pneumatization;

- 1.09.2016: lung infiltration density decrease in the lower lobe of the left lung. Without clear dynamics in the upper lobe of the left lung, in the right lung.

Paraclinically: from 1.09.2016: COE 63 mm/hour, anemia, hemoglobin level 90 g/L; hyperfibrinogenemia 7.5 g/L (normal: 2-4 g/L). In single urine portions, proteinuria from 1 to 1.75 g/l.: microhematuria changed to macrohematuria, cylinduria. Anti-dsDNA (antibodies to double-stranded DNA) IgG - 36.5 (normal 0 to 25), total ANCA - 3.24 (normal to 1.0).

Clinical diagnosis: ANCA-associated systemic vasculitis with lung and kidney damage.

Since 2.09.2016 he has been receiving methylprednisolone 12 mg/day. Since September 13, 2016, she has been receiving mycophenolate mofetil 250 mg/day, also received deaggerant therapy, captopril, inhalation with pulmicort. The child was hospitalized in SPbGPMU. Nephrobiopsy of the kidneys was performed: picture of ANCA-associated glomerulonephritis, focal variant, with cellular-fibrous semilunions (37%), with segmental and global sclerosis (49%), tubulointerstitial nephritis with minimal inflammatory activity, without necrotizing capillaritis. Baseline therapy was changed to cyclophosphamide at an age-appropriate dose of 1000 mg/m2/month (6 months total).

Computed tomography of the chest organs dated January 11, 2017: positive dynamics was noted due to a decrease in the size and density of the thickened areas of the left lung. Due to failure to achieve remission, therapy with rituximab at a dose of 500 mg, 2 injections every 2 weeks, change of baseline therapy with cyclophosphamide to mycopherolate mofetil (MMF) was prescribed. First administration of rituximab in 500 mg dosage on February 28, 2017, second administration on March 14, 2017 at the place of residence. Due to pronounced B-cell depletion and development of hypoimmunoglobulinemia, a six-month course of therapy with intravenous immunoglobulin (IVIG) drugs 1 g/kg -1 once a month was administered, a gradual reduction of methylprednisolone dosage was performed.

In summer 2017 the patient had no infectious diseases, received a full course of IVIG, methylprednisolone at a dosage of 6 mg/day. In October 2017, the patient received a course of rituximab in a dosage of 500 mg intravenous drip. At the end of November 2017, against the background of an acute respiratory infection, proteinuria up to 1 gram in a single portion of urine was observed. The dosage of MMF drug was recalculated, the dose of methylprednisolone was decreased, treatment with VBIH 1 g/kg once a month was continued.

In the next six months, there were recurrences of proteinuria in the field of acute respiratory infections; no clinical manifestations of vasculitis were noted. The patient grew by 3 cm and added 2 kg.

In June 2018, MMF therapy was continued, against the background of decreasing the dose of methylprednisolone, a course of VBIH treatment was prescribed for 6 months.

In November 2018, another administration of rituximab once in a dosage of 500 mg, since January 2019 prednisolone was completely abolished. There were no pathological changes in clinical and biochemical tests, proteinuria in single urine tests was up to 0.3 g/l. The patient grew by 6 cm, added 2 kg. Severe hypoimmunoglobulinemia IgA - 0.3 mg/ml (normal: 0.7-3.0 mg/ml), IgG - 3.5 mg/ml (normal: 8.0-16.0 mg/ml); IgM - 0.94 mg/ml (normal: 0.6-2.0 mg/ml); IgE - 0.5 ME/ml (normal: 0.0-100.0 ME/ml) persisted.

Computed tomography of the chest organs on 10/27/221: Focal interstitial changes in the lungs, no changes in the dynamics of 2020. Increased size of the thymus gland. Consultation of ophthalmologist on 10/27/2021: OU - Hyperopia of 1st degree. Initial complicated posterior capsular cataract. Retinal angiopathy.

