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Professor A.R. Varfolomeev is 80 years old

КОЛОНКА ГЛАВНОГО РЕДАКТОРА

Dear colleagues!

Here is the fourth issue of the Yakut Medical Journal of 2019. Another year has passed, filled with good deeds, creative and professional plans fulfilled, difficulties surpassed and new heights reached.

We continue to draw the attention of the authors and users of our publication to the main sections of the journal. If in the second issue of the journal of 2019 we discussed “Arctic medicine” section, which has been active and fruitful from the very beginning, then in this final issue of the year, we turn to “Clinical case” section, which is in our opinion, is very relevant and has an undeniable scientific and practical appeal. In this issue of the magazine you will get acquainted with an extremely rare clinical case of sex cord-stromal tumor of the fallopian tube (Biryukov A.E. et al.), as well as a clinical description of a genetic disease - Bruton agammaglobulinemia in a child from Yakutia (Ivanova O.N. et al.).

The Yakut Medical Journal is and remains a scientific and practical medical publication, covering a wide range of health problems, prevention, diagnosis and treatment of widespread diseases, promoting the achievements of medical science and medical education in one of the Arctic regions of the Russian Federation. The priority research areas of the journal are issues of cardiology, neurology, pediatrics, genetic and immunological studies. The doors of our journal are open to anyone who is interested in the health problems of the population of our country.

We will continue to improve the website of our journal. The editorial board, in order to improve the quality of articles, as well as to increase its competitiveness, inform ativeness and accessibility, will facilitate the functioning of stable feedback with users of the Yakut Medical Journal. The editorial board is working with authors with great inspiration and is doing everything so that readers can get acquainted with the interesting results of scientific research on the pages of our journal. We are always ready to listen to your opinion about the magazine and accept suggestions for its improvement.

December came, and with it frost grows stronger, thick fog covers the streets and houses. Despite this, all is calm, a premonition of something secret, unknown and joyful lifts our spirit. Frost and fog go by the wayside. The end of the year, the debriefing – it’s exciting and solemn.

New Year celebrations are coming, and a well-earned January vacation is coming with it. On the eve of the New Year of 2020, I wish our dear authors and readers good health and good spirits, new wonderful ideas and achievements, and the realization of good intentions! May the New Year bring luck and success for all of us! Harmony, prosperity and happiness! Longevity and prosperity to our journal, as well as relevance and high demand by authors and readers!

Editor-in-chief ***Anna Romanova***

EDITORIAL

L.N. Afanasieva, A.S. Golderova, L.C. Burnasheva, T.I. Nikolayeva, S.A. Myreeva, M.M. Vinokurov, N.N. Makarova, P.M. Ivanov

MALIGNANT NEOPLASMS AS THE MOST IMPORTANT ECONOMIC AND SOCIAL PROBLEM IN THE NORTH

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The analysis of the data of 18.117 cases of death of the official statistics of the Republican Statistical Office of the Republic Sakha (Yakutia) for 2001 - 2015 was carried out. We presented the results of the analysis of socio-economic damage related to mortality from malignant neoplasms (MN). Analysis of mortality showed that tumors of gastroenterological localization in the male population of Yakutia account for 41.3% of all deaths from malignant neoplasms, and in the female - 40.7%. Similar indicators for Russia were respectively 35.6% - in men and 36.7% - in women. The second highest frequency in men in the RS (Ya) is occupied by malignant tumors of respiratory organs (32.6; Russian Federation - 30.2%), and women - genital organs (16.4 and 15.3%, respectively). Men have the third highest ranking of urinary neoplasms (4.7%) and women have breast cancer (12.1%).

In both populations MN of digestive organs remain the dominant localizations, their total share was at the beginning and end of the analyzed period (2001, 2015), respectively, 52.8 and 45.2% in men and 41.3 and 40.0% in women.

Between 2001 and 2015, mortality trends in both populations are estimated to be upward (with average annual growth rates for men and women 0.55 and 0.35%, respectively). By 2020, the projected level of total mortality rates from malignant tumors in men will be $145.0^0/_{0000}$. (with an average annual growth rate of 0.70%). Mortality rates from rectal cancer are likely to be high - $5.3^0/_{0000}$ (3.60%), pancreas - 7.0 (1.15), liver - 14.4 (0.75) and respiratory disease - $44.3^0/_{0000}$ (0.85%).

Keywords: malignant neoplasms, mortality, socio-economic damage.

Introduction. As estimated, 40 million deaths from non-communicable diseases occurred globally in 2015, accounting for 70% of the world 's 56 million deaths. Most of these deaths were caused by four major non-communicable diseases, namely, cardiovascular disease - 17.7 million deaths (accounting for 45% of all non-communicable diseases deaths); cancer - 8.8 million deaths (22%); chronic respiratory diseases - 3.9 million deaths (10%); And diabetes - 1.6 million deaths (4%) [3].

In 2017 in Russia it is for the first time revealed nearly 541 thousand cancer patients (more than 617 thousand new tumors), died of malignant new growths of 290.7 thousand patients (15.9% in the general structure of mortality) - the second reason after cardiovascular diseases. About 40% of the first detected malignant neoplasms have the III-IV stage of the disease, which causes a rather high one-year fatality (22.5%) [5].

In the Russian Federation, about 1/3 (29.5%) of men 's deaths are caused by MN, and stomach tumors caused 12.6% of men 's death. Further, the wound sites were distributed as follows: malignant tumors (MT) of the urinary system (7.0%), prostate (6.6), colon (5.8) and rectum (5.2%), pancreas (5.0%), head and neck (4.7%) and hemoblastosis (4.6%) [1, 2].

In Yakutia, one in six women and one in nine men among those who died in the Republic during the year of the MN are the main cause of their death. Their share is 14.8% (in the Russian Federation - 13.8%) from all deaths in the republic and in importance they take the second place after cardiovascular pathology [4].

The aim of the study is to analyze the data of population mortality from the MN of the population of Yakutia. The results obtained will be of interest to specialists in the development of a targeted, reasoned anti-cancer program.

Materials and methods of research. The analysis of the official statistics of the Republican Statistical Office of the Republic Sakha (Yakutia) for 2001 - 2015 has been carried out. During this period, 18.1 thousand deaths from the MN have been registered in the Republic.

Considering that the results of socio-economic analysis at the regional level are important for determining the priorities of health care on the ground, we estimate the socio-economic damage associated with mortality from health care. In order to rank certain forms of MN according to the degree of their socio-economic importance, we have used a method of counting based on a derivative of the average life expectancy, expressed in the loss of man-years of life.

The population, territorial and temporary patterns of mortality of the population of Yakutia have been established, the forecast and socio-economic damage have been calculated. In order to estimate social and economic losses in connection with death from the MN, a model based on the identification of the difference between actual and actual average life expectancy was used.

Results and discussion. In 2015 in RS (YA) the number of deaths from carcinoma reached 1227, which is 3.8% higher than in 2001 (1182) at an average annual growth rate of 0.25%. Men were

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54.2% and women were 45.8%, the ratio of men to women was 1.2: 1.0 (Figure 1).

Similar indicators for Russia were respectively 35.6% - in men and 36.7% - in women. The second highest frequency in men in RS (Ya) is occupied by malignant tumors (MT) of respiratory organs (32.6; RF - 30.2%), and women - genital organs (16.4 and 15.3%, respectively). In men, the third place is taken by neoplasms of urinary organs (4.7%), and in women - breast cancer (12.1%).

Characterizing the dynamics of mortality from malignant neoplasms of the population RS (Ya), it can be noted that in both populations malignant tumors of digestive organs remain the dominant localizations, their total share was 52.8 and 45.2% in men and 41.3 and 40.0% in women at the beginning and end of the analyzed period (2001, 2015), respectively.

In 2015, men ranked first in mortality rates: lung cancer (42.1 $^{0}/_{0000}$), liver cancer (16.8), stomach cancer (15.3), pancreas cancer (8.8) and esophagus cancer (7.7), and women's cancer in

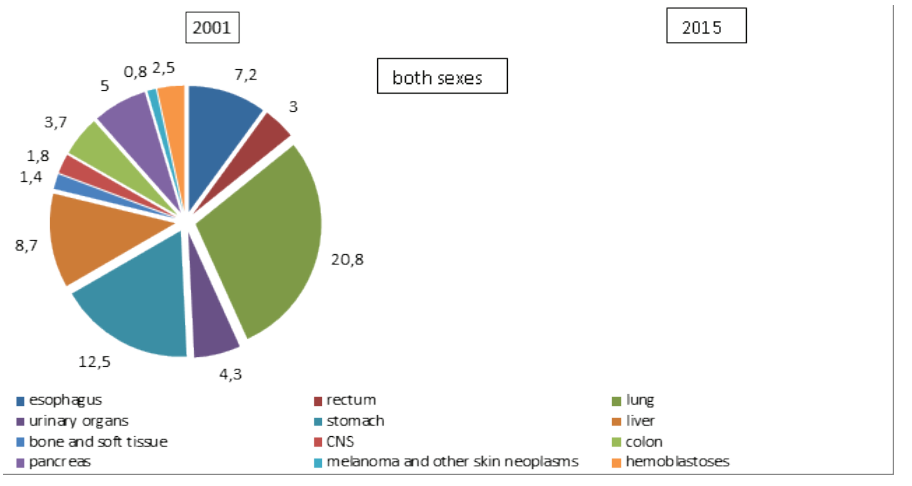


Fig. 1. Structure of mortality in the Republic Sakha (Yakutia) from malignant neoplasms in 2001 and 2015 (%)

mortality rates: breast cancer (13.8), lung cancer (12.8), stomach cancer (10.9), liver cancer (9.9) and cervical cancer (8.5 $^{0}/_{0000}$), respectively. Between 2001 and 2015, mortality trends in both populations are estimated to be upward (with average annual growth rates for men and women 0.55 and 0.35%, respectively) (Table 1).

The highest annual mortality rate of the population of Yakutia from MN is in

Table 1

Dynamics of mortality from malignant neoplasms of RS (Ya) population for 2001-2015 and probable characteristic for 2020

Localization	Years															Forecast 2020
	2001	2002	2003	2004	2005	2006	2007	2008	2009	1010	2011	2012	2013	2014	2015	
Both sex																
Malignant neoplasms - total	120.1	124.6	130.5	127.0	125.1	126.9	129.6	125.2	131.6	120.3	125.3	127.7	125.5	126.9	128.0	126.8
MN of head and neck	3.9	3.3	3.4	4.4	3.1	3.9	4.3	3.4	4.2	2.9	2.7	3.1	3.9	4.4	3.9	3.7
Digestive organs	56.4	59.0	59.4	58.3	56.1	54.3	52.6	53.1	53.3	48.5	49.0	50.5	53.4	48.4	52.6	54.2
Respiratory organs	30.4	30.6	30.1	30.4	33.3	31.9	29.8	28.4	35.2	26.6	31.5	28.6	29.1	28.6	29.6	30.3
Bones and soft tissues	1.7	3.5	2.8	3.7	2.3	2.1	3.2	2.9	2.9	2.0	3.5	3.0	2.2	1.8	3.0	2.8
Skin cancer and melanoma	1.1	0.7	1.3	0.9	1.5	0.9	1.1	1.8	1.3	1.6	0.9	1.0	1.3	1.6	1.7	1.4
Uric bodies	6.0	6.4	6.5	5.1	4.2	6.8	7.0	5.5	4.6	5.1	5.5	6.7	4.6	5.1	4.6	5.5
CNS	2.2	2.0	3.2	2.1	3.3	2.5	4.1	2.4	3.2	2.6	2.7	3.1	3.2	3.2	2.6	2.8
Hemoblastoses	3.1	3.7	5.1	4.5	4.4	4.5	3.2	5.6	3.5	5.2	3.4	5.7	4.3	5.8	4.8	4.5
Men																
Malignant neoplasms – total	132.1	143.1	153.4	145.5	145.5	142.8	147.4	137.4	147.8	133.9	146.4	147.3	139.9	150.0	143.0	145.0
MN of head and neck	5.5	4.3	5.8	8.0	5.4	6.9	6.7	5.0	7.6	4.4	3.9	5.0	4.7	4.5	5.8	5.7
Digestive organs	69.9	72.4	76.8	74.5	74.0	60.5	63.1	60.4	59.6	53.6	59.3	60.1	59.5	75.9	59.1	65.9
Respiratory organs	39.1	43.4	42.9	44.7	46.1	48.1	40.3	42.6	50.7	39.4	48.2	43.1	44.2	45.5	46.7	44.3
Bones and soft tissues	2.4	4.3	2.8	5.0	2.8	2.4	4.4	4.0	4.3	2.9	3.0	3.9	2.8	4.5	3.6	3.7
Skin cancer and melanoma	1.0	0.6	1.5	0.8	2.1	1.1	2.2	1.5	1.8	1.7	0.8	1.1	1.5	0.6	2.0	1.4
Urinary organs	2.7	2.7	3.2	3.2	1.9	2.2	4.6	2.8	3.7	3.7	4.9	5.4	2.4	2.8	5.8	3.4
CNS	6.3	4.1	4.7	5.8	5.4	8.6	8.7	5.6	5.7	5.2	7.9	8.6	5.9	8.8	6.2	6.4
Hemoblastoses	1.8	2.5	4.3	2.6	3.5	3.3	4.3	3.7	3.3	3.5	2.6	3.2	4.1	2.6	2.6	3.2
MN of head and neck	4.1	5.1	5.0	5.2	4.3	4.8	3.7	5.9	4.4	5.9	4.3	6.9	5.0	6.0	4.9	5.0
Women																
Malignant neoplasms - total	108.2	106.5	108.6	109.3	105.8	112.0	112.8	113.7	116.5	107.5	105.3	109.1	111.9	105.1	114.0	111.3
Lips. oral cavity	2.2	2.2	1.0	1.0	0.8	1.0	2.0	1.8	1.0	1.6	1.6	1.4	3.1	4.3	2.0	1.8
Digestive organs	43.1	45.8	42.9	42.9	39.1	48.5	42.7	46.3	47.3	43.7	39.2	41.5	47.6	22.6	46.4	43.1
Respiratory organs	21.8	18.2	17.9	16.8	21.1	16.6	19.8	15.1	20.6	14.7	15.7	14.9	14.9	12.6	13.6	17.0
Bones and soft tissues	1.0	2.8	2.7	2.4	1.8	1.8	2.0	1.8	1.4	1.2	3.8	2.0	1.6	0.6	2.2	1.9
Skin cancer and melanoma	1.2	0.8	1.2	1.0	1.2	0.8	2.0	2.0	1.0	1.4	0.9	1.0	1.2	2.6	1.6	1.4
Mammary gland	14.1	12.9	12.8	14.0	11.7	14.5	12.9	12.7	14.1	8.0	13.0	14.5	12.4	13.4	13.8	12.9
Genital organs	14.5	15.7	17.1	17.9	16.8	14.5	16.5	18.4	16.5	12.6	14.2	15.3	15.9	18.9	18.7	16.1
Urinary organs	5.0	4.4	3.7	4.3	2.9	4.5	4.1	5.3	3.5	4.9	2.8	4.1	3.3	1.6	2.6	3.7
CNS	2.6	1.6	2.1	1.6	3.1	1.8	3.9	1.2	3.1	1.8	2.8	3.1	2.4	3.9	2.6	2.5
Hemoblastoses	2.2	2.2	5.2	3.9	4.5	4.3	2.7	5.3	2.7	4.5	2.6	4.5	3.7	5.5	4.7	3.9

the age group over 70 years (910.8$^{0}/_{0000}$). Within this age group, both male (1,452.7$^{0}/_{0000}$) and female (802.0 $^{0}/_{0000}$) age mortality rates are the highest (Table 2).

It should be noted that malignant tumors of hepatobiliary zone organs, which make up 1/3 of all deaths from malignant tumors of digestive organs, allow classifying them as leading forms of oncological pathology in conditions of the North as causing significant social and economic damage to the population of the Republic.

