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FREQUENCY OF HETEROZYGOUS CARRIAGE OF MUTATIONS IN THE GENES OF NOTCH SIGNAL PATH IN PATIENTS WITH CLEAR CELL KIDNEY CANCER AND IN THE POPULATIONS OF THE VOLGA-URAL REGION

Aim of the study: to determine the frequency of mutations in the Notch signaling pathway (*DLL4* (rs35748882), *HEY2* (rs61737181), *JAG1* (rs1801140, rs1801139, rs45575136), *NOTCH1* (rs61751542), *NOTCH2* (rs3795666), *NOTCH4* (rs8192576, rs8192579, rs8192585) identified earlier as a result of exome sequencing in an expanded group of patients with clear cell renal cell carcinoma.

Materials and methods. The study included 238 paired samples of tumor and normal kidney tissue from patients with clear cell renal cell carcinoma. Detection of nucleotide sequence alterations of genes was performed using PCR followed by RFLP analysis. Restriction enzymes were selected using the NEBcutter V2.0 Internet resource.

Results. On average, the frequency of detected changes in the group of clear cell renal cell carcinoma patients was higher than the general population values. The highest frequency was found for rs8192579 and rs8192585 NOTCH4 gene. Clinical and pathological characteristics of the tumors in which mutations were identified, were heterogeneous and included patients with both early and late stages.

Conclusions. The results obtained in this study may indicate the contribution Notch signaling pathway gene alterations to the pathogenesis of clear cell renal cell carcinoma, as well as the possibility of their use in creating a molecular markers panel for the diagnosis and prognosis of the course of the disease.

Introduction. Renal cancer (RC) is a heterogeneous group of malignant tumors, the overwhelming majority of which are renal cell carcinomas of various morphological types. More than 300 thousand new cases of RC are registered in the world every year (Mohammadian et al., 2017). Due to the asymptomatic course of renal cancer, the disease is often detected in the late stages, aggravated by metastasis. In this regard, there is a clear need for an in-depth molecular genetic study of the pathogenesis of renal cancer, which will make it possible to identify new molecular markers for the early diagnosis of RC, to carry out more effective risk assessments, to select patients for more aggressive treatment methods, and to select molecules that will serve as new drug targets. The main molecular genetic event in the development of renal cancer is the change in the activity of the von Hippel-Lindau tumor suppressor gene (*VHL*), which accompanies about 70% of cases of sporadic renal cancer. Along with the VHL gene, a number of genes involved in different molecular pathways are involved in the pathogenesis of renal cancer. Transmembrane receptors of the Notch family carry out regulatory actions, affecting proliferation, apoptosis, differentiation, angiogenesis, metastasis, and other cellular processes that induce the onset and development of malignant tumors. Signaling through Notch receptors protects cells from a variety of apoptotic stimuli [10]. The four Notch receptors (Notch-1, -2, -3, and -4) are single-pass heterodimeric transmembrane proteins that are activated by binding to one of five ligands, Delta-like 1/3/4 or Jagged 1/2, expressed on adjacent cells [11]. Several studies have shown that the Notch signaling pathway plays an important role in the formation of mammalian kidneys. It has been shown that inhibition of Notch signaling in mice leads to a decrease in the epithelial compartment in the developing kidney with degradation of the proximal tubules [13].

It is known that abnormal activation of the Notch signaling pathway genes is observed in various types of tumors. It is believed that the Notch and Wnt pathways can be used as therapeutic targets. In contrast to *VHL*, mutations in Wnt and Notch pathway members in renal cell carcinoma are rare [5]. However, *VHL* and other important molecular genetic factors responsible for the development of kidney cancer activate the Wnt and Notch pathways. For example, loss of *VHL* stabilizes β-catenin via *JADE1*. B-catenin activation, in turn, is associated with advanced renal cancer and lower patient survival. At the same time, it was shown that Notch pathway signaling does not depend on the activity of *VHL*, *HIF1α*, *HIF2α* and the level of cell oxygenation. [8].

Previously, we performed exome analysis in patients with clear cell renal cell carcinoma, as a result of which the most pathogenic changes in the nucleotide sequence were found in the genes of the Notch pathway. The purpose of this work was to determine the frequency of mutations in the Notch signaling pathway (*DLL4* (rs35748882), *HEY2* (rs61737181), *JAG1* (rs1801140, rs1801139, rs45575136), *NOTCH1* (rs61751542), *NOTCH2* (rs3795666), *NOTCH4* (rs8192576, rs8192579, rs8192585) identified earlier as a result of exome sequencing in an expanded group of patients with clear cell renal cell carcinoma.

Materials and methods. The study included 238 paired samples of tumor

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and normal kidney tissue from patients with clear cell renal cell carcinoma. All examined were patients of the clinic of the Bashkir State Medical University in Ufa. The collection of tissue samples was carried out by the staff of the Department of Urology. The study was approved by the Bioethical Committee of the Institute of Biochemistry and Genetics. In the study group, 56.7% of patients had early stages of the disease (stages I-II of the malignant process according to the TNM classification) and 43.3% of patients had late stages (III-IV stages of the malignant process according to the TNM classification). The age of the patients ranged from 37 to 89 years.

The mutation frequency was also studied in a group of healthy individuals from the population control of Bashkir, Russian and Tatar ethnicity (50 individuals in each ethnic group).

Isolation of genomic DNA from paired samples of kidney tumor tissue and adjacent normal renal parenchyma was carried out by phenol-chloroform extraction. The frequency of mutations was determined in the genes of the Notch pathway identified by exome sequencing. The most pathogenic variants were selected for analysis using six in silico programs (SIFT, PolyPhen-2, LRT, Mutation Assessor, Mutation-Taster, phyloP, and GERP ++) from dbNSFP v. 3.0a. Detection of changes in the nucleotide sequence of genes performed using PCR followed by RFLP analysis. Restriction enzymes were selected using the NEBcutter V2.0 Internet resource [12].

Results and discussion. We analyzed 10 gene loci of the Notch signaling pathway in tumor and normal kidney tissue in 238 patients with clear cell renal cell carcinoma: (*DLL4* (rs35748882), *HEY2* (rs61737181), *JAG1* (rs1801140, rs1801139, rs45575136), *NOTCH1* (rs61751542), *NOTCH2* (rs3795666), *NOTCH4* (rs8192576, rs8192579, rs8192585). The frequencies of Notch pathway gene mutations in the study group of patients are shown in Table 1.

All mutations studied here were found in a heterozygous state. On average, the frequency of detected changes in the group of patients with clear cell renal cell carcinoma was higher than the general population values. Clinical and pathological characteristics of the tumors in which mutations were identified, were heterogeneous and included patients with both early and late stages. There were also no significant differences in mutation frequencies with the sex and age of patients. No changes were found in the population control.

The highest frequency of occurrence among the studied loci was demonstrated by changes in the NOTCH4 gene (rs8192579 and rs8192585). The NOTCH4 protein is a single-pass transmembrane receptor containing extracellular (NECD) and intracellular domains (NICD). The extracellular domain NECD contains repeats similar to Epidermal Growth Factor 29 (EGF) and serves to bind ligands and calcium. When bound to ligands (including Jag 1 and 2, Delta-like 1, 3, and 4), NOTCH proteolysis occurs, which releases the intracellular NICD domains from the cell membrane. The NICD then moves to the nucleus. NICD, in turn, activates the expression of a group of downstream genes such as *Hes* and *Hay*. Notch signaling is an important pathway involving cell proliferation, differentiation, and apoptosis [1]. It has been shown that *NOTCH4* plays an important role in the regulation of breast growth and development. Moreover, abnormal expression of *NOTCH4* can inhibit the differentiation of breast stem cells, and mutations in this gene are associated with increased proliferation of epithelial cells [9]. Increased expression of *NOTCH4* is also noted in tumor tissues in liver and colorectal cancer [7], as well as in prostate cancer cell lines [8]. On the other hand, mutations in the *NOTCH4* gene were found to be associated with an increase in the overall survival of patients with gastric cancer who received immunotherapy with PD-1/PD-L1 inhibitors [2].

It is known that the activity of the *NOTCH4* gene is associated with proliferation, invasion, and migration of renal cancer cells, as well as with the size of the tumor and the level of its differentiation [6]. In addition, a recent study has demonstrated that mutations of the Notch signaling pathway genes can influence the effectiveness of immunotherapy in clear cell renal cell carcinoma [3].

Conclusions. The results obtained in this study may indicate the contribution of the studied changes in the nucleotide sequence of the Notch signaling pathway genes to the pathogenesis of clear cell renal cell carcinoma, as well as the possibility of their use in creating a molecular markers panel for the diagnosis and prognosis of the course of the disease. However, further studies are required in larger patient populations.

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Frequency of nucleotide sequence alterations of Notch signaling pathway genes in patients with clear cell renal cell carcinoma

Gene	Type of substitution	Frequency, n (%)	Average frequency in the general population according to Ensembl DB - 1000 Genomes Project Phase 3 (%)*
DLL4 c.C1239T (rs35748882)	synonymous	0/238 (0)	1.0
HEY2 c.G588C (rs61737181)	synonymous	1/238 (0.42)	5.0
JAG1 c.A2214C (rs1801140)	synonymous	2/238 (0.81)	1.0
JAG1 c.C1578T (rs1801139)	synonymous	5/238 (2.10)	1.0
JAG1 c.C924T (rs45575136)	synonymous	1/238 (0.42)	3.0
NOTCH1 c.C4129T (rs61751542)	nonsynonymous	5/238 (2.10)	9.0
NOTCH2 c.C6421T (rs3795666)	synonymous	0/238 (0)	5.0
NOTCH4 c.T4828C (rs8192576)	synonymous	3/238 (1.26)	5.0
NOTCH4 c.A5427G (rs8192579)	synonymous	7/238 (2.94)	8.0
NOTCH4 c.C731T (rs8192585)	nonsynonymous	8/238 (3.36)	2.0

* No changes were found in the populations of Russians, Tatars and Bashkirs from the Volga-Ural region of Russia.

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ASSESSMENT OF RISK FACTORS FOR BRONCHIAL ASTHMA ASSOCIATED WITH CONNECTIVE TISSUE DISPLASIA IN CHILDREN LIVING IN SAKHA REPUBLIC (YAKUTIA)

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The article presents the results of the examination of 33 children with bronchial asthma in the pulmonology department of the children's consultation clinic of the Pediatric Center of the Republic of Sakha (Yakutia). 2 groups were formed due to the detected external signs of connective tissue disorder. Comparative analysis of BA clinical characteristics was described. The BA course associated with moderate and severe CTD was characterized by moderate forms and tendency to lower disease control, worse prognosis. Most children with BA in both groups had body weight deficient. All children with BA associated with CTD had musculoskeletal pathology as well as other comorbid diseases. Significant risk factors have been identified, such as the effects of parental smoking, the presence of pets, and low rates of breastfeeding.

Keywords: bronchial asthma in children, connective tissue disorder, children, allergies.

Introduction. Bronchial asthma (BA) is one of the important problems of pediatrics and clinical medicine, in general. [6, 19–21]. International and domestic program documents on BA emphasize the clinical heterogeneity of the disease, manifesting both in differences between individual patients, and also in the pathological process dynamics in each patient [21]. Connective tissue disorder (CTD) deserves special attention out of many causes for the development of individual features of BA course - this is a heterogeneous group of diseases of connective tissue of a polygenic-multifactorial nature, combined into phenotypes based on the commonality of external and/or visceral features [17].

CTD is a widespread pathology from 13 to 85.4% according to various researchers [7, 13, 14, 16]. The works on CTD effect on the structure and function of the bronchopulmonary system noted disorders of the elastic framework of the lungs: a change in the architectonics of pulmonary tissue in the form of interalveolar septum destruction and underdevelopment of elastic and muscle fibers in small bronchi and bronchioles, leading to reduced elasticity of pulmonary tissue with the formation of emphysematous bulls; polycystic disease on the background of bronchial obstruction and the formation of spontaneous pneumothorax. Congenital defect of the cartilage and connective tissue framework of the trachea and bronchi leads to impaired mobility (dyskinesia), the emergence of bronchiectases, pneumosclerosis. Tracheobronchial dyskinesia promotes bronchospasm [6, 18, 19]. The involvement of several organs and systems in the pathological process in children with CTD at the same time can explain more severe, non-classical manifestation of clinical symptoms in respiratory diseases, including BA [2, 4, 9, 13].

Attention to the BA problem associated with connective tissue disorder is explained by the early development of severe forms of the disease, complications, difficulties in selecting management programs for both adult patients [8, 11, 14] and children [5, 12, 13, 15].

The research aim is to study BA risk factors in children with CTD living in the Republic of Sakha (Yakutia).

Research materials and methods. The study included 33 patients with BA of Yakut nationality aged from 4 to 16 years old, examined in the pulmonology department of the children's clinic of the Pediatric Center of the Republic of Sakha (Yakutia). The research criteria included: proven diagnosis of bronchial asthma; informed consent of patients' parents to participate in the research, Yakut nationality. Criteria for exclusion from the research were: patients under 4 years of age; lack of informed consent to participate in the study, children with established hereditary connective tissue disorder; tuberculosis and other chronic lung diseases, other nationalities.

Diagnosis, severity and indicator of bronchial asthma control level was carried out with criteria of clinical recommendations "Bronchial asthma in children"

(2017) taking into account clinical (detailed anamnesis, a case history), laboratory (clinical blood test, rhinocytogram), functional (results of spirography and daily picflowmetry) and allergic (performing scratch test according to a standard procedure on the inner surface of the forearm, allergen-specific immunoglobulins E in blood serum) examination.

Connective tissue disorder was diagnosed by the external signs of connective tissue involvement (CT) [17]. The criterion for CTD severity was the point assessment of phenotypic signs of CT systemic involvement in children (screening algorithm) according to the classification of T. Milkovskaya-Dimitrova in the modification of L.N. Abbakumova: mild - 0-12, moderate - 13-23, expressed - over 24 points [1].

Two groups were formed due to the severity of CTD external manifestations: 1st (n = 15) - children with bronchial asthma and moderate and pronounced degree of CTD (sum of points over 12), 2nd (n = 18) - BA patients with mild connective tissue disorders (sum of points less than 12). In each BA patient, the level of stigma was determined according to the criteria proposed by V.G. Arsentiev, where a score of 40 or more was considered to be significant for CTD. The result from 30 to 40 points was treated as increased dysplastic stigma [3].

For each child, an individual questionnaire was issued with data from a case history, clinical examination. The BA pattern was evaluated, the level of control of the disease was determined by the asthma control test, the peak expiratory rate was monitored daily with a picflowmeter and the results were recorded in the patient's diary. The identification of possible risk factors determining the course of BA was carried out by analyzing family and allergological history, as well as assessing the quality of anti-inflammatory (basic) therapy, BA frequency per year, the duration of the disease, and the patient's living conditions. All children and parents were given recommendations how to achieve asthma control. Ultrasound examination of organs of the abdominal cavity, kidneys, heart, radiography, as well as specialists' examination was performed to identify clinical-instrumental signs of connective tissue disorders. Body mass index (BMI) was calculated by the formula: body weight (kg)/body length (estimated as normal indicator (18.5 - 30); body weight deficiency (< 18.5); obesity (> 30) [10]. Statistical processing of the material was carried out using a package of SPSS-22 programs using Mann-Whitney U-test, Spearman correlation analysis, differences at $p<0.05$ were statistically significant.

Results and discussion. Clinical and demographic characteristics of BA patients associated with CTD are shown in Table 1.

Boys were dominated in both groups. The groups were comparable in age, the average age in the 1st group was 9.1 ± 3.2 years old, in the 2nd - 8.7 ± 2.9 years old. The vast majority of patients in both groups were characterized by body weight deficiency.

Hereditary predisposition to BA was detected in 38.9% of patients from the 2nd group. Allergic rhinitis is equally common in both groups, in half of cases - from mothers, in 27-28% - fathers. Eczema from both parents was observed more often in the 1st group (46.7%). Atopic dermatitis in Sibs was detected 2 times more frequently in the 2nd group (44.4%) ($p = 0.002$) (Table 1).

Analysis of the structure of comorbid allergic pathology in children of both groups showed that BA was more likely to be associated with diseases such as allergic rhinoconjunctivitis, atopic dermatitis and pollen disease. Less often there were urticaria, Quinke's edema (Table 1).

According to allergotesting, sensitization to household allergens was more often detected in patients of the 2nd group than in the 1st group (Table 1).

The assessment of BA risk factors showed that the majority of children of the 1st group and half of the 2nd group lived in urban conditions (Table 2). There was a residence in a wooden house (barrack) in half of the cases of both groups. 27.8% of patients from the 2nd group and one child from the 1st group grew up in incomplete family. Breastfeeding has been found to prevent the development of atopy. The 2nd group patients were on natural feeding 3 times less often than in the 1st one ($p = 0.03$). The presence of pets was detected with equal frequency in families of the 1st (20%) and 2nd (16.7%) groups. 53.3% of children of the 1st group and 77.7% of children of the 2nd group were subjected to passive smoking by parents, the fathers of the 2nd group smoke most often in families ($p = 0.01$) (Table 2).

The analysis of laboratory data revealed the increased levels of total IgE serum in patients of both groups, but this indicator was shown 3 times more often in patients of the 2nd group ($p=0,03$). A third of patients in both groups had eosinophilia. An increased number of eosinophils were found 2 times more often in patients of the 2nd group, according to the rhinocytogram (Table 2).

The BA diagnosis was made at the age of 7,4±3,9 years old in the 1st group, in the 2nd group - 6,3±3,2,3 years old. The average duration of the disease in the 1st group was 1,8±2,4,8 years and in the 2nd - 2,4±2,6 years. The BA duration less than 1 year was established in 53,3% patients of the 1st group and 61.1% – in the 2nd group. The duration of the disease from 1 year to 5 years old was determined in 33.3% patients of the 1st group and in 11.1% patients of the 2nd group. The BA duration from 5 to 7 years old was detected in 1 and 2 children, respectively. The BA experience for more than 7 years was in 1 patient of the 1st group and 3 - in the 2nd group.

In the 1st group, a diagnosis of mild BA was established in 1 patient, moderate - in the rest of patients.

In all patients of the 2nd group, BA of moderate severity was stated. No patients with severe BA were recorded in the groups. All patients in both groups received baseline therapy according to the clinical guidelines "Bronchial Asthma in Children" (2017) and were followed up at the place of residence. To correct the therapy, children of both groups were referred to the NCM clinic to a pulmonologist, who revealed that the uncontrolled course of BA was recorded in 80% of patients of the 1st group. In the 2nd group, 50% of patients had partial or complete control over the disease. This circumstance required additional research by narrow specialists, correction of baseline treatment, dynamic control, and increased compliance in this category of patients.

At the 2nd stage, after in-depth multi-specialist study, the prevalence of comorbid diseases was analyzed (Table 3).

Table 3 shows that the musculoskeletal system was affected in all patients of the 1st group and half of the 2nd group. The correlation links between external and internal features were found in the 1st group of patients: scoliosis and flatulence $r = 0.76$, $p < 0.01$, myopia and muscle hypotension $r = 0.50$, $p < 0.05$. 26.7% of children in the 1st and 22.2% in the 2nd group showed cervical spine instability.

Cervical spine instability was revealed in almost a quarter of children of both groups, signs of juvenile osteochondrosis were in one child from the 1st group.

Connective tissue disorder of the heart was diagnosed at the 2nd place. According to ECHO-CG, children in both groups showed additional trabecula, an open oval window, mitral valve prolapse, etc.

The gastrointestinal system pathology

Table 1

Clinical and demographic characteristics of BA patients enrolled in the research

Indicators	1st group (n = 15)		2nd group (n=18)		p
	Абс.	p	Абс.	%	
Средний возраст	9.1 ±		8.7 ±		
Sex					
Male	10	66.7	12	66.7	
Female	5	33.3	6	33.3	
Body mass index (BMI)					
Normal (18.5-30)	1	6.7	4	22.2	
Body weight deficit (<18.5)	14	93.5	14	77.8	
Excess body weight (>30)	0	0	0	0	
Average CTD score					
CTD average score	25.2±7.2*** (14-38)		5.7±2.5 (3-10)		0.0001
Increased stigma from 30 to 40 points	7	46.7	0	0	
Diagnostically significant stigma > 40 points	4	26.7	0	0	
Average Stigma Score	32.2±10.4*** (15-48)		9.5±6.0 (2-27)		0.0001
Hereditary predisposition					
Asthma at Mother	0	0	4	22.2**	0.003
Asthma at Father	1	6.7	3	16.7**	0.027
Atopy in Sibs	3	20	8	44.4**	0.002
Eczema at mother	7	46.7	3	16.7	
Eczema at father	7	46.7	3	16.7	
Allergic rhinitis in mother	8	53.3	8	44.4	
Allergic rhinitis in father	4	26.7	5	27.8	
Concomitant allergopathology					
Atopic dermatitis	10	66.7	10	55.6	
Allergic rhinoconjunctivitis	15	100	16	88.9	
Pollinen disease	5	33.3	4	22.2	
Quinke's edema	0	0	3	16.7	
Urticaria	1	6.7	3	16.7	
Allergoanamnesis					
Home dust	5	33.3	10	56.6	
Library dust	2	13.3	6	33.3	
Mites Pteronissimus. farinea	2	13.3	7	38.9	
Animal allergens	5	33.3	9	50	
Citrus	4	26.7	7	38.9	
Cow's milk proteins	2	13.3	5	27.8	
Chicken egg	3	20	3	16.7	
Birch	2	13.3	1	5.6	
Wormwood	4	26.7	3	16.7	
Other herbs	5	33.3	4	22.3	

*p<0.05. **p<0.01. ***p<0.001.

was diagnosed in half of patients from both groups: more often gastroesophageal reflux disease, less often bile dyskinesia.

Visual impairment occurred in patients in both groups, myopia and, less often, accommodation spasm were found with almost the same frequency. Nephroptosis was detected in one child from the 1st group.

The analysis of cumulative pathology of internal organs in the 1st group, damage to three or more systems was noted in 20%, two systems in 40% of patients, one in 26.7%, no visceral pathology was detected in 13.3%. In the 2nd group, involvement of three systems was diagnosed in 11.1% of patients, two in 44.4%, one system in 22.2%, no pathology was detected in 22.2% (Table 3).

Conclusion. Thus, BA patients, regardless of CTD presence, often show hereditary predisposition. Patients with moderate and severe CTD on the maternal line more often had manifestations of eczema (46.7%) and allergic rhinitis (53.3%) than bronchial asthma.

Among the risk factors were the presence of animals at home and smoking parents, which is assessed as lack of compliance leading to uncontrolled asthma type. Patients with mild CTD had a low rate of breastfeeding (p = 0.03).

Most BA patients had a body weight deficit with the same frequency in the study groups (93.5% and 77.8%).

BA associated with a moderate and severe degree of CTD has been found to be characterized by a medium-severe course tendency to lower disease control, a worse prognosis.

BA patients, regardless of the presence of the severity of external signs of CTD had comorbid diseases of the musculoskeletal system, cardiovascular system, digestive organs, pathology of the visual organs, kidneys with almost the same frequency.

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Table 2

Risk factors and clinical-laboratory characteristics of BA patients, included in the research

Indicators	1st group (n = 15)		2nd group (n=18)		p
		%	Абс.	%	
Risk factors					
Accommodation in the city	11	73.7	8	44.4	
Wooden house, barrack	7	46.7	11	61.1	
Incomplete family	1	6.7	5	27.8	
Operative delivery	1	6.7	4	22.2	
Breastfeeding < 6 months	2	13.4*	11	55	0.03
Maternal smoking	2	13.3	4	22.2	
Father smoking	6	40	10	56.6**	0.01
Cat in the house	3	20	3	16.7	
Severity of bronchial asthma					
Mild	1	6.7	0	0	
Average	14	93.3	18	100	
Severe	0	0	0	0	
Level of control					
Controlled	0	0	1	5.6	
Partially controlled	3	20	8	44.4	
Uncontrolled	12	80	9	50	
Laboratory indicators					
Total IgE	341.6±188.3		379.6±202.1*		0.03
Rhinocytogram	8.3±5.7		18.8±13		
Eosinophils in the blood	8.9±3.2		8.9±2.5		

*p<0.05. **p<0.01. ***p<0.001

Table 3

Visceral signs of systemic CT involvement in BA children

Characteristics	1 group		2 group	
	Абс.	%	Абс.	%
Musculoskeletal pathology	15	100	11	55.6
Cervical spine instability	4	26.7	4	22.2
Juvenile osteochondrosis	1	6.7	0	-
Mitral valve prolapse/other MAC	8	53.3	11	61.1
Visual pathology	5	33.3	4	22.2
Reflux Disease	5	33.3	4	22.2
Abnormality of gallbladder development	1	6.7	2	11.1
Nephroptosis and/or ptoses of other organs	1	6.7	0	0

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EMOTIONAL DISORDERS IN PATIENTS WITH MOTOR NEURON DISEASES IN THE REPUBLIC SAKHA (YAKUTIA)

The article describes the study of patients with motor neuron disease and their families according to the Hospital Anxiety and Depression Scale (HADS). Motor neuron diseases (MND) are a group of neurodegenerative diseases of unknown etiology and pathogenesis, accompanied by the death of central and / or peripheral motor neurons , steady progression and inevitable death. Objective: To investigate the incidence and severity of anxiety and depression in patients with MND and their families.

Keywords: motor neuron diseases, amyotrophic lateral sclerosis, anxiety, depression, hospital anxiety and depression scale, HADS

Introduction. Motor neuron diseases (MND) are a group of neurodegenerative diseases of unknown etiology and pathogenesis, accompanied by the death of central and / or peripheral motor neurons, steady progression and inevitable death. MND in adults includes: sporadic and familial forms of amyotrophic lateral sclerosis (ALS), progressive muscle atrophy (PMA), progressive bulbar palsy (PBP), primary lateral sclerosis (PBS). Among the scientists of the world scientific community, there are different points of view on the form of diseases from the MND group: is it worth separating them or should it be considered phenotypic variants of ALS? [14,12,16]. The incidence of ALS in the world is 1.89 per 100 thousand of the population, and the prevalence is 5.2 cases per 100 thousand of the population [17]. Among ALS patients, 7% have been ill for more than 5 years. Their average life expectancy is 2.5 years with bulbar and 3.5 years with spinal ALS onset. In recent years, there has been an increase in the incidence of MND in the world. For example, the direct age-standardized incidence in 2016 in Scotland, which maintains a national registry, was 2.89 per 100 thousand population (95% CI 2.50-3.34), which was higher than in previous years ... However, researchers attribute this to improved diagnostics [10]. In Yakutia, the incidence as of 2018. was 0.5 cases per 100,000 population.

The clinical picture of the disease is manifested by the development of paresis and paralysis, atrophy of the muscles of the trunk and limbs, involuntary contractions of muscle fibers. At the onset of the disease or as it progresses, symptoms of pseudobulbar and bulbar syndromes join.

A characteristic feature of the clinical picture of ALS, in contrast to other neurodegenerative diseases, is the absence of oculomotor disorders, dementia (with the exception of some subgroups: the familial form and with the complex "parkinsonism-ALS-dementia'on the island of Guam and ALS-front-temporal dementia syndrome) [1,9], dysfunctions of the pelvic organs and the absence of bedsores, despite the fact that patients are bedridden for a long time.

The main cause of death in ALS is restrictive or restrictive obstructive respiratory failure, which develops due to paresis of the diaphragm muscles, respiratory muscles and aspiration of food and saliva in bulbar disorders. According to Hong Kong researchers, pneumonia (54.8%) and respiratory failure (40.5%) were the main causes of death in patients with MND [5].

Anxiety-depressive disorders can be attributed to the non-motor manifestations of MND. Given the steady progression of the disease and the fatal outcome, a high prevalence of depressive and anxiety disorders can be expected in patients with MND, as well as in their family members or their close associates. Published studies have described the presence of subclinical and clinical manifestations of anxiety and depressive disorders in patients with ALS. Different methods for detecting depressive disorders, together with different representativeness of patient samples used in previous studies, may partially explain the different incidence of anxiety-depressive disorders in this pathology [6].

The aim is to investigate the incidence and severity of anxiety-depressive disorders in patients with motor neuron disease and their relationship with clinical forms and the rate of progression of the disease.

Materials and methods. In our study, we used data from the personalized register of patients with MND of the Center for Neurodegenerative Diseases of the Yakutsk Scientific Center for Complex Medical Problems of the Republic of Sakha (Yakutia). Patients from 1986 were retrospectively included in the register. until now. The register has been maintained since 01.01.2006. As of 01.01.2019. the

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personalized register consisted of 165 patients. The register includes patients with significant ALS according to El Escorial criteria [2], as well as patients with PBS, PBS, and PMA. In the current study, 55 patients with an established diagnosis of ALS, PBS, PBS and PMA were selected from this MND register for the period from 2006 to 2018. In addition, we included in the study a group of 55 people, which consisted of members of their families and close associates, to assess their emocional state. All study participants gave written informed consent to participate in the study.

Study inclusion criteria:

1.patients with clinically significant ALS using El Escorial criteria;

2.patients with progressive bulbar paralysis,

3. Patients with progressive muscular atrophy;

4. patients with primary lateral sclerosis;

5. relatives or close people who take part in caring for patients with MND.

Exclusion criteria for patients from the study:

1.patients with ALS-mimicking syndromes;

2. patients with MND with severe cognitive impairment;

3. patients in the terminal stage of the disease who are on a ventilator;

5. relatives of patients who do not take part in caring for patients with MND.

Exclusion criteria for patients from the study:

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3. patients in the terminal stage of the disease who are on a ventilator;

5. relatives of patients who do not take part in caring for patients with MND.

Research methods

1. Psychometric - using the HADS (Hospital Anxiety and Depression Scale) to identify states of depression, anxiety and emotional distress among patients and their families or loved ones.

2. Clinical research method (assessment of somatic and neurological status).

3. Using the ALS Functional Rating Scale (ALSFRS) to determine the rate of disease progression, functional deficit was assessed using a 4-point ALSFRS scale. The rate of progression was defined as: fast, if the patient lost more than 10 points per year; average - with a loss of 5 to 9 points per year; slow - with a loss of up to 5 points per year.

4. Statistical analysis of the research results was carried out using the Statistica v.12 software (StatSoft, USA) using descriptive statistics, analysis of variance and the Kruskal – Wallis method to compare mean values. The critical level of significance (p) was taken equal to 0.05.

Results and discussion. Of the 55 patients included in the sample, 35 patients are patients with significant ALS, 5 with PBP, 5 with PBS, 10 with PMA. Distribution of patients by ethnicity: 12 (21.8%) representatives of the Russian ethnic group; 43 (78.2%) the Yakut ethnic group. The distribution of patients by sex: men - 31 (56.3%) people, women - 24 (43.7%) people. The age ranged from 30 to 72 years. The average age was 53 ± 11.8 years. At the same time, the age group 30-50 years old was 15 people. (27.2%), 51-60 years old - 14 people. (25.4%), 61 years and older - 26 people. (47.7%). According to the ALSFRS scale, a fast rate of disease progression was revealed in 50.9% of patients, an average rate - in 21.8%, a slow rate - in 27.3%. The onset of the disease was established in 12 (21.8%) cases.

Drug treatment of depression was carried out with a drug from the group of tricyclic antidepressants - amitriptyline 50-75 mg orally at night in 10 patients, of which 6 patients had severe sialorrhea. The use of anxiolytics for anxiety in patients and relatives was irregular and rare.

Anxiety and depression in patients with MND on the HADS scale

We found that in patients with established ALS the level of anxiety averaged 17.74 ± 0.48 points, depression - 13.60 ± 0.68, with PBP the level of anxiety was 21.20 ± 1.27 points, depression 16, 60 ± 1.8 points. With PBS, the level of anxiety averaged 14.60 ± 1.27 points, depression - 10.50 ± 1.27 points. In the group with PMA, an average level of anxiety was revealed - 13.40 ± 0.9 points, and depression - 10.50 ± 1.27 points. Figure 1. As can be seen from the figure, the level of clinically expressed anxiety was significantly higher in the group of patients with ALS. and PBP than in the group of patients with PBS and PMA (F = 6.014; p = 0.0002).

Figure 2. Figure 2 shows that the level of depression was also significantly higher in patients with ALS and PBS than in patients with PBS and PMA (F = 3.51; p = 0.042).

Anxiety and depression in relatives and close people from the patient's environment according to the HADS scale

Since the indicators of anxiety and depression in this group do not correspond to the law of normal distribution, the median with quartiles was calculated. In relatives of patients with ALS, the median anxiety was 14 points, with PBS - 15 points, and PBS and PMA - 12 points. The median of depression in family members in all groups was 6 points.

There were no statistically significant results of the dependence of the level of anxiety and depression on age in both patients and their relatives (p = 0.08). In the general group, anxiety and depression did not depend on the rate of progression of MND (p = 0.09 and p = 0.9, respectively). Separate analysis, depending on the form of MND, also revealed no differences (p> 0.05). The HADS survey showed that all patients experience clinically significant anxiety and depression, which they associated with their illness. At the same time, the level of anxiety and depression was statistically significantly higher in patients with ALS and PBS than in patients with PBS and PMA. However, a HADS examination of family members and close people of patients in the entire MND group revealed clinical manifestations of anxiety disorders without depressive disorders.

Thus, our study shows that all patients had pronounced anxiety-depressive disorders, which can be attributed to non-motor manifestations of MND. These data correlate with the data of researchers from Brazil (2017), in whose studies the symptoms of anxiety and depression were correlated and often met in patients with ALS [8]. Motataianu Anca et al. (2020, Romania) published data from a small sample of ALS patients (n = 50). The prevalence of depression in the sample after excluding ALS patients with cognitive impairment was 42.8%, which indicates a high prevalence of depression in ALS patients. In addition, they showed a relationship between sociodemographic factors and the development of depression: a low level of education, lack of psychological support from relatives, severe physical weakness of patients, as well as custody of sick children or parents were associated with the development of depression. In contrast, a high level of education, psychological support, high ALSFRS scores, and spousal custody of the patient were associated with the absence of depression in ALS patients [13]. Researchers from the University of Normandy (France, 2019) cite the conclusion of Rabkin et al. (2009) and Burke et al. (2015) that it is cognitive and behavioral disorders, and not the physical disability of patients, that increase the burden on caregivers and increase their anxiety [4]. A Chinese study (2015) found a very strong correlation between depression and anxiety between patients and their caregivers.

However, the severity of depression and anxiety in caregivers of ALS patients correlated with their age. [7] Scientists from Sweden and Norway (2016) concluded that ALS patients are at higher risk of developing depressive disorders and a consequence of taking antidepressants both immediately before and after the diagnosis. In their studies, they showed that within 1 year after the diagnosis of depression, the risk of ALS increased 3.6 times. There was also a higher risk of ALS in the second and third years after the diagnosis of depressive disorder. Patients with ALS are more likely to use antidepressants than in the control group, especially during the year before diagnosis [15].

In addition, depression can become an obstacle to treating a patient. Thus, researchers from Poland published a protocol for the complex treatment of a 71-year-old patient with ALS, which included the method of electroencephalography with biofeedback (EEG-BFB). The method is based on the use of the interaction between the patient's mental state and brain activity, allowing the patient to actively and consciously participate in the management of their neurophysiological processes. The inclusion of this method in the aggravation of depressive disorders and the refusal of the patient with ALS to continue physiotherapy sessions made it possible to complete the planned course of complex treatment, since after the first three sessions of EEG-BFB there was a clear improvement in the patient's mood and interest in continuing the physiotherapy sessions [3]. A group of researchers from Korea also published research results (2019) that suggest that biofeedback may be an effective method as an additional treatment not only for comorbid depressive disorders, but also for functional recovery in patients with drug-resistant depression [11].

Conclusion. Thus, despite the small sample of patients with MND, our data are consistent with the data of foreign researchers. In the surveyed sample, all patients (n = 55) suffered from anxiety-depressive disorders, which are non-motor manifestations of MND. At the same time, the relatives were worried about isolated anxiety without symptoms of depression. Patients with MND may have anxiety and depressive disorders, both at the onset of the disease and at subsequent stages of its development. The high incidence of comorbidity of anxiety-depressive disorders in ALS patients requires the development of an integrated approach to the treatment of MND, including medication, psychotherapeutic, physiotherapy, and other methods. Also, taking into account the previously published data on the development of depression in ALS, which can be both a non-motor symptom in ALS + frontotemporal degeneration, and the beginning of the development of damage to the upper motor neurons in classical ALS, it can be assumed that the clinical picture of ALS consists of non-motor symptoms at the beginning disease and the subsequent attachment of movement disorders in the advanced stage of the disease. Biomarkers, taking into account behavioral and mood disorders, as well as the search and investigation of other probable non-motor manifestations of MND, as well as screening of the population using questionnaires adapted to MND, would help diagnose the disease in the early stages.

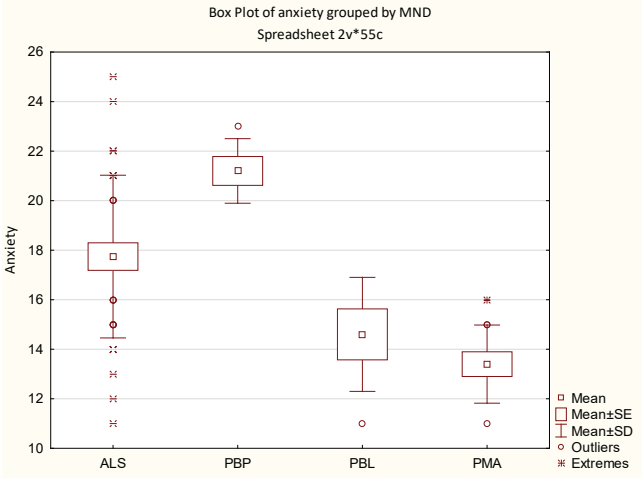

Fig. 1. Anxiety levels in patients with ALS, PBP, PLS, PMA

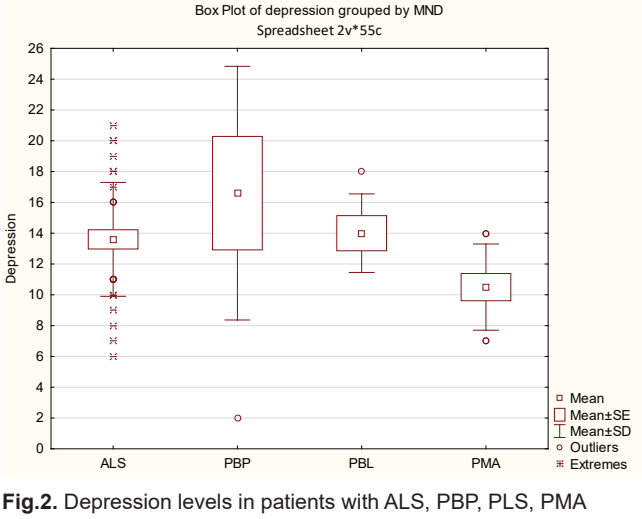

Fig.2. Depression levels in patients with ALS, PBP, PLS, PMA

Conflict of interest

The authors report no conflicts of interest regarding the concepts discussed in this article.

Financing. The study was conducted without sponsorship.

Respect for the rights of patients and the rules of bioethics

All patients and family members signed informed consent to participate in the study.

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STUDY OF THE PARAMETERS OF ESTERIFIED FATTY ACIDS IN BLOOD PLASMA IN PERSONS WITH VIBRATION PATHOLOGY

Objective: to study the spectrum of esterified polyunsaturated fatty acids in the blood of persons with vibration pathology.

Materials and methods. 97 people were examined, of which 2 groups were formed: the main group I included 52 workers with an established diagnosis of vibration disease (average age 49.0 ± 0.8 years), group II (comparison group) consisted of 45 conditionally healthy men (average age - 52.0 ± 0.8 years), who had no contact with vibration. The determination of esterified fatty acids was carried out by gas chromatography-mass spectrometry on a gas chromatograph Agilent 7890A with a mass-selective detector Agilent 5975C. The data were processed in the program Statistica 6.1.

Results. The distribution of parameters of polyunsaturated fatty acids (PUFA) ω-3 and ω-6 in the examined groups was studied. In the group of persons with vibration disease, a statistically significant increase in the level of ω-3 docosahexaenoic acid was noted. The ω-3 index was calculated, according to which the representatives of the cohorts were divided into 4 subgroups (less than 2.5%, 2.5 - 5%, 5 - 7.5%, more than 7.5%). The main group was dominated by persons with an ω-3 index in the intervals of 2.5-5% and 5-7.5%, while in the comparison group there was a uniform distribution of persons between 4 subgroups ($\chi 2 = 11.2$, $p = 0.011$). Comparison of the sums of the main representatives of ω-3 PUFAs (eicosapentaenoic and docosahexaenoic acids) and ω-6 (arachidonic and linoleic acids) showed that the sum of the main ω-6 PUFAs was statistically significantly higher than the sum of the main ω-3 PUFAs in both groups.

Conclusion. The conducted study of esterified fatty acids parameters in blood plasma in persons with vibration disease revealed a higher content of C22:6ω3. It was found that the ω-3 index in both groups and varied in the range: 2.0–9.2% in persons with vibration disease and 1.3–12.7% in the comparison group.

Keywords: polyunsaturated fatty acids, omega-3 index, chromatography-mass spectrometry, vibration disease.

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Introduction. In the structure of occupational morbidity, vibration disease (VD) occupies one of the leading places [3, 13]. The factors that aggravate the harmful effects of vibration on the body include unfavorable climatic conditions of carrying out production activities and living, especially low temperature of environment. It is known that cold enhance the negative exposure of vibration on the organism and increases the risk of developing vibration disease due to increased vascular reactions [1]. It should be borne in mind that one of the key roles in its pathogenesis is played by endothelial dysfunction, which, along with changes in the nervous system, leads to the formation of systemic microangiopathies [6]. It is believed that these disorders are caused both by the direct exposure of vibration on the vascular endothelium, and by an imbalance of redox processes, neurohumoral, neuroimmune mechanisms, metabolic disorders [2]. As the latter, changes in lipid metabolism of a proatherogenic orientation are noted. At the same time, the study of lipid profile indicators does not always answer the question of the possible mechanisms of the development of these disorders.

One of the approaches to solving this problem is study blood lipids in terms of their primary components, namely fatty acids, assess the balance of their various fractions for the diagnosis, prognosis and treatment of dyslipidemia, cardiovascular pathology and other diseases [5, 8, 12]. One of the fractions of blood fatty acids are esterified polyunsaturated fatty acids (PUFAs), the ratio between the components of which can play an important role in the development of vascular disorders caused, among other things, by exposure to vibration.

In this regard, the aim of the work was to study the spectrum of esterified polyunsaturated fatty acids in the blood of persons with vibration pathology.

Materials and methods. The present study involved 97 people who were examined at the clinic of our institute, of which 2 groups were formed: the main

group I included 52 workers with an established diagnosis of VD (average age 49.0±0.8 years), group II (comparison group) consisted of 45 conditionally healthy men (average age - 52.0±0.8 years) who did not have contact with vibration in the professional route. The exclusion criteria from the study were the presence of acute and chronic non-infectious diseases in the exacerbation stage at the time of the examination, diagnoses established in the anamnesis of ischemic heart disease, stroke, myocardial infarction, cerebrovascular accident, as well as age over 65 years and the use of dietary supplements containing PUFA. All surveyed lived in the conditions of Eastern Siberia for at least 10 years. The studies were carried out in accordance with the principles of the Declaration of Helsinki of the World Association "Ethical principles of scientific medical research with human participation" (as amended in 2008), "Rules of clinical practice in the Russian Federation" (approved by the Order of the Ministry of Health of the Russian Federation of June 19, 2003, No. 266), all studies were carried out with the informed consent of the subjects, approved in accordance with the established procedure by the Committee on biomedical ethics of the FSBSI ESIMER. The studies conducted did not infringe on the rights, did not endanger the well-being of the research subjects, and did not harm their health.

Vacutainers containing ethylenediaminetetraacetic acid were used to collect blood plasma samples. To obtain plasma, the collected blood was centrifuged for 15 min at 3000 rpm. Plasma samples were aliquoted into eppendorfs and stored at -20 ° C.

The determination of esterified fatty acids (EFA) was carried out by a two-stage technique using extractive alkylation by gas chromatography-mass spectrometry [4] on a gas chromatograph Agilent 7890A with an mass-selective detector Agilent 5975C on an HP-5MS capillary column.

The results were statistically processed using the Statistica 6.1 software, using the nonparametric Mann-Whitney test. The normal distribution of quantitative indicators was tested using the Shapiro – Wilks test. Comparison of relative values was performed using the χ2 test. In all cases, the differences were considered statistically significant at p <0.05. The results of the studies performed are presented as the median and interquartile range, mg/*l*.

Results and discussion. The distribution of quantitative indicators of PUFA of the ω-3 and ω-6 families in the examined groups was studied (table). In the group of individuals with VD, there was a st atistically significant increase in the level of ω-3 docosahexaenoic acid.

The content of esterified polyunsaturated fatty acids of the ω-3 and ω-6 families in the blood plasma of persons with vibration pathology. Me (Q25 – Q75). mg/*l*

Parameter	Group with VD. n = 52	Comparison group. n = 45	p
ω3 – Fatty acids			
Eicosapentaenoic acid (C20:5ω3)	27.8 (19.9–48.4)	37.5 (24.8–54.9)	0.066
α- Linolenic acid (C18:3ω3)	13.6 (9.5–23.3)	14.4 (9.9–29.0)	0.820
Eicosatrienoic acid (C20:3ω3)	2.8 (0.2–3.3)	3.0 (0.2–3.3)	0.321
Docosahexaenoic acid (C22:6ω3)	110.1 (85.7–133.8)	89.4 (38.7–105.2)	0.003
Σ ω3 FA	151.5 (123.7–193.0)	139.4 (111.0–176.0)	0.154
ω 6 – Fatty acids			
γ- Linolenic acid (C18:3ω6)	8.7 (6.2–14.0)	10.2 (7.3–20.6)	0.063
Linoleic acid (C18:2ω6)	468.1 (414.8–559.2)	449.6 (380.7–643.8)	0.834
Arachidonic acid (C20:4ω6)	184.4 (153.8–207.1)	181.6 (160.3–227.1)	0.546
Dihomo-γ-linolenic acid (C20:3ω6)	96.3 (71.8–115.8)	85.8 (76.9–121.9)	0.919
Eicosadienoic acid (C20:2ω6)	15.6 (11.7–18.8)	12.5 (10.5–16.3)	0.096
Σ ω6 FA	761.9 (673.4–923.7)	746.5 (613.6–997.6)	0.868
ω6/ω3	4.7 (4.1–6.4)	5.4 (4.4–9.4)	0.114

According to the literature, of all PUFA of the ω-3 family, docosahexaenoic (DHA) and eicosapentaenoic (EPA) are significant, and of ω-6 - arachidonic (AA) and linoleic (LA) [7]. For the first, the ω-3 index was calculated as a percentage of the sum of eicosapentaenoic (C20:5ω3) and docosahexaenoic (C22:6ω3) acids of the total amount of fatty acids (FA) in the blood. This index in the examined groups varied in a wide range: from 2.0 to 9.2% in patients with VD and from 1.3 to 12.7% in the comparison group. According to the obtained data of the ω-3 index, the representatives of the co-

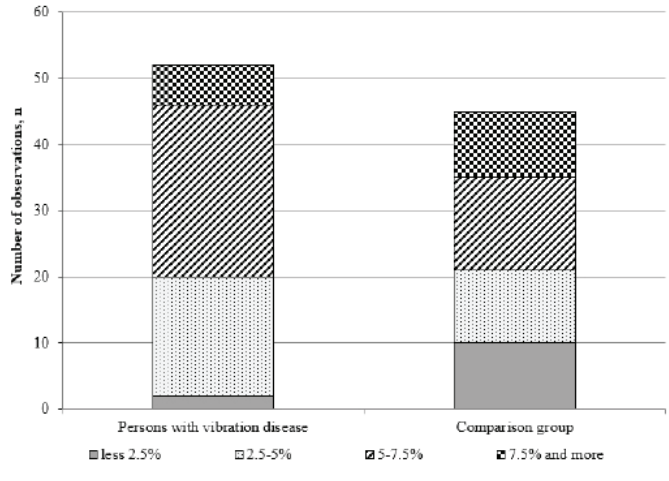

Fig. 1. Distribution of the surveyed persons by the level of the ω-3 index

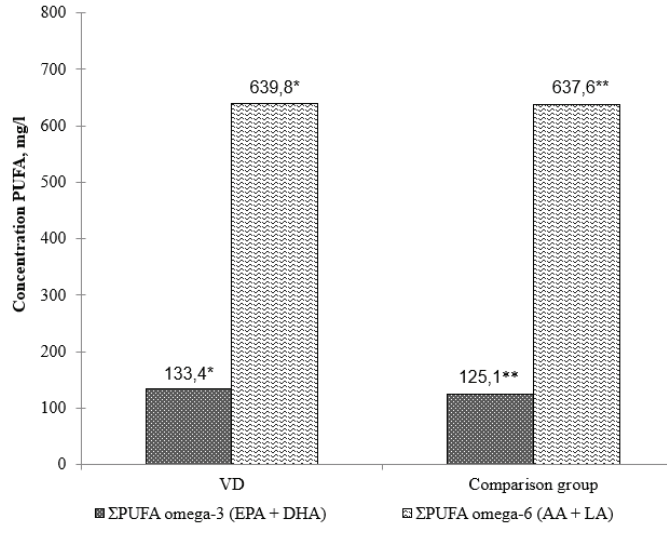

Fig. 2. The ratio of the sum of the concentrations of the main representatives of FA of the family ω-3 and ω-6
Note *, ** - differences are statistically significant at p <0.05

horts were divided into 4 subgroups (less than 2.5%, 2.5 - 5%, 5 - 7.5%, more than 7.5%). The main group was dominated by persons with an ω-3 index in the intervals of 2.5-5% and 5-7.5%, while in the comparison group there was a uniform distribution of persons between 4 subgroups ($\chi 2 = 11.2$, $p = 0.011$) (Figure 1).

The studied ω-3 index is currently proposed to determine the risk of cardiovascular diseases (CVD). It is believed that in individuals with an ω-3 index <4%, the risk of CVD is 10 times higher than in patients with an index> 8% [14]. In our observation, in the main group, the number of patients with ω-3 index> 7.5% was 11.5%, and in the comparison group - 22.2%, however, the intergroup differences were statistically insignificant ($\chi 2 = 2.0$, $p = 0.157$). Noteworthy is the fact that among the persons of the comparison group, the relative number of persons with an ω-3 index less than 2.5 was statistically significantly higher (22.2%, $\chi 2 = 7.5$, $p = 0.006$) than in the main group of subjects (3.8%).

Comparison of the sums of the main representatives of the ω-3 PUFAs (EPA and DHA) and ω-6 (AA and LA) showed that the sum of the main ω-6 PUFAs was statistically significantly higher than the sum of the main ω-3 PUFAs in both groups (Figure 2).

It is known that esterified fatty acids reflect the transfer of exogenous FAs from enterocytes to the liver and then to all cells [10]. Wherein, ω-3 and some ω-6 FAs are essential, act as a substrate for energy production and for the synthesis of biologically active humoral regulators. Therefore, with a deficiency of their intake into the body, the regulation of physiological processes is disrupted. In the same time, a violation of the ratio between them in the direction of the prevalence of ω-6 PUFA indicates the activation of pro-inflammatory processes. This is determined by the conversion of PUFA in the body. When oxidized with cyclooxygenase, PUFAs are converted into prostaglandins (PGs): from ω-6 PUFAs PGs of classes 1 and 2 are formed, from ω-3 PUFAs PGs of class 3 are synthesized [15]. The transformation of PUFAs by the lipoxygenase pathway gives classes of leukotrienes (LT): 3 and 4 for ω-6 acids, 5 for ω-3 acids. With an increase in the class, the vasodilating and antiaggregatory effect of PG increases and the proinflammatory and atherogenic properties of LT decrease [9, 11].

Considering that one of the links in the pathogenesis of VD is a dysfunction of the endothelium, the formation of vascular inflammation as a result of the prevalence of esterified ω-6 over ω-3 PUFAs in the organism can be considered as a mechanism of its development. It should be noted that the representatives of the comparison group have disorders of a similar nature in the metabolism of PUFA, which requires, on the one hand, studies to determine whether they have a metabolic syndrome, and, on the other hand, dictates the need to study the prevalence of such changes in the population as a whole.

Conclusion. Thus, the study of the quantitative parameters of EFA in the blood plasma of persons with VD revealed a higher content of C22: 6ω3. It was found that the ω-3 index in both groups and varied in the range: 2.0–9.2% in persons with VD and 1.3–12.7% in the comparison group.

The work was performed within the framework of research work on a fragment of the laboratory of analytical ecotoxicology and biomonitoring of the FSBSI ESIMER "Study of the mechanisms of metabolic disorders and their role in the formation of sensitivity to the exposure of production factors", state registration number AAA-A18-1180 2089005-6.

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ANALYSIS OF ASSOCIATIONS OF *PPARGC1A* AND *PPARG* GENE POLYMORPHISMS WITH METABOLIC SYNDROME IN PERSONS WITH VIBRATION DISEASE

Abstract. Vibration disease (VD) has a significant authority in the structure of occupational pathology and is often accompanied by diseases associated with impaired lipid and carbohydrate metabolism. The increased risk of their development may be due to a genetic predisposition to them. Information about the associations of polymorphisms of the peroxisome proliferation activating gamma receptor (PPARγ) gene and its coactivator with metabolic syndrome is presented in the literature. The aim of this work was to study the relationship between the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC 1A* gene with metabolic syndrome in individuals with VD. The frequency of alleles and genotypes of these polymorphisms was studied in patients with VD and in the comparison group, and their role in the development of metabolic syndrome (MS) was assessed. It was found that the frequency of MS among individuals with VD was higher with the same distribution of alleles and genotypes of Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene in the examined groups. Carriage of the ProPro genotype of the *PPARG* gene is associated with resistance to MS development in the comparison group. A significant effect of the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene on the formation of MS was not revealed in patients with vibration disease.

Key words: polymorphisms, PPARG, PPARG coactivator, vibration disease, metabolic syndrome.

Introduction. From 2007 to 2017, about 7% of employees of enterprises in the Far North of the Russian Federation who have contact with hazardous production factors were exposed to general and local vibration [10]. The combined effect of unfavorable production factors (vibration, pronounced cooling and functional overstrain of the musculoskeletal system) leads to the development of vibration disease (VD). This disease takes a significant place in the structure of occupational pathology and is 20-22% [9, 10]. It is characterized as a concomitant pathology of cardiovascular disease (CVD), disorders of lipid and carbohydrate metabolism [13]. It is possible that the sensitivity of people to the action of industrial vibration, as well as an increased risk of metabolic disorders and CVD, can be determined, among other things, by the peculiarities of their genetic status. Associations have been identified between some genotypes of the protease inhibitor alpha-I-antitrypsin, acid phosphatase isoenzyme and vibration disease [7]. Relationships have been established between polymorphic variants of genes for nitric oxide synthase, endothelin, plasminogen activator type 1 and arterial hypertension [1, 3]. It has been shown that polymorphisms of the peroxisome proliferation-activating gamma receptor (PPARγ) gene are associated with changes in the levels of fatty acids, cholesterol and its fractions in blood lipoproteins and tissue sensitivity to insulin, metabolic syndrome (MS) [12, 14, 18]. However, data on the influence of minor allele of the Pro12Ala polymorphism of the *PPARG* gene on metabolic processes and lipid metabolism are ambiguous, the peculiarities of its phenotypic manifestations may be due to the combined influence of race, the presence of mutations in other genes, and the action of external factors, including industrial factors [5, 18]. The functioning of the PPARγ receptor depends on its coactivator, which is encoded by the *PPARGC1A* and *PPARGC1B* genes [4, 16, 17]. The literature provides data on the association between the Gly482Ser polymorphism of the *PPARGC1A* gene and arterial hypertension in men with type 2 diabetes [20]. The **aim** of this work was to study the relationship between the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene with metabolic syndrome in individuals with vibration disease.

Materials and methods. The study included men after they signed an informed consent for examination approved by the Biomedical Ethics Committee of the East Siberian Institute of Medical and Environmental Research, who had no history of cancer, renal, liver failure, stroke, myocardial infarction and coronary heart disease. There were two groups: main group included 121 patients with VD (age 51.0 ± 0.6 years), the comparison group – 69 men who were not exposed to vibration in their professional activity (mean age 51.4 ± 0.8 years).

Individuals with MS were identified in each of the surveyed groups. They had abdominal obesity (waist volume> 94 cm) and two of any of the criterion indicators of impaired lipid or carbohydrate metabolism, blood pressure (triglyceride content more than 1.7 mmol / L, high-density lipoprotein cholesterol below 1.0 mmol / L, lipoprotein cholesterol low density above 3.0 mmol / l, blood pressure more than 140/90 mm Hg, plasma glucose levels above 6.1 mmol / l or impaired glucose tolerance). Individuals without this syndrome and those with it were subgroups 1 and 2 in the comparison group, in main group – 3 and 4, respectively. Subgroup 1 included 45 people aged 50.3 ± 1.0 years, subgroup 2 – 24 mens 53.5 ± 1.0 years old, the 3rd subgroup consisted of 60 patients 50.4 ± 0.9 years old, 4th – 61 individuals (average age 52.5 ± 0.9 years).

We ascertained the ethnicity of the respondents using a questionnaire to ascertain the ethnicity of their parents. Persons of the Caucasian race (Russians, Ukrainians) accounted for 89%, individuals of the Mongoloid race (Buryats, Ya-

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kuts, Tatars) among the surveyed were 11%. The incidence of representatives of the Mongoloid race did not differ significantly in subgroups 1-4 and amounted to 8.9%, 12.5%, 11.6% and 9.8%, respectively.

Whole blood using K3 EDTA as an anticoagulant was used for genetic studies. DNA was isolated from blood leukocytes using a DNA-express reagent (Litekh, Russia) by a modified method [2]. Genotyping of the Gly482Ser polymorphisms of the *PPARGC1A* gene and Pro12Ala of the *PPARG* gene was performed by real-time PCR with allele-specific primers in accordance with the protocol of the manufacturer of reagent kits (Litekh, Russia).

The analysis of the research results was performed using the STATISTICA 6.0 and SNPstats software (access https://www.snpstats.net/start.htm). The chi-square test ($\chi 2$) was used to compare genotype frequencies. The assessment of the association of the genotype with the disease was determined by the odds ratio (OR), taking into account the 95% confidence interval (95% CI). The critical level of statistical significance of the differences (p) was 0.05. When describing the age characteristics of the studied samples, the values of the arithmetic mean and its error (M ± m) were used.

Results and discussion. The Pro-12Ala mutation (rs1801282) is most common for the *PPARG* gene localized on chromosome 3 (3p25.2), the Gly-482Ser polymorphism (rs8192678) - for the *PPARGC1A* gene, which is located on chromosome 4 (4p15.1) [5, 16, 17, 21, 22]. Data on the frequency of allelic variants and genotypes of these polymorphisms in the comparison group and patients with VD are presented in Table 1.

It was found that the distribution of the studied genotypes in the investigated samples corresponded to the expected values at the Hardy-Weinberg equilibrium. The Ala allele of rs1801282 polymorphism was carried by 17% of individuals from the comparison group and 15% from group I. Our data are consistent with the results of studies carried out on the European population and residents of Russia, in which the frequency of the Ala allele of the *PPARG* gene was 20% and 13.9 % respectively [4, 21]. The occurrence of alleles and genotypes of the Pro12Ala polymorphic locus of the *PPARG* gene among persons with and without occupational pathology did not differ. The frequencies of nucleotide substitutions in the Gly482Ser polymorphism of the *PPARGC1A* gene were also comparable in the groups. The incidence of carriers of the minor allele Ser in the studied groups was the same as the average for the population of Russia (32.6%) and amounted to 32-37% [21]. The absence of differences in the frequencies of alleles and genotypes of the studied polymorphisms of the *PPARG* and *PPARGC1A* genes between the groups indicates that the cohorts had a similar pattern of genetic predisposition to the development of dyslipidemia and impaired glucose metabolism, since these receptors are involved in the metabolism of fats and carbohydrates. Due to the fact that PPARγ and its coactivator are involved in the pathogenesis of a number of diseases, including obesity, MS and diabetes mellitus, at the next stage of the study, we analyzed the occurrence of MS in the comparison group and among patients with VB.

The number of individuals with MS among patients with an occupational disease was higher than in the comparison group (50.4% and 34.8%, p = 0.037). According to the literature, metabolic syndrome is detected in 20-50% of the population of Russia, it is observed in 30-40% of cases in people over 30 years old, and its frequency varies depending on the region, age, gender [8, 19]. Higher numbers of MS incidence among patients with VD are consistent with the data of other studies, which examined the individual components of the syndrome – abdominal obesity, dyslipidemia and arterial hypertension, detected in 34%, 59% and 94% of people with vibration pathology, respectively [6].

Further analysis of the association of gene polymorphism was carried out in the subgroups identified taking into account the presence of MS. It was found that the risk of MS is reduced in persons who are not in contact with vibration in professional activities and who are carriers of the ProPro genotype of the *PPARG* gene (OR = 0.43; 95% CI 0.21-0.91, p=0.046). The *PPARG* gene belongs to the key regulators of adipogenesis, and the presence of the minor allele Ala of the Pro12Ala polymorphism leads to a decrease in the binding of the receptor to its target (lipoprotein lipase and acetyl-CoA synthetase), and, as a consequence, to a change in the intensity of lipid metabolism, an increase in free fatty acids in adipocytes, insulin resistance [4, 18, 21, 22]. Therefore, the carriage of the Pro allele can have a protective effect and be a marker of resistance to the development of MS in the absence of vibration. In the presence of vibration pathology, the protective effect of the considered genetic factors is leveled. In this study, we did not reveal a relationship between the Gly-482Ser polymorphism of the *PPARGC1A* gene and the risk of developing MS in the examined groups.