Discussion: Our article describes a case of early debut of AAV (at the age of 4 years) as HPA with predominant kidney and lung involvement. The peculiarities of our case were early debut, absence of upper respiratory tract (URT) involvement. A multicenter retrospective study showed that the median time to diagnosis of AAV was 1.6 months for IPA and 2.1 months for HPA, with a maximum delay in diagnosis of up to 39 and 73 months, respectively [8]. The median age of debut was 12 and 14 years, with the earliest cases reported in the study being 1 and 2 years, respectively [8]. Among children with HPA, up to 30% may not have an AFD lesion, whereas MPA is usually 100% without an AFD lesion. Joint syndrome is about 1.5 times more common in patients with HPA. Renal damage is more frequent and severe in patients with MPA, they have a more frequent nephrotic syndrome and a higher need for renal replacement therapy [8]. Pulmonary involvement, on the contrary, is more typical for HPA, and is represented by cough, pulmonary bleeding, pleurisy, presence of nodules, infiltrative changes and decay cavities on lung radiological examination. Abdominal symptoms are more typical for MPA, while ENT lesions (chronic destructive otitis media, septal perforation, orbital and sinus granulomas, chronic sinusitis, granulomatous lesions of the larynx and trachea) are typical for GPA [8]. Cutaneous lesions: nodules, hemorrhages, purpura, ischemic necrosis are more common in patients with MPA. Nonspecific symptoms (fever, myalgia, intoxication, weakness, weight loss >10%) and increased CRP are more typical for patients with HPA. Among the immunological tests, the detection rate of antibodies to MPO (p-ANCA) was 55% for IPA patients and 27% for HPA patients, whereas antibodies to proteinase-3 (c-ANCA) were more common in HPA patients (67%) than in IPA patients (17%). At the same time, 26% of children with SMI and 5% of children with HPA were negative for all ANCA types [8]. Among treatment approaches, corticosteroids (97%) and cyclophosphamide (76%) were the main therapeutic agents; methotrexate, azathiaprine, and mofetil mycophenolate were used less frequently. Plasmapheresis was used in 21% of cases [8]. Rituximab was used in 12% of children with AAV.

Conclusions: AAV in children is a rare pathology with little coverage in the available scientific literature. The peculiarity of the case is an unusually early debut, the need for anti-B-cell therapy due to the lack of effect of hormonal-cytostatic therapy.

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A SEVERE CLINICAL CASE REPORT OF A NOVEL CORONAVIRUS INFECTION (COVID-19) OF A PATIENT WITH DIABETES MELLITUS

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The article describes a clinical case of a severe course of a novel coronavirus infection (COVID-19) in a woman with comorbid pathology from the practice of the infection department of the Yakutsk Republican Clinical Hospital (YRCB). Type 2 diabetes mellitus, obesity, and arterial hypertension in an elderly woman were predictors of the severe course of a new coronavirus infection, which led to the development of ARDS and caused the death of this patient.

Keywords: COVID-19, viral pneumonia, diabetes mellitus, obesity, "cytokine storm", Yakutia.

Introduction. According to March 14, 2022, the total number of COVID-19 cases worldwide is more than 458 million, with more than 6 million deaths.

People with serious comorbidities are at a higher risk of severe disease caused by COVID-19 [1]. For example, an analysis of 1,099 diabetic patients hospitalized with COVID-19 showed that the severe course of infection (16.2%) was almost 3 fold more common than the mild course (5.7%) [2].

Regarding mortality, according to the results of the Chinese Center for Disease Control and Prevention, among 44,672 patients diagnosed with COVID-19, the mortality rate among people with diabetes was also significantly higher (7.3%) than in the general population (2.3%) [3].

In type 2 diabetes mellitus (T2DM), both humoral and cellular immunity are affected as a result of primary immune impairment. Poor glycemic control, in turn, impairs the immune response to viral infection and potential bacterial infection in the lungs. In addition, T2DM is associated with obesity, a risk factor for severe infection through systemic inflammation, bronchopulmonary pathology, and sleep apnea. Moreover, in DM the frequency of comorbidity and the presence of vascular pathology is high: cardiovascular disease, chronic heart failure (CHF), chronic kidney disease (CKD), diabetic foot, etc. [4, 5, 6].