Table 2

Dynamics of mortality from malignant neoplasms of RS (Ya) population for 2001-2015 and probable characteristic for 2020

Localization	Years a	Abs. number	ИП	Per 100,000 population of appropriate age														
				0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70 +.
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
both gender																		
Malignant neoplasms - total	2001-2005	6039	127.3	3.0	4.2	5.4	4.6	5.7	10.8	19.6	37.4	66.9	136.0	252.0	386.7	628.9	873.2	1139.2
	2006-2010	6077	127.9	3.1	2.8	2.6	4.3	5.1	8.1	15.1	23.7	65.5	102.0	203.8	373.1	570.1	801.0	1083.5
	2011-2015	5640	126.4	2.0	0.6	3.1	3.1	5.8	4.5	18.1	29.8	42.2	99.0	180.8	306.3	491.4	741.5	910.8
Lip, Oral cavity, throat	2001-2005	173	3.6	0.3	0.0	0.0	0.0	0.0	0.8	0.0	0.9	2.1	6.1	8.9	15.6	17.2	22.8	21.9
	2006-2010	131	2.8	0.3	0.0	0.0	0.0	0.0	0.8	0.0	1.2	2.4	4.2	6.4	9.3	16.7	7.9	11.3
	2011-2015	165	3.5	0.2	0.0	0.0	0.0	0.3	0.5	0.0	0.6	0.6	3.2	6.8	8.8	8.3	32.6	23.1
Digestive organs	2001-2005	2785	58.7	0.3	0.3	0.2	0.4	1.3	3.5	8.1	12.0	25.6	56.6	105.9	164.5	288.7	443.2	608.3
	2006-2010	24.9	52.8	0.3	0.3	0.0	0.7	0.0	1.3	4.2	7.2	20.4	37.6	74.8	129.8	235.2	349.8	528.2
	2011-2015	2224	50.6	0.0	0.0	0.0	0.0	0.8	1.6	5.2	9.4	15.9	34.4	67.2	115.3	182.7	318.5	409.3
Respiratory organs	2001-2005	1491	31.4	0.0	0.6	0.0	0.2	0.5	0.5	0.9	3.7	11.9	33.2	64.1	110.7	180.7	232.6	278.1
	2006-2010	1443	30.4	0.3	0.0	0.0	0.5	0.4	0.8	0.6	0.6	12.0	20.4	48.0	102.7	166.7	209.9	241.5
	2011-2015	1348	30.1	0.0	0.0	0.6	0.0	0.5	0.0	0.8	1.5	7.0	21.4	46.2	81.9	139.5	167.9	210.1
Bones and soft tissues	2001-2005	135	2.8	0.3	0.3	1.1	1.2	0.8	0.3	0.3	1.5	2.1	3.3	9.3	8.2	10.0	11.0	14.0
	2006-2010	123	2.6	0.0	0.0	0.3	1.2	0.7	1.0	0.6	1.5	1.8	3.4	5.0	6.3	7.6	16.0	12.0
	2011-2015	118	2.8	0.0	0.2	0.0	0.3	0.3	0.0	0.3	1.5	2.3	1.2	5.2	6.5	7.9	12.0	19.0
Melanoma, skin cancer	2001-2005	55	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.6	1.2	1.4	1.3	2.3	2.5	6.3	7.9	6.9
	2006-2010	74	1.5	0.0	0.0	0.0	0.0	0.2	0.0	0.3	0.0	1.2	0.9	2.8	4.8	5.4	5.0	16.0
	2011-2015	58	1.3	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.9	0.6	0.9	1.9	4.9	2.8	3.9	8.9
Urinary organs	2001-2005	272	5.7	0.0	0.0	0.2	0.0	0.0	0.0	0.3	1.4	1.6	4.8	11.5	16.3	37.5	42.1	54.7
	2006-2010	276	5.8	0.0	0.0	0.0	0.0	0.0	0.3	0.3	0.3	2.4	3.7	7.8	21.6	28.9	44.3	45.7
	2011-2015	241	5.1	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.0	1.9	4.1	6.3	12.4	21.3	27.8	44.5
CNS	2001-2005	123	2.6	1.5	1.1	1.6	0.8	0.8	0.3	1.7	2.6	2.1	3.3	6.1	6.3	7.0	10.5	7.5
	2006-2010	141	3.0	1.4	0.3	1.1	0.2	0.9	0.3	1.1	2.7	3.6	3.2	5.6	8.6	6.9	14.8	11.3
	2011-2015	132	2.9	0.0	0.2	0.6	0.9	1.0	0.0	2.1	4.1	0.3	2.8	4.4	3.9	12.1	17.3	11.0
Hemoblastoses	2001-2005	212	4.5	0.9	1.7	2.2	1.5	2.1	1.6	2.3	1.7	3.0	4.3	8.0	6.9	15.6	18.4	32.8
	2006-2010	208	4.3	0.6	2.1	1.1	0.9	1.7	1.9	1.4	2.4	2.1	4.4	7.0	14.1	16.7	17.7	19.8
	2011-2015	215	9.8	0.0	0.6	3.0	2.1	4.3	1.5	3.2	5.6	5.1	11.0	17.5	23.1	30.0	63.5	24.7

Continuation of table 2

Men																		
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Malignant neoplasms - total	2001-2005	3399	146.7	4.1	5.5	4.8	6.6	4.7	6.4	17.7	38.3	70.0	169.6	341.3	529.5	889.6	1248.6	1667.0
	2006-2010	3294	143.0	4.4	3.6	3.9	6.5	6.1	7.4	11.7	20.0	72.0	122.2	268.1	528.1	802.8	1116.8	1427.4
	2011-2015	3364	146.4	1.1	1.8	4.3	5.9	6.6	15.1	26.1	37.5	113.8	239.6	239.6	435.7	701.5	1034.6	1452.7
Lip, throat	2001-2005	137	5.9	0.6	0.0	0.0	0.0	0.0	1.1	0.0	1.1	3.3	10.1	14.9	32.6	30.8	43.4	48.1
	2006-2010	141	6.1	0.0	0.0	0.0	0.0	0.0	0.5	0.6	1.8	3.1	5.2	15.6	28.2	19.5	45.1	54.4
	2011-2015	121	5.2	0.0	0.0	0.0	0.5	0.0	0.0	0.6	0.6	5.9	12.1	12.1	18.2	21.8	48.7	7.2
Digestive organs	2001-2005	1736	74.9	0.6	0.6	0.0	0.4	0.5	3.7	9.1	16.6	35.5	82.4	160.8	244.4	436.6	712.3	968.4
	2006-2010	1368	59.4	0.6	0.0	0.0	0.9	0.0	1.1	5.0	7.3	26.4	49.4	113.0	187.4	336.7	460.7	705.2
	2011-2015	1369	59.0	0.0	0.0	0.6	1.0	2.6	7.3	12.5	19.4	49.1	95.9	95.9	166.6	263.6	426.0	657.7
Respiratory organs	2001-2005	1021	44.1	0.0	1.1	0.0	0.4	0.5	1.1	1.1	7.4	20.3	55.8	116.7	190.1	293.5	347.4	443.4
	2006-2010	1018	44.2	0.0	0.0	0.0	0.9	0.9	0.5	0.6	1.2	21.5	36.9	85.4	189.9	303.1	358.1	370.4
	2011-2015	1035	44.6	0.0	0.6	0.0	0.5	0.0	1.0	2.4	8.4	33.4	78.5	78.5	159.3	252.7	326.2	391.0
Bones and soft tissues	2001-2005	82	3.6	0.6	0.0	1.3	1.6	1.0	0.0	0.6	2.2	2.8	5.3	11.5	15	12.6	8.6	23.0
	2006-2010	82	3.6	0.0	0.0	0.0	2.3	1.3	1.1	1.2	2.4	3.7	5.8	5.4	8.3	12.4	27.5	20.4
	2011-2015	71	3.1	0.0	0.0	0.0	1.0	0.0	0.5	3.0	0.6	2.7	6.9	6.9	5.8	14.1	12.2	30.7
Melanoma, skin cancer	2001-2005	29	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.6	1.7	1.8	1.0	2.1	1.4	9	10.8	10.5
	2006-2010	38	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.5	3	8.3	8.9	7.5	20.4
	2011-2015	48	2.1	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.6	2.0	4.0	4.0	5.1	9.8	7.3	24.3
Prostate	2001-2005	65	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.6	4.1	12.2	10.9	30.4	56.5
	2006-2010	78	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8	5.0	19.5	50.1	64.6
	2011-2015	112	4.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.9	2.9	5.1	28.3	48.7	33.9
Urinary organs	2001-2005	172	7.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.9	1.4	6.4	12.9	24.4	68.8	73.8	87.8
	2006-2010	167	7.3	0.0	0.0	0.0	0.0	0.0	0.5	0.6	0.6	3.1	6.2	10.2	32.3	37.2	75.1	68.0
	2011-2015	172	7.4	0.0	0.0	0.0	0.0	0.0	1.0	0.0	1.3	6.5	13.3	13.3	23.3	34.9	51.1	80.8
CNS	2001-2005	69	3.0	0.0	1.7	0.9	1.2	0.0	0.0-	1.7	2.9	1.9	3.2	10.2	9.5	12.7	15.2	4.2
	2006-2010	83	3.6	2.2	0.6	2.2	0.5	1.7	0.5	1.1	1.2	4.3	3.6	7.2	13.3	8.9	20.0	15.3
	2011-2015	74	3.2	0.6	0.0	0.6	1.0	0.0	1.6	5.3	0.0	3.9	6.4	6.4	6.5	14.2	12.2	19.4
Hemoblastoses	2001-2005	118	5.1	0.6	2.2	2.6	2.1	2.1	0.0	3.4	1.1	3.8	6.9	10.9	10.9	23.6	21.7	39.7
	2006-2010	113	4.9	0.0	0.6	3.0	1.7	0.9	0.8	2.6	1.1	3.0	2.4	4.7	9.0	23.8	16.0	25.0
	2011-2015	126	5.4	0.0	0.6	2.4	1.5	2.2	1.5	1.2	3.8	3.9	9.8	9.8	15.3	16.3	41.3	40.4

End of table 2

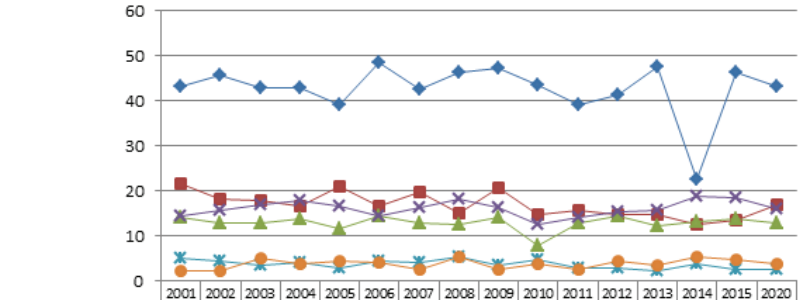
Women																		
Malignant neoplasms - total	2001-2005	2640	108.8	1.9	2.9	6.0	2.6	6.6	15.3	21.4	36.4	63.9	104.9	172.7	264.6	430.9	618.6	883.0
	2006-2010	2787	113.8	1.7	1.9	1.2	1.9	4.0	8.7	18.5	27.5	59.3	83.4	148.0	247.0	395.0	596.1	912.5
	2011-2015	2773	105.4	0.0	0.0	1.9	1.9	5.2	4.2	20.1	35.3	46.2	88.9	214.6	214.6	334.1	535.1	802.0
Lip, oral cavity, throat	2001-2005	36	1.5	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.6	0.9	2.5	3.6	1.2	6.9	8.8	9.1
	2006-2010	37	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.5	2.6	3.4	6.7	6.5	13.5
	2011-2015	51	2.08	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.6	0.0	2.98	3.0	3.23	17.41	18.6
Digestive organs	2001-2005	1049	43.2	0.0	0.0	0.5	0.4	2.0	3.3	6.9	7.4	16.1	32.9	57.2	96.3	176.2	260.7	433.4
	2006-2010	1119	45.7	0.0	0.6	0.0	0.5	0.0	1.5	3.4	7.2	14.7	26.7	41.7	83.0	158.8	277.8	440.2
	2011-2015	1060	43.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.0	81.0	81.1	109.7	251.7	358.3
Respiratory organs	2001-2005	470	19.4	0.0	0.0	0.0	0.0	0.5	0.0	0.6	0.0	3.7	12.3	17.5	42.9	95.0	154.6	197.9
	2006-2010	425	17.3	0.6	0.0	0.0	0.0	0.0	1.0	0.6	0.0	2.9	5.2	15.6	31.7	64.0	113.7	177.4
	2011-2015	374	15.2	0.0	0.0	0.0	0.0	0.0	0.5	0.0	1.2	0.0	0.0	18.4	18.5	60.5	47.4	144.3
Bones and soft tissues	2001-2005	53	2.1	0.0	0.6	1.0	0.0	0.5	0.5	0.0	0.6	1.4	1.5	7.2	2.3	8.3	13.2	10.2
	2006-2010	41	1.7	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.6	0.0	1.5	4.7	4.7	4.0	8.1	8.5
	2011-2015	57	2.3	0.0	0.0	0.0	0.0	0.5	0.0	8.0	8.8	10.6	14.0	5.4	5.4	3.2	12.7	17.8
Melanoma, skin cancer	2001-2005	26	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.6	1.0	1.5	2.4	3.5	4.2	5.9	5.1
	2006-2010	36	1.4	0.0	0.0	0.0	0.0	0.4	0.0	0.6	0.0	1.2	1.4	2.6	2.0	2.7	3.2	14.4
	2011-2015	33	1.3	0.0	0.0	0.0	0.0	0.0	0.5	1.6	5.3	7.4	14.6	3.0	3.0	1.6	6.3	10.8
Mammary gland	2001-2005	318	13.1	0.0	0.0	0.0	0.0	0.0	0.5	1.2	5.7	15.6	22.1	24.7	56.9	38.5	61.9	67.0
	2006-2010	298	12.2	0.0	0.0	0.0	0.0	0.0	0.0	2.8	4.2	6.5	17.2	28.7	29.7	38.7	52.0	66.8
	2011-2015	326	13.2	0.0	0.0	0.0	0.0	0.5	0.5	1.1	1.2	0.6	3.0	32.1	32.2	52.4	58.5	69.8
Genital organs	2001-2005	402	16.6	0.0	0.0	0.0	0.0	0.0	6.0	8.1	15.4	17.9	22.1	44.5	39.5	71.6	54.5	70.0
	2006-2010	385	15.7	0.0	0.0	0.0	0.0	0.9	3.1	7.3	8.4	21.1	17.2	28.7	49.3	40.0	61.7	69.3
	2011-2015	408	16.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	2.4	38.7	38.7	46.0	55.4	62.8
Urinary organs	2001-2005	100	4.1	0.0	0.0	0.5	0.0	0.0	0.0	0.6	0.0	1.8	3.4	10.2	9.3	13.8	20.6	38.6
	2006-2010	109	4.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8	1.4	5.7	12.8	22.7	24.4	34.6
	2011-2015	82	3.3	0.0	0.0	0.6	0.6	0.5	0.0	2.1	2.9	0.6	0.2	5.9	6.0	11.3	12.7	32.6
CNS	2001-2005	54	2.2	0.6	0.6	2.3	0.4	1.5	0.5	1.7	2.3	2.3	3.4	2.4	3.5	2.8	7.4	9.1
	2006-2010	58	2.4	0.6	0.0	0.0	0.0	0.0	0.0	1.1	4.2	2.9	2.9	4.2	4.7	5.3	11.4	9.3
	2011-2015	69	2.8	0.0	0.0	0.6	0.6	0.5	0.0	2.1	2.9	0.6	3.0	6.56	6.6	7.26	14.25	9.3
Hemoblastoses	2001-2005	29	3.9	1.2	1.2	1.8	0.9	2.0	3.3	1.2	2.3	2.3	2.0	5.4	3.5	9.6	16.2	29.4
	2006-2010	95	3.9	0.6	1.3	0.6	1.0	2.7	1.0	1.7	1.8	1.8	4.4	5.2	7.4	17.4	13	17.7
	2011-2015	108	4.4	0.0	0.0	0.6	0.6	2.1	0.0	2.0	1.8	1.2	1.2	7.75	7.8	13.7	22.1	24.0

The results of the analysis allow noting that by 2020 the projected level of total mortality rates from containment in men will be 145.0 $^0/_{0000}$ (with an average annual growth rate of 0.70%). Mortality rates from rectal cancer are likely to be high - 5.30/0000 (3.60%), pancreas - 7.0 (1.15), liver - 14.4 (0.75) and respiratory disease - 44.3 $^0/_{0000}$ (0.85%) (Fig.2).