This syndrome was less common among the examined patients with the protective ProPro genotype of rs1801282 polymorphism in the comparison group than among patients with VD (p=0.025) (Table 2). This shows that under the influence of external factors, in particular, vibration, the role of genetic predisposition in the development of MS decreases.

Among individuals with the GlySer genotype of rs8192678 polymorphism, the frequency of MS in the comparison group was lower (p = 0.061) compared to the group of patients with occupational pathology. This fact may also indicate that nucleotide substitutions in the genes of the PPARγ receptor and its coactivator,

Table 1

Frequency distribution of alleles and genotypes of polymorphic variants of the PPARG and PPARGC1A genes

Gen/SNP	Allele / Genotype	All examined % (number)	Comparison group % (number)	Main group % (number)	p
PPARG Pro12Ala (rs1801282)	Pro	84 (320)	83 (115)	85 (205)	0.606
	Ala	16 (60)	17 (23)	15 (37)	
	ProPro	71 (134)	70 (48)	71 (86)	0.884
	ProAla	27 (52)	27 (19)	27 (33)	1.00
	AlaAla	2 (4)	3 (2)	2 (2)	0.663
PPARGC1A Gly482Ser (rs8192678)	Gly	66 (198)	63 (87)	68 (111)	0.327
	Ser	34 (104)	37 (51)	32 (53)	
	GlyGly	45 (68)	42 (29)	48 (39)	0.425
	GlySer	42 (64)	45 (31)	40 (33)	0.502
	SerSer	13 (19)	13 (9)	12 (10)	0.840

Note: p - level of statistical significance of differences in allele and genotype frequencies between groups.

Table 2

The incidence of metabolic syndrome among individuals with different genotypes of polymorphic loci Pro12Ala of the PPARG gene and Gly482Ser of the PPARGC1A gene

Gen/SNP	Genotype	Comparison group, % (quantity)	Main group, % (quantity)	p
PPARG Pro12Ala	ProPro	31 (15)	51 (44)	0.025
	ProAla	47 (9)	45 (15)	0.889
	AlaAla	0 (0)	100 (2)	1.000
PPARGC1A Gly482Ser	GlyGly	41 (11)	41 (16)	1.000
	GlySer	29(9)	52 (17)	0.061
	SerSer	44 (4)	50 (5)	0.794

Notes: p is the level of statistical significance of differences between groups.

causing changes in their functional activity, do not significantly affect the development of MS in individuals with VD. It can be assumed that its formation is caused by a violation of other mechanisms of regulation of lipid and carbohydrate metabolism, which are characteristic, among other things, for persons with vibration pathology. [3, 15]. Since MS is one of the main causes of atherosclerotic lesions of the coronary arteries [11], in order to reduce the risk of developing cardiovascular disease, it is necessary to carry out diagnostic and preventive measures aimed at identifying this syndrome and reducing its frequency in people with VD.

Conclusion. As a result of the study, it was found that, despite the same distribution of alleles and genotypes of the Pro12Ala polymorphism of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene in the examined groups, the frequency of MS among persons with WD was higher. It was shown that the carriage of the ProPro genotype of the *PPARG* gene in the comparison group marks resistance to the development of MS, while the role of genetic factors in patients with occupational pathology has not been established. It can be concluded that in the examined persons exposed to vibration, the formation of MS is caused by disturbances in the mechanisms of regulation of lipid and carbohydrate metabolism, which are not associated with the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene.

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VARIANTS OF SINGLE NUCTEOTIDE SUBSTITUTIONS IN THE GENES OF MATRIX METALLOPROTEINASES *(MMP-2 AND MMP-9)* IN ARTERIAL HYPERTENSION IN PEOPLE OF WORKING AGE

Point substitutions were studied in the genes MMP-2 c.-1306C> T (rs243865) and MMP-9 c.-1562C> T (rs3918242) in people under the age of 60 living in the Primorsky Territory. It was found that the differences between the shares of the MMP-2 CC, CT, and TT genotypes in the groups of persons with AH and the control group were statistically insignificant (mid-p = 0.16), while for the MMP-9 CC, CT, and TT genotypes, these differences were determined (α = 0.05). In the distribution of patients with hypertension, depending on the indicators of relative cardiovascular risk (CVR) in persons with hypertension under 40 years of age in the group with a CVR value of 2, a significant increase in the minor alleles of MMP-9 1562 C/T was found, compared with individuals with a CVR value 1, the presence of the T allele in the MMP-9 gene c.-1562C> T (rs3918242) is associated with a higher risk of cardiovascular catastrophes in young people with hypertension. Thus, the definition of the aforementioned polymorphism is of particular importance for young patients.

Keywords: arterial hypertension, metabolic syndrome, matrix metalloproteinases MMP-2 and MMP-9, genetic polymorphisms

Introduction. One of the discussed problems in the risk of occurrence and prognosis of an unfavorable course of AH is the search for genetic polymorphisms and other significant biomarkers that allow to assess the individual cardiovascular risk with a high degree of accuracy and timely carry out personalized corrective preventive measures [3].

The direction of predictive medicine associated with the search for genes encoding enzymes of connective tissue metabolism, the imbalance in the state of which, in turn, determines early damage to target organs, regardless of the degree of increase in blood pressure (ABP) is of interest. The processes of cardiovascular remodeling in hypertension (AH) and preclinical damage to target organs are associated with the inversion of the phenotypes of the smooth muscle cell of the vessel from contractile to proliferative, changes in the state of the cytoskeleton and cellular memory of cardiomyocytes, restructuring of the extracellular matrix as a result of the action of factors that activate hemodynamic stress, and as a result of discoordination of the response at the genetic level [3]. The family of matrix metalloproteinases (MMP) occupies a special place in the formation of the proinflammatory potential of the cell microenvironment, followed by elastin degradation and accumulation of collagen I, II, and III and fibronectin [8]. The unbalanced activity of the *MMP-2* and *MMP-9* genes caused by single nucleotide substitutions in the promoter zone at the rs243865 and *rs3918242* loci, respectively, in hypertension (AH) attracts the attention of many researchers, and their results are not unambiguous. Interest in studying the contribution of SNV to the *MMP-2* and *MMP-9* genes at the *-1306 C / T* and *-1562 C / T* loci indicates the need to accumulate data for their identification in the population of persons with AH in order to be able to use them as predictors of the risk of AH, predicting the occurrence of target organ damage and organizing personalized prevention of cardiovascular accidents, which is especially important for people of working age and young people, including due to the high prevalence of "masked" hypertension (AH) in this category of patients.

Objective: to determine the conjugation of SNV in genes *MMP-2 c.-1306C>T* (rs243865) and *MMP-9 c.-1562C> T (rs3918242)* with the presence of hypertension (АГ) in people of working age.

Materials and methods. The study included 271 volunteers aged 25 to 60 years of Caucasian race, Slavic ethnicity, living for at least three generations in the Primorsky Territory. These individuals took part in the ESSE-RF study. Of these, 161 patients with hypertension (AH), 91 men and 70 women, the control group

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consisted of 110 practically healthy volunteers (50 men and 60 women) of the corresponding age without hypertension (AH).

For genetic studies, DNA samples were used, isolated from whole venous blood. The fragments were obtained by the polymerase chain reaction (PCR) method.

Quantitative indicators of the clinical characteristics of patients were expressed as mean (M) plus or minus standard error (SE); Student's test was used for comparative assessment. The correspondence of the observed distribution of genotype frequencies to the theoretically expected equilibrium distribution according to the Hardy – Weinberg law was evaluated using the Pearson χ^2 test. When comparing the frequencies of alleles and genotypes in the groups of healthy and sick individuals, the $\chi 2$ test was used with Yates' correction for 2x2 contingency tables. The strength of associations of genotypic characteristics with the risk of developing hypertension (AH) was assessed by the odds ratio (OR). The confidence interval (CI) was calculated using the Woolf method with a 95% confidence interval.

Results and Discussions. The average age in the group of patients with hypertension (AH) was 39.5 ± 2.3 years (range from 33 to 44), in the control group –39.2 ± 3.5 years (range from 35 to 46). In the group of people with AH, AH of the 1st degree prevailed, which was diagnosed in 135 individuals. Half of the 110 subjects in the control group were smokers. Among 161 patients with hypertension (AH), 92 smoked. The smoking index in both groups did not differ and was 5.35 ± 1.6 in the group of people with hypertension (AH) and 4.75 ± 1.5 in the control group (p> 0.05). In the group of patients with hypertension (AH), there was a significant increase in the level of triglycerides (TG), weight, waist circumference, BMI compared with the control group (p <0.05, table 1).

The frequencies of the genotypes of the studied SNV variants in the genes of metalloproteinases *MMP-2* and *MMP-9* in healthy individuals (p = 0.7122, p = 0.2109) and patients with hypertension (AH) (p = 0.0855, p = 0.0821) corresponded to equilibrium Hardy-Weinberg, which confirmed the independent distribution of alleles in the studied variants and the absence of errors during genotyping. The frequencies of the *MMP-2 CC, CT* and *TT* genotypes in healthy subjects were 50%, 40%, and 10%, and in patients with AH, 48.3%, 35% and 16.7%, respectively (table 2). A number of authors have associated a relationship between the *1562 T* alleles of *MMP-9* and AH [4,5,10]. In our

Table 1

Comparative analysis of the clinical characteristics of the examined healthy individuals and patients with hypertension (AH)

Indicators	Control group (n=110)	Patients with AH (n=161)
Age	39.2±3.5	39.5±2.3
Weight, kg	69±3.0	79±3.4*
BMI, kg/m^2	22.1±3.5	24.0±3.2*
Waist circumference, cm	73.7±4.8	87.3±5.6*
ABP (SBP and DBP), mm Hg	118 и 79 (±9.2 и ±7.0)	151 и 91(±7.5 и 8.0)*
HR, beats per minute	72 ±7.0	80 ±8.0
Smoking status (n, persons)	55	92
Smoking person index, pack / years	4.75±1.5	5.35±1.6
Blood glucose, mmol / l	4.82 ±0.7	5.22 ±0.8
GC, mmol / l	4.95±0.6	5.01±0.7
ApoA - g/l	1.79 ±0.4	1.81 ±0.3
ApoB - g/l	0.92±0.3	0.83 ±0.3
LDL, mmol / l	3.13±0.8	3.35 ±0.7
HDL, mmol / l	1.31±0.5	1.28±0.4
TLC, mmol / l	1.21±0.7	1.75 ±0.9*

Note: * - at p <0.05 between the group of patients and control. BMI - body mass index, BP - blood pressure (systolic and diastolic), GC - general cholesterol, HR - heart rate, ApoA - apolipoprotein A, ApoB - apolipoprotein B, LDL - low density lipoproteins, HDL - high density lipoproteins, TLC - triglycerides.

Table 2

Frequency distribution of alleles and genotypes of the rs243865 polymorphic locus of the MMP-2 gene in the population of healthy individuals and patients with hypertension (AH)

Polymorphic variant of the *MMP-2 gene c.-1306C> T (rs243865)*	**Frequency in healthy (n=120), absolute number (%)**	**Frequency in patients with arterial hypertension (n=120), absolute number (%)**	**$\chi 2$**	**OR (95% CI)**
CC	60 (50)	58 (48.3)		1
CT	48 (40)	42 (35)	0.13 p=0.05	0.905 (0.52-1.57)
TT	12 (10)	20 (16.7)	1.51 p=0.05	1.72 (0.77-3.84)
Dominant form of inheritance *CT* + *TT* versus *CC*	60 (50) 60 (50)	62 (51.7) 58 (48.3)	0.058 p=0.05	1.07 (0.64-1.77)
Recessive form of inheritance *TT* versus *CC* + *CT*	12 (10) 108 (90)	20 (16.7) 100 (83.3)	1.9 p=0.05	1.8 (0.84-3.87)
Super dominance *CC*+*TT* versus *CT*	72 (60) 48 (40)	78 (65) 42 (35)	0.5 p=0.05	1.24 (0.73-2.1)

Note: *MMP* is metalloproteinase, n is the number of groups, $\chi 2$ (p) is the assessment of the significance of differences in the distribution of genotype frequencies between the two groups, OR is the odds ratio, 95%, CI is the confidence interval

Table 3

Frequency distribution of alleles and genotypes of the rs3918242 polymorphic locus of the MMP-9 gene in the populationof healthy individuals and patients with hypertension (AH)

Polymorphic variant of the *MMP-2 gene c.-1306C> T (rs243865)*	Frequency in healthy individuals (n=120), absolute number (%)	Frequency in patients with hypertension (n=120), absolute number (%)	χ2 (P-value)	OR (95% CI)
CC	76 (63.3)	70 (58)		1
CT	38 (31.7)	34 (28.3)	0.38 p=0.05	0.971 (0.55-1.71)
TT	6 (5)	16 (13.7)	5.55* p=0.05	2.895 (1.073-7.81)
Доминантная форма наследования *CT+TT* versus *CC*	44 (36.7) 76 (63.3)	50 (42) 70 (58)	0.59 p=0.05	1.234 (0.73-2.07)
Рецессивная форма наследования *TT* versus *CC+CT*	6 (5) 114 (95)	16 (13.7) 104 (86.3)	4.47* p=0.05	2.92 (1.1-7.75)
Сверхдоминирование *CC+TT* versus *CT*	82 (68.3) 38 (31.7)	86 (71.7) 34 (28.3)	0.275 p=0.05	1.17 (0.67-2.04)

study, with regard to the distribution of the frequency of the *MMP-9 CC, CT* and *TT* genotypes, it was determined that in the control group they were 63.3%, 31.7% and 5%, and in patients with AH 58%, 28.3% and 13.7% respectively. Thus, the differences between the proportions of the *MMP-2 CC, CT*, and *TT* genotypes in the groups of persons with AH and the control group were statistically insignificant (mid-p = 0.16), while the indicated differences were determined for the *MMP-9 CC, CT*, and *TT* genotypes (α = 0.05). Thus, the proportion of persons with *TT* genotype *MMP-9*, in whom the studied effect manifested itself, in the sample with hypertension (AH) was higher than in the control group (p = 0.045), which is consistent.

Considering the highest frequency of occurrence of the minor T allele in patients with hypertension (AH), we combined the *CT + TT* genotypes into one group and viewed them relative to individuals with the *CC* genotype. Single nucleotide substitutions in genes encoding matrix metalloproteinases can change the level of their expression, which, according to researchers, increases the susceptibility to cardiovascular diseases [1].

As follows from the data in Table 3, the odds ratio (OR) calculated from the occurrence of the *T*-allele *MMP-9* in patients with hypertension (AH) exceeded that in people without hypertension (AH) by 2 times (OR = 2.9) with significant differences at p = 0.05. In other words, the presence of the T allele in the *MMP-9* gene *c.-1562C> T (rs3918242)* correlates with the presence of AH. Along with this, with the dominant *(CT + TT* versus *CC)* and overdominant (*CC + TT* versus *CT*) models of inheritance, the carriage of the *T* allele slightly increased the risk of developing AH (1.234 95% CI = 0.73-2.07; 1.17 CI = 0.67-2.04, respectively, with a significance level of p <0.05). Whereas, in the recessive model (*TT* versus *CC + CT*) of inheritance in hypertensive patients, this risk significantly increased (2.92 95% CI = 1.1-7.75, p <0.05), confirming the hypothesis that the presence of the *T* allele at the rs3918242 polymorphic locus of the *MMP-9* gene is directly related to the likelihood of developing AH. Thus, the results of this replicative study confirm the data obtained during the GWAS, which identified the polymorphic locus as a marker of an increased risk of hypertension in European and Asian populations [3, 9].

Taking into account the heterogeneity of the group of people with hypertension, depending on the degree of relative risk (for persons under 40 years old), determined on a scale for assessing the relative risk of developing cardiovascular complications and absolute (for persons aged 40 and older) cardiovascular risk (CVR) determined by the SCORE scale, we found it interesting to analyze the presence of the T allele of the genes *MMP-2 c.-1306C> T (rs243865)* and *MMP-9 c.-1562C> T (rs3918242)* in individuals with AH with varying degrees of CVR.

Analysis of the situation in real clinical practice demonstrates that most cardiovascular accidents occur more often in individuals with low and intermediate cardiovascular risk [2]. In our study, it was found that the vast majority of people under 40 years of age (n = 95) had a CVR value of 2 (76%, n = 72) and only 24% (n = 23) had a reference CVR value = 1. Among persons aged 40 years and older (n = 66), an opposite tendency was observed: 35% (n = 23) had a moderate absolute CVR (≥1% and <5%), and 55% (n = 37) had a high (≥ 5% and <10%) and 10% (n = 6) of patients had a very high risk (≥10%).

Alessandra M.V. Ritter et al. and Sabbatini A.R. et al. suggests that *rs243865* in the *MMP-2* gene may be associated with an increase in blood pressure (ABP) in patients with resistant hypertension (AH) [6, 7]. In our study, it was found that the distribution of the frequency of the *CC, CT* and *TT* genotypes *MMP-2 c.-1306C> T (rs243865)* in persons under 40, depending on the degree of relative risk, as well as in the general group of patients, did not statistically differ (table 4). When comparing the frequency of genotypes *MMP-9 c.-1562C> T (rs3918242),* it was found that patients with the minor allele *T (CT* and *TT*) were more common in the subgroup with CVR = 2 (OR 2.26 95% 0.42-1.84, p = 0.04). Probably, these substitutions can phenotypically manifest themselves as an imbalance in the state of connective tissue metabolism and associated damage to target organs in hypertension (AH).

In the group of patients with hypertension (AH) older than 40 years of age, no difference was found in the distribution of genotypes of the *rs243865* polymorphic locus of the *MMP-2* gene depending on the degree of absolute cardiovascular risk on the SCORE scale (Table 5). Moreover, in contrast to persons under 40, there was no difference in the distribution of frequencies of genotypes *MMP-9 c.-1562C> T (rs3918242)* depending on the degree of cardiovascular risk.

Conclusions. No statistically significant difference in SNV in the *MMP-2 gene c.-1306C>T* (rs243865) depending on the presence of AH was found.

Table 4

Distribution of the frequency of genotypes of polymorphic loci *rs243865* of the *MMP-2* gene and *rs3918242* of the *MMP-9* gene in patients with hypertension (AH) younger than 40, depending on the degree of relative cardiovascular risk

Genotypes	Frequency in persons with CVR=2 (n=72)	Frequency in persons with CVR=1 (n=23)	OR (95% CI)	P-value
MMP-2 c.-1306C>T (rs243865) TT+CT	38(52.7)	10 (43.4)	0.34 (0.16-0.71)	0. 52
MMP-2 c.-1306C>T (rs243865) CC	34 (47.2)	13 (56.5)		
MMP-9 c.-1562C>T (rs3918242) TT+CT	48 (66.6)	8 (34.7)	2.26 (0.42-1.84)	0.04
MMP-9 c.-1562C>T (rs3918242) CC	24 (33.3)	15 (65.2)		

Note: MMP - metalloproteinase, OR - odds ratio, CI - confidence interval. P-value - significance level p≤0.05.

Table 5

Distribution of the frequency of genotypes of polymorphic loci *rs243865* of the *MMP-2* gene and *rs3918242* of the *MMP-9* gene in patients with hypertension (AH) over 40, depending on the degree of absolute cardiovascular risk (SCORE scale)

Genotypes	Frequency in persons with moderate CVR (n = 23)	Frequency in individuals with high and very high CVR (n = 43)	OR (95% CI)	P-value
MMP-2 c.-1306C>T (rs243865) TT+CT	13 (56.5)	22 (51.1)	0.81 (0.46-1.42)	0.35
MMP-2 c.-1306C>T (rs243865) CC	10 (43.4)	21 (48.8)		
MMP-9 c.-1562C>T (rs3918242) TT+CT	10 (43.4)	19 (44.1)	1.42 (0.59-1.82)	0.55
MMP-9 c.-1562C>T (rs3918242) CC	13 (56.5)	24 (55.8)		

In persons with AH, the presence of a minor *T*-allele at the *rs3918242* polymorphic locus of the *MMP-9* gene occurs 2.04 times more often than in healthy individuals. These data allow us to consider *MMP-9 c.-1562C> T (rs3918242)* as a candidate gene for detecting genetically determined connective tissue dysmetabolism with the development of hypertension (AH).

In hypertensive patients under 40 years of age with a relative cardiac risk index equal to two, the proportion of the *T* allele in the *rs3918242* polymorphic locus of the *MMP-9* gene was 2.2 times higher than that in individuals with a relative cardiovascular risk equal to one. In persons over 40 years of age, such a difference has not been distinguished. Accordingly, the presence of the *T* allele in the *MMP-9 gene c.-1562C> T (rs3918242*) is associated with a higher risk of cardiovascular catastrophes in young people with hypertension (AH).

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DIAGNOSTIC AND TREATMENT METHODS

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RISK OF ACUTE KIDNEY INJURY IN PATIENTS WITH ISHEMIC HEART DISEASE AND CONCOMITANT METABOLIC SYNDROME AFTER ON-PUMP CORONARY BYPASS GRAFTING

The aim of the research was to study the incidence and risk factors of developing AKI, its patterns in patients with CHD and concomitant MS after the coronary artery bypass grafting off-pump.

Materials and methods. The study covered two groups: patients with CHD and MS (the main group, n=82); and patients with CHD but without MS (the control group, n=51). Here are the inclusion criteria for the study: CHD with HF of Class III-IV; normal left ventricular ejection fraction (LVEF) - 55% and above; 45-69 years of age. The exclusion criteria were as follows: complications during and after the surgery, diabetes mellitus, kidney diseases, low LVEF (<54%), over 70 years of age. The criteria for MS: central obesity, arterial hypertension, increased triglycerides (≥1.7 mmol/L), and impaired glucose tolerance (IGT).

Results. Signs of AKI were detected in 61 (45.9%) patients, out of which 56 (68.3%) patients had MS. The patients with MS demonstrated initial reduced in GFR (71.2 ± 13.2 ml/ min/1.73 m^2), with its values reducing further on the 2nd day to 55.2 ± 14 ml/min/1.73 m^2 and the low values remaining on the 10th day after the surgery (69.5 ± 12.8 ml/min/1.73 m^2). The patients with MS had longer artificial lung ventilation (17.1 ± 9.1 hours against 10.8 ± 8.6 in the control group, p <0.01), longer stay at ICU (4.1±1.7 days against 2.9±0.9 in the control group, p<0,01) and in the hospital (24.3±3.2 days against 21.39±2.3 in the control group, p<0.015), and higher mortality (5.4% against 1.9% in the control group). The statistically reliable risk factors were revealed: the patient's age (p<0.01), high-density lipoprotein in blood (p <0.01), total cholesterol (p<0.039), and creatinine (p<0.01).

Conclusion. The presence of MS is a factor contributing to the high probability of AKI development after coronary artery bypass grafting off-pump (68.3% of the cases), which requires monitoring of the renal function during perioperative period, as well as prevention of AKI in patients with CHD and concomitant MS.

***Keywords*:** coronary heart disease, coronary artery bypass grafting off-pump, metabolic syndrome, risk factors, acute kidney injury.

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Relevance. Coronary heart disease (CHD) is a leader among all causes of death in the world [1]. At present, myocardial revascularization by artery bypass surgeries is a common solution for CHD. However, despite its high efficiency, there surgeries are accompanied by various undesirable dysfunctions of organs and systems in the organism, as well as the development of severe complications, including acute kidney injury (AKI) [2]. The recent data show that after coronary artery bypass grafting, AKI is observed in 17.5 % of cases [3], leading to a changed patient treatment tactic, prolonged treatment duration and significantly worse prognosis, with hospital mortality rate increasing from 7.6 % to 26.3% [2].

It has been established that MS is one of the negative factors contributing to renal dysfunction in patients with cardiovascular pathologies [4]. Typically, patients with MS are overweight and suffer from dyslipidemia, insulin resistance, and arterial hypertension [5]. Due to a high risk of developing various complications in the postoperative period, this category of patients constitutes a serious medical, social, and economic challenge of the present time [2, 4].

The comparison of the data from different researchers on AKI after bypass surgeries demonstrates a wide scatter of the incidence and outcomes of treating this complication. This is explained by the fact that they use different criteria of evaluating kidney injuries, present heterogeneous age groups of patients, sometimes do not take into account the presence of chronic kidney diseases, or cover different methods of surgeries – bypass grafting with mechanical ventilation or off-pump.

In this regard, the study of the incidence and predictors of developing AKI, its patterns in patients with CHD and concomitant MS having undergone coronary artery bypass grafting off-pump is relevant.

The aim of the research was to study the incidence and risk factors of developing AKI, its patterns in patients with CHD and concomitant MS after the coronary artery bypass grafting off-pump.

Materials and methods. The study covered 133 patients (104 men and 29 women), aged 45-69 (mean age of 58.2±6.4 years). All the patients underwent semi-elective coronary artery bypass grafting off-pump at the Sakha (Yakutia) Republic's Hospital No. 1 - National Center of Medicine in the period 2017-2020. During the postoperative period, the patients were supervised and treated at the Anesthesiology, Reanimation and Intensive Therapy Unit (ARITU).

The diagnostics of AKI and evaluation of its severity was done in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [9]. The calculation of the glomerular filtration rate (GFR) was done with the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) [10] before the surgery, on Day 1, 2, 3, and 10 following the surgery.

The continuous sampling of all the patients was divided into two groups: Group 1 – 82 patients with CHD and concomitant MS (main group); and 51 patients with CHD without MS (control group).

The inclusion criteria for the study were as follows: diagnosed CHD with HF of Class 3 and 4; normal left ventricular ejection fraction (LVEF) – 55% and above; 45-69 years of age.

The exclusion criteria were as follows: complications during and after the surgery (major bleeding, repeated exploration, perioperative myocardial infarction, and stroke), diabetes mellitus of Type 1 and 2, kidney diseases, and low LVEF (<54%).

The criteria for MS: waist over 80 cm in women and over 94 in men, systolic blood pressure >140 and diastolic – above 90 mm Hg, increased level of triglycerides (≥1.7 mmol/l), IGT – an increased level of plasma glucose in 2 hours after the load of 75 g of anhydrous glucose with the oral glucose tolerance test ≥7.8 and <11.1 mmol/l, under the condition that the level of fasting plasma glucose makes less than 7.0 mmol/l [1].

All the patients fell into Class 3 and 4 under the classification of anesthesiology risks by the American Society of Anesthetists (ASA).

All the patients were measured and their body mass indexes (BMI) were calculated. Before the surgery, the patients underwent standard tests: ECG, holter monitoring, duplex vascular scans. Two-three weeks before the surgery, they had a selective coronary angiography (SCAG), angiography of major and peripheral arteries. Laboratory tests: general clinical (complete blood count and urinalisys, coagulogram, biochemistry tests, lipid profile, finding out the acid-base balance and blood electrolytes, glycemic profile). The tests were run on the following stages: *Stage 1* – before the surgery; *Stage 2* – Day 1 after the surgery; *Stage 3* – Day 2 after the surgery; *Stage 4* – Day 3 after the surgery; *Stage 5* – Day 10 after the surgery.

The anesthetic managements of all the patients was carried out under cardio anesthesiology standards following the management protocol of patients undergoing coronary artery bypass grafting off-pump.

The type of the study is retrospective and prospective, longitudinal observational.

The processing of the statistical data was performed using SPSS Statistics, version 23, and included: at different stages of the study, calculating the mean value and standard deviation assuming a normal distribution (M±SD), the median and interquartile range (Me, IQ RQ3-Q1); a logistic regression analysis to assess the predictors of reduced GFR; the

Table 1

The indicators and dynamics of laboratory-instrumental and clinical data in the studied groups (M±SD)

Indicators	All patients (n=133)	Patients with MS (n = 82)	Patients without MS (n=51)	p
Overweight BMI>25 kg/m^2	29.7±4.8	32.4±3.26	25.3±3.7	0.297
HbA1c, %	4.99±1.0	5.44±1.08	4.27±0.6	<0.01
EuroSCORE index, %	8.95±2.83	9.55±2.99	7.92±2.23	<0.01
Surgery duration, min.	156.5±18.9	157.43±20.2	155.1±16.7	0.496
Number of bypasses, Me(IQR)*	1(1;1)	1(1;1)	1(1;1)	0.895
Number of bypasses, n (%)				
1 bypass	115 (86.5)	70 (85.4)	45 (88.2)	
2 bypasses	17 (12.8)	12 (14.6)	5 (9.8)	
3 bypasses	1 (0.8)	-	1 (2)	
LVEF, %				
before surgery	59.9±6.1	59.6±5.2	60.3±7.5	<0.01
after surgery (Day 2)	60.8±6.1	60.4±6.25	61.5±6.6	0.036
Microalbuminuria, mg/day				
before surgery	18.6±13.7	22.4±13.1	12.64±12.6	0.387
Urea, mmol/l				
before surgery	7.5±1.4	7.6±1.3	7.2±1.56	0.243
Day 1 after surgery	8.9±2.2	9.3±2.3	8.1±1.71	0.002
Day 2 after surgery	9.6±2.7	10.3±2.8	8.4±1.9	0.001
Day 3 after surgery	9.6±2.8	10.0±3.1	8.92±2.0	0.011
Day 10 after surgery	8.2±1.9	8.3±2.0	8.0±2.0	0.341
Creatinine, μmol/l				
before surgery	96.6±16.5	100.4±17.8	90.5±12.18	0.012
Day 1 after surgery	96.3±15.7	119.6±20.3	100.9±13.2	<0.01
Day 2 after surgery	119.6±29.7	130.4±29.2	102.2±21.4	0.013
Day 3 after surgery	111.1±26.3	120.0±26.1	96.7±19.8	0.081
Day 10 after surgery	96.3±15.7	102.1±14.7	87.1±12.6	0.971
Osmolarity, mOsm/l				
before surgery	279.8±10.1	283.2±6.4	274.5±12.4	<0.01
Day 1 after surgery	286.4±10.4	291.4±7.6	278.8±9.9	0.279
Day 2 after surgery	288.7±11.0	292.7±10.3	283.4±10.1	0.159
Day 3 after surgery	285.5±10.5	289.8±6.6	279.8±12.4	<0.01
Day 10 after surgery	279.4±12.3	283.6±6.3	272.7±16.1	<0.01

Note: * Me, IQR – the median, interquartile range Q3-Q1.

two-tailed criterion of Student's t-test for comparing the mean values of two independent groups, and the x^2 criterion for comparing the dichotomous variables. The statistical significance was set at $p < 0.05$

Results and Discussion. Out of 133 patients covered in the study, the signs of AKI were observed in 61 (45.9%) patients. The changes in the excretory function of the kidneys were registered as early as on Day 1 after the surgery and reached the maximum on Day 2. The two studied groups demonstrated significant differences. In the control group, the sign of AKI under the KDIGO criteria were observed in 5 (9.8%) patients only, whereas in the group of the patients with MS the signs manifested in 56 (68.3 %) of the patients. Indeed, the analysis of the concomitant MS contribution to the development of AKI in the patients revealed their definite relation: the odds ratio (OR) = 12.9; confidence interval (CI) = 4.6–36.0; $x^2 = 31.153$ ($p<0.05$).

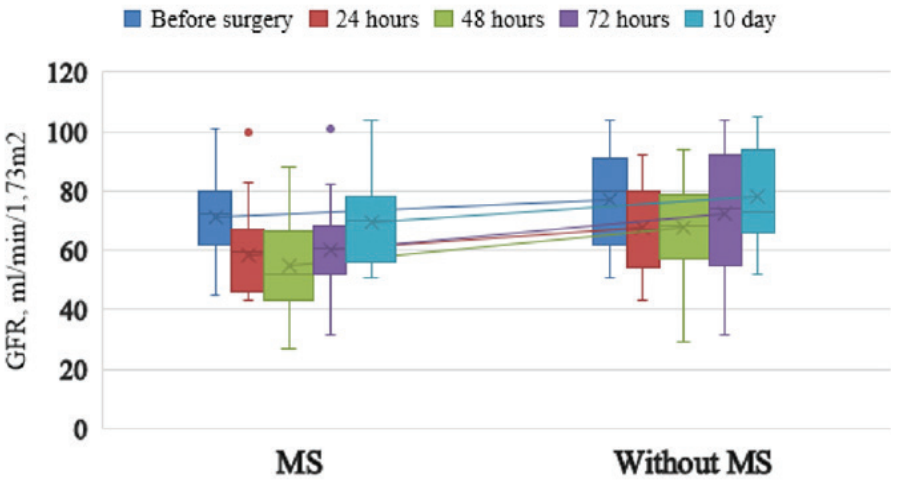
Table 1 and Figure present the detailed comparative analysis of the values obtained in the laboratory research and instrumental analysis on the patients in the studied groups.

In the preoperative period, the study groups demonstrated significant baseline differences ($p<0.05$) in the values of the adverse outcome index of coronary artery bypass grafting (EuroSCORE index), glycosylated hemoglobin (HbA1c), LVEF, creatinine and blood osmolarity. For instance, before the surgery, the blood creatinine level in the patients with MS was 100.4±17.8 μmol/l, in the control group – 90.5±12.2 μmol/l ($p<0.012$). The exceptions were BMI ($p=0.297$) and albuminuria level ($p=0.387$) (Table 1).

The most pronounced changes in the indices were observed in the both groups on Day 2 after the surgery, when the maximum level of increased blood creatinine was noted. The patients with MS also demonstrated a more pronounced increase in creatinine, which reached 130.4±29.2 μmol/l.

The postoperative dynamics of GFR, as an objective predictive criterion of AKI, confirms the above dynamics of the creatinine level in blood at the different stages of treatment (Figure).

In the patients with MS, in contrast to the patients in the control group, an initial decrease in GFR was observed in the preoperative period – 71.2±13.2 ml/min/1.73 m^2 ($p<0.01$). After the surgery, it decreased further, reaching 55.2±14 ml/min/1.73 m^2 on Day 2, which is 1.3 times lower than the initial values ($p<0.01$). In the following days, there was an increasing trend; however, on Day 10 after the surgery, the GFR level remained below the initial values – 69.5±12.8 ml/min/1.73 m^2. It can be seen that similar dynamics in the level of GFR in the postoperative period is also characteristic of the patients in the control group, which indicates the need for mandatory monitoring of the renal function and targeted prevention of its disorders for all patients with coronary artery disease having undergone bypass grafting.



Glomerular filtration rate dynamics in the studied groups (M±SD).

Given the obvious relationship between MS and decreased renal function, as well as the presence of numerous risk factors for the development of AKI with MS, it is of interest to identify the key factors among them. In order to determine the main predictors of a decrease in GFR in patients with MS, we performed a regression analysis of a number of AKI factors (Table 2).

Among the presented risk factors for AKI, the statistical significance of the factors was revealed: the patient's age ($p<0.01$), the level of high-density lipoproteins (HDL) in blood ($p<0.01$), total cholesterol ($p<0.039$), and creatinine ($p<0.01$). All other factors were of no statistical significance (Table 1). Obviously, the risk factors for the development of AKI also include the specifics of a certain surgery (duration, number of bypasses, technical difficulties) and anesthetic support (for example, unstable hemodynamics). However, we excluded the cases with a complicated course of surgical intervention and anesthesia from our study.

The treatment outcomes of the patients in the studied groups demonstrated significant differences (Table 3).

The duration of mechanical ventilation in the patients with MS in the postoperative period was 17.1±9.1 hours against 10.8±8.6 hours in the control group ($p<0.01$).

The duration of treatment of the patients with MS at ARITU and in-patient ward was 4.1±1.7 and 24.3±3.2 days, respectively, which also reliably exceeds the duration of treatment of the patients in the control group ($p<0.01$).

The mortality in the patients with MS made 5.4%, in the patients without MS – 1.9%.

Conclusions. In our study, the patients with coronary heart disease who underwent bypass surgery off-pump

Table 2

The regression analysis of the main predictors of a decrease in GFR in patients with MS (M±SD)

AKI risk factors	GFR 89-60 ml/min/1.73m2 (n=26)	GFR < 60 ml/min/1.73m2 (n=56)	p
Age, years	55.0±7.0	59.4±6.5	<0.01
BMI, kg/2	31.3±3.2	33.5±2.9	0.094
Osmolarity of blood plasma, mOsmol/l	284.0±7.6	282.0±5.6	0.819
HDL, mmol/l	1.68±0.23	1.49±0.2	<0.01
LDL, mmol/l	2.53±0.36	2.5±0.5	0.486
Total cholesterol, mmol/l	6.75±1.2	6.94±1.26	0.039
Triglycerides, mmol/l	1.78±0.2	1.71±0.3	0.599
Creatinine, μmol/l	97.8±15	101.9±20.6	<0.01
LVEF, %	61±5.9	60.2±5.9	0.551

Table 3

The treatment outcomes of the patients in the studied groups (M±SD)

Indicator	All patients (n=133)	Patients with MS (n=82)	Patients without MS (n=51)	p
Duration of MV at ARITU, hours	14,7±9,4	17,1±9,1	10,8±8,6	<0,01
Duration of treatment, bed/days at ARITU at in-patient ward	 3,6±1,6 23,2±3,1	 4,1±1,7 24,3±3,2	 2,9±0,9 21,39±2,3	 <0,01 0,015
Mortality, abs (%)	5(4)	4(5,4)	1(1,9)	<0,01

manifested early signs of AKI in 45.9% of the cases, with the signs most pronounced on Day 2 after the surgery. The signs of AKI in the patients without MS were noted in 9.8% of the cases, whereas with concomitant MS, they were observed far more often – in 68.3% of the patients. In this case, unlike the patients in the control group, the patients with MS were characterized by both an initial decrease in GFR (71.2 ± 13.2 ml/min/1.73 m^2) and its low values on Day 10 after the surgery (69.5 ± 12.8 ml/min/1.73 m^2).

Among the risk factors for AKI, the statistical significance of the factors was revealed: the patient's age ($p<0.01$), the level of high-density lipoproteins (HDL) in blood ($p<0.01$), total cholesterol ($p<0.039$), and creatinine ($p<0.01$).

Thus, the management of patients with coronary heart disease and concomitant MS who underwent surgical treatment, in particular bypass surgery off-pump, requires a special approach, a mandatory assessment of the initial state of the renal function, and the implementation of measures for the targeted prevention of the kidney decreased function in pre- and postoperative periods.

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STATE OF THE HEMOSTASIS SYSTEM IN PATIENTS WITH CHRONIC GENERALIZED PERIODONTITIS IN ALTERNATIVE METHODS OF TREATMENT

Abstract: The aim of the research was to study the indicators of the hemostasis state in the blood and oral fluid in chronic generalized periodontitis (CGP) of moderate severity before and after the standard treatment and with the use of the neurotropic drug «Cortexin». The study included 60 patients aged 25-60 years, divided into 4 groups of 15 persons with moderate CGP and 15 healthy individuals aged 18-24 years forming the control group. The analysis shows the insufficient effectiveness of standard treatment in chronic generalized periodontitis of moderate severity, and the inclusion of «Cortexin» in therapy leads to an improvement or normalization in the hemostasis system in young and middle-aged people.

Keywords: periodontitis, oral fluid, hemostasis, fibrinolysis, 'Cortexin'.

Introduction. Inflammatory periodontal diseases are quite common pathologies, in particular chronic generalized periodontitis - one of the most complex pathologies of the maxillofacial region, with physical, psychological suffering, leading to early tooth loss, reduced functional capabilities of the denture system, foci formation of chronic infection, leading to the development of somatic pathology and sensitization of the body [2. 4. 10. 11. 15-17]. Various scientific researches present that the life quality in chronic generalized periodontitis is characterized as low [16, 18-20].

Hemostasis system changes in chronic generalized periodontitis are widely discussed in studies [3, 8, 9, 12-14]. We need a multilateral study of the mechanisms of disease development in order to study and understand etiopathogenesis, as well as prevent exacerbation of the course of the disease and its complications due to the prevalence of chronic generalized periodontitis and the insufficient effectiveness of treatment.

The aim of the research is to identify the dynamic features of the hemostasis system condition in blood and oral fluid in the complex treatment of chronic generalized periodontitis by using the neurotropic drug Cortexin.

Research materials and methods. During 2016-2018, 60 patients with chronic generalized periodontitis (CGP) aged from 25 to 60 years old were examined, who were treated in the clinic dental department No. 1 of Chita State Medical Academy. All patients had the moderate chronic generalized periodontitis. 4 clinical comparison groups were formed for the research: the 1st Group - 15 patients aged 25-44 years old with CGP receiving standard treatment; Group 2 - 15 CGP patients aged 45-60 years old receiving standard treatment; Group 3 - 15 patients aged 25-44 years old with CGP receiving Cortexin (a dose of 10 mg 10 days, intramuscularly) in standard therapy; Group 4 - 15 patients aged 45-60 years old with CGP receiving Cortexin (a dose of 10 mg 10 days, intramuscularly) in

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Table 1

The effect of therapy on the state of hemostasis system in patients with CGP [Me (25-75 0/00)]

Indicator	Control (n = 15)	Standard treatment (n = 15)		Standard treatment + Cortexin (n = 15)	
		before treatment	after treatment	before treatment	after treatment
CGP patients of young age (25-44 years old)					
APTT, c	43.10 (40.5; 44.9)	38.9* (37.8; 39.7)	39.6*▲- (38.8; 39.8)	37.9* (37.5; 39.5)	40.95▲▪ (40.6; 41.4)
MHO	1.05 (1.0; 1.1)	1.2* (1.2; 1.2)	1.1 (0.95; 1.21)	1.19* (1.1; 1.3)	1.05▲ (1.0; 1.14)
Thrombin time, s	17.2 (17.2; 17.3)	15.8* (15.6; 16.2)	16.1*▲ (15.7; 16.6)	15.0* (14.5; 15.4)	17.1▲ (16.9; 17.4)
Fibrinogen, g/l	2.75 (2.3; 3.0)	4.3* (3.9; 4.6)	4.1*▲ (3.8; 4.4)	4.2* (3.9; 4.4)	3.5▲▪•
FMC, mg/100 ml	3.00 (2.90; 3.0)	5.1* (5.0; 5.8)	5.3*▲ (5.0; 5.4)	5.2* (5.0; 5.5)	3.5▲▪•
Fibrinolysis, min	141.00 (138.0; 147.0)	178.5* (177.0; 182.5)	164.00*▲ (159.0; 167.0)	179.2* (176.0; 182.0)	146.0▲▪•
CGP patients of young age (45-60 years old)					
APTT, s	43.10 (40.50; 44.90)	34.8* (29.5; 36.5)	37.60*▲ (36.4; 38.5)	34.7* (32.5; 36.5)	40.4▲▪•
INR	1.05 (1.00; 1.10)	1.2* (1.13; 1.2)	1.2* (1.11; 1.21)	1.2* (1.13; 1.2)	1.07▲▪ (1.0; 1.1)
Thrombin time, s	17.20 (17.20; 17.30)	14.8*▪ (14.3; 14.9)	15.40*▲•	14.6*▪ (14.3; 14.6)	16.9▲▪ (16.5; 17.0)
Fibrinogen, g/l	2.75 (2.30; 3.00)	5.4* (5.1; 5.6)	5.3*• (5.2; 5.6)	5.5* (4.8; 5.7)	3.2▲▪• (3.1; 3.5)
FMC, mg/100 ml	3.00 (2.90; 3.00)	6.1* (6.0; 6.6)	6.0*▲ (5.8; 6.2)	6.0* (5.8; 6.2)	4.10*▲▪ (3.8; 4.20)
Fibrinolysis, min	141.00 (138.0; 147.0)	189.1* (183.0; 194.5)	177.00*▲ (175.0; 180.0)	188.9* (181.8; 189.8)	154.0▲▪• (152.25; 158.0)

Note: n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); ▲ - differences in values compared to the baseline (Wilcoxon test); ▪ - differences in values between groups; • - differences in values between treatment options (Mann-Whitney test).

standard therapy. The control group was 15 practically healthy individuals without acute and chronic periodontal diseases at the time of research aged from 18 to 24 years old.

Standard treatment of patients with CGP included: hygiene training of oral cavity, professional hygiene and sanitation of oral cavity, antiseptic processing of tissues of the parodont with 0.06% Chlorhexidine solution, hardening bandage with Cholisal and "Metrogyl Denta" for 20 min. 2 times a day within 10 days, the Vector therapy, ozonterapy, a selective grinding, splinting with "GlasS-pan". Cortexin was used intramuscularly in complex treatment with a dose of 10 mg, the course of treatment was 10 days in the 3rd and 4th clinical groups.

The tissue factor of plasminogen (t-PA) and PAI-1 was determined in blood plasma and oral fluid by a set of reagents "Cloud-Clone Corp." (USA) with ELISA sandwich method. To examine hemostasis, donor blood from the ulnar vein was taken with a wide needle into centrifugal siliconized tubes with addition of 3.8% sodium citrate solution in a ratio of 1:9. To obtain platelet-rich and platelet-depleted plasma, sodium citrate-stabilized blood was centrifuged at 1000 rpm for 7 minutes and 3000 rpm for 15 minutes, respectively.

Coagulation hemostasis was evaluated by the following tests: activated partial thromboplastin time (Larrien M.G., Weillard C., 1957), prothrombin time (Quick A.J., 1943), thrombin time (Syrmai E., 1957). Euglobulin fibrinolysis was investigated by M. Kowarzhyk (1953). Fibrinogen concentration was determined coagulometrically. Fibrin monomer complexes (FMC) content was determined by phenatroline test. All methods used in this research were published in hemostasis system instructions [1, 5-7].

Statistical processing was carried out in the program "StatSoft Statistica 10.0 Advanced" (StatSoft Ins., USA) (License No. AXAR507G794202FA-B). According to the results of visual and quantitative analysis according to the Shapiro-Wilk statistics for compliance with the normal distribution, some indicators were not to the law of normal distribution. In case of non-compliance with the normal distribution, according to the recommendations of A.M. Grizhbovsky et al. (2016), a median quartile assessment was performed. Wilcoxon criterion was used for analyzing dependent samples. Mann-Whitney criterion was used for comparing independent samples.

Results and discussion. The obtained data of the hemostasis system indicate that there is an increase in the coagulation blood properties in young and middle age patients with moderate CGP. Concentration of compounds having procoagulant activity and inhibiting fibrinolysis in oral fluid was increased in those patients compared to healthy ones.

After standard therapy, hypercoagulation signs decreased in blood of young patients, but maintained a shortened APTT (Table 1). The latter indicates that the internal coagulation pathway remains initiated. At the same time, INR reached the normal level, and the concentration of fibrinogen and fibrin clot lysis time approached the control values. It should be especially noted that there was an increased concentration of FMC in this group of patients, which indicated an increase in constant intravascular blood coagulation and microcirculatory disorders. After Cortexin therapy, all the examined indicators of the hemostasis system in young patients reached control values, which contributed to the restoration of microcirculation in periodontal tissues.

In middle-aged patients, after standard treatment, shortened APTT, increased INR and reduced thrombin time were preserved. At the same time, in patients, compared with healthy ones, the concentration of fibrinogen and FMC remained increased, as well as suppressed fibrinolysis, which indicated serious microcirculation damage and thrombus preservation. Meanwhile, the dynamics of hemostasis system indicators in complex treatment with Cortexin was more pronounced. Thus, APTT, thrombin time and fibrinogen content approached the normal level, INR achieved control indicators, and fibrinolysis accelerated by more than 18% compared to conventional therapy.

In young patients with CGP, standard therapy led to a decrease in the concentration of procoagulants in the oral fluid, an extension of APTT, prothrombin and thrombin time, as well as an acceleration of fibrin clot dissolution in comparison to the course of treatment. The procoagulant activity of saliva was increased with Cortexin treatment, which is characterized by approaching the APTT values and prothrombin time to the normal level, as well as normalization of thrombin time and fibrinolysis (Table 2). In the oral fluid of middle-aged patients after standard therapy, procoagulant activity increased poorly and the antifibrinolytic effect remained at the same level, but Cortexin therapy led to the restoration of APTT, INR and thrombin time in the bloodstream to reference values, and at the

Table 2

Effect of oral fluid on blood clotting and fibrinolysis during the therapy in patients with CGP [Me (25-75 0/00)]

Indicator	Control (n = 15)	Standard treatment (n = 15)		Standard treatment + Cortexin (n = 15)	
		before treatment	after treatment	before treatment	after treatment
CGP patients of young age (25-44 years old)					
Prothrombin time, %	75.8 (74.6; 78.6)	62.1* (59.0; 63.0)	68.4* (62.10; 69.5)	62.7* (59.5; 63.6)	72.3*▲■ (68.60; 74.40)
APTT, %	80.1 (79.8; 81.8)	59.2* (58.3; 61.0)	71.0*▲ (67.9; 70.8)	59.7* (58.3; 61.0)	77.8*▲■ (76.6; 79.4)
Thrombin time, %	80.3 (78.8; 82.8)	63.4* (62.2; 65.3)	68.3* (65.6; 70.65)	63.3* (62.4; 65.6)	75.3▲■ (73.3; 79.4)
Fibrinolysis, %	73.5 (73.0; 75.5)	86.1* (84.0; 89.0)	82.8* (82.0; 83.5)	87.0* (84.00;90.0)	78.1▲■ (77.00; 80.00)
CGP patients of young age (45-60 years old)					
Prothrombin time, %	75.80 (74.63; 78.60)	62.0* (58.0; 64.3)	67.1*▲ (64.4; 67.90)	61.7* (59.8; 61.9)	71.1▲■ (69.2; 71.5)
APTT, %	80.10 (79.80; 81.80)	65.0* (57.2; 69.5)	69.2*▲ (67.3; 70.75)	65.1* (57.4; 68.5)	79.5▲• (76.8; 81.0)
Thrombin time, %	80.28 (78.80; 82.81)	63.3* (62.2; 63.8)	68.5*▲ (65.7; 70.65)	63.3* (62.5; 63.5)	77.6▲■ (73.3; 78.4)
Fibrinolysis, %	73.50 (73.00; 75.75)	85.7* (85.0; 89.0)	83.0*▲ (82.0; 84.0)	85.8* (85.3; 88.4)	76.5■ (74.5; 81.0)

Note: n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); • - differences in values compared to the baseline; ■ - differences in meanings between treatment options.

Table 3

Dynamics of tPA and PAI - 1 content in blood plasma in patients with CGP moderate severity [(Me (25-750 / 00)]

Indicator	Control (*n*=15)	Standard treatment		Standard treatment + Cortexin (*n*=15)	
		before treatment (*n*=15)	after treatment (*n*=15)	before treatment (*n*=15)	after treatment (*n*=15)
CGP patients of young age (25-44 years old)					
tPA, нг/мл	0,728 (0,537; 0,825)	5,07* (4,482; 5,197)	1,849*• (1,59; 1,925)	5,395* (4,482; 5,585)	3,592*▪ (2,667; 4,115)
PAI – 1, пг/мл	585,35 (556,05; 591,3)	28325,00* (27195; 28850)	13780*• (12850; 13920)	26810* (26540; 26960)	8570*•▪ (8212; 8820)
CGP patients of young age (45-60 years old)					
tPA, нг/мл	0,728 (0,537; 0,825)	5,246* (5,07; 5,615)	1,438*• (1,219; 1,608)	5,525 * (4,125; 6,825)	4,608* (3,425; 5,315)
PAI – 1, пг/мл	585,35 (556,05; 591,3)	30196* (28998,5; 31005)	18250*• (17923; 18550)	29590* (28954; 30440)	14020*•▪ (13445; 14880)

Note. n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); • - differences in values compared to the baseline; ■ - differences in meanings between treatment options; p <0.05.

Table 4

Dynamics of the content of tPA and PAI - 1 content in oral fluid in patients with CGP moderate severity [(Me (25-750 / 00)]

Indicator	Control (*n*=15)	Standard treatment		Standard treatment + Cortexin	
		before treatment (*n*=15)	after treatment (*n*=15)	before treatment (*n*=15)	after treatment (*n*=15)
CGP patients of young age (25-44 years old)					
tPA, нг/мл	0.06 (0.052; 0.078)	0.19* (0.15; 0.21)	0.24* (0.17; 0.28)	0.17* (0.13; 0.19)	0.073•▪ (0.065; 0.078)
PAI – 1, пг/мл	156.072 (135.5; 169.6)	1800.5* (1676; 1936)	1677* (1535; 1717)	1802* (1697; 1929)	1621* (1575; 1763)
CGP patients of young age (45-60 years old)					
tPA, нг/мл	0.06 (0.052; 0.078)	0.457* (0.374; 0.493)	0.48* (0.44; 0.55)	0.445* (0.363; 0.472)	0.186*•▪ (0.174; 0.199)
PAI – 1, пг/мл	156.072 (135.5; 169.6)	2165* (2097.0; 2206)	1555*• (1435; 1641)	2180* (2112; 2321)	1738* (1617; 1944)

same time a weakly expressed inhibition of fibrinolytic activity was preserved. The effect of oral fluid on the examined indicators of the hemostasis system when using Cortexin had practically no difference in comparison to healthy people.

The research revealed a high blood content of plasminogen activator inhibitor (PAI-1) in young patients, which decreased by 2 times with standard treatment and by 3 times with Cortexin (Table 3) after the treatment. The level of tissue factor plasminogen (tPA) was increased 4-5 times before treatment, and decreased 2.5 (standard treatment) and 1.5 times (standard treatment with Cortexin) after therapy. A high content of plasminogen activator inhibitor (PAI-1) in blood was also detected in patients aged 45-60 years old, which after treatment decreased by 1.5 (standard treatment) and 2 times (standard treatment and Cortexin). The tissue factor of plasminogen (tPA) in patients receiving standard therapy decreased 3.5 times from the original, and it remained the same in patients using Cortexin.

There is a high content of plasminogen activator inhibitor (PAI-1) in the oral fluid of patients with CGP aged 25-44 years old, which decreased in both methods of treatment. The tissue factor of plasminogen (tPA) with standard treatment remained the same, and the use of Cortexin normalized these indicators (Table 4). After treatment in patients aged 45-60 years old, the oral fluid showed a decrease in the content of the plasminogen activator inhibitor (PAI-1) with standard treatment and with the use of Cortexin. The tissue factor of plasminogen (tPA) with standard treatment remained at the same level, and Cortexin decreased it by 2 times. Standard therapy reduced the content of activator inhibitor and tissue factor plasminogen, but the effect in complex with "Cortexin" was significant.

Conclusion. The obtained data indicated hemostasis system disorders in chronic generalized periodontitis of moderate severity in patients of young and middle age, which was confirmed by the researches.

Standard treatment improved blood

hemostasis - INR and fibrinogen reached the normal level, but at the same time, APTT was shortened and the concentration of FMC was increased. Tissue factor and plasminogen activator inhibitor decreased but did not reach control numbers. A similar situation was observed in the indicators of hemostasis in the oral fluid. Complex Cortexin treatment in young and middle-aged patients led to a significant reduction or elimination of hypercoagulation shifts and restoration of procoagulant and antifibrinolytic activity of oral fluid. Use of "Cortexin" in patients of young age with chronic generalized periodontitis of moderate severity led to normalization of the analysed parameters of the hemostasis system in the bloodstream and oral fluid.

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ANTI-RELAPSE TARGETED CHEMOEMBOLIZATION AS AN ADJUNCT TO RENAL CANCER RESECTION

Aim: to assess the saturation of the surgical margin of the kidney resection with a chemotherapy drug in order to determine the effectiveness Aim: to assess the saturation of the surgical margin of the kidney resection with a chemotherapy drug in order to determine the effectiveness of targeted balloon chemoembolization during parenchymal organ resection for the prevention of tumor recurrence

Materials and methods. The study is based on the results of experimental experiments on laboratory animals. The concentration of the marker in the parenchyma of the organ was determined for 8 days with its transarterial administration when simulating the resection process followed by wound closure.

Results and discussion. The data obtained clearly demonstrated the prolonged fixation of the marker in the tissues of the surgical edge of the resected organ.

Conclusion. Transarterial balloon embolization with a targeted drug for resection of the parenchymal organ may be effective for the prevention of tumor recurrence due to the duration of high concentrations in the surgical margin of resection.

Keywords: Kidney cancer, renal tumor recurrence, targeted balloon chemoembolization

Introduction. Kidney cancer occupies 2–3% of all human malignant neoplasms, and 90% of kidney tumors are localized in the renal parenchyma. The annual global increase in the incidence of kidney tumors is 2%, [13]. In Russia, this figure is slightly higher and amounts to about 3-4% [2]. Given the high growth rates of this pathology, the search for the most effective methods of treatment is an urgent problem of modern medicine.

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Rudolf Virchow in 1865 noted the abundant blood supply to tumor tissue, but only 100 years later J. Folkman in 1971 suggested the dependence of tumor growth on the development of capillary blood supply, under the influence of certain substances produced by the tumor itself [7]. Since that time, an extensive search for angiogenesis inhibitors and their use in the treatment of oncological diseases began. For a long time, it was believed that a tumor mass with a volume of less than 2 mm3 does not have its own blood supply and that vital functions in it are supported by its own supply of energy substrates and diffusion of oxygen from the surrounding tissue. When a tumor grows beyond this volume, oncocytes located in the center of the formation undergo acute hypoxia and stimulate the processes of oncoangiogenesis [8]. The results of studies of C. Li showed that oncoangiogenesis is triggered in a formation consisting of 100-300 cells, when microvessels are formed to feed the tumor mass [12]. Substances that activate angiogenesis were first described by N. Ferrara in 1989 and constitute a group of vascular endothelial growth factors (VEGF) [6].

When VEGF interacts with the corresponding receptor on the endothelial cell surface, the receptor is activated, which leads to the launch of a cascade of intracellular mediators reaching the cell nucleus and the final result of which is the initiation of genes responsible for angiogenesis [15]. Disclosure of the mechanisms of onconeoangiogenesis led to the creation of a whole group of drugs that block angiogenesis in malignant tumors of various localization [1].

The first targeted drug, bevacizumab, which is a monoclonal antibody, was presented in 2003 and showed an increase in oncological patient survival in clinical studies [9, 14]. In the treatment of advanced renal cell carcinoma, the use of bevacizumab led to a decrease in tumor size and increased the duration of the relapse-free period [5]. Inhibitors of vascular endothelial growth factors block the site that binds to the corresponding receptor and thereby prevent its activation and further transmission of the angiogenic impulse, which in turn inhibits the proliferation of endothelial cells, preventing the formation of a pathological vascular network. In addition, the action of bevatsimab induces apoptosis of endothelial cells of tumor vessels [4]. It is noteworthy that the effect of antiangiogenic therapy

with monoclonal antibodies develops on the first day after the start of treatment [10], which is associated with the extracellular mechanism of action of drugs of this series.

Materials and research methods. The currently existing methods of organ-preserving operations for malignant neoplasms, with all their positive characteristics, are devoid of a specific anti-relapse component. Prevention of relapse consists in resection of the affected area of the organ with a supply of healthy tissue, determined macroscopically, and removal of the tissues adjacent to the formation. As a result, the inevitable acute ischemia of tumor tissue is accompanied by a massive release of vascular endothelial growth factors, which, entering the systemic circulation, act on the receptors of epithelial cells, and thereby trigger recurrent neo-oncoangiogenesis. At the same time, relapse can give not only marginal continued growth from the remaining tumor, but also the emergence of a tumor de novo from microscopic oncocytes located outside the resection zone in the primary-multiple nature of the disease.

Taking into account the mechanism of oncoangiogenesis and the principle of antiangiogenic targeted therapy, a method of balloon chemoembolization and resection of malignant tumors of parenchymal organs has been proposed (RF patent for invention No. 2711549 "Method for balloon chemoembolization and resection of malignant tumors of parenchymal organs", Maksimov A.V., Neustroev P.A., 17.01.2020, State Register of Inventions of the Russian Federation).

The essence of the method is as follows: under X-ray control, selective angiography is performed, which determines the segmental artery of the organ supplying blood to the segment with the formation. A balloon catheter with a central channel for the administration of drugs, with a balloon size sufficient to block blood flow, is inserted into the selected artery under X-ray control. Inflation of the balloon stops arterial blood flow in the parenchyma segment of the organ. Then, bevacizumab is injected through the central canal of the balloon catheter into the ischemic segment, after which the tumor is resected within the intact tissue. The wound of the organ parenchyma is sutured with hemostatic sutures, after which the balloon is deflated and removed from the vessel lumen.

The current practice of prescribing targeted chemotherapy in the long term after the operation is not effective enough due to the late onset: the vascular growth factor formed as a result of acute hypoxia of tumor tissue provides active growth of the pathological vascular network, and the action of angiogenesis antagonists does not apply to already formed tumor vessels, which contributes to the recurrence of the oncological process. Thus, the timely saturation of the parenchyma adjacent to the tumor with a targeted drug creates a trap barrier for the VEGF secreted by the formation, thereby preventing its influence on potential recurrent foci.

An important role in this protection is played by the time factor - how long the targeted drug can persist in the resection margin, since oncocytes have an increased potential for survivability. In this regard, the goal of our study is to assess the saturation of the surgical margin with a chemotherapy drug and the duration of saturation during resection of the parenchymal organ for the prevention of tumor recurrence. To assess the duration of drug fixation in the surgical margin of resection of the parenchymal organ, we performed an experiment on laboratory animals, simulating the transarterial administration of the drug during resection by the example of using a marker - food dye Ponso S introduced into the parenchyma of the kidney of laboratory rabbits.