Discussion: The article presents a clinical case of a novel coronavirus infection in the presence of many risk factors of a severe form of the disease, which resulted in a fatal outcome.

Patient P., 73 years old, first symptoms appeared on December 4, 2021 - fever up to 38.5°C, weakness, chills, pains in joints, body aches and pains. On December 6, 2021, she called a physician, and on December 7, 2021, a PCR test was taken for SARS CoV-2 RNA. During the outpatient phase of treatment, arbidol and antipyretic drugs was prescribed.

The patient had concomitant diseases: type 2 diabetes mellitus, grade 3 arterial hypertension, grade 1 obesity

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(BMI 30.11 kg/m2), chronic pyelonephritis, COPD. For BP stabilization she took Lorista 50 mg and Capotene 25 mg on an irregular basis. She suffered from diabetes mellitus since 2015, and took oral antidiabetic drugs irregularly. Periodically she received courses of Metformin (850 mg 2 times a day), Galvus (50 mg 2 times a day). She was not vaccinated against influenza, novel coronavirus and pneumococcal infections.

On the 4th day of the disease, i.e., on 08.12.21, the patient was hospitalized with a confirmed diagnosis in the infectious diseases department of the YRCB.

Objective status at admission: Condition of moderate severity, body temperature +36.2 °C. Alert. Appetite and sleep were preserved. The position was active. The skin and visible mucous membranes were clean, of normal color, no rashes. The pharynx had no catarrhal phenomena, and the tongue was clean and moist. Peripheral lymph nodes were not enlarged, painless. Respiration was independent, free, auscultatory in all fields, respiratory rate 18 per minute, SPO2 96% without supplementation with humidified oxygen. Heart tones are rhythmic, muffled. Hemodynamics are stable, BP 120/80 mmHg, heart rate 100 beats/min. The abdomen was soft, not swollen, painless on palpation, the liver was not enlarged. Urination was independent and free. Diuresis was adequate. Stool was normal. There were no edemas.

On admission the blood tests showed moderately elevated CRP 13.6 mg/l, ferritin - 106.7 mcg/l, LDH - 281 units/l, in the general blood test the leukocytes were 7.1 x 109/l, segmented neutrophils - 44%, stab neutrophils - 7.0%, lymphocytes - 36%, platelets - 226 x 109/l, ESR 19 mm/h, as well as there was hyperglycemia 16.6 mmol/l, moderate increase of transaminases ALT - 45.3 units/l, AST - 45.4 units/l. Computed tomography of the chest organs diagnosed bilateral polysegmental pneumonia, volume of lung lesion less than 25%, CT - 1.

Based on complaints, medical history, objective examination, the clinical diagnosis was established: U07.1 Novel coronavirus infection COVID-19 (confirmed on December 7, 2021), moderate form. Bilateral polysegmental viral pneumonia of CT-1 (09.12.2021). DN-0. Diabetes mellitus type 2. Hypertension 1 st., arterial hypertension 3 st., risk of CCO 3. Obesity 2 st.

The patient was treated as an inpatient in the infectious disease department for 4 days and received: Favipiravir 800 mg 2 times a day, with anticoagulant purpose Heparin 7.5 thousand units 3 times a day by p/k, With proactive anti-inflammatory purpose Metipred 60 mg every 6 hours (at 06:00, at 12:00, at 18:00, at 00:00). and also taking into account exacerbation of chronic bronchitis with presence of purulent sputum, Ceftriaxone 2 g once a day was appointed. Besides, the patient was prescribed short-acting insulin Apidra and long-acting insulin Tresiba 18 units at 21:00, Amlodipine 5 mg once a day, Omeprazole 20 mg twice a day, Bromhexin 8 mg three times a day with hypotensive purpose.

Despite the ongoing therapy, respiratory failure increased, hyperglycemia was not stabilized: glucose averaged 16.4 mmol/l, glycated hemoglobin - 11.7%. Given the negative dynamics, chest X-ray was performed repeatedly, where the progression of lung lesions up to 50% was detected, CT 2-3. Blood tests showed CRP 67.7 mg/L, LDH 364 units/L, creatinine 87 mmol/L, urea 8.4 mmol/L, general urinalysis showed moderate leukocyturia 4-6 per field of view, yeast-like fungi.