In the female population over the period from 2001 to 2015, the average annual growth rate of mortality from the MN of

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2020
Digestive organs	69,9	72,4	76,8	74,5	74	60,5	63,1	60,4	59,6	53,6	59,3	60,1	59,5	75,9	59,1	65,9
Respiratory system	39,1	43,4	42,9	44,7	46,1	48,1	40,3	42,6	50,7	39,4	48,2	43,1	44,2	45,5	46,7	44,3
Urinary organs	6,3	4,1	4,7	5,8	5,4	8,6	8,7	5,6	5,7	5,2	7,9	8,6	5,9	8,8	6,2	6,4
Hemoblastoses	4,1	5,1	5	5,2	4,3	4,8	3,7	5,9	4,4	5,9	4,3	6,9	5	6	4,9	5

Fig. 2. Dynamics of mortality of the male population of the Republic Sakha (Yakutia) from malignant neoplasms by localization in 2001 - 2015 and probable characteristic in 2020 (per 100 thousand of the population)



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2020
Digestive organs	43,1	45,8	42,9	42,9	39,1	48,5	42,7	46,3	47,3	43,7	39,2	41,5	47,6	22,6	46,4	43,1
Respiratory system	21,8	18,2	17,9	16,8	21,1	16,6	19,8	15,1	20,6	14,7	15,7	14,9	14,9	12,6	13,6	17
Breast	14,1	12,9	12,8	14	11,7	14,5	12,9	12,7	14,1	8	13	14,5	12,4	13,4	13,8	12,9
Genitals	14,5	15,7	17,1	17,9	16,8	14,5	16,5	18,4	16,5	12,6	14,2	15,3	15,9	18,9	18,7	16,1
Urinary organs	5	4,4	3,7	4,3	2,9	4,5	4,1	5,3	3,5	4,9	2,8	3,1	2,4	3,9	2,6	2,5
Hemoblastoses	2,2	2,2	5,2	3,9	4,5	4,3	2,7	5,3	2,7	4	2,6	4,5	3,7	5,5	4,7	3,9

Fig. 3. Dynamics of mortality of the female population of the Republic Sakha (Yakutia) from MT for 2001-2015 on localizations and its probable characterization in 2020 (per 100 thousand population)

the lymphatic and hematopoietic systems (2.1 - a multiple increase in the initial indicators), from colon cancer (1.8 times), and ovary - (1.7), cervix (1.5), genitalia (1.3) and liver cancer (1.1 times).

According to the forecast, by 2020 the total mortality rate from malignant neoplasms will be 111.3$^0/_{0000}$, while maintaining the average annual growth rate of 1.05%. Including: from colon cancer - 6.4$^0/_{0000}$ (1.8%), hemoblastosis - 4.7 (2.1), liver cancer - 9.93 (1.1), from саTcer of genitalia organs - 18.7 (1.3), including ovarian and cervical cancer - 5.5 and 8.5$^0/_{0000}$ (1.5%) respectively (Fig.3).

Given that socio-economic analysis at the regional level is important for determining local health priorities, we estimate the socio-economic damage associated with cancer mortality. In order to rank certain forms of cancer according to the degree of their socio-economic importance, we have used a method of counting based on a derivative of life expectancy, expressed in the loss of man-years of life.

According to official statistics of the Ministry of Health of the Russian Federation, the losses of the population of Russia related to mortality from malignant neoplasms amounted to 4,288.8 thousand people-years. The most significant damage is caused to society by cancer of the lung (678.2), stomach (511.9), breast (401.7) and hemoblastose (268.5). The greatest losses of human-years of life of the working-age population of Russia are related to mortality: from lung cancer (101.2), stomach cancer (72.2), hemoblastosis (61.5), breast cancer (48.0), neck cancer (27.4), colon (21.1) and rectum (20.4) [1].

According to the results of the analysis in Yakutia, the average life expectancy of men due to death from malignant neoplasms is reduced by 1.53 and for women - by 1.74 years. Including men from colon cancer - 1.72 years, rectum - 1.71, primary gland - 1.70, esophagus - 1.69, stomach - 1.60, liver - 1.58, lung - 1.27. In women, life expectancy is shortened due to death from cancer of the lip, throat by 1.92 years, esophagus - 1.94, rectal - 1.92, uterine bodies - 1.92, ovarian - 1.91, colon - 1.88, stomach - 1.85, cervical cancer - 1.84, breast - 1.75, lung - 1.75, liver - 1.85 years.

A comparison of the average number of lost years of life by one deceased in RS (YA) and in Russia as a whole showed that during the analyzed period in the North men and women die from cancer at a relatively young age (under-life years in RS (I) - 13.1, and in women - 14.8 years, in the Russian Federation - 14.5 and 16.7 years respectively). In men, liver cancer (13.6 years), hemoblastosis (13.5), pancreas (12.5), lung cancer (11.8) and rectal cancer (11.7 years) follow in terms of the extent of "lost years of life." In women, in descending order of "lost years of life by one deceased," the first five places are: cervical cancer (19.2), lips (17.8), rectum (16.3), liver (14.6) and breast (14.5). The following are kidney cancer (12.8), stomach cancer (12.6), lung cancer (12.1), bladder cancer (11.9), etc.

In RS (YA) the general losses were about 17.3 thousand person-years of life, of them: from MN of digestive organs - 6.3 thousand (36.4%), respiratory organs - 3.4 (19.6), gemoblastoes - 0.7 (4.0), uric bodies - 0.2 (1.2), a female mammary gland - 1.0 thousand (5.8% - at women) and genitals at women - 0.05 thousand (0.3%).

The data of the analysis on the loss of human-years of life in working age show that the working-age population of the Republic loses 4.9 thousand people-years of life due to mortality from the MN, including 1.7 thousand people-years of life from the digestive organs, 0.8 hemoblastosis - 0.2, female genital organs - 0.05 thousand people-years.

In the North, the average number of lost years of life by one person of working age is 11.0 (in the Russian Federation-8.5), and in the female population - 18.5 (9.4). In men, mortality from larynx cancer (22.7), hemoblastosis (14.2), rectum (13.5), liver (13.5), pancreas (10.1), kidney (9.07), prostate (8.1), and in women - from hemoblastosis (34.6), uterine body (24.9), kidney (23.6), breast (21.5). Women have significant rates of damage in cervical cancer (17.2), lung cancer (15.8), ovarian cancer (13.2) and liver cancer (11.6 years).

The male working-age population of the Republic loses 5.6 years of life annually, including from cancer of the digestive organs of the 2.4 (48.9%), breathing - 1.3 (20.1%) and urinary organs - 0.12 (3.1%). For the female population, the same figures reach 5.9 life years, with the highest losses caused by mortality from digestive cancer (1.25), hemoblastosis (0.24), respiratory organs (0.22), and female genital organs (0.09). In men from certain forms of malignant neoplasms, the first three places of the ranked row occupy p liver (1.21), lung (1.04) and stomach (0.38), and in women - cervical cancer (0.81), breast cancer (0.58 life years).

In conclusion, inflation, which continues for more than a quarter of a century, does not make it very likely to determine the amount of conditionally underexploited national income in monetary terms. However, the overall economic damage caused by deaths from malignant formations to the population of Yakutia was quite significant. Due to the death of the population of the Republic from malignant neoplasms every year loses 3.1 thousand person-years of life, including 0.72 thousand of working age, which is 23.3% of the total loss.

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ORIGINAL RESEARCHES

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THE ANALYSIS OF ASSOCIATIONS OF *HELICOBACTER PYLORI BABA* GENE IN PATIENTS WITH CLINICAL OUTCOMES OF GASTRODUODENAL DISEASES IN YAKUTIA

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УДК 616.34 (571.56)

Introduction: *Helicobacter pylori* has several of the most characteristic adhesins that have the property of a targeted effect on epithelial cells of human stomach, among which the *babA* gene is the most studied and exists in several variants – *babA1*, *babA2*. The BabA protein is high-affinity and binds to mono or difucosylated blood group antigens and each can be modified into blood group A, B, or 0 and expressed on epithelial cells of the stomach. The clinical outcomes of gastroduodenal diseases, depending on the *babA* variants of *Helicobacter pylori* circulated in Yakutia, has not been previously studied. The aim of this work is to analyze of associations of *Helicobacter pylori babA* gene in patients with clinical outcomes of gastroduodenal diseases in Yakutia.

Materials and methods: Gastric biopsy specimens were obtained from 322 patients. According to the results of histological analysis, 188 patients had the presence of *Helicobacter pylori* and divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Results: Chronic gastritis was established in 96 samples (51,1%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 92 samples (48,9%). *Helicobacter pylori babA2* gene variant were identified in 65 samples (34,5%), and *babA1* in 123 samples (65,4%). In the male patients the frequency of the *babA2* gene was almost two times higher (69,6%) than in the female patients (38,3%) (p<0,001). In contrast, in female patients more common was the *babA1* gene (61,6%) than in male patients (30,3%) (p<0,001). It was found that the *babA2* gene variant was significantly more common in samples of patients with chronic gastritis associated with erosions and ulcers of stomach and duodenum (43,4%) than in patients with chronic gastritis (26,0%) (p<0,05). Patients diagnosed with chronic gastritis had more often the *babA1* gene variant (73,9%), than patients with erosive gastritis (56,5%) (p<0,05). In comparing group of patients with different degrees of inflammation there were no statistically significant difference in the activity of inflammation with the presence of the *babA* gene, but there was a slight statistical difference with the second degree of dissemination which had the *babA1* gene variant.

Conclusion: We showed relationship between *babA2* gene of *Helicobacter pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known about data *babA2* which are more virulent and pathogenic than *babA1* gene of *Helicobacter pylori*. The data about *babA2* gene was more frequent in male patients and it may be an additional risk factor for more severe gastroduodenal diseases.

Keywords: *Helicobacter pylori*, gastroduodenal diseases, *babA* gene, Yakutia.

Introduction. In 1994, the US National Institute of Health published an expert opinion stating that the majority of recurrent gastric ulcers and gastritis with increased acidity are caused by infection with the bacterium *Helicobacter pylori* (*H. pylori*). Since then, evidence has gradually accumulated that duodenal ulcers and duodenitis are also associated with *H. pylori* infection. [17, 18]. In 2005 Robin Warren and Barry Marshall were awarded the Nobel Prize in Medicine about the medical significance of the bacteria. Recently, a lot of research has been done on the *H. pylori*. Most studies have found that *H. pylori* is a proven cause of gastroduodenal diseases (chronic gastritis, erosion, ulcers, and cancer of the human stomach). According to the latest data, the proportion of peptic ulcer associated with *H. pylori* infection accounts for 38% of gastric ulcers and 56% of duodenal ulcers worldwide [1].

These facts contributed to the emergence of a large number of works that devoted to the study of characteristics, prevalence and clinical significance of various on the genetic structure and on the virulence of *H. pylori* strains, including its molecular genetic characteristics. It has been shown that genetic factors of *H. pylori* – virulence and pathogenicity can have a great influence on the development and clinical outcomes of diseases of the upper gastrointestinal tract, as well as on the morphological changes in the gastric mucosa. Recently, the spectrum of genetic factors of pathogenicity of *H. pylori* is expanding and their role in

the development of pathological changes at gastroduodenal diseases is becoming more and more obvious [2].

Currently it is known that the genome of the *H. pylori* strain "26695" is represented by 1 667 867 base pairs, and contains 1 630 genes, which 1 576 encode proteins [15]. The study of the *H. pylori* genome is conducted mainly in order to improve the understanding of the pathogenesis of gastritis and peptic ulcer disease, the causes of ability to be the cause of disease. Currently, in the database of *H. pylori* genome, 62 genes are classified as "pathogenic" (their presence in the bacterium correlates with its pathogenicity).

In 2002, the results of study of two sequences of *H. pylori* genomes were published, which has a large family of 32 bound outer membrane proteins (*Helicobacter* outer membrane protein) was discovered. They include the most well-known adhesin *H. pylori* [15], which allow firmly attached to epithelial cells due to numerous bacterial components. The most typical for *H. pylori* are few adhesins, which have the property of a targeted action on epithelial cells of the human stomach, among which the *babA* gene is the most studied and exists in the form of several variants – *babA1*, *babA2* [19]. The *babA2* gene variant creates a start codon in the signal peptide sequence and functions as an adhesin that is identical to the *babA1* variant (91% identity) except for 10 b.p. insertion with a repeat motif that ends with the creation of a translational initiation codon and has the ability to bind Lewis-like antigens (Le^b) in the blood of a human.

The BabA protein is high-affinity and binds to mono- or difucosylated blood group antigens, and each can be modified into blood group A, B, or 0 and expressed on epithelial cells of the stomach [4, 9, 10, 14]. There is a hypothesis that the bacterial adhesion factor BabA, may contribute to the pathogenesis of gastric ulcer and/or gastric cancer by mediating anchorage to the epithelium of the stomach [3]. The clinical outcomes of gastroduodenal diseases, depending on the *babA* gene variants of *H. pylori* circulating in Yakutia, has not been previously studied.

The purpose of this work is to analyze the associations of *Helicobacter pylori babA* gene in patients with clinical outcomes of gastroduodenal diseases in Yakutia.

MATHERIALS AND METHODS. Gastric biopsy specimens were obtained from April 2014 to January 2018 from 322 patients that admitted to the endoscopic department for fibrogastroduodenoscopy (FGDS) in endoscopic department of State autonomous institution of Republic Sakha (Yakutia) «Republican Hospital No. 1 – National Center of Medicine» (RH No.-1 NCM). To confirm the presence of *H. pylori* infection, gastric biopsy specimens were sent for histological examination to the pathoanatomical department of RH No.-1 NCM. According to the results of histological analysis, 188 patients (out of 322) were included in the study, who had the presence of *H. pylori*. The average age was 25,2 years (from 3 to 70). In accordance with macroscopic analysis of the mucosa and histological results, patients were divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Genomic DNA of *H. pylori* was isolated from frozen gastrobiopsies of the examined patients by using phenol-chloroform extraction [7]. To perform the genotyping of babA H. pylori DNA fragments, the sequences of oligonucleotide primers proposed earlier by Rad R. et al., which flanks the region containing the babA gene, were used. (817 b.p.) – 5'-AATCCAAAAAGGAGAAAAAACATGAAA-3' (babA2-F), 5'-TGTTAGTGATTTCGGTGTAGGACA-3' (babA2-R) [16]. Polymerase chain reaction (PCR) was performed on «Bio-Rad» thermocycler. Separation of amplification products was carried in the horizontal electrophoresis camera in a 2% agarose gel. Visualization of PCR products was performed by «Bio-Rad» gel video documentary device using Image Lab ™ Software.

The surveys, provided by the framework of research work, were carried out strictly after the informed consent of participants, parents or legal representatives of minor patients without violations of ethical standards. This study was approved by the local committee on biomedical ethics of the Yakutsk Scientific Center for Complex Medical Problems. Protocol No. 41 of November 12, 2015. Decision №5.