We used 14 laboratory rabbits weighing 2400-2600 g, New Zealand White breed. When working with laboratory animals, we used the recommendations of the “Animals in Research: Reporting In Vivo Experiments” manual [11], in compliance with international standards and bioethical norms, in accordance with the European Convention for the Protection of Vertebrate Animals used for Experiments or Scientific Purposes , Declaration of Helsinki on the Humane Treatment of Animals [3]

A diagram of the experimental operations is shown in Fig. № 1. Laparotomy was performed on two rabbits under mask ether anesthesia (Fig. №. 1) with further isolation of both kidneys. After isolation, the upper third of both kidneys were sutured with U-shaped sutures, in the transverse direction, while the nodes were not tightened. Then a 21 G cannula, 25 mm long, was inserted into the lumen of the aorta below the renal artery discharge, its end was inserted proximally, above the renal arteries. Through the cannula into the lumen of the aorta, a jet infusion of a solution of food coloring Ponso S in physiological saline was carried out at a rate of 100 mg / l in a volume of 5 ml. At the time of administration of the marker solution, knots were tied on the renal parenchyma, so as to

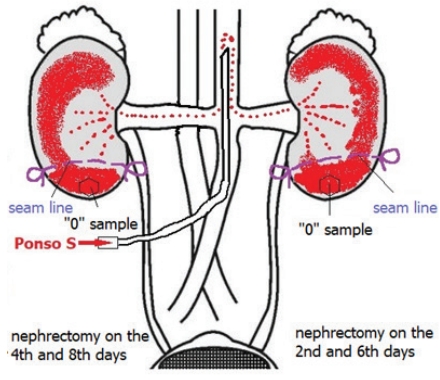

Fig. 1. Scheme of the operation on experimental animals

cause ischemia of the organ site. The resulting model of kidney resection with preliminary saturation of the parenchyma of the resection zone with a marker and with the imposition of hemostatic sutures clearly demonstrated the process of fixation of the targeted drug injected through the artery into the parenchyma adjacent to the tumor. After suturing the kidney, a 2 x 3 mm tissue fragment was taken from the ischemic region of the kidney for an initial assessment of the concentration of the marker in the parenchyma and a similar fragment of the parenchyma from the blood supplied part of the organ. In this way, zero dye values were obtained. The operation was completed by suturing the abdominal wound. After 2 days, one rabbit underwent nephrectomy of kidney №1, after 4 days, the same animal underwent nephrectomy of kidney №2 on the other side. In the second rabbit, the kidneys №3 and №4 were removed after 6 and 8 days. At the end of the last operation, all experimental animals were injected into the aorta with a solution of potassium chloride for cardioplegia, whereby the animals were removed from the experiment.

Thus, we obtained the values of the Ponso S marker concentration in the parenchyma of the ischemic and blood-supplied areas of the kidneys at the time of dye injection and with the dynamics of elimination within 2, 4, 6 and 8 days after the operation.

Results and discussion. The quantitative assessment of the concentration of the introduced dye into the renal parenchyma and the determination of the rate of marker elimination from the resection margin made it possible to estimate the duration of high concentrations of the chemotherapy drug in the organ parenchyma. For this, the initial specific gravity of the marker in the parenchyma at the time of administration was determined in both experimental animals, then the con-

Ponceau S concentration in kidney parenchyma, mg/l (p=0,024)

	Kidney №1	Kidney №2	Kidney №3	Kidney №4
Initial, on the day of administration	27,25 (100)	26,4 (100)	22,96 (100)	28,4 (100)
Study timing	2-й	4-й	6-й	8-й
Ischemized parenchyma (margin of resection)	16,55 (60,73)	15,18 (57,5)	12,65 (55,09)	14,82 (52,85)
Healthy parenchyma	7,7 (28,25)	3,36 (12,72)	2,45 (10,67)	2,46 (8,77)

tent of the substance in the tissue was assessed after 2 and 4 days in one rabbit, after 6 and 8 days in the second of this pair. For comparison, the concentration of the dye in the healthy, non-ischemic part of the kidneys was evaluated. Data were analyzed using statistical packages SPSS (Windows version 7.5.2). The reliability of differences in quantitative indicators was determined by the Student's t test for normally distributed values. Differences were recognized as significant at p <0.05. The data obtained as a result of the experiments are presented in table.

Taking the initial, on the day of administration, the content of the marker in the parenchyma as 100%, to eliminate the effects of individual characteristics (age, condition of the animal, organ size, speed and amount of the injected drug), the concentration of the substance can be presented as a percentage of the initial one. The data obtained as a result of the experiments are presented in table No. 1. A clear dynamics of elimination is shown in Figure 2.

The graph shows that the clearance of the drug injected into the parenchyma and fixed with sutures at the edge of the resection is less than the separation from the parenchyma marker, the blood-supplied part of the organ. The quantitative expression of this process: the concentration of the substance in the stitched part of the organ decreases after 2 days by 1.64 times, and in the blood-supplied part of the kidney - a decrease from the initial figures by 3.57 times. Elimination of the drug from the kidneys continues throughout the observation period, but its rate in the zone of organ ischemia is less than the rate of decrease in the concentration of the substance from the tissue of the intact kidney area.

The presented data prove the fact of long-term persistence of the substance introduced into the renal parenchyma through the arterial bed and fixed with hemostatic sutures. Moreover, more than 50% of the initial level remains for 8 days. A substance introduced into an organ and not fixed by sutures loses more than 90% of its original concentration.

Conclusion. The performed study proves that the duration of high concentrations of targeted chemotherapy drugs in the surgical margin of resection may be sufficient for effective prevention of tumor recurrence.

Methods of nephrons-sparing surgery have recently firmly occupied their niche in the arsenal of surgical treatment of malignant kidney tumors. The functional safety, low invasiveness and radicality of these methods certainly deserve the highest assessment, but at the same time one important aspect of the treatment of malignant neoplasms of the parenchymal organs is missed - the danger of tumor recurrence. Supplementing surgical organ-preserving treatment with local targeted chemotherapy, based on one of the mechanisms of tumor recurrence and the principles of antiangiogenic therapy, will block this vector of disease recurrence.

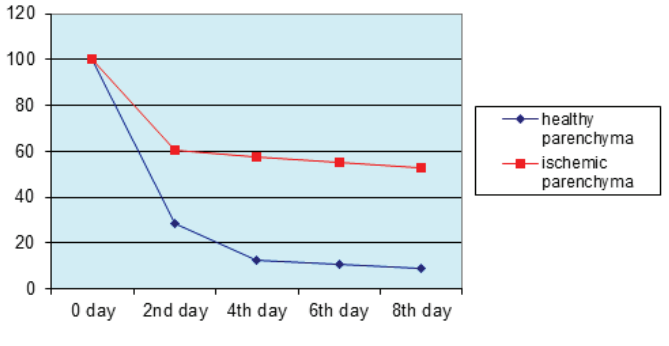

Fig. 2. The dynamics of Ponceau S elimination from kidney parenchyma, %.

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METABOLIC CHANGES IN CHILDREN WITH LIVER DISEASE IN THE TERRITORY OF THE REPUBLIC SAKHA (YAKUTIA)

The article presents the review of metabolic changes in children with liver pathology from clinical and laboratory-instrumental positions. The aim of the study was to study the biochemical and metabolic parameters in children and adolescents with obesity and liver pathology in the territory of the RS(Y).There are two groups of children, depending on the liver damage. According to ethnicity, it was found that liver damage prevailed in children of the Mongoloid race. The comparison of average biochemical parameters in groups with and without liver damage was carried out. Markers have been identified to identify liver damage in children at an early stage.

Key words: children, obesity, liver pathology, metabolic changes, ROC analysis.

Introduction. Currently, the comorbid course of diseases is an actual problem of medicine not only in Russia, but also in the whole world [2,3]. It is known that obesity is accompanied by damage to almost all organs and systems, including the digestive system [5,7]. Worldwide, there is a disastrously rapid increase in the number of obese people, not only among adults, but also among children [6,1]. Adipose tissue affects the digestive organs both mechanically and through metabolic action [9]. Non-alcoholic fatty liver disease (NAFLD) is considered the most common liver disease of non-infectious etiology in adults and children, which is primarily due to an increase in the prevalence of obesity, which is the main etiological factor of this pathology [10]. In children and adolescents, NAFLD is characterized by a chronic course, and its spread is global [8,4].

Materials and methods. 250 obese children with pathology of the gastrointestinal tract (GI) were examined. The study was conducted at the Department of Pediatrics and pediatric surgery, Medical Institute FGAOU VPO "northeastern state University named after M. K. Ammosov" of the Ministry of education and science of the Russian Federation, and Clinic of Pediatrics SBI RS(Y) "Republican hospital №1-national medical center" 2015 to 2018 selection criterion in the group of "cases" was the presence of liver pathology in children with obesity – 98 children (the main group). The control group was represented by children with obesity, but without liver damage-152 children. Patients were divided into Mongoloid and Non-mongoloid populations. To the Mongoloid population was classified as indigenous ethnic groups of Yakutia (Yakuts, Evens, Evenks) – 69 (70,4%) patients of the main group and 97 (63,8%) of the control group, not mongoloid – representatives of other ethnic groups - 29 (29,6%) patients of the main group and 55 (36.2%) of control group.

Laboratory tests included: biochemical blood tests (including lipidogram), glucose tolerance test (GTT), determination of basal blood insulin and C-peptide levels. Markers that allow identifying liver damage in children were identified: HOMA index - insulin resistance index (IR), FIRI index of insulin resistance, FABC index - functional activity of β cells. Values higher than 2.77 were used as a criterion for insulin resistance (IR).

Statistical data analysis was performed in the IBM SPSS STATISTICS 22 package. Verification of compliance of the distribution of quantitative variables with the normal law was carried out using the Shapiro-Wilk test and visual evaluation of the distribution. The distribution of quantitative variables was presented as a median (IU) and an interquartile (25 and 75 %) distribution in the IU format (Q1-Q3). When comparing independent groups, we used the Mann-Whitney criteria and the Pearson criterion $\chi 2$.

Results. In the main group, 98 children were diagnosed with liver damage (Table.1). Of these, 64 (25.6%) have fatty hepatosis (LH), and 34 (13.6%) have non –alcoholic steatohepatitis (NASG) (table.1). When analyzing ethnicity, it was found that in both groups of children with obesity, representatives of the mongoloid population prevailed both in the main group of 69 people (69.9%) and in the control group of 97 people (63.8%), representatives of the non - mongoloid population were respectively 29 people (29.6%) and 55 people (36.2%). The age structure in both groups was dominated by 11-14-year-olds 48 people (48.9%) and 70 people (46%) (table.1). The average age in the group with liver damage was 11.8 (±2.9) years, in the group without this pathology 11.2 (±2.7) years.

The comparative analysis of the average biochemical parameters in groups of children with liver damage and without, IU (Q1-Q3) (Table.2). Table 2 shows that children in the group with liver damage had significantly higher biochemical parameters than children without liver damage, with the exception of" good cholesterol " of high-density lipoproteins (HDL), which was significantly lower in the main group compared to the control group ($p<0.001$).

In the group of children with liver damage, an increase in intracellular enzymes was determined: alanine aminotransferase (ALT) indicators ranged from 40 to 136 u/l, these levels were statistically significantly higher than in the control group, aspartate aminotransferase (AST) in patients in the main group ranged from 40 to 69.3 u /l, compared to the control group, which was considered in the absence of markers of viral hepatitis in the blood, as a manifestation of NAFLD (table. 2). The children of the main group noted atherogenic type of dyslipidemia, by increasing low-density lipoprotein (LDL), compared with the control group, and lower HDL, compared to the control group, ($p<0.001$).

All indicators of carbohydrate metabolism were also significantly higher in the group of children with liver damage ($p<0.001$) (table 3). Indicators of fasting blood glucose in children with NAFLD

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Table 1

Distribution by age group and ethnicity

Age, years	There is liver damage, n=98				Liver damage no, n=152		p
	mongoloid		not mongoloid		mongoloid	not mongoloid	
	GG	NASG	GG	NASG			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
6-10	15 (15.3)	8 (8.2)	6 (6.1)	3 (3.0)	38 (25)	22 (14.5)	0.201
11-14	21 (21.4)	12 (12.2)	10 (10.2)	5 (5.1)	51 (33.5)	19 (12.5)	
15-17	8 (8.2)	5 (5.1)	4 (4.1)	1 (1.0)	8 (5.3)	14 (9.2)	
Всего	44 (44.9)	25 (25)	20 (20)	9 (9)	97 (63.8)	55 (36.2)	

Table 2

Data of biochemical analysis of blood in groups

Indicator	There is liver damage, n=98			Liver damage no, n=152			N
	Q25	Q 50	Q 75	Q 25	Q 50	Q 75	
ALT, u / l	30.3	48.3	88.6	25.3	31.6	40.7	≥40
AST, u / l	31.7	38.7	47.3	28.7	34.7	39.7	≥40
Total cholesterol, mmol / l	5.7	6.2	6.8	3.9	4.4	5.7	≥ 5.2
HDL cholesterol, mmol / l	0.8	0.9	1.0	1.0	1.2	1.4	≥ 1.3
LDL cholesterol, mmol / l	3.0	3.3	3.6	2.1	2.6	3.1	≥ 3

Примечание. В табл. 2-3 p - достигнутый уровень статистической значимости различий при сравнении групп по критерию Манна-Уитни, для всех показателей p<0,001.

Table 3

These indicators of carbohydrate metabolism in the IU groups (Q_1-Q_3)

Indicator	There is liver damage, n=98			Liver damage no , n=152			N
	Q 25	Q 50	Q 75	Q 25	Q 50	Q 75	
Fasting glucose, mmol\l	5.0	5.3	5.6	4.3	4.8	5.3	≥ 5.5
Glucose 2 hours after OGTT	5.9	7.9	10.9	5.1	6.0	6.9	≥ 7.8
Insulin, u / ml	29.1	32	34.8	8.2	13.3	18.3	0-29
C-peptide, ng / ml	3.4	5.6	7.4	1.2	1.4	2.4	0.9-4
HOMA index	4.8	7.5	8.5	1.5	1.7	4.4	≥ 2.77
FIRI index	4.3	6.7	7.7	1.4	1.6	3.9	≥ 2.7
FABC index	79.0	110.0	129.9	38.6	43.3	71.0	≥ 3.5

Table 4

The area under the ROC curve (with 95% CI) for identifying liver lesions

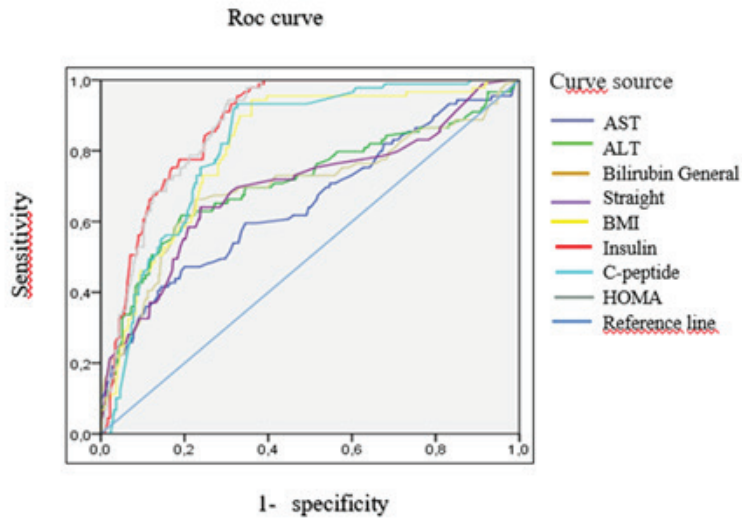
Text variable	Area	Standard error	p	95% confidence interval	
				lower limit	upper limit
ALT, u / l	0.65	0.04	<0.001	0.58	0.72
AST, u / l	0.71	0.04	<0.001	0.64	0.78
bilirubin general	0.70	0.04	<0.001	0.63	0.77
Bilirubin straight	0.70	0.03	<0.001	0.63	0.77
Body mass index, kg / m^2	**0.82**	**0.02**	**<0.001**	**0.77**	**0.86**
Insulin u / ml	**0.88**	**0.02**	**<0.001**	**0.85**	**0.91**
C-peptide ng / ml	**0.82**	**0.02**	**<0.001**	**0.78**	**0.86**
HOMA	**0.88**	**0.02**	**<0.001**	**0.85**	**0.91**

had a slight increase from 5.0 to 5.6, compared with the control group, while the violation of glucose tolerance according to the oral glucose tolerance test (GTT) was observed statistically significantly more often in children with NAFLD (with an increase in glucose level from 7.8 mmol\l up to 11 mmol\l – the diagnosis of impaired glucose tolerance), compared with the control group. In children with liver damage, an increase in fasting insulin was observed, ranging from 29 to 35.2 u/ml, compared with the control group, as well as the level of C - peptide from 4.1 to 7.5 ng\ml, compared with the control group. The indices of insulin resistance of NOMA, FIRI, and FABC in children with NAFLD were also significantly higher compared to the control group (p<0.001) (table. 3). Among the patients from the group without liver damage with the expected normal biochemical parameters, there were several patients who had changes in the indicators of carbohydrate and lipid metabolism. These patients were 20, which was 13.1%. All representatives of this subgroup were of the Mongoloid race (Yakuts), as well as all children, according to the anamnesis, had an early onset of obesity at the age of one to three years. All patients had impaired glucose tolerance, according to GTT data, with an increase in glucose levels from 7.8 mmol \ l to 10.7 mmol\l, as well as a decrease in HDL to 0.9 mmol\l. According to the data of ultrasound examination of the liver, 14 (70%) children of this subgroup were diagnosed with hepatomegaly without increasing echogenicity and changing the structure of the liver parenchyma.

To compare the ability of biochemical and metabolic indicators to identify the presence of liver damage, a ROC analysis was performed. A binary variable — the presence or absence of liver damage-is accepted as a classifiable variable. ROC curves are constructed for body mass index (BMI), ALT, AST, total bilirubin, direct bilirubin, insulin, C-peptide, and HOMA index (Fig.1).

The quality of the classification corresponds to the average and good. The largest area under the curve was observed in insulin, C-peptide, HOMA index, and BMI (p<0.001) (table.4).

Conclusions. In RS (Y) in children with obesity, the features of metabolic exchange were noted. In both groups of obese children adolescents are dominated by the Mongoloid race. In children with NAFLD, there were more pronounced changes in average biochemical parameters in the form of an increase in ALT, AST, LDL, a decrease in HDL, an in-



ROC curves for identification of lesions of the liver.

crease in insulin, C-peptide, NOME, FIRI, and FABC insulin resistance indices, and a decrease in glucose tolerance, compared with a group of children without liver pathology, which indicates more pronounced violations of carbohydrate and lipid metabolism in these patients.

According to the ROC analysis, important highly sensitive and highly specific indicators were identified to identify liver pathology (NAFLD): insulin, C-peptide, and HOMA index in obese children.

We identified unfavorable prognostic markers (nationality, early onset of obesity in history, impaired glucose tolerance, decreased HDL, hepatomegaly) that will serve as early diagnostic signs of the initial stage of liver damage in obese children.

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FIFTEEN-YEAR EXPERIENCE OF USING THE INTEGRAL SCALE 'ABDOMINAL CAVITY INDEX' IN ESTABLISHING INDICATIONS FOR STAGED SURGICAL TREATMENT OF GENERALIZED PERITONITIS

The analysis of fifteen years of experience in the use of an integral scale for assessing the degree and nature of damage to the abdominal organs in peritonitis 'Abdominal index' in routine surgical practice of the multidisciplinary surgical hospital was conducted. The extensive use of these scale criteria in clinical practice in the hospitals has led to significant improvements in the results of treatment of patients with peritonitis. There has been a decrease in the number of post-operative complications and fatalities.

The results of our clinical experience of using the integral scale for assessing the degree and nature of damage to the abdominal organs in peritonitis allow us to recommend its widespread use in the practice of urgent clinics.

Keywords: common peritonitis, abdominal index, surgical treatment tactics.

Introduction. Despite constant improvements in surgical treatment tactics, diagnostics and surgical technique for common peritonitis, surgeons continue to dissatisfy the immediate results of treatment. Evident evidence of this is the data of modern researchers, who note that the mortality rate with this formidable complication of a number of diseases or traumatic injuries of the abdominal organs remains very high, stably holding at the level of 4,5-58%, and with the development of systemic complications it can reach more than 70% [1,3,5,8,10].

Considering the issues of a modern multidimensional approach to surgical treatment of common peritonitis, in recent decades, the most acceptable are the classical principles of surgical interventions [3,6,7,9]. Such methods include staged operations using half-open / half-closed technologies (relaparotomy "according to plan", relaparotomy "on demand"), which allow achieving a comprehensive and adequate sanitation of all parts of the abdominal cavity, establish direct control over the infectious focus, if it is impossible to complete its full-fledged one-step elimination, create favorable conditions for the delimitation of the inflammatory process and ensure its relief.

According to most authors, relaparotomy after the first operation (taking into account the known indications) [2,4,5,8] should be performed 24-48 hours after the correction of the arisen metabolic disorders and before the beginning of fixation of signs of the development of a systemic inflammatory reaction. It should be noted that none of the operations would be sufficiently effective without clear criteria for its implementation (including relaparotomy). In recent decades, a large number of different systems for assessing the severity of the general condition of patients with peritonitis (MPI, PIA, MOSF and others) have been developed [2,5,11]. In our country, the system for assessing the severity of common peritonitis - the "Abdominal Cavity Index" (ACI), developed by the staff of the department of faculty surgery of the PMU named after N.I. Pirogov under the guidance of academician V.S. Saveliev [2]. According to the authors of the developers, the original scale allows a more objective assessment of the severity of peritonitis, in particular, to assess the effectiveness of staged reoperations and, therefore, to optimize the choice of treatment tactics.

The **aim** of the study. In our clinic, we have more than fifteen years of experience in using the original scale - "Abdominal Cavity Index", which was the reason for the analysis of clinical material in order to assess the effectiveness of its use in routine surgical practice in a multidisciplinary surgical hospital.

Material and methods. The presented work is based on a retrospective analysis of the results of complex treatment of 278 patients with peritonitis who were treated in the emergency surgical departments of the Republican hospital № 2 - Emergency Medical Aid Center of the Republic of Sakha (Yakutia) in the period from 2005 to 2020. The diagnosis of peritonitis was verified on the basis of a comprehensive examination, which included data from physical, laboratory, instrumental and instrumental research methods. The average age of patients was 35,2 ± 6,5 years, with 156 men (56,1%), women - 122 (43,9%). Out of 278 patients with peritonitis, 70 (25,2%) patients were operated on in the relaparotomy mode - "on demand" and 120 (43,2%) patients with generalized peritonitis, underwent staged surgical treatment - "according to the program" (2015-2020 years), taking into account the common introduction of the ACI scale in the clinical practice of urgent surgical departments of the clinic. According to the data of the retrospective analysis, the main reasons for the development of peritonitis, which required reoperations in the "on demand" and "according to the program," modes were: destructive cholecystitis - 28 (14,7%), perforated gastroduodenal ulcer - 7 (3,7%), acute intestinal obstruction of non-tumor genesis - 15 (7,9%), acute intestinal obstruction of tumor genesis - 21 (11,1%), destructive appendicitis - 19 (10,0%), destructive pancreatitis - 58 (30,5%), mesenteric thrombosis - 18 (9,4%), abdominal trauma (including stab and cut, gunshot wounds and ruptures of hollow organs)

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- 11 (5,8%), decay malignant liver tumor - 2 (1,1%), perforation of the pancreatic pseudocyst - 5 (2,6%), perforation of the parasitic liver cyst - 2 (1,1%), strangulated diaphragmatic hernia with perforation in the splenic angle of the colon - 4 (2,1%).

The basis for the integral assessment of the degree and nature of damage to the abdominal organs - the "Index of the abdominal cavity" - consists of seven groups of factors, such as: the prevalence of peritonitis, the nature of the exudate in the abdominal cavity, fibrinous deposits and adhesive process, the state of the intestine and the source of peritonitis, as well as performing repeated operations, the state of the laparotomic wound [2] (Table 1).

Following the example of the authors of the developers of the scale [2], the following signs (indicators) were identified as significant: the frequency of the need to perform repeated operations associated with the progression of peritonitis or the development of its complications, as well as mortality. At the same time, the need to perform relaparotomy "on demand" arose in 70 (25,2%) patients and was determined by such reasons or their combination as: persistent or progressive common peritonitis - 19 (27,1%) patients, the emergence of new sources of peritonitis - 11 (15,7%) patients, including incompetent sutures of hollow organs - 6 (8,6%) patients, abscesses (single or multiple) of the abdominal cavity - 5 (7,1%) patients, eventration - 19 (27,1%) patients, non-resolving intestinal paresis - 2 (2,9%) patients, adhesive intestinal obstruction - 7 (10,1%) patients, intra-abdominal bleeding - 1 (1,4%) patient.

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

Results and discussion: The results of the analysis of the ACI indicators in 70 (25,2%) patients with various forms of peritonitis, operated on in the “on demand” relaparotomy mode, are presented in

As well as the authors of the scale, we assessed the influence of each of the groups of factors and their contribution to the overall assessment of the severity of peritonitis and indications for the choice

Table 1

Integral scale "Abdominal Cavity Index "

Sign	Points
Prevalence of peritonitis:	
local (abscess)	1
diffuse	2
common	3
The nature of the exudate and pathological impurities:	
serous	1
purulent	3
hemorrhagic	4
fecal	4
The nature of the fibrinous overlays and the adhesive process:	
in the form of a shell fixed to the peritoneum	1
in the form of loose masses	4
the formation of a conglomerate of intestines and greater omentum	1
the adhesive process is not expressed or absent	4
Bowel condition:	
wall infiltration more than 3 mm	3
lack of spontaneous * and stimulated peristalsis	3
intestinal fistula	4
Unresolved source or emergence of new sources of peritonitis	4
Suppuration or necrosis of the edges of the surgical wound **	3
Eventration **	3

* Response to mechanical irritation; ** postoperative peritonitis.

Table 2

Frequency of performing relaparotomy "on demand" and mortality depending on the values of the criteria for ACI in patients with peritonitis

Sign	Total patients	The frequency of performing relaparotomy, abs. (%)	Mortality, abs. (%)
Prevalence of peritonitis:			
local (abscess)	33	2 (6.0)	1 (3.0)
diffuse	107	10 (9.3)	6 (5.6)
common	138	58 (42.0)	28 (20.2)
The nature of the exudate and pathological impurities:			
serous	68	5 (7.4)	5 (7.4)
purulent	145	49 (33.8)	21 (14.5)
hemorrhagic	21	4 (19.0)	4 (19.0)
fecal	44	12 (27.3)	5 (11.4)
The nature of the fibrinous overlays and the adhesive process:			
in the form of a shell fixed to the peritoneum	31	3 (9.7)	3 (9.7)
in the form of loose masses	89	17 (19.1)	12 (13.5)
the formation of a conglomerate of intestines and greater omentum	39	5 (12.8)	2 (5.1)
the adhesive process is not expressed or absent	119	45 (37.8)	18 (15.1)
Bowel condition:			
wall infiltration more than 3 mm	148	38 (25.7)	21 (14.2)
lack of spontaneous * and stimulated peristalsis	109	26 (23.9)	18 (16.5)
intestinal fistula	21	6 (28.6)	6 (28.6)
Unresolved source or emergence of new sources of peritonitis	17	11 (64.7)	5 (29.4)
Suppuration or necrosis of the edges of the surgical wound **	29	4 (13.8)	4 (13.8)
Eventration **	21	19 (90.5)	4 (19.0)

of reoperation mode - "on demand" or "according to the program." When analyzing the data obtained in the course of observations, we tried to focus on the most significant groups of factors, as well as to give them some of our own assessment, taking into account the many years of experience in using ACI in the clinic.

The first groups of factors characterizing the prevalence of peritonitis, the nature of exudate and pathological impurities, in assessing the severity of this disease, are generally accepted and do not raise doubts [5]. In our study, the number of patients with high ACI scores due to these factors was quite impressive - at least 38,5%, which indicates a continuing high percentage of patients with a complicated course of acute surgical diseases and / or late treatment of patients, including number (given the size of the Republic of Sakha (Yakutia)) due to the remoteness and inaccessibility of some settlements, late evacuation for medical reasons.

The next group of ACI factors, including such important criteria as the severity of the adhesive process in the abdominal cavity and the nature of fibrinous overlays, from our point of view, are the leading ones. To assess this group of factors, the scale uses the following parameters: "in the form of loose masses" - turbid effusion, fibrin is located in the form of free fragments (greenish-gray clots and films), there is not much of it, there is practically no adhesion of the abdominal organs. "In the form of a shell, it is fixed to the peritoneum" - fibrous overlays are transparent or light gray, occupy more than 1/3 of the surface of the parietal and visceral peritoneum, are tightly fixed to it and ensure the formation of a conglomerate of organs. Undoubtedly, it is worth agreeing with the authors and developers of the integral scale that these factors are integral components of the delimited and common inflammation of the peritoneum. It is these groups of factors that determine the physiological potential of delineating the process of inflammation, that is, the possibility of resolving (recovering), or in another case of overspending of plastic means of compensatory mechanisms, exhaustion and progression of the disease. As V.S. Saveliev, the transition of a common form of peritonitis to a delimited one - an abscess that poses an incomparably less threat, probably should not be considered a complication of surgical treatment, but on the contrary, its success, albeit not ideal [2]. According to our observations, after the appearance of the adhesive process due to the organization of fibrin films and other plastic processes, one can always note a decrease in the amount of peritoneal exudate that is evacuated from the abdominal cavity through drainage structures, a change in its color and character. All this, apparently, occurs according to the stages of the inflammatory process, the peculiarities of the restoration of the reabsorption function of the parietal peritoneum and is characterized by a redistribution of the content of low- and medium-molecular metabolites in the peritoneal exudate, as well as protein fractions. The predictive value of these factors begins to clearly manifest itself in the second, third and subsequent operations. In confirming the correctness of the authors, it was noted that it was the decrease in the area of the peritoneal lesion, primarily due to adhesion and the formation of the delimiting conglomerate of the intestine and the greater omentum, that determined the potential for recovery. It should be noted that often the surgeon's desire to achieve complete "cleanliness" of the abdominal cavity during reoperations is erroneous. In fact, a reduction in the number of relaparotomies should be achieved by eliminating the source of peritonitis, optimal drainage of the abdominal cavity to maximize the removal of exudate (we consider one of the most important conditions) and adequate intensive care. In the course of our observations, it was noted that even in the presence of a persisting source of peritonitis and antibiotic resistance of the microflora, with optimal drainage of the abdominal cavity and, taking into account the factors of incipient adhesion (this is especially often the case with destructive pancreatitis), it is possible to transfer the common inflammatory process into a delimited one - the formation of intra-abdominal or retroperitoneal abscesses. In this case, this is the first step towards successfully resolving the inflammatory process. The influence of these factors is clearly reflected in the data given in the table of the frequency of reoperations and mortality in staged surgical treatment, depending on the value of the selected criteria for ACI (Table 3). During the first operation, in patients with a disease period of 12-24 hours, there were practically no visual signs of the localization of the inflammatory process, and these parameters of the "Abdominal Cavity Index" scale were always high.

Another criterion, which is indicated by the authors of the scale, is "an unrepaired source or the appearance of new sources of peritonitis", and implies the presence of any source of endogenous infection of the abdominal cavity: incompetence of the sutures of hollow organs, perforation of acute ulcers, intestinal perforation due to pressure ulcers from drains and nasointestinal probes, and also destructive cholecystitis, perforation of abscesses, complications and progression of pancreatic necrosis. To assess the severity of the lesion of the gastrointestinal tract, the authors used morphological and functional signs of intestinal failure, such as the presence of edema (wall thickness), the state of motor activity and violation of the integrity of the organ in the form of fistula formation.

The criterion "unrepaired source of peritonitis" was registered by us in 6,1% of patients and was associated with the technical difficulties of its complete elimination and the extreme severity of the patient's condition - the ACI values were more than 13 points. In particular, such complications were observed as: multiple perforations of the jejunum, perforation of a disintegrating tumor of the bladder, the formation of infected forms of pancreatic necrosis with the spread of the process to the retroperitoneal tissue (phlegmon of the retroperitoneal tissue), perforation of the rectosigmoid colon. In our case, the probability of performing relaparotomy when fixing the criterion "unrepaired source or the appearance of new sources of peritonitis" was at least 64,7%. Continuing the topic of complications, it is necessary to mention such criteria as - "suppuration and necrosis of

Table 3

The number of subsequent reoperations and mortality, depending on the value of the selected criteria for ACI in staged surgical treatment of peritonitis

The nature of fibrinous overlays and the adhesive process	Total sick	Number of reoperations	Mortality, abs. (%)
in the form of a shell fixed to the peritoneum	35	3.9±1.6	9 (25.7)*
in the form of loose masses	23	4.1±1.8	9 (39.1)*
the formation of a conglomerate of intestines and greater omentum	41	3.1±1.4	11 (26.8)*
the adhesive process is not expressed or absent	21	5.6±2.5	5 (23.8)*

* - intergroup differences are significant (p <0,05).

the edges of the postoperative wound." In patients with common peritonitis, the state of the surgical wound (suppuration of the postoperative wound) often acts as an independent factor in choosing the tactics of staged reoperations and as a source of persistent peritonitis [2]. In this case, if such a complication is detected, we advise not to suture the wound tightly at the time of performing relaparotomies, expose only the muscular-aponeurotic layer of the anterior abdominal wall to suturing, followed by tamponing with ointment napkins, or connect VAC hardware therapy until it is completely cleansed and good granulations begin to form. According to our observations, it was the suppuration of the postoperative wound with the spread of the infectious process into the abdominal cavity that caused repeated relaparotomies in at least 10,4% of patients included in the study group.

Thus, despite the existence of a large number of integral scales for assessing the severity of peritonitis, used in modern times, developed by employees of the department of faculty surgery of the PMU named after N.I. Pirogov scale called "Abdominal Cavity Index" remains in high demand and is included in the clinical guidelines of the Russian society of surgeons. In our opinion, the integral scale "Index of the abdominal cavity" allows to reliably detail the degree of damage to the abdominal organs during peritonitis and makes it possible to clarify the indications for the choice of management tactics in the "on demand" and "according to the program" modes. In addition, the scale presented has a significant potential for detailing some positions in its structure, as well as searching for new criteria for improving and optimizing the choice of treatment tactics for this severe category of patients.

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REPEATED VERTEBRAL FRACTURES IN CHILDREN

The main epidemiological indicators of the problem of recurrent uncomplicated vertebral fractures in somatically healthy children have been studied. In the overwhelming majority of clinical observations with repeated trauma, fractures of those thoracic and lumbar vertebrae not initially damaged were diagnosed. The average age of children with primary vertebral fractures was 7 years 7 months, the same children repeatedly injured the spine at average age of 11 years 3 months. In more than half of the clinical observations, the main mechanism of injury is a fall onto the buttocks from height of one's own height. More often than others, the bodies of ThV and ThVI vertebrae were damaged in the primary injury, while the body of ThIV vertebra was observed in the repeated injury,. Key words: children, repeated vertebral fractures.

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Relevance. Various aspects of vertebral fractures in children are fairly well presented in the modern medical literature. At the same time, despite a large volume of science research on this topic, we failed to find any publications devoted to cases of repeated vertebral fractures in somatically healthy children. Two scientific articles devoted to the problems of osteoporosis and osteogenesis imperfect provide information on the possibility of receiving repeated vertebral fractures in children with these diseases [10,13]. The lack of modern scientific information on the problem of recurrent vertebral fractures in somatically healthy children motivated this study.

Objective. To study the maim epidemiological indicators of the problem of recurrent uncomplicated vertebral fractures in somatically healthy children.

Materials and methods. At the stages of planning and implementation of this study, in order to determine its type and design, we were guided by the recommendations presented in the journal "Traumatology and Orthopedics of Russia" [7]. According to these recommendations, the type of research carried out is defined as "applied", aimed at gaining knowledge for solving a specific practical problem, namely, studying the main epidemiological indicators of repeated vertebral fractures in children. Design-analytical sample cross-sectional study.

We had 9 years of experience in dynamic observation and treatment of 1,000 children and adolescents aged 2 to 17 years inclusive, who received uncomplicated compression fractures of the vertebral bodies of the cervical, thoracic and lumbar localizations. Of this number, 16 (1.6%) children received vertebral fractures twice. These 16 patients constituted the observation group that served as the clinical material for the present study. For the diagnosis of vertebral body fractures in children, both in primary and in repeated injuries, we used the methods of examination traditional for emergency traumatology: collection of complaints and anamnesis, clinical examination, radiation diagnostics (plain radiography, computed tomography (CT), magnetic resonance imaging). tomography (MRI)).

Children who received repeated compression fractures of the vertebral bodies were consulted by an endocrinologist. Anthropometric parameters were determined in patients with the calculation of the body mass index. All patients underwent a blood test (ionogram, ionized calcium, total protein, alkaline phosphatase, bilirubin) and urine (daily excretion of calcium and phosphorus).

To determine the severity of injuries to the vertebral bodies, the AO/ASIF classification was used [12]. In accordance with the criteria of this classification, fractures of all vertebrae in the studied children with primary and repeated injuries were attributed to type A. More detailed detailing of the nature of fractures made it possible to ascertain the A1 subtype in 15 (93.75%) children and in 1 (6.25 %) clinical observation, with repeated trauma, a ThXII vertebral body fracture was attributed to the A3 subtype.

For statistical processing of data, the Microsoft Excel and Statistica 6.0 software package was used. The specific weight of each of the variants of the studied indicators is presented in the form P ± m, where P is the relative value of the indicator variants in%, m is the error in the representativeness of the relative value.

The study was approved by the Ethics Committee at the Tyumen State Medical University Federal State Budgetary Educational Institution of Higher Education of the Ministry of Health of Russia (protocol No. 59 of June 27, 2014).

Results and discussion. Among 16 children who received vertebral fractures twice, there were 9 (56.25%) boys, and 7 (43.75%) girls. The average age of patients at the time of their primary injury was 7 years 7 months, and the second injury was 11 years 3 months. The average time elapsed between the dates of the spinal injury was initially and again equal to 3 years 8 months. The minimum period between episodes of obtaining vertebral fractures was 8 months, the maximum period was 8 years. In more than half of the cases, the main cause of vertebral fractures in children, both in primary and in repeated injuries, was a fall on the buttocks from their own height - in 75.0% and 56.25% of cases, respectively (t <2). The data published in the literature confirm the fact that more than half of cases of vertebral fractures in the pediatric population arise from falls on the back from a low height [11]. The high incidence of vertebral fractures in children with minor trauma is due to the action of the so-called arc-keyboard mechanism, described by the staff of the Central Institute of Traumatology and Orthopedics [2].

Less often, children injured the spine as a result of an automobile injury and as a result of a fall from a height of 2 floors - (according to one clinical observation with primary and repeated injuries).

The information about the number of vertebrae was broken in the children of the studied cohort is of undoubted interest. Analysis of the clinical material showed that in more than half of the

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cases - 56.25% - patients received fractures of one vertebra, both in primary and in repeated injuries. Fractures of two vertebrae were diagnosed in 37.5% and 25.0% (t <2) clinical cases, respectively. Three vertebrae were fractured in 6.25% of the patients at the time of the primary injury and in 12.5% (t <2) of the patients at the time of the second injury. Four vertebrae were injured only in 1 (6.25%) patient, at the time of receiving a fracture again. A total of 24 vertebrae were broken in children with the primary injury, and 27 vertebrae in the repeated injury.

In primary trauma, the bodies of ThV (16.68%), ThVI (16.68%), ThX (12.5%) and ThXII (12.5%) vertebrae were most often compressed. With repeated trauma, fractures of the bodies of ThIV (14.87%), ThIII (11.11%), ThXII (11.11%) and LII (11.11%) vertebrae were most often diagnosed. In none of the analyzed cases were the vertebrae of the upper thoracic, middle and lower lumbar spine broken.

The predominant localization of the compressed vertebrae in the thoracic spine in children is due to the anatomical and physiological characteristics of the growing child's spine [6].

In the course of the study, in 2 (2.97%) clinical cases, compression of the same vertebra was established twice - the bodies of the ThIII and ThXII vertebrae, respectively. In one of these observations, an 8-year-old girl received a ThXII vertebra body fracture while riding a slide. After 8 years, she repeatedly injured the same vertebra when falling from a height of 2 floors. As a result of this falling from height, the patient required surgical treatment in order to stabilize the fracture and prevent the formation of symptoms of mechanical and (or) neurological instability at the level of the spinal motion segments ThXI-ThXII and ThXII-LI [8]. In the remaining 14 clinical observations, the re-injured vertebrae in 8 (54.17%) cases were located caudally in relation to the already consolidated vertebrae, and in 6 (42.86%) cases - cranially. The clinical picture of vertebral fractures was typical when children received both primary and repeated injuries, and is well and fully described in the literature [6]. There were no clinical features of the course of the acute period of trauma in the studied children.

In order to objectively confirm compression fractures of the vertebral bodies in children, we used radiological diagnostic methods. Objective X-ray diagnosis of the injured spine began with plain X-ray or CT. The choice in favor of one or another research method was determined individually and depended on the characteristics of the child's response to the injury received, the mechanism of injury, and the severity of clinical symptoms.

Upon confirmation of compression fractures of the vertebral bodies by X-ray or CT, the children were admitted to the traumatology and orthopedic department of the children's hospital, where they were treated. This course consisted of adhering to strict bed rest on a reclinator roller in the projection of the compressed vertebrae, physiotherapy procedures, physical therapy sessions with an instructor. In cases of diagnostics of fractures of the lower thoracic and lumbar vertebrae in 6 patients with primary injury and in 7 patients with repeated injury, traction was performed for the pelvis along an inclined plane. We consider this procedure to be effective not only in terms of treatment, but also in terms of compliance with the orthopedic regime in the department.

On days 2–3 of hospital stay, as the severity of vertebral pain syndrome decreases, all patients underwent MRI of the spine, which is currently the most informative research method in the diagnosis of compression fractures of vertebral bodies in children [1]. It was MRI that made it possible to finally formulate the clinical diagnosis and determine the method of immobilization of the spine, before the patients were discharged from the hospital for outpatient treatment.

For the purpose of immobilization of the spine, plaster corsets, made individually for each injured child, were used more often than others [9]. In total, immobilization with a plaster brace was performed in 12 (75.0%) children with primary injury, and in 7 (43.75%) patients with repeated injury ($p<0.05$). The use of plaster braces in clinical practice ensures reliable immobilization of the injured spine, creates favorable conditions for the processes of remodeling of compressed vertebrae and, importantly, fully complies with the program of state guarantees of free medical care to victims in case of injuries of the musculoskeletal system. In addition to plaster corsets, such orthopedic products as reinforced posture corrector "Orlett", frame hyperextension corrector by "Otto Bock" company, "Orlett" orthopedic thoracic-lumbar corset were used for therapeutic purposes. The listed products are also widely used in the clinical practice of orthopedists [5].

The analysis of anthropometric indicators of children made it possible to register that all 16 patients with repeated vertebrogenic fractures “were” within their age norms [4]. The average body mass index in the study group of patients was 21.4 ± 1.3.

Table shows the average biochemical parameters of blood and urine in the same children.

As the studies have shown, all the studied parameters in patients were within the age norm [4]. Considering the normal blood and urine parameters in the studied patients, a more detailed study of bone mineral density was not carried out in them.

A paraclinical study of blood and urine prescribed by an endocrinologist for all children in cases of repeated spinal injury did not reveal any deviations from the age norm. The average hospital stay for patients with the initial injury was 9.6 days, with the repeated one - 11.7 days.

As our experience in providing emergency vertebral care to children who have received uncomplicated vertebral fractures repeatedly, there are no specific measures to prevent these injuries. Although, as follows from literary sources, recently, on the basis of large medical institutions, whole "services for the prevention of recurrent fractures" are being created, but only patients suffering from osteoporosis are provided with assistance in these units [3].

Conclusion. The relevance of this study is primarily due to the lack of modern scientific medical information on repeated vertebral fractures in children. In the course of the study, several important epidemiological indicators were obtained, which, in our opinion, are of interest to interested medical specialists. Thus, in the course of the study it was found that the frequency of repeated fractures of the vertebral bodies in children is 1.6% of cases. In the overwhelming majority of clinical observations - 87.5% of cases - with repeated trauma, fractures of those thoracic and lumbar vertebrae that were not initially damaged were diagnosed. Only in 2 (12.5%) clinical ob-

Biochemical parameters of blood and urine in children with repeated vertebral fractures

Investigated parameters	Average results
Magnesium	0.95±0.3 ммоль/л
Potassium	4.2±0.9 ммоль/л
Chlorine	98±3.1 ммоль/л
Ionized calcium	1.19±0.5 ммоль/л
Total protein	64±3.7 г/л
Alkaline phosphatase	170±5.3ед/л
Total bilirubin	9.6±1.6 ммоль/л
Daily urinary calcium excretion	3.2±1.1 ммоль/л
Daily urinary phosphorus excretion	36±3.4 ммоль/л

servations were vertebral fractures that were injured earlier. The average age of children who received vertebral fractures was initially 7 years 7 months, the same children repeatedly injured the spine at an average age of 11 years 3 months. The average time elapsed between the dates of primary and repeated vertebral injury was 3 years 8 months. In more than half of the clinical observations, the main mechanism of injury is a fall on the buttocks from a height of one's own height - 75.0% of cases with primary injury and 56.25% of clinical observations with repeated injury. More often than others, the bodies of the ThV and ThVI vertebrae were damaged during the primary injury - in 16.68% of cases, respectively. In case of repeated trauma, the body of the ThIV vertebra is most often compressed - 14.87% of clinical observations. Therapeutic tactics, both in primary and in repeated spinal injuries, is to conduct a course of conservative therapy aimed at relieving vertebrogenic pain syndrome, creating conditions for a more favorable course of the remodeling processes of compressed vertebrae. Only in 1 (6.25%) clinical observation, with repeated spinal trauma, it was required to perform surgical treatment of the damaged spinal motion segments. In order to immobilize the injured spine, a plaster corset was used more often than others from orthopedic products, made individually, taking into account the physique of each patient. The use of plaster braces in clinical practice has found application in 75.0% of patients with primary injuries and in 43.75% of patients with repeated vertebral fractures. Examination of children with repeated injuries to the spine, carried out by an endocrinologist, did not reveal any deviations from the age norm in any of the clinical observations.

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HEALTHY LIFESTYLE. PREVENTION

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POLYGRAPHIC PATTERN OF NIGHT SLEEP IN OLDER ADOLESCENTS WITH OVERWEIGHT OR OBESITY: A CROSS-SECTIONAL STUDY

The aim of the study was to identify features of the structure, cyclic and segmental organization of the night sleep by polysomnography (PSG) in overweight/obese (Ow/Ob) older adolescents.

Materials and methods. Adolescents aged 15–17 years with Ow/Ob and normal body weights (NBW) were examined using PSG on wearable equipment AURA PSG GRASS-TECHNOLOGIES (USA) according to the standard method. Total sleep time (TST), representation of stages, their latent periods (LPs), wake time after sleep onset (WASO), number of awakenings (NA), sleep efficiency (SE), sleep cycle's and segment's architectonic were assessed.

Results and discussion. The study included 38 patients with Ow/Ob and 15 adolescents with NBW (controls). After PSG, 14 Ow/Ob patients with obstructive sleep apnea were excluded from the study. In adolescents with Ow/Ob, shortening rapid eye movement sleep (REM) and delta sleep latencies ($p < 0.0001$, for both variables), an increase in NA by 4 times ($p = 0.0001$), a significant decrease in SE ($p = 0.005$) and delta sleep ($p = 0.018$), an increase in WASO ($p = 0.0002$) and REM sleep ($p < 0.0001$) relative to controls were revealed.

Additionally, a decrease in superficial sleep duration from the 1st to the 3rd cycle ($p < 0.0001$) and an increase in REM sleep in the 1st cycle ($p < 0.0001$), and more stable REM sleep and less stable delta sleep were demonstrated. The obtained results partially agree with the data of previous studies of children's sleep, and are also an interesting finding of this research.

Conclusion. These specific sleep patterns in older adolescents with Ow/Ob can be considered both initial changes in sleep homeostasis under conditions of endocrine pathology, and adaptive mechanism to restore psychological defense system violation in the adolescent's daily life.

Keywords: older adolescents, sleep, polysomnography, overweight, obesity.

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Introduction. According to experts from the World Health Organization (WHO), obesity is one of the greatest threats to humanity today and an important component of the causes of premature mortality [14]. Globally, it affects over 650 million adults and 213 million children aged 5 to 19 years [21]. According to the results of a multicenter study, about 20% of children and adolescents in the Russian Federation are overweight, and another 5% are obese [9]. It is known that the main cause of overweight/obesity (Ow/Ob) is considered to be an energy imbalance, in which the caloric content of the diet exceeds the energy requirements of the body [6]. However, it should be noted an increase in the number of scientific studies aimed at identifying new associations and disclosing the pathophysiological mechanisms underlying excessive weight gain [11,18]. In recent years, awareness of the role of sleep and the circadian rhythms in the development and progression of obesity has increased [1,12,13]. Wherein, research aimed at analyzing the relationships between sleep quality and Ow/Ob in adolescent population are mainly reduced to analysis of its subjective characteristics [12] and/or standard objective characteristics [24]. At the same time, changes in the temporal organization of sleep (cyclicity) and its internal structure (segmentation) in older adolescents are not reflected in modern research. It should be noted that it is the late adolescence (15-17 years) that is transition period between childhood and adulthood, which is characterized by completion of the formation of the body's regulatory systems. During this period, various functional disorders often occur, and the risk of pathology of the endocrine and nervous systems (including sleep disorders), which often proceed comorbid and tend to become chronic, increases [23].

The purpose of this study was to identify features of the structure, cyclic and segmental organization of the night sleep by polysomnography (PSG) in Ow/Ob older adolescents.

Materials and methods. A cross-sectional study of adolescents aged 15-17 years from October 2018 to April 2019 was carried out in Department of Pediatrics of Scientific Center for Family Health and Human Reproduction Problems (SC FHHRP), Irkutsk. The sample of adolescents with Ow/Ob was formed from 64 patients of the appropriate age, referred for examination and clarification of the diagnosis in SC FHHRP. After anthropometry procedure, 43 adolescents were selected, 38 of whom signed voluntary informed consent to participate in this study. The exclusion criterion was the presence of obstructive sleep apnea/hypopnea syndrome (OSA/HS) in the patient, established during PSG, with diagnostic criterion - apnea/hypopnea index (AHI) ≥ 2 episodes per hour of sleep [17]. According to this criterion, 14 Ow/Ob patients were excluded from the

study. Thus, the main group consisted of 24 adolescents with Ow/Ob. Among adolescents with NBW (21 people), only 15 adolescents signed voluntary informed consent (the control group). All patients at the time of inclusion in the study and throughout its entire duration did not have signs of acute diseases, did not take drugs with a hypnotic, sedative or psychotropic effect.

Anthropometric parameters (body weight and linear height) of adolescents were assessed once when they were included in the study, the body mass index (BMI, kg/m2) was calculated. Body weight was measured on an electronic medical balance (error value ± 50 g), height measurement was performed using a medical stadiometer in a standing position (error value ± 0.1 cm). The assessment of weight and height indicators of adolescents was carried out using tables of Standard variables of physical development of children [22] and the AnthroPlus calculator. Ow/Ob was determined when the actual BMI exceeded the median value by more than 1 and 2 standard deviations (SD), respectively; NBW - when BMI deviates from -1 to +1 SD.

PSG was performed using a wireless monitor AURA PSG GRASS-TECHNOLOGIES (USA). An electroencephalogram was recorded in 4 standard leads with the imposition of reference electrodes on the mastoid processes (O1 / A2, O2 / A1, C3 / A2, C4 / A1); eye movements - electrooculogram; electromyogram from the chin muscles. To detect respiratory disorders during sleep, we used registration of the oronasal air flow, thoracic and abdominal respiratory efforts, and the degree of blood oxygen saturation. PSG procedure, definition and assessment of sleep stages were carried out according to the standard method [10]. Analyzed such variables as: total sleep time (TST), min; wake time after sleep onset (WASO), min; number of awakenings (NA); sleep efficiency (SE) as TST in relation to total recording time, expressed in%; representation (%) of slow-wave sleep (SWS), delta sleep and rapid eye movement sleep (REM) in the total sleep pattern; latent periods duration (LPs) of each sleep stage, min; duration and architectonics of sleep cycles (duration of stages and WASO in the first 3 cycles, min.); the stability of sleep segments (a section of the sleep polygram, from the moment of the appearance of any sleep stage to the moment of its change by another stage) and the character of interstage transitions [7].

Statistical data processing was carried out using the Statistica 10.0 software package (StatSoft Inc, USA). The description of quantitative variables was performed with the indication of the median, Me (25th; 75th percentiles) and % of occurrence. The nonparametric Mann – Whitney (U) test was used to assess differences between groups for continuous variables (age, SDS BMI, PSG scores). In cases of categorical variables (gender), the value of Pearson's χ2 test was assessed. Differences were considered statistically significant at $p < 0.05$.

The study protocol was approved at a meeting of the Local Committee on Biomedical Ethics (Protocol №2 dated 23.02.2018).

Results and discussion. Comparison of study groups by baseline characteristics and PSG variables, depending on the presence or absence of excess weight, is presented in Table 1.

The absence of significant differences in clinical and demographic data, except for the grouping parameter (weight status), was demonstrated. At the same time, in patients with Ow/Ob, certain changes in the structure of sleep were revealed in comparison with similar variables in controls, namely: a tendency towards a decrease in TST; a significant increase in latency to sleep ($Z = 3.09$; $p = 0.0002$) and WASO ($Z = 3.47$; $p = 0.0002$); an increase in NA by 4 times ($Z = 3.59$; $p = 0.0001$); a decrease in SE ($Z = -2.69$; $p = 0.005$); a significant increase in REM sleep ($Z = 4.01$; $p < 0.0001$) and a decrease in SWS ($Z = -2.29$; $p = 0.018$); a significant shortening of LP both to stage 3-4 of non-rapid eye movement sleep (NREM) ($Z = -4.37$; $p < 0.0001$ and $Z = -4.17$; $p < 0.0001$, respectively) and REM sleep ($Z = -4$, 37; $p < 0.0001$).

When studying the cyclic structure of sleep, there were no statistically significant changes in the total number of sleep cycles in patients with Ow/Ob compared with NWB peers (4 (3; 5) and 4 (3; 6), respectively ($Z = -0.15$; $p = 0.856$). At the same time, the average duration of one cycle was 92 (89; 94) minutes versus 94 (92; 98) minutes in adolescents with NBW ($p = 0.257$). However, analysis of sleep cycle's architectonics revealed certain changes in Ow/Ob adolescents, depending on the ordinal number of the cycle: a significant decrease in duration of the 1st cycle and superficial sleep duration (1-2 stages of NREM sleep) from the 1st to the 3rd sleep cycle; an increase in REM sleep duration in the 1st sleep cycle (Table 2).

Interesting results were also obtained when analyzing the segmental organization of sleep in adolescents with different weight status. For example, participants with Ow/Ob showed a lower stability of 3-4 stages of NREM sleep with the appearance of episodes of superficial sleep (intersegmental transitions) mainly in the 2nd and the 3rd sleep cycles, and a greater REM sleep stability in the 1st and the 2nd sleep cycles compared to those in NBW adolescents.

Table 1

Comparative analysis of clinical and demographic characteristics and PSG data in adolescents with Ow/Ob and NBW, Me (25%; 75%).

Variables	Ow/Ob adolescents, n=24	NBW adolescents, n=15	P value
Age, years	16 (16;17)	16 (15.5;17)	0.824
Male sex, %	62.5	60.0	0.751
SDS BMI, kg/m^2	2 (1.7;2.5)	-0.06 (-0.05;-0.2)	< 0.001
TST, min.	448 (419;468)	454 (431;485)	0.399
Latency to sleep, min.	16 (14;19)	12 (10;14)	0.0002
WASO, min.	10 (8;11)	7 (6;8)	0.0002
NA, event	4 (3;6)	1 (1;2)	0.0001
SE, %	92 (91;94)	95 (93-95)	0.005
LP to N1, min.	13 (11;14)	11 (10;13)	0.052
Stage N1, %	2.5 (2;3)	3 (2.5;5)	0.054
LP to N2, min.	2.5 (2;3)	3.5 (2.5;4)	0.051
Stage N2, %	50 (47;51)	51 (50;53)	0.167
LP to N3, min.	42 (41;45)	53 (51;56)	< 0.0001
Stage N3, %	10 (9;12)	10 (10;12)	0.792
LP to N4, мин.	52 (50;57)	67 (62;69)	< 0.0001
Stage N4, %	9 (8;10)	11 (9;13)	0.103
SWS, %	20 (19;20)	23 (22;24)	0.018
LP to REM, min.	64 (59;68)	84 (81;88)	< 0.0001
REM, %	25 (22;27)	21 (21;22)	< 0.0001

Studies conducted earlier among patients with Ow/Ob have shown that changes in sleep patterns are a frequent polysomnographic finding [16,20]. In turn, a decrease in duration and quality of sleep negatively affects the course of metabolic processes in the body [19], especially in childhood and adolescence [4]. As a result, a "vicious circle" is formed, elimination of which is possible only when the cause-and-effect relationships are broken. Our study revealed a clear tendency towards disturbance of night sleep structure in older adolescents with Ow/Ob compared with their NBW peers. They fell asleep longer and woke up more often during the night, less often immersed themselves in delta sleep, had a reduced SE, which does not contradict the well-known literature data on the state of hypnogenic function in obesity [5,25]. However, an interesting finding of our study was the fact of a change in the order of sleep stages appearance in cycles (an earlier appearance of REM sleep and delta sleep epochs after falling asleep), as well as an increase in REM sleep proportion and its high stability in the first half of the night in Ow/Ob patients relative to controls.

It is known that REM sleep can play a role in restoring emotional balance and psychological state [3]. It has been found that obese people experience stress differently than healthy individuals. Studies have shown that they experience higher levels of stress at work, school, in family, and are less able to tolerate negative moods. Wherein, obese patients experience great difficulties with the expression of their emotions in comparison with people with NBW, and prefer to overcome stress, for example, by displacing unpleasant events into the "unconscious" [8]. With a weakening of control over protective mechanisms, for example, during sleep, a spontaneous "return of the repressed" to the level of consciousness can occur, which is carried out trough dreams [2]. However, studies among children and adolescents with Ow/Ob did not show a pronounced tendency to change parameters of SWS and REM sleep in comparison with NBW peers [15]. At the same time, in a 3-year population study HypnoLaus, conducted among persons over 35 years old, obese patients have been demonstrated a significant increase in the duration of REM sleep and a decrease in delta sleep, compared with the control group [26], which was reflected in the present study in Ow/Ob adolescents.

Conclusion. So, there are some features of night sleep pattern in older adolescents with Ow/Ob. In our opinion, this is reflection of changes in their homeostasis in endocrine pathology, and also plays the role of an adaptive mechanism to restore psychological defense system violation in the adolescent's daily life. However, under certain conditions (an increase in obesity degree, the appearance of OSA/HS, etc.), tension in self-regulation system and breakdown in adaptation mechanisms may occur, which can lead to formation of severe neuropsychiatric and somatic disorders. The our results determine the need for dynamic medical observation and examination (including PSG use) of adolescents and young people with Ow/Ob, as well as timely adequate correction of the identified disorders to preserve labor and reproductive reserve of humanity.

Table 2

The difference between sleep stages duration, depending on the ordinal number of the cycle * in study groups, Me (25%; 75%).

Variables	Ow/Ob adolescents, n=24	NBW adolescents, n=15	P value
The 1st sleep cycle			
Stages N1-2 duration, min.	42 (39;46)	61 (59;67)	< 0.0001
Stage N3-4 duration, min.	21 (19;23)	19 (18;21)	0.103
REM sleep duration, min.	24 (22;26)	11 (10;13)	< 0.0001
Wake, min.	1.5 (1;2)	1 (1;1.5)	0.051
Total the 1st cycle duration, min.	87 (84;92)	93 (91;95)	0.085
The 2nd sleep cycle			
Stages N1-2 duration, min.	47 (45;49)	57 (55;59)	< 0.0001
Stage N3-4 duration, min.	20 (19;24)	21 (20;23)	0.867
REM sleep duration, min.	22 (20;26)	15 (13;17)	0.051
Wake, min.	2.5 (2;3)	1.5 (1;2)	0.121
Total the 2nd cycle duration, min.	92 (91;96)	94 (93;99)	0.156
The 3rd sleep cycle			
Stages N1-2 duration, min.	52 (51;56)	45 (40;46)	< 0.0001
Stage N3-4 duration, min.	19 (17;22)	24 (21;25)	0.075
REM sleep duration, min.	21 (20;22)	28 (25;30)	0.053
Wake, min.	1.5 (1;2)	2 (1.5;2)	0.052
Total the 3rd cycle duration, min.	93 (92;95)	95 (95;98)	0.102

Note. * - comparative data for the first 3 sleep cycles were presented; Me is the median; Ow/Ob – overweight/obesity; NBW - normal body weight; N1-N4 – non-rapid eye movement sleep stages 1-4; REM – rapid eye movement sleep.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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DISPARITIES OF CERVICAL CANCER AND MORTALITY INDICES IN THE REPUBLICS LOCATED IN SIBERIA AND ALL OVER RUSSIA IN THE PERIOD FROM 2007 TO 2019

The article presents a research of disparities in cervical cancer incidence (CCI) and mortality (CCM) in the period 2007 - 2019 among the republics Altai (RA), Buryatia (RB), Tyva (RT), Khakassia (RKh), Sakha (Yakutia) (RSYa) and Russia as a whole. In this period the CCI in the republics was significantly higher than in Russia as a whole, the highest CCI was in RT, while the lowest was in the RSYa and the increase of CCI in the republics exceeded such in Russia as a whole. In this period CCM in the republics, except of RSYa, was also significantly higher than in Russia as a whole, and the highest CCM was in RB, while the lowest was in RSYa. CCM in 2019 compared to 2007 significantly increased in RT and decreased in RA. CCI and CCM have a statistical relationship in RB. Obtained results confirm the expediency to carry out vaccination against HPV in the republics first of all.