On 12/12/21, due to the severity of the disease, persisting temperature up to +37.2 °C, increased degree of lung damage to CT-3, decreased saturation to 89% when inhaled with atmospheric air, 94% with humidified oxygen, with the threat of ARDS, interleukin-6 inhibitor was prescribed with anti-inflammatory proactive purpose. With negative dynamics, on the 9th day of the disease the patient was transferred to the pulmonology department with ICU support.

An endocrinologist was consulted in the pulmonology department in connection with hyperglycemia up to 32 mmol/l, and hypoglycemic therapy was readjusted. The inflammatory process could not be controlled against the background of the therapy. Blood tests on December 13, 21 showed a significant increase in CRP level to 127.6 mg/L, ferritin 301.9, LDH 325 units/L, neutrophilic leukocytosis - leukocytes 10.1 x 10 9 9/L, neutrophils 81.9%, as well as elevated sedimentation to 33 mm/h. Given the increase in CRP level from 67.7 mg/L to 127.6 mg/L, high ferritin level of 301 mcg/L, low saturation, 94-95% with humidified oxygen supply, presence of severe KT-3 pneumonia with proactive anti-inflammatory purpose, intravenous levilimab 648 mg was re-injected.

On the 12th day of the disease, patient P. with deterioration was transferred to the emergency room with complaints of dyspnea, marked weakness, desaturation up to 85%. On December 15, 21, the volume of pulmonary lesions on CT scan. The volume of pulmonary involvement was 72-76%, CT 3/4, Lab tests showed white blood cells 32.4 x 109/L, neutrophils - 91.3%, sed rate 1.0 mm/h, platelets 231, glycated hemoglobin 12.5%, glucose 10.2 mmol/L, CRP 3.4 mg/L, ferritin 320 µg/L, LDH 730 units/L, creatinine 97.0 µmol/L, urea 7.6 mmol/L. Her condition progressively worsened, her respiratory and cardiovascular signs grew, her blood count increased to 27.1*109/l, neutrophils 85, Lymphocytosis up to 27.1*109/l, neutrophils - 85%, ALT - 67.4 units/l, AST - 153.7 units/l, urea - 23.7 mmol/l, creatinine - 801 µmol/l, ferritin - 406 µg/l, LDH - 1171 units/l, CRP - 7.2 mg/l, glucose - 10 mmol/l. According to the results of computed tomography on December 24, 21, compared to CT investigation on December 19, 2021, there was negative trend, the lesion volume was more than 75%, CT-4. Effusion in the left pleural cavity.

The patient died on December 30, 21, the cause of death was respiratory failure, progressive pulmonary and cardiac failure, multiple organ failure syndrome. Диагноз клинический посмертный:

Main disease: U07.1 - COVID-19, virus identified (07.12.2021), severe form.

Complication: community-acquired bilateral viral-bacterial polysegmental pneumonia of severe grade, CT-3-4. DN 2-3. On December 25, 21, he was placed on a ventilator. Syndrome of systemic inflammatory reaction. Syndrome of multiple organ failure. Pulmonary edema, cerebral edema.

Background disease: Diabetes mellitus type 2, decompensation stage. Target level of glycated hemoglobin less than 7.5%. Diabetic micro-, macroangiopathy. Diabetic nephropathy. Chronic kidney disease, stage 5, GFR 4 ml/min as of 12/29/2021. Mixed genesis dyscirculatory encephalopathy (hypoxic, diabetic).

Associated diseases: J12.8 - Other viral pneumonia. Atherosclerosis of the aorta, aortic and mitral valves. Minor pericarditis. Hypertensive disease, 3rd stage. Grade II arterial hypertension, risk of CCO4. Bilateral hydrothorax. Chronic heart failure, ejection fraction 64%, stage 2a. Chronic bronchitis, exacerbation. Grade I obesity. Adipose hepatosis. Urinary tract infection.