RESULTS. *Analysis of the H. pylori babA frequency occurrence in patients with gastroduodenal diseases*

Endoscopic and histological studies carried out in the first step of work have shown that only in 188 (58,3%) out of 322 patients confirmed the presence of *H. pylori*. The diagnosis of chronic gastritis was established in 96 cases (51,1%), and the diagnosis of chronic gastritis with erosions and ulcers in 92 cases (48,9%). We analyzed the frequency of the *H. pylori babA* gene occurrence among 188 samples with histologically confirmed of *H. pylori* infection. The *babA2* gene variant was identified in 65 samples (34,5%), and *babA1* in 123 (65,4%).

Comparison of the occurrence of H. pylori babA1 and babA2 gene variants in patients depending on the clinical outcomes of *gastroduodenal diseases (erosive or chronic gastritis)*

It was found that the *babA2* gene variant was significantly more common in sample of patients with chronic gastritis associated with erosions and ulcers of stomach and duodenum (43,4%). Patients diagnosed with chronic gastritis more often had the *babA1* gene variant (73,9%) (p<0,05) (Table 1).

Comparison of the occurrence of H. pylori babA1 and babA2 gene variants in patients depending on the activity of inflammation and dissemination degree

There were no found statistically significant difference between comparing group of patients with different degrees of inflammation and with presence of the *H. pylori babA* gene variants (Fig. 2). However, a slight statistical difference was found in comparison with the second degree of dissemination and the variant of the *babA1* gene (Fig. 3).

Comparison of H. pylori babA1 and babA2 gene variants in group of patients depending on gender, age, place of birth and residence

There were no significant differences depending on age, place of birth or residence in patients with *H. pylori babA* gene variants (p>0,05), however, statistically significant differences were found while comparing male and female group (p<0,001) (Table 1). Thus, the frequency of occurrence of the *babA2* gene variant was almost twice as high in group of male patients (69,6%) than in female patients (38,3%) (p<0,001). On the contrary, *babA1* gene (61,6%) was significantly more common in female patients than in male patients (30,3%) (p<0,001) (Table 1).

DISCUSSION. In this paper, for the first time in Yakutia, the frequency of occurrence of *H. pylori babA* gene variant in patients with gastroduodenal diseases was investigated. Thus, it was found that the frequency of the *babA2* gene variant in patients with erosive gastritis was 43,4% (Table 1). Earlier, a meta-analysis of the frequencies of the *babA* gene variants in different countries of the world was performed by Chen M. Y. Obtained results are concordant with data from Turkey, China-1, Portugal-1, Brazil-1 and Italy (46,6%, 39,5%, 47,3%, 40,0% and 48,7%, respectively), but differ from the results of most other countries (India 52,7%, Iran from 18,1-74,1%, Japan from 84,8-100%, South Korea from 96,5-

Comparison of the frequency of *babA* genes depending on the presence of erosions and ulcers, age and sex and demographic factors

Factors	n (188)	*babA1* (%)	*babA2* (%)	χ^2	*p*
Dependence on the presence of erosions and ulcers					
CG with erosions and GU/DU	92	52 (56.5%)	40 (43.4%)	**6.314**	**<0.05**
CG	96	71 (73.9%)	25 (26.0%)		
Dependence of age					
Children (3-17 years)	112	77 (68.7%)	35 (31.2%)	1.354	>0.05
Adults (18-70 years)	76	46 (60.5%)	30 (39.4%)		
Comparison by gender					
♂	89	27 (30.3%)	62 (69.6%)	**18.417**	**<0.001**
♀	99	61 (61.6%)	38 (38.3%)		
Comparison on place of residence					
Urban population	32	23 (71.8%)	9 (28.1%)	0.709	>0.05
Rural population	156	100 (64.1%)	56 (35.8%)		

Note: GU/DU – gastric ulcers/chronic ulcers, CG – chronic gastritis; ♂ – male, ♀ – female.

100%, Thailand 91,1%, China 64,9%-2, Taiwan 100%, Portugal 50,0%-2, France 81,4%, Sweden 83,3%, Germany-1 77,7%, USA 84,8%, Brazil 20,0%-2, Finland 70,9%, Colombia from 82,8-85,0% and Germany-2 100%) (Fig. 1) [3].

Comparison of *H. pylori babA* gene variants depending on the clinical outcomes of gastroduodenal diseases (erosive or chronic gastritis) showed that patients with erosions and ulcers of the stomach, *H. pylori babA2* gene variant (43,4%) was significantly more common than in patients with chronic gastritis (26,0%) (p<0,05) (Table 1). In this regard, obtained result may indicate a more expressed pathogenic potential of *H. pylori babA2* gene variant. The results of our study are consistent with previous data that the presence of the *babA2* gene variant in the *H. pylori* genome was found to be associated with a higher incidence of duodenal ulcer, a complicated course of *H. pylori* infection, and also with adenocarcinoma of the stomach [2].

When comparing the *H. pylori babA1* and *babA2* genes with the inflammation activity, there were no statistically significant differences. However, insignificant difference was found in comparison with the second degree of dissemination and the *babA1* gene variant (Fig. 3), which is probably due to stochastic causes and is a consequence of the small number of subgroups of observations.

When comparing of *H. pylori babA1* and *babA2* gene variants in patients depending on age, place of birth and residence, no statistically significant differences were obtained (p>0,05). However, in the analysis, depending on the gender of the patients, a higher frequency of *H. pylori babA2* gene variant occurrence was found among men – 69,6%, almost two times more often than among women – 38,3% (p<0,001). In the case of the *babA1* gene variant, the opposite picture was observed: female patients had *H. pylori babA1* gene variant (61,6%) twice often than in male patients (30,3%) (Table 1). Our obtained result is consistent with the study of Mattar et al., where the *babA2* gene variant was also more common in men than in women [12]. Recent studies have conducted studies on mice and macaques to study the determining factors of the host organism that affect the expression of *H. pylori* BabA proteins [5-8, 11, 13]. The determining factor was the gender of the host, which was associated with a higher bacterial load and loss of BabA expression, and generally was preserved in male mice. These results may indicate the possibility that the loss of BabA protein expression is not due to adaptive immunity or signaling toll-like receptors. This evidence may indicate that BabA may have other unrecognized functions besides adhesion that binds to Le^b antigens which do not require the effect of gender differences in glycosylation for loss of BabA expression [11].

CONCLUSION

1) An association has been established between *H. pylori babA2* gene with more severe cases of gastroduo-

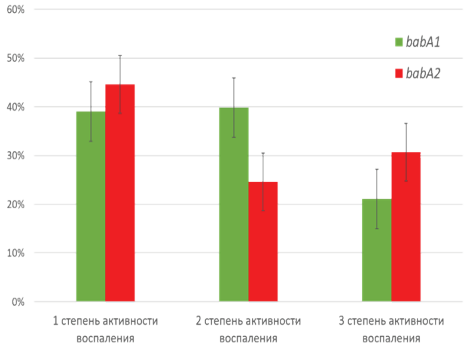

Fig. 1. Results of the frequency distribution of the *babA H. pylori* in the World. Note: China-1 – a study performed in 2006; China-2 – a study performed in 2004; Portugal-1 – a study performed in 2010; Portugal-2 – a study performed in 2009; Brazil-1 – study performed in 2006; Brazil-2 – study performed in 2005; Germany-1 – a study performed in 2009; Germany-2 – a study performed in 1999.

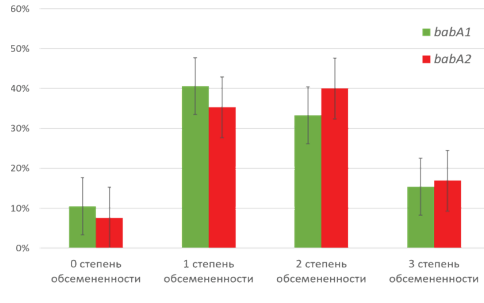

Fig. 2. Comparative analysis of *babA* gene with inflammation activity in patients with gastroduodenal diseases.

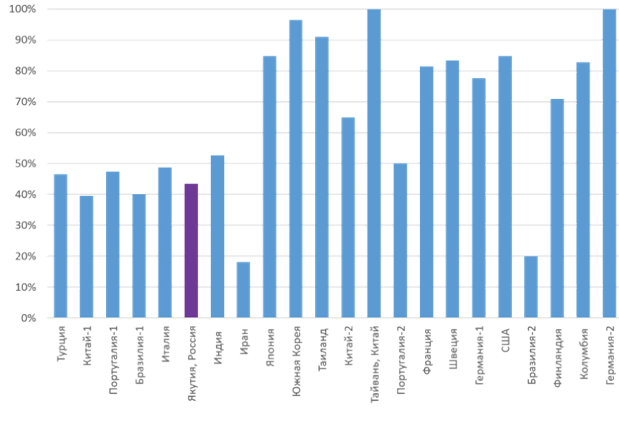

Fig. 3. Comparative analysis of *babA* gene with dissemination degree in patients with gastroduodenal diseases.

denal diseases (erosions and ulcers) in patients of Yakutia. Our results are consistent to previously known evidence that the presence of the *H. pylori babA2* gene may contribute to an increased risk of erosions and stomach ulcers.

2) It has been established that the *H. pylori babA2* gene was more often found in males than in female patients, which suggests that the infection of men with the *H. pylori* strain with a *babA2* gene variant may be an additional risk factor for more severe gastroduodenal diseases.

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REPLICATIVE ANALYSIS OF HEREDITARY THROMBOPHILIA FACTORS IN THE DEVELOPMENT OF PREECLAMPSIA IN THE YAKUT POPULATION

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The study of the contribution of hereditary thrombophilia to the etiopathogenesis of preeclampsia (PE) is of particular interest, since the formation of blood clots in the microvasculature vessels have affects to the processes of implantation and placentation, which subsequently leads to disorders of uteroplacental perfusion, which is a key link in the pathogenesis of this disease.

The **aim** of this work was to conduct a replicative associations analysis of the single-nucleotide polymorphisms the four most significant genes of hereditary thrombophilia with the development of PE in the Yakut population: rs1801133 (C677T) in the *MTHFR* gene, rs1799963 (G20210A) in the *F2*, rs6025 (G999A) in the *F5* gene and rs1799889 (-675 4G/5G) in the *SERPINE1* gene.

The results of this study indicate a statistically significant association of 4G allele of polymorphic variant rs1799889 (-675 4G/5G) in the *SERPINE1* gene in formation of a hereditary predisposition to the development of this pregnancy complication in Yakuts, both in the general group of patients and in the subgroup of patients with severe PE.

Keywords: preeclampsia, hereditary thrombophilia, association study.

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Introduction. Preeclampsia (PE) is a severe multisystem complication of pregnancy, which is characterized by the presence of arterial hypertension and significant proteinuria after 20 weeks of gestation. For a long time, this pathology continues to be one of the leading causes of maternal mortality, accounting for at least 63,000 cases per year worldwide [27]. According to the study, which covered about 39 million women from 40 countries, the incidence of PE for the period from 2002 to 2010 was 4.6%, in addition, the frequency of this complication of pregnancy varied widely among different regions [19]. It should be noted that differences in the frequency of PE development in modern human populations are due to the characteristics of racial and ethnic affiliation of the studied individuals [21, 23, 28, 29]. In the Russian Federation, among healthy first-time pregnant women, PE is detected in 6-12% of cases, while in the presence of extragenital pathology, the frequency increases to 20-40%. In addition, in recent years, there has been an increase in the number of cases of this complication of pregnancy and its contribution to the structure of maternal mortality, which is from 6 to 29.6% depending on the region [5], the excess of the average Russian rate of PE is 1.5 times observed among the regions of Siberia and the Far East [10].

According to the Ministry of health of the Republic of Sakha (Yakutia) PE plays a significant role in the structure of diseases of pregnant women. Thus, for the period from 2000 to 2016, the frequency of this pathology of pregnancy varied within 12.8 – 22.2%, which means the development of PE in every sixth pregnant woman on average for this region. According to the Ministry of health of the Republic of Sakha (Yakutia) PE plays a significant role in the structure of diseases of pregnant women. Thus, for the period from 2000 to 2016, the frequency of this pathology of pregnancy varied within 12.8 – 22.2%, which means the development of PE in every sixth pregnant woman on average for this region. In addition, the results of the analysis of critical obstetric conditions in maternity institutions in 2016 among the regions of the far Eastern Federal district showed the largest number of cases of "near miss"("Almost lost" or "nearly dead" women) for the Republic of Sakha (Yakutia) it is noteworthy that a significant number of these cases (54.5%) is due to the development of severe PE and eclampsia [6]. This high incidence of "near miss" cases due to severe PE and eclampsia, along with the high incidence of PE among the population of this region, shows the importance of studies studied at studying the etiopathogenesis of this pregnancy complication in women from the Yakut population.

According to the most recognized hypothesis of PE, the basis for the forma-

tion of this complication of pregnancy is placental pathology, which develops due to violation of cytotrophoblast invasion and insufficient remodeling of the uterine spiral arteries in the early stages of gestation [2, 11]. Of particular interest in this context is the study of the contribution of hereditary thrombophilia, which leads to thrombosis of the vessels of the microcirculatory bed and thus has an impact on the processes of implantation of the fetal egg, placentation, and later violations of uteroplacental perfusion [1, 3, 7].

According to the "HuGE Navigator" genes of hereditary thrombophilia are widely studied genes-candidates of PE, among which are the leaders in the number of conducted studies: the fifth coagulation factor gene (*F5*), the methylenetetrahydrofolate reductase gene (*MTHFR*), the prothrombin gene (*F2*), and the gene plasminogen activator inhibitor (*SERPINE1*). Thus, using samples from various populations and the case-control method, it was possible to demonstrate a significant contribution to the development of this pregnancy complication of four single nucleotide polymorphic variants (SNPs): rs1801133 (C677T) of the *MTHFR* gene, rs1799963 (G20210A) of the *F2* gene, rs6025 (G1691A) of the gene *F5* and rs1799889 (-675 4G / 5G) of the *SERPINE1* gene [4, 13, 18, 24, 26, 30, 31]. However, at present, there are also a large number of publications whose results could not confirm the contribution of SNP data to the genetic architecture of PE [8, 13, 16, 25, 30]. According to the results of our previous study [1], four SNPs of three genes of hereditary thrombophilia are associated with the formation of PE in the Russian population: rs6025 of the F5 gene, rs1799889 of the SERPINE1 gene, rs1801133 and rs1801131 of the MTHFR gene, whereas for rs1799963 the F2 gene did not show statistically significant differences comparing the patient group and the control group. In addition, it should be noted that the results of the meta-analyzes performed to date also demonstrate conflicting results on the role of the SNPs of the studied genes in the formation of a hereditary predisposition to the development of PE [9, 12, 15, 17]. Such differences can be due to both racial and ethnic variability of the frequency of development of pathology, clinical heterogeneity of this disease, and the use of various methodological approaches [9].

Thus, the **objective** of the study was to conduct a replicative analysis of SNP associations of the most significant genes of hereditary thrombophilia with the development of PE, identified earlier by the results of our own research in persons of russian nationality [1] and the results of several meta-analyzes, with the development of this pathology of pregnancy in the Yakut population.

Material and research methods. The study analyzed 428 DNA samples of Yakut women. The group of patients with PE contained 218 patients with moderate (119 women) and severe (99 women) degrees of PE and was heterogeneous in the presence of previous and concomitant background diseases. The control group was represented by 210 women with a physiologically occurring pregnancy, childbirth and the absence of an unfavorable obstetric history. The average age of patients in the studied group of patients with PE and the control group was 30 ± 7 and 32 ± 7 years, respectively. Blood samples of the examined patients were collected on the basis of the Perinatal Center of RB No. 1 in Yakutsk.