Key words: human papilloma virus (HPV), vaccination, Altai, Buryatia, Tyva, Khakassia, Sakha, Yakutia.

Introduction. Cervical cancer (CC) is a fourth most frequent cancer among women worldwide. Now more than 300,000 women have been dying from it annually. CC burdens more in low- and middle-income countries where public healthcare services are restricted [1].

In Russia CC has significant rate in the structure of cancer incidence among women too. So, in 2019 CC incidence (CCI) percentage rate (5%) took up fifth place after breast cancer incidence (21.2%), skin cancer (15.2%, with melanoma – 17.2%), uterine cancer (7.8%), colon cancer (7.3%) [2].

Also the CC mortality (CCM) rate was significant at the structure of women's cancer mortality; in 2019 this rate was on a 9-th place (4.7%), after mortality from breast cancer (15.9%), colon cancer (9.7%), stomach cancer (8.3%), pancreatic cancer (7.3%), tracheal, bronchial and lung cancers (7.1%), cancer of lymphoid and hematopoietic tissues (6.1%),rectal cancer (5.8%), ovarian cancer (5.5%) and uterine cancer (5.0%) [2].

There are significant disparities in CCI and CCM among countries [3] and different territories of the same country [4,5,6], including the territories of Russia [7,8].

To design optimal approaches to CC preventive vaccination scientific research of CC territorial, ethnic and gender disparities are needed [9,10].

Basically all cases of CC are caused by infection of the Human Papilloma Virus (HPV). A study of an archival biological samples related to prior to vaccination against HPV period (1993-2005) showed that HPV DNA was found out in 90.6% cases of CC and also in 98.8% cases of CC in situ [10].

Research in this scientific area in Russia including in Siberia are few in number. Possibly it may be related that vaccination against HPV is not included in the national vaccination calendar and the vaccination by epidemic indications approved by Order of Ministry of Health of the Russian Federation, March 21, 2014, N 125n.

Meanwhile on the 73-rd session of World Health Assembly, in May 2020, countries- members of World Health Organization approved the resolutions to develop world public health including the global strategy of WHO to accelerate CC elimination as a problem of public health. In this strategy a main attention in the period 2020-2030 is paid to prevent CC by the vaccination against HPV along with screening and treatment precancerous lesions and management of patients with CC invasive forms, including palliative care [1].

The research realized in USA showed that the vaccination against HPV can avoid not only invasive CC (prevent 66.2% cases) but other cancer sites associated with HPV, - anal cancer (79.4%), oropharyngeal cancer (60.2%), vaginal cancer (55.1%), penile cancer (47.9%) and vulvar cancer (48.6%). The 9-valent vaccine, which additionally targets HPV 31/33/45/52/58, can prevent an additional 4.2% to 18.3% of the above sites cancer [11].

In our previous studies, we found disparities in CCM among national-state entities (NSEs) located in Siberia - in the republics Altai (RA), Buryatia (RB), Tyva (RT), Khakassia (RKh), Sakha (Yakutia) (RSYa) in the period from 2007 to 2018. It was shown that during this period according to the values of annual age-standardized rates per 100 thousand of the population the lowest CCM was observed in RSYa [7,8], the highest in RB [8]. For the majority of peoples inhabiting these NSEs, the fact of genetic relationship has been established [12].

The aim of this study was to establish the disparities of CCI and CCM in the period from 2007 to 2019 among RA, RB, RT, RKh, RSYa and Russia as a whole. The following tasks were set: to compare the rates of CCI and CCM in NSEs with the rates in Russia as a whole; to identify NSEs with the highest and lowest rates of CCI and CCM; to establish the changes of NSEs' and Russia's CCI and CCM in 2019 in comparison to 2007; to identify NSEs with a statisti-

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cal relationship between CCI and CCM.

Materials and Methods. To establish the disparities of CCI and CCM, the data of national medical cancer statistics from 2007 to 2019 were used. This data is annually published in the books of the P. Hertsen Moscow Oncology Research Institute - a branch of the Federal State Budgetary Institution "National Medical Research Radiological Center" of the Ministry of Health of the Russian Federation from 2008 to 2020, which can be found on the website for medical and pharmaceutical workers "ONCOLOGY.ru" [13].

The CCI and CCM were estimated according to CCI age-standardized rates (ASIR) and to CCM age-standardized rates (ASMR) per 100 thousand. In the above-mentioned books to standardize by the age the world standard for the age distribution of the population was used. The period used in this study was from 2007 to 2019, state formations - RA, RB, RT, RKh, RSYa and Russia as a whole, cite - the cervix (C53).

Since the annual ASIRs and ASMRs did not have a normal distribution, to identify differences in the total (multiple) sample Friedman's analysis of variance by ranks was used. To identify paired differences the Wilcoxon signed ranks test was used. The $p < 0.05$ was chosen as a significance level.

The t-test was used to determine if CC ASIRs and ASMRs in 2019 and 2007 are equal. The $p < 0.05$ was chosen as a significance level of inequality (difference).

To identify the statistical relationship between the annual values of CC ASIR and ASMR, the Spearman correlation coefficient (r) was calculated using the formula for small sample sizes. The Chan scale was used to assess the strength of statistical relationship [14], r were considered significant at $p < 0.05$.

Results and discussion. The annual values of CC ASIR from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole are presented in Table 1. An analysis of their distribution revealed their heterogeneity (p=0.000).

The average ranks of the annual values of CC ASIR from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole are shown in Figure 1. Based on these ranks the highest CC ASIRs in this period were in RT, the lowest were in RSYa. At the same time CCI in Russia as a whole was significantly lower than in all NSEs: in comparison with RT - 5.01 times (p=0.001), with RB - 4.14 times (p=0.001), with RKh by 3.01 times (p=0.001), with RA by 2.73 times (p=0.002), with RSYa by 2.34 times (p=0.002).

Analysis of CCI changes in 2019 compared to 2007 showed that CCI increased significantly in RB - by 1.75 times (p=0.000), in RT - by 1.68 times (p=0.002) and in Russia as a whole - by 1.23 times (p=0.000), in RKh and RSYa the increase in incidence also exceeded the all-Russian rate - by 1.4 and 1.31 times respectively and approached to the level of significance we have selected (p=0.052 and p=0.070, respectively). In RA with a visible decrease in the value of CC ASIR in 2019 compared to 2007 (1.55 times), the difference of these indicators did not reach the level of significance (p=0.108). The CC ASIR values in 2017 and 2019 in the republics located in Siberia and in Russia as a whole are graphically presented in Figure 2.

Analysis of the CC ASMRs distribution from 2007 to 2019 in RA, RB, RT, RKh, RSYa and in Russia as a whole also revealed heterogeneity of these indicators (p=0.000). The annual values of the indicators are presented in Table 2.

The average ranks of the annual CC ASMRs from 2007 to 2019 in RA, RB, RT, RKh, and RSYa and in Russia as a whole are shown in Figure 1. According to the ranks the highest CCM in this period was in RB, the lowest was in RSYa. At the same time, CCM in Russia as a whole was also lower than in all NSEs: in comparison with RB by 3.74 times (p=0.001),

Table 1

Annual values of CC ASIRs in the republics located in Siberia and RF as a whole

Year	RA		RB		RT		Rkh		RSYa		RF	
	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error
2007	22.55	3.91	22.83	1.98	30.49	4.34	15.79	2.14	14.07	1.62	12.48	0.11
2008	18.6	3.77	22.9	1.98	27.54	3.98	14.04	1.99	17.21	1.74	12.84	0.11
2009	27.03	4.83	18.66	1.75	17.45	3.12	16.36	2.09	17.44	1.72	13.4	0.12
2010	14.15	3.45	15.57	1.62	20.66	3.54	16.97	2.11	13.36	1.52	13.71	0.12
2011	18.56	3.88	21.09	1.86	27.94	4.11	22	2.47	16.68	1.7	13.7	0.12
2012	18.97	3.87	18.86	1.76	20.2	3.43	20.15	2.34	16.58	1.69	13.9	0.12
2013	22.43	4.16	31.27	2.27	24.07	3.66	20.55	2.37	20.3	1.84	14.17	0.12
2014	16.46	3.35	27.83	2.1	30.97	4.15	26.57	2.69	19.59	1.83	14.47	0.12
2015	21.86	4.04	29.91	2.2	35.4	4.48	17.2	2.12	19.2	1.79	15.01	0.12
2016	16.75	3.71	30.03	2.25	43.88	4.96	17.26	2.1	22.85	1.94	15.45	0.12
2017	17.08	3.6	42.55	2.67	44.98	4.92	20.29	2.3	20.2	1.82	15.76	0.13
2018	18.19	3.59	35.64	2.43	49.01	5.09	19.48	2.33	21.57	1.89	15.8	0.12
2019	14.50	3.14	39.92	2.56	51.37	5.33	22.10	2.44	18.38	1.75	15.38	0.12

Note: See the explanation of abbreviations in Tables 1-3 and Fig.1-2 in the text

Table 2

Annual values of CC ASMRs in the republics located in Siberia and in RF as a whole

Year	RA		RB		RT		Rkh		RSYa		RF	
	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error	Value	Error
2007	15.97	3.57	11.46	1.37	5.38	1.71	8.32	1.47	5.04	0.91	5.11	0.07
2008	10.28	2.96	11.69	1.42	6.24	1.90	8.39	1.45	6.77	1.09	4.99	0.07
2009	12.91	3.28	11.60	1.38	9.20	2.33	6.60	1.27	5.29	0.96	5.13	0.07
2010	10.98	3.00	8.71	1.17	10.44	2.48	4.31	1.02	3.82	0.79	5.12	0.07
2011	6.18	2.21	11.13	1.33	13.46	2.85	5.77	1.23	4.91	0.93	5.27	0.07
2012	6.93	2.21	10.57	1.31	9.04	2.29	8.08	1.43	5.58	0.99	5.23	0.07
2013	11.19	2.82	12.47	1.42	12.00	2.59	10.55	1.72	6.95	1.06	5.35	0.07
2014	8.95	2.54	12.48	1.39	9.38	2.22	7.46	1.42	6.47	1.03	5.18	0.07
2015	8.21	2.37	11.46	1.36	12.21	2.64	8.50	1.50	6.21	0.97	5.39	0.07
2016	9.18	2.68	11.39	1.36	9.11	2.23	8.78	1.53	6.84	1.07	5.26	0.07
2017	7.61	2.12	13.09	1.47	9.41	2.17	8.55	1.45	6.11	1.01	5.18	0.07
2018	2.14	1.07	11.41	1.30	12.62	2.62	6.21	1.18	4.61	0.84	5.07	0.07
2019	5.12	1.86	14.32	1.53	13.60	2.81	7.93	1.40	5.49	0.93	5.01	0.07

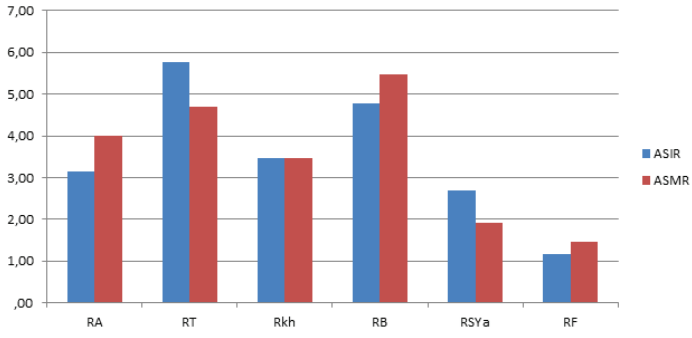

Fig. 1. Average ranks of CC ASIRs and ASMRs in RA, RB, RT, Rkh, RSYa and in RF as a whole from 2007 to 2019

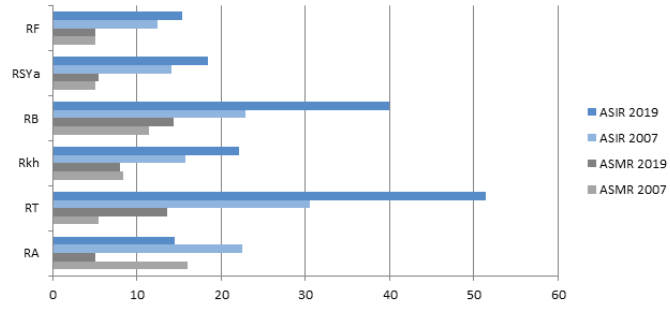

Fig 2. Values of CC ASIRs and ASMRs in RA, RB, RT, Rkh, RSYa and in RF as a whole in 2019 and in 2007.

with RT by 3.21 times (p=0.001 with RT), with RA by 2.73 times (p=0.006), with RKh by 2.37 times (p=0.002). CCM in RSYa also exceeded the all-Russian one by 1.32 times, and the significance of the differences was close to the level we have chosen (p=0.075).

Analysis of the differences in CCM in NSEs in 2019 compared to 2007 showed that CCM significantly increased in RT - 2.52 times (p=0.012) and decreased in RA - 3.11 times (p=0.007). The changes of CCM in these years in Russia as a whole and in the other republics did not reach the required significance. The CC ASMRs in 2017 and in 2019 in the republics located in Siberia and in Russia as a whole are shown in Figure 2.

The analysis of the relationship between the annual values of CC ASIR and ASMR in the state formations (see Table 3) showed the presence of moderately strong links only in RB.

Revealed in our study increased CCI and CCM in territories that are distinguished by a variety of races and ethnic groups have correlated with international studies [6, 11, 15].

The WHO global strategy to accelerate the elimination of CC as a public health problem contains a clause that in order to that all countries must achieve (and maintain) an incidence rate of less than 4 cases per 100,000 women per year [1]. That is, in NSEs located in Siberia, urgent medical and preventive measures are needed to reduce CCI. Based on the data of 2019, it is necessary to reduce the CCI from 3.6 times (in RA) to 12.8 times (in RT). The WHO strategy also calls on all countries to achieve CC vaccination of 90% girls by 2030 (by age 15) [1].

Our research shows that vaccination against HPV in the republics located in Siberia for the CC elimination is an urgent present time task.

Table 3

Spearman correlation coefficient (r) between the annual values of CC ASIR and ASMR (2007-2019)

ASIR		ASMR					
		RA	RB	RT	RKH	RSYa	RF
RA	r p N	0.456 0.117 13					
RB	r p N		0.641* 0.018 13				
RT	r p N			0.434 0.138 13			
RKH	r p N				-0.049 0.873 13		
RSYa	r p N					0.533 0.061 13	
RF	r p						0.165 0.590 13

Note: * - the r has the required significant p-value

Conclusion. CCIs in the period 2007-2019 in the republics, located in Siberia and inhabited by different ethnic groups with a close genetic portrait - RA, RB, RT, RKh, RSYa, were significantly higher than in Russia as a whole. In this period the highest CCI was in RT, while the lowest was in the RSYa and the increase of CCI in the republics exceeded such in Russia as a whole. In this period CCMs in the republics, except of RSYa, were also significantly higher than in Russia as a whole, and the highest CCM was in RB, while the lowest was in RSYa. CCM in 2019 compared to 2007 significantly increased in RT and decreased in RA. CCI and CCM have a statistical relationship in RB.

In our study we established significantly higher rates of CCI and CCM in the republics then in Russia as a whole and therefore there is a need for priority vaccination against HPV in the republics. In RT and RB, which have the highest CCI and CCM rates, the increase in CCM and the relationship between CCI and CCM, there is a need for urgent vaccination.

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FEATURES OF IMMUNE AND METABOLIC PROFILE OF AUTONOMIC DYSFUNCTION ASSOCIATED WITH POLYMORPHISM OF CANDIDATE GENES

Introduction. To preserve employable population's health is a most vital task contemporary medicine has to face. Chronic exposure to occupational factors can induce disorders in the immune, humoral, and nervous regulation in workers employed at an oil extraction enterprise and consequently result in work-related pathology. **Our research aim** was to examine peculiarities of immune and metabolome profile of workers who were employed at an oil-extracting enterprise and suffered from vegetative dysfunction that were related to working experience and combined with candidate gene polymorphism. **Materials and methods**. We examined 137 workers employed at an oil-extracting enterprise who had vegetative dysfunction including 66 workers with their working experience at the examined enterprise exceeding 10 years and 71 workers with working experience being shorter than 10 years. Contents of $CD3^+CD95^+$-lymphocytes, TNFR, Bax, and p53 were determined via flow cytometry. Leukocytes phagocytosis was examined with formalinized ram erythrocytes; contents of IL-6, NO, and homocysteine were determined via ELISA technique. We applied PCR in real time mode to identify SNP of *ApoE*(rs429358), *MTHFR*(rs1801133), *SULT1A1* (rs9282861) genes. **Results**. Immune and metabolome profiles of workers employed at an oil-extracting enterprise with their working experience being longer than 10 years had the following peculiarities: apoptosis, IL-6, and phagocytosis were hyper-activated (Bax, p53, TNFR), and homocysteine contents were elevated as well. These established changes are likely to reflect a pathogenetic relation with T-allele in *MTHFR*(rs1801133) gene which occurred among these workers more frequently than among those whose working experience didn't exceed 10 years ($\chi2=4.89$; $p=0.027$); this relation may well lead to atherosclerotic vascular disorders. Workers with their working experience being shorter than 10 years had higher NO levels, dopamine production, and greater CD3+CD95+-marker inhibition than reference levels ($p<0.05$). These established deviations are likely to reflect a pathogenetic relation with the highest frequency of C-allele in *ApoE* (rs429358) gene and A-allele in *SULT1A1* (rs9282861) gene which occurred in them authentically more frequently than among workers with working experience exceeding 10 years ($\chi2=4.77$-699; $p=0.008$-0.028). This, combined with established negative effects, indicates there is a risk than the immune system will be involved (excessive IL-6 and Bax deficiency), disorder in neuro-metabolome regulation will take place (excessive dopamine), and as a result vegetative dysfunction and vascular atherosclerotic changes will occur. Therefore, established imbalance in the immune (excessive apoptosis and phagocytosis), nervous (elevated dopamine), and metabolome (homocysteine hyper-expression and elevated NO due to its unstable forms) regulation that occurs against polymorphism of genes that participate in enzyme detoxification and metabolism such as *MTHFR*(rs1801133), *SULT1A1* (rs9282861), and *ApoE*(rs429358) characterizes peculiarities of immune and metabolome profiles that are related to working experience; workers with such profiles who suffer from vegetative dysfunction run a serious risk of atherosclerosis and hypertension. These peculiarities that are related to working experience and detected in immune and

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metabolome profiles are recommended to be used as markers for identifying early regulatory immune, vegetative, and metabolome disorders in homeostasis regulation in workers employed at an oil-extracting enterprise.

Key words: immune status, genetic polymorphism, risk of atherosclerosis and hypertension, working experience at an oil-extracting enterprise, vegetative dysfunction

Introduction. Preserving the health of the working-age population, prevention and early diagnosis of occupational diseases is the most important task of modern medicine. Harmful and dangerous chemical (aromatic hydrocarbons), physical (noise intensity, vibration, unfavorable climatic conditions), as well as psychophysiological production factors of oil production enterprise have a negative impact on the health of people employed in oil production [4]. Excessive exposure of occupational groups to these factors over a long period of time might lead to disorders of adaptive reactions, including imbalance of immune, humoral and nervous regulation of physiological functions of the body and, as a result, the development of occupationally pathology [1, 6, 11].

The aim of the research was to examine peculiarities of immune and metabolome profile of workers who were employed at an oil-extracting enterprise and suffered from vegetative dysfunction that were related to working experience and combined with candidate gene polymorphism.

Materials and methods. The study of features of immune and neurohumoral regulation depending on work experience by employees involved in oil production and having autonomic dysfunction associated with candidate gene polymorphisms (autonomic dysfunction syndrome) was carried out. 137 men having autonomic dysregulation were examined. They were chronically exposed to the production factors of the oil production enterprise during their work. At that, 66 men have more than 10 years of work experience and 71 men have less than 10 years of work experience. The persons examined have the same ethnicity and social status.

The study was conducted as per the standards outlined in the World Medical Association's Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”. All patients signed a voluntary informed consent for the examination.

The content of CD3+CD95+-lymphocytes, tumor necrosis factor receptor TNFR, apoptosis regulator proteins Bax and p53 was determined using flow cytometry using a FACSCalibur instrument (Becton Dickinson, USA).

The content of IL-6, dopamine, homocysteine and NO were determined by enzyme immunoassay (EIA) using an Elx808 analyzer (BioTek, USA).

The phagocytic activity of peripheral blood leukocytes was studied using formalized ram red blood cells.

Single-nucleotide polymorphisms (SNP) of 3 gene loci were studied by real-time PCR technique using CFX96 Real Time System C1000 Thermal Cycler (BioRAD, Singapour). Genetic material was received from buccal scrapings using a reagent kit AmpliPrime DNA-sorbB Form 2 Variant 100 (NextBio LLC, Russia) by a sorbent method. To determine the genetic polymorphism of the examined genes, test following systems (Syntol, Russia) were used: Cys130Arg of apolipoprotein E *ApoE* gene (rs429358); C677T of methyltetrahydrofolate reductase *MTHFR* gene (rs1801133), Arg213His of the sulfotransferase *SULT1A1* gene (rs9282861). The allelic discrimination method in the TaqMan program was applied to determine the human genotype.

For statistical processing of the study results, mathematical statistics methods were implemented using Statistica 10.0 application software package (StatSoft, USA). To assess the data reliability, Student's t-distribution considering the normal distribution of variables in the groups was used. In the case of deviation from the normal distribution, the nonparametric Mann–Whitney U test was used to compare data.

Calculation of the allele frequency distribution, as well as the $\chi 2$, OR odds ratio and its 95% confidence interval (CI) were calculated in Microsoft Excel. Differences between the groups were considered statistically significant at $p<0.05$.

Results and discussion. The clinical and laboratory examination of blood samples of employees involved in oil production and having autonomic nervous regulation disorders revealed functional changes in immune and metabolic regulation of physiological functions of the body associated with the work experience (tab. 1).

Inhibition of CD3+CD95+-marker lymphocyte expression level in workers having autonomic disorders is characterized by a significant decrease in its content relative to the reference level regardless of the age of the examined persons ($p<0.05$).

The detected increase in the content of intracellular molecular inducers and regulators of apoptosis shows hyperactivation of transcription factors of immunocyte apoptosis in employees working in oil production enterprise with a charac-

Table 1

Features of immune and neurohumoral status depending on work experience by employees involved in oil production and having autonomic nervous regulation disorders

Indicator	Reference range	Employees having >10 years of work experience (n=66)	Employees having <10 years of work experience (n=71)
Bax, %	5 – 9	13.815±1.473*	10.127±1.598
CD3+CD95+-lymphocytes, abs., 10^9/l	0.63 – 0.97	0.457±0.094**	0.355±0.109**
CD3+CD95+-lymphocytes, %	39 – 49	22.857±2.507**	17.800±2.845**
TNFR, %	1 – 1.5	4.730±0.917**	3.167±1.211**
p53, %	1.2 – 1.8	10.403±2.851**	9.447±1.993**
Absolute phagocytosis, 10^9/cdm	0.964 – 2.988	2.418±0.190*	2.001±0.141
Percentage of phagocytosis, %	35 – 60	54.682±2.078*	49.333±1.606
Phagocytic number, c.u.	0.8 – 1.2	1.061±0.059*	0.924±0.043
IL-6, pg/ml	0 – 10	1.552±0.115	3.105±0.553*
Dopamine, pg/cc	10 – 100	74.837±3.372	80.247±1.387*
Homocysteine, μmol/l	6.26 – 15.01	11.400±2.295*	7.600±0.940
NO, μmol/cdm	70.4 – 208.6	136.867±6.871	167.154±8.920*

* - the differences between the groups are statistically significant ($p<0.05$);
** - differences with the reference level are statistically significant ($p<0.05$)

teristic tendency to increase associated with work experience. Thus, the examined persons having more than 10 years of work experience with autonomic regulation disorders revealed an increased (p<0,05) level of proapoptotic protein Bax relative to the same value in the group of workers having less than 10 years of work experience and the reference level. The content of transcription factor p53 and tumor necrosis factor receptor TNFR significantly (p<0.05) exceeded the established reference levels for these parameters regardless of the work experience of the examined persons, but with higher expression in the group with more than 10 years of work experience.

It was found out that the neuro-metabolomic profile of employees working in oil production enterprise with less than 10 years of work experience and having autonomic dysregulation was associated with increased (p<0.05) dopamine levels relative to the group with more than 10 years of experience. According to the available literature, dopamine affects the processes of proliferation, differentiation, apoptosis, lymphocyte migration and cytokine production [7, 10]. Consequently, activation of dopamine expression and its receptors may cause the development of atherosclerosis and hypertension associated with an imbalance of immune and nervous regulation. Excessive levels of cytokine IL-6 expression shows the development of inflammatory reactions in workers with less than 10 years of experience. The literature provides the information that increased levels of IL-6 and its receptors sIL-6R activate sympathetic nervous regulation with inhibition of parasympathetic mechanisms due to the direct effect on hypothalamic areas, nucleus of solitary pathway of medulla oblongata and baroreceptors of blood vessels (p<0.05) [5, 13].

The detected features of immune and metabolomic regulation depending on work experience by employees involved in oil production and having autonomic dysfunction are significantly (p<0.05) associated with polymorphic variants of candidate detoxification and metabolism genes: *MTHFR* (rs1801133), *SULT1A1* (rs9282861) and *ApoE* (rs429358) (table. 2). Gene polymorphism is described by the multiplicative model of inheritance ($\chi 2$ test, df = 1).

Changes in the immune and metabolomic profile of workers having more than 10 years of work experience are associated with increased frequency of the T-allele (p<0,05) of *MTHFR* gene (methylene tetrahydrofolate reductase) (rs1801133), which causes inhibition of the expression product activity and, as a result, an increase in homocysteine concentration. Homocysteine has a cytotoxic effect not only on endotheliocytes, but also on neurons when nitric oxide levels decrease under oxidative stress, which causes an increased risk of both neural and cardiovascular pathologies [3, 8, 14]. The results of our study also demonstrate an increase in homocysteine levels against the background of a decrease in NO (table 1) in the group of men with autonomic dysregulation having more than 10 years of work experience (p<0.05).

The gene pool of the group of employees involved in oil production and working less than 10 years and having autonomic dysregulation revealed significantly (p<0.05) increased frequency of the A-allele (69.1%) of the gene of the thermally stable isoform of the detoxification enzyme-sulfotransferase *SULT1A1* (rs9282861) when compared to the group having longer work experience. It is associated with inhibition of drug conjugation reactions, xenobiotics and neurotransmitters, inactivation of estrogen and their metabolites in order to protect against estrogen-mediated mitosis and mutagenesis [12].

In addition, the group of workers having less than 10 years of work experience revealed significantly (p<0.5) increased frequency of the C-allele of the apolipoprotein E apoe gene (rs429358) relative to the group of workers with more than 10 years of work experience. According to the literature, the protein encoded by this allele also has a reduced functional activity, which causes disorders of lipid metabolism, as well as a reduced neuroprotective potential of apolipoprotein E [2, 9]. It creates an additional increased risk for the development of atherosclerosis and hypertension against the background of the established autonomic regulatory disorders.

Conclusions. The group of employees involved in oil production and working more than 10 years and having autonomic dysregulation was characterized by hyperactivation of apoptosis processes (p53, TNFR, Bax) and phagocytosis, as well as increased homocysteine levels. The changes identified might reflect a pathogenetic link with the minor T-allele of the *MTHFR* gene (rs1801133), the frequency of which is increased in relation to employees working less than 10 years. In the group of workers having less than 10 years of work experience, excessive levels of nitric oxide (due to its unstable forms), IL-6 against the background of CD3+CD95+ marker deficiency were established relative to the reference values (p<0.05). At the same time, dopamine expression levels were increased relative to workers having high work experience (p<0.05). The revealed abnormalities might reflect a pathogenetic link with the highest frequency of C-allele of *ApoE* gene (rs429358) and A-allele of *SULT1A1* gene (rs9282861), the frequency of which is significantly increased in relation to employees working over 10 years, which proves the participation of the immune system and neurometabolome regulation in the risk of further development of atherosclerosis and hypertension. Thus, the established imbalance of immune (excess of apoptosis and phagocytosis), nervous (excess of dopamine) and metabolic (hyperexpression of homocysteine and excess of NO) regulation along with the polymorphism of genes of detoxification and metabolism enzymes - *MTHFR* (rs1801133), *SULT1A1* (rs9282861) and *ApoE* (rs429358) characterize the features of immune and metabolome regulation depending on work experience by employees having autonomic dysfunctionthe and risk of forming atherosclerosis and hypertension and are recommended to use as marker indicators when identifying the early regulatory immune, autonomic and metabolomic disorders of homeostasis regulation in employees involved in oil production depending on work experience.

Table 2

Distribution of allele frequencies of candidate genes in employees involved in oil production and having autonomic dysregulation disorders

Gene / allele		Group of employees having >10 years of work experience (n=66)	Group of employees having <10 years of work experience (n=71)	$\chi 2$	OR (CI 95%)	p
ApoE (rs429358)	T	96.2	86.1	4.77	4.03 (1.06 – 15.02)	0.028
	C	3.8	13.9		0.25 (0.09 – 0.70)	
MTHFR (rs1801133)	C	65.4	81.8	4.89	0.42 (0.19 – 0.92)	0.027
	T	34.6	18.2		2.38 (1.06 – 5.27)	
SULT1A1 (rs9282861)	G	52.6	30.9	6.99	0.40 (0.21 – 0.77)	0.008
	A	47.4	69.1		2.48 (1.25 – 4.84)	

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MORTALITY OF THE INDIGENOUS POPULATION OF YAKUTIA IN THE XIX AND EARLY XX CENTURIES (ACCORDING TO METRIC BOOKS)

The article assesses the level, seasonality, and structure of mortality of the indigenous population of Yakutia in the late 19th - early 20th centuries, based on the analysis of information from the birth registers of the Bilyuchansky, Nikolaevsky, and Sheinsky Georgievsky churches of the Vilyui district. The scientific novelty of the work lies in the fact that such studies in Yakutia have never been conducted before. The sample size was 3014 people, including 1518 men, 1496 women.

The proportion of children under 5 years old was 41.7% for the total number of deaths, and this corresponds to the official statistics of the beginning of the 20th century. In addition, the data established by the medical and sanitary detachment of the Yakut expedition of the USSR Academy of Sciences in 1925-1926 on infant mortality among the Yakut population, are exaggerated due to the inclusion of children under 5 years. This indicator is similar to those in Germany (1910-1914) or Japan (1920-1922). The data on the mortality of Yakut women in the pre-revolutionary period due to childbirth or postpartum complications were specified. A significant part of the population died from respiratory diseases, such as tuberculosis. In contrast to other regions of Russia, the peak of mortality of the population, regardless of age, fell in the spring, which was primarily due to the deterioration in the nutrition of the population at this time of the year. Presumably, the widespread of diseases identified by the authors of the article as infectious diseases (typhus, scarlet fever, measles, smallpox, influenza, and others) could be hindered by the dispersed residence of the local population across the territory of parishes. In the general structure of mortality, mortality from external causes was insignificant (1.4%). However, most of the deaths in this group were due to careless handling of fire and drowning.

Keywords: historical demography, history of Yakutia, Yakut, mortality, infant mortality, causes of mortality, metric books.

Introduction. The data of the registers of births (metric books) are a valuable source for the study of the local history of the population, although they have some problems related to the reliability and accuracy of the data, for example, with regard to the diagnosis of some deaths, which were recorded by priests, and sometimes only from the words of the relatives of the deceased. Often, even the alleged cause of death was missing. Nevertheless, church documents make it possible to quite accurately trace such indicators as the level, seasonality or structure of mortality of the local population, as well as some other issues of demography in the pre-revolutionary period.

Materials and research methods. The analysis of mortality was carried out according to the metric books of the Bilyuchansky Nikolaevsky (1897-1917) and Sheinsky Georgievsky churches of the Vilyui district of the Yakutian region (1891-1919), published in "Write my name" books [11; 12]. The sample size is 3014 people, including 1518 men, 1496 women.

The causes of death indicated in the documents are conventionally divided into the following groups: 1) diseases of the abdominal organs ("pain in the stomach", "abdominal disease", "abdominal", "bloating", "internal", "dropsy", "catarrh") ; 2) diseases of the respiratory system ("pneumonia", "chakhotka", "cough", "kolotyo"); 3) nervous diseases ("head", "hysterical seizure", "opiectal (apoplexy) stroke"); 4) infectious diseases ("fever", "typhoid", "scarlet fever", "measles", "smallpox", "flu", "zhelunitsa", "scrofula"); 5) surgical diseases ("osteomyelitis", "tumor", "gangrene"). Separate groups also include mortality "infant", "childbirth", "old age", "unknown" and mortality from external causes (accidents, suicides, murders). The results were processed using Microsoft Excel.

Results and discussion. Calculations have shown that the average life expectancy of the indigenous population in the study period was 27.9 ± 0.8 years (27.7 ± 0.8 years for men and 27.9 ± 0.8 for women). Low values are due to the high mortality rate of children under 5 years of age, whose share was 41.7% of the total number of all deaths, or 1,255 people, including 665 boys, 590 girls. These figures are similar to the data of official statistics for the Vilyui district for 1910, according to which the proportion of deaths under the age of 5 was 44.9%, or 922 people, including 480 boys, 442 girls [13, C . 276]. By the way, according to R. Maack [9, p. 69], the mentioned indicator was equal to 18.9% (from 1850 to 1854), but he explained this by the share of "unwritten in church books" for various reasons was still significant. A later, in 1866, according to the memorable books, this figure was 15.6%, in 1879 - 29.4%.

At the age of less than 1 year, 15.9% died, although it is possible that the calculated figure may be somewhat underestimated due to the fact that stillborns or those who died before the baptism ceremony could remain unaccounted for. Nevertheless, these data are also similar (14.6%) with the official statistics for 1910 [13]. For comparison, at the beginning of the XX century in the Oryol province, about 25% of babies died, and in some areas of Buryatia in the 1920s-1930s. - 39.2% [2; 6]. Thus, the information of P.

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Bushkov [4] that both in the Vilyui district and “in other parts of Yakutia” infant mortality was 64.9-68.8%, is doubtful. This assumption is confirmed by the words of S.E. Schreiber [19, p. 365], who admitted that “the percentage is increased by many incorrect data obtained from parents who have forgotten in what year their children died, and confusing age up to a year with an age of up to 5 years” (it is necessary to indicate that in the dictionary “Russian words adopted and mastered by the Yakuts”, compiled by A.E. Kulakovsky [8, p. 351], the word “myladyanas” means a deceased child, that is, without indicating his age). At the same time, among the Yakuts examined by Schreiber under the age of 50 (n = 287), the average number of children was 5.1 ± 0.2 people, and 16.0% gave birth at least 10 times, and only 9.4% were childless. According to the calculations made by us based on the materials of statistical collections of the Yakutsk region for 1866, 1970, 1879, 1884, 1895, 1910, the coefficient of natural growth of the population in the district averaged 8.6 ‰.

Analysis of the structure of infant mortality showed that the level among boys was significantly higher (471 people) than among girls (387 people), however, after the onset of reproductive age, these indicators change in the opposite direction (Table 1).

Regardless of age, people more often died in spring than in winter, as indicated in the work of Schreiber [19, p. 146]. As can be seen from Fig. 1, the main peak fell in May, during which the mortality rate was 1.8 times higher than the average annual indicators. It is interesting that in other regions of Russia, similar peaks of mortality occurred in the summer period [1; 3; 7, p. 121; ten; 15]. Some authors, referring to the work of doctors, associated this fact with the difficult living conditions of the peasant population and outbreaks of infectious diseases [5]. As for Yakutia, the main reason for the high mortality rate of the population in the spring was most likely the deterioration in the nutrition of the population during this period, as evidenced by such researchers as R.K. Maak [9, p. 52] or V.L. Seroshevsky [16, p. 315]. Perhaps it is due to the facts noted that Russians traditionally calculate their age in years, and *Yakut*s - in springs. By the way, *Yakut*s also has a stable expression “*күөх окко үктэммит*” (“stepped on the green grass”), implying that a person survived the spring, passed all the hardships of the current year.

In the majority of children who died before 1 year (55.9%, or 480 cases) the cause of death was indicated as "infant" (Table 2). Infectious diseases (21.8%, or 187 cases) and respiratory diseases (18.9%, or 162 cases) occupied a special place in this age group. As they got older, the risk of dying in children gradually decreased, and the most “safe” period was considered as the age from 6 to 17 years (8.6% of all deaths).

The risk group for *Yakut*s of reproductive age included women. So, in the age group from 17 to 50 years (n = 401) 23.4% or 94 people died during childbirth or due to postpartum complications, including at the age of 17 - 1 person, 18-20 years old - 9 people, 21-30 years old - 40 people, 31-40 years old - 33 people, 41-45 years old - 6 people, 46-49 years old - 4 people, 50 years old - 1 person For comparison, among the peasant women of the Southern Trans-Ural, this figure was 13.6-16.0% [18]. The age indicators above demonstrate that the high mortality rate of women during childbirth was not due to early marriages, as stated by Bushkov [4], but primarily due to

Table 1

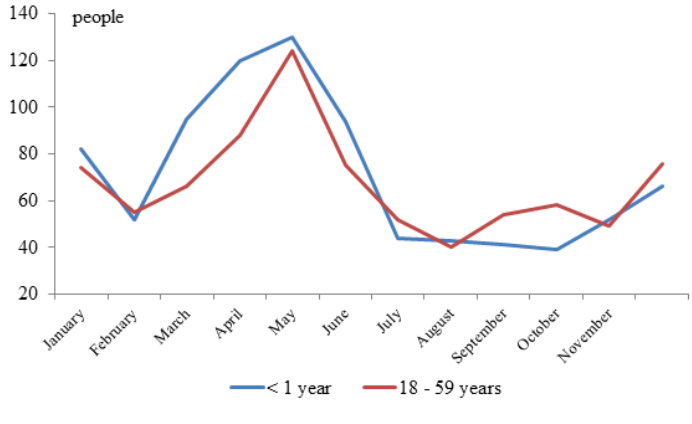
Distribution of deaths by age and sex (1897-1919)

Age (years)	Male		Female		Total	
	N	%	N	%	N	%
< 1	471	31	387	25.9	858	28.5
2 - 5	194	12.8	203	13.6	397	13.2
6 - 17	137	9.0	124	8.2	261	8.6
8 - 44	234	15.4	333	22.3	567	18.8
45 - 59	123	8.1	120	8.0	243	8.1
60 - 74	201	13.2	198	13.2	399	13.2
75 - 90	148	9.8	125	8.4	273	9.1
> 91	10	0.7	6	0.4	16	0.5
Total	1518	100	1496	100	3014	100

Table 2

Causes of death of parishioners (people) in Bilyuchansky Nikolaevsky and Sheinsky Georgievsky churches of the Vilyui district of the Yakutian region (1897-1919)

Age, years	Sex	Cause of death									
		«Infant»	Diseases of					Labor mortality	«old age»	Eternal causes	«Unknown»
			Abdominal organs	Respiratory system	Nervous	Infectious	Surgical				
0-1	m	264	12	82	1	109	-	-	-	3	-
	f	216	10	80	1	78	1	-	-	1	-
2-5	m	18	22	41	6	83	-	-	-	3	21
	f	27	12	49	9	74	-	-	-	5	27
6-17	m	-	24	36	19	42	2	-	-	2	12
	f	-	17	33	16	47	1	1	-	3	6
18-44	m	-	29	122	20	40	4	-	-	8	11
	f	-	26	153	22	31	3	83	-	4	11
45-59	m	-	28	62	11	10	4	-	-	2	6
	f	-	28	54	8	12	-	10	2	1	5
60-74	m	-	35	92	18	8	1	-	36	5	7
	f	-	30	78	18	5	1	-	55	1	10
75-90	m	-	15	29	7	5	1	-	79	2	9
	f	-	8	14	5	3	-	-	92	1	2
90+	m	-	-	2	-	-	-	-	8	-	-
	f	-	-	-	-	-	-	-	6	-	-
Total	m	282	165	466	82	297	12	-	123	25	66
	f	243	131	461	79	250	6	94	155	16	61



Suntarsky ulus local population seasonality of mortality in the period from 1891 to 1918.

difficult social and living conditions, lack of elementary obstetric and gynecological care for the population, as well as the use of useless and sometimes extremely harmful measures. For example, S.E. Schreiber mentioned that he more than once had to see "fresh cow droppings in the vagina of a woman in labor during difficult childbirth and delay of the placenta" [19, p. 356].

Both during this period and at a mature age, the main causes of death of the population were respiratory diseases (30.7%), especially tuberculosis (410 cases), pneumonia (106 cases), "kolotyo" (330 cases), implying, according to N.A. Romanov et al. [14], pleuritis, and pleuropneumonia.

The share of diseases that we classified as infectious was 18.1%. The most common deaths were from dysentery (173 cases), measles (149 cases), scarlet fever (76 cases), typhoid (30 cases), smallpox (25 cases), etc. Perhaps the widespread of these diseases was hampered by the dispersed residence of the local population across the territory of parishes. Nevertheless, it should be recognized that the figures are given only superficially reflect the real epidemiological situation at that time.

Death "from old age" in some rare cases was stated at 57-58 years old, and the bulk of those who died, for this reason, were noted in the range from 75 to 90 years. The share of those who crossed the 90-year line of life was 0.5% (16 people), but it is also possible that these data may be overestimated due to the widespread distortion of age data among the elderly Yakut population [17].

The proportion of mortality from external causes was about 1.4%, or 41 cases, of which 19 people died due to careless handling of fire, including 15 children, 9 people drowned. There were also cases of death from freezing, a bear attack, "cutting a leg", "bruising", etc. There were 3 cases of suicide, 1 case of murder.

Conclusion. The studies have shown that the first statistics on the mortality of children under 5 years of age in Yakutia were underestimated due to insufficient coverage of the population. Conversely, the infant mortality data at the beginning of the 20th century were overestimated by including older children in this group. Moreover, the calculated values of this indicator allow us to conclude that its level on the territory of the Vilyui district was even lower than in some regions of Russia and was at the level of the indicators of Germany (1910-1914) or Japan (1920-1922) - 16.3-16.6% [19, p. 363].

The most unfavorable period for the life of the local population was the spring, during which the mortality rate increased 1.8 times higher than the average annual indicators. The main causes of death, regardless of age, were respiratory diseases, mainly tuberculosis. The mortality rate of women during or shortly after childbirth was extremely high.

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TOPICAL ISSUE

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ANALYSIS OF THE EPIDEMIOLOGICAL SITUATION ON COVID-19 : A SECOND WAVE

Summary. The analysis of prevalence, morbidity, mortality and lethality from COVID-19 for the period from September 1, 2020 to January 4, 2021 was carried out. It was revealed that during the analyzed period (18 weeks), the prevalence and incidence rates of new coronavirus infection increased significantly. The highest prevalence of COVID-19 is registered in the USA, Spain, France. China and Thailand have the lowest prevalence and incidence rates for new coronavirus infection.

Key words: new coronavirus infection, COVID-19, epidemiology, prevalence, morbidity, mortality, lethality.

Introduction. On December 31, 2019, the Chinese authorities informed the World Health Organization (WHO) of an outbreak of unknown pneumonia. The pandemic of the new coronavirus infection began with the detection of a group of cases of idiopathic pneumonia in hospitals in Wuhan (Hubei Province, China) as of December 31, 2019 [3, 4]. Coronavirus 2019 (COVID-19) as an infectious viral disease has spread throughout the world, leading to an ongoing pandemic [9, 13]. As of 01/04/2021, the total number of infected COVID-19 around the world was 83,934,188, and the number of deaths was 1,840,028. [15-23].

It was assumed that the disease would be cyclical in its course for an indefinite time. According to forecasts of epidemiologists, the beginning of the second wave should cover the autumn months [2, 6, 7]. The repeated increase in the number of patients with a new coronavirus infection was associated with the absence of the so-called herd immunity and the weakening of anti-epidemic measures [8, 12]. Since November 2021, vaccination of the population began, primarily from risk groups, which should affect the rate of spread of infection in the future through an increase in the population stratum with persistent immunity [5, 10].

In a previous article, we analyzed the dynamics of the spread of COVID-19 in the Republic of Sakha (Yakutia) in comparison with other regions of the Russian Federation and a number of foreign countries from the beginning of the pandemic to July 31, 2020.The highest prevalence of a new coronavirus infection was registered in the USA - 1433.8 , in Brazil - 1227.7, in Spain - 712.3, followed by Russia with an indicator of 572.4 cases per 100 thousand of the population. Three zones were identified on the basis of the analysis of the spread of infection [1]. As the pandemic continues, we decided to continue our analysis of the COVID-19 epidemiological situation for a "second wave" in the same countries that were included in the previous study.

Aim of the work: to analyze of the dynamics of the spread of COVID-19 during the second wave in the Republic of Sakha (Yakutia) in comparison with other regions of the Russian Federation and a number of foreign countries.

Tasks:

1. Calculate the growth rate of the spread of COVID-19 in different regions during the "second wave"
2. Conduct a comparative analysis of the spread of COVID-19 during the "first" and "second wave"
3. Compare mortality and lethality in the first and second waves of a new coronavirus infection.

Materials and methods. Epidemiological data for SARS-CoV-2 was obtained using an online platform that collects data from government agencies from September 1, 2020 to January 4, 2021 December, the coverage was 18 weeks of observation [15-23]. The study included countries the following countries: China, USA, Spain, Italy, France, Germany, Great Britain, Russia, Brazil, Norway, Finland, Thailand. For the Russian Federation, a comparison was made of data in Moscow, St. Petersburg and the Republic of Sakha (Yakutia). We analyzed the following indicators: the number of confirmed cases, new cases of COVID-19 in 18 weeks, mortality per 100 thousand of the population, lethality in % during the observation period as of 01/04/2021.

Research results. Analysis of the total number of patients in the compared countries in dynamics in terms of 100 thousand of the population (prevalence) for 18 weeks of follow-up (end date 01/04/2021) showed that the highest prevalence of new coronavirus infection was registered in the USA - 6342.8, then

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in Spain - 4210, in France - 4162.6, the UK is in fourth place - 4062, in fifth place Italy - 3593.1 cases per 100 thousand of the population (Figure 1). The lowest prevalence of COVID-19 remains in China, amounting to 6.9 cases per 100 thousand of the population. Compared to the previous analysis, the structure of the leading countries in terms of the number of confirmed cases of COVID-19 has changed: the number of cases in Europe, such as Spain, France, and the United Kingdom, has significantly increased. Overall, there is a widespread exponential increase in the number of patients with COVID-19.

We also calculated new cases of coronavirus infection per 100 thousand of the population weekly (Figure 2). According to the analysis results, the "red" zone included (more than 100 cases per 100 thousand of the population per week): Great Britain, USA, Italy, France, Germany, Russia, Brazil, where there is a steady increase in the number of cases and the highest prevalence rates, trends no decrease in morbidity was noted. In France, at week 10, there was a sharp increase in the number of new cases to 606 per 100 thousand of the population. Norway is in the “yellow” zone (weekly incidence rates range from 40 to 90 cases per 100 thousand). China and Thailand are still in the "green" zone, where the weekly incidence is extremely low. In the first place in terms of incidence are Great Britain, then the USA, Italy.

As can be seen from the data presented, in the second wave of COVID-19, we note a significant increase in both the total number of confirmed cases and new cases. Such an increase in the incidence by the beginning of November can be explained by public protests against quarantine measures with a mass gathering of people at the end of October in most European countries. In the United States, there were also riots in connection with

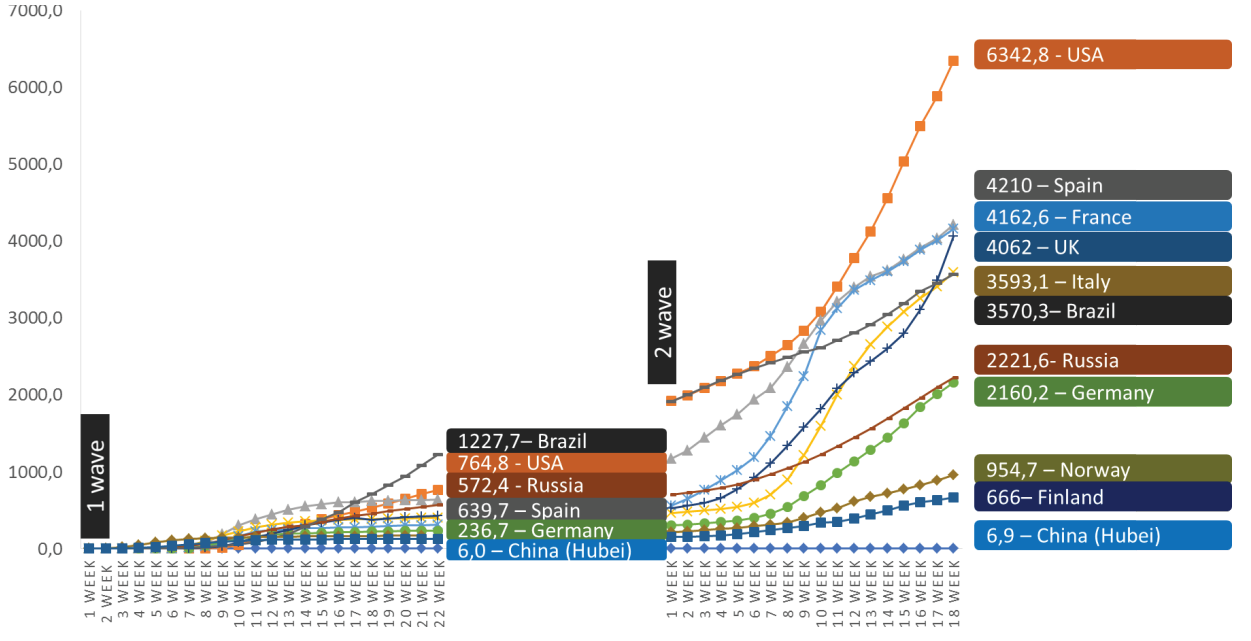

Fig. 1. The number of confirmed cases of COVID-19 (per 100 thousand of the population) in the compared countries (in the first and second wave)

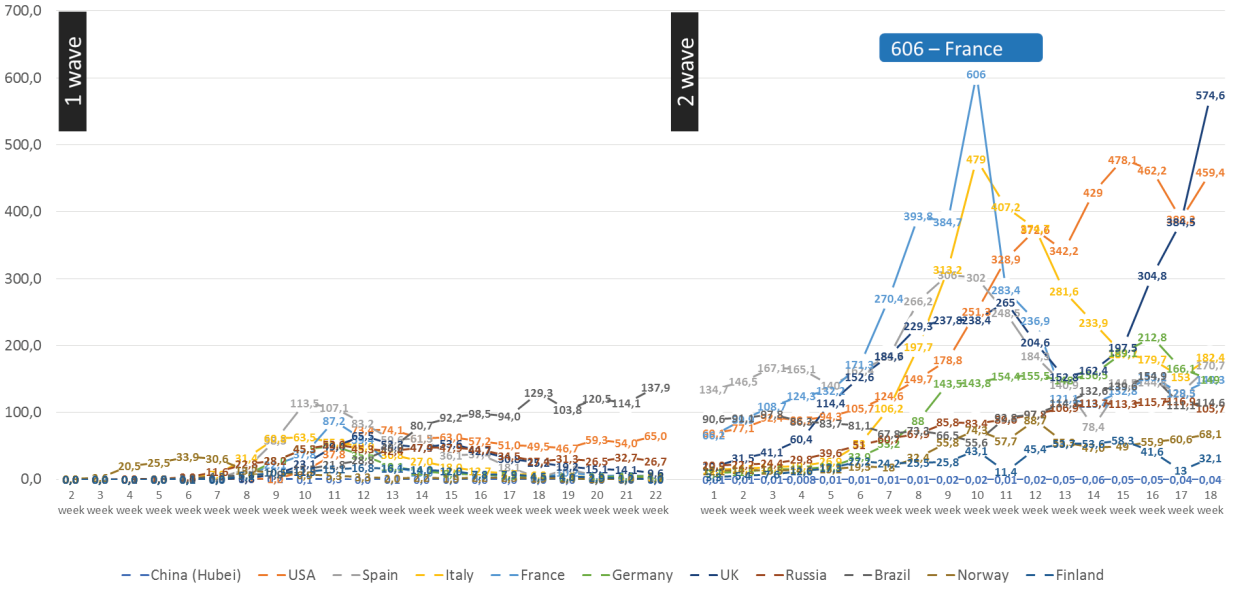

Fig. 2. New cases of COVID-19 (per 100 thousand of the population) over 18 weeks (09/01/2020 to 01/04/2021) in the compared countries

the presidential elections in the country. China and Thailand have the lowest prevalence and incidence rates for new coronavirus infection.

We calculated the mortality and lethality in the compared regions, taking into account the total number of deaths over 18 weeks of observation as of 01/04/2021 (Figure 3). The highest mortality rate in Italy is 55, followed by the United States - 43.8, then Great Britain - with an indicator of 42.8 per 100 thousand of the population. The lowest mortality rates were found in China and Thailand, at 0.004 and 0.003, respectively. It should be noted that in comparison with the mortality rates of the first wave, there is a twofold increase in Italy (from 27.5 to 55 per 100 thousand of the population), 2.8 times in Germany (from 8.9 to 25.2 per 100 thousand.), 2.75 times in Russia (from 8.9 to 24.5 per 100 thousand). Lethality in the countries included in the study ranged from 0.02 to 1.5%, that is, we note a decrease in this indicator during the second wave. The lowest lethality rate in Thailand is 0.02%. Italy is in first place in lethality (1.5%), in second - Germany (1.2%), in third - Great Britain and Russia (1.1%).

During the analyzed period in the

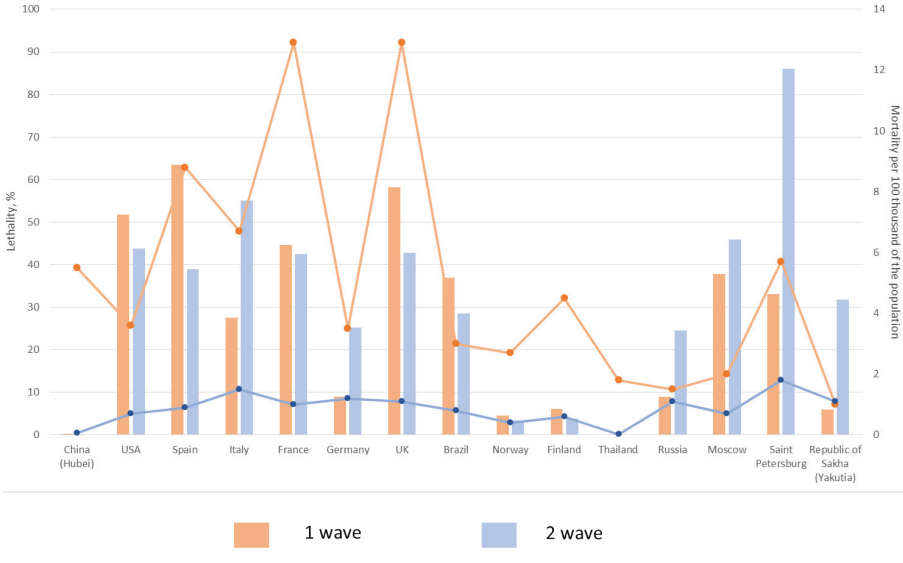

Fig. 3. Indicators of lethality and mortality from COVID-19: lines - lethality in%, columns - mortality per 100 thousand of the population

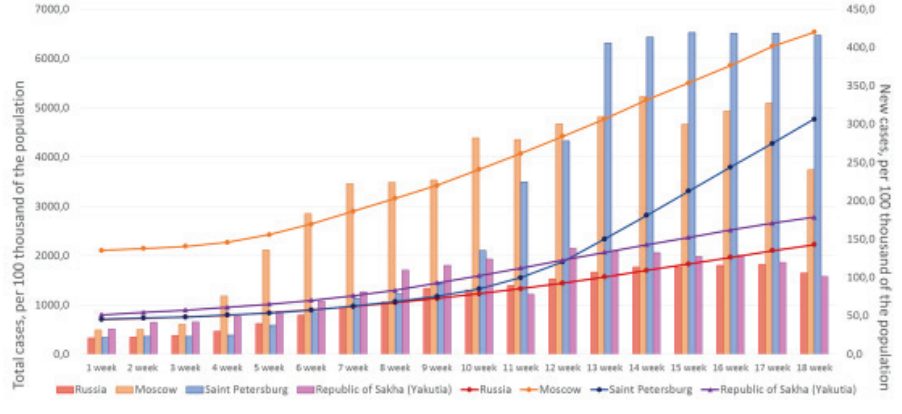

Fig. 4. The number of confirmed and new cases of COVID-19 in the Republic of Sakha (Yakutia) and Russia (per 100 thousand of the population), as of 01/04/2021

Republic of Sakha (Yakutia), the prevalence of COVID-19 by week 18 reached 2,774.9, and the incidence - 101.3 per 100 thousand of the population. When compared with the epidemiological situation in Russia, the indicators of both prevalence and morbidity in the Republic of Sakha (Yakutia) are comparable. In Russia, Moscow and St. Petersburg are in first place in terms of prevalence and incidence of COVID-19. Starting from the 13th week, St. Petersburg was ahead of Moscow in terms of the analyzed indicators (Figure 4).

Conclusion. The analysis of the prevalence and incidence of new coronavirus infection during the first and second waves showed that a significant increase in the number of patients with COVID-19 was registered in the autumn-winter period, which corresponds to the seasonal increase in respiratory infections. Noteworthy is the decline in mortality rates in the analyzed countries as a whole, which was noted against the background of an overall increase in the number of cases. Although in three countries (Italy, Germany, Russia), mortality per 100 thousand of the population has increased. But the lethality rate decreased everywhere, reaching a maximum in Italy (1.5%), while in the first wave the highest lethality rate was in the UK, amounting to 12.9%. This suggests that, despite the widespread increase in the number of patients with COVID-19, the health system has learned to cope with the most severe consequences of the disease since the beginning of the pandemic.

In all likelihood, factors such as mass protests by the population and refusal to comply with quarantine measures played a huge role in increasing the number of patients in Europe and the United States. Another possible reason for the increase in the incidence of COVID-19 is a new variant of coronavirus-19, which was discovered in the UK, where the London government has now imposed quarantine with restrictions on international movement. The new variant of the virus has already infected 1/4 of the total number of cases, and in December 2020 it reached 2/3 of those infected in the UK. It is assumed that the spread of the British variant may exceed 70% of cases compared to the normal SARS-CoV-2 virus [11].

As the experience of China in the fight against the COVID-19 epidemic has demonstrated, the right model of anti-epidemic measures, which includes such principles as adaptive management, a culture of moral standards, reliable cooperation between the government and the public, including through the media, is paramount. As the authors emphasize, the culture of moral observance by the population is a key success factor in the fight against COVID - 19 [14].

The beginning of vaccination of the population presupposes the formation of collective immunity, which should make adjustments to the pandemic process through the formation of collective (population) immunity. In this regard, in the future it will be interesting to analyze the prevalence and incidence of COVID-19 after mass vaccination of the population.

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EPIDEMIOLOGICAL AND CLINICAL ASPECTS OF CARDIOVASCULAR DISEASES IN NOVEL CORONAVIRUS INFECTION

A review of the published data on the epidemiological and clinical aspects of cardiovascular diseases in the novel coronavirus infection is presented. Summarizing the results of studies by many authors, we state that the tropism of the new coronavirus infection to the cardiovascular system is manifested through ACE2 receptors, immune, cytokine inflammation, increased coagulation activity. These pathophysiological characteristics are especially evident in concomitant cardiovascular pathology, leading to decompensation of the existing pathology and often to a fatal outcome. Thus, cardiovascular disease is a dangerous risk factor for the development of fatal consequences in the current pandemic situation.

Keywords: SARS-CoV-2, COVID-19, cardiovascular disease, ACE2, arterial hypertension, myocarditis, arrhythmia.

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The novel coronavirus infection (SARS-CoV-2) was first reported in December 2019 in Wuhan, Hubei province, China. This viral infection quickly spread throughout the world at an alarming rate. The SARS-CoV-2 virus is characterized by high virulence and lethality. The World Health Organization declared COVID-19 a pandemic in March 2020. According to WHO, as of February 15, 2021, 108.2 million confirmed cases of COVID-19 were registered worldwide, with more than 2.3 million deaths [32]. In Russia, according to epidemiological data, as of February 15, 2021, more than 4 million cases and 82 thousand deaths were registered [1].