Conclusion: In the presented clinical case the patient had many factors aggravating the course of the infection process, such as type 2 diabetes mellitus, obesity, the presence of a focus of chronic infection (chronic bronchitis), arterial hypertension, diabetic nephropathy

and advanced age, which contributed to the unfavorable course of the new coronavirus infection.

Patients with diabetes mellitus should monitor glucose levels more closely throughout the day and continue taking the blood glucose-lowering drugs recommended by their physician. The presence of diabetes mellitus is a significant risk factor for the rapid progression and poor prognosis of novel coronavirus infection (COVID-19). This group of patients needs priority vaccination against COVID-19 and pneumococcal infection, which can significantly reduce the risk of developing viral-bacterial pneumonia.

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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (CLINICAL OBSERVATION)

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Multisystem inflammatory syndrome is the most severe manifestation of a new coronavirus infection in children. The article presents the clinical case of the multisystem inflammatory syndrome features associated with COVID-19 in a teenager. The purpose of the work is to provide information on this topical clinical problem.

Keywords: multisystem inflammatory syndrome (MIS-D), fever, toxic erythema.

Introduction. Since April 2020, in some European countries and in the USA, children have been observed with signs of Kawasaki disease and toxic shock syndrome, causing inflammation of the whole body [6,8]. The new disease was given the name - children's multisystem inflammatory syndrome (MIS-D), associated with COVID-19. This disease occurs after infection with COVID-19 and affects mainly school-age children [4,5,6].

MVS-D is an inflammatory response of the body that occurs approximately 3-4 weeks after infection with a coronavirus infection. The initial symptoms of the disease are often manifested as fever, rash all over the body, redness of the eyes, abdominal pain, diarrhea and vomiting. The heart, blood vessels, and central nervous system are also affected, which requires emergency care [2,5].

According to the literature, almost 100% of patients with MVS-D have a fever, in one retrospective study of 21 patients it was reported that all had gastrointestinal symptoms, which usually occurred in the early stages of the disease [7]. Respiratory symptoms such as cough and rhinorrhea were relatively rare. Half of the patients had cardiogenic shock [9,10]. Another study reported that 56% of patients had macrophage activation syndrome (MAS), and Kawasaki-like symptoms were in 16-25% of patients [11].

The pathophysiology of multisystem inflammatory syndrome remains largely unclear. Apparently, it is based on a virus-induced hyperimmune reaction [3,8,5]. The most important role in the pathogenesis is played by the activation of T-lymphocytes, hyperproduction of pro-inflammatory cytokines (TNF-α, interleukins 1, 2, 6, 8, 10, granulocyte-macrophage colony-stimulating factor), deposition of immune complexes in the vascular wall. These mechanisms determine the development of a multisystem inflammatory response and explain most of the clinical and laboratory signs of the syndrome, such as fever, hyperferritinemia, coagulopathy, and an increase in inflammation markers [1,9].

Treatment. In accordance with the CDC (Centers for disease control and prevention) algorithm, therapy depends on the clinical manifestations and severity of the disease. Antibiotics are selected

empirically, at the onset of the disease, they should be prescribed to all patients [2]. Intravenous immunoglobulin is also prescribed at the rate of 1-2 g/kg, acetylsalicylic acid, low molecular weight heparins, infusion therapy, depending on the severity of the condition, glucocorticosteroids and genetically engineered biological preparations [1,2].