The criterion for the selection of markers for the case-control analysis was the presence of a statistically significant association with the development of PE identified in our previous study among Russians [1], along with the results of several meta-analyzes [9, 12, 15, 17]. Thus, four SNPs were included in the study: rs6025 (G1691A) gene of the fifth coagulation factor (F5), rs1799963 (G20210A) of the prothrombin gene (F2), rs1799889 (-675 4G / 5G) plasminogen activator inhibitor gene (SERPINE1), rs1801133 C677T) of the methylenetetrahydrofolate reductase gene (MTHFR). For genotyping, a polymerase chain reaction method was used, followed by analysis of the polymorphism of the lengths of restriction fragments obtained using specific endonucleases (PCR-RFLP), as described previously [1, 8]. The correspondence of the frequency distribution of alleles and genotypes to the Hardy-Weinberg equilibrium was carried out using the Fisher exact test. To compare the frequencies of alleles and genotypes between the studied groups, the Pearson χ^2 criterion was used. To assess the association of rSNP with the development of PE, the odds ratio (OR) and its 95% confidence interval (95% CI) were calculated.

Experimental studies were carried out on the basis of the Center for the collective use of scientific research equipment and experimental biological material "Medical Genomics" (Scientific Research Institute of Medical Genetics, Tomsk Scientific and Research Center). This study was approved by the Committee on Biomedical Ethics, Scientific Research Institute of Medical Genetics, Tomsk State Research Center.

Results and discussion. The frequencies of the studied alleles and genotypes for the studied polymorphic variants were in the world range, however, two SNPs in the studied ethnic sample were characterized as monomorphic: rs6025 of the *F5* gene in the group of PE patients, while rs1799963 of the *F2* gene in all the examined groups (Table 1). The frequency distribution of genotypes corresponded to Hardy-Weinberg equilibrium.

Among the SNPs of the four genes of hereditary thrombophilia studied, the association with the development of PE in the Yakut population was revealed only for one polymorphic variant - rs1799889 of the SERPINE1 gene. So, in the group of patients with PE there was a statistically significant increase in the 4G allele (p = 0.02, OR = 1.42, CI: 1.06-1.90) and a decrease in the frequency of the 5G allele (p = 0.02, OR = 0 70, CI: 0.53-0.94). For the 4G / 4G and 5G / 5G genotypes, the threshold value of the significance level was not reached: p = 0.06, OR = 1.48, CI: 1.01-2.17 and p = 0.06, OR = 0.56 CI: 0.30-1.05, respectively.

Table 2 presents the results obtained by studying the contribution of four SNPs to the development of individual clinical manifestations of this pathology, divided by severity according to the current classification of the disease [3]. Among patients with moderate PE, the frequency of the 4G allelic variant did not statistically significantly differ from the control group, but tended to associate (p = 0.06, OR = 1.39, CI: 0.98-1.95). With the development of severe PE, an association was found for the 4G allele (p = 0.04; OR = 1.47; CI: 1.01-2.13), while the 5G allele (p = 0.04; OR = 0.68 ; CI: 0.47-0.99) has protective properties. Thus, it can be assumed that the increased frequency of the 4G allele in the general group of patients with PE, in comparison with the control group, may be due to the even higher frequency of this allele in patients with a severe form of the disease.

Thus, the results of the study revealed the important role of rs1799889 of the SERPINE1 gene in the formation of a hereditary predisposition to the development of PE in Yakuts. The associations obtained in this work are consistent with the results of some case-control studies conducted in different ethnic samples, as well as with data from several meta-analyzes [1, 4, 9, 13, 14, 20, 22].

The product of the SERPINE1 gene is a type 1 plasminogen activator inhibitor (PAI-1), whose function is to block the activation of the fibrinolysis system [7]. The polymorphic variant rs1799889 (-675 4G / 5G) is located in the promoter region of

Table 1

Frequency distribution of genotypes and alleles in the studied groups

Gene, localization	SNP	Genotype, MA	The frequencies of genotypes and alleles, %		Value χ^2 (p)*
			Control group	PE patients	
MTHFR 1p36.22	rs1801133 (C677T)	CC	70.5	75.5	2.87(0.24)
		CT	26.7	23.6	
		TT	2.9	0.9	
		T	16.2	12.7	1.79(0.18)
F2 11p11.2	rs1799963 (G20210A)	GG	100.0	100.0	-
		GA	0	0	
		AA	0	0	
		A	0	0	-
F5 1q24.2	rs6025 (G1691A)	GG	99.0	100.0	2.09(0.35)
		GA	1.0	0	
		AA	0	0	
		A	0.5	0	0.54(0.46)
SERPINE1 7q22.1	rs1799889 (-675 4G/5G)	5G/5G	13.9	8.3	5.57(0.06)
		5G/4G	44.5	40.3	
		4G/4G	41.6	51.4	
		4G	63.9	71.5	**5.69(0.02)**

Note. MA - mutant allele; PE - preeclampsia. Statistically significant differences are highlighted in bold for ($p<0.05$). * - significance level p for criterion $\chi 2$ with Yeats correction obtained by comparing the frequencies of alleles and genotypes of the patient group and the control group.

the gene, while carriers of the 4G / 4G genotype have a higher level of PAI-1 protein in the blood compared to homozygous carriers of the 5G allele [9], which in turn leads to decreased activity of the thrombolytic system and increased risk of thrombosis [1, 7]. It should be noted that in the process of preparing the blastocyst for implantation, an increased level of PAI-1 is necessary, which is a physiological mechanism to prevent the formation of hemorrhage during further trophoblast invasion into the decidual uterine membrane. However, under hypofibrinolysis conditions (for example, in the case of 4G / 4G genotype carriage), local processes of fibrin formation and fibrinolysis during implantation are violated, thus, the number of proteases synthesized by the blastocyst becomes insufficient to ensure the necessary level of invasion, which ultimately leads to disruption of the mother - the placenta is the fetus [7].

Table 2

Frequency distribution of genotypes and alleles (%) in subgroups of patients with moderate and severe PE

Gene, SNP	Genotype, MA	FGA in the control group	PE of moderate degree		Severe PE	
			FGA	Value χ^2 (p)*	FGA	Value χ^2 (p)*
MTHFR, rs1801133 (C677T)	CC	70.5	76.4	3.59(0.17)	76.5	1.24(0.54)
	CT	26.7	25.4		21.4	
	TT	2.9	0		2.0	
	T	16.2	12.7	1.17(0.27)	12.8	0.97(0.32)
F2, rs1799963 (G20210A)	GG	100.0	100.0	-	100.0	-
	GA	0	0		0	
	AA	0	0		0	
	A	0	0	-	0	-
F5, rs6025 (G1691A)	GG	99.0	100.0	1.15(0.56)	100.0	0.94(0.62)
	GA	1.0	0		0	
	AA	0	0		0	
	A	0.5	0	1.11(0.74)	0	0.04(0.83)
SERPINE1, rs1799889 (-675 4G/5G)	5G/5G	13.9	9.2	3.34(0.19)	7.2	4.12(0.13)
	5G/4G	44.5	39.5		41.3	
	4G/4G	41.6	51.3		51.5	
	4G	63.9	71.0	3.46(0.06)	72.2	**4.09(0.04)**

Note. MA - mutant allele, PE of moderate degree - moderate preeclampsia, Severe PE. - severe preeclampsia. FGA - frequencies of genotypes and alleles (%). Statistically significant differences are highlighted in bold for ($p<0.05$). * - significance level p for criterion $\chi 2$ with Yeats correction obtained by comparing the frequencies of alleles and genotypes of the patient group and the control group.

Table 3 shows the allele frequencies of the three SNPs for which no association with PE development was identified in this study: rs6025 (G1691A) of the F5 gene, rs1799963 (G20210A) of the F2 gene, and rs1801133 (C677T) of the MTHFR gene. It can be assumed that the lack of replication of associations identified in Russians in our previous study [1], as well as in other populations (the results are presented in a number of meta-analyzes) [9, 12, 15, 17], may be due to the population specificity of the genetic structure of PE and is associated with a lower frequency of mutant alleles of SNP data in the Yakut population. So, for rs1801133 of the MTHFR gene in all studied groups and for rs6025 of the F5 gene in the control group, the frequency of mutant alleles in the Yakut sample was lower than their frequency in Russians and in populations from the 1000 Genomes project. At the same time, polymorphisms rs1799963 of the F2 gene and rs6025 of the F5 gene were monomorphic in all the studied groups and in the group of patients with PE, respectively.

Conclusion. To date, there are no unambiguous results on the association of factors of hereditary thrombophilia with the formation of such a pregnancy complication as PE [1, 9, 12, 13, 15, 16, 17, 18, 24, 25, 26, 30, 31]. The conflicting results of a large number of studies can be due to both the population specificity of the pathology, heterogeneity of the analysis (incorrect composition of the studied samples, their small volume), and gene- and / or gene-medium interactions [1].

In the present work, of the four SNPs of the most significant genes of hereditary thrombophilia for only rs1799889 of the SERPINE1 gene, an association with the occurrence of PE in the Yakut population was revealed. A statistically significant increase in the frequency of the 4G allelic variant was also shown in a subgroup of patients with severe PE compared with its frequency in the control group. In addition, for the 4G allele, there was a tendency to association in the subgroup of patients with moderate PE. Thus, for a

Table 3

Comparison of the frequencies (%) of mutant alleles of the three studied SNPs in the studied samples and world populations from the 1000 Genomes project

Gene, SNP	MA	Project populations "1000 genomes" *				Control group		PE patients	
		ALL	EUR	EAS	SAS	Rus.	Yak.	Rus.	Yak.
MTHFR, rs1801133 (C677T)	T	24.5	36.5	29.6	11.9	20	16.2	32	12.7
F2, rs1799963 (G20210A)	A	0.4	0.8	0	0	1	0	1	0
F5, rs6025 (G1691A)	A	0.6	1.2	0	1.1	1	0.5	3	0

Note. * - According to the Ensembl database. MA is a mutant allele. ALL is a general sample of populations from the 1000 Genomes project. EUR - Caucasoid populations: Europeans, Finns, British, Iberians, Tuscans; EAS - East Asian populations: Chinese, Japanese, Viet; SAS - South Asian populations: Bengalis, Indians, Punjabis, Sri Lankan Tamils. Rus - Russian population, results obtained in our previous study [1]; Yak. - The population of the Yakuts.

more complete understanding of the role of the polymorphic variant rs1799889 of the SERPINE1 gene in the structure of the hereditary component of PE in Yakuts, it is necessary to increase the size of the studied sample, divided into separate clinical forms of this pregnancy pathology. Of great interest is also expanding the list of currently known genes for hereditary thrombophilia and evaluating their contribution to the genetic architecture of PE for various ethnic groups.

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POLYMORPHISM OF THE *NOS3* GENE IN THE YAKUT POPULATION

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Several studies confirm the role of nitric oxide in the development of inflammatory and fibrous changes in liver parenchyma. However, the role of nitric oxide synthase – *NOS3* gene in LF formation remains unclear. The **aim** of our research was to study the polymorphism of rs1799983 of the NOS3 gene in healthy individuals of the Yakut population. Materials and methods of research: The experimental part of the work was carried out in the Laboratory of Hereditary pathology of the Department of Molecular Genetics of the Yakut Science Center of Complex Medical Problems (YSC CMP). A total of 146 DNA samples of healthy volunteers of Yakut ethnicity from the YSC CMP biomaterial collection were examined. Single nucleotide polymorphism (SNP) was determined by polymerase chain reaction (amplification of specific gene sites) followed by RFLP analysis. As a result of genotyping of the *NOS3* gene polymorphism rs1799983 among the Yakut population, the prevalence of the *G allele* (91.44%) was determined. An analysis of the frequency of occurrence of genotypes of the polymorphic variant rs1799983 of the *NOS3* gene revealed that carriers of the *GG* homozygous genotype prevailed among all examined individuals (83.56%), the heterozygous *GT* genotype was 15.75%, while the homozygous genotype of the *T* allele was found only in 0.69 % of cases. Thus, the study of the *NOS3* gene polymorphism rs1799983 in various ethnic groups may have a perspective in the development of personalized medicine, for the prediction of pathological conditions associated with endothelial dysfunction: liver fibrosis, cardiovascular diseases, obstetric and gynecological pathology, dysfunction of various organs and systems.

Keywords: nitric oxide synthase 3 gene, nitric oxide, polymorphism, *NOS3*, *G894T*, endothelial dysfunction, liver fibrosis, Yakut population.

Introduction. Liver fibrosis (LF) is a key element in the pathogenesis of liver diseases, specifically the degree of LF is clearly associated with the progression of clinical manifestations of socially significant diseases such as chronic viral hepatitis (CVH) [12]. Despite the whole range of preventive and therapy measures being taken to combat viral hepatitis, the number of people with CVH is steadily growing. Thus, from 2013 to 2016 in the Republic of Sakha (Yakutia), the hospitalization rate of people with CVH increased by 130%, with liver cirrhosis - 141%. There is a predisposition of indigenous people to the progressive course of HCV with frequent formation of cirrhosis and liver cancer, mainly in the outcome of HDV infection-52.2 % [2].

Therefore, the urgent issue is the search for new non-invasive methods for diagnosing and predicting fibrotic changes in liver tissue. It is known that the pathogenesis of LF is closely associated with oxidative stress, due to which there is an increase in the production of free radicals, one of which is nitrogen oxide (NO). NO is an active free radical that acts as a key mediator of vasodilation and contributes to the inflammation in liver tissue affected by hepatitis virus [8, 12].

A number of studies confirm the role of NO in the development of inflammatory and fibrous changes in liver parenchyma [10-11]. However, the role of nitric oxide synthase – *NOS3* gene (*eNOS*, *nitric oxide synthase 3*) in LF formation remains unclear. Nitric oxide synthase induces the conversion of L-arginine to endogenous nitrogen monoxide. At this point, polymorphisms at 11 loci have been studied, 8 *NOS3* polymorphisms associated with cardiovascular diseases have been described, one of which is the single nucleotide polymorphism rs1799983 *(Glu-298Asp, E298D, G894T),* the action of the risk allele *T* can be associated with endothelial dysfunction [3, 13].

The rs1799983 polymorphism of the *NOS3* gene has been studied in many human populations, but this polymorphism has not been sufficiently studied in the Yakut population.

The aim of our research was to study the polymorphism of rs1799983 of the *NOS3* gene in healthy individuals of the Yakut population.

Materials and methods of research: The experimental part of the work was carried out in the Laboratory of Hereditary pathology of the Department of Molecular Genetics of the Yakut Science Center of Complex Medical Problems (YSC CMP). DNA samples from the YSC CMP biomaterial collection were used for the research. A total of 146 DNA samples of healthy volunteers of Yakut ethnicity were examined (including Yakuts in the third generation). Of these, 31 DNA samples belonged to male individuals and 115 samples to female individuals. The average age of the study subjects was 30.51 ± 10.92. Criteria for exclusion from the study were: age under 18, chronic cardiovascular disease, oncological diseases, viral hepatitis, alcohol abuse. All the studied individuals filled out a questionnaire with informed consent to genetic research, approved by the Local Committee on biomedical ethics at the YSC CMP.

DNA was extracted by a standard method from frozen whole blood. Single nucleotide polymorphism (SNP) was determined by polymerase chain reaction (amplification of specific gene sites) followed by RFLP analysis.

Table 1 presents the amplification protocol, the sequences of oligonucleotide primers used, the PCR temperature and amplification length.

The restriction conditions, the used restriction endonuclease and the length of the restriction fragments are presented in table 2. For restriction, 5 µl of amplification, 1 µl of restriction buffer, 0.2 µl of restriction endonuclease *MboI* (New England Biolabs Inc., USA) and 8.8 µl of deionized water were used.

The resulting genotypes were determined by analysis of the lengths of restriction fragments (restricts) by gel

Table 1

PCR primers and conditions

SNP	Primer Sequence	Temperature	Amplicon size
rs1799983	F: TCACGGAGACCCAGCCAATGAG R: TCCATCCCACCCAGTCAATCCC	1. 95°C – 5 min 2. (95°C – 35 s; 64°C – 35 s; 72°C – 35 s) * 35 cycles 3. 72°C – 5 min	292 bp

Table 2

Restriction conditions

SNP	Endonuclease	Conditions	Restriction fragments size
rs1799983	*MboI*	37°C - 15 min	292 bp - *GG* 197 and 95 bp - *TT* 292. 197. and 95 bp - *GT*

electrophoresis on a 2% agarose gel with ethidium bromide (3,8-Diamino-5-ethyl-6-phenylphenanthridium bromide, Ethidium bromide) at 120 V in standard tris- acetate buffer for 1 hour. The results were visualized using a gel-documenting system in UV rays (Vilber Lourmat, France) (Fig. 1).