The standard clinical picture of the novel coronavirus infection was characterized as follows. The incubation period of the disease lasted from 3 to 7 days. The most common symptoms of the disease in patients with COVID-19 were fever (91.7%), cough (75.0%), fatigue (75.0%) and diarrhea (39.6%), and the most common comorbidity was hypertension (30.0%) and diabetes mellitus (12.1%) [54]. 80% of patients suffered from the disease in a mild and asymptomatic form, 15% - in severe and 5% - critical, requiring intensive therapy and mechanical ventilation [36]. One of the main diagnostic signs of the novel coronavirus infection is developing pneumonia with characteristic changes in the computed tomography of the chest - a "frosted glass" seal.

In a retrospective study by Navaratnam AV et al. [2] for the period from March 1 to May 31, 2020, out of 91,541 adult patients who were hospitalized in

England, 30.8% died in hospital, with the largest percentage of deaths occuring at the beginning of March 2020 - 52.2 % and up to 16.8% at the end of May 2020. The most susceptible to hospital mortality are the elderly, men and people of Asian or mixed ethnicity. The ratio of patients by race to Caucasians, Asians, and Blacks was 13.0:1.4:1.0. Asian ethnicity was associated with higher odds of death, although this differed between South Asian ethnicity (OR-1.246; 95% CI 1.152-1.48; n = 5117) and other Asian ethnicities (OR-1.108; 95% CI 0.973 -1.262; n = 2000). The higher hospital mortality among people of Asian or mixed ethnicity requires more detailed further study.

Despite the fact that the disease is mainly characterized by damage to the respiratory system, there is growing evidence of an increase in the number of COVID-19 patients with cardiovascular comorbidity, which has led to higher mortality among patients with COVID-19.

In the study of deaths from COVID-19 by age group 54 and under, 55 to 64, and 65 and over, across 6 weeks as of April 12, 2020 in 16 countries including Austria, Belgium, Brazil, Canada, China, France, Germany, India, Iran, Israel, Italy, the Netherlands, Portugal, Russia, South Korea, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States - 178,568 deaths from COVID-19 were registered, with a total population of about 2.4 billion people [50]. The mortality rate was 8.1 times higher in patients older than 55 compared to people younger than 55 years old, and with the age of 65 years and older, the mortality rate was 62 times higher. In men, the mortality rate is 77% higher than in women. The United States has the highest number of COVID-19 deaths per week, followed by several Western European countries initially affected by COVID-19, followed by Canada and Brazil, then Germany and Austria. China and South Korea had the lowest death rates from COVID-19 among the countries in the sample. Comorbidities such as hypertension, diabetes mellitus and obesity are associated with higher mortality from COVID-19 [21]. Since the number of comorbid conditions increases with age, this logically explains the increased mortality in older patients. Although disease-related mortality is higher in the elderly and in patients with other conditions such as cardiovascular disease, changes associated with reduced immunity may explain the increased susceptibility to infection and high mortality due to novel coronavirus infection in the elderly [23].

Most publications on the analysis of the course and clinical outcomes of COVID-19 relate to middle-aged and elderly patients. However, due to the rapid spread of the SARS-CoV-2 virus, it is important to note the course of the disease and the risk of adverse events and death in young patients. In a study by Cunningham JW. et al. [13] for the period from 01.04. to 30.06.2020, 3222 patients with COVID-19 aged 18 to 34 years were hospitalized in 419 US hospitals, their average age being 28.3 ± 4.4 years, 57% of which were of the Negroid race and Hispanics. In the study group, comorbid pathology was widespread: obesity (36.8%), arterial hypertension (16.1%), diabetes mellitus (18.2%). The mortality rate was 2.7%, which is lower than in the older age group, but twice as high as the mortality rate in young patients with acute myocardial infarction without COVID-19. Patients with multiple risk factors (obesity, arterial hypertension and / or diabetes mellitus) were characterized by a comparable risk of adverse outcomes to patients with COVID-19 in the 35-64 age group without the listed cardiovascular risk factors.

Given the rising incidence of COVID-19, the study's findings highlight the importance of COVID-19 prevention measures across all age groups. The high prevalence of comorbid pathology and the associated increase in mortality even in the subgroup of young patients with COVID-19 determine the need to promote healthy lifestyles and correct modifiable risk factors such as hypertension and obesity.

Previous outbreaks of the novel coronavirus infection, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), have had cardiovascular complications as well as cardiovascular comorbidities [14,57]. The most frequent complications were hypotension, myocarditis, arrhythmias and sudden cardiac death [49,52]. The novel coronavirus infection also has similar complications from CVS.

In China, in a large retrospective analysis of 72,314 patient histories, of which 44,672 (61.8%) had confirmed cases of COVID-19, 16,186 (22.4%) were suspected of having it, and 889 (1.2%) had asymptomatic cases [15]. Among the confirmed cases, 12.8% had hypertension, 5.3% - diabetes and 4.2% - cardiovascular disease [15]. Interestingly, these figures are lower than the prevalence of cardiovascular risk factors in a typical Chinese population, but it is important to mention that they are not age-standardized and that there was no data on comorbidities in 53% of cases [56].

A study of 5700 patients with COVID-19 from New York, Long Island and Westchester County (USA) showed that 56.6% of them had hypertension, obesity - 41.7%, diabetes - 33.8%, coronary heart disease - 11.1% and congestive heart failure 6.9%, which were the most common comorbidities [35]. For comparison, according to the US Centers for Disease Control and Prevention in 2017, the prevalence of hypertension, obesity and diabetes was 45%, 42.4% and 10.5%, respectively [7,8,9].

In an early retrospective analysis of 138 patients in Wuhan, China, approximately 50% of patients with COVID-19 had one or more comorbidities. Moreover, in patients admitted with severe COVID-19, this proportion reached 72% [48]. It remains unclear whether diabetes, hypertension and other cardiovascular diseases are causally related or age-related. However, it is important to note that patients with a severe form of the disease are more likely to have comorbidities, including cardiovascular disease.

In a study by Li S. et al. in patients with a severe form of the disease, there was a high expression of inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α), the so-called "cytokine release syndrome" or "cytokine storm "[29]. Many researchers argue that the level of serum interleukin-6 is a biomarker for the severe, highly-lethal form of the disease [12,18,31,44,47]. In the meta-analysis of 6212 patients [45], IL-6 and IL-10 were biomarkers of the severe, more lethal form of COVID-19; these biomarkers were significantly higher in severe patients compared to non-severe patients (OR - 18.63, 95% CI 10.91 - 26.35, P <0.00001; OR - 2.61, 95% CI 2.00-2.32, P <0.00001; respectively), it was also higher in patients with fatal outcomes compared to survivors (OR - 57.82, 95% CI 10.04 -105.59, p=0.02; OR - 4.94, 95% CI 3.89 - 6.00, p <0.00001; respectively).

In patients with pre-existing heart failure, there was an increased expression of angiotensin converting enzyme 2 (ACE2) both at the mRNA level and at the protein level, causing dysfunction of capillary endothelial cells, thereby affecting small vessels. This means that when infected with the SARS-CoV-2 virus, these patients have a higher risk of heart attack and severe form of the disease. The results of this study explain the high rate of severe cases among COVID-19 patients with cardiovascular disease [10]. The PURE study [41], which included 10,753 participants from 14 countries of 5 continents of the world, where the effect

of ACE2 level on the risk of death from CVD, an increase in heart failure (OR - 1.27; 95% CI 1.10-1.46), myocardial infarction (OR - 1.23; 95% CI 1.13-1.33), stroke (OR - 1.21; 95% CI 1.10-1.32) and diabetes (OR - 1.44 ; 95% CI 1.36-1.52) was researched. The results were not influenced by gender, age, nationality, and traditional risk factors. Compared to other risk factors, such as smoking, hypertension, diabetes, dyslipidemia, obesity, the ACE2 level was the most informative predictor of death from heart failure, stroke and myocardial infarction. Thus, an increased concentration of ACE2 is closely associated with the risk of death, cardiovascular complications and diabetes. It was also noted that ACE2 levels were higher in men, the elderly, people who had a history of smoking, had diabetes, had a higher BMI, high blood pressure, and higher blood lipid concentrations.

In a study by Shi S. et al. [39] of 416 patients, 57 were fatal. Among the deceased, heart damage accounted for 19.7%, coronary heart disease - 10.6%, heart failure - 4.1%, and 5.3% - cerebrovascular diseases.

It is noted that more than 7% of patients have had cardiovascular complications in the form of myocardial damage [24,51]. Cardiac manifestations in COVID-19 patients included myocardial infarction (MI), cardiac arrhythmias, cardiac arrest, heart failure, and blood clotting disorders ranging from 7.2% to 33%. Heart damage in patients with COVID-19 is caused both by direct damage to myocardial cells, mediated by ACE2 receptors, as suggested by some studies, and systemic inflammation, which causes indirect damage to myocytes [16]. The risk of morbidity and mortality from COVID-19 is higher in patients with CVD. An increase in ACE2, and in response, an increase in angiotensin II associated with the renin-angiotensin-aldosterone system, are key mechanisms for the development of hypertension, atherosclerosis, and heart failure [5,17]. In a study of 187 patients infected with SARS-CoV-2, 35% had a history of cardiovascular disease. The mortality rate from COVID-19 was 10.5% higher in patients with concomitant CVS pathology, and 52% higher in patients with heart failure. In patients with CVD, an elevated cardiomarker troponin T was detected (up to 55%) [40].

Myocardial damage of non-ischemic origin can manifest itself in the form of myocarditis, cardiomyopathy. Acute myocardial injury can be accompanied by increased levels of lactate and other inflammatory markers, including C-reactive protein, procalcitonin, cardiac enzymes such as troponin I, troponin T, and N-terminal-pro hormone BNP (NT-proBNP). ProBNP and BNP levels are usually elevated in myocarditis due to acute myocardial injury and possible ventricular dilatation [20,25,37,53]. Although a negative troponin result does not exclude myocarditis, especially for atypical forms or for chronic patients, in patients with COVID-19, the level of cardiac troponins and NT-proBNP may increase due to myocardial stress, a possible complication of severe respiratory illness, indicating an unfavorable course [22]. But one cannot exclude the development of type 1 myocardial infarction due to rupture, thrombosis of atherosclerotic plaques as a result of hypercoagulation. A history of concomitant ischemic heart disease should be especially taken into account. This requires selective coronary angiography in these patients. Also, the development of myocardial ischemia due to sepsis, leading to increased myocardial oxygen demand, is not excluded [11]. Myocardial ischemia in this case may be aggravated by the development of type 2 myocardial infarction.

It is believed that the pathophysiology of myocarditis is associated with the direct damaging effect of the virus on the myocardium and damage due to the immune response of the human body caused by a cytokine storm [28]. The cytokine storm triggers the activation of T-lymphocytes and further release of inflammatory cytokines that stimulate more T-lymphocytes, resulting in a positive feedback loop of immune activation and myocardial damage. It is believed that the sensitivity of T-lymphocytes to cardiomyocytes results from the interaction between the heart-produced hepatocyte growth factor (HGF) and the HGF receptor on naive T-lymphocytes (c-Met) [27].

The clinical picture of SARS-CoV-2 myocarditis varies depending on the severity. Some patients may have relatively mild symptoms such as fatigue and shortness of breath [20,25], while others may have chest pain or tightness during exertion [37,53]. The condition of many patients with deterioration of the condition is manifested by symptoms of tachycardia and acute heart failure up to cardiogenic shock [20,25,53]. Mild cases of myocarditis often remain undetermined. It may manifest on an electrocardiogram (ECG) and in an increase in cardiomarkers (troponins I and T). In myocarditis, ECG changes similar to those in pericarditis, such as elevation or depression of the ST segment, can be observed, however, these data are not sensitive in detecting the disease, and their absence is no exception [6]. With myocarditis, other ECG changes can also be observed, including new-onset bundle branch block, lengthening of the QT interval, ventricular premature beats and bradyarrhythmia with the development of atrioventricular block, pseudoinfarction. For a more accurate diagnosis of myocarditis, imaging methods such as echocardiography (ECHOKG), magnetic resonance imaging (MRI) or computed tomography (CT) of the heart with enhanced contrast, which exclude damage to the coronary arteries, are used, since many patients have concomitant cardiovascular pathology. Echocardiography is easier to deploy under time constraints, portable, affordable, easy to quickly disinfect and monitor. Signs of myocarditis on echocardiography may include an increase in wall thickness, dilatation of the heart chambers, and pericardial effusion in the presence of systolic ventricular dysfunction [26]. More informative methods are MRI and CT of the heart with enhanced contrast, allowing differentiation from other cardiac pathology. But these methods require more thorough deep disinfection after use, given the high infectivity of the new coronavirus infection. For definitive diagnosis, some researchers recommend endomyocardial biopsy [6,26]. The difficulties in carrying out this study lie in the lack of proper experience and false negative results. Biopsy specimens should be immunohistochemically tested for inflammatory changes and RNA / DNA isolation to check for viral genomes [55]. This method involves the identification of biomarkers for the development of a diagnostic test for SARS-CoV-2 myocarditis.

The mechanism of heart rhythm disturbances has not yet been clarified and remains controversial, although manifestations of arrhythmia are also not uncommon. Arrhythmia was one of the possible clinical characteristics of cardiovascular complications in patients with COVID-19. In one observational study in Hubei Province of China, 137 COVID-19 patients had heart palpitations and they accounted for 7.3% of the clinical manifestations [30]. Wang D. et al. [48] in their study reported that 16.7% of 138 patients had arrhythmias, manifested in severe cases of the disease, characterized in the form of paroxysms of atrial fibrillation. The nature of the development of arrhythmia remains unexplored, the real figures are unknown due to the small sample size. Perhaps the arrhythmias were the result of electrolyte imbalance or the occurrence of pre-existing arrhythmias, or as a result of the development of myocardi-

tis. Peretto G. et al. reported that 78.7% of patients with myocarditis had ventricular arrhythmias that depended on the stage of myocardial injury. Monomorphic ventricular tachycardia and regular ventricular arrhythmias were more common in patients with cured than with acute myocarditis [33]. The pathophysiology of arrhythmias includes, in addition to direct damage to cardiomyocytes, possible infection of pericytes, causing myocardial ischemia as a result of multivessel disease [10,34]. The influence of pro-inflammatory cytokines on the occurrence of arrhythmias is not excluded.

Research by Arentz M. et al. showed that 67% of critically ill COVID-19 patients needed vasopressors, and 33% developed cardiomyopathy [3]. This study does not exclude sepsis-associated cardiomyopathy characterized by reversible myocardial dysfunction. Previous studies have shown that myocardial damage occurs due to increased production of nitric oxide, which suppresses the response of cardiomyocytes to calcium and β1-adrenergic receptors [38]. The main signs of sepsis-associated cardiomyopathy were left ventricular dilatation, impaired ejection fraction, and recovery in 7-10 days. Difficulties arise in the differential diagnosis of stress-induced cardiomyopathy, sepsis-induced cardiomyopathy, and acute coronary syndrome.

The novel coronavirus infection with concomitant CVS pathology can also be complicated by heart failure. In a study carried out in Israel, which included 100 patients with COVID-19, whose average age was 66 years, in 90% of cases - ejection fraction was intact, and the most frequent pathological findings were right ventricular dilatation (39%) and left ventricular diastolic dysfunction (16%) [42]. Similar results were obtained in New York in a study of 105 patients of similar age [4].

Dwelling on the treatment of the novel coronavirus infection and associated cardiovascular diseases is not the purpose of this literature review. Vaccination is at the forefront of stopping the spread of this viral infection around the world. Given that there are new variants of SARS-CoV-2 501Y.V1 (B.1.1.7) in the UK [46] and 501Y.V2 (B.1.351) in South Africa [43], the end of the pandemic is possible only when vaccines effective against circulating variants will be evenly distributed around the world.

Conclusion. In conclusion, we state the tropism of the novel coronavirus infection to the cardiovascular system, exerting an effect through the ACE2 receptors, immune, cytokine inflammation, increased coagulation activity, etc. These pathophysiological characteristics are especially evident in concomitant cardiovascular pathology, leading to decompensation of the existing pathology and often to a fatal outcome. Thus, cardiovascular disease is a dangerous risk factor for the development of fatal consequences in the current pandemic situation.

The COVID-19 pandemic has proven the need for a more thorough study of the effect of SARS-CoV-2 on cardiovascular pathology, both during the period of illness and in the long-term, as well as making adjustments to many pathogenetic mechanisms and clinical features of the consequences of the disease for the cardiovascular system, to further develop the latest guidelines for curation of such patients.

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COGNITIVE IMPAIRMENT IN PATIENS WITH COVID-19

The assessment of changes in the level of cognitive functions in patients who underwent COVID-19 was carried out. An analysis of more than 30 modern scientific studies for 2019-2021 showed that patients who have suffered a new coronavirus infection in varying degrees of severity, there are significant changes in the level of cognitive functioning in the form of reduced memory, executive functions, attention, etc.

Keywords: cognitive functions, cognitive deficits, memory, attention, new coronavirus infection, COVID-19.

Introduction. Almost a year after the first COVID-19 outbreak, we still have a lot to learn about how the virus affects our health. However, it is becoming increasingly clear that many patients who have had a new coronavirus infection subsequently experience a number of neurological, psychiatric, and cognitive complications. According to various studies, these symptoms are observed in about a third of patients who have experienced COVID-19 in varying degrees of severity [4]. These symptoms also persist for a long time after recovery, which negatively affects the quality of life of patients. There is now growing evidence that COVID-19 can have a damaging effect on the brain. The main neurological symptoms of COVID-19 include ischemic stroke, encephalopathy, encephalitis, and peripheral neurological disorders. However, it is estimated that about 30% of patients with neurological symptoms also suffer from cognitive impairment, with deficits in attention, control functions, short-term memory, and psychomotor processes. The prevalence of cognitive complications remains an open question, but it is safe to conclude that they are not uncommon in patients with COVID-19. Several early studies described cognitive impairment in some patients after discharge from the hospital [5, 8]. The potential mechanisms underlying these symptoms are not fully understood, but are likely multifactorial, including the direct neurotrophic effect of SARS-CoV-2, the effects of prolonged stay in the intensive care unit, the use of artificial ventilation and sedatives, brain hypoxia, systemic inflammation, secondary effects of drugs used to treat COVID-19, and peripheral organ and system dysfunction. For example, in a study conducted in France, more than one-third (15 out of 40) of patients demonstrated cognitive impairment upon discharge from the intensive care unit in the form of a dyslexic syndrome characterized by inattention, disorientation in space and impaired executive functions [20]. In addition, in a sample of 71 patients with COVID-19, those with a history of delirium (42%) had lower cognitive performance in a screening interview after hospital discharge [10].

In general, there are very few studies of patients who have undergone COVID-19 with regard to neurocognitive data, especially in Russia. In addition to rough clinical assessments of the outcome of the disease (survival and duration of hospitalization), the medical community should take into account neurological, psychological and psychiatric outcomes.

This article attempts to summarize the currently available scientific data and clinical observations on the impact of COVID-19 on human cognitive functions.

The functioning of memory. As mentioned above, it is currently unknown whether the cognitive symptoms are caused by a virus that directly affects nerve tissue, or whether they are the result of brain damage caused by low oxygen levels or an extreme immune response known as a cytokine storm. There is some evidence that the hippocampus, a region of the brain involved in memory processes, is particularly vulnerable to damage associated with COVID-19 [2, 23]. The specific vulnerability of the hippocampus to respiratory infections was indicated in earlier studies using different strains of the influenza virus. For example, in a study by Hosseini et al. Changes were found in both the morphology and functioning of the hippocampus, which was associated with short-term learning impairment and impaired spatial (short-term) memory in mice infected with the influenza virus [18]. This may explain to some extent the presence of persistent memory disorders in patients after COVID-19. If the damage to the hippocampus is indeed a consequence of COVID-19 infection, then the question arises whether this can lead to an acceleration of hippocampal-related degeneration, as occurs, for example, in Alzheimer's disease, and accelerate the onset of the disease in individuals who have not previously had symptoms. Animal studies show that inflammation associated with viral infection significantly increases the content of tau proteins and leads to a deterioration in the functioning of spatial memory [15], which in turn is considered one of the first symptoms of Alzheimer's disease.

Despite the fact that COVID-19 infection is accompanied by damage to many organs and systems, the respiratory system is in the most serious condition. A recent small study showed that 70% of critically ill patients admitted to the intensive care unit with COVID-19 needed artificial lung ventilation (ventilator) [5], who subsequently developed acute respiratory distress syndrome (ARDS) within 3 days. According to a number of clinical observations, patients who required a ventilator for various reasons had impaired attention, memory, speech fluency, information processing speed, and executive functions in 78% of cases 1 year after discharge and in about half of patients within 2 years [25, 27]. Adhikari et al. memory problems persisted up to 5 years after ARDS, which significantly affected the daily functioning of patients, especially in relation to medication intake and compliance with medical prescriptions [24]. At the same time, anxiety, depression, and post-traumatic stress syndrome, which are also common in ARDS patients, may contribute to cognitive impairment [24] in COVID-19 patients. There is some evidence that cognitive impairment occurs independently of psychological problems

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and is associated with the severity of an infectious disease [25].

Executive functions. Violations of executive functions are usually associated with pathology of the frontal lobes of the brain [16]. Violations of executive functions are based on defects in attention control, difficulties in planning, abstraction, behavioral control and orientation [1]. Thus, defects can be detected, both in cognition and in behavior. A detailed review of the literature on COVID-19 shows that, in at least 26-40% of cases, there is a violation of executive functioning [3, 20]. Also, many articles talk about confusion and difficulties with attention in patients [7, 22], which indicates a violation of executive functions. It is known that encephalopathy, which is often mentioned in patients with COVID-19 [21, 29], is usually accompanied by generalized cognitive disorders, including disorders of executive functions [6].

It is also important to note that cognitive impairment may be associated with the length of hospitalization. Although the long-term effects of COVID-19 on cognitive function are not yet fully understood, early studies have shown that many patients report increased fatigue long after recovery [4, 13, 14]. Preliminary data show that recovered COVID-19 patients who experienced fatigue syndrome 2-3 months after the onset of the disease also had deficits in control functions and visual-spatial information processing [19]. Violations of executive functioning and attention have also been reported in patients after COVID-19 and in a number of other studies [12, 23]. Long-term cognitive changes are often observed after a viral infection, as part of the post-intensive care syndrome and the "post-viral fatigue" syndrome, respectively. Both syndromes are associated with a deterioration in physical, cognitive, and mental health and persist for a long time after the disease. Up to 80% of patients with ARDS experience this syndrome after intensive care, often with impaired executive functions [12, 17].

Non-specific cognitive functions. Due to the high interest of researchers in changes in cognitive functions in patients who have undergone COVID-19, many authors have simultaneously studied various aspects of cognition in the literature. For example, in a study by Zhou H. et al. The effects of COVID-19 on the cognitive functions of recovered patients (n=29) and their relationship with the immune system parameters were evaluated [26]. Cognitive functions were assessed using online neuropsychological tests: the Pathway Test (TMT). Trial Making Test) and continuous performance test (CPT, from the English Continuous Performance Test). Patients with COVID-19 showed lower CPT scores (lower reaction time and more errors), which correlated with blood levels of C-reactive protein (CRP) (r=0.557 and 0.41). Similar results were obtained in the study of Wilcox S. [28], devoted to the study of the effect of COVID-19 on cognitive functions in patients in China who were hospitalized in the infectious diseases department, and subsequently recovered. Statistically significant differences in test results were found between the COVID-19 patients and the control group only in the Continuous Performance test (CPT). Patients with COVID-19 showed more missed responses and errors in the more complex section of this test. In another study, Baker H. A. et al. [4], we studied the level of cognitive deficits in 13 patients admitted to a hospital in Lausanne, Switzerland, during the post-critical acute stage of severe COVID-19. The neuropsychological assessment consisted of two standard sets of tests: the Montreal Cognitive Assessment Scale (MoCA) and the Frontal Dysfunction Battery (FAB). MoCA data showed that 4 (30.8%) patients had moderate cognitive deficits, and 5 (38.5%) had moderate to severe deficits. The MoCA subtests revealed a selective cognitive pattern with lower control function scores in patients with relatively normal MoCA test scores, and more extensive cognitive impairments of executive functions, memory, attention, and visual-spatial functions with relatively preserved orientation and speech, in patients with severe cognitive deficits. FAB data showed executive system dysfunction in 8 (61.5%) patients. According to the FAB subtests, speech function was most affected: pronounced fluency was found in 12 (92.3%) of the 13 patients. In a study by Marcel S. et al. [9] 18 patients were examined 20-105 days after treatment for mild to moderate COVID-19. 14 (78%) patients had sustained moderate cognitive deficits in the form of worse results in the "Modified Telephone Interview for Cognitive Status screening test" (TICS-M) for mild cognitive impairment compared to 10 healthy people from the control group of the same age. To a greater extent, the authors noted a decrease in short-term memory, attention and concentration, however, the results of screening did not correlate with the duration of hospitalization and treatment. Hampshire A. et al examined a group of patients who had suffered from COVID-19, and showed an average decrease of 8.5 points in IQ level [11].

Conclusion. Over the past few months, our understanding of the prevalence, pathogenesis, and clinical heterogeneity of the new coronavirus infection has been significantly supplemented and modified. The few publications devoted to changes in cognitive functions associated with COVID-19 indicate significant cognitive disorders. It is becoming increasingly clear that one of the most important consequences of COVID-19 is cognitive deficits, even in patients with mild symptoms. Together, there is growing evidence that the CAVID-19 infection itself, as well as the consequences of an intensive course of therapy, can independently and synergistically contribute to the development of cognitive decline (Figure).

However, these studies do not provide an exhaustive answer to whether cognitive deficits are caused by the direct neu-

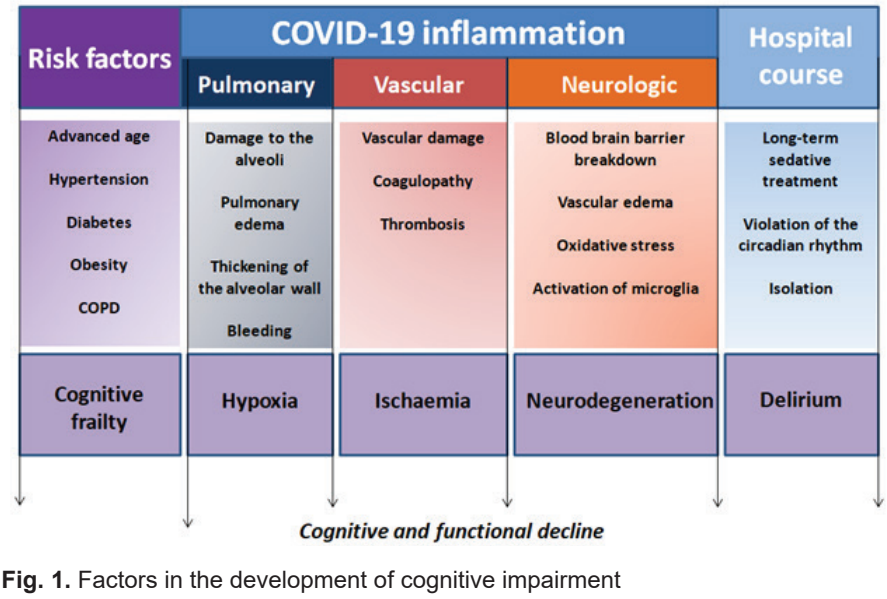

Fig. 1. Factors in the development of cognitive impairment

rotropic action of the virus or are mediated by an immune response, or other reactions.

The lack of more accurate information about functional brain disorders, including cognitive impairment, in patients with COVID-19 can be attributed to the impact that the pandemic has had on health systems, as well as the difficulty of conducting a comprehensive neuropsychological assessment. However, this information will be of great importance for identifying risk factors associated with neuropsychological symptoms, both in people with and without prior cognitive impairment, and will also shed light on the underlying mechanisms of pathogenesis. Also, to improve the quality of medical care, it is necessary to offer neuropsychological rehabilitation to those who need it. It is important and urgent to minimize the potential negative impact on cognitive and psychosocial functions and quality of life in patients who have undergone COVID-19.

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ARCTIC MEDICINE

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FEATURES OF MEDICAL CARE AND MEDICAL-DEMOGRAPRHIC INDICATORS IN THE ARCTIC REGIONS OF THE REPUBLIC OF SAKHA (YAKUTIA)

A net of medical and prophylactic institutions in the Arctic regions of the Republic of Sakha (Yakutia) for the period of 2000-2018, medical and demographic data of indicators are represented in the article. A comparative analysis of indicators for the whole Republic with the Arctic regions is carried out. The main tendencies in changes of the medical and demographic indicators of the Arctic regions of the Republic of Sakha (Yakutia) are revealed. Well-based concepts of the development of medical care in the Arctic regions of the Republic of Sakha (Yakutia) are suggested in the concluding part of the article.

Keywords: birth rate, mortality rate, natural growth of population (natality), air medical services, Yakutia

Introduction. The main reasons for inefficient functioning of healthcare system in the regions of the Far North of the Russian Federation are in its natural climatic features, transport infrastructure, low density of population and medical understaffing associated with vast and unpopulated territories. A present normative legal regulation of healthcare resources in the Arctic regions does not take into account the density of population of the Russian Federation resulting in decreased availability of medical service in such regions. Due to geographic and climatic factors, a historically prevailing lifestyle of the Arctic regions presupposes a great number of low-populated villages located at a great distance from each other as well as away from administrative and medical centers. Nowadays a transport infrastructure in the Arctic regions is underdeveloped, and the tendency of its development does not show any considerable improvement for the next decades. It contributes to the development of a very specific life support system. The medical service in these regions is represented by rural hospitals for any available medical service, there is high demand in emergency service including specialized and air medical services, organization of mobile team for initial and specialized medical service and high level of hospitalization.

Materials and methods: The initial materials are represented by official reports of 'Yakut Republican medical center of informatics and analysis under the healthcare ministry of the Republic of Sakha (Yakutia)' for the period of 2000-2018. All the tables represent the data for the period of 2000-2018. Medical and demographic indcators of the Arctic regions of the Republic of Sakha (Yakutia) for the period of 2000-2018 have been analyzed. Main tendencies of medical and demographic processes in the Arctic regions of the Republic of Sakha (Yakutia) are revealed. Positive and negative trends in medical and demographic indicators are determined.

Results: There are 97 medical institutions in the Arctic regions of the Republic of Sakha (Yakutia). The system of initial in-patient and out-patient healthcare service is represented by 13 central

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Table 1

A net of medical institutions in the Arctic regions of the Republic of Sakha (Yakutia), (2018)

Regions	a	b	c	d	e	f	g	Total
Abiyskiy	1	5	-	-	1	1	-	8
Allaikhovskiy	1	-	-	1	-	3	-	5
Anabarskiy	1	1	-	-	1	-	-	3
Bulunskiy	1	4	-	1	1	2	-	9
Verkhne-Kolimskiy	1	1	-	2	-	2	-	6
Verkhoyanskiy	1	6	1	1	1	11	-	21
Zhiganskiy	1	1	-	-	1	2	-	5
Momskiy	1	1	-	-	-	4	-	6
Nizhne-Kolimskiy	1	2	-	-	1	-	1	5
Olenyokskiy	1	2	-	1	-	-	-	4
Sredne-Kolimskiy	1	8	-	1	1	-	-	11
Ust-Yanskiy	1	4	-		1	5	-	11
Eveno-Bytantaiskiy	1	1	-	-	-	1	-	3
Total for the Arctic regions	13	36	1	7	8	31	1	97

Note: a – Central Republican hospital, b – district hospital, c – city hospital, d – out-patient departments, e – TB dispensaries, f – first-aid and obstetric stations, g – first-aid station.

Table 2

Medical staff and medical staff provision (medical and paramedical personnel) in the Arctic regions of the Republic of Sakha (Yakutia). 2018

Regions	Medical personnel				Paramedical personnel			
	Established staff number	Actual staff number	Medical staff provi sion. %	Medical staff provision per 10 000	Established staff number	Actual staff number	Medical staff provi sion. %	Medical staff provision per 10 000
Abiyskiy	29	15	51.7	37.7	72	64	88.9	160.8
Allaikhovskiy	22	11	50.0	40.6	48.5	34	70.1	125.6
Anabarskiy	18.75	9	48.0	25.0	38.5	30	77.9	83.4
Bulunskiy	56.25	26	46.2	31.2	141	79	56.0	94.7
Verkhne-Kolimskiy	27.5	15	54.5	37.0	65.25	39	59.8	96.3
Verkhoyanskiy	61.5	37	60.2	33.2	209.25	155	74.1	139.2
Zhiganskiy	26.5	22	83.0	52.7	58.5	46	78.6	110.1
Momskiy	22	16	72.7	40.3	70.5	58	82.3	146.0
Nizhnekolimskiy	35.25	19	53.9	44.3	97.5	50	51.3	116.6
Olenyokskiy	28.5	24	84.2	57.9	61.5	52	84.6	125.4
Srednekolimskiy	47.25	31	65.6	41.8	117.25	100	85.3	134.7
Ust-Yanskiy	59.25	34	57.4	48.4	153	81	52.9	115.3
Eveno-Bytantaiskiy	14	9	64.3	31.8	33	31	93.9	109.7
Total for the Arctic regions	448	268	59.9	39.6	1165.75	819	70.3	121.0
The Republic of Sakha (Yakutia)	6489.5	4947	76.2	51.2	13414.5	11044	82.3	114.2

regional hospitals, 36 district hospitals, 1 city hospital, 7 out-patient departments, 8 TB dispensaries, 31 first-aid and obstetric stations and 1 first-aid station (Table 1).

448 of medical staff of physicians is required for the Arctic regions, in fact only 268 specialists were occupied by the end of 2018; the hospitals are understaffed 59.9%, this number is lower than the mean value for the Republic (76.2%). The medical staff provision per 10 000 of population was 39.6 in 2018, and it was 42.9 and 41.8 in 2016 and 2017 respectively.

The total capacity of medical organization in the Arctic regions is 673 day-and-night beds it is 7.5% of the total hospital bed fund of the Ministry of healthcare of the Republic of Sakha (Yakutia). Since 2013 the number of day-and-night beds reduced by 24.5% (219 beds). A bed provision for 10 000 of population is 99.4%, which means that totally the number is higher than in the Republic (the total Republican index is 91.8%).

The analysis of dynamics of the health service indicators for the Arctic regions showed high demand of such kind of medical assistance and increased by 110% (from 2.8% to 5.9%) since 2000 (Table 3).

At the beginning of 2019 there were 68 159 people, or 7% from the total number of population, living in the Arctic regions of the Republic. The number of population in the Arctic regions has reduced by 29.1% or 27997 people since 2000 (Table 4).

The children population in the Arctic regions has reduced by 30.8% or 7947 children since 2000 (Table 5).

The number of the labour potential in the Arctic regions reduced by 23.0% or 11200 people since 2005 (table 6).

The birth rate in the Arctic regions varies from 8.8 (Verkhnekolimskiy region) to 23.6 (Olenyokskiy region) per one thousand in 2018. The number has decreased in dynamics by 0.6% (from 14.5% to 14.3%). However the birth rate number in the Arctic regions is steadily higher than the average level of the whole Republic (table 7).

The mortality rate in the Arctic regions varies from 7.5 (Abiyskiy region) to 13.5 (Verkhnekolimskiy region) per one thousand in 2018. The number has reduced by 5.7% in dynamics (from 10.5 to 9.9). The mortality rate indices are higher in the Arctic regions than in the whole Republic (table 8).

The natural increase of population in the Arctic regions varies from -4.7 (Verkh-

Table 3

The dynamics of indices of the air medical services in the Arctic regions of the Republic of Sakha (Yakutia)

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	5.5	7.1	3.7	6.3	4.9	7.4	4.8	
Allaikhovskiy	6.8	11.4	4.0	3.7	2.2	2.2	4.8	
Anabarskiy	0.8	5.4	4.8	5.9	3.8	4.2	3.4	
Bulunskiy	0.7	8.9	10.2	9.8	10.1	8.8	10.1	
Verkhnekolimskiy	0.9	3.3	4.7	8.9	3.8	6.7	3.7	
Verkhoyanskiy	1.2	9.0	6.8	7.9	6.8	8.6	6.0	
Zhiganskiy	8.1	5.2	2.2	1.6	2.4	2.4	4.0	
Momskiy	1.7	4.3	4.0	5.5	5.6	4.4	4.0	
Nizhnekolimskiy	1.7	2.9	3.8	5.0	3.7	4.2	4.0	
Olenyokskiy	3.5	2.7	4.2	9.1	4.8	4.0	6.6	
Srednekolimskiy	2.1	10.5	13.1	8.4	8.6	10.8	11.4	
Ust-Yanskiy	0.7	9.2	5.1	7.6	6.3	8.1	7.7	
Eveno-Bytantaiskiy	2.8	7.9	12.2	9.0	9.0	8.6	5.7	
Mean number for the Arctic regions	2.8	6.7	6.1	6.8	5.5	6.2	5.9	+110
Republic of Sakha (Yakutia)	1.5	1.5	1.4	1.6	1.5	1.5	1.5	

Table 4

The number of population living in the Arctic regions of the Republic of Sakha (Yakutia), absolute numbers

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	5228	4649	4112	4125	4095	4058	4018	
Allaikhovskiy	4421	3203	2904	2733	2682	2718	2716	
Anabarskiy	3757	4113	3682	3387	3431	3500	3567	
Bulunskiy	10420	9495	9366	8404	8366	8404	8339	
Verkhnekolimskiy	6662	5314	4712	4287	4288	4220	4123	
Verkhoyanskiy	15928	12695	11765	11528	11371	11385	11352	
Zhiganskiy	4849	4187	4047	4246	4258	4238	4222	
Momskiy	5243	4699	4383	4218	4139	4099	4073	
Nizhnekolimskiy	8147	5460	4879	4426	4386	4366	4290	
Olenyokskiy	4206	4111	4026	3967	3983	4009	4072	
Srednekolimskiy	9415	8240	7774	7497	7538	7512	7499	
Ust-Yanskiy	15097	9398	8262	7244	7242	7202	7075	
Eveno-Bytantaiskiy	2783	2781	2811	2798	2778	2782	2813	
Total for the Arctic regions	96156	78345	72723	68860	68557	68493	68159	-29,1%
The Republic of Sakha (Yakutia)	962479	950668	949400	956896	959700	962835	964330	-0,2%

Table 5

The number of the children population in the Arctic regions of the Republic of Sakha (Yakutia), absolute numbers

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	1541	1182	937	1048	1017	975	964	
Allaikhovskiy	1072	679	620	712	687	694	698	
Anabarskiy	1256	1230	1094	1024	1030	1051	1057	
Bulunskiy	2812	2140	2044	1953	1947	1960	1924	
Verkhnekolimskiy	1659	1047	878	837	851	846	820	
Verkhoyanskiy	4229	3216	2749	3046	3027	3009	2970	
Zhiganskiy	1352	1031	931	1219	1246	1239	1229	
Momskiy	1735	1391	1230	1306	1305	1268	1254	
Nizhnekolimskiy	1892	1085	948	1149	1158	1165	1142	
Olenyokskiy	1517	1299	1085	1199	1214	1214	1220	
Srednekolimskiy	2966	2196	1858	2065	2090	2074	2065	
Ust-Yanskiy	2952	1807	1430	1719	1744	1770	1733	
Eveno-Bytantaiskiy	799	784	724	774	759	766	759	
Total for the Arctic regions	25782	19087	16528	18051	18075	18031	17835	-30,8
The Republic of Sakha (Yakutia)	251287	217105	206200	221119	223900	226449	226891	

Table 6

The number of the labour potential in the Arctic regions of the Republic of Sakha (Yakutia), absolute numbers

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	…	2688	2353	2284	2240	2233	2189	
Allaikhovskiy	…	2017	1741	1492	1457	1468	1467	
Anabarskiy	…	2391	2051	1975	1996	2015	2026	
Bulunskiy	…	6148	5824	5282	5132	5147	5036	
Verkhnekolimskiy	…	3432	2938	2483	2440	2335	2263	
Verkhoyanskiy	…	7853	7226	6552	6361	6334	6286	
Zhiganskiy	…	2547	2398	2315	2308	2238	2191	
Momskiy	…	2631	2424	2184	2077	2050	2039	
Nizhnekolimskiy	…	3534	3039	2467	2390	2348	2277	
Olenyokskiy	…	2272	2279	2199	2188	2163	2199	
Srednekolimskiy	…	4917	4778	4022	3978	3933	3883	
Ust-Yanskiy	…	6470	5466	4239	4172	4063	3897	
Eveno-Bytantaiskiy	…	1609	1594	1602	1570	1549	1556	
Total for the Arctic regions	…	48509	44111	39096	38309	37876	37309	-23,0
The Republic of Sakha (Yakutia)	…	616724	609000	579209	571800	566053	560256	

nekolimskiy region) to 11.7 (Eveno-Bytantaiskiy region) per one thousand in 2018. The indicators have increased by 2.3% in dynamics (from 4.3 to 4.4), however it should be noted that the indicators are lower than the average rate for the whole Republic (table 9).

Annual analysis of the natural increase of the Arctic population shows that in Bulunskiy, Ust-Yanskiy, Srednekolimskiy and Nizhnekolimskiy regions an average number is not high. There is an annual population loss in Verkhnekolimsk, which tends to increase in dynamics.

Conclusion: The analysis of the period 2000-2018 shows the following negative trends for the Arctic regions of the Republic of Sakha (Yakutia):

Low medical and paramedical personnel provision and understaffing;

Low bed provision;

Decreasing density of population, including labor potential, and children population respectively;

Relatively high mortality rate indicators.

The following positive trends have been noticed in the Arctic regions of the Republic of Sakha (Yakutia) since 2000:

Positive natural increase of population;

Relatively high indicators of birth rate;

Decrease of mortality rate.

One of the key points is high demand in air medical services.

To increase the accessibility and the quality of the medical aid in the Arctic regions population of the Russian Federation it is necessary to introduce such legal term as "the Arctic model of healthcare service". Such attitude will enable to differentiate the norms according to the extents and financing, taking into account specific territorial features. It will require development of federal normative acts, regulating the concept of rural hospitals for the regions of the Far North and the Arctic regions, with the establishment of the norms of medical staffing, institutional capacity, financing, organizing mobile medical aid and improvement of mobile medical service, including unrestricted use of air medical services for urgent and emergency cases.

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Table 7

Birth rate in the Arctic regions of the Republic of Sakha (Yakutia), per 1000

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	15.4	10.6	15.1	13.6	9.6	13.6	12.5	
Allaikhovskiy	15.3	17.3	12.4	19.6	18.1	14.7	13.6	
Anabarskiy	19.7	20.3	17.9	20.5	20.8	21.8	16.2	
Bulunskiy	14.6	11.9	15.2	14	14.1	14.3	11.4	
Verkhnekolimskiy	10.0	10.1	10.3	11.7	12.0	11.0	8.8	
Verkhoyanskiy	15.0	15.5	18.7	19.8	18.3	16.8	13.5	
Zhiganskiy	12.6	19.9	22.4	22.8	17.9	18.0	16.9	
Momskiy	17.3	19.2	17.9	23.2	18.0	17.6	14.4	
Nizhnekolimskiy	11.6	12.8	14.3	17.9	15.5	12.9	14.5	
Olenyokskiy	11.6	13.7	24.1	22.1	22.5	22.8	23.6	
Srednekolimskiy	13.9	12.8	17.5	19.3	15.1	16.3	13.4	
Ust-Yanskiy	9.0	10.3	11.9	17.9	17.6	15.5	13.2	
Eveno-Bytantaiskiy	22.6	11.5	16.8	16.1	18.3	17.9	22.0	
Average number for the Arctic regions	14.5	14.3	16.5	18.3	16.6	16.2	14.3	-1.3
The Republic of Sakha (Yakutia)	13.5	14.3	16.8	17.1	16.0	14.5	13.7	

Table 8

Mortality rate in the Arctic regions of the Republic of Sakha (Yakutia), (per 1000)

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	11.3	12.1	10.6	11.2	15.7	12.9	7.5	
Allaikhovskiy	10.5	13.2	15.7	11.4	7.4	12.5	11.4	
Anabarskiy	11.6	11.7	10.3	9.1	8.1	7.1	7.0	
Bulunskiy	9.9	10.1	12.0	8.6	8.1	8.0	8.2	
Verkhnekolimskiy	10.2	13.3	16.0	12.4	13.2	13.9	13.5	
Verkhoyanskiy	11.5	14.6	13.8	11.7	9.8	11.5	10.8	
Zhiganskiy	9.8	12.7	13.8	13.6	9.7	9.5	10.5	
Momskiy	10.2	14.7	14.3	10.3	10.0	10.5	8.2	
Nizhnekolimskiy	10.3	15.2	15.2	15	11.0	11.6	9.1	
Olenyokskiy	7.9	12.9	11.9	10.3	7.0	10.1	12.9	
Srednekolimskiy	10.3	11.5	14.2	9.4	12.1	10.5	10.9	
Ust-Yanskiy	9.5	11.4	10.9	13	12.2	12.9	9.4	
Eveno-Bytantaiskiy	14.1	10.0	10.8	9.3	9.4	10.7	10.3	
Average number in the Arctic regions	10.5	12.6	13.0	11.2	10.4	10.9	9.9	-5.7
The Republic of Sakha (Yakutia)	9.6	10.2	9.8	8.5	8.4	8.1	7.8	

Table 9

Natural population growth in the Arctic regions of the Republic of Sakha (Yakutia), per 1000 population

Regions	2000	2005	2010	2015	2016	2017	2018	%
Abiyskiy	4.0	-1.5	4.5	2.4	-6.1	0.7	5.0	
Allaikhovskiy	4.8	4.1	-3.3	8.2	10.7	2.2	2.2	
Anabarskiy	7.6	8.6	7.6	11.4	12.7	14.7	9.2	
Bulunskiy	4.7	1.8	3.2	5.4	6.0	6.3	3.2	
Verkhnekolimskiy	-0.5	-3.2	-5.7	-0.7	-1.2	-2.9	-4.7	
Verkhoyanskiy	3.5	0.9	4.9	8.1	8.5	5.3	2.7	
Zhiganskiy	2.8	7.2	8.6	9.2	8.2	8.5	6.4	
Momskiy	7.1	4.5	3.6	12.9	8.0	7.1	6.2	
Nizhnekolimskiy	1.2	-2.4	-0.9	2.9	4.5	1.3	5.4	
Olenyokskiy	9.1	0.8	12.2	11.8	15.5	12.7	10.7	
Srednekolimskiy	3.8	1.3	3.3	9.9	3.0	5.8	2.5	
Ust-Yanskiy	-0.4	-1.1	1.0	4.9	5.4	2.6	3.8	
Eveno-Bytantaiskiy	8.5	1.5	6.0	6.8	8.9	7.2	11.7	
Average number for the Arctic regions	4.3	1.7	3.5	7.2	6.2	5.4	4.4	+2.3
The Republic of Sakha (Yakutia)	3.9	4.1	7.0	8.6	7.6	6.4	5.9	

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TYPOLOGICAL FEATURES OF HEART RATE VARIABILITY IN ATHLETES INVOLVED IN MARTIAL ARTS

The aim of the study is to determine typological features of the heart rate autonomic regulation in adolescents and young men who are systematically engaged in martial arts.

Materials and methods of research. In total 60 martial arts athletes of Magadan region aged on average 16.1±0.16, all indigenes of the North (Evens, Koryaks), were involved in the screening surveys of 2007-2019. All the subjects exercised 18 hours a week. The VK 2.5 Varikard and Iskim-6 (LLC Ramena) program were used in the orthotest mode to register the HRV followed by analyzing the obtained indices. The classification by N.I. Shlyk was applied to ascertain the predominant type of autonomic regulation.

Results. Among all the examinees, 50.0% demonstrated a moderate predominance of autonomic regulation, which indicates their good reserves in heart rate regulation (group III) while moderate and pronounced prevalence of central regulation (41.6% of athletes) is considered an unfavorable indicator for doing sports (groups I and II). They experience a tension in the body regulatory systems, unlike students from group III. The predominance of centralization in the heart rate regulation makes the Amo, SDNN, MxDMn, TP, HF, LF, and VLF values decrease while the HR, AMo50 and SI indices tend to increase. After the active orthostatic test (AOT), the optimum functional response got to prevail in group III (with sympathetic activity becoming higher and parasympathetic activity becoming lower). In groups I and II, the subjects showed reduced versions of changes in HRV indicators as compared to their initial values indicating low functional capabilities. In group IV, a pronounced functional response to AOT was observed that requires dynamic monitoring of the young athletes to determine the causes of such a reaction.

Conclusion. Specifying the type of autonomic regulation makes it possible to determine the adaptive and regulatory capabilities of the body of young athletes and take a proper model of physical exercise, which can help preserve the health of the younger generation.

Keywords: Russia' Northeast, indigenous peoples of the North, sports, heart rate variability, initial type of autonomic regulation.

Introduction. Martial arts refer to sports (all sorts of wrestling and boxing) which suggest dynamic changes in the competitive situation. The athlete needs to quickly assess the situation and correctly respond to it with effective and accurate actions. For doing that significant morphofunctional reserves of the body are necessary. In northern regions, low comfort climatic environments additionally affect the processes of adaptation to physical exercises [3, 4]. Proper physical activity contributes to the formation of the body general resistance while excessive exercise breaks down the adaptation [2, 5]. Moreover, the problem of more frequent cardiac pathologies and sudden deaths from cardiovascular diseases in young athletes remains common [7]. One of the reasons for the rapid onset of dysregulation and overtraining among younger beginners may be the initial functional state of the body regulatory systems that is not considered by physicians and coachers prior to accepting children for training [5].

Indicators of heart rate variability (HRV) are known to be informative criteria for assessing mechanisms of autonomic regulation [1]. The regulation has individual characteristics and depends on the age, gender, and fitness of the body. Each athlete has their own physiological capabilities which can be used to assess their functional readiness to perform exercises [5]. An active orthostatic test has proved to be one of the highly informative methods for determining the body adaptabilities as well as early and hidden changes in the heart regulation. For a practically healthy person, the test does not bring any pronounced stress but suggests a working tension to the body regulatory systems, unlike people with autonomic disorders [2, 8].

The aim of the study was to determine typological features of the heart rate autonomic regulation in adolescents and young men regularly involved in martial arts.

Materials and methods of research. Screening studies of 2007-2019 involved 60 students from secondary schools of Magadan region, Evens and Koryaks by origin. The average age of the subjects was 16.1±0.16 years old. Four people responded going in for boxing, six people – for freestyle wrestling, and 50 – for Greco-Roman wrestling. Training sessions were held for 18 hours a week. The level of sports qualification was different: from the youth category to the candidate for master of sports. Prior to the study, all students and their authorized representatives gave their informed consent.

General HRV indicators were recorded using the VK 2.5 Varicard hardware complex and the Iskim-6 program (Ryazan city, Ramena LLC) in the Ortho Test mode (11 min.) [1]. A predominant type of autonomic regulation was determined according to the classification proposed by N.I. Shlyk: moderate and pronounced predominance of sympathetic and central regulation of the heart rate (group I and II), and moderate and pronounced predominance of the autonomic regulation (group III and IV) [5]. After Doctor of Medical Sciences, Professor, Honored Scientist of the Russian Federation R.M. Baevsky "... these groups of regulation correspond to the generally accepted division into sympathotonic, normotonic and vagotonic types. At the same time, the normotonic type is considered in two versions: sympatho-normotonic (group I) and vago-normotonic (group III)" [5].

Statistical analysis of the data was performed with the Statistica 6 program using nonparametric methods: Kruskal-Wallis one-way analysis of variance (Kruskal-Wallis test), and Wilcoxon criterion. The values are presented as the median (Me) and the 25th and 75th percentiles (C25; C75). The critical significance level was taken at $p<0.05$.

Results and discussion. In the sample of subjects, their initial types of autonomic regulation were determined. We observed moderate (group I) and pronounced (group II) predominance of central regulation in 11 (18.3%) and 14 (23.3%) students, and moderate (group III) and pronounced (group IV) predominance of autonomous regulation in 30 (50.0%) and 5 (8.4%) subjects, respec-

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Heart rate indicators in athletes with different types of autonomic regulation at active orthostatic test. Me (25th; 75th percentile)

Indicator	Group I. n = 11		Group II. n = 14		Group III. n = 30		Group IV. n = 5		Difference significance level Kruskal-Wallis test	
	Baseline	Orthostatic test	Baseline	Orthostatic test	Baseline	Orthostatic test	Baseline	Orthostatic test	Baseline	Orthostatic test
HR. beats per min	75 (71; 83)	96 (85; 103)	83 (75; 85)	99 (91; 106)	69 (62; 75)	84 (79; 93)	60 (56; 64)	90 (83; 93)	p<0.001	p=0.011
Mo. ms	807 (732; 831)	623 (572; 667)	714 (698; 823)	592 (558; 644)	868 (796; 960)	712 (624; 764)	876 (871; 1128)	680 (589; 705)	p<0.01	p=0.011
AMo_{50}. %	55 (50; 60)	50 (43; 74)	56 (47; 62)	63 (52; 84)	35 (31; 42)	45 (38; 54)	20 (19; 21)	46 (42; 48)	p<0.001	p=0.002
MxDMn. мс	221 (193; 245)	206 (154; 251)	170 (151; 202)	150 (130; 207)	315 (278; 345)	240 (195; 273)	480 (471; 499)	250 (228; 250)	p<0.001	p=0.003
SDNN. мс	43 (36; 45)	39 (28; 45)	34 (29; 37)	31 (26; 37)	60 (51; 67)	44 (39; 53)	100 (92; 111)	51 (44; 52)	p<0.001	p<0.001
SI. arb. units	150 (142; 189)	180 (142; 363)	223 (186; 273)	374 (195; 527)	62 (52; 84)	137 (105; 193)	20 (20; 25)	155 (131; 158)	p<0.001	p=0.002
TP. ms^2	1809 (1618; 2253)	1651 (684; 2044)	1142 (967;1485)	796 (464; 1760)	3304 (2422; 4476)	1742 (1468; 2216)	8376 (8261; 9118)	2335 (2319; 2715)	p<0.001	p=0.010
HF. ms^2	438 (251; 664)	200 (57; 567)	408 (290; 586)	125 (71; 246)	1197 (783; 1730)	258 (190; 393)	3273 (3000; 3832)	296 (198; 309)	p<0.001	p=0.076
LF. ms^2	492 (377; 861)	498 (258; 1351)	295 (167; 495)	399 (155; 540)	1085 (610; 1383)	857 (496; 1086)	2856 (1616; 3162)	1174 (938; 1185)	p<0.001	p=0.024
VLF. ms^2	325 (291; 412)	252 (137; 546)	135 (111; 171)	183 (114; 295)	425 (326; 629)	420 (344; 675)	1798 (1273; 1817)	425 (396; 666)	p<0.001	p=0.004

Note: In the table and in the figure presented on the abscissa axis is the indices of heart rate variability: HR heart rate; Mo is Mode; AMo50 is the amplitude of Mode; MxDMn is the difference between maximum and minimum values of cardiointervals; SDNN is standard deviation of cardiointervals; SI is Stress Index; TP – Total Power; HF is High Frequency; LF is Low Frequency; VLF is for Very Low Frequency

tively (Table). The categorized groups demonstrated changes of HRV indices with the running influence of the central regulation on the heart rhythm: the Mode (Mo), the standard deviation of the full array of cardiac intervals (SDNN), the variation range of the dynamic series of cardio intervals (MxDMn), the power of high-, low- and very low frequency spectral component (HF, LF, VLF, ms2) proved to become lower. Groups I and II tended to have a low-frequency component (LF > HF > VLF) to prevail in the total spectrum power. The growth of the LF component at rest was associated with the pronounced activity of cardiovascular system which resulted in an emergency mechanism for increasing myocardial contractility that contributed to the formation of negative metabolic and rheological abnormalities [2]. Groups III and IV showed respiratory waves (HF > LF > VLF) to predominate which reflected physiological respiratory arrhythmia in healthy individuals. However, despite the similar ratio of spectral components, subjects from group IV were high in the SDNN index that exceeded the standard values of 40-80 ms [1, 5]. The MxDMn values in these athletes were combined with high values of the total power of the spectrum (TR > 8000 ms2), which may have indicated a multifactorial nature of the effects on the heart rhythm. That is often observed in various sinus node dysfunctions. To find out whether these HRV changes correspond to physiological or pathological autonomic regulation of the heart rate is only possible by making dynamic analyses of the cardiorhythm parameters and doing functional tests [5].

It was found that the perfect response to orthostatic exposure was characterized by moderate activation of the central regulation and a decrease in parasympathetic effects. That was reflected in the following changes of the HRV indicators: along with the running HR, SI, and AMo50, there was a decrease in Mo, MxDMn, SDNN, and the spectral components of HRV – TP, HF, LF, and VLF [5]. We could see differences between the categorized groups in the analyzed HRV parameters at orthostasis to remain, with the exception for the HF-wave index (Table), which may have indicated a different level of reactivity of the autonomic regulation in maintaining

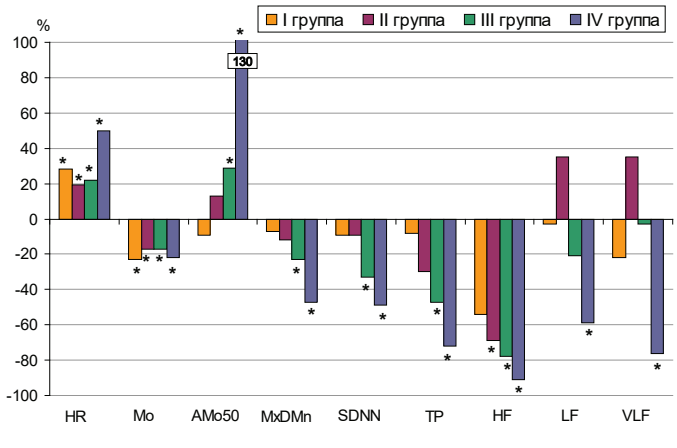

Fig. Changes in the median of heart rate variability indicators during orthotest as compared to the baseline (initial) level
Note:
* is for statistical reliability between the indicators in the lying and standing positions

the activity of the heart. The examinees differed in functional reserves of the heart regulation and autonomic responses to stress (Fig.). In group III, changes in HRV statistical indicators corresponded to the optimum response to orthostatic exposure, with an increase in the SI index median by 2.2 times from the initial values, $p<0.05$. The total power of the spectrum changed at the expense of the HF waves that had been the only to significantly decrease reflecting the inhibition of vagotonic influences [4]. We found no reliable changes in LF- and VLF-wave parameters which indicated insignificant reactivity of vasomotor and ergotropic suprasegmental centers, respectively.

In group IV, the orthostasis test resulted in pronounced changes in all the considered HRV indicators with an increase in SI by 7.8 times from the initial values at $p<0.05$. Such a functional response to AOT was typical for highly trained or overtrained athletes. That can be considered a hyperreaction with the overtrained athletes. With young athletes, it may indicate an accelerated, irrational way of a rise in the heart adaptation and its overload to training [5]. It remains unclear whether the identified changes occurred before starting sports or occurred during the course of training. Therefore, for subjects of that group, explanation of the changes observed in their heart rate regulation is still to be made.

We observed a different reaction to the orthostatic test in the central regulation groups: no changes in most HRV indicators were found as compared to their background values, and the diametrically opposite reaction of the low-frequency components (LF and VLF) of the spectrum in group II (Fig.). Examinees from groups I and II were 1.2 and 1.7 times as high in SI index in comparison with the initial values. It has been proved that the more pronounced is the stress of the central regulation structures, the greater is growth in SI, and LF and VLF values. This may indicate the predominance of low reactivity of the ANS and a decrease in its adaptabilities. Such changes in HRV are most often found at severe fatigue as well as at prenosological conditions and pathologies [2, 5].

According to researchers, for doing sports it is necessary to select individuals with moderate predominance of autonomic regulation since they have a ready physiological "platform". Such athletes have a normal level of the sinus node functioning, economical type of respiratory and cardiovascular systems in the initial state, and they demonstrate a quick recovery rate after physical exercises. With the central control getting involved in the regulation process, the body system to be controlled is destabilized, which completely suppresses self-regulation [5]. The sympathicotonic type of autonomic regulation does not agree with the concepts of fitness and adaptability in sports [2]. When planning exercising, it is necessary to consider the initial type of autonomic regulation of the athlete since the same physical activity can cause different adaptive reactions in the body. Special attention should be paid to individuals with both autonomic and central parts of the ANS strongly influencing their heart rate (group II and IV) [5]. As shown by N.I. Shlyk [6] these types of autonomic regulation are acquired as a result of various long-term stress states. Individuals with these types of regulation often have pronounced or low variants of autonomic reactivity considered unfavorable for the body [2, 5, 8].

Conclusion. Among the examinees, moderate (group III) and pronounced (group IV) predominance of the autonomic regulation was found in 50.0% and 8.4%, respectively. Moderate (18.3%) and pronounced (23.3%) predominance of central and sympathetic regulation of heart rhythm (groups I and II, 41.6% in total) has been an unfavorable indicator for doing sports. These subjects prove to have a strain within the body regulatory systems, compared to group III. With the centralization prevailing in the heart rhythm regulation, there was a directed decrease in Mo, SDNN, MxDMn, TP, HF, LF, VLF and an increase in the HR, AMo50 and SI indices, which was consistent with the physiological approaches to their interpretation of other authors. In group III, the optimum functional response (moderate increase in sympathetic activity and decrease in parasympathetic activity) could be seen. In groups I and II, changes in heart rate control were less expressed as related to the baseline values indicating low functional capabilities of the body. Athletes of group IV require more dynamic observation to make clear the causes of their pronounced functional response to AOT and prevent possible prenosological states or even adaptation failure. Specifying the initial type of autonomic regulation allows avoiding overload in young athletes' regulatory capabilities and taking a proper model of physical exercise.