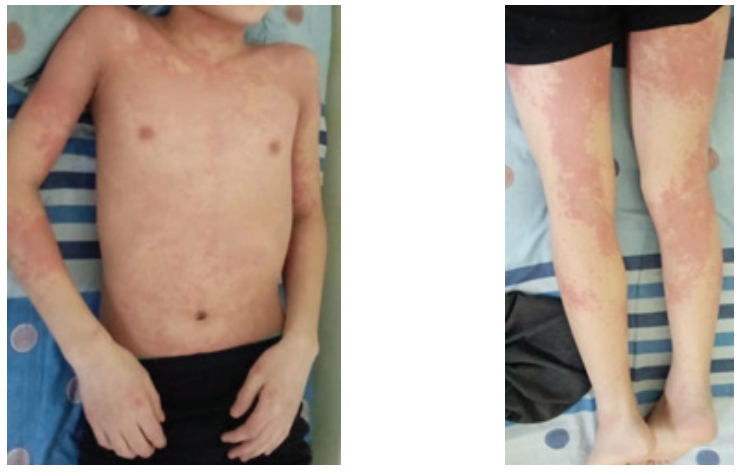
Material and research methods. A retrospective analysis of the medical history of a patient who was hospitalized in the cardio-rheumatology department of the Pediatric Center of the SAI RS (Yakutia) "Republican Hospital No. 1 - NCM" was carried out, where an in-depth examination and treatment was carried out according to all standards and clinical recommendations.

Clinical case. Patient A., aged 14, nationality - Sakha, was admitted to the cardio-rheumatology department of the Pediatric Center of the SAI RS (Yakutia) "Republican Hospital No. 1 - NCM" for examination and treatment. Complaints at admission: increased body temperature up to 38.5C - 40C, severe headaches, pain along the spine and in the cervical region when bending the head, turning the head, pain in the muscles of the thighs, legs and arms, rashes on the body, fatigue.

Anamnesis of life. A child from 1 pregnancy, 1 birth, birth weight - 2880g, Height - 50cm. Apgar score - 7/8 points. Development by age. Past illnesses: acute respiratory infections - rarely, atopic dermatitis, residual encephalopathy, recurrent urticaria with annual relapses, more often in winter. Heredity from words is not burdened.

Anamnesis of the disease: fell ill acutely, there was an increase in body temperature up to 38C, bright erythema, pruritus on the body. The temperature did not stop within 3 days, he was examined by the pediatrician of the Gornyi Central District Hospital, inpatient treatment was recommended with a diagnosis of multisystem inflammatory syndrome, toxic erythema. Linked immunosorbent assay for SARS-CoV-2 from 12/18/2020: IgM - 3.1 (norm < 1.0 U / ml); IgG - 13.6 (norm < 10.0 U / ml). Treatment was prescribed: cefotaxime, infusion therapy with saline solutions, antihistamine therapy, corticosteroids, symptomatic treatment. On the 4th day of the disease, no improvement was noted during treatment. After the consultation, he was sent to the cardio-rheumatology department of the Pediatric Center of the SAI RS (Yakutia) "Republican Hospital No. 1 - NCM".

On admission: the patient is in a serious condition, feeling low, correct phy-



Eruptions in a patient with multisystem inflammatory syndrome

Table1

Biochemical parameters of blood serum in dynamics

Serum index	19.12.2020	29.12.2020	11.01.2021	Reference values
ALT (u/l)	12.56	138.10	33.30	0-27
AST (u/l)	25.26	61.10	19.90	0-29
Urea (mmol/l)	4.61	8.40	5.80	1.8-6.4
Bilirubin total (μmol/l)	9.11	6.00	10.70	3.4-17.1
Creatinine (μmol/l)	60.66	51.64	47.81	27-62
Albumin (g/l)	43.26	36.20	38.20	38-54
Total protein (g/l)	72.30	77.60	72.10	60-80
Glucose (mmol/l)	7.01	4.11	4.73	3.3-5.6
GGTP (gamma-glutamyl transpeptidase) (u/l)		27.90	25.80	0-45
Phosphorus (mmol/l)		1.49	1.65	0.87-1.45
Lactate dehydrogenase (u/l)		175.70	139.40	0-250
CPK (u/l)		20.30	9.99	0-270
Calcium total (mmol/l)		2.34	2.41	2.1-2.55
Sodium (mmol/l)		135.50	138.10	138-145
Potassium (mmol/l)		4.49	4.05	3.4-4.7

Table2

Complex ultrasound of the heart (M-and B-mode, TsDK, dopplerography)