The research data were processed by statistical programs "Office Microsoft Excel 2010" and "IBM SPSS Statistics 23". Frequency of alleles and genotypes of rs1799983 polymorphism of the *NOS3* gene was checked for compliance with Hardy - Weinberg equilibrium. Frequency of alleles and genotypes between groups of men and women was compared using the criterion χ2 with Yates correction for continuity. The results were considered significant, with a value of *p* less than 0.05 ($p<0.05$).

Results and discussion. As a result of genotyping of the *NOS3* gene polymorphism rs1799983 among the Yakut population, the prevalence of the *G allele* (91.44%) was determined, which corresponds to the previously published results of a study conducted by Mestnikova E.N. et al. (2018) [1], according to which the Yakut population was also characterized by the predominance of the G *allele.* An analysis of the frequency of occurrence of genotypes of the polymorphic variant rs1799983 of the *NOS3* gene revealed that carriers of the *GG* homozygous genotype prevailed among all examined individuals (83.56%), the heterozygous *GT* genotype was 15.75%, while the homozygous genotype of the *T* allele was found only in 0.69 % of cases (Table 3).

Analysis of genotype distribution depending on gender revealed no significant differences (χ2=1.131, *p*=0.288). It was found that among women, as well as men, carriers of the homozygous genotype *GG* prevailed (83.87%, 83.48%, respectively). The GT genotype was found in 16.13% of men and 15.65% of women. The incidence of the T allele was 8.07% in the male group and 8.7% in the female group, without statistically significant differences (table 4).

According to open sources of the project "1000 genomes" [15], a high incidence of *allele* T was observed in the European population (indigenous people of Northern Europe - 36%, Finns - 23%, British - 34%, Spaniards - 38%, Tuscans - 40%), as well as in Colombians – 27%, Mexicans – 20%, Puerto Ricans – 28%. Most rarely the *T* allele is found in the African population (Kenyans - 4%, residents of Sierra Leone - 5%, Yoruba, Nigeria - 6%). Among Asian populations, the *T* allele is more common among Vietnamese (16%), Chinese (15%), more rarely - among Japanese (8%) (figure 2).

When compared with world populations according to the "1000 genomes", the *T* allele among Yakuts is less common than among the population of North America, South America, Europe, India, Oceania and China. The prevalence of this allele is comparable to Japan, where the *T* allele is found in 8% of the population [15].

When comparing the results of this study, allele *T* polymorphism of rs1799983 gene *NOS3* in the Yakut population was less common than in previous population studies. Thus, in the research by *Bae* et al (2010), the incidence of the *T* allele in the indigenous people of Korea was 18.6% [7]. In the Japanese population, the *T* allele was found in 15.6%, according to the research by Tamemoto et al (2008) [14]. In 2015 Huo et al. examined 420 young healthy Chinese and found the *T* allele in 28.09% of those examined [5]. Similar results were obtained by Indonesian geneticists Thaha et al. The *T* allele was found in 28.84% [6], while in the Asian population of India - 32.89% [4] (table 5).

Thus, the study of the *NOS3* gene polymorphism rs1799983 in various ethnic groups may have a perspective in the development of personalized medicine, for the prediction of pathological conditions associated with endothelial dysfunction: liver fibrosis, cardiovascular diseases, obstetric and gynecological pathology, dysfunction of various organs and systems.

Conclusion. The results of this research showed that the healthy population of the Yakuts living in the territory of the Sakha Republic (Yakutia), is characterized by a significant predominance

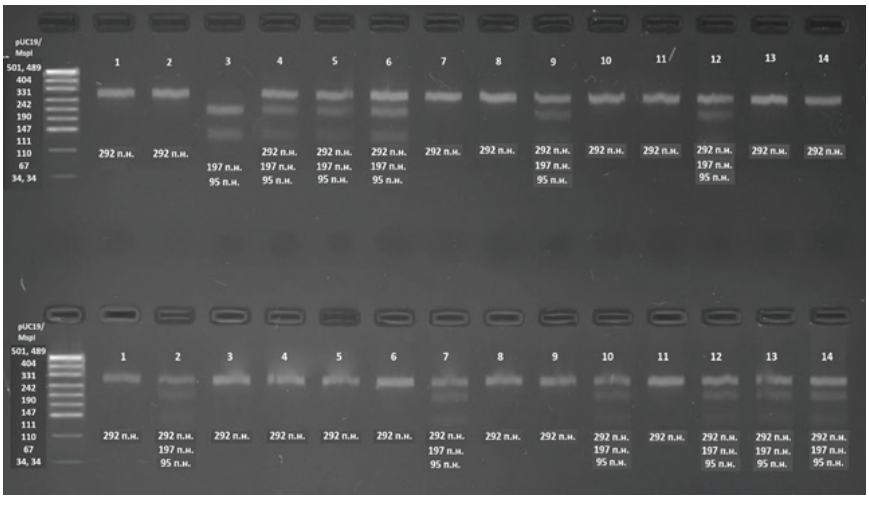

Fig. 1 Electrophoregram of PCR- RFLP. M - marker PUC19/+Msp I. Series 1. 1, 2, 7, 8, 10, 11, 13, 14 – GG genotype, 4, 5, 6, 9, 12 – GT genotype, 3 – TT genotype. Series 2. 1, 3, 4, 5, 6, 8, 9, 11 – GG genotype, 2, 7, 10, 12, 13, 14 – GT genotype. П.н. – bp.

Table 3

The frequency of occurrence of genotypes and alleles of polymorphism rs1799983 of the NOS3 gene among the Yakut population

Group	Распр	Genotype			Allele		χ2	p
		GG	GT	TT	G	T		
n=146	H	122 (83.56)	23 (15.75)	1 (0.69)	267 (91.44)	25 (8.56)	0.06	0.94
	O	122.07 (83.61)	22.86 (15.66)	1.07 (0.73)				

Note: O is the observed distribution, E is the expected distribution.

Table 4

The prevalence of genotypes and alleles in groups of men and women

Groups	Genotype			Allele		χ2	p
	GG	GT	TT	G	T		
Men (n=31)	26 (83.87)	5 (16.13)	0	57 (91.93)	5 (8.07)	1.131	0.288
Women (n=115)	96 (83.48)	18 (15.65)	1 (0.87)	210 (91.3)	20 (8.7)		

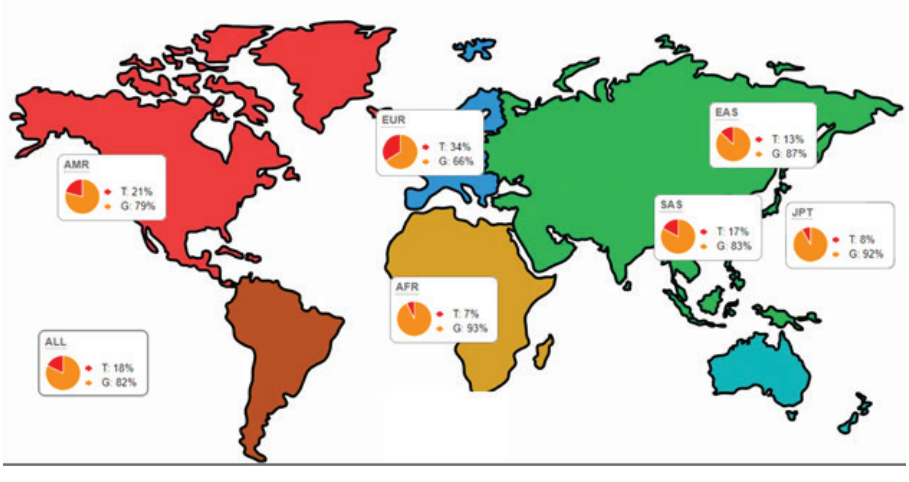

Рис. 2. Частота встречаемости аллелей, по данным «1000 геномов»

of carriers of allele *G* (91,44%) and *GG* genotype (83,56%) polymorphic variant rs1799983 *NOS3* gene.

Credits. *The study was carried out within the framework of the research project Study of the genetic structure and burden of congenital defects of the populations of the Sakha Republic (Yakutia) using the UNU "Genome of Yakutia" (reg. No. USU_507512).*

Table 5

The prevalence of the G allele of the polymorphic variant rs1799983 of the *NOS3* gene in Asian populations of the world

Populations	Genotypes			p	Authors
	GG	GT	TT		
Yakutia (n=146)	122	23	1	-	-
South Korea (n=161)	131	30	0	0,192	[7]
Japan (n=211)	181	27	3	0,101	[14]
China (n=420)	315	92	13	0,047	[5]
Indonesia (n=104)	76	26	2	0,845	[6]
India (n=152)	114	46	2	0,263	[4]

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ETHNIC DIFFERENCES IN DISTRIBUTIONS OF ALLELIC AND GENOTYPIC FREQUENCIES OF *NAT2* POLYMORPHIC VARIANTS IN PATIENTS WITH PULMONARY TUBERCULOSIS

Ethnic differences in allele frequencies and genotype distribution for polymorphic variants of *NAT2* gene (NAT2*5, NAT2*6, NAT2*7) were studied among ethnic Yakuts and Russians with newly diagnosed pulmonary tuberculosis.

This is the first study to establish allele and genotype frequencies for polymorphic variants of *NAT2* gene (NAT2*5, *6, *7) among ethnic Yakuts and Russians, who permanently reside in the Sakha Republic (Yakutia). Prevalence of NAT2*5, *6, *7 polymorphisms among Yakuts and Russians was determined, and ethnic differences were shown in allele frequencies and genotype distribution of NAT2 polymorphic variants: rs1801280 (341T>C), rs1799930 (590G>A), and rs1799931 (857G>A).

Keywords: *NAT2* gene polymorphism, Yakuts, Russians, tuberculosis, adverse drug effects

Introduction. Treatment success indicators are remaining at low levels in Russia. Based on official statistical data, in 2016, effective chemotherapy outcomes were registered in 74.3% out of all new pulmonary TB cases treated with regimens I–III (irrespective of microscopy results at case notification), or in 64.3% of cases with positive sputum microscope results [4]. Clinically, low treatment effectiveness in new TB cases resulted from nonadherence to chemotherapy duration, treatment interruptions, temporary cancellation of drugs due to adverse drug effects (ADE) (up to 61% cases [3] treated for drug-sensitive TB). Development of ADE is associated with variations in drug kinetics, and can be stemming from both transient (inhibition of biotransformation enzymes, as a result of drug interactions, eating habits) and constant causes (sex, concomitant diseases, genetic mutations in genes encoding enzymes involved in drug metabolism) [15, 24].

Genetic polymorphisms have been established and thoroughly researched for N-acetyltransferase (NAT) 2. NAT2 is an enzyme participating in biotransformation phase II, and is responsible for acetylation of more than 70% of xenobiotics, including therapeutic agents [21]. Single-nucleotide substitutions in the structural region of NAT2 gene determine genetic variations in enzyme activity [1,12], and have been linked to decreased or increased rates of xenobiotic metabolism [2]. NAT2 polymorphisms considered the most clinically important in terms of effective and safe TB chemotherapy are: *4, *5, *6, *7, *12, *13, *14. Patients with slow acetylation alleles (NAT2*5, *6, *7, *14) have been shown to be at risk for

developing liver injury [7, 23]. Presence of NAT2 slow metabolism alleles induces damage to hepatocyte cell structures due to significantly reduced amount of N-acetyltransferase in liver, slowdown in metabolic rate, and delayed elimination of antituberculosis drugs from the body. Distribution of NAT2 polymorphic alleles is widely variable between different populations and ethnic groups [19]. Only scarce data are available in current scientific literature regarding genotype prevalence of NAT2 polymorphic variants (NAT2*5, *6, *7) among Yakut and Russian patients with newly identified pulmonary TB permanently residing in the Sakha Republic (Yakutia).

Aim: study ethnic differences in allele frequencies and genotype distribution of NAT2 polymorphic variants (NAT2*5, NAT2*6, NAT2*7) among ethnic Yakuts and Russians with newly diagnosed pulmonary TB.

Material and methods: The study comprised 197 patients newly diagnosed with pulmonary TB. Of the patients examined, all of them permanently residing in Yakutia, 132 (67%) were referred to ethnic Yakuts (77 women, 55 men), and 65 (33%) to Russians (35 women, 30 men). Ethnicity was determined by a self-definition method comparable to SSR analysis [10]. Mean patient age was 43.3 with a standard deviation of 14.4 years. All patients completed informed consent to participate in the study. Sequencing of a particular NAT2 region was performed in several steps, using Sanger method with dideoxynucleotide tripshosphates (ddNTP): 1) DNA fragment under study was hybridized with primer; 2) molecule was enzymatically synthetized; 3) substance was further subjected to electrophoresis; 4) radioautographic analysis of results. Sequencing chromatograms were estimated visually, analyzed using Finch TV 1.4 software, and matched with reference NAT2 sequence for determination of individual single-nucleotide polymorphisms (SNP) https://www.ncbi.nlm.nih.gov/nuccore/NM_000015.2. Sequencing was performed for 3 polymorphic variants: rs1801280 (341T>C), rs1799930 (590G>A), rs1799931 (857G>A).

Concordance of genotype frequency distributions with Hardy-Weinberg law was checked using Pearson's chi-squared test. Threshold statistical significance level was 0.05. Statistical analysis was performed in IBM SPSS Statistics 23 software (licensed to North-Eastern Federal University), utilizing classical Pearson χ^2 test, and a modified version with likelihood adjustment applied in case expected frequencies took value of less than 5 in 15 or more cells in contingency table.

Results and discussion. All sought-for polymorphic variants of NAT2 were detected during the study. Distributions of allelic and genotypic frequencies for NAT2 polymorphic markers rs1801280 (T341C) and rs1799931 (G857A) among Yakuts and Russians were concordant with Hardy-Weinberg distribution ($p>0.05$). Significant differences between Yakuts and Russians ($p<0.05$) were observed in allelic and genotypic frequencies of polymorphisms NAT2*5 and NAT2*7 (Table 1).

The T allele of polymorphism NAT2*5(T341C) occurred reliably higher among Yakuts (0.82) than in Russians (0.58). Mutant C allele had the highest observed frequency in Russians (0.42), and was much less frequent in Yakuts (0.18) ($p<0.05$). Estimated frequencies of C allele are 0.45 for European population, 0.35 for South Asia, and 0.04 for East Asia [20]. It is noteworthy, that frequency of C allele of NAT2*5 (T341C) in Yakuts was considerably higher, compared to the population of East Asia. T/T genotype of NAT2*5 (T341C) was prevalent in 68.9% of individuals of Yakut origin. Meanwhile, Russian patients were 2 and 3 times more often carriers of T/C and C/C genotypes, respectively (55.4% and 13.8%, correspondingly) ($p<0.05$) (Table 1).

Meaningful ethnic differences in frequencies of polymorphism NAT2*5 (T341C) among Yakuts and Russians were established (31.1% vs. 69.2%, respectfully) ($p<0.05$). The highest prevalence rates of polymorphism NAT2*5 have been observed among Europeans (35% to 55%) [5,11,13], and among people originating from West Asia (up to 40%) [13], according to Gra O. et al. (2010); frequency among Russians varies between 38% and 45% [16].