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RISK FACTORS FOR CONGENITAL HEART DEFECTS IN CHILDREN OF THE REPUBLIC OF SAKHA (YAKUTIA)

Summary. The aim of the study was to examine the association between the risk of congenital heart defects in children and some perinatal factors, health status and ethnicity of parents. According to the Perinatal Center of the National Center for Medicine for the periods 2001-2003 and 2013-2015 diagnosis of congenital heart defects was more common in children of native parents. The presence of congenital heart disease in parents was associated with a greater frequency of confirmed defects in children. No statistically significant associations were established between the studied perinatal factors and the incidence of congenital heart defects in children. Probably, genetic factors should be considered as one of the main causes of the development of congenital heart defects in the population of Yakutia.

Key words: congenital malformations, congenital heart defects, native peoples of the North, Yakutia, risk factors for congenital heart defects.

Introduction. Congenital heart defects are one of the main problems of modern pediatrics. In the regions of the Russian Federation, congenital heart defects occupy a leading position in prevalence compared to other developmental defects in children and remain the leading cause of their death.

Cardiovascular lesions according to the national register of degenerate malformations have the largest specific gravity, occupying 18,1%. In different regions of the Russian Federation, the incidence rates and structure of congenital heart defects differ significantly from each other. Since 2000, a regional register has been operating in the Republic of Sakha (Yakutia), which includes data on the birth of children with developmental defects, including those with congenital heart defects. Data from this register are the basis for research and statistical work on congenital heart defects. In 2011, in the Republic of Sakha (Yakutia), the incidence of congenital heart defects amounted to 29,1 cases per 100 thousand children. The number of congenital heart defects detected increases steadily over the years and heart defects for a long time occupy the second place in the structure of infant mortality.

In the genesis of congenital heart defects, we should talk about a combination of social, hereditary, medical, as well as environmental factors. Very often, these effects can be combined. Genetic factors are considered as one of the main reasons for the development of degenerate heart defects (chromosomal mutations and deletion, fresh mutations). In isolated populations (for example, in places of compact residence of native people), genetic manifestations can arise as a result of homolocal and national marriages. According to the Yakutsk Republican Medical Information Center for the period 2002-2006,congenital heart defects were the second most common cause of death of patients under the age of 14 among evenks, evens, dolgans and yukagirs. For the period from 1995-2012, the maximum incidence of congenital heart defects was recorded in the Olekminsky, Ust-Maysky and Nizhnekolymsky districts of the Republic of Sakha (Yakutia). When analyzing the incidence of congenital heart defects in various zones of the Republic of Sakha, Yakutia, significant growth is described in the industrial, Arctic and Vilyu groups of regions.

In the structure of congenital heart defects in Yakutia, the most common are the defects of the so-called “big six”: a defect in the interventricular septum, an open arterial duct, transposition of main vessels, a defect in the intervertebral septum, tetralogy of fallot, aortic coarctation.

Due to the high significance of the problem of congenital heart defects, the aim of the study was to study the association between the risk of developing congenital heart disease and some factors of the period, the state of health and ethnicity of parents.

Materials and methods. A retrospective clinical trial was conducted on the basis of the perinatal center of the national center of medicine. The analysis included all cases of congenital heart defects (n=1824) among newborns born alive for periods of 2001-2003, and 2013-2015. The primary documentation was statistical maps of the inpatient (form №066/y-02) and inpatient journals (form №010). All cases were divided into 2 groups (confirmed and unconfirmed congenital heart defects).

In all patients with complex congenital heart defects, except for echocardiographic methods, the diagnosis was confirmed by computed tomography with contrasting vascular amplification, aortography, selective coronaroangiography.

The nationality of parents was determined by self-identification. Representative of the indigenous peoples of Yakutia included Yakuts and indigenous small peoples of the North – evens, evenks, dolgans, yukagirs, chukchi. For the analysis, 2 approaches were used, the first – with the unification of one group of children, one or both of whose parents, were representatives of the indigenous peoples of the Republic of Sakha (Yakutia) – yakuts or natives (n=1319). In the second approach, this group was divided into 2 subgroups – 1246 cases, where both parents were representatives of the native peoples of Yakutia and 73 cases where one parent was a representative of the native peoples of Yakutia. In 503 cases, parents were from other ethnic groups (Russian, peoples of Central Asia (Kyrgyz, Tajiks, Uzbeks); peoples of the Caucasus (Chechens, Ingush, Armenians); representatives of other nation-

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alities (Kumyks, Khakass, Ukrainians, Poles, Germans, Tatars, Buryats)).

Statistical calculations were performed using IBM SPSS Statistics 17 (IBM, USA) software. The Pearson X2 and Mann-Whitney criteria were used to compare the groups. The critical value of the significance level in testing statistical hypotheses was taken to be 5%.

Results and discussions. The diagnosis of congenital heart disease was confirmed in 625 out of 1822 children (34,3%). Statistically significant more often these were children of parents of native people (Table 1). These differences persisted when dividing the native group into subgroups.

Of the children with confirmed congenital heart defects 549 (87,8%) had a simple heart defect, and 76 (12,2%) – complex. When comparing the structures of confirmed congenital heart defects, no statistically significant differences were found in the proportion of simple and complex defects in children of different nationalities (Table 2).

Differences in congenital heart disease rates between native and non-native ethnos may have been due to differences in parental age, lower health quality, presence of adverse factors during pregnancy, higher incidence of genetic disorders, etc. To test these hypotheses, a comparative analysis was consistently conducted in 2 groups.

Comparison of groups by age of parents and ordinal number of pregnancy revealed no statistically significant differences (Table 3).

When studying history, it was found that in the general group in 3,8% of cases, one of the parents had a congenital heart defect. At the same time, this factor was somewhat more often noted in the group of parents of native people, the level of significance was close to critical. When dividing natives into 2 subgroups, in the group where both parents are natives, the incidence of congenital heart defects in parents was 4,4% (Table 4).

The presence of congenital heart disease in parents was associated with a greater frequency of confirmed heart defects in children. Moreover, these differences were more clearly traced in native children. The chances of having this risk factor were 2,9 times higher in children with congenital heart defects (Table 5).

All perinatal factors studied were grouped into 5 modules. Module 1 – aggravated obstetric anamnesis, module 2 – pathology of pregnancy, module 3 – harmful environmental factors, module 4 – maternal health disorders, 5 – harmful maternal habits. When comparing groups

Table 1

Incidence of confirmed congenital heart defects in different ethnic groups, n (%)

Groups	Confirmed vice		p
	No (n=1197)	Yes (n=625)	
1 approach			
Коренные (n=1319)	836 (63.4)	483 (36.6)	0.001
Некоренные (n=503)	361 (71.8)	142 (28.2)	
2 approach			
Both parents is a native (n=1246)	785 (63.0)	461 (37.0)	0.002
One of the parents is a native (n=73)	51 (69.9)	22 (30.1)	
Parents of a different nationality (n=503)	361 (71.8)	142 (28.2)	

Note: p – level of significance achieved when comparing groups (Pearson test χ2).

Table 2

Structure of confirmed congenital heart defects, n (%)

Groups	Simple (n=549)	Complex (n=76)	p
1 approach			
Native (n=483)	422 (87.4)	61 (12.6)	0.508
Non-native (n=142)	127 (89.4)	15 (10.6)	
2 approach			
Both parents is a native (n=461)	403 (87.4)	58 (12.6)	0.794
One of the parents is a native (n=22)	19 (86.4)	3 (13.6)	
Parents of a different nationality (n=142)	127 (89.4)	15 (10.6)	

Note: p – level of significance achieved when comparing groups (Pearson test χ2).

Table 3

Comparison of groups by age of parents and ordinal number of pregnancy

Indicator	Group	N	Me (Q1-Q3)	p
Mothers age, years	Non-native	142	28 (23-34)	0.262
	Native	481	27 (23-32)	
Fathers age, years	Non-native	125	30 (26-35)	0.055
	native	435	29 (25-35)	
Pregnancy sequence number	Non-native	142	2 (1-4)	0.490
	Native	482	2 (1-4)	

Note: p – level of significance achieved when comparing groups (Mann-Whitney test).

Table 4

Rate of congenital heart defects in parents, n (%)

Group of children	Congenital heart desease in parents		p
	non (n=1753)	yeah (n=69)	
1 approach			
Native (n=1319)	1262 (95.7)	57 (4.3)	0.053
Non-native (n=503)	491 (97.6)	12 (2.4)	
2 approach			
Both parents are native	1191 (95.6)	55 (4.4)	0.118
One of the parents of the native	71 (97.3)	2 (2.7)	
Parents of a different nationality	491 (97.6)	12 (2.4)	

Note: p – level of significance achieved when comparing groups (Pearson test χ2).

Table 5

Incidence of confirmed heart defects in children with heart defects in parents, n (%)

CHD in parents	Confirmed heart disease in a chald		OR (95%CI)	p
	non	year		
The whole group (n=1822)				
non (n=1753)	1169 (66.7)	584 (33.3)	2.9 (1.8-4.8)	<0.001
year (n=69)	28 (40.6)	41 (59.4)		
native (n=1319)				
non (n=1262)	814 (64.5)	448 (35.5)	2.9 (1.7-5.0)	<0.001
year (n=57)	22 (38.6)	35 (61.4)		
Non-native (n=503)				
non (n=491)	355 (72.3)	136 (27.7)	2.6 (0.83-8.2)	0.089
year (n=12)	6 (50.0)	6 (50.0)		

Note: p — level of significance achieved when comparing groups (Pearson test $\chi 2$).
Note: p — level of significance achieved when comparing groups (Pearson test $\chi 2$): OR-odds ratio with 95% Confidence Interval.

Table 6

Maternal risk factors for congenital heart defects in infants, n (%)

	There is no vice	There is a vice	p
Module 1 Aggravated obstetric anamnesis			
Non risk factor	610 (66,7)	305 (33,33)	0,381
There is a risk factor	587 (64,7)	320 (35,3)	
Module 2 Pregnancy pathology			
Non risk factor	80 (65,6)	42 (34,4)	0,976
There is a risk factor	1117 (65,7)	583 (34,3)	
Module 3 Environmental hazards			
Non risk factor	937 (66,1)	480 (33,9)	0,471
There is a risk factor	260 (64,2)	145 (35,8)	
Module 4 Maternal health disorders			
Non risk factor	579 (65)	312 (35)	0,530
There is a risk factor	618 (66,4)	313 (33,6)	
Module 5 Mothers bad habits			
Non risk factor	1106 (66, 2)	564 (33,8)	0,114
There is a risk factor	91 (59,9)	61 (40,1)	

Note: p — level of significance achieved when comparing groups (Pearson test $\chi 2$).

of children without congenital heart disease and with confirmed heart disease, no statistically significant differences in the frequency of risk factors were found (Table 6, p>0,05). Segregation by ethnicity also showed no statistically significant dependence. The health quality of pregnant women was extremely poor regardless of ethnicity.

Genetic syndrome was observed in 24 children, of which in 14 cases the child had a confirmed congenital heart defect (p=0,013). The incidence of genetic syndrome in native children was 15 (1,1%) and 9 (1,8%) in non-native children (p=0,275). In native people, the presence of genetic syndrome was statistically significantly more often associated with the presence of confirmed congenital heart disease (Table 7). It should be noted that the absence of a similar association in non-native people may be due to a small number of observations with genetic syndrome.

No statistically significant differences were found in the incidence of multiple malformations between native and non-native children (5,2% in both groups, p=0,991). In 44 cases out of 94, children with multiple malformations had a confirmed congenital heart defect (p=0.009).

Table 7

Frequency of confirmed congenital heart disease in children with genetic syndrome, n (%)

Group	Genetic syndrome	Confirmed heart disease		p
		non	year	
Non-native (n=494)	non	356 (72.1)	138 (27.9)	0.276
	year	5 (55.6)	4 (44.4)	
Native (n=1304)	non	831 (63.7)	473 (36.3)	0.015
	year	5 (33.3)	10 (66.7)	

Note: p — level of significance achieved when comparing groups (Pearson test $\chi 2$)

Conclusion. Thus, according to the Perinatal Center of the Republican hospital №1 – The National Medicine Center, for the periods 2001-2003 and 2013-2015, the diagnosis of heart disease was statistically significantly more common in children of native parents. The presence of congenital heart disease in parents was associated with a greater frequency of confirmed defects in children. There are no statistically significant differences in the proportion of simple and complex vices in children of different nationalities. The health quality of pregnant women is characterized as “poor” regardless of ethnicity. No statistically significant associations were established between the studied perinatal factors and the incidence of congenital heart defects in children. Probably, genetic factors should be considered as one of the main reasons for the development of congenital heart defects in the native population of Yakutia.

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PSYCHOLOGICAL MARKERS OF THE RISK OF DEPRESSION DEVELOPMENT IN THE INDIGENOUS POPULATION AND MIGRANTS IN THE REPUBLIC OF SAKHA (YAKUTIA)

The aim of the study was to compare psychological markers of the depressive disorder in indigenous people and migrants in the polar regions of Yakutia. The study involved 50 healthy students of a medical college in the Khandyga village and 50 medical students who moved to Yakutia from the southern regions. The migrants were examined twice – during one month after the move and six months after the move. All participants completed a set of psychological tests that assessed their psychological personality traits and degree of depression. In all participants, the degree of depression positively correlated with scores of neuroticism and negatively with scores of extraversion, collectivism, and social activity. The first examination showed that migrants had an increased level of trait and state anxiety in comparison with the local people, as well as an increased degree of depression. Upon re-examination, the level of anxiety in all migrants significantly decreased. The dynamics of the degree of depression in the migrant group was multidirectional. For a majority of migrants, the degree of depression decreased significantly, but for 11 of them it increased. The group of migrants with an increased level of depression was characterized by low values of collectivism and family attachment in comparison with migrants whose degree of depression decreased. In general, according to the results of the study, it can be concluded that an increased risk of depression in both the indigenous population and among migrants was associated with low scores on many scales of psychological tests, reflecting the level of social activity of an individual. The study is executed under support of grants of RFBR № 18-415-140021 и 18-29-13027. Study of A.N. Savostyanov also supported by budgetary project of ICG SB RAS № 0324- 2019-0040-C-01.T.

Keywords: predisposition to depression, migrants, polar region, neuroticism, collectivism, extraversion

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Introduction. Adaptation to extreme climates is often accompanied by increase in the risk of affective pathology, including disorders of the anxiety-depressive spectrum [5, 6]. Early diagnosis of such disorders is necessary for their timely prevention and reduction of negative consequences from morbidity. Until recently, most medical research on depression has focused on comparing clinical patients with healthy controls. Such comparisons have several significant drawbacks. First of all, they do not allow identifying those people who, for some reason, hide the symptoms of depression from others and do not seek medical help. In addition, clinical examinations are carried out on patients who are already receiving medication, which does not allow identifying the underlying causes of depression, since the effect of therapy distorts the ratio of various factors that determine the predisposition to the disease [31]. In this regard, it seems relevant to conduct research aimed at establishing markers of predisposition to depression in healthy people [13, 14, 20, 32].

Most often, as psychological markers of depression, individual assessments are considered on various scales of psychological tests proposed in the framework of the "Big Five" concept developed by G. Ayseng [15] and his followers [11, 26, 33, 27]. In a series of studies carried out under the guidance of G.G. Knyazeva [2, 4, 22] it was shown that such factor of the "Big Five" as neuroticism and its facets has a positive correlation with the risk of depression, and the assessments of extraversion and, in particular, agreeableness, on the contrary, negatively correlate with the risk of depression. With according most neurobiological concepts personal characteristics, markers "Big Five" primarily determined genetically [11, 26] , and slightly dependent on the formation conditions and the residence of the individual. On the contrary, sociocultural factors related to the choice of various moral and ethical regulators of human behavior turn out to be highly dependent on the social environment and can change during a person's life. Indicators of individualism and collectivism are often cited as such socio-culturally defined markers of depression [33, 17]. These two concepts relate primarily to the method of self-assessment of a person in the context of social relations. Collectivism reflects the desire of the individual to determine his own properties through belonging to a community (family, state, religious group, etc.). Individualism, on the contrary, is as-

sociated with the desire to define one's personality regardless of the collective. It should be noted that at the cultural level, collectivism and individualism are opposed characteristics [29]. However, at the level of individuals, these two indicators turn out to be orthogonal to each other, i.e. personal assessments of the severity of individualism and collectivism using psychological tests are not statistically related to each other [30] .

A number of studies have shown that collectivism and individualism are associated with neurophysiological indicators reflecting the functional state of the so-called structures of the "social brain" [23]. It has also been shown that these two psychological indicators change the relationship between behavioral, psychogenetic and neurophysiological markers of depression in non-clinical subjects [21, 25]. However, these relationships are not permanent and can change in different communities. Thus, for the majority of Asian samples, a significant negative dependence of the risk of developing depression on the level of collectivism was shown [18]. At the same time, G.G. Knyazev et al. showed that in Russia a high level of collectivism does not reduce the risk of developing depression [24]. Thus, the question of the role of sociocultural personality traits in the formation of the risk of depression remains open.

The aim of this study is to investigate the relationship between psychological markers of depression among healthy young people who have moved on long-term resident in a circumpolar e area s Republic of Sakha (Yakutia) from the southern regions, compared with people constantly Residential E in these regions. Severity of depression implicit symptoms has been well appreciated and we use the psychological techniques Beck and questionnaires for adults Achenbach. As psychological markers of depression, we have selected both the traditional indicators of the "Big Five" and the values of individual assessments of individualism and collectivism and related scales. We assumed that the selected indicators not only correlate with the severity of depressive symptoms in the nonclinical subjects we examined, but are also associated with the long-term dynamics of the severity of depression in migrants during their long-term residence in Yakutia.

Materials and methods. Survey participants: The survey involved 50 migrants who arrived in Yakutsk in 2018 (all men, average age 24.1±3.2 years). The migrants were examined twice. The first survey took place in September-October 2018, about a month after the migrants moved to Yakutsk, and the re-examination took place in April 2019, i.e. six months after their move. The first survey involved 50 migrants. However, three people subsequently left Yakutia and did not take part in the second survey. Most of the migrant participants arrived in Yakutia from the republics of Central Asia (Tajikistan - 28 people, Kyrgyzstan - 11 people, Turkmenistan - 4 people, Uzbekistan - 2 people). In addition, some migrants came to Yakutia from Egypt (5 people), Zambia (1 person) and Peru (1 person). All of the migrant participants were medical students at the North-Eastern Federal University. All migrants either received higher education in Russian, or were full-time students at NEFU, studying in Russian-language programs. As a control sample in 2019, a group of medical college students in the Khandyga village of the Tomponsky district of Yakutia (23 men, 27 women, average age 25.2 ± 3.1 years), which is officially classified as a region with an Arctic climate. All people gave their voluntary written consent to participate in the survey. The survey was conducted in accordance with the ethical standards of the Declaration of Helsinki on Biomedical Ethics. The survey protocols were reviewed and approved by the ethics committee of NEFU.

Psychological testing: All survey participants underwent psychological testing using a package of questionnaires and an implicit association test. To measure personality within the framework of the five-factor model, the “Big Five Factor Markers” questionnaire was used [10]. In addition, we used the well-known questionnaires for measuring personal anxiety (State Trait Anxiety Inventory) [7] and aggression (Aggression Scale) [10]. Emotional intelligence was measured using the questionnaire K. Barchard, translated and validated by Knyazev et al. [3]. To assess the severity of individualistic and collectivist tendencies, two questionnaires were used. The first is the well-known questionnaire of Singelis’s (Self Construal Scale) [28] collective and independent self-concept. The second questionnaire measures the affiliation tendencies selectively towards the next of kin, or a loved one (RISC, The Relational-Interdependent Self-Construal) [12]. Both questionnaires have been translated and validated [1]. Depressive symptomatology used the Beck’s questionnaire (Beck depression inventory) [9], the Achenbach’s questionnaire for adults on the severity of a wide range of psychopathological symptoms (Adult Behavior Checklist) [8], and the WHO Self-Reporting Questionnaire (SRQ20) [16] . The Holmes and Reich questionnaire [19] was also used to measure sensitivity to stress and the presence of stress in the environment. It should be noted that the results of psychological testing were thoroughly checked when re-examining migrants. According to the indicators of personality scales, which should not change under the influence of adaptation (extraversion, neuroticism, responsibility, intelligence, etc.), high values of the coefficients of intrasubjective self-correlation were revealed ($r > 0.95$; $p < 0.0001$), which indicates that the participants understood the questions of the tests and about the meaningfulness of filling them out.

Statistical processing of results. For the definition the relationship between the risk of developing depression and personality and psychological characteristics of people calculated Pearson's correlation coefficients between individual scores of different scales of personality questionnaires and assessments on various scales s depression questionnaire Beck’s and Achenbach's questionnaire scales. However, we found that the scales of the Beck’s and Achenbach’s questionnaires were highly correlated with each other ($r > 0.4$; $p < 0.03$). Therefore, within the framework of this publication, only correlations of assessments of personality scales with assessments according to the total Beck’s scale will be presented.

To compare migrants and the indigenous population, a one-way ANOVA was used with the “group” factor (migrants vs indigenous population). For intragroup comparisons of migrants, repeated measures ANOVA was used with the factor “adaptation period” (first survey vs second survey).

Results. Correlation of the severity of depression with personality traits in both groups. In both groups of the patients, severity of depression implicit symptoms, rated by Beck’s questionnaire, showed a highly significant positive correlation personality traits Eiseng’s questionnaire: neurotism ($r = 0.43$; $p<0,0001$) and its anxiety ($r =0.34$; $p<0.0001$), instability to uncertainty ($r = 0.46$; $p<0.0001$), psychoticism ($r = 0.30$; $p<0.0001$) and impulsivity ($r = 0.28$; $p=0.001$) and irresponsibility ($r =0.29$; $p<0.0001$). Furthermore, the severity depression positive correlated well with the level neurotism by questionnaire “Big Five markers” ($r =0.24$; $p=0.003$), as well as the scale of anger ($r =0.25$; $p=0.002$)

and hostility (r =0.19; p=0.002) of the Bass-Perry's questionnaire.

Negative correlations were found between the severity of depression and the level of extraversion according to the Eiseng's test (r = -0.25; p=0.002) and its activity facet (r = -0.26; p=0.009), as well as for extraversion (r =- 0.36; p < 0.00010), friendliness (r =-0.24; p=0.003) consciousness (r =-0.27; p=0.001), and intelligence (r =-0.23; p=0.005) of the "Big Five marker" questionnaire. In addition, the severity of depression negatively correlated a with the collectivism index of the Singelis's questionnaire (r =-0.38; p<0,0001), and the level of affiliation tendencies selectively towards close relatives (RISC, r =-0.25; p=0.002) and also with the ability to empathy according to K. Barchard's questionnaire of emotional intelligence (r =-0.24; p=0.004).

Comparison of psychological indicators in migrants and the indigenous population. The severity of depression according to the summary Beck's scale in migrants during their first examination was significantly higher (11.6 ± 1.2) than among the indigenous population (7.2±1.2), F (1,97) = 6.31; p =0.014. Severity of depression among immigrants positively correlated well with the stress level (r =0.65; p <0,0001). Also, the level of personal anxiety according to the Spielberger's test was significantly higher among migrants (34,3 ± 1,0) in comparison with the indigenous population (25,1±1,0), F (1,99)=38.16; p <0. 0001. An increased level among migrants was also observed for the indicator of situational anxiety. In addition, migrants showed reduced, in comparison with indigenous populations, affiliation tendencies towards close relatives (RISC test, for migrants 4.3 ± 0.1; for indigenous people 4.8±0.1, F (1,99)=3,48;p=0,055) , a reduced level of teamwork (questionnaire Singelis, migrants 4,5 ± 0,1; native 4 9 ± 0.1, F (1,99) = 3.40; p=0 ,05), but an increased level of social activity (Iseng's questionnaire, 34.4 ± 0.8 among migrants; 32.1±0.8 among indigenous people, F (1,98) = 4.43; p=0.038).

Comparison of psychological indicators in migrants during their initial and repeated examination. The level of personal anxiety in migrants upon repeated measurement six months after moving to Yakutia was significantly lower (32.2±0.9) than during the first measurement immediately after the move (34.4±0.9), F (1,46) = 4.34; p=0.042. Similar changes were observed for the indicator of situational anxiety. All indicators of personality traits, as well as indicators of the severity of depression in migrants during the six months of their residence in Yakutia did not change significantly. However, when comparing the indicator of the severity of depression according to the Beck scale individually for each of the 47 twice surveyed migrants, it was noted that this indicator decreased in 29 people, increased in 15 people and did not change in 3 people. Thus, the severity of depression decreased and with s for most migrants, but one third of them, depression increased. We performed additional statistical analysis to find out which of the psychological factors may be associated with these differences. To do this, migrants in each of the scales of personality traits was conducted univariate ANOVA with the factor of "a group". Most of the analyzed personality indicators did not give any reliable effects on the dynamics of depression. Significant values were found for the collectivism index according to the Singelis's test and according to the affiliation tendencies towards the next of kin (RSIC test). The level of collectivism was the highest for migrants, in whom the severity o depression during their life in Yakutia decreased (4.8 ± 0.2), was slightly lower in migrants, in whom the severity of depression did not change (4.7 ± 0.4) and was significantly reduced migrants for which the severity of depression increased (4,1 ± 0.2), F (2, 46) = 3.35; p=0.044. Similar results were found for the RISC scale. An increase in the severity of depression is associated with a low severity of affiliation with relatives.

Discussion. General analysis of the dependence of the severity of depression on psychological personality traits in both groups, both migrants and the indigenous population in Yakutia, generally confirmed the results that were previously obtained by domestic [4, 16] and international [2, 6] researchers. Depression more pronounced as people with high neuroticism and its facets, as well as indicators of psychoticism and its facets. On the contrary, high values of extraversion, friendliness and intelligence are associated with low values of the severity of depression. However, we also revealed a significant relationship between collectivism and low severity of depression. According to G.G. Knyazeva [2, 4], such a relationship is not revealed for the Russian sample, although it is typical for respondents from Asian countries such as China [18]. It may be noted that the respondents surveyed by us are either

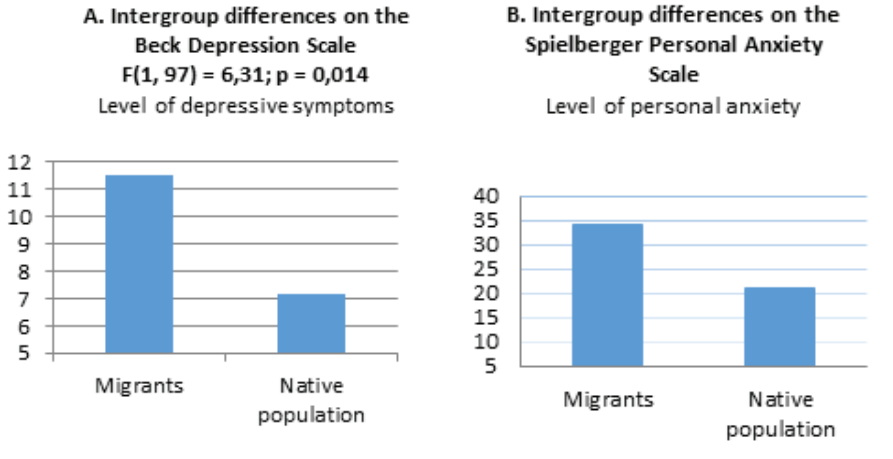

Fig. 1. Intergroup comparison of migrants at the initial examination and permanent residents of Yakutia in terms of the severity of depression (A) and the level of personal anxiety (B)

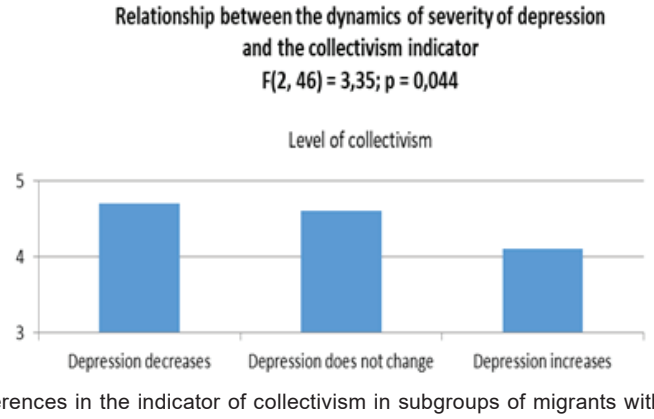

Fig. 2. Differences in the indicator of collectivism in subgroups of migrants with different dynamics of the severity of depression

indigenous population of Yakutia (Yakuts and Evenks), or are representative of s Asia (Tajiks, Uzbeks, Kyrgyz) or North African (Arab) nations. Accordingly, for this indicator, we got a result typical for Asian countries, but not typical for the Russian population of Russia.

In the first month after moving to Yakutia, migrants showed increased values of the level of anxiety and the severity of ьdepression. Six months after the move, the level of anxiety among the entire group of migrants significantly decreased, which can be considered as a result of adaptation to new conditions. The indicator of the severity of depression in migrants showed multidirectional dynamics. In a large migrants severity of depression decreased, but approximately 30%, on the contrary, has increased. Two psychological indicators of similar value - collectivism and affiliation with relatives - turned out to be significant for the formation of the dynamics of the severity of depression. Low levels of collectivism is a poor predictor of the dynamics of depression, when in the course of life in Yakutia depressive trend is growing, while a high level of teamwork and determines the decrease in severity of depression over time to adapt.

Conclusion. Thus, the collectivism indicator can be considered as one of the main markers that determine the risk of developing depression in migrants when they adapt to sub-extreme living conditions.

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SCIENTIFIC REVIEWS AND LECTURES

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ACTIVATION OF BROWN ADIPOSE TISSUE IN THE HUMAN BODY

This literature review presents current data on the influence of physiological factors such as cold, nutrition, and fasting on the activation of brown adipose tissue in the adult body, since the activation of this tissue stimulates human metabolism and can be a potential therapeutic method in the fight against obesity and concomitant diseases.

Keywords: cold, brown adipose tissue, thermogenesis, insulin, positron emission tomography, postprandial, obesity.

Introduction. Obesity is a major public health problem in this decade, reaching epidemic proportions not only in high-income countries, but also in middle-income countries.

According to the WHO, the number of obese people has more than doubled worldwide [37]. So, from 1980 to the present time, overweight and obesity are more frequent causes of death in 65% of people than underweight [10]. Obesity was found in approximately 1/3 of the adult population, the same number of people were found to be overweight [37].

Brown adipose tissue (BAT) is a unique adipose tissue whose main function is to generate heat by dissipating chemical energy. This tissue has been extensively studied in the past in small mammals and until recently it was believed that in humans, BAT is present only in newborns [6]. In addition, many studies have shown that BAT thermogenesis increases energy expenditure in mammals, affects excess lipids and fat accumulation. Active BAT is controlled by the sympathetic nervous system, in which the adrenergic response initiates the absorption of energy in fatty acids and carbohydrates in the BAT and stimulates thermogenetic activity. This activity is associated in particular with the hypothalamus and is regulated by a wide range of transcription factors and regulators. Currently, it is believed that BAT is active not only in small mammals and newborns, but also in adults. By scanning including recognizing and measuring the mass and activity of BAT in humans, current research has expanded the understanding of the prevalence, clinical correlations, activators and regulators of BAT systems. These findings prove the ability of BAT to be metabolically active in adults, and it is possible that this tissue could be a potential therapeutic option in the fight against obesity and metabolic disease. Cold activation of brown adipose tissue

In the human body, during fasting and at room temperature, the functions of brown adipose tissue are neutral in metabolic activity and are comparable to white adipose tissue [19, 32]. Cold is one of the most effective natural and physiological activators of human BAT [32]. In persons with active BAT during acute exposure in the cold, the temperature of the skin does not decrease in the supraclavicular region, in this area is the most significant depot of BAT in humans [35]. A number of studies have shown that the effect of cold increases energy expenditure at rest in the human body [14, 22, 27, 32], especially in individuals with high metabolic BAT activity in the cold [35].

A non-invasive combined PET/CT (positron emission tomography / computed tomography) imaging technique is used to determine tissue-specific BAT activity in humans in vivo. The physiological and metabolic functions of BAT can be determined using various indicators. The most commonly used BAT assay is quantitative tissue-specific glucose uptake or semi-quantitative 18FDG (18F-fluoro-D-deoxyglucose) uptake. The 18FDG indicator is a glucose analogue and its uptake provides an overall assessment of the metabolic activity of a tissue.

Acute exposure to cold increases the probability of detecting the metabolic activity of BAT, so in people with normal weight, this probability can be 60-90% [14,19]. In the absence of exposure to cold, increased metabolic activity of BAT can be detected only in 0,6-25% of patients [8, 12]. With regular daily exposure to the cold in the study group, the level of metabolic activity of BAT was increased [2, 9, 36], which was characteristic of natural seasonal acclimatization during the thermal winter.

Oxidative metabolism with active brown adipose tissue

Oxidative metabolism in BAT can be measured indirectly using 11C-acetate-PET or radio guides, as well as directly by measuring oxygen absorption in BAT using ^{15}O-O^2-PET [19, 22, 30]. Indicators of oxidative metabolism are more descriptive indicators of thermogenesis and oxidation of the mitochondrial substrate than the absorption of the substrate itself, since exposure to cold significantly activates oxidative metabolism [22]. Also, the perfusion of BAT significantly increases during cold weather, approximately twofold [19], which further confirms the increased oxidative role of brown adipose tissue when exposed to cold.

Thus, it was revealed that oxygen consumption was 50% higher in subjects with functionally active BAT - their tissue oxygen consumption was also high at rest compared to the control group with non-functional BAT [15]. In general, the oxygen uptake of BAT doubles during acute cold exposure along with double perfusion [30], and oxygen consumption and perfusion are interrelated. Taken together, they indicate the activation of thermogenesis in human FAT during exposure to cold.

Tissue-specific oxygen consumption can also be used to estimate the energy expenditure in BAT, which is strongly associated with the absorption of fatty acids by brown tissue both at cold and at room

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temperature [30]. Fatty acid absorption in FAT is measured using PET and 18F-fluoro-TIA-heptadecanoic acid (18F-FTHA), a palmitate analog that can enter either the intracellular lipid pool or directly into the mitochondria. During cold weather, activated BAT uses both glucose and fatty acids, but if intracellular triglyceride lipolysis is inhibited by nicotinic acid during cold weather, oxidative metabolism in BAT slows down and muscle tremors increase [4]. The importance of intracellular lipolysis for oxidative metabolism in BAT is additionally confirmed by the data that the radiodensity of BAT does not change with the introduction of nicotinic acid [4].

The X-ray density of tissue is measured by computed tomography (CT), which is measured in Hounsfield units (HU) for tissue as an indirect measure of triglyceride content. It was shown that after a 3-hour exposure to the cold, the subjects were found to have an increased level of HU, reflecting the degree of oxidation of one third of the intracellular lipid pool [22].

In mild cold (- $4C^0$), a high consumption of fatty acids in BAT was observed [3]. In addition, other methods such as magnetic resonance imaging (MRI) and proton spectroscopy (PS) can be used to assess the content of lipid profile and triglycerides in tissue. The content of triglycerides in BAT, measured using PS, is significantly lower in subjects with functionally active BAT compared to subjects with inactive BAT and is associated with the sensitivity of the whole organism to insulin [25].

Interestingly, when exposed to cold for 2 to 3 hours, lipid oxidation predominates [30], while prolonged exposure to cold (5 to 8 hours) in patients with functionally active BAT and increased insulin sensitivity increases glucose consumption [7].

Insulin-stimulated glucose uptake in brown adipose tissue. Despite the fact that cold is a powerful activator of BAT function, people do not currently spend significant time in the cold. A number of authors have found that nutrition and physical activity directly affect the activation of this tissue [5, 26].

Food intake is a complex chain of reactions in which the first signals of metabolic changes and the body's preparation for food intake and nutrient utilization occur even before the meal begins. The head phase of appetite and eating begins with the thought of food or the smell of food, accelerating the secretion of saliva. During this phase, a number of hormonal signals are transmitted, and among others, early release of insulin and peak insulin concentration are recognized [28].

Insulin also plays an important role after meals, in the postprandial state. After the first phase of increasing insulin, the concentration is gradually increased to facilitate digestion. Typically, in healthy people, the fasting plasma insulin level is approximately 3-10 IU/L (20-60 pmol / L), and in the postprandial state, the insulin level rises to 70-100 IU / L (420-600 pmol / L).

The postprandial level reflects the fasting level; the higher the fasting insulin concentration, the higher the postprandial concentration. Knowledge of postprandial insulin concentrations is used in an experimental setting, and the stimulation of insulin produced by the euglycemic hyperinsulinemic clamp is aimed at achieving an insulin concentration of 70-100 IU/L similar to postprandial clamping levels. During this type of insulin stimulation, the uptake of tissue-specific substrate can be measured by PET, and especially the rate of glucose uptake increases [17]. In part, the clamping stimulation of insulin can be viewed as mimicking the postprandial state, at least in terms of plasma insulin concentration.

Like cold, insulin activates the sympathetic nervous system (SNS), and through SNS activation, insulin can increase BAT thermogenesis. However, during steady state hyperinsulinemic clamping, BAT perfusion does not increase in the same way as when exposed to cold [19], suggesting that insulin may not have a direct effect on BAT thermogenesis. It is noteworthy that the steady state in hyperinsulinemic clamping is usually achieved 45-60 minutes after the start of the insulin infusion, and the acute effect of insulin may have already passed.Thus, BAT can be considered an insulin sensitive tissue type. Despite the fact that BAT is a small tissue in size and the contribution of this tissue to glucose consumption and to the sensitivity of the whole body to insulin is small, the rate of glucose uptake by insulin in BAT correlates with the M-value, a measure of the sensitivity of the whole body to insulin [19].

The effect of cold and insulin stimulation on BAT metabolism is somewhat different. Both stimulations increase the absorption of glucose by BAT and energy expenditure throughout the body [19], while the concentration of glucose in the blood plasma remains unchanged. However, with cold sympathetic activation results in high plasma fatty acid concentrations, and with insulin stimulation, a decrease to low fatty acid concentrations is observed. So, when exposed to cold, lipolysis predominates in adipocytes of white adipose tissue, and with insulin stimulation, it is suppressed by a high concentration of insulin. This is due to high plasma norepinephrine levels during cold periods, but such changes in norepinephrine concentration cannot be detected during insulin stimulation. Plasma insulin concentration is evidently high during hyperinsulinemic clamping, but during cold exposure, insulin levels decrease in all subjects, even those with higher fasting levels (obese and insulin-resistant subjects) [19]. The levels of thyroid hormones, thyroxine (T4) and especially triiodothyronine (T3), decrease during exposure to cold in patients with functionally active BAT [19]. No changes in the content of thyroid hormones were detected with insulin stimulation.Activation of brown adipose tissue through food intake and fasting

Food-induced thermogenesis refers to the production of heat that occurs in response to food intake. Thermogenesis reflects tissue respiration, in which mitochondria play a key role. Thus, tissues with a higher content and function of mitochondria have a greater contribution to thermogenesis of the whole organism.

The role of human BAT, which contains a large number of mitochondria, has been the focus of this debate, and it has been questioned whether BAT thermogenesis has any role in energy balance, especially in obesity. In the 1980s, results from studies in mice [26] prompted researchers to hypothesize that thermogenesis induced by fasting or food intake may explain why some people gain weight more easily than others [13]. However, the question of whether food-induced thermogenesis plays a role in human metabolism remains poorly understood.

During a diagnostic 18FDG-PET scan for tumor detection, the goal is to reduce the accumulation of the indicator by other metabolically active tissues. Such tissues include, in particular, skeletal muscle and brown adipose tissue. The accumulation of 18FDG tracer in BAT in diagnostic scans has been successfully reduced with beta-blockers [23], but equally effective results can be achieved by keeping the patient warm before and during the scan. In addition to premedication and controlled ambient temperature during scans, fatty foods have been used to reduce the uptake of 18PDHv BAT [34]. One group of patients (n = 741) prepared for a high-fat, very low-carb, protein-free diet scan, and another group of patients (n = 1229) was on an empty stomach. The high-fat group had a lower incidence of high uptake of 18FDG in BAT [34].

Thus, food composition can influence substrate preference in FAT, and the Randle cycle appears to function in FAT as well, in addition to other tissues such as myocardium and skeletal muscle [16]. Provided that a healthy person is given a high-calorie, carbohydrate-rich food, the postprandial uptake of 18FDG in BAT is higher than in subcutaneous or visceral adipose tissue [33], but it is not known whether the uptake of 18FDG after a meal is increased compared to the fasting state prior to a meal. In general, postprandial uptake of 18FDH remains lower than during acute cold exposure [33].

With oral glucose after 3,5 hours at ambient temperatures of 20 °C and 25 ° C, the insulin response appears to be higher at 20 ° C, based on the higher ratio of insulin to glucose at 2 hours of GTT (glucose tolerance test) [24]. At a temperature of 20 °C, the concentration of insulin in the blood of the subjects decreases, since the lipolysis process is activated by catecholamines, the glucose load can cause a pronounced and compensatory release of insulin in favor of glucose oxidation after exposure to moderate cold. However, insulin concentrations at various temperatures have not been shown, nor have the levels of catecholamines or fatty acids been measured, and therefore the previous assumption remains validated under controlled conditions.

Thus, postprandial FAT substrate uptake may be influenced by food composition, although postprandial insulin levels can be expected to be sufficient to increase glucose uptake by this tissue. Since glucose uptake is not an ideal indicator of thermogenesis, postprandial oxidative metabolism may provide a better understanding of food-induced thermogenesis. Thus, eating food with a caloric content within the normal range, with a predominance of carbohydrates, increases blood supply and oxygen absorption in the BAT as well as during cold exposure [29].Prolonged fasting for 54 h leads to a decrease in the cold-induced rate of glucose uptake in the BAT, which is approximately half the rate measured under normal ambient temperature [15]. In addition, obesity reduces the likelihood of detecting metabolically active BAT, and only 30% of obese patients have shown a significant increase in cold-induced absorption of glucose in BAT [20]. The metabolic activity of BAT in obesity is impaired, and insulin-stimulated glucose uptake is less than half of the absorption measured in subjects with normal weight [20]. It is possible that the brown adipocytes of obese subjects are transdifferentiated into white adipocytes completely filled with triglyceride, or isolation by thick subcutaneous adipose tissue in obesity is effective enough to prevent a similar degree of FAT activation than in lean subjects. On the other hand, some people may be prone to obesity due to poorly functioning BAT.

Recruiting BAT (browning) to other fat depots, such as visceral white fat depots or perirenal white fat depots, may be beneficial in the fight against obesity. Patients with morbid obesity have a lower content of uncoupling protein 1 (UCP1) in intraperitoneal adipose tissue than lean subjects [18]. Weight loss predominantly targets intra-abdominal fat, and thus UCP1 expression and function can be increased following weight loss at these depots. Routine weight loss through diet and exercise for 5 months results in a 12% reduction in baseline weight, while cold-induced metabolic activity of BAT tends to be higher than before weight loss [20].

It was found that in patients with severe obesity, bariatric surgery leads to a noticeable weight loss (by about 30% of the initial weight), and one year after surgery, the metabolic activity of BAT in these patients increases [31].

Conclusion. Modern studies on the physiology of brown adipose tissue have shown that the effect of cold increases energy expenditure at rest in the human body, especially in persons with a high metabolic activity of this tissue, which contributes to a decrease in body weight. The activation of brown adipose tissue most effectively occurs during exposure to cold, but in the modern world we spend less time in natural cold conditions, therefore nutritional factors can serve as inhibitors for the activation of this tissue. Short-term regulation of the functional activity of brown adipose tissue by nutritional factors is possible mainly due to insulin. Insulin helps to reduce the absorption of glucose in brown adipose tissue by 5 times under fasting conditions.The activation of brown adipose tissue most effectively occurs during exposure to cold, but in the modern world we spend less time in natural cold conditions, therefore nutritional factors can serve as inhibitors for the activation of this tissue. Short-term regulation of the functional activity of brown adipose tissue by nutritional factors is possible mainly due to insulin. Insulin helps to reduce the absorption of glucose in brown adipose tissue by 5 times under fasting conditions.

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SIGNALING FUNCTIONS OF FATTY ACIDS IN THE PLACENTA

This review summarizes the current understanding of FA-activated signal transduction systems in the placenta. Their effect on membrane and nuclear receptors, as well as their participation in the processes of decidualization and modulation of inflammation in the placenta, associated with G-protein-coupled receptors, has been shown. The effects of peroxisome proliferator-activated receptors mediated FAs in the placenta are described. Particular attention is paid to the Toll-mediated inflammatory signaling pathways of the FAs in the placenta. Research data on the effect of FAs on the expression of genes involved in placenta angiogenesis are summarized.

These data demonstrate that FAs and their derivatives are signaling molecules that regulate the metabolic and inflammatory processes in the placenta through a family of trans-membrane receptors associated with G-protein and Toll-like receptors that activate pro-inflammatory transcription factors: activating protein-1, nuclear factor kappa B and anti-inflammatory nuclear transcription factors - PPAR. Saturated FAs and unsaturated FAs in the placenta activate inflammation and apoptosis via TLR2/TLR4, while ω-3 polyunsaturated FAs inhibit their expression and further pathways of inflammation, which is associated with their anti-inflammatory effect.

In this review, FAs are considered as signaling molecules involved in the regulation of implantation, placentation, trophoblast differentiation, angiogenesis, modulation of inflammation and apoptosis in the placenta, and the pathogenesis of pregnancy complications.

Keywords: lipids, fatty acids, receptors, signal transduction, pregnancy, placenta.

Introduction. It has now been established that FAs are not only structural components of cell membranes and energy substrates, but also act as signaling molecules that regulate cell function. FAs modify the activity of phospholipases, protein kinases, G-proteins, adenylate and guanylate cyclases, as well as ion channels and other biochemical events involved in stimulus-response interaction mechanisms.

The effect of FAs on the signal transmission pathway can be direct and / or indirect (by the catabolic conversion of arachidonic acid-AA to eicosanoids). However, studies clearly show that FAs themselves are molecules of the messenger and modulator of several signal transduction pathways [14, 25, 34].

FAs can function as signaling molecules, acting through receptors in the cytosol or on the cell surface. Most of the effects of FAs in the placenta are mediated by their nuclear receptors that regulate transcription. The interaction of nuclear receptors with the FAs ligand leads to the formation of a ligand-receptor complex with subsequent translocation into the nucleus and activation of the expression of specific genes.

Depending on the structure of the carbon chain, FAs can act as inhibitors or activators of gene expression by directly regulating the activity of nuclear receptors (PPAR, X-receptor of the liver, nuclear factor of hepatocytes 4α) and transcription factors (sterol regulatory element-binding protein (SREBPs), protein binding elements sensitive to carbohydrates and NF-kB) or indirectly, through physicochemical changes in the properties of the membrane and activation of signal transmission paths [26].The study of the signal functions of FAs and their derivatives for a long time remains an important scope of an inquiry in medicine and biology due to the diversity and importance of the functions performed by these compounds. Despite the observed progress in this research area, comprehensive reviews, including new data on the mechanisms of signal transduction of FA in the placenta, have not yet been conducted.

The search for scientific publications in PubMed, Google Scholar databases was conducted. Information search was about the signal function of the FAs in the placenta. Notice has been focused on studies of FAs signaling pathways mediated by G-protein receptors (G-protein receptors 120, 41, 43), PPAR γ, Toll-like receptors (TLR2 and TLR4). Articles were searched in English and Russian using keywords in various combinations. All abstracts and full-text articles have been considered, and the most relevant are included in this review. The literature review used an analytical research method.

The action of fatty acids through membrane receptors. As pointed above, FAs can affect cells through several different mechanisms, including receptors on the surface of the cell. Recently, there is increasing evidence that FAs serve as natural ligands for a group of G-protein coupled receptor (GPCRs), which are called free FAs receptors, essentially intertwining metabolism and immunity in several ways, for example, by regulating inflammation and secretion of peptide hormones. Several receptors that are activated by free FAs with different chain lengths have been identified and characterized. So, A. Hirasawa et al. (2005) identified the G-protein receptor (GPR) 120 as a long chain polyunsaturated fatty acid (LC PUFA) receptor [15], which is involved in the regulation of various cellular and physiological functions, including during pregnancy, and mediates anti-inflammatory and insulin-sensitizing effects of docosahexaenoic acid (DHA) [10].

The data obtained in the study of the placenta in obese women showed that GPR120 is expressed mainly in the microvilli of human placenta and its expression level does not changes depending on the mother's body mass index. Thus, it was found that FAs in maternal circulation can affect the cellular transmission of trophoblast signals mediated by activation of the GPR120 receptor [13]. Other researchers have shown the involvement of GPR120 in the processes of decidualization during pregnancy. GPR120 stimulates decidualization processes by enhancing the absorption of glucose and the pentose phosphate pathway of human stromal endometrial cells. The

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enhancement of decidualization with GPR120, in researcher's opinion, can be mediated by the signaling pathway ERK1/2-MAPK-FOXO1 [29]. However, the functional significance and subsequent effects of GPR120 activation in the placenta have yet to be determined.

Other G-protein coupled receptors studied in the placenta are GPR41 and GPR43, which have been identified as short-chain FAs receptors (S-CFA). Studies conducted by C. Voltolini et al. (2012) showed the role of GPR43 expression in the tissues of the uterus and placenta, as well as the importance of S-CFAs themselves in modulating inflammatory reactions in the in fetuses born to women at term and in preterm delivery. At the same time, there was an increased expression of GPR41 and GPR43 in the myometrium and fetal membranes in women with preterm birth. The action of S-CFAs contributed to a decrease in lipopolysaccharide-induced expression of inflammatory genes, including IL-6, IL-8, COX-2, IL-1α, intracellular adhesion molecule-1, and platelet-endothelial cell adhesion molecule-1 [4]. Thus, while studying the interaction of GPR43 - S-CFAs, the authors showed new ways of regulating inflammatory processes during childbirth.

The action of fatty acids through nuclear receptors. Other mechanisms associated with the effects of FAs relate to their ability to bind to PPAR. There are three PPAR isotypes: PPAR*α*, PPAR*γ* and PPAR*β/δ.* Several studies have demonstrated the role of PPAR in implantation, placentation, trophoblast differentiation, and angiogenesis [35]. PPAR*γ*, like other nuclear receptors, binds lipophilic ligands and regulates transcription in the active state. Among endogenous PPAR*γ* ligands, unsaturated, oxidized, and nitroxylated FAs, AA metabolites were found: 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, 15-hydroxyeicosatetraenoic acid, 9-hydroxyoctadecadienoic acid, 13-oxo-octadecadienoic acid, phosphatasidinoic acid, components of oxidized low-density lipoproteins (LDL) [34]. Some studies show that PPAR*γ* are able to bind not one specific FA, but whole FAs patterns, including two FA molecules simultaneously. Such binding of the ligand, according to the researchers, indicates that PPAR*γ* is not a specific factor of FA alone, but a sensor of the intracellular mixture of FAs, the ratio of which may affect physiological processes. Moreover, FAs and their derivatives (eicosanoids) have been shown to regulate gene expression through direct interaction with PPAR*α* and PPAR*γ* [22].

Summarizing the results of studies about the role of PPAR*γ* in the processes of trophoblast invasion and the growth of human placenta, F. Wieser, L. Waite, C. Depoix, R.N. Taylor (2008) indicate that PPAR*γ* is expressed in the invasive trophoblast in the first trimester of pregnancy, while PPAR*γ* expression is shown in the syncytio and cytotrophoblast of the anchoring villi in the second trimester. In the third trimester, PPAR*γ* is localized mainly in the extravillous trophoblast and villus syncytiotrophoblast, where this transcription factor regulates the secretion of placental hormones [27].

The important role of PPAR*γ* in the differentiation of trophoblasts and the growth of placenta is also emphasized by studies using agonists. The main processes of placental growth were evaluated by V. Garnier et al. (2015) in the absence or presence of prokinetin receptor antagonists (PROKR) 1 and PROKR2. Both in human trophoblast cells and in placental explants, the researchers demonstrated that rosiglitazone, a PPAR*γ* agonist, increased secretion of EG-VEGF, expression of EG-VEGF mRNA and its receptors, and also increased the process of placental vascularization through PROKR1 and PROKR2; but at the same time inhibited trophoblast migration and invasion via PROKR2 [28].

J. Zhang et al. (2017) showed that PPARγ has a pro-angiogenic effect on the growth of animal placenta. This transcription factor mediates the vascularization process by modulating isoforms and receptors of vascular endothelial growth factor (VEGF): VEGF120/VEGFRs, VEGF188/VEGFRs and PlGF/VEGFRs by enhancing the expression of angiopoietin-1 mRNA. In addition, the authors suggest that PPARγ can interact with hypoxia-induced factor (HIF) and thereby activate VEGF transcription. Therefore, PPARγ can be involved in the process of angiogenesis by stimulating the adhesion, proliferation and migration of endothelial cells, as well as by enhancing the formation and stability of capillary-like tubules [25]. Thus, the researchers proved that different VEGF isoforms and VEGFR subtypes can be differently involved in different stages of the angiogenic process and differentially regulate vascularization processes.

PPARγ is also known for its role in promoting the accumulation of lipids in the placenta. An increase in PPARγ activity increases FAs absorption and accumulation in primary human trophoblast cells by regulating the expression of fatty acid binding proteins (FABP). In turn, it was shown that oxidized LDLs are able to activate PPARγ in primary cytotrophoblast cells and even inhibit trophoblast invasion [21]. Therefore, the authors conclude that PPARγ regulates and is itself regulated by lipid metabolites. At the same time, the potential role of PPARγ in the regulation of oxidative stress in the placenta across pregnancy is emphasized. PPARγ plays an important role in many metabolic pathways during placentation and across pregnancy. These include trophoblast differentiation, inflammatory and oxidative reactions, nutrient sensitivity, in particular FAs metabolism. Thus, one of the mechanisms of FAs signal transduction in the placenta is the regulation of gene expression by direct activation of the PPARγ nuclear receptor.

Toll-mediated signaling pathways of fatty acids in the placenta. FAs are able to stimulate an inflammatory response through the signaling pathway of Toll-like receptors (TLRs). TLRs refer to pattern-recognizing receptors that respond to the constituent elements of various pathogens, the so-called molecular patterns. In particular, they distinguish the molecular structures of various causative agents of infectious diseases, they are expressed on the surface of cells of the myelomonocytic line, endothelial and epithelial cells, as well as on the surface of placental cells, uterine and trophoblast epithelial cells [17]. The ligands of these receptors are both components of microorganisms and saturated fatty acids (SFA). SFAs are an important component of bacterial endotoxins. Lipid A lipopolysaccharide (LPS) contains 6 SFAs and 2 phosphate residues. The carbon chain length of these acids in lipid A varies from 12 to 16 carbon atoms. An interesting fact is that the replacement of SFA mono- or PUFA reduces the pro-inflammatory activity of LPSs. It was shown that SFAs acylated on lipid A of LPS or bacterial lipoproteins playing an important role in ligand recognition and activation of TLR4 and TLR2 [14]. A specific ligand for TLR4, which is a single chain transmembrane protein, is LPS from the wall of gram-negative bacteria. A specific ligand of TLR2 is a bacterial lipoprotein. In the process of binding TLRs to ligands, their coreceptors also have a role: CD14 (lacking an intracellular part) and MD-2, which increase the affinity and stability of the whole complex. The activated signaling transduction after binding of LPSs or bacterial lipoprotein is provided mainly by the adapter molecule MyD88 (myeloid differentiated factor 88). At the final stage of intracellular signal chains, there is a nuclear transcription factor NF-κB, which, moving from the cytosol to the cell nucleus, stimulates the expression of genes

encoding the synthesis of inflammatory regulatory substances, including cytokines, chemokines, and other components of the immune system [20]. However, it has been shown that TLR4 can also transmit signals independently of MyD88. This signaling occurs through an adapter protein containing a Toll/IL-1 receptor domain that induces IFN-β (TRIF), which not only activates the NF-κB pathway, but also leads to phosphorylation of regulatory factor-3 IFN (IRF-3) [17].

In human placenta, mRNA expression of ten TLR, coreceptors, and auxiliary proteins was established. However, we focused on the TLR4 and TLR2-mediated FAs signaling pathways in the placenta.

Currently, it has been established that SFAs and PUFAs differently regulate placental viability, antioxidant ability, inflammation and the effects of gram-positive and gram-negative endotoxins [32].

The combination of many studies shows the activation of TLR4 SFAs and their inhibition of PUFAs caused by both SFAs and LPSs. However, data were obtained proving the mutual modulation of the activation of TLR4 SFA (lauric - LA) and PUFA - (DHA) by regulating the dimerization and recruitment of TLR4 to lipid rafts. In addition, it was found that the dimerization and recruitment of TLR4 to lipid rafts were associated events mediated by the generation of NADPH oxidase-dependent reactive oxygen species. These results provide a new understanding of the mechanism by which FAs differentially modulates the TLR4-mediated signaling pathway and subsequent inflammatory responses that are involved in the development and progression of many chronic diseases [14]. X. Yang et al. (2015) investigated the effect of FAs on the synthesis and secretion of cytokines in trophoblast cells isolated from human placenta. It has been demonstrated that SFAs (stearic - SA and palmitic - PA) stimulate the synthesis and release of TNFα, IL-6 and IL-8 by trophoblast cells, while HUFA (palmitoleic, oleic - OA, linoleic - LNA) do not significantly affect expression of pro-inflammatory cytokines. Moreover, the authors note that palmitate-induced inflammatory effects are mediated by activation of TLR4, phosphorylation, and nuclear translocation of NF-kB [31]. In animal experiments, it was also shown that a high concentration of PA in the uterine endometrium induces the development of oxidative stress and high secretion of pro-inflammatory cytokines (IL-6, IL-8, TNFα) by activating the NF-κB signaling pathway [24]. Therefore, activation of TLR4 in the placenta leads to the recruitment of the transcription factor NF-kB and an increase in the synthesis of proinflammatory cytokines, and the induction of TLR4 pathways under the influence of FAs largely depends on the length of their carbon chain and the number of double bonds.

Other authors have shown that SFAs (LA, PA, and SA) can induce the expression of cyclooxygenase-2 (COX-2) via NF-kB-dependent mechanisms in macrophage cell lines. It was noted that LA had the highest ability to activate COX-2 via TLR4. Unlike SFAs, monounsaturated and PUFAs did not contribute to TLR4 signal activation. In addition, it was indicated that pretreatment of in vitro cells with DHA and OA significantly reduced the pro-inflammatory effect caused by LA and contributed to the reduction of inflammation [30]. The obtain results indicate that the TLR4 signaling pathway can be modulated by PUFA.

There is evidence showing the involvement of TLR2 in the induction of COX-2 and prostaglandin E2 in trophoblast cells via the NF-kB and MAPK pathways [33]. Thus, SFA and bacterial products (LPS) induce pro-inflammatory reactions by binding to TLRs, activating JNK and p38 MAPK signaling and downstream transcription factors.

Other options that FAs can function as TLR signaling pathway modulators are studies by S. Lager, F. Gaccioli, V.I. Ramirez (2013), who showed that OA regulates cellular signaling and placental transport of amino acids via TLR4, by increasing the phosphorylation of the JNK signal protein and activator of transcription 3 (signal transducer and activator of transcription, STAT3) [18]. Later it was found that DHA, OA and PA FAs differentially regulate trophoblast amino acid transport. DHA promotes inhibition of cell trophoblast signaling (p38 MAPK, STAT3 and mechanical target of rapamycin (mTOR) and amino acid transport activity. On the contrary, OA increases amino acid transport and phosphorylation of ERK, mTOR, S6 kinase 1 and rpS6. The combination of DHA with OA increases the transport of amino acids and phosphorylation of rpS6. PA does not affect the transport of amino acids, but it contributes to a decrease in the expression of Iκ-Bα [19].

Thus, FAs mediate the inflammatory response in the placenta via the TLR signaling pathway. However, the exact molecular mechanisms regulating pro-inflammatory reactions in the placenta remain to be determined.

Recently, research of TLR-mediated trophoblast apoptosis has been of great interest. It was shown that some pathogenic microorganisms can cause apoptosis in the trophoblast, and TLR mediate this process. In trophoblast, apoptosis can be activated via TLR2 and TLR4 [3].

Three microRNAs (miRs) have been identified that regulate TLR2-mediated responses in human trophoblast cells: miR-329, miR-23a and let-7c. Activation of TLR2 by bacterial peptidoglycan (PDG) induces the expression of miR-329, which plays a key role in the regulation of trophoblast apoptosis and inhibition of IL-6 expression by targeting the p65, the NF-κB subunit. Other researchers indicate that overexpression of TLR6 blocks apoptosis, production of IL-6 and IL-8 by trophoblast cells [3].

The results obtained indicate that TLR10 is highly expressed in trophoblast cells in early pregnancy, as well as the important role of TLR10 in stimulating PDG-induced apoptosis.

There are publications that show that trophoblast cells respond to the viral ligand via the TLR3 system. TLR3 is able to recognize mRNA of viruses located in the genital tract of women - herpes simplex virus, human papilloma virus, hepatitis B and C virus, cytomegalovirus, HIV. Data are also presented on the role of TLR2 in the identification of herpes simplex virus type I and cytomegalovirus [3].