Date	Conclusion
19.12.2020	MK regurgitation of the 1st degree. The cavities of the heart are not dilated. EF - 76%. Separation of pericardial sheets along the posterior wall of the left ventricle - 3 mm.
21.12.2020	Expansion of the coronary arteries. Ectopic attachment of PSMK chords with minimal regurgitation. Regurgitation on TC 1 degree. Separation of the sheets of the pericardium. The cavities of the heart are not dilated. EF 69.7%.
28.12.2020	Ectopic attachment of mitral valve chords with minimal regurgitation. Regurgitation of the tricuspid valve 1 degree. Additional trabecula in the cavity of the left ventricle. The pressure gradient at the isthmus of the aorta is 14.0-15.0 mm Hg. The cavities of the heart are not dilated. PV - 69%. Splitting of the sheets of the pericardium along the posterior wall of the left ventricle up to 3 mm, in the region of the apex - up to 4.9 mm, along the anterior wall of the right ventricle - up to 2.5 mm.
12.01.2021	Expansion of the coronary arteries. Ectopic attachment of PSMK chords with minimal regurgitation. Separation of the sheets of the pericardium. The cavities of the heart are not dilated. EF - 71%.

sique, moderate nutrition. On the skin of the neck, chest, abdomen, upper and lower extremities, there is an erythematous diffuse spotty rash that does not rise above the skin (Fig. 1-2). Palpated small submandibular and inguinal lymph nodes, painless. Tongue with prominent papillae. Respiration is vesicular. Heart tones are clear, rhythmic, rough systolic murmur with a maximum in the 2-3 intercostal space to the left of the sternum. The abdomen is soft and painless. Hyperesthesia. Blood pressure - 90/60, heart rate - 76 beats per minute, respiratory rate - 18 per minute.

Research results. Complete blood count dated 12/25/2020: neutrophilia - 10.2x109 / l and an increase in ESR - 45 mm / h. In the biochemical blood test dated 12/29/2020: signs of cytolysis and an increase in the level of urea (Table 1). Immunological blood test dated 12/21/2020: CRP - 59.3 mg / dl (norm - up to 1.0), ASLO - 150 IU / ml (norm - up to 150.0).

In the dynamics of the ECHO-KG, an increase in the ejection fraction is observed. The separation of the sheets of the pericardium is preserved (table 2).

Chest X-ray dated 12/19/2020: no focal and infiltrative changes in the lung parenchyma were detected. Electroencephalography from 12/28/2020: Focal and epileptic activity was not detected. MRI of the brain from 12/21/2020: no pathological changes in the brain were detected.

Based on clinical and anamnestic data, laboratory and instrumental studies, the main diagnosis was established: Multisystem inflammatory syndrome associated with COVID-19 (M 35.8). Complications: Toxic erythema. Condition after acute coronavirus infection (asymptomatic).

Treatment was carried out: intravenous immunoglobulins ("Privigen"), cefotaxime, dexamethasone, clexane, aspirin, diacarb, asparkam.

Discharged with improvement on the 25th day of illness. The condition is satisfactory, feeling does not suffer. Body temperature - 36.1, heart rate - 80 beats per minute, respiratory rate - 20 per minute, blood pressure - 112/60 mm Hg. The skin is clean, the lymph nodes are not palpable, the pharynx is calm, the tongue is clean. Respiration is vesicular. Heart sounds are muffled, rhythmic, not coarse systolic murmur. Follow-up with a district pediatrician at the place of residence is recommended. Dispensary registration - at least 5 years. Examination by a cardiologist in a month.

Conclusion. This clinical case demonstrates a severe course of multisystem inflammatory syndrome in a teenager who had a new coronavirus infection in an asymptomatic form. A feature of the manifestation of the disease is the long-term preservation of changes in the cardiovascular system (dilation of the coronary vessels, separation of the sheets of the pericardium).

Thus, heart damage in multisystem inflammatory syndrome is the main symptom of the disease [3]. Based on diagnostic criteria, it is important to recognize the disease in a timely manner, differentiate from Kawasaki disease, and prescribe adequate therapy to prevent serious complications.

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