Frequency of G allele of NAT2*7 was 0.84 in Yakuts, and 0.93 in Russians. Mutant A allele occurred in 0.16 of Yakuts, and 0.07 of Russians ($p<0.05$). Global frequencies of A allele of NAT2*7 are 0.02 in Europeans, 0.18 in East Asia, and 0.07 in South Asia [20]. Our findings suggest the highest prevalence of A allele of NAT2*7 among ethnic Russians of Yakutia, exceeding that in residents of Europe by 3.5 times. Individuals of Yakut origin were 1.9 times more often carriers of G/A genotype of NAT2*7 (G857A), compared to Russians (26.5% vs. 13.8%, respectively) ($p<0.05$). Genotype A/A was detected in none of Russian patients, while 2.3% of Yakuts carried it (Table 1). Existing evidence on link between hepatotoxicity and NAT2*7 genotypes is scarce and contradictory. Increased risk of hepatotoxicity was suggested in carriers of G/A genotype receiving chemotherapy with anti-tuberculosis first line drugs, compared to carriers of G/G genotype [14,18], although this association was never detected in other studies [6, 9].

Polymorphic variant NAT2*7 (G857A) was more frequent in Yakuts (28.8%), than in Russian patients (13.8%) ($p<0.05$). This finding is coherent with reported data, and is in agreement with average 20% frequency observed in Asian population of Central, East, and South-East Asia. Compared to Europeans, Russian population of Yakutia, showed notably higher prevalence of this polymorphism (5%) [5, 11, 13].

Frequencies of rs1799930 (G590A) NAT2 genotypes had no statistically significant differences between Yakuts and Russians, which is consistent with reported data. Frequencies of G and A alleles of NAT2*6 (G590A) were 0.78 and 0.22

Distribution analysis of polymorphic variants of *NAT2* gene in Yakut and Russian patients with pulmonary tuberculosis

Genotype	Yakuts, n (%)	Russians, n (%)	χ^2	p
NAT2*5 (T341C)				
T/T	91 (68.9)	20(30.8)	26.54	0.000*
T/C	35 (26.5)	36(55.4)		
C/C	6(4.5)	9(13.8)		
NAT2*6 (G590A)				
G/G	78(59.1)	29(44.6)	5.57	0.062
G/A	49(37.1)	29(44.6)		
A/A	5(3.8)	7(10.8)		
NAT2*7 (G857A)				
G/G	94(71.2)	56(86.2)	7.06	0.029*
G/A	35(26.5)	9(13.8)		
A/A	3(2.3)	0		

Note: χ^2 – Pearson chi-squared value. *- statistically significant differences are bold-typed. ($p<0.05$)

in Yakuts, and 0.67 and 0.33 in Russians, respectively. Reported frequencies of G and A alleles of NAT2*6 are 0.74 and 0.26 in East Asia, and 0.72 and 0.28 in Europe, respectively [20]. Compared to Russians, and residents of East Asia and Europe, while Yakuts had the lowest frequency of A allele.

Genotype G/G of NAT2*6 was prevalent in predominating 59.1% of Yakuts, while Russians had genotypes G/G and G/A, with the same frequencies of 29.0%. Genotype A/A was common in patients of Russian origin, and occurred 2.8 times more frequent, than in Yakut patients (Table 1). A allele of NAT2*6 (G590A) has been linked with increased risk of ADE [9]. Studies have found the highest hepatotoxicity risk during chemotherapy in residents of Turkey, China, and Tunisia with confirmed TB diagnosis, who had A/A genotype of rs1799930 (G590A) NAT2 gene, compared to patients with the same diagnosis, who were carriers of genotypes G/G and G/A [8,18,22]. Residents of Korea with AA or GA genotype receiving treatment for TB were found to have slower drug acetylation, than patients with GG genotype [9].

Polymorphism NAT2*6 is reportedly prevalent all over the world with approximately the same frequency (10%-35%) [5,11]. In our study, the frequencies of this polymorphism among Yakuts and Russians with pulmonary TB were higher than the rates reported in literature: 55.4% in Russians, and 40.9% in Yakuts, without notable ethnic differences.

Conclusion. This was the first study to establish allelic and genotypic frequencies of NAT2 polymorphic variants (NAT2*5, *6, *7) among ethnic Yakuts and Russians newly diagnosed with pulmonary TB and permanently residing in the Sakha Republic (Yakutia). Prevalence of polymorphisms NAT2*5, *6, *7 among Yakuts and Russians was determined. Ethnic differences in allele frequencies and genotype distributions of NAT2 polymorphic variants rs1801280 (341T>C), rs1799930 (590G>A), and rs1799931 (857G>A) were analyzed.

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RESTRUCTURING OF HEART RATE VARIABILITY, GAS EXCHANGE AND MICROCIRCULATION AT CYCLE-ERGOMETRY IN PERSONS WITH DIFFERENT DEGREES OF EXERCISE TOLERANCE

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An objective criterion for assessing the functional state of the human body, as well as the degree of balance of its physiological systems may be the study of physical performance. The **purpose** of this work was to study the specific features of urgent adaptations of a number of functional systems of the body in response to a cycle-ergometric test, and to identify marker criteria for assessing the level of exercise tolerance.

Based on the study of heart rate variability, indirect calorimetry, capillary blood flow and a modified PWC170 test, a comparative study was carried out on 63 young men aged 17-19 who were students from among Caucasians born in the North in the 1st and 2nd generations. Analysis of the data showed that during the stress test, most values of heart rate variability, microcirculation and metabolism increase as compared with the background level or at different stages of cycle-ergometry. At the same time, these changes are different for people with different degrees of tolerance to the load.

The results of the study made it possible to establish that the most important and informative indices reflecting the degree of tolerance to the load are the heart rate, the concentration of carbon dioxide in the exhaled air, the oxygen utilization factor, and the rate of capillary blood flow. During the performance of the stress test, such criteria are heart rate, MxDMn in relation to heart rate, reflecting the degree of decrease in parasympathetic activation, as well as the level of oxygen consumption, whose values in individuals with normal load resistance continue to increase until the end of the test.

Keywords*:* young men, heart rate variability, gas exchange, microcirculation, exercise test.

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Examination of physical working capacity is an important element of the quantitative assessment of the level of health, and an assessment of the degree of exercise tolerance can serve as a prognostic and objective criterion of the functional state and a quantitative indicator of individual human health [6]. A reduced level of motor activity is accompanied by a decrease in the overall working capacity of the organism and an increase in the "physical cost of the load," which is associated with a high tension of functioning systems involved in response to this load [10]. The autonomic nervous system plays an important role in modulating the cardiovascular system in various situations [16], including physical exercise [17]. To maintain cardiovascular homeostasis during exercise, it is necessary to connect mechanisms based on the rapid action of the autonomic nervous system [17]. Heart rate variability (HRV) characteristics are available and fast in use indicators reflecting changes in cardiovascular homeostasis, and also are indirect indicators of vagal nerve activity of the heart. In doing so, they allow us to determine the relative contribution of the parasympathetic and sympathetic link in the regulation of the rhythm of the heart in stress testing, being an accessible measure of the overall function of the ANS [8, 15].

Cardiovascular reactions, in response to physical exertion, are characterized by a direct expressed decrease in the activity of the parasympathetic link of the autonomic nervous system at the beginning of the test, with an increase in heart rate due to the activation of sympathetic activity. Immediately after the end of exercise, the heart rate decreases due to vagal reactivation [19].

It is important to judge the peculiarities of the changes in metabolic processes during the performance of load tests, preferably using indirect calorimetry,

which consists in the fact that the combustion of products generates thermal energy, the value of which can be determined from the results of measuring the body's consumption of oxygen and carbon dioxide [22].

The functional state of the capillary bed and the lability of the dynamic characteristics of microcirculation create conditions for the adaptation of blood flow to external loads [20]. Recent studies have shown that the values of capillary blood flow can differ significantly among comparable groups of people who lead a similar way of life [4].

The purpose of this work was to study the urgent adaptation changes in the indices of cardiorhythm, gas exchange, the characteristics of capillary blood flow in response to the cycle-ergometric test, as well as the identification of marker criteria for assessing the level of exercise tolerance.

Materials and methods. For the purpose, 63 young men were studied - students aged 17 to 19 years from among the Caucasians born in the region in the 1-2 generation who are students of the Northeastern State University (Magadan). The examination was conducted in physical education classes before the load, which implies the presence of medical admission, the absence of chronic diseases in the stage of exacerbation and complaints about the state of health, which was the direct criterion for inclusion in the studies.

Subjects were offered a modified PWC170 test with a standard load, according to which a load of 900 kgm / min (150 W) was set on a cycle-ergometer with a pedaling speed of 60 rpm and duration of 6 minutes. We showed earlier [5] that the degree of load tolerance can be determined on the 3rd minute of the cycle-ergometric load, so that the pedaling time was reduced to 3 minutes. The differentiation of the subjects according to the level of resistance to physical activity was carried out on the basis of the heart rate at the 3 minute of the sample. In the case of an increase in this index above 139 bpm at the peak of the load, the subject was assigned to 1 group with reduced exercise tolerance, whereas at a heart rate of less than 139 bpm, the examinee was assigned to group 2 with normal load resistance. Body length and body weight in the first group were 66.8 ± 1.0 kg, 178.4 ± 0.08 cm, and in the second group they were 72.1 ± 1.1 kg and 180.1 ± 0.9 cm, respectively.

The recording of the heart rate variability was carried out both at rest and during the cycle-ergometric exercise with the help of the Varicard device and the VARICARD-KARDi software and taking into account the methodological recommendations of the group of Russian experts [1]. Further the following HRV parameters were analyzed: the difference between the maximum and minimum values of the cardiointervals (MxDMn, ms); the square root of the sum of the differences in the series of cardiointervals (RMSSD, ms); number of pairs of cardiointervals with a difference of more than 50 ms in % of the total number of cardiointervals (pNN_{50}, ms); standard deviation of the full array of cardiointervals (SDNN, ms); the index of the tension of regulatory systems (SI, unit units); total power of the heart rate spectrum (TP, ms^2), the power of the spectrum of the high-frequency component of the heart rate variability in the range 0.4-0.15 Hz (respiratory waves) (HF, ms^2); power spectrum low-frequency component of heart rate variability in the range of 0.15-0.04 Hz (LF, ms^2); the power of the spectrum of a very low-frequency component of the heart rate variability in the range 0.04-0.015 Hz (VLF, ms^2). The total power of the cardiorhythm spectrum (TP) in the process of rebreathing was calculated without taking into account the ultra-low frequency component (ULF) based on the requirements for the correctness of the application of the analysis of short time series using the Fourier transform method. In addition, the ratio of the low-frequency and high-frequency components of the heart rate variability (LF/HF, conventional units) was determined. To analyze the spectral characteristics of HRV, a 3-minute stretch of the cardio-intervalogram was used to perform the cycle-ergometric exercise, which allowed having more than 250 cardiointervals in the analyzed area, which is a necessary criterion for the analysis of cardiac rhythm [1].

The levels of energy metabolism, as well as the parameters of the external respiration system were studied using the Medgraphics VO2000 (USA) metabolograph. Energy expenditure in the state of rest per minute (Kcal / min, kcal), energy consumption in a state of rest per day (REE day, kcal), respiratory quotient (RQ, conventional units), respiratory rate (RR, cycle / min), total volume of low voluntary ventilation, TV LVV (Vt BTPS, ml), low voluntary ventilation (VE BTPS, L), carbon dioxide emission (VCO_2, mL / min), oxygen consumption (VO_2, mL / min), carbon dioxide concentration and oxygen in the exhaled air (FET CO_2, FET O_2,%), the proportion of carbohydrates and fats in the energy substrate (CHO / REE, Fat / REE,%), oxygen consumption per kilogram weight, OC (Ox. Cons / kg, mL / kg) and oxygen utilization factor (Ox. Util. Fact., mL / L).

The rate of capillary blood flow was measured by the movement of erythrocytes in the capillary in the area of the cutaneous ridge of the nail bed using a computer capillaroscope "Capillaroscan-1" (Russia, LLC "New Energy Technologies"). The software of the device made it possible to evaluate the average speed of the erythrocyte movement over the specifically studied capillaries, as well as the length and diameter of the capillary sections. The temperature in the microcirculation study zone was measured using an infrared receiver built into the capillaroscope.

Examinations of young men were conducted in a room with a temperature of 19-21 °C, mainly in the first half of the day. The study was carried out in accordance with the principles of the Helsinki Declaration (2008). The study protocol was approved by the Ethics Committee of Biomedical Research at the All-Russia Research Center of Far Eastern Branch of the Russian Academy of Sciences (Ethical Protocol No. 004/013, dated December 10, 2013). All subjects were informed of the nature, purpose of the study and gave written consent to participate in it.

The obtained results were subjected to statistical processing with application of the package of applied programs Statistica 7.0. The normal distribution of the measured variables was checked based on the Shapiro-Wilk test. The results of nonparametric processing methods are presented as a median (Me) and interquartile range in the form of 25 and 75 percentile (C_{25} and C_{75}), and parametric ones are mean value (M) and its standard error (± SE). For independent samples, the significance level of differences for samples with a distribution not differing from normal was determined using Student's t-test for independent samples and in the case of samples with a distribution different from normal-the Mann-Whitney criterion was used. In dependent samples, the statistical significance of the differences was determined using Student's t-test with parametric distribution and the non-parametric Wilconson criterion for coupled samples with a distribution different from normal. The critical level of significance (p) was assumed to be 0.05; 0.01; 0.001.

Results and discussion. Table 1 presents the main indicators of the frequency characteristics of the heart rate variability at each stage of the cycle-ergometric exercise in representatives of two groups. An analysis of the minute

increase in the dynamics of heart rate revealed a number of differences depending on the type of resistance to the load. For example, the boys of the 1st group showed statistically significantly higher HR values at each stage of the load relative to those in the 2nd group, as well as a higher rate of increase in heart rate, reaching 150 beats / min by the 3rd minute, whereas in the group with a normal tolerance to the load, this value was 129 bpm. Obviously, regardless of the type of load resistance, there were qualitatively similar shifts in the dynamics of RMSDD, the indices which, from the third minute, did not differ in the dynamics between the groups studied. But at the same time the RMSDD index had statistically significantly lower values, in the group with a low tolerance at the 3rd minute of the load.

The higher informative value of the degree of assessment of load tolerance can be attributed to the MxDMn and SDNN, in the dynamics of which there were differences in the representatives of the two groups: in persons with normal stability, there was a lack of dynamics in response to the load already in the 2nd minute, whereas in the group with low resistance the decrease in these indicators was fixed until the end of the load. It is necessary to note significantly higher SI indices from the 3rd minute of the load in the representatives of the 1st group. Analysis of the spectral characteristics of HRV (Table 2) revealed a decrease in all parameters in response to the cycle-ergometric test, with a more pronounced dynamics observed in the group with reduced tolerance to the load. Table 3 presents the calculated coefficients reflecting the degree of influence in the provision of the heart rate sympathetic and parasympathetic link of the ANS. The obtained results indicate different dynamics of the estimated coefficients in the representatives of the two groups, which is more pronounced in the group with low resistance to the load.

Table 4 shows the parameters of gas exchange and external respiration against the background and load during the performance of the cycle-ergometric test in young men with different levels of tolerance to the load. In the intergroup comparison of people with different resistance to exercise, it was found that the differences were observed against the background and at the 3rd minute of the sample, in contrast to the 2nd minute, where no significant differences were noted. At rest, the oxygen concentration in the exhaled air was higher in people with low, and carbon dioxide - in people with normal tolerance to the load. In this case, the individuals from the second group had a significantly higher oxygen utilization factor. By the third minute of the load, the number of differing values doubled, affecting the ratio of fats and carbohydrates in the energy substrate, as well as oxygen consumption. At the initial stage of the cycle-ergometric exercise on most indicators, the young men of both groups start to register statistically significant differences. Note that this affects both time intervals: "background - the 2nd minute" and "2-minute - 3-rd minute", while the increase in the indicators for young men of the two groups are observed.

Table 5 presents the indices of blood microcirculation at rest and at the peak of the cycle-ergometric test in young men with different levels of tolerance to the load. In a state of rest, both groups practically did not differ in terms of microcirculation, significant differences were noted only in the rate of blood flow in the arterial part of the capillary against the background. In response to the cycle-ergometric test, when comparing the two groups of subjects, an increase in the diameter of the venous and transitional part of the capillary was detected, and the temperature of the examined area of the skin also increased.