The trophoblast apoptosis associated with the infection attracts close attention as an alternative mechanism of placental pathology. To date, there is enough information about the role of FAs in the implementation of apoptosis in trophoblast cells. It was shown that FAs can act either as inducers of apoptosis, in the case of a high content in the extracellular space, or inhibit this process in the placenta [8]. We found a cytomegalovirus-dependent induction of oxidative stress and an imbalance of FAs triggering apoptosis of trophoblast cells [1]. However, it should be noted that the molecular mechanisms of the implementation of cell apoptosis are determined not only by the action of free radical molecules, but also by a signal-transmitting system of lipid nature, including AA and PA. The induction of placental apoptosis in viral infection, apparently, is the result of the action of PA on the membrane of the endoplasmic reticulum, which, as shown by studies, causes modulation of lipid components and creates an unfavorable environment for the correct conformation of the protein, both along the proteasome and non-proteasome pathways. According to T. Liu et al. [24], PA can cause endoplasmic reticulum stress associated with increased expression of the proapoptotic transcription factor CHOP and activation of Akt.

According to Y. Zhang et al. (2011), PA induces caspase-3 and apoptosis [12], which is also confirmed by our studies [2]. The mechanism by which PA induces endoplasmic reticulum stress can be associated with TNF-induced apoptosis realized through activation of the nuclear transcription factor NK-kB [23]. The data presented emphasize the need for further research to elucidate the detailed molecular mechanisms underlying the FAs signal transduction in the placenta.

Fatty acids and expression of genes involved in angiogenesis. A number of studies have been conducted to research the effect of FAs on the expression of genes involved in angiogenesis. G.M. Johnsen et al. (2011) investigated the effect of PUFAs (AA, eicosapentaenoic - EPA, DHA and OA) on tube formation (as a measure of angiogenesis) and on the expression of genes involved in angiogenesis (VEGF and angiopoietin-like protein 4 - ANGPTL4) on the trophoblast cell line HTR8/SVneo. It was shown that only DHA upregulated the expression level of VEGF mRNA, while the remaining PUFAs stimulated the expression of ANGPTL4 mRNA. This study demonstrated that PUFAs selectively affects the placentation process through pro-angiogenic action [11]. Evidence of the selective effect of various FAs on angiogenesis, expression of lipid metabolic genes in a cell model was the study of S. Basak, A.K. Duttaroy (2013), which shows the dependence of the angiogenic properties of FAs (AA, EPA, DHA, OA) on their level of saturation. It has been demonstrated that DHA has the highest angiogenic properties; further, the angiogenic effect of FAs decreases in the following order: EPA>AA>OA [7]. It was also confirmed that DHA and conjugated linoleic acid (LNK) mediate angiogenesis in placental cells in the first trimester through stimulation of gene expression not only of the main angiogenic factors (VEGF and ANGPTL4), but also by increasing the expression of intracellular proteins that bind FAs (FABP), FABP4 and FABP3, which are known to directly modulate angiogenesis [5].

Studies of S. Basak, A. Sarkar, S. Mathapati, A.K., Duttaroy (2018) are also indicate the pro-angiogenic role of FABP4 in the cells of the first trimester placental trophoblast. They showed the effects of exogenously added FABP4 (Exo-FABP4) and its inhibitor (BMS309403) on cell growth, proliferation, and tube formation (as a measure of in vitro angiogenesis) in HTR8/SVneo. The dose-dependent pro-angiogenic effect of FABP4 was noted. Exo-FABP4 stimulated gene expression of pro-angiogenic mediators, such as a tissue inhibitor of matrix metalloproteinase-1 (TIMP1), insulin-like growth factor (IGF1), and prokinetin 2 (PROK2) [9].

It should be noted that the expression of FABP4 in trophoblast cells increases under the action OA, and VEGF [63]. It was also shown that expression of FABP1, FABP3, FABP4, and FATP2 is regulated by HIF-1α and/or HIF-2α in placentas of women with preeclampsia [16]. In addition, it was found that the c9, t11-cisLNA isomer can regulate angiogenic processes during early placentation through increased expression and other pro-angiogenic factors such as COX-2 and adipose differentiation-related protein (ADRP), with a concomitant increase in DHA absorption in these cells [6]. Consequently, PUFAs stimulate placental angiogenesis through gene expression of both major angiogenic factors (VEGF, ANGPTL4) and other pro-angiogenic mediators (FABPs, eicosanoids, COX-2, ADRP).

Conclusion. Thus, scientists are currently paying much attention to the mechanisms of signal transduction of FAs in the placenta. Despite a sufficiently large number of studies, many regulatory mechanisms and components of signaling systems in the placenta, associated with FAs and their derivatives, remain unknown. However, despite outstanding issues, convincing evidence suggests that FAs are a separate class of lipid mediators acting on PPARγ, TLR1, TLR2, GPR120, GPR41, GPR43 receptors that activate various signal transduction systems and have a wide range of regulatory effects in the placenta. PPARγ, TLR, GPR and other FAs receptors were involved in the processes of implantation, placentation, differentiation of trophoblasts and angiogenesis, modulation of inflammatory responses, placental apoptosis, pathogenesis of the most common disorders across pregnancy. This fact provides a sustainable interest to the study of FAs receptors from both fundamental science and the pharmacological industry. The presented data expand the understanding of the mechanisms of FAs signal transduction and emphasize the need for further targeted study of the unique aspects of FAs signal functions in the placenta, which will allow us to move from fundamental research to practical aspects of the use of these substances in obstetrics and perinatology.

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THE ROLE OF LEPTIN GENES AND LEPTIN RECEPTOR GENES IN THE DEVELOPMENT OF CHILD OBESITY

The role of polymorphic variants of the leptin (*LEP rs2167270*) and leptin receptor (*LEPR rs1137100*) genes in the development of childhood obesity and eating behavior was assessed. Eating behavior was assessed using the CEBQ questionnaire. There was no association with the development of obesity when comparing children's groups with each other. At the same time, the association of the *LEP* (rs2167270) was established according to the following scales of the CEBQ questionnaire: “pleasure from eating, EF”, “slowness in eating, SE” and glucose level. For the *rs1137100* locus of the *LEPR* gene, associations are shown with such anthropometric parameters as birth weight, weight at present, Z-score, and percentile level.

Keywords: obesity in children, eating behavior, CEBQ, polymorphism, leptin, leptin receptor.

According to the WHO, the number of childhood obesity cases has reached alarming levels in many countries and continues to grow (https://www.who.int/end-childhood-obesity/facts/ru/). Pediatric obesity remains an ongoing serious in Russian, especially in boys aged 11 years [4]. It was found that only 60% of the school children had a normal weight, the prevalence of obesity and overweight reached 40% and 10% of children with underweight.

It is known that the main cause of childhood obesity is energy imbalance as result from excessive energy intake (WHO https://www.who.int/end-childhood-obesity/facts/ru/). However, only physical activity and frequent consumption of fatty foods cannot be explained cases of familial obesity. Besides more than 79 obesity-related syndromes are known. Identification of genes for morbid obesity will allow for corrective therapy starting from childhood [9].

One of the most well-known genes for obesity is the gene for the peptide hormone leptin, which is responsible for anorexigenic action or appetite suppression. Leptin, on the one hand, reduces the formation of insulin, and on the other, it increases the sensitivity of cells to insulin. In turn, this may contribute to the development of insulin resistance and the formation of type 2 diabetes mellitus (T2DM) in patients with high leptin levels. The *rs2167270* polymorphic marker of the *LEP* gene correlates with leptin levels and is also associated with metabolic syndrome, T2DM and is a risk factor for cardiovascular diseases [5, 14, 16]. The polymorphic marker causing the *A* to *G* substitution at position -2548 upstream of the ATG start site in the 5'-region of the leptin gene promoter is responsible for altered expression. Thus, in comparison with the *G* allele, the *A* allele is associated with a twofold increase in gene expression [18]. Obese people develop leptin resistance; they have both high concentrations of leptin in the blood plasma and very low. High concentration can be the cause of leptin resistance and responsible for activating the molecular mechanisms underlying leptin resistance. On the other hand, a well-known leptin defect leading to structural disruption and a decrease in leptin levels lead to a constant feeling of hunger in patients and leads to obesity. The manifestation of leptin is also mediated by binding to the leptin receptor (*LEPR*) located on the membrane of hypothalamic cells [12]. *LEPR* belongs to the family of cytokine class receptors [13]. There are functionally significant polymorphic variants of the leptin receptor gene with a possible biological effect on metabolic regulation. The polymorphic marker *rs1137100* of the *LEPR* gene is located in exon 4 and leads to an amino acid substitution in the protein sequence (K109R). In our study, Kochetova OV, 2019, an association of the *rs1137100* locus of this gene with the BMI level in the population of Tatars with type 2 diabetes mellitus was revealed [1].

Leptin leptin interacts with hypothalamic receptors to induce satiety, inhibiting the neuronal activity of orexigenic neuropeptide Y (NPY) / agouti-related peptide (AgRP), and stimulating anorexigenic neuronal activity. Children's eating behavior is provided by both genes and the environment [17]. Martín-Pérez C, et al., 2018 revealed a violation of the functional activity of the hypothalamic-pituitary system during overeating and obesity in adolescents; eating disorders were determined using the CEBQ questionnaire [11].

The aim of our work was to analyze the associations of polymorphic variants of the *LEP* and *LEPR* genes with childhood obesity and the assessment of eating behavior in children.

Material and methods. The study used DNA samples from 380 children living in the city of Ufa. Of these, 170 are obese and overweight patients and 270 children without signs of obesity. The description of the samples is given in table. 1. The average age of children in the obese group was 7.1 ± 2.3 years, in the control group 7.3 ± 2.5 years (the age ranged from 2 to 10 years). Anthropometric measurement was carried out according to standard methods. To assess anthropometric status, reference tables of the World Health Organization (WHO) for 2006 and 2007 were used, which are based on Z-scores for body mass index (BMI) depending on gender and age. For statistical analysis, overweight was determined as follows: for children under 5 years of age (z> +2 points) (http://who.int/childgrowth/standards/ru/), for children aged 5 to 10 years (z > +1) (http://who.int/growthref/who2007_bmi_for_age/en/index.html). The sample was formed on the basis of a multidisciplinary hospital (City Clinical Hospital No. 17, Ufa).

Genotyping. DNA was isolated from peripheral blood leukocytes using phenol-chloroform purification. Conditions for PCR, primer sequences are presented in the study of M. Krylov et al., 2010 [2]. The results of amplification and restriction were assessed using vertical electrophoresis in 6–8% polyacrylamide gel. The gel was stained with a solution of ethidium bromide (0.1 μg / ml) for 15 min and photographed in transmitted ultraviolet light. To determine the size of the product, a molecular weight marker with a step of 100 bp (SibEnzyme, Russia) was used.

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Eating behavior analysis (BP) was carried out using the Child Eating Behavior Questionnaire (CEBQ) [8]. The questionnaire consists of 8 scales, such as: Food responsiveness (FR); Enjoyment of food (EF), Satiety responsiveness, (SR); Slowness in eating (SE); Food fussiness (FF); Emotional over-eating (EOE); emotional under-eating (EUE); Desire to drink (DD). CEBQ has good psychometric properties: internal consistency, test reliability, and dynamic stability. Used to analyze the eating behavior of young children.

Statistical processing of results. Statistical processing of the data was performed using the SPSS Statistics 22 software packages. The association between polymorphic variants of the studied genes and obesity was assessed using the Pearson χ^2 test. The groups of obese patients and children of the control group were compared in pairs. The frequencies of alleles and genotypes, the correspondence of the distribution of genotype frequencies to the Hardy – Weinberg equilibrium (χ^2 and P) were calculated. Logistic regression was used to identify the association of polymorphic variants of the studied genes with the development of obesity and eating behavior; the exponent of the individual regression coefficient (beta) was interpreted as the odds ratio (OR) with the calculation of a 95% confidence interval. The contribution of allelic variants of the studied candidate genes to the variability of quantitative clinical and biochemical parameters (glucose, lipid levels, etc.) and CEBQ scores was determined using the Kruskal-Wallis test (in the case of three groups) or Mann-Whitney (in the case of two groups).

Results and discussion. An analysis was carried out for the correspondence of the frequency distribution of the genotypes of polymorphic loci to the Hardy – Weinberg equilibrium, and the frequency of a minor allele frequency (MAF) was tested in the patient and control samples. The following results were obtained in control group: for *LEPR rs1137101* gene (PX-B = 0.06, MAF=0.3019), for *LEP rs2167270* gene (P=0.53, MAF=0.3241), in the group of patients for *LEPR rs1137101* gene (PX -B = 0.23, MAF = 35.59) and for *LEP rs2167270* gene (PX-B=0.23, MAF=35.59).

N is the number of individuals in the group. P * is the significance level comparing the frequencies of alleles or genotypes of the control group and the group of patients, P ** is the significance level of the Armitage trend test, P *** is the significance level adjusted for gender, age of gestation, and feeding. Statistically significant differences (P<0.05) are marked in bold.

The analysis of the scales of the CEBQ questionnaire showed differences in the compared groups of children in terms of the indicators Food responsiveness (FR) (P=0.01) and Enjoyment of food, (EF) (P=0.03). These indicators determined low satiety, increased appetite and interest in food, that contributes to the development of obesity. Hirsch Ya. V. et al., 2018 confirmed the results [3]. Analysis of allele and genotype frequencies for polymorphic markers of *LEP* and *LEPR* genes between overweight children and the control group statistically significant differences were not obtained (Table 2).

Analysis of quantitative parameters of obesity and eating behavior (CEBQ) is presented in table 3. Statistically significant associations were also observed for gene *LEP* (*rs2167270*) with Enjoyment of food (EF) (P=0.03) and Slowness in eating (SE) (P=0.0096). Carriers of allele *A* had higher scores for the EF scale and low scores for the SE scale (Table 3). The association was also found with fasting glucose for the *rs2167270* locus of the *LEP* gene (P=0.032). Carriers of the *AA* genotype had high blood glucose levels, reaching 6.25 mmol/L. It can be assumed that allele *A* is an eating disorder risk allele in children, and also leads to the development of insulin resistance. Poitou C et al. (2005) showed a decrease in the leptin level in children with morbid obesity, carriers of the GG genotypes *LEP* (*rs2167270*) [15]. However, allele *G* was associated with decreased blood leptin levels according to other authors [6]. Our study confirms the absence of a relationship between *LEP rs2167270* gene polymorphic locus and the risk of obesity in children and indicates the ambiguity of the results obtained [7].

Associations with birth weight, current weight, Z-scores and percentiles were established for the *LEPR rs1137100* marker (P=0.02, P=0.032, P=0.028, P=0.04). Carriers of the genotypes *AA* and AG had a higher birth weight and currently weight, high Z-score and percentile levels. Obesity in adolescents was associated with both the *A* and *G* alleles [10]. *A* allele of the *LEPR rs1137100* locus is characterized by an increased level of leptin and impaired glucose tolerance in girls with an android fat mass; for the *G* allele, an association was found in girls with a gynoid fat mass[10]. Several studies have shown severe leptin resistance in obese that its level is much higher than in patients with obesity. The association is most likely associated with leptin resistance mediated by the leptin receptor.

Conclusion. These results indicate the association of polymorphic variants of the gene LEP with the nutritional characteristics of children (CEBQ) and glucose level and LEPR with anthropometric characteristics.

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Table 1

Clinical and biochemical characteristics of children

Parameters	Control group (N = 270)	Obesity (N=170)	P
Boys, N (%)	118 (56.2%)	92 (54.1%)	0.67
Girls, N (%)	92 (43.8%)	78 (45.9%)	0.71
Age, years	7.3±2.5	7.1±2.3	0.81
Weight, kg	19.7±3.5	22.4±2.6	**0.002**
Height, cm	113.1±8.9	106.8±7.3	0.08
Percentile	38.9±10.1	92.5±3.2	**0.0001**
BMI, kg / m^2	15.5±2.1	19.6±3.4	**0.0001**
Gestational age, weeks	39.1±1.1	39.0±1.4	0.78
Birth weight, g	3313±100	3376±110	0.69
CEBQ			
FR, Food responsiveness	1.9±0.47	2.2±0.77	**0.01**
EOE, Emotional over-eating	1.6±0.54	1.7±0.63	0.89
EF, Enjoyment of food	3.0±0.63	3.35±0.82	**0.03**
DD, Desire to drink,	2.9±0.84	2.8±0.81	0.13
SR, Satiety responsiveness	3.1±0.57	2.99±0.60	0.22
SE, Slowness in eating	2.5±0.58	2.6±0.70	0.94
EUE, Emotional Malnutrition	2.8±0.78	2.8±0.87	0.87
FF, Food fussiness	2.9±0.43	3.1±0.49	0.73

Note: - statistically significant differences are in bold, P - significance level.

Table 2

Frequency distribution of genotypes and alleles of LEP and LEPR genes

Genotypes and alleles	Obesity (N = 170) N (%)	Control (N = 270) N (%)	P*	P**	P***
	LEP rs2167270				
GG	73 (42.94)	126 (46.67)	0.63		
AG	73 (42.94)	113 (41.85)			
AA	24 (14.12)	31 (11.48)		0.07	0.66
G	219 (64.41)	365 (67.59)			
A	121 (35.59)	175 (32.41)	0.37		
	LEPR rs1137100				
AA	69 (40.59)	125 (46.30)	0.31		
AG	84 (49.41)	127 (47.04)			
GG	17 (10.00)	18 (6.67)		0.13	0.36
A	222 (65.29)	377 (69.81)			
G	118 (34.71)	163 (30.19)	0.19		

N is the number of individuals in the group. P * is the significance level comparing the frequencies of alleles or genotypes of the control group and the group of patients, P ** is the significance level of the Armitage trend test, P *** is the significance level adjusted for gender, age of gestation, and feeding. Statistically significant differences (P <0.05) are marked in bold.

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Table 3

Analysis of associations of polymorphic loci of genes *LEP, LEPR*, clinical and anthropometric parameters and eating behavior scales (CEBQ) in children

Parameter	*LEP rs2167270*			*P**	*P***	*LEPR rs1137100*			P*	P**
	GG	*AG*	*AA*			*AA*	*AG*	*GG*		
FR	1.82 (0.09)	1.81 (0.1)	1.95 (0.45)	0.89	0.72	1.78 (0.08)	1.90 (0.24)	2 (0.14)	0.51	0.12
EOE	1.53 (0.12)	1.73 (0.14)	1.69 (0.53)	0.58	0.75	1.52 (0.1)	1.86 (0.21)	2 (0.49)	0.16	0.07
EF	2.62 (0.2)	3.04 (0.13)	3.62 (0.41)	**0.03**	**0.04**	2.9 (0.13)	3.08 (0.29)	0.86 (0.75)	0.84	0.12
DD	3.12 (0.22)	2.79 (0.19)	2.92 (0.25)	0.52	0.15	2.87 (0.15)	3.5 (0.25)	2.75 (0.21)	0.34	0.36
SR	3.25 (0.12)	3.12 (0.17)	3.05 (0.39)	0.75	0.79	3.19 (0.11)	3.1 (0.25)	2.95 (0.15)	0.75	0.37
SE	2.92 (0.15)	3.75 (0.37)	2.64 (0.14)	**0.0096**	**0.045**	2.88 (0.12)	2.96 (0.25)	3.19 (0.58)	0.43	0.29
EUE	2.84 (0.19)	2.62 (0.19)	2.81 (0.43)	0.72	0.83	2.76 (0.14)	2.71 (0.31)	2.94 (0.68)	0.80	0.73
FF	3.05 (0.12)	2.81 (0.09)	3.38 (0.22)	0.063	0.19	2.96 (0.09)	3.11 (0.09)	3.12 (0.38)	0.49	0.56
ИМТ, kg/m^2	15.86 (0.31)	20.68 (2.25)	18.24 (1.18)	0.17	0.19	18.35 (2.07)	19.05 (1.38)	18.18 (1.03)	0.96	0.80
Age, month	52.11 (7.53)	56.55 (7.91)	28.36 (9.42)	0.2	0.14	47.35 (6.41)	63.12 (9.52)	26.58 (7.14)	0.076	0.04
Birth weight, g	3226.32 (109.4)	3237.17 (112.93)	3282.5 (169.04)	0.97	0.96	3248.19 (110.19)	3264.92 (112.13)	2855.56 (226.15)	**0.02**	**0.03**
Weight, kg	18.16 (1.68)	20.92 (2.31)	14.84 (3.47)	0.34	0.32	17.37 (1.52)	23.3 (2.88)	12.38 (1.94)	**0.032**	**0.03**
Z-score	-0.29 (0.3)	0.67 (0.35)	1.01 (0.92)	0.13	0.05	-0.22 (0.31)	0.78 (0.41)	1.53 (0.79)	**0.028**	**0.015**
Precentiles	40.06 (5.02)	55.44 (4.73)	60.13 (10.47)	0.059	0.06	70.74 (9.95)	52.21 (5.43)	44.12 (4.56)	**0.041**	**0.015**
Glucose, mmol /l	5.32 (0.23)	5.18 (0.16)	6.25 (0.45)	**0.032**	**0.04**	5.35 (0.18)	5.46 (0.22)	5.1 (0.38)	0.73	0.46

P * significance for the Kruskal–Wallis H-test, P ** significance for the Kruskal–Wallis H-test adjusted for gender, age of gestation, and feeding. Statistically significant differences (P <0.05) are marked in bold.

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RADIOMICS AND RADIOGENOMICS OF PROSTATE CANCER (LITERATURE REVIEW)

Imaging plays an important role in the detection, diagnosis and staging of cancer, as well as in treatment planning and therapeutic response assessment. In recent years, there has been considerable interest in the extraction of quantitative information from images in order to obtain more complete information about the phenotype of the neoplasm image. Research has demonstrated that deeper analysis can reveal new imaging features that can provide useful diagnostic and prognostic information as well as data on tumor size and volume. In addition, imaging phenotypes can be associated with genomic data, which contributes to understanding their biological basis, improving the accuracy of predicting clinical outcomes. The aim of this review is to provide an update on the application of radiomics-based approaches and to discuss the potential role of radiogenomics in prostate cancer.

Keywords: prostate cancer, radiomics, radiogenomics.

Epidemiology of prostate cancer. Death from cancer is the second leading cause of death in the world. In 2018, 9.6 million people died for this reason. Cancer is the cause of almost one in six deaths in the world.

Prostate cancer (PCa) is one of the most common malignant diseases in men. About 1.6 million cases of prostate cancer are registered annually in the world, and 366 thousand men die annually from this pathology. In connection with these data, more and more attention has recently been paid to the diagnosis and treatment of this pathology, both in the Russian Federation and abroad. High incidence rates of prostate cancer are noted in the USA, Canada and in a number of European countries, where it comes out on top in the structure of cancer in men. According to the National Cancer Institute of the USA, from 1986 to 1992. the incidence of prostate cancer among the white population increased by 108% and by 102% - for African Americans [1]. The global incidence of prostate cancer has increased in most countries, and this increase has been most pronounced in Asia, Northern and Western Europe [13]. In the Russian Federation, the incidence of prostate cancer is constantly increasing. In the structure of the incidence of malignant neoplasms in the male population of Russia, prostate cancer takes the second place, which corresponds to 14.5% of all diagnosed neoplasms in men.

In the last decade, an increase in life expectancy has been observed throughout the world [3]. From 2000 to 2015, male life expectancy increased from 64.1 years to 69.1 years worldwide [37]. This poses serious problems for global health, as some diseases, such as cancer, tend to develop with age [36]. It was found that 5% of men under the age of 30 and 59% of men over 79 years of age had PCa at autopsy [21]. It is a common and serious medical condition that poses serious challenges to the health care system.

Genetic predisposition, genomics and epigenomes in prostate cancer. Numerous studies, especially epidemiological studies, twin studies and large-scale genome-wide association studies (GWA study, GWAS) have demonstrated the genetic component of the etiology of prostate cancer [34]. In particular, epidemiological studies have found that a family history of prostate cancer significantly increases the risk of developing prostate cancer [33]; twin studies have shown that prostate cancer is one of the most inherited cancers [8]; GWAS identified locus of susceptibility to prostate cancer [11], such as the single nucleotide polymorphism (SNP) rs339331, which increases the expression of the RFX6 gene, which promotes the development of cancer, through functional interaction with the HOXB13 gene, the role of which is the normal development of prostate tissue, and changes in its structure, indicate a predisposition to malignant cell changes in the prostate) [4]; genomic studies have identified family mutations in *HOXB13* [5] and DNA repair genes such as *BRCA2, ATM, CHEK2, BRCA1, RAD51D*, and *PALB2* [14]. Moreover, differences in the incidence and outcomes of prostate cancer were observed in men from different racial / ethnic groups. Men of African descent had the highest rates of morbidity and mortality [6], which may be due in part to genetic factors [9].

Cataloging the genetic factors of PCa underlies the definition of disease subtypes and associated therapeutic strategies. Several large-scale genomic studies of primary prostate tumors and metastatic castration-resistant prostate cancer have revealed repetitive changes in DNA copy numbers, mutations, rearrangements and gene fusion [10], [35]. Primary tumors of the prostate gland and metastatic castration-resistant prostate cancer are characterized by an increase in the altered copy number across the entire genome, but show only a small increase in the number of mutations [15]. Genetic changes target the AR, PI3K - PTEN, WNT pathways, as well as the repair of DNA and cell cycle components in almost all metastatic prostate tumors and in a high proportion of primary prostate cancer [16].

Radiomics and radiogenomics of prostate cancer. Imaging plays an important role in the diagnosis and staging of cancer, as well as in patient treatment planning and therapeutic response assessment. Recently, there has been considerable interest in extracting quantitative information from images that conform to the standard of clinical care, i.e. radiomics, in order to provide a more complete characterization of tumor image phenotypes. Several studies have demonstrated that

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deeper radiome analysis can reveal new imaging features that can provide useful diagnostic and prognostic information beyond standard data on tumor size and volume. In addition, imaging phenotypes can be linked to genomic data, that is, radiogenomics, to understand their biological basis or further improve the accuracy of predicting clinical outcomes.

The purpose of this article is to provide a brief overview of the progressive changes in the application of approaches to radiomics and to discuss the potential role of radiogenomics in PCa.

The shift of interest from qualitative interpretation of medical imaging with a bias towards obtaining quantitative information to medical imaging (radiomics) is due to the hypothesis that macroscopic heterogeneity in the image reflects the biological diversity of the underlying disease [25, 29]. The use of radiomics in localized prostate cancer is particularly interesting given the widespread but underutilized use of imaging. Currently, the main method of risk stratification in men is the diagnosis of localized prostate cancer. A "diagnosis of prostate cancer" is made after evaluating the biopsy material, serum PSA levels and clinical staging [12]. However, the complex anatomical structure and incomplete tissue sampling leads to spatial sampling bias when using standard biopsy methods. This high level of misclassification is thought to be due to spatial heterogeneity.

In addition to morphological variability, there is growing evidence of the existence of genetic heterogeneity in prostate cancer in the same patient [32]. An insufficient assessment of biological heterogeneity can lead to an underestimation of the risk in localized PCa.

Thus, prognostic tests are needed that can provide a complete model or complement current therapies for prostate cancer.

Multiparameter magnetic resonance imaging is the standard imaging technique for detecting localized disease and demonstrates high sensitivity in identifying and localizing lesions in the prostate gland [20]. Despite its high sensitivity, multivariate MRI (mpMRI) is limited to false positives.

Radiomics refers to a method for extracting higher order objects from images. There are several functions of radiomics - this is extraction from medical images based on the research task or research goal (Fig. 1). Scoring and scoring has remained a highly controversial topic in recent years due to the large number of functions available to use and changing implementation methods. The technical description and implementation of radiomic analysis is outside the scope of this review; however, brief descriptions of the features of radiomics relevant to study evaluation are listed below. From a methodological point of view, most can be classified as describing the intensity, texture, or shape of an area of interest.

The scheme of operation of the radiomics process consists of four main stages [2]:

- receiving and collecting images,
- image segmentation (the process of dividing a digital image into multiple segments (superpixels); accurate segmentation of the prostate is important for many applications, including radiation therapy planning, biopsy preparation, PSA assessment, and tumor localization. Ultrasound is most commonly used to visualize the prostate from because of its real-time implementation and low cost [30]. Because of this, many researchers have attempted to create semi-automatic and automatic segmentation algorithms to reduce workload and standardize results [19]. Recently, a number of studies have been segmentation of zonal structures prostate [38],
- extraction of features, their statistical processing (actually radiomics);
- 3D visualization and model creation [24] (Fig. 1)

1. Standard mpMRI analysis of the prostate includes T2-weighted images (imaging) (T2W), diffusion-weighted images (b2000) and calculated diffusion coefficient maps (ADC), dynamic contrast-enhanced imaging sequence (DCE) MRI.

2. Areas of interest are identified and the prostate is segmented. In the prostate gland, the areas of interest are its peripheral zone and then the transition zone, the urethra, tissues with normal structure, tumor focus or foci. Extracts the quantitative characteristics of the image associated with volume / shape

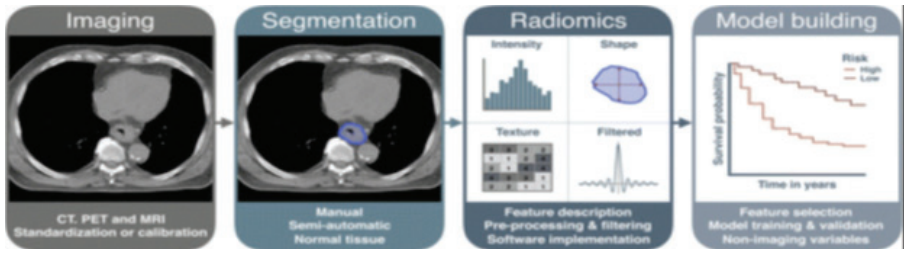

Fig. 1. Stages of the radiomic process using positron emission tomography (PET)

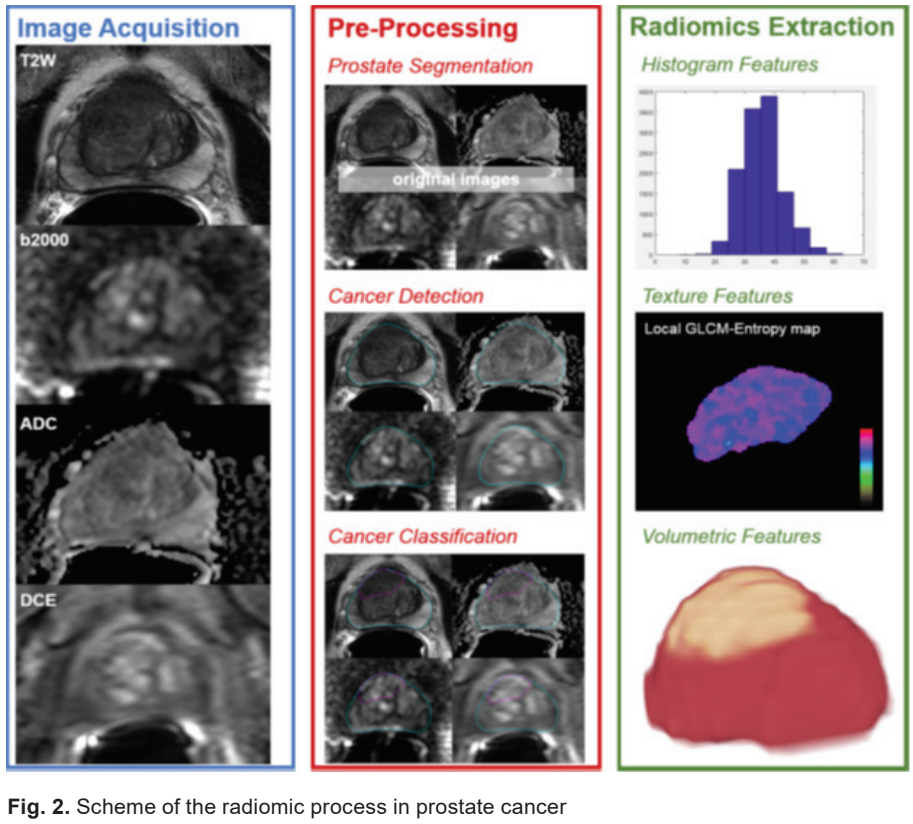

Fig. 2. Scheme of the radiomic process in prostate cancer

(shown in blue) or lesion volume (shown in pink), intensity volume histogram (first order functions), texture function (second order functions) and transformation analysis functions. Extraction of radiomic features can be performed on a voxel (voxel is a volumetric image element containing the value of a raster element in three-dimensional space) or a volumetric basis, depending on the method.

3. The data obtained through radiomic analysis is combined with clinical, genomic, proteomic and metabolic data.

4. The Scanning Diffusion Coefficient Map (ADC) is calculated on the MRI console.

The resulting images are transferred to an image processing station. There are many platforms for medical imaging. The choice of volumes for analysis affects the entire further analysis process.

Thus, radiomic analysis can become a "virtual biopsy", providing additional information about the disease, but not replacing the standard biopsy, which at the moment remains necessary for a more detailed analysis of the pathological process.

Radiogenomics in the diagnosis of prostate cancer/. In recent years, more and more articles have been published on radiomics in prostate cancer. The terms radiomics and radiogenomics are easily confused and are often used interchangeably. But both terms describe different areas of imaging. Radiogenomics was originally described as a method of linking pretreatment diagnostic imaging with genomic profiles that are associated with various toxic reactions to radiation therapy. The concept of radiogenomics has changed quite recently [31, 27]. The term “radiogenomics” is a combination of the morphemes “radiomics” and “genomics”. Radiomics is a technique for extracting visual cues from diagnostic images [28]. The data obtained can be used as non-invasive biomarkers for the detection [17], as well as for assessing the aggressiveness of prostate cancer [22]. Genomics provides a different approach to personalized medicine and correlates genomic profiles obtained from biopsy samples with clinical outcomes [26]. New technologies such as microarrays [23] and next generation sequencing (NGS) [7] are emerging, and genomic analysis is becoming widely available. Radiogenomic methods rely on information obtained from radiomic analysis to determine imaging biomarkers in order to predict genomic profiles [18].

Radiogenomics is an interesting new approach that can take oncology to a new level, from detecting cancer to predicting genomic systems that are associated with different clinical outcomes. The existing data on the diagnosis of prostate cancer are promising, but further research is needed in this direction.

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MICROARRAYS IN CLINICAL DIAGNOSTICS AND PROSPECTS FOR THEIR APPLICATION AS A SCREENING TOOL

Abstract. In this paper diagnostic microarrays and its application in various fields of clinical medicine are reviewed. The use of DNA microarray based diagnostics for carrying out the genetic carrier screening has been proposed.

Keywords: hereditary diseases, molecular genetic screening, biological microchips, practical medicine

Introduction. A series of outstanding discoveries: DNA and the genetic code gave a big impact to the development of genetics and methods in molecular biology. In 1977, Frederick Sanger developed the first in the modern sense of the method of DNA sequencing, which at that time was called the "chain termination method". Soon in 2001Human genome project were completed. In parallel with sequencing, after the discovery of the polymerase chain reaction in 1983, another method rapidly began to gain popularity and develop, which combines the developments of several areas from biology to electronics - microarray technology. Biological microchips are microarrays with various kinds of biopolymers deposited on a solid substrate as probes, and the biological material under investigation as targets.

There are two types of microchips, high and low density, which are widely used in basic research and in various fields of clinical medicine. High density microarray fabrication is characterized by the synthesis of probes directly on the substrate. For example, the GeneChip microchip photolithography technology developed by Affimetrix is designed to analyze large DNA fragments and the entire genome of an organism. Such types of microchips require expensive equipment and specially trained bioinformatics specialists to interpret a huge amount of information [21].

A slightly different approach is used in the manufacture of low-density microchips, in which the probes are applied to the prepared substrate surfaces. In clinical medicine, low-density microarrays are gaining more and more popularity due to their low cost and specificity of the studied DNA fragments.

Application of biological microchips in practical medicine. A significant part of ongoing genetic medical research is currently aimed at diagnose monogenic and multifactorial diseases caused by point mutations in the genome - single nucleotide polymorphisms. DNA microarrays are used to identify mutations and genetic polymorphisms to detect hereditary diseases, hereditary predisposition to various widespread diseases, for example, diabetes, cardiovascular diseases, oncology, ophthalmology, as well as for the diagnosis of infectious diseases. Table 1 presents a list of diagnostic microchips developed for use in clinical medicine.

Gene expression profiling using DNA microarrays provides information on the relative differences in gene expression between two different cell populations, for example, in a comparative analysis of certain drugs tested on cultured cells, or a comparison of gene expression in cancer cells with normal cells. The human genome is made up of 3.2 billion nucleotides. According to some estimates, it contains about 10 million nucleotide substitutions - the so-called single nucleotide polymorphisms (SNPs). SNPs are distributed throughout the genome and can be used as genomic markers to find links between genes and diseases. SNP is essentially the replacement of one nitrogenous base in DNA with another. For example, guanine is replaced by cytosine, while all other bases located nearby remain unchanged. Since SNP can be located within one gene, or in several at once, therefore, the probe for the microchip must be designed in such a way that the entire genome is covered. This can be a serious obstacle to genome-wide analysis [34]

Microchips for the biomarker detection in multifactorial disease diagnostics. The discovery of new specific biomarkers associated with a specific disease is very important for making an accurate diagnosis and drug development. The search for a biomarker using a DNA microarray is carried out by analyzing a large amount of data on expression levels under various genotypic, phenomical, and environmental conditions, which makes it possible to identify a larger number of candidates. It allows the simultaneous identification of candidate biomarkers by analyzing differentially expressed genes in comparison with normal and pathological conditions. By carefully applying clinical specimens at different stages or conditions to the DNA microarray, it is possible to identify those

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Microarrays in clinical diagnostics

Classification / name	Disease /causative agent	references
Microarray for biomarker detection in multifactorial disease diagnostics	Crohn's disease	[11]
	Type 1 diabetes mellitus	[26]
	Oncological diseases, SNPs in the genes of the biotransformation, SNPs in the genes of the renin-angiotensin system	[3]
	Sporadic Alzheimer's Disease	[4]
	Breast cancer	[12]
	Chemotherapy resistance for uterine cancer	[36]
Microarray for infectious disease diagnostics	Tuberculosis and its drug-resistant forms; pathogens of HIV, hepatitis B and C, smallpox, 2 types of herpes simplex, anthrax, influenza A virus	[12]
	Oncogenic variants of human papillomavirus type 18 (HPV-18).	[33]
	Adenoviruses, bocavirus, Chlamydia trachomatis, coronaviruses types 229E, OC43, NL63, HKU1, human metapneumovirus (hMPV) types A and B, influenza A, influenza B viruses, influenza C - Mycoplasmae. 4, respiratory syncytial virus (RSV) types A and B, and rhinoviruses	[13]
	Neutropenia	[18]
	Resistance to the anti-tuberculosis drug Ethambutol	[25]
	Pathogens in Bacterial and Fungal Brain Infections	[9]
	AIV, NDV, IBV and IBDV for use in routine mass epidemiological monitoring.	[31]
Microarray for genetic disease diagnostics	Chromosomal disorders associated with developmental delay and congenital malformations (Down's syndrome, Patau's syndrome, Edward's syndrome, Turner syndrome, Klinefelter's syndrome, alpha-thalassemia syndrome, Charcot-Marie-Tooth neuropathy 1A, cri-du-chât syndrome, hereditary neuropathy with a tendency to paralysis from compression (HNPP), Prader-Willi syndrome, Rubinstein-Tybee syndrome, Williams syndrome, and Wolf-Hirschhorn syndrome)	[16]
	Gemoglobinopatiya	[30]
	Primary immunodeficiency	[32]
	Cystic fibrosis	[3,4]
	Tay-Sachs disease, Bloom syndrome, Canavan disease, Niemann-Pick disease, familial dysautonomia, torsion dystonia, mucolipidosis type IV, Fanconi anemia, Gaucher disease, glycogen storage disease type 1A, maple syrup urine disease, nonsyndromic hearing loss, familial Mediterranean hearing loss and type III glycogen storage disease	[15]
	Wilson's syndrome	[22]

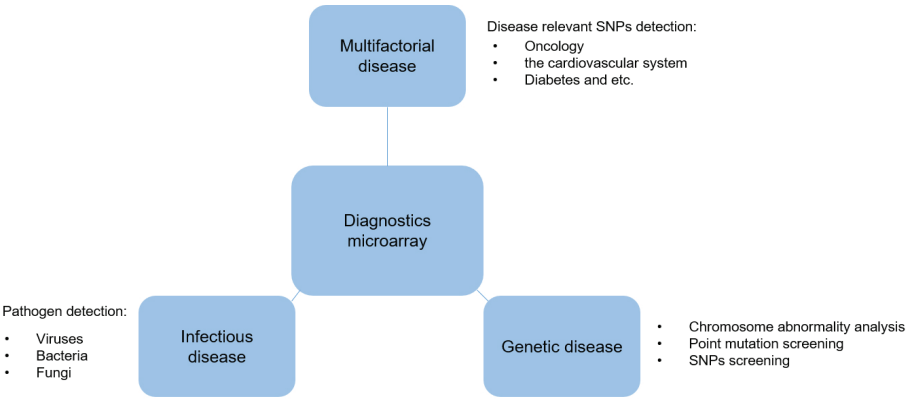

Fig. Application of diagnostic microchips in clinical medicine.

genes that are specifically associated with different stages of the disease. DNA microarray approaches for searching for biomarkers have been used to study several chronic diseases, including diabetes, arthritis, cardiovascular and oncological diseases. For example, biomarkers for the diagnosis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), which are chronic autoimmune and inflammatory diseases, can be tested by profiling expression in leukocytes, since differential gene expression in leukocytes is clearly related to SLE and RA. Osteoarthritis, a degenerative joint disease that can be confused with RA, can also

be diagnosed by leukocyte expression profiling. Based on these facts, Wohlgemuth et al. Developed a method for diagnosing and monitoring autoimmune or chronic inflammatory disease, especially SLE, based on differentially expressed genes. The selected genes were further studied by comparing them with clinical data. The nucleotide sequences of the selected genes were determined and used to diagnose these diseases [5]. Crohn's disease, ulcerative colitis, and inflammatory bowel disease (IBD) can also be diagnosed using biomarker genes selected from gene expression profiles using DNA microarrays. In particular, a diagnosis of high incidence and incidence of IBD is important for assessing prognosis and treatment. Mannick and his colleagues made a diagnostic chip for diseases based on sequences of overexpressed and underexpressed genes selected using high-density chips Affymetrix GeneChip.As a result, in patients with IBD, 25 sequences were identified as genes related to IBD, giving a sensitivity of 84% and specificity 100%. In Crohn's disease in patients with ulcerative colitis, 36 genes were identified as genes related to Crohn's disease with ulcerative colitis, giving a sensitivity of 89% and a specificity of 80% [11].

Scientists Natarajan and Myao have developed a DNA microarray to map histone modifications in the coding regions of genes involved in gene regulation and expression. They compared the patterns of histone modifications in the coding regions of disease-specific genes by analyzing the localization of the entire genome using chromatin immunoprecipitation coupled to cDNA microarrays. Were selected those genes that showed increased (more than 2-fold) and decreased (less than 0.5-fold) expression under certain conditions. This patent proposes a method for determining the risk of developing a disease by examining the presence or absence of histone modification (H3-K9 dimethylation) associated with type 1 diabetes, which is an autoimmune disease that can be accompanied by complications such as retinopathy, neuropathy and nephropathy [25]. In Russia, Institute of Molecular Biology. V.A. Engelhardt RAS microchips for the analysis of single nucleotide polymorphisms in humans with various diseases have been developed: a biochip for the diagnosis of lymphoproliferative diseases, microchips for detecting and diagnosing a genetic predisposition to the development of oncological diseases of various etiologies and for determining individual sensitivity to certain drugs, and others designed for the analysis of polymorphism in the genes of the biotransformation system, for the determination of polymorphism in the genes of the renin-angiotensin system and for hemostasis genes, and are used to analyze the genetic predisposition to the development of complications during pregnancy [1]. A biological microchip has been developed to study the hereditary predisposition to the sporadic form of Alzheimer's disease. The biochip is capable to detect 10 polymorphic markers in the *APOE, TOMM40, APOJ, EXOC3L2, GAB2, A2M, CR1, BIN1* and *PICALM* genes. The genotyping procedure includes the amplification of the nucleotide sequences of the selected genes and subsequent hybridization of the fluorescently labeled regions with allele specific DNA probes, immobilized on a biochip [2]. A low-density microchip was developed, which contains markers of 132 genes that are differentially expressed in breast cancer and also associated with signs of a malignant tumor (cell cycle disorders, hormonal sensitivity, proteolysis) and the developed system has shown itself as an alternative way to diagnose breast cancer at an early stage [12]. Scientists from China proposed a method based on a low-density microchip, which allows to identify 83 differentially expressing genes that indicate resistance to chemotherapy in uterine cancer [36]. An oligunocleotide biochip was created by a Mexican group of scientists to detect 19 point mutations in the 5th, 7th and 9th exon of the *TP53* gene, which is a known oncogene and mutations in which lead to malignancy and are observed in most patients with various types of cancer, and this approach has been proposed as a screening tool and early detection of malignant cancer for timely treatment [23]. An oligonucleotide biochip was developed to detect the carriage of 182 mutations in the *LDLR* and *APOB* genes that cause hypercholesterolemia, which in turn leads to early diseases of the cardiovascular system [10].

Microchips for the infectious diseases diagnostics. DNA microarrays are widely used and improved in the field of diagnostics of various infectious diseases. So, developed at the Institute of Molecular Biology. V.A. Engelhardt RAS hydrogel microchips allow to determine the causative agent of tuberculosis and its drug-resistant forms; pathogenš HIV, hepatitis B and C (22 subtypes), smallpox, 2 types of herpes simplex, anthrax, infections of newborns, 30 subtypes of influenza A virus, including avian influenza H5N1 [24]. Scientists from the University of Mexico have developed a low-density oligonucleotide microchip for the rapid screening of oncogenic variants of the human papillomavirus type 18 (HPV-18) strain. The technology used in the development can be used to differentiate three possible phylogenetic branches of HPV-18 [33]. Scientists at University College Dublin described the development of a test system based on oligonucleotide microarrays for the simultaneous detection, differentiation and typing of 18 viral and bacterial respiratory pathogens, including 16 viruses and two atypical bacteria: adenoviruses, bocavirus, chlamydia (Chlamydophila) pneumoniae, coronaviruses of types 229 , NL63, HKU1, human metapneumovirus (hMPV) types A and B, influenza A, influenza B viruses, influenza C - Mycoplasmae. 4, respiratory syncytial virus (RSV) types A and B, and rhinoviruses [13]. A similar approach was used in the development of a microchip for the rapid diagnosis of bloodstream infections caused by bacterial pathogens in pediatrics and general therapy [27]. PCR amplification in combination with an oligonucleotide microchip was used to identify the bacterium Bacillus anthracis based on the ITS region in rRNA. Several studies have reported the use of microarrays to identify pathogenic yeasts and molds by targeting the ITS region in fungal rRNA genes [14]. In another study, a DNA microarray was created to detect and identify 14 common fungal pathogens in clinical specimens from neutropenic patients [18]. At the University of Barcelona, a method based on a DNA microchip was proposed for the simultaneous diagnosis of mutations in the embB gene, which indicates resistance to the anti-tuberculosis drug Ethambutol [25]. DNA microchip for the detection of 14 strains of bacteria (Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Haemophilus influenza, Stenotrophomonas maltophilia, Neisseria meningitidis, Enterobacter spp. Candida tropicalis, Candida glabrata, and Cryptococcus neoformans pathogens in bacterial and fungal infections of the brain [9].

Scientists from Kazakhstan have described a method for the rapid detection of viral diseases AIV, NDV, IBV and IBDV simultaneously for use in routine mass epidemiological monitoring [31].

Microchips for the genetic disease diagnostics. Foreign companies Affymetrix and Illumina present biochips for genotyping 2,800,000 and 1,000,000 SNPs, respectively. The technologies of these companies are based on the methods of allele-specific hybridization and allele-specific primer extension, respectively. In allele-specific hybridization,

probes are concentrated in the center of the mutation site so that the variable base is in the middle of the probe. This allows the formation of nonspecifically bound hybrids to be maximized, and the sensitivity of the probe to the target is significantly increased. Two probes are used to detect a specific SNP: one probe corresponds to one allelic variant, and the other probe is intended for the second allelic variant. The genotype is determined by analyzing the relative signal strength of the two probes. Despite this, Affymetrix uses about 20 probes for each SNP analyzed in order to obtain more accurate analysis results [20]. The same technology used for SNP analysis is used to genotype specific mutations that cause monogenic diseases. Biochip technology here effectively replaces labor-intensive and time-consuming sequencing technology. Considering the methods used in biochip technologies and sequencing methods, biochips have a number of advantages: they are cheaper, faster and less laborious. Diseases caused by chromosomal abnormalities include several types, such as Down syndrome (associated with chromosome 21), Edwards syndrome (chromosome 18), Patau syndrome (chromosome 13), Turner syndrome (XO) and Klinefelter syndrome (XXY), which leads to irreversible physical and mental abnormalities and even death. Microchips are widely used in cytogenetics to detect various chromosomal pathologies. For example, chromosomal microarray analysis (CMA) to detect variations in copy number, homozygosity, and triploidy, replacing karyotyping as a diagnostic tool for many cases where chromosomal is suspected. CMA is significantly more sensitive (from 10 to 100 kb) than traditional karyotyping (from 5 to 10 Mb). In addition, CMA does not require cell culture, which reduces processing time and is an excellent alternative tool when cell division is not available for analysis. This method can be used for various purposes, for example, to determine the cause of miscarriage or to identify aneuploidies such as Down's syndrome [7]. CMA uses comparative genomic hybridization (CGH) technology, a molecular cytogenetic technology that combines the standard cytogenetic karyotyping technique and the method of fluorescence in situ hybridization. CHG is based on a comparison of test and control DNA labeled with different fluorochromes, which mix in a 1: 1 ratio and hybridize on the metaphase chromosomes of a karyotypically healthy person. After chromosome isolation, the program automatically calculates the fluorescence ratio for each point of the chromosome and, based on the data obtained, builds a color-coded image. CGHs have been designed to cover the entire genome, for targeted analysis of known microdeletions / microduplications, and for known loci of inherited mutations [6]. Chip sensitivity depends on the size and type of probes used. The most common are oligonucleotide probes (~ 60 bp) or probes with single nucleotide polymorphism (SNP) (32-40 bp). Oligonucleotide probes can be used to cover the entire genome with an average resolution of about 35 kb. Modern SSG chips typically use a combination of copy number probes (oligonucleotides) to detect increases and decreases in copy numbers and single nucleotide polymorphism (SNP) probes to detect single nucleotide sequence similarity (homozygosity). The combination of probes detects a series of homozygosity between the maternal and paternal copies of each chromosome, which allows the diagnosis of triploidy, homogeneous disomy and consanguinity, and also improves the detection of low levels of mosaicism [8]. Several commercial CMA tests are available today, including GeneDx's GenomeDx CMA. GenomeDx can confirm clinical diagnoses, distinguish between de novo and familial cases, and assist in the prenatal diagnosis of high-risk pregnant women. This test takes three weeks to complete, and both blood and buccal scraping can be used as the test sample. GenomeDx is a full genome CMA containing 118,000 oligonucleotide probes that detect copy number variations [17]. LabCorp has developed the Reveal® microchip that detects chromosomal abnormalities associated with developmental delay and congenital malformations [29]. Scientists from South Korea have also developed a microchip for diagnosing chromosomal abnormalities that cause various diseases: Down's syndrome, Patau's syndrome, Edward's syndrome, Turner's syndrome, Klinefelter's syndrome, alpha-thalassemia, Charcot-Marie-Tooth disease, hereditary neuropathy with a tendency to paralysis from compression, Prader-Willi syndrome, Rubinstein-Tybee syndrome, Williams syndrome and Wolff-Hirschhorn syndrome [16].

A DNA microchip was developed for neonatal screening for hemoglobinopathy. The following approach to the manufacture of a microchip was used - a fragment of the human beta-globin gene was amplified and immobilized on a glass substrate, on which the solution was then applied with the test sample-labeled with a fluorescent dye oligonucleotide probes corresponding to either the wild-type or mutant alleles S, C, and E of the beta-gene. Globin [30].

Research team from the Netherlands, the United Kingdom and Thailand has developed a biochip for the diagnosis of primary immunodeficiency (PID), which is a group of heterogeneous diseases that includes more than 400 different monogenic hereditary diseases that affect the development and function of the immune system. Modern approaches to genetic diagnosis of PID are based on Sanger sequencing, next generation sequencing (NGS), and copy number variant (CNV) analysis. However, these methods are time-consuming, expensive and require complex data interpretation, which up to now limits the number of analyzes. For this development, the biochip platform of Illumina The Illumina Custom GSA was used, which includes 9,415 mutations in 277 genes associated with PID. The test system allows high-precision screening for known mutations in a short time and at a lower cost [32].

Also, the Alkor Bio group of companies (St. Petersburg) has developed a test system for detecting the 25 most common mutations in the CFTR gene “Cystic fibrosis-biochip” in the Russian Federation and Europe [3]. Every year biological microchips are being introduced more and more in various fields of clinical medicine. Many different types of microchips are being developed. Microarray technology continues to improve in terms of performance in terms of sensitivity and accuracy, and is becoming the most economical research method.

Prospects for the use of diagnostic DNA microarray in genetic carrier screening. Modern microchips can contain millions of markers for thousands of diseases, which makes it possible to significantly reduce the cost of screening diagnostics of the population. However, as noted earlier, due to the great complexity and laboriousness of the technology for printing microchips at the moment, they have not yet become widespread in clinical practice. In addition, since mass screening of people from various populations for thousands of genetic diseases (most of which are not common) is not an urgent task at this time. The most intensive introduction of microchips of medium and low print density, containing tens and hundreds of genetic markers. Such microchips have a relatively low cost and affordable printing technology, and also allow screening only for the most common mutations. In addition, the method of microchip DNA diagnostics has a high speed of analysis and high reliability of the results obtained, which, according to

scientists, ensures the future leadership of this method in the segment of DNA diagnostics.

In isolated populations, for example, in the Yakut ethnic group, there is an accumulation of certain forms of monogenic disorders caused by ethnospecific mutations, the frequency of heterozygous carriage of which significantly exceeds the global data [4]. In this regard, the development and implementation of new effective methods of DNA diagnostics is an integral task of medical genetic services. An excellent example is the research of scientists from Stanford University, who proposed the development of a microchip to identify ethnospecific mutations responsible for the occurrence of hereditary diseases common among the Ashkenazi Jewish population - Tay-Sachs disease, Bloom syndrome, Canavan disease, Niemann-Pick A, familial dysautonomia , torsion dystonia, mucolipidosis type IV, Fanconi anemia, Gaucher disease, glycogen storage disease type 1A, maple syrup urine disease, non-syndromic hearing loss, and glycogen storage disease type III [15]. Also, a research group of scientists from India developed a low-density oligonucleotide biochip to detect the carriage of 62 mutations of the *ATP7B* gene, characteristic of the Indian population, that are the cause of Wilson's syndrome. The frequency of heterozygous carriage of these mutations in India is 1: 90. In their development, the method of allele-specific primer extension was used. This development has already been introduced into the practice of clinical medicine in India for the diagnosis of Wilson's syndrome in the Indian population [22].

Programs to prevent the spread of hereditary diseases have been introduced and are being practiced in several countries. For example, such measures have been shown to be effective in reducing the incidence of β-thalassemia, sickle cell anemia by 70% in Mediterranean populations, and by 90% the incidence of TSD (Tay-Sachs disease) in the Jewish population in the United States of America and Canada [35, 19]. Currently used classically diagnostic methods such as PCR-RFLP, real-time PCR, sequencing methods have a number of disadvantages that limit the number of analyzes performed due to the laboriousness and high cost of consumable reagents, which greatly complicate the conduct of DNA diagnostics on a large scale and, therefore, the introduction of such preventive measures. Also, as we mentioned earlier, ready-made high-resolution microchips from large companies "Illumina", "Affimetrix", "PerkinElmer" and others include simultaneous detection for thousands and millions of SNPs, which makes them very expensive and not in demand in clinical the practice of a geneticist and a doctor of another specialty. To process the huge information obtained from these microchips, it is necessary to use special programs and trained personnel. Commercially available off-the-shelf microchips often do not correspond to the interests of research in a specific area, for example, in the Republic of Sakha, due to the specificity of mutations characteristic of the Yakut ethnic group, which have a high frequency in the region, but are completely rare for other populations in the world. Thus, the independent production of microchips at the workplace is very important for regions burdened with hereditary diseases for the detection of heterozygous carriers and application in molecular genetic screening.

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SURGICAL TREATMENT OF POST-OPERATIVE STERNOMEDIASTINITIS (LITERATURE REVIEW)

Postoperative sternomediastinitis is an infectious complication occurring after sternotomy with the sternal bone tissue and mediastinal tissues being involved into the infectious process, with the involvement or noninvolvement of superficial soft tissues and with the stable or unstable sternum. According to domestic authors [3], up to 8,000 reconstructive surgical operations for postoperative sternomediastinitis are performed annually in the developed countries. According to various sources, infectious complications occur up to 6.9% of cases [8]. Due to the rapid development of cardiac surgery in the late 20th century, the number of studies on postoperative sternomediastinitis has increased significantly. At present cardiosurgical patients are people of older age with multiple comorbid diseases determining a great number of risk factors, which lead to the complicated healing of surgically operated tissues. Postoperative sternomediastinitis morbidity increases the early in-hospital mortality to 7% as compared to patients having no inflammatory changes in the sternum with mortality rate of 1.8% [30], and the risk ratio of decreased long-term survival of patients after a deep sternal infection is 1.91 [30]. Postoperative sternomediastinitis aggravates the clinical status of the patient and increases the duration of the treatment, and the long-term expensive treatment of post-operative complications caused by cardiac surgery interventions makes us consider the economic dimension [15]. The cost of treatment of deep postoperative sternum infection doubles the cost of overall treatment of cardiac patients [15]. Thus in the US specialized centers this cost is about 500,000 dollars which even with an infection rate of less than 1% presents impressively high expenses for a country.

Keywords: thoracic surgery, postoperative sternomediastinitis, purulent complications of cardiac surgery

Historical stages of treatment of postoperative sternomediastinitis. First, sternomediastinitis was treated by an open method which included re-exploration and surgical revision of the wound with dressings of the wound applied constantly, and the expectation of spontaneous closure of the wound with granulations followed by epithelization. The treatment took a long time. The mortality reached 50%, with the death usually being caused by the development of sepsis, bleeding or the direct damage to the heart inflicted by the sharp bone fragments or the edges of the sternum [31].

Later a surgical treatment of the wound was proposed in combination with the system of continuous flow irrigation of the wound with antibiotics or antiseptics, among which 0.5% povidone-iodine solution was most often used. According to the data of foreign authors [34], treatment with the system of continuous flow irrigation of the wound lasted 12.7 days on the average, with 87% of such cases recognized as being treated effectively, 13% of cases characterized by sternal instability, and 13% of lethal cases due to deep infection.

Another technique suggested an open management after surgical treatment with further using a variant of musculoplasty, or with the preservation of the wound until complete granulation. In this case, the mortality rate reached 50%, and the development of a new technology for surgical treatment of the pathology in question was required.

In 1975, a radical surgical d-bridement of sternotomy wounds with myoplasty or omentoplasty but without continuous flow irrigation of the wound or open treatment were proposed, which decreased the mortality to 10% [14].

By the end of the XX-th century foreign researchers [22] offered a more active use of the surgical treatment technique applying reconstructive methods of

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plasty with muscle flaps or omentoplasty which allowed to decrease the mortality from 15.3% to 8.1%.

Gottlieb L.J. et al. [28] began to perform reosteosynthesis of the sternum using titanium microplates after the surgical treatment of the wound and a thorough sternum vascularization.

R. Wettstein et al. [26] performed a radical removal of the sternum along the cartilaginous joints of the ribs and the sternoclavicular joints using plastic surgery of the chest wall defect with flaps of the rectus abdominis muscle or the lat. His method resulted in early mortality of 5.1% and limited local complications in 44% of cases, which required minor surgeries. No recurrence of the disease was noted.

Later on, the risk for the recurrence of the disease in case of instantaneous surgical treatment was proven, and the double-staged treatment with reconstructive plasty after the wound infection resolution was recommended.

Vacuum therapy. In 1997, LC. Argenta and MJ. Morykwas [12] conjointly proposed negative pressure wound therapy for infected wounds, which in its turn, being used widely in clinical practice showed its efficacy and sufficient reliability in the management of wounds. Evenly distributed negative pressure provides complete drainage of the wound surface while the structure of the vacuum therapy system implies the restoration of the chest frame. The use of a porous material to fill the wound cavity allows the stress to be evenly distributed, bringing the wound edges closer together. At the same time, direct and complete contact of the bottom of the wound with the bandage, and the continuous removal of the wound discharge, stimulates metabolic processes in the tissues of the wound. As a result, swelling is reduced, creating faster wound clearance, reducing microbial colonization of the wound, and preventing recontamination from the skin.

Comparing the open method of treatment with the negative pressure wound therapy technique in patients with sternomediastinitis has confirmed that vacuum therapy accelerates decolonization of the infected wound, speeds up the decrease of C-reactive protein, reduces the mortality and shortens the treatment duration. Gorbunov V.A. et al. [9] carried out a comparative analysis of the continuous flow irrigation and drainage of postoperative sternomediastinitis method with the negative pressure therapy. The results of histological examination of wounds showed that during vacuum therapy, an increase in the lymphoid-plasmacytic reaction of the tissue and the proliferation of the vessels of the microvasculature are observed by the end of the second week of treatment, which is clinically manifested by the cleansing of the wound and the formation of granulation tissue.