It is known that physical exercise, especially aerobic activity, affects the balance of the autonomic nervous system by increasing parasympathetic tone and reducing sympathetic activity [21] and improves the MOC (maximum oxygen consumption). Thus, our data obtained, along with the results of other authors [11] give us reason to conclude that the values of the heart rate of the background loading period may be a criterion for assessing the level of physical performance, the numerical values of which are known to be due to greater activity of the parasympathetic link of the ANS [21]. The physical load intensity of more than 100 W is now considered as a sufficiently high load leading to physiological stress and to a complete depression of parasympathetic modulation (which results in a significant activation of the sympathetic link of the ANS). An analy-

Table 1

Frequency characteristics of heart rate variability in young men with different levels of exercise tolerance during the cycle-ergometric test performance

Parameter	Cycle test stages				Differences significance between groups		
	Baseline	1st min	2nd min	3rd min	Baseline-1st min	1st -2nd min	2nd -3rd min
Low exercise tolerance group (1)							
HR, BPM	*70.9 (63.7;79.5)	*117.9 (112.4;123.4)	*140.1 (131.8;144.8)	*150.1 (143.2;152.9)	p<0.001	p<0.001	p<0.001
MxDMn, ms	366.1 (277.9;417.3)	207 (174;268)	66 (59;78)	*41 (33;61)	p<0.001	p<0.001	p<0.001
RMSSD, ms	39..9 (33.6;53)	11.2 (8.9;17.5)	5.9 (4.6;7.4)	*5.7 (3.9;8)	p<0.001	p<0.001	p=0.16
SDNN, ms	72 (49.6;83)	45.3 (40.4;57.4)	15.3 (12.5;17.6)	*8.4 (6.2;12.3)	p<0.001	p<0.001	p<0.001
SI., c. u.	51.1 (30.8;82.6)	302.3 (208.6;435.3)	2364.9 (1615;3106.8)	*4757.9 (2447.4;10416)	p<0.001	p<0.001	p<0.001
Normal exercise tolerance group (2)							
HR, BPM	63.1 (58.6;67.7)	106.9 (104.6;112.3)	124.5 (121;129.3)	129.7 (126.5;137.6)	p<0.001	p<0.001	p<0.001
MxDMn, ms	424.4 (312.7;535)	245 (199.8;333.3)	72.6 (48.8;98.8)	52.5 (45.8;76)	p<0.001	p<0.001	p=0.15
RMSSD, ms	52.2 (41.5;64.2)	13.6 (10.3;16.7)	7.1 (4.8;14.1)	7.3 (5.8;15.7)	p<0.001	p<0.05	p=0.20
SDNN, ms	73.9 (53.2;100)	53.9 (45.8;69.2)	15.6 (10.4;19.7)	10.8 (8.8;12.5)	p<0.001	p<0.001	p=0.09
SI., c. u.	34.5 (22.3;71.6)	206.8 (150.5;331.1)	2003.1 (993.4;4324.5)	3901.1 (1794.7;5439.3)	p<0.001	p<0.001	p<0.05

Note: here and below the * sign denotes statistically significant differences between groups with different exercise tolerance

Table 2

Heart rate variability spectral parameters in young men with different tolerance to exercise during the cycle-ergometric test performance

Parameter	Cycle test stages		Differences significance between groups
	Baseline	1st -3rd min of exercise	
Low exercise tolerance group (1)			
TP, ms^2	3242.4 (1889.8;5472.2)	*222.6 (141;389)	p<0.001
HF, ms^2	629 (361.1;1771.4)	*32.8 (20.6;70.2)	p<0.001
LF, ms^2	1157.1 (898.9;1963.2)	*101.2 (50.6;180)	p<0.001
VLF, ms^2	516.1 (361.3;768.8)	*71.1 (46.7;128.1)	p<0.001
LF/HF, c. u.	1.7 (1.1;3.4)	2.2 (2.1;3.7)	p<0.001
Normal exercise tolerance group (2)			
TP, ms^2	3506.6 (2107.1;6361.4)	442 (292.5;565.5)	p<0.001
HF, ms^2	932.4 (582.2;1421.8)	57 (42.4;103.3)	p<0.001
LF, ms^2	1138.735 (715.992;1971.212)	218.6 (120.6;255.1)	p<0.001
VLF, ms^2	710.2 (301.0;1129.6)	132 (94.6;152.2)	p<0.001
LF/HF, c. u.	1.3 (1.0;2.3)	2.1 (1.8;3.8)	p<0.001

Table 3

Coefficients reflecting the degree of the parasympathetic and sympathetic link contribution in providing the heart rate at each exercise stage in groups with different exercise tolerance

Parameters studied	Cycle test stages			
	Baseline	1st min	2nd min	3rd min
Heart Rate / MxDMn	0.19	0.61	2.12	3.61
	0.14	0.43	1.71	2.52
Heart Rate / SI * 1000	1387	390	59	32
	1828	516	62	33

Note: in the numerator there are indices of the low exercise tolerance group, in the denominator – normal tolerance group indices

sis of the minute increase in heart rate (Table 1) in response to the cycle-ergometric test showed a more pronounced increase in its degree in the group with low resistance to exercise, reaching 150 bpm to the 3rd minute of the load, whereas in the group with normal exercise tolerance the heart rate was only 129 beats per minute. The rapid increase in HR at the beginning of the load is the result of a sharp parasympathetic decline, whereas sympathetic activation causes a relatively slow increase in heart rate in submaximal performance [9].

Per-minute analysis of changes in the statistical indices of heart rate variability (Table 2) revealed a number of differences in their dynamics, depending on the group of subjects. At the same time, the MxDMn, SDNN parameters were characterized by the highest degree of informativeness with respect to the parasympathetic link of regulation, the significant decrease of which in response to the load reflected the degree of decrease in parasympathetic activity. It should be noted that in the sample with normal exercise tolerance, already from the 2nd minute, the decrease relative to the previous minute segment of the cycle-ergometer was not observed, and the subjects of this group were characterized by higher numerical values of MxDMn, SDNN at the peak of the load. In the group with reduced resistance to physical activity, the SI index, reflecting the degree of assessment of sympathetic effects on autonomic cardiac modulation, had statistically higher values in individuals of the 1st group at the 3rd minute of the load.

To assess the contribution of sympathetic and parasympathetic supply of heart rate, we performed calculations of the ratio of cardiac rhythm and heart rate at rest and at each load minute and analyzed their dynamics, depending on the degree of resistance to physical activity. Considering the high degree of informativeness for the evaluation of the parasympathetic link, the MxDMn index was chosen, and SI for the sympathetic contribution (Table 3). The HR/MxDMn ratio had a more pronounced increase in the group with low resistance to exercise due to high HR values against the background of low MxDMn values. The positive dynamics of this coefficient indicates a decrease in the contribution of parasympathetic modulation in ensuring the level of heart rate at each stage of the load, which is more typical for young men of the 1st group. This fact may indicate a constant decrease in the inhibitory effect of the parasympathetic link at the heart rate, which leads to such high values when the peak load is reached in persons of this group. The coefficient reflecting the degree of activation of the sympathetic link (HR/SI * 1000) did not differ in dynamics and numerical values in the representatives of the two groups, which indicates that there is no difference in the degree of activation of the sympathetic link in providing the loading heart rate. Based on the dynamics of the coefficients analyzed, it can be concluded that even at the 3rd minute of the load it is possible to assess the degree of resistance to the load, while the design coefficients reflecting the degree of decrease in the parasympathetic link of the ANS will be the markers of the autonomic maintenance of the level of the loading heart rate.

Analysis of the spectral characteristics of the cardiorhythm (Table 2) in response to the stress test also revealed the presence of a pronounced dynamics of all the studied indicators, but having certain features depending on the degree of resistance to the load. Note that against the background of the absence of statistically significant background intergroup differences between these indicators at the peak of the load, differences were observed due to a more pronounced decrease in the 1st group. A significant decrease in the loading cardiorhythmogram of LF, HF and VLF waves, accompanied by a decrease in the duration of the cardiointervals, indicates a consistent increase in sympathetic and a decrease in parasympathetic influences reaching their poles at maximum heart rate [6]. However, in the group with a low degree of resistance to the load, the shifts to the area of decrease in the activity of the parasympathetic link were more pronounced than in young men with a normal level of tolerance to the cycle-ergometric sample. The balance of sympatho-vagal influences on the heart rhythm (LF/HF) at the peak of the load sharply shifted towards the predominance of activity of the sympathetic link with the same degree of severity in the representatives of the two groups, which is also confirmed by the

Table 4

Indirect calorimetry and external respiration indicators in young men with different exercise tolerance during the cycle-ergometric test performance

Cycle test stages				Differences significance between groups	
Parameter	Baseline	2nd min	3rd min	Baseline -2nd min	2nd-3rd min
Low exercise tolerance group (1)					
REE day, kcal	1975±117.5	12818±166.8	13754±259.6	1.3×10^{-43}	0.01
RQ, c. u.	0.85±0.03	0.93±0.02	1.08±0.02	0.05	3.7×10^{-05}
RR, cycle/min	13.9±0.86	23±1.11	24.2±1.26	5.9×10^{-8}	0.23
Vt BTPS, mL	641±40	1961±96	2222±144.8	8.7×10^{-17}	0.07
VE BTPS, L/min	8.6±0.48	41.9±1.17	50.1±1.09	1×10^{-29}	5.1×10^{-06}
V CO_2, ml/min	240.6±17.5	1660±41.2	1996±43.3	2.3×10^{-33}	1×10^{-06}
V O_2, mL/min	280.4±16.2	1791±23.1	*1858±38.4	9.1×10^{-44}	0.07
FET CO_2, %	*3.5±0.1	5±0.09	5±0.1	2.6×10^{-14}	0.35
FET O_2, %	*16.8±0.15	15.5±0.11	*16±0.11	7.7×10^{-09}	6.9×10^{-04}
CHO/REE, %	50.5±8.7	69.9±5.73	*96.2±2.21	0.05	9.2×10^{-05}
Fat/REE, %	48.9±8.7	37.8±6.21	*3.8±2.21	0.15	4.8×10^{-06}
Ox. Cons/kg, mL/kg	4.1 ±0.25	26.6±1.08	27.5±1.23	6×10^{-25}	0.29
Ox. Util. Fact., mL/L	*33±1.37	43.2±1.06	*37.3±0.98	4.2×10^{-07}	1.5×10^{-04}
Normal exercise tolerance group (2)					
REE day, kcal	2092±67.6	13069±285.5	14362±270.8	1.3×10^{-36}	1.9×10^{-03}
RQ, c. u.	0.84±0.02	0.89±0.02	1.03±0.02	0.05	4.6×10^{-06}
RR, cycle/min	13.6±0.71	21.6±0.95	23.4±1.34	2×10^{-08}	0.13
Vt BTPS, mL	668±30.8	2144±113.4	2286±123.9	1.3×10^{-16}	0.2
VE BTPS, L/min	8.2±0.37	40.9±1.14	49±1.24	1.8×10^{-30}	1.6×10^{-05}
V CO_2, mL/min	249.6±9.42	1635±40.6	1984±41.5	2.7×10^{-34}	2.6×10^{-07}
V O_2, mL/min	298.5±9.52	1843±41.85	1968±41.4	7.3×10^{-36}	0.05
FET CO_2, %	3.9±0.09	5±0.11	5.2±0.1	1.5×10^{-10}	0.17
FET O_2, %	16.3±0.12	15.2±0.12	15.6±0.13	2.1×10^{-07}	0.01
CHO/REE, %	46.8±4.8	61.6±4.5	89.9±2.51	0.05	1.5×10^{-06}
Fat/REE, %	53.5±4.9	41.8±4.2	10.3±2.49	0.05	5.1×10^{-08}
Ox. Cons/kg, mL/kg	4±0.1	24.8±0.72	26.4±0.67	1.7×10^{-31}	0.05
Ox. Util. Fact., mL/L	37.3±1.1	45.6±1.09	40.7±1.1	2.4×10^{-06}	2.9×10^{-03}

Table 5

Blood microcirculation indices in young men with different exercise tolerance before and after performing the cycle-ergometric test

Parameter	baseline	exercise, 3 min	Differences significance
Low exercise tolerance group (1)			Baseline - Exercise
Diameter of arterial department of capillaries, mcm	9.3±0.3	*8.7±0.3	0.10
Venous department diameter, mcm	13.9±0.4	*15.8±0.3	$1.4*10^{-3}$
Transition department diameter, mcm	18.1±0.5	20.7±1.1	0.05
Capillary length, mcm	337.2±17.8	325.0±18.4	0.32
Arterial department speed, mcm/s	*239.0±15.8	*260.8±18.8	0.19
Venous department speed, mcm/s	170.3±14.1	*179.7±13.3	0.32
Transition department speed, mcm/s	189.3±13.0	186.8±16.1	0.45
Frequency of sludges, units	2.7±0.2	2.3±0.2	0.10
Temperature, °C	30.1±0.6	*31.7±0.2	0.01
Normal exercise tolerance group (2)			Baseline - Exercise
Arterial department diameter, mcm	9.0±0.4	9.8±0.3	0.08
Venous department diameter, mcm	12.6±0.5	14.8±0.2	$2.7*10^{-4}$
Transition department diameter, mcm	17.7±0.7	21.9±0.7	$2.4*10^{-4}$
Capillary length, mcm	326.2±14.3	349.2±11.7	0.11
Arterial department speed, mcm/s	374.4±30.0	317.6±11.2	0.05
Venous department speed, mcm/s	217.8±19.7	241.1±13.4	0.39
Transition department speed, mcm/s	222.2±23.1	169.5±9.1	0.05
Frequency of sludges, units	3.0±0.2	2.2±0.3	0.01
Temperature, °C	31.2±0.6	34.1±0.1	$6.9*10^{-5}$

similar dynamics of the calculated heart rate / SI * 1000 (Table 3).

The results of the survey show that of the 13 indicators characterizing the state of gas exchange and external respiration, background differences in the young men of the two groups were observed only in 3 values characterizing metabolic processes in the body (Table 4). Thus, the value of the carbon dioxide content in the exhaled air (FET CO_2) and the oxygen utilization factor (Ox. Util. Fact) were higher for young men resistant to the load. At the same time, the oxygen level in the exhaled air (FET O_2) was statistically significantly higher in non-load resistant individuals, reaching 16.8%. The obtained results indicate a more intensive course of energy processes in young men from group 2. At the peak of the stress test, the oxygen consumption (VO_2), carbon dioxide (VCO_2) and oxygen consumption (Ox. Cons / kg) were significantly increased in them, which indicates a more intensive flow energy exchange processes in the body, whose values (REE) were significantly higher than the normative values [14]. It should also be noted that these individuals had a higher fat content as an energy substratum - 10%, while in the other group almost all the energy in the body was produced by the metabolism of carbohydrates. It is known that in a few minutes after the beginning of the cyclic loading the anaerobic processes of providing work begin to give way to a much more efficient aerobic stage of energy production - oxidative phosphorylation. Strengthening lipolysis makes it possible to optimize the energy supply of muscle tissue, allowing more than an order to increase the amount of synthesized ATP. Previous studies have shown that people with a high level of performance during physical work, there is an accelerated transition of carbohydrate metabolism to fat [2].

In this connection, attention is drawn to the fact that in young men with a low tolerance to the load, a higher value of the respiratory quotient (RQ) was observed, which also reflects the utilization of one or another energy substratum. The increase of this indicator is higher than one, due to the increase in the ratio of VCO_2 to VO_2, signals an increase in the anaerobic nature of metabolic processes, in which the only way to regenerate ATP is an energy-poor glycolysis process [7].

One of the main compensatory mechanisms aimed at maintaining the level of oxygen in the blood, as well as satisfying the oxygen demand of the body in mus-

cle activity is activation of the respiratory function [3]. In previous studies by other authors, it was shown that