Atkins BZ et al. [16] propose to use the negative pressure treatment system as preparation for reconstructive surgery. The use of this technique makes it possible to preserve the sternum tissue and to perform sternum reosteosynthesis in 50% of patients in the future, with the average duration of vacuum therapy before the debridement of the infected wound being 26 days. Domestic authors [10] note that the use of vacuum therapy in preparation for the reconstructive stage of surgical treatment can reduce the treatment time in half.

Today, vacuum therapy is actively used as an intermediate stage before the reconstructive myoplastic stage of surgical treatment of the pathology under consideration, allowing preliminary preparation of the soft tissues of the wound and sternum for the forthcoming surgical intervention [16].

Myoplasty in the treatment of postoperative sternomediastinitis. Foreign authors in the 90s of the XX century [23] proposed to perform plastic surgery of the chest wall defect with flaps of the greater pectoral muscles in sternomediastinitis, while achieving satisfactory functional and cosmetic results. The close location to the wound, sufficient muscle volume, and low difficulty in isolating the flaps further led to the most frequent plasty of the defect in this area by the pectoral muscles.

However, in the case of an extensive defect of the chest wall, flaps of the greater pectoral muscles are not always sufficient, since the latter are over-tensioned, especially in the distal regions where a residual space is formed, which may result in the failure of reconstructive surgery and requires a combination of various vascularized flaps.

Depending on the degree and extent of the lesion of the sternum, some authors [18] proposed to perform additional plasty with a flap of the rectus abdominis muscle; less often the broadest muscle of the back (latissimus dorsi muscle) is used, and myoplasty with a scapular skin flap is possible.

The role of the greater omentum in the management of postoperative infection of the anterior mediastinum and sternum. In addition to the myoplastic reconstruction of the chest wall, plasty of the chest wall defect with a flap of the greater omentum is carried out, especially in extensive defects of the chest wall.

A.B. Lee Jr. et al. [33] first proposed the use of the omentum in postoperative sternomediastinitis. Later on, omentoplasty found its application in the chest wall reconstruction and began to be actively used in thoracic surgery. The main advantages of the greater omentum are its big size, the ability to fill any cavities, a long pedicle and an abundant vascular and lymphatic network. However, Cartier R. et al. [11] revealed through experiment angiogenic activity of the omental lipid fraction stimulating the formation of new vessels in the ischemic tissue.

T. Krabatsch et al. [19] carried on the analysis of the omental flap vascularization in the postoperative period of the reconstructive surgery, which revealed the presence of vascular anastomoses of the advanced flap and surrounding tissues. At that, the greater omentum is characterized by a pronounced immunocompetent function, which makes it possible to isolate and eliminate the purulent process. Korymasov E.A. et al. [8] believe that the best method for reconstructive surgery stage in sternomediastinitis is omentoplasty in combination with a mesh implant.

R. Saltz [29] was the first to propose the laparoscopic extraction of the greater omentum flap with the aim of decreasing the injury rate, lowering the risk of postoperative complications and increaseing cosmetic efficiency, the idea which was later developed by the domestic and foreign authors.

A.A. Pechetov et al. [5] presented their own results of step-by-step management of sternomediastinitis. The first step is to perform the surgical treatment of the wound with the resection of nonviable tissues, economical resection of the sternum, followed by the complex therapy including the use of antibiotics, treatment of concomitant pathology, local treatment of the wound with bacterial contamination control. Provided that the wound is macroscopically clean and the bacterial load is less than 10^3, the second stage – final thoracoomentoplasty with endoscopic harvesting of the greater omentum flap - is performed. The authors pointed out minor local complications in 2 (14.3%) of patients; there were no severe complications requiring repeated surgery. No recurrences of the underlying disease were noted.

Complications of reconstructive surgery. Despite the long experience of myoplastic and omentoplastic reconstructive operations for sternomediastinitis, the recurrence of chest wall wound

infection is still possible. Meta-analysis conducted by J.J. Van Wingerden et al. [24] highlighted reoperation rate associated with flap necrosis or recurrent infection from 3% to 18%, mortality rate reaching 29%, chronic pain syndrome noted in 50% of patients, and postoperative ventral abdominal hernia present in 5% of cases.

According to [35], recurrent hernia with the rate of up to 21% is the most frequently occurred disease on the donor's side after laparotomy harvesting of the greater omentum flap, which can significantly affect the patient.

PC. Pairolero et al. [25] analyzed the treatment of 98 patients. 79 patients with myoplasty with various muscle flaps were analyzed, in 4 patients with omentoplasty and in 15 patients with omentomyoplasty, when assessing long-term results of treatment (on average 4.2 years), recurrence of infection was noted in 26% of cases.

Kokhan E.P. [4] believes that the recurrence of sternomediastinitis is due to the insufficient removal of the affected tissues of the sternum and costal cartilages and that improved diagnostics and active surgical tactics are required when the disease process becomes chronic.

P.R. Ringelman et al [21] assessed the remote results of sternomediastinitis treatment using omentomyoplasty in 48 months on the average. The study revealed constant dull pain and discomfort in the chest and shoulders in 51% of patients, feeling of numbness and paresthesia in the anterior surface of the chest in 44% of patients, instability of the chest in 42.5%, and general dissatisfaction with the quality of life in 36% of patients who could not perform the actions they carried out before the primary surgery. Besides, 52% of patients failed to return to previous work.

Current treatment of postoperative sternomediastinitis. At present, the treatment of postoperative sternomediastinitis requires a complex multidisciplinary approach of cardiac surgeons, thoracic and plastic surgeons. Still there is no consensus on the most optimal surgical technique and a universal treatment protocol [17]. However all researchers agree that the early sternotomy wound exploration with an extensive surgical treatment of the affected tissues is necessary.

At present, the most prevalent management of sternomediastinitis is a two-stage treatment [6] including an early initial surgical d-bridement of the wound, preparation of the wound for reconstruction, more often using vacuum therapy, with the final stage consisting of reconstructive surgeries preserving the sternum tissue or its complete removal. In case the bone tissue is preserved, the restoration of the sternum integrity is achieved by interrupted, Z-shaped or circlage sutures made with a surgical wire. Gorbunov V.A. et al. [9] also perform sternum reosteosynthesis using titanium nickelide clips with a memory effect. In case of the sternum tissue incompetence, reosteosynthesis is carried out with U-shaped sutures through the body of the sternum or cartilages on metal perforated plates. At this, the recurrence rate was 16.2%, while reoperations occurred in 5.4% of the observed cases.

According to domestic specialists [10], the extent of the sternum resection must be determined for each individual case depending on the degree of the sternal tissue and cartilages involvement into the inflammatory process, and the presence of concomitant pathology aggravating reparation of the bone. Belov Iu.V. et al. [10] very rarely recommend to resort to sternum extirpation with costal cartilages resection. The final stage of surgical intervention involves different types of myoplasty and omentoplasty with harvested flaps of greater pectoral muscle (pectoralis major) being used more often.

Carlesimo B. [20] reported positive remote results of myoplasty performed with flaps of pectoral muscles. Frequently enough the rectus and the lat are used for plasty of the sternal defect, while for the prevention of seromas, tissue adhesive was proposed for use at the point of flap harvesting. V.V. Golovteev et al. [2] offered to combine cellular implants with myoplasty in case of an extensive defect of the chest wall after removal of the sternum.

Domestic authors [1] use deepithelized fasciocutaneous flaps of the chest wall for sternal defects plasty. In superficial forms (osteomyelitis of the sternum and the ribs), E.A. Korymasov et al. [8] performs limited sequestrectomy and removal of ligatures, with further wound healing occurring by secondary intention. In deep forms, debridement of the mediastinum is carried out using vacuum therapy, and depending on the result of the wound cleansing the pus pocket is opened widely which leads to the adequate drainage of pus, removal of foreign bodies and abnormal tissues. After that, a reparative surgery for elimination of the cavity in the sternum or in the mediastinum along with stabilization of the sternum is performed. The second stage includes removal of ligatures after debridement therapy with negative pressure which is aimed at prevention of the impairment of external respiration due to the possible instability of sternocostal framework.

Foreign authors [32] propose a method of reconstructive surgery including myoplasty and the use of 3-4 titanium plates in order to preserve the skeleton and stability of the chest. Domestic authors [9] also highlight the importance of the restoration of the sternal structure on finishing the sternomediastinitis treatment as it maintains the satisfactory breathing biomechanics and allows to prevent such complications as hernias of the anterior chest wall.

M. Kalab et al. [27] effectively used allogeneic bone transplantation to stabilize the sternum, while other specialists successfully treated patients with extensive defects of the anterior part of the chest using cellular titanium implant.

Dornseifer U. et al. [13] described the cases of successful application of the free musculocutaneous flap of anterolateral femoral surface in sternomediastinitis treatment.

The efficacy of sternomediastinitis treatment, according to A.V. Potemkin et al. [7], depends on how soon the disease was diagnosed after the complications appeared, on the stability of the sternum and the extent of its damage, the condition of the surrounding soft tissues, concomitant pathology as well as the intensity of exudative and destructive inflammation. As E.A. Korymasov et al. [8] point out, one should strictly follow a certain sequence of steps and timely come up with the indications for the final stage of the reconstructive surgery to achieve a positive result in sternomediastinitis treatment. The above-mentioned measures can be provided if the continuity of patient's treatment is observed in the same thoracic surgery unit with the aim of implementing a comprehensive set of actions for the treatment of a purulent complication.

Thus, in spite of the long history and solid experience in the field of the pathology studied, some unsolved problems remain in the treatment of postoperative sternomediastinitis so far. Complications of transsternal approach are still possible regardless of the preventive measures taken during the cardiac surgery. Expensive long-term treatment of patients with this complication and frequently unfavorable outcome make the problem of postoperative sternomediastinitis extremely urgent. At the same time, the possibility of the infection recurrence after the treatment of the pathology under review can not be excluded, which indicates the necessity of further active development of

innovative technologies for the complex treatment of postoperative sternomediastinitis.

Summary. The study of the historical development of the treatment of postoperative sternomediastinitis, based on the literature data, was carried out. At the initial stages, open treatment of chest wounds was performed, then treatment was carried out using the flow-washing system, both methods were accompanied by a high incidence of complications and mortality. Later, a more active use of the surgical method of treatment in combination with volumetric reconstructive operations was proposed as the wound was cleared, which contributed to a decrease in the mortality rate (from 50 to 5.1%) from this pathology. However, the likelihood of complications of trans-sternal access and recurrence of infection persists regardless of the preventive measures taken during cardiac surgery. which indicates the expediency of active development at the present time of innovative approaches to the complex treatment of postoperative sternomediastinitis.

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POINT OF VIEW

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EFFECTIVENESS OF ANTIHYPERTENSIVE ARTERIAL THERAPY CONSIDERING EQUILIBRIUM OF CORTICAL PROCESSES IN THE CENTRAL NERVOUS SYSTEM AND PARTS OF THE AUTONOMIC NERVOUS SYSTEM

In the last 20 years, there has been no significant reduction in the level of cardiovascular diseases. At the same time, arterial hypertension and coronary heart disease are leading in the structure of overall morbidity. Various environmental conditions Influence the course of arterial hypertension and coronary heart disease. The latter is able to significantly potentiate emotional stress. In connection with the above, solving issues of effective therapy and secondary prevention play a significant role in the clinical management of patients suffering from cardiovascular diseases. However, in equal conditions, the clinical course of diseases differs in different patients. some individuals have more pronounced changes, while others have less. This may be due to the activity of the Central nervous system, the type of higher nervous activity, and the state of equilibrium of cortical processes. It is assumed that the course of hypertension may have its own characteristics in patients with different characteristics of excitatory or inhibitory processes in the Central nervous system, and the establishment of effective antihypertensive therapy in the process of a differentiated approach to higher nervous activity will contribute to the justification of targeted (targeted) or personalized antihypertensive therapy. The aim of the study was to determine the effectiveness of personalized pharmacotherapy in patients with arterial hypertension with different characteristics of excitatory or inhibitory processes in the Central nervous system. The prevailing type of higher nervous activity (equilibrium of cortical processes) was determined by the reaction to a moving object. The presence and severity of depression were determined using psychological tests by Je. Akhmetzhanov. The quality of life was determined using the «SAN» test (health, activity, mood, score). The effectiveness of antihypertensive therapy was also judged by the value of the hand endurance coefficient (spring dynamometer with a fixed arrow). The coefficient of endurance of the hand was determined by the ratio of the strength of the hand in the 3rd press to the strength in the 1st (× 100%). The activity of the autonomic nervous system was determined by calculating the initial vegetative tone of the body. The results of the study determined the significant effectiveness of personalized pharmacotherapy of arterial hypertension, depending on the prevalence of excitatory (correction of sympathicotonia with highly selective beta-blockers) and inhibitory processes in the Central nervous system (blockade of mineralocorticoid receptors with spironolactone/eplerenone) in comparison with the empirical treatment option. Randomized clinical trials of this new promising approach are appropriate.

Keywords: arterial hypertension, personalized antihypertensive therapy, the activity of the Central nervous system.

Introduction. In the last 20 years, there has been no significant reduction in the level of cardiovascular diseases (CVD). At the same time, arterial hypertension (AH) and coronary heart disease (CHD) are leading in the structure of overall morbidity) [1, 6, 11, 12]. Various environmental conditions affect the course of hypertension and CHD [3, 8, 10, 16]. The latter can significantly potentiate psychoemotional stress. In connection with the above, the solution of issues of correction of the peculiarities of the psychoemotional status of patients, effective pharmacotherapy, secondary prevention play a significant role in the clinical management of patients suffering from CVD [5, 7, 9, 17]. However, under equal conditions, some individuals have more pronounced changes, while others have less [13, 14]. The latter is probably related to the activity of the Central nervous system, the type of higher nervous activity (GNI), and the state of equilibrium of cortical processes. It is assumed that the clinical course of hypertension may have its own characteristics in patients with different characteristics of excitatory or inhibitory processes in the Central nervous system, and the establishment of effective antihypertensive therapy in the process of a differentiated approach to GNI will contribute to the justification of targeted (targeted) or personalized antihypertensive therapy (AHT).

Objective: to evaluate the results of treatment of men with hypertension who differ in psychosomatic status, in the coefficient of hand endurance and the coefficient of oxygen utilization by tissues using the "well-being, activity, mood" test; to determine the effectiveness of personalized pharmacotherapy in patients with hypertension with different characteristics of excitatory or inhibitory processes in the central nervous system. After establishing patients men features of hypertension (hypertension of stage II) with high and low anxiety level and prevalent type of GNI, a standard empirical AHT (EAT) compared with personalized AHT (PAT), aimed at correction of in patients with sympathicotonia predominance of excitatory processes in the CNS or in other patients with the prevalence of inhibitory processes – the blockade mineralokortikoidna receptors of the renin-angiotensin-aldosterone system (RAAS).

Material and methods. Study design: outpatient, single – center, cohort, prospective, controlled, non-randomized, long-term clinical trial (2011-2018). Contingent: patients with AH (n=328,41 patients with high (HA) and low (LA) anxiety on the background of EAT and PAT), engineering and technical workers, aged 44-62 years (average 54±1,8 years) were divided by type of GNI into equal groups with the prevalence of excitatory (sympathotonia) or inhibitory (parasympathotonia and activation of RAAS) processes in the Central nervous system, taking into account anxiety (HA and LA). The

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examination revealed hypertension in stage II (GB-II, grade 2, risk 3) according to the criteria set out in [11, 12]. The average duration of the disease was 11,6±1,4 years. The control indicators were data from 164 healthy men who were compatible in terms of anthroposocial parameters. The prevailing type of GNI (equilibrium of cortical processes) was determined by the reaction to a moving object [4]. The value of reactive and personal anxiety was determined by the method of Yu.L. Khanin [15]. Persons who scored 32,0±0,6 points are classified as LA, and those who scored 42,8±0,4 points or higher are classified as HA. The study took into account the degree of depression (D, score) on the depression scale of Je.A. Akhmetzhanov [2], which was taken into account in the process of conducting AHT. Quality of life (QOL) was determined using the «SAN» test (health, activity, mood, score) [4]. The effectiveness of AHT was also judged by the value of the coefficient of endurance of the hand (CEH,%) (spring dynamometer with a fixed arrow). CEH, % was determined by the ratio of the hand strength in the 3rd press to the strength in the 1st (x 100%) [4]. The activity of the VNS departments was determined by calculating the initial vegetative tone of the body according to the method of a.m. vane [4]. In individuals with a predominance of excitatory processes, the activity of the sympathetic, and in individuals with inhibitory processes in the Central nervous system – the parasympathetic part of the ANS. It was found that a mild degree of neurogenically induced depressiveness (D) was observed only in HA patients with a predominance of braking processes (BP) in the Central nervous system. For the rest of the examined individuals, the values were lower than mild D. In this regard HA ill with the prevalence of excitatory processes was obtained in 96% anxiolytic diazepam 2,5 mg morning and night, and HA ill with the prevalence of TP in the Central nervous system in 96% of the antidepressant tianeptine 12,5 mg in the morning and at night in 4% of cases, sertraline 25 mg /day. The content of cortisol and aldosterone in blood serum was determined by radioimmune method (CEA-IRE-SORIN, France – Italy). The minute volume of blood flow (MVB) was taken into account on the 6-NEG device and by the calculation method. Determination of the coefficient of oxygen utilization by tissues (COUT, %) was performed using the blood gas analyzer «STAT PROFILE. pHOx». AHT included: highly selective beta-blocker metoprolol, 100 (for LA) - 200 (for HA) mg/day, angiotensin converting enzyme (iACE) inhibitor enalapril, 20 mg/day, diuretic hydrochlorothiazide, 12,5-25 mg/day. HA-patients with predominance of excitatory processes in the Central nervous system received hydrochlorothiazide, 25 mg/day, and HT with excitable processes (EP) in the Central nervous system – 12.5 mg/day. Of the iACE, HA patients in 96% took enalapril, 20 mg/day + spironolactone 100-200 mg/day (in 75%), less often (25%)-hydrochlorothiazide, 25 mg/day, since their blood potassium content was lower than in patients with EP. LA patients with a predominance of inhibitory processes in the Central nervous system received enalapril, 10 mg/day + hydrochlorothiazide, 12,5 mg/day. A special feature of the appointment of personalized at: sympathicotonia in patients with a predominance of EP, compared with individuals with BP, the activity of the sympathetic part of the ANS and HGNS (cortisol) was high. The latter was blocked by beta-blockers. In individuals with BP, compared with those who had a predominance of excitatory processes in the Central nervous system, against the background of parasympathicotonia, the activity of RAAS (for aldosterone) was high, which was blocked by iACE. All other variants of at are called empirical, or EAT. This approach, taking into account GNI (by temperament), which is consistent with the presented scheme of AHT, made it possible to effectively and at an earlier time reduce the manifestations of left ventricular hypertrophy in patients [9].

The data were processed using variational statistics (M±m) using the standard software package «Statistica 7.0» and the student's parametric t–test, the Mann-Whitney U-test. The values at $p<0.05$ were considered statistically significant. The study was performed in compliance with the provisions of the Helsinki Declaration on the examination and treatment of people and approved by the ethics Committee of the Novosibirsk state medical University on 27.10.2009, Protocol No. 19.

The results of the study and their discussion. The study showed that on the background of both variants of AHT quality of life (test SAN) (table 1), the magnitude of CEH (table 2) and COUT, as well as the MVB have HA (LA) healthy and HA (LA) patients, was significantly reduced in sequences from individuals with a prevalence of excitatory processes in the Central nervous system to persons with the prevalence of the brake.

From HA individuals quality of life (for the SAN) and CEH was significantly lower than in lowanxiety, and HA (LA) patients on the background of EAT lower than that of HA (LA) healthy individuals of appropriate state of cortical processes of the CNS. However, against the background of PAT's quality of life (for the SAN) and the magnitude of ICC, IOC and KUCT was the same as in healthy individuals of the appropriate type GNI. Analysis of the data showed that the magnitude of KOUT have HA (LA) individuals was significantly reduced in the sequential series from those with a prevalence of excitatory processes to persons with a prevalence of brake processes in the Central nervous system (fig. 1). Against the background of both variants of AHT, the value of AHT in high-anxiety individuals was significantly lower than in low-anxiety individuals. However, HA (LA) patients on the background of EAT amount COUT was lower than in healthy HA (LA) individuals of the corresponding type of activity of the cortical processes in the CNS, and patients who have used the CAT, the value of COUT did not differ from that in healthy HA (LA) individuals of the appropriate type of HNA.

Fig. 1. The coefficient of oxygen utilization by tissues in high (VOT) and low-anxiety (NT) patients with hypertension with a predominance of excitatory or inhibitory processes in the central nervous system against the background of ET and PAT for the study period 2011-2018.

Thus, if the treatment was aimed at arresting the activity of the RAAS (by aldosterone) in patients with the prevalence of the BP in the Central nervous system, and of sympathicotonia in patients with the prevalence of EP in the Central nervous system, the amount of oxygen utilization by tissues (for COUT) was higher than on the background of EAT, and approached that in healthy HA (LA) individuals of the appropriate type HNA by equilibrium of cortical processes in the CNS. The success of the study is consistent with the results of other studies [9], where the authors reduced the time for remodeling left ventricular hypertrophy using PAT, in contrast to EAT.

The value of MVB (calculated and determined by tetrapolar rheovasography) from healthy HA (LA) and patients with hypertension HA (LA) males was significantly reduced in the sequential series from those with a prevalence of excitatory processes in the Central nervous system to the persons with predominance of inhibitory processes in the CNS (Fig. 2, 3). This decrease was observed both on the background of EAT and on the background of PAT. The peculiarity is that against the background of PAT, in contrast to empirical therapy, the MVB indicators (calculated and hardware) did not

Table 1

Quality of life according to the level of "well-being, activity, mood" (score) on the " SAN " test in patients with ET and PAT for the study period from 2011 to 2018.

		The equilibrium of cortical processes in the central nervous system is shifted towards the predominance of processes	
		excitatory	brake systems
Highanxiety	EAT	4.2±0.1 41	3.0±0.1 41
	PAT	5.8±0.1 41	4.3±0.1 41
	Health	5.7±0.1 41	4.7±0.1 41
Lowanxiety	EAT	5.0±0.1 41	4.3±0.1 718
	PAT	6.7±0.1 41	5.8±0.1 41
	Health	6.8±0.1 41	5.9±0.1 41

Note. Here and further on, the denominator indicates the number of persons in the group

Table 2

Coefficient of hand endurance (%) by the ratio of the force in the third press (kg) of the dynamometer spring to the force in the First press (kg) in patients with ET and PAT during the study period from 2011 to 2018.

		The equilibrium of cortical processes in the central nervous system is shifted towards the predominance of processes					
		excitatory			brake systems		
Dynamometer press		I, kg	III, kg	CEH, %	I, kg	III, kg	CEH, %
Highanxiety	EAT	54.7±0.9 41	42.2±0.9 41	78.1±0.8 41	50.1±0.9 41	37.6±0.7 41	75.0±0.8 41
	PAT	54.6±0.5 41	53.6±0.5 41	98.2±0.2 41	52.0±0.3 41	50.1±0.4 41	96.4±0.4 41
	Health	54.7±0.4 41	53.6±0.4 41	98.1±0.3 41	51.7±0.5 41	49.5±0.5 41	95.7±0.3 41
Lowanxiety	EAT	51.3±0.5 41	45.3±0.5 41	88.3±0.5 41	47.5±0.4 41	39.7±0.4 41	83.5±0.3 41
	PAT	53.4 ±0.4 41	51.9±0.3 41	99.3±0.4 41	49.5±0.3 41	48.8 ±0.3 41	98.6±0.3 41
	Health	53.3±0.3 41	52.9±0.5 41	99.3±0.1 41	50.6±0.3 41	49.5±0.4 41	97.8±0.2 41

Note. I, kg – the force of the brush in the 1st fluid of the dynamometer; III, kg-the force of the brush in the 3rd press of the dynamometer

significantly differ from those in HA (LA) healthy individuals of the corresponding state of equilibrium of cortical processes.

An important component of PAT is that the achievement of the target MVB by PAT was combined with an earlier and more pronounced approximation of the left ventricular mass to that of healthy HA (LA) individuals of equal temperament.

The data obtained by us showed that the utilization of oxygen by tissues decreased in a sequential series from individuals with a predominance of excitatory processes to those with TP in the Central nervous system, both in healthy and in patients. In the background of any at the sympathotonics minute volume of blood flow was higher than parasympathotony. Despite the lower MVB, parasympathotonics with TP in the Central nervous system, in contrast to those with EP in the Central nervous system, have higher anxiety and a tendency to depression. We considered this to be a consequence of a lower level of oxygen utilization by tissues (according to COUT), which also indicated the peculiarities of the course of hypertension depending on the type of HVA.

A review of the scientific literature over the past 20 years shows a great interest of cardiologists and therapists in studying the psychosomatic features of hypertension in conditions of chronic stress [3, 4, 8, 10], as well as the influence of psychosocial factors and stress on the course of AH [13]. However, in various reports, the authors investigated anxiety across the entire group of patients, without identifying HA and LA individuals, and without taking into account the type of HNA for the equilibrium of cortical processes. The majority of outpatients with hypertension and CHD showed a predominance of signs of anxiety and depression. However, this was less common in this study compared to previous studies in Russia. In the available literature, such approaches to personalized pharmacotherapy have not been developed.

The observed progress in the treatment of hypertension is associated with the introduction of new antihypertensive drugs, including combined dosage forms. However, the level of mortality and morbidity remains high [6]. The reasons for this are different, including stressful situations, low adherence of patients to treatment [5, 12]. Against the background of our results, we can assume that in the course of empirical therapy, the use of combined drugs contributes to a decrease in the activity of RAAS, but increases the already pronounced prevalence of parasympathicotonia in patients with a predominance of inhibitory processes in the Central nervous system.

It should be noted a certain novelty of the proposed approach to at. It lies in the fact that the correction of sympathicotonia in patients with the prevalence of excitatory processes, and in other patients with a prevalence of brake processes in the Central nervous system activity of the renin-angiotensin-aldosterone system (aldosterone), as well as anxiety from HA individuals combined with the increase of utilization of oxygen by the tissues (cells) to the level of that in healthy individuals of the appropriate type of HNA. With this you can link the decline in the propensity to depression in patients with inhibitory processes in the Central nervous system and tension in the cardiovascular system (for MVB) in patients with a predominance of excitatory processes in the CNS.

In contrast to EAT, in PAT, the values of the studied indicators (anxiety, propensity to depressiveness, COUT, MVB) did not differ from those in healthy individuals of the corresponding type of HNA. The effectiveness of PAT is also evidenced by the fact that the time of remodeling of left ventricular hypertrophy can be reduced in comparison with EAT [9]. It is promising to further study the long-term results of long-term correction of changes in the thickness of the intima-media complex of arteries in patients with hypertension with different CNS activity and HNA type against the background of personalized at.

Conclusion. The differences between the studied indicators of patients with VP and TP on the background of AGT and AGT indicate the feasibility of separation of patients with psychosomatic status and activity of the cortical processes of the CNS and ANS divisions. A greater effectiveness of personalized pharmacotherapy of hypertension was determined depending on the prevalence of excitatory (correction of sympathicotonia with beta-blockers) and inhibitory processes in the central nervous system (block-

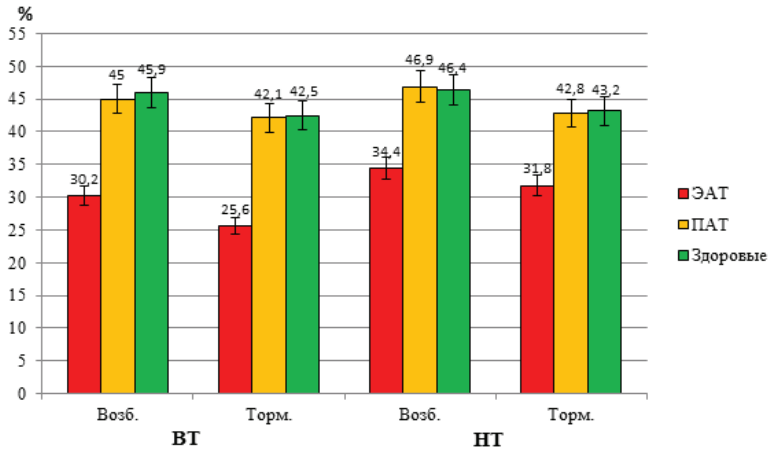

Fig. 1. The coefficient of oxygen utilization by tissues in high (VOT) and low-anxiety (NT) patients with hypertension with a predominance of excitatory or inhibitory processes in the central nervous system against the background of ET and PAT for the study period 2011-2018.

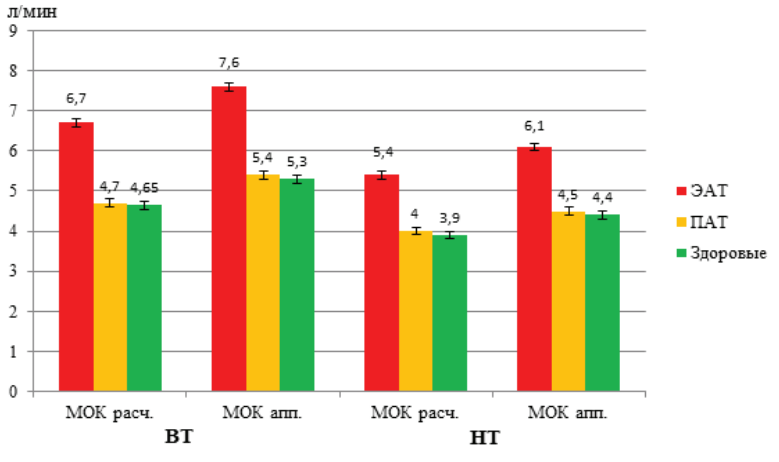

Fig. 2. Minute volume of blood flow in high (VOT) and low-anxiety (NT) patients with hypertension with predominance of excitatory processes in the central nervous system against the background of ET and PAT during the study period 2011-2018.

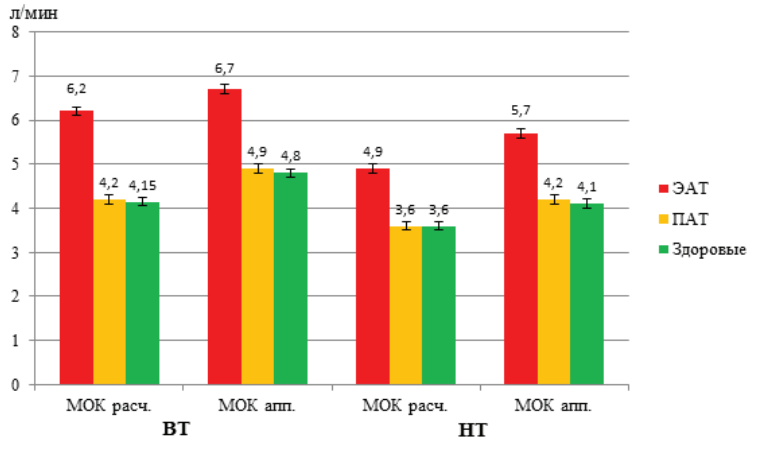

Fig. 3. Minute volume of blood flow in high (VOT) and low-anxiety (NT) patients with hypertension with a predominance of inhibitory processes in the Central nervous system against the background of EAT and PAT during the study period 2011-2018.

ade of mineralocorticoid receptors with spironolactone/eplerenone) compared to the empirical treatment option. Randomized clinical trials of this new promising approach are appropriate.

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CLINICAL CASE

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COMBINATION OF AUTOIMMUNE HEPATITIS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. CLINICAL OBSERVATION

Abstract: The autoimmune hepatitis (AIH) is a chronic disease of the liver with different clinical phenotypes where significant roles have autoimmune processes of failed self-tolerance mechanism to own hepatocytes. Some other autoimmune diseases such as lupus are also observed with AIH. On the example of clinical observation we present features of course of the AIH with lupus on the background, the challenges of the diagnosis and treatments. During the research we identified a relationship between two autoimmune diseases based on association of autoimmune disorders with major histocompatibility complex.

Keywords: Autoimmune hepatitis, lupus, autoantibodies, liver encephalopathy, immunosuppressive therapy.

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Autoimmune hepatitis (AIH) is a chronic diffuse liver disease with various clinical phenotypes, laboratory and histological manifestations. The worldwide prevalence of AIH is increasing annually, currently at <30 cases per 100,000 people, regardless of age and ethnicity, with a gender ratio of 4:1 for women over men [7].The most important issue in the study of this disease is the search for trigger factors and genetic predisposition. In clinical practice, there are also acute problems of early diagnosis and differentiation with other diseases. Thus, most cases are observed among women with increased gamma globulin titers, Immunoglobulin G (IgG), presence of antibodies (Abs) as well as human leukocyte antigen (HLA) DR3 and DR4, morphological signs of periportal hepatitis and a favorable response to immunosuppression [6].

To date, the pathogenesis of AIH remains incompletely understood. It is known that autoimmune processes with impaired tolerance to the liver's own cells are crucial. In clinical practice, timely diagnosis of AIH is difficult, the disease may have a fulminant course, which not infrequently leads to the omission of the possibility of timely therapy in the initial stages of the disease, as well as the development of other autoimmune or immune-mediated pathological diseases. Among them, there is an association of AIH with systemic lupus erythematosus (SLE).

Autoimmune or immune-mediated diseases such as autoimmune thyroiditis, rheumatoid arthritis, type-1 diabetes, systemic lupus erythematosus, Sjögren's syndrome, celiac disease and immune thrombocytopenic purpura may develop at any stage of AIH. SLE is characterized

by a genetic abnormality of B- and T-lymphocytes, which in turn synthesize cytotoxic Abs. The resulting immune complexes containing antinuclear antibodies (ANA) stimulate Th1-induced connective tissue inflammation. According to the literature, it is known that AIH with HLA-DR4 is predominantly prevalent in Southeast Asia, Japan the clinical course of the disease is characterized by frequent systemic manifestations [1, 2, 7, 8] .

The association of AIH with SLE suggests the presence of common links in the pathogenesis of these diseases. There are insufficient data in literature on peculiarities of course and treatment of comorbid patients. The aim of our study is to study clinical case of concomitant autoimmune pathology of AIH and SLE, peculiarities of the course, diagnostics and treatment tactics of the disease.

We present a clinical case of combination of AIH with SLE in a patient residing in the Republic of Sakha (Yakutia).

Patient V., born in 1968, was hospitalized for inpatient treatment in January 2020 at the gastroenterological department of Yakutsk Republican Clinical Hospital (YRCB).

Complaints upon admission: pain, sense of gravity in the right subdermal region, jaundice of the skin, general weakness, loss of body weight, swelling of the lower extremities.

Past medical history: Patient B. had 5 pregnancies, 5 births (4 girls, 1 boy). Heredity: Mother and elder sister died of severe liver failure on the background of liver cirrhosis of unknown etiology, the rest had no pathology.

Anamnesis: Considers himself sick since 2010. when, within 2 months, an ulcer appeared in the region of the left tibia, fever, arthralgia, a symptom of a «butterfly» on the face, Le-cells were detected in the blood and the diagnosis of SLE, Raynaud syndrome were verified. Prescribed steroid therapy with prednisone 15 mg/day resulted in stable clinical remission. Until 2019 the patient had no complaints, she did not take any further steroid therapy. During the period from 2010-2019, the patient was operated for a falxmeningioma of the brain (2017), diagnosed with type-2 diabetes, insulin-independent variant (2018). In May 2019, during the check-up, the level of the cancer marker alpha-fetoprotein (AFP) increased to 48.1 IU/ml, with a subsequent increase to 159 IU/ml (Nov. 22, 2019) and 201.6 IU/ml (Jan. 20, 2020) on the background of weight loss and an increase in general weakness.

In November 2019, in order to rule out carcinogenic pathology, she was referred to the National Center of Medicine - Yakutsk City Hospital No. 1. In the course of diagnostics oncopathology was excluded. Serum cytolysis and cholestasis syndrome values were within the reference values (Table 1). In January 2020 due to increasing pain syndrome in the right subcostal area, jaundice of skin, mucous membranes and diarrhea the patient was urgently admitted to the regional hospital with suspicion of acute cholecystitis, mechanical jaundice. Further, 7 days later, given the severity of her condition and the ineffectiveness of the therapy she was urgently hospitalized by ambulance to the Emergency Medical Center - Yakutsk Hospital No. 2. Blood chemistry on January 13, 2020: total bilirubin (BIL-T) -182.1 μmol/L, direct bilirubin (D-BIL) -126 μmol/L, alanine transaminase (ALT) - 88 U/L, alkaline phosphatase (ALP) - 513 U/L, total protein (BELOK) -75.7 g/L, glugose (GLU) - 3.09 mmol/L. In the hospital, weakness and jaundice progressed. On January 15, 2020 the blood chemistry showed signs of marked cytolysis syndrome (ALT/aspartic transaminase (AST) - 417.5/1533.8 U/L), marked cholestasis (BIL-T 165.1 μmol/L, D-BIL - 149.6 μmol/L, gamma-glutamyl transpeptidase (GGT) - 77.5 U/L, ALP - 378 U/L), hepatosuppression syndrome (albumin - 20.1 g/l, Quik prothrombin - 28%, international normalized ratio (INR) 2.45). There was an increase in the dynamics of serum oncomarkers (AFP) to 201.6 IU/ml, antibodies to ds-DNA (anti-dsDNA) concentration of 118.80 IU/ml, Immunoglobulin E (IgE) concentration of 248 IU/ml, and detection of positive antinuclear antibodies (ANA). Components of the complement system C3/C4 were not detected (Table 2).

Ultrasound of the abdominal cavity organs, computed tomography with contrast revealed signs of hepatosplenomegaly, diffuse changes of the parenchyma, signs of cholelithiasis (GI). On the basis of high cytolytic serum transaminase values, a steroid therapy with Prednisolone 60 mg/day was started. During the first days against the background of this treatment, the patient's serum transaminase values decreased: ALT 195.8 U/l, AST 347.7 U/l, ALP 315.2 U/l, BIL-T to 135.2 μmol/l, D-BIL 97.8 μmol/l, C-reactive protein (CRP) 12.93 mg/l (Table 1). On the fourth day of steroid therapy, signs of progressive hepatic encephalopathy suddenly appeared, with somnolence, disorientation, left-sided hemiparesis, and sensory impairment on the left side. Infusion of Hepa-Mertz (Ornithine) 20 mg/day, purging enemas, Dufolac (Lactulose) 30 ml/day, Ursosan (Ursodexycho-

Table 1

Blood chemistry in dinamics

Serum indicators	22.11. 2019	15.01. 2020	20.01. 2020	27.01. 2020	04.02. 2020	11.02. 2020	03.03. 2020	21.04. 2020	29.06. 2020	17.08 2020	05.10. 2020
GGT, units/L		77.5	54.0	53.0	52.0	58.0		32.0	37		
BIL-T, μmol/L	15.0	182.1	201.0	161.0	117.0	136.0	113.6	68.0	29.5	28.1	16.9
D-BIL, μmol/L		149.6	169.6	136.1	99.5	115.9	91.9	53.9	21.1	8.4	3.5
ALT, U/L	9.0	417	299.1	173.9	181.5	178.4	117.2	37.8	24.7	39	53
AST, U/L		1533.8	981.4	397.4	455	436.4	341	66.4	76.9		
Urea, mmol/L		2.6	2.8	3.6	3.6	3.8	4.2	4.8		5.62	5.62
Albumin, g/L		20.1	29	38	36	36	26.8	30	29.8		
Creatinine, mmol/L	93	54	78.0	83.0	77.0	84.0	77	78.0		74.5	83
Cholesterol, mmol/L		3.6	2.9	4.6	4.1	3.9	2.36	3.0	4.2	3.66	5.1
ALP, U/L		378	293	275	255	272		196		765	
CRP, mg/l			9.8	14.8	14.8	11.4		20.4			
BELOK, g/L		75.6	75.1	84.4	81.5	84.4		72.0	69.4	64.5	73
Glucose, mmol/L	4.0	4.30	4.45	3.85	7.93	4.53	4.04	4.25	6.34	5.01	5.51

lic acid) 750 mg/day were performed. For correction of blood coagulopathy-Dicinon 4 ml and Vikasol 10 mg/ml. The patient's condition slightly improved against the background of the therapy, but her general weakness, rapid fatigability, and weakness in the left extremities persisted. Subsequently, according to the decision of the medical council, it was decided to refrain from the prescription of targeted therapy and continuation of maintenance dosage of steroids due to the high risk of re-progression of hepatic encephalopathy. In mid-February 2020, she was discharged in stable condition with the diagnosis: Mixed etiology liver cirrhosis, Child-Pugh class B, decompensated. SLE, chronic course. Raynaud's syndrome. In April 2020, the patient again progressed symptoms of hepatic encephalopathy, against the background of reappointed therapy with Prednisolone 90 mg/day, for which the treatment with Ornithine and Ursodeoxycholic acid was cancelled and prescribed. The differential diagnosis was made in March 2020 with the purpose of immunological analysis of the blood markers of AIH: IgG-30.67 g/l; ANA - positive; determination of the antibody titers to smooth muscles class (S-SMA) IgG, IgA, IgM 1:160; Abs to microsomal fraction of the liver and kidneys (anti-LRM) <1:40. The diagnosis of AIH 1 type was confirmed (Table 3).

Taking into account clinical and anamnestic, laboratory results, the patient was clinically diagnosed:

Primary: Autoimmune hepatitis type 1, high degree of activity. Liver cirrhosis of mixed genesis, grade B according to Child-Pugh, decompensated.

Complications: Portal hypertension, varicose esophageal veins, coagulopathy. Chronic hepatic insufficiency. Hepatic encephalopathy type C, class II, recurrent, provoked (stool retention).

Concomitant: Systemic lupus erythematosus, chronic course, activity 1, test ANA, anti-dsDNA positive. Type-2 diabetes, subcompensated. GIBS. Chronic calculous cholecystitis in remission. Condition after bifrontal bone-plastic craniotomy microsurgical removal of falxmeningioma dated May 15, 2017.

Against the background of ongoing therapy, there is a decrease in cytolysis syndrome indices from 29.06.2020. (ALT/AST - 24,7/76,9 U/L), cholestasis (total bilirubin - 29,5, direct - 21,1 μmol/l, GGT - 37 U/L) (Table 1). In dynamics there was some increase of transaminases and ALP in blood.

Based on the above history, clinical picture of the disease course, the diagnosis of SLE in this patient B. was made before AIH verification. It can be assumed that these diseases are characterized by common links of pathogenesis. Thus, there is an association of autoimmune disorders with human major histocompatibility complex. It is known that most autoimmune diseases, particularly SLE and AIH, are associated with the presence of the following antigens in the HLA phenotype: DRB1, DR2 and DR3, DR4, respectively [2, 3]. Presumably, the genes of the HLA system are involved in T-lymphocyte selection, a process that is impaired in the presence of certain alleles, resulting in the failure to eliminate sensitized T-lymphocytes to autoantigens. This relationship has significance in the diagnosis of AIH: the presence of a history of SLE indicates impaired immune tolerance associated with the HLA-complex.

Table 2

Иммунологические маркеры крови СКВ от 19.12.2019 г.

Показатель крови	Результат	Референсное значение
Антитела IgG к двуспиральной (нативной) ДНК (анти-dsDHA), МЕ/мл	118,80	< 10
Иммуноглобулин Е (IgE) (total), МЕ/мл	248	0–100
С3 компонент комплемента, г/л	0,86	0,9–1,8
С4 компонент комплемента, г/л	0,13	0,1-0,4
Антинуклеарные антитела, IgG (АНА)	Положительно	Отрицательно

According to the literature, often one of the variants of the onset of AIH is observed by the manifestation of extrahepatic manifestations, fever, arthralgia for several years and can be mistakenly regarded as SLE, rheumatoid arthritis [1, 3, 7, 8]. The course of AIH in association with SLE is characterized by the following features: manifestation of clinical manifestations of AIH with a sharp increase in laboratory indices occurs in a shorter period of time. In our clinical observation it was 8 months. During this period, the patient had pronounced clinical symptomatology of hepatic encephalopathy, which developed lightning fast against the background of glucocorticosteroid treatment. According to literature data, in most cases of AIH without treatment, cirrhosis develops within three years, and the prognosis is more serious than in patients with chronic viral hepatitis [3, 4, 5]. In this patient with pathogenetic therapy, cirrhosis developed within less than 1 year. It could be related to variability of disease course connected with peculiarities of antigenic histocompatibility, with the role of transcription factor designated as autoimmune regulator of type 1, which causes predisposition to AIH development.

Conclusion: The present clinical observation shows the course of AIH against the background of SLE, which is characterized by rapid progression with the outcome in liver cirrhosis, early manifestation of clinical symptomatology, as well as a pronounced manifestation of hepatic encephalopathy. For final verification of AIH type 1, liver biopsy with detection of characteristic morphological picture of AIH - lobular hepatitis with bridging or massive necroses, emperipolysis, hepatocytic rosettes - is required.

If a patient has signs of liver damage with impaired immune system tolerance, it is recommended to rule out AIH at an early stage. In the diagnosis of AIH, the first sign is increased titers of the AFP oncomarker, often detected in screening. It is necessary to consider that AIH can occur under the mask of other clinical signs for several years and can be mistakenly regarded as SLE, rheumatoid arthritis, which is a prerequisite for determining AIH markers [1, 2, 3, 4, 7, 8].

Table 3

Autoimmune hepatitis blood immunological results from 23.03.2020 г.

Variable	Result	Valeurs de reference
Immunoglobulin G (IgG), g/L	30,67	7-16
Antinuclear antibodies IgG (ANA IgG)	Положительный	Отрицательно
Smooth muscle antibodies (S-SMA), IgG +A +M	1:160	< 1:100
Anti-liver kidney microsomal (aLKM), IgG +A + M	< 1:40	< 40

If AIH is verified to be highly active with positive markers, early initiation of pathogenetic therapy is necessary, despite the absence of results of liver morphological analysis (biopsy). At the same time, it is necessary to consider the risk of hepatic complications in response to treatment with glucocorticosteroids, development of systemic inflammatory reaction. Genetically engineered biologics and liver transplantation can be an alternative therapy option.

If AIH is verified to be highly active with positive markers, early initiation of pathogenetic therapy is necessary, despite the absence of the results of morphological analysis of the liver (biopsy). At the same time, it is necessary to consider the risk of hepatic complications in response to treatment with glucocorticosteroids, development of systemic inflammatory reaction. Genetically engineered biologics and liver transplantation can be an alternative therapy option. The presented clinical observation demonstrates the necessity of early diagnosis for exclusion of AIH in predisposed patients, timely and competent use of systemic and topical immunosuppressive therapy and decision on the indication of alternative therapy as indicated.

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THE FAMILY CASE OF OCULOPHARYNGEAL MYODYSTROPHY IN UST-ALDANSKY DISTRICT OF THE REPUBLIC SAKHA (YAKUTIA)

Abstract: This study was carried out to study the clinical and genetic characteristics of a family with oculopharyngeal muscular dystrophy in the Ust-Aldan district and to draw up a plan for the introduction of such patients. As a result, it was revealed that in two patients (proband and sibs) examined earlier, there was a progression of symptoms in the form of an increase in muscle weakness and movement disorders. Given the course of the disease, characterized by the steady development of symptoms of the disease, which leads to a decrease in the quality of life, patients with OPMD need to undergo symptomatic therapy courses in a specialized neurological department, inform the population about the pathways of disease transmission, about prenatal diagnosis and adequate available interventions and supportive care to reduce risk of suffocation and other complications of OPMD.

Key words: oculopharyngeal myodystrophy, autosomal dominant inheritance, *PABPN1* gene, family case, eyelid ptosis, progressive muscle weakness, hypotrophy of the proximal extremities, dysphagia, dysphonia, Yakuts.

Introduction. The staff of the YSC CMP together with the Research Institute of Medical Genetics (Tomsk) have been conducting research on a number of hereditary diseases of the nervous system for several years. Based on the analysis of the results of genetic and epidemiological studies, several hereditary diseases were identified that have a high prevalence in the Yakuts in comparison with the world population: type 1 spinocerebellar ataxia (46 cases per 100,000), myotonic dystrophy (21.3 cases per 100,000), hereditary enzymopenic methemoglobinemia (14.9 cases per 100,000), oculopharyngeal muscular dystrophy (12.6 cases per 100,000), Kennedy spinal bulbar amyotrophy (15.3 cases per 100,000), Friedreich's ataxia (2.8 cases per 100,000), 3M syndrome (12.7 cases per 100,000) [2].

Oculopharyngeal muscular dystrophy (OMIM 164300) is a rare progressive, hereditary, disabling disease of the neuromuscular system. The highest frequency of OPMD is found in populations with the "founder effect", such as Bukharian Jews - 1: 600 people. (Israel) [8] and the French-Canadian population (Quebec, Canada) - 1: 1000 people. [12]. In Europe, the incidence of this disease is 1: 100,000 [12], in the Republic of Sakha (Yakutia) it is 12.5 per 100,000 people and occurs mainly among the indigenous Yakut population. To date, more than 47 families (60 patients) from all over the republic have been registered, the largest number of families (11 families, 15 patients) with OPMD is observed in the Ust-Aldan district [4], where this disease is most common along with type 1 spinocerebellar ataxia (SCA 1, the prevalence is 46 cases per 100,000 population [7]). The cause of the disease is a mutation - expansion of trinucleotide GCN repeats in the *PABPN1* gene.

The disease is late manifesting, the onset of the disease is manifested in 40-60 years. An accurate diagnosis can only be made by a molecular genetic research method. Molecular genetic diagnosis of OPMD (mutation identification (GCN) 14) was introduced into the medical genetic consultation in Yakutia in 2008 [1].

In the clinical picture, progressive hypotrophy and muscle weakness in the proximal extremities, bilateral ptosis of the eyelids, hoarseness and dysphagia are observed. Death usually occurs from respiratory failure, due to impaired swallowing, leading to aspiration pneumonia, pulmonary infections and asphyxia [9].

Oculopharyngeal muscular dystrophy has an autosomal dominant mode of inheritance, but cases with a recessive mode of inheritance have been described [6, 10].

The age of onset of eyelid ptosis in patients with OPMD is on average 48 years (26-65 years), dysphagia is 50 years (40-63 years). Other symptoms are observed in patients as the disease progresses. Atrophy and weakness of the tongue (82%), atrophy and weakness of the proximal lower extremities (71%), dysphonia (67%), ophthalmoplegia (61%), weakness of the facial muscles (43%) and atrophy and weakness of the proximal upper extremities (38 %). At the same time, it was found that the earlier bilateral ptosis of the eyelids and dysphagia appeared in patients with OPMD (up to 45 years old), the earlier muscle weakness developed in the proximal regions (up to 60 years old), which led to a more severe course of the disease. The cases of severe course of the disease were 5-10%. [11, 12]. - raise from the results above to the introduction.

The aim of the study was to study the clinical and genetic characteristics of a family with oculopharyngeal muscular dystrophy in the Ust-Aldan district and draw up a plan for the introduction of such patients.

Materials and research methods. The material was collected during an expedition trip to the Ust-Aldansky district of the RS (Y), v. Borogontsy, v. Syrdaakh and v. Arylaakh under a bilateral agreement between the YSC CMP and the administration of these villages to examine the population in order to identify new cases of OPMD and other hereditary diseases. Were collected 102 samples of biological material (blood), of which 14 were taken from family members with a burden of heredity according to OPMD. Samples of biological material were placed in the collection of biomaterial at the YSC CMP.

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Research methods.

1. Genealogical method. The pedigree of a family from the Ust-Aldan district was studied. The pedigree (Fig.) included 5 generations, a total of 64 people in the pedigree fragment. I, II generation - deceased parents, III generation - patients and their siblings, IV - children of the proband and siblings of the proband, V - children who have not reached the age of onset of the disease. In the I-IV generations there are patients with OPMD, a total of 8. Presymptomatic carriers of the mutation out of those studied in the IV-V generations - 4 people.

2. Molecular genetic method.

All participants in the study underwent DNA diagnostics of the subject carriage of the mutation in the *PABPN1* gene. Molecular genetic research was carried out in the laboratory of hereditary pathology of the OMG YSC CMP. DNA was isolated from 10 ml of peripheral blood by the standard method using proteinase K followed by phenol-chloroform extraction (Medical laboratory technologies, 1999). Previously, written informed consent was obtained from all subjects for molecular research.

3. The clinical research method included an assessment of the somatic and neurological status. Two patients with OPMD (proband and sibs) were examined and examined by the molecular genetic method in 2008 and were examined again during an expedition trip in 2018.

Results and discussion. Of the 14 patients of the burdened family (n = 14), 7 (n = 7) had two alleles: normal - 6th and pathological allele - 10th. For the first time, a mutation in the PABPN1 gene — an expansion of the GCN repeat in the PABPN1 gene — was found in 5 patients from the same family (the genealogical scheme is shown in Fig.). The remaining 7 patients were found to have two normal alleles - 6/6. Thus, out of 14 members of one family, 7 carriers of the mutant gene were found with the development of a clinical picture of the disease after 60 years in 2 family members. The rest of the family members are in the preclinical stage of the disease.

Were examined 14 members from 1 burdened family (Fig.). At the same time, in two patients (proband and sibs), examined earlier, there was a progression of symptoms in the form of an increase in muscle weakness and movement disorders. In the clinical picture of the disease in both patients, drooping of both eyelids (eyelid ptosis), difficulty in swallowing liquid and solid food, nasal voice and hypotrophy (weakness) of the shoulder and thigh muscles are observed.

Proband N., (III-5, fig.) 1945 y. First examined at the age of 62. In the clinical picture of the disease: bilateral ptosis, dysphagia, external ophthalmoplegia, dysarthria, weakness of the facial muscles, hypotrophy of the shoulder, sub- and supraclavicular, subscapularis, gluteal muscles. At the age of 72, complaints: difficulty in walking, inability to cross a small threshold, to get up from a sitting position on their own. He considers himself ill from the age of 46, when rapid fatigability appeared and the upper eyelids began to drop. After 50 years, choking and nasal symptoms appeared. In the neurological status: a patient of high stature, asthenic constitution. Distinguishes odors. Visual acuity is reduced due to presbyopia. Pupils D = S, rounded. Already the left palpebral fissure, the eyelids close the upper third of the pupil (operated on for ptosis in 2008). The photoreaction is reduced. External ophthalmoplegia. No nystagmus. Trigeminal points are painless on palpation. The chewing muscles are affected. Sunken temporal fossa. The nasolabial fold on the right is less pronounced. Puffs out her cheeks and bares her teeth weakly. Hearing acuity is reduced on both sides, there is a hearing aid on the right. The pharyngeal reflex is reduced, the perception of taste is not impaired. Snuffiness, dysphagia. The soft palate is inactive during phonation. Raises shoulders and turns head satisfactorily. Tongue - deviation to the right, without fibrillation and atrophy. Marinescu-Radovic's symptom D = S ++.

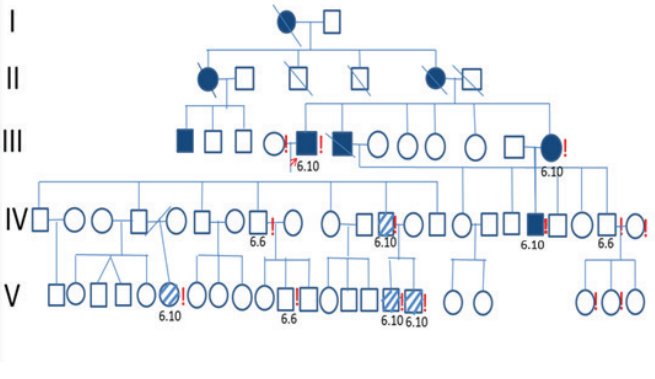

Fig. Fragment of the pedigree of a family with OPMD with the results of DNA analysis for a mutation in the PABPN1 gene;
Note. 6/6; 6/10 - results of DNA analysis for mutation in the PABPN1 gene ;! - personally examined patients; filled square - patient with OPMD, empty square - clinically healthy; the shaded square is a clinically healthy carrier of the mutation in the PABPN1 gene. I, II generation - deceased parents, III generation - patients and their siblings, IV - children of the proband and siblings of the proband, V - children who have not reached the age of onset of the disease.

He cannot raise his arms and legs, bend his legs at the knee joints, does not stand up independently from lying and sitting positions. Hand strength D = 13kg, S = 19kg. In the proximal parts of the arms, the strength was reduced to 3 points, in the distal parts to 4 points, in the proximal parts of the legs to 2 points. Muscle tone is diffusely reduced. Wide interscapular space. Hypotrophy of the subscapularis and subclavian muscles, more on the right, hypotrophy of the biceps and triceps muscles, Weakness of the iliopsoas on both sides. Hypotrophy of the gluteal muscles, quadriceps muscles. Deep tendon reflexes from the arms and legs are reduced, no difference in sides. There are no pathological signs. Coordination tests, PNP performs satisfactorily, CPR cannot raise his legs. Stands in the Romberg position. Duck gait. Superficial and deep sensitivity are not disturbed.

Sibs probanda T. (III-12, fig. 1), born in 1943 for the first time independently applied to a medical genetic consultation at the age of 64. Considers himself a patient since 51 years old, when complaints of general weakness, periodic coughing when swallowing, nasal voice, drooping of the upper eyelids appeared within 2 years. In the clinic in 2008: ptosis, external ophthalmoplegia, dysphagia, nasal tone, poorly intelligible speech, weakness of facial muscles, weakness of the subscapularis muscles and lower extremities. Objectively at the moment: general condition of moderate severity, general emaciation is expressed, asthenic. Neurological status: hypomimia, dysphonia. Low standing of the eyelids, almost complete ptosis on both sides. Pupils S> D, photoreaction is reduced, paresis of abduction in both directions, paresis of gaze upward. Diplegia n. facialis. The soft palate is motionless during phonation. The pharyngeal and palatal reflexes are absent. There are no atrophies and fasciculations. Severe atrophy of all muscle groups of the trunk and limbs. Tendon reflexes are absent from the hands, knee and Achilles are reduced. Tetraparesis is predominantly proximal. Does not move independently. No sensitivity disorders. He does not perform coordination tests due to weakness in the limbs.

Neurological examination in the dynamics of the proband and siblings of the

N. family showed that both patients had a pronounced progression of the disease in the form of an increase in bilateral ptosis, impaired swallowing, and the development of flaccid tetraparesis. At the same time, the proband could hardly move, and the sibs had a pronounced deep tetraparesis, as a result of which the patient could not move independently. Both patients required palliative therapy and nasogastric tube placement. The rest of the family members examined during the expedition had no symptoms of OPMD. In the clinical picture of the disease, as the symptoms progress, the greatest danger is dysphagia, which leads to aspiration of food into the respiratory tract and, as a consequence, to the development of aspiration pneumonia. Palliative neurology in OPMD involves tube feeding or stoma placement. There is currently no effective treatment. Techniques have been described to dissect the cricopharyngeal muscle to improve swallowing but not prevent aspiration. If ptosis interferes with vision, use special adhesive tape on the eyelids, wire eyelid holders, which are attached to the frame of glasses, or, if there is no pronounced weakness of the facial muscles, they resort to surgical treatment [3, 5]. From the anamnesis of patients and their medical records, it was established that patients received once a year symptomatic drug treatment at the place of residence. The drugs were prescribed for oral administration, in view of movement disorders, such as Carniel 2.0 mg 2 times - for a long time, Cytoflavin, milgamma, Dibazol 5 mg 3 times a day, Neuromidin. Such a course of treatment is insufficient for the restorative treatment of such patients, let alone palliative therapy. Patients do not have the opportunity to receive massage, physiotherapy exercises, physiotherapy electrical procedures. Although adequately prescribed therapy cannot cure the patient, it can improve his quality of life and prolong his life.

Conclusion. Taking into account the course of the disease, characterized by the steady development of the symptoms of the disease, which leads to a decrease in the quality of life, patients with OPMD need to undergo courses of symptomatic therapy 2 times a year in a specialized neurological department. Physicians should advise patients on what to expect as OPMD progresses, and discuss available interventions and supportive care to reduce the risk of choking and other complications of OPMD.

Such counseling can reduce the emotional burden of the disease. Patients with burdened families of OPMD, medical workers responsible for managing patients, as well as all people with rare diseases, need reliable, up-to-date information about the disease. For a timely diagnosis, it is necessary to conduct health education among the population and among families with a burdened heredity of OPMD, observing all the rules of bioethics. Early diagnosis in burdened families will allow prenatal diagnostics to reduce the burden of the disease in the population, as well as presymptomatic treatment in case of carriage of the pathological PABPN1 gene. The difficulty of making a diagnosis is associated with the late onset of the disease (40-60 years), especially in families with an undetected burdened heredity. Therefore, public health education plays an important role in timely diagnosis. In addition, timely diagnosis will provide an opportunity for early career guidance of the patient. Develop useful habits of a healthy lifestyle, limit hard physical labor, while receiving all symptomatic therapy, such as correction of ptosis of the eyelids using blephoroplasty and cricopharyngeal myotomy, will improve dysphagia in the early stages of the disease, as well as chemodenervation with botulinum toxin A into the cricopharyngeal muscle. In the later stages, surgical methods of treatment will not be effective. It is necessary to continue cooperation with the Ust-Aldan district for further work on health education of the population.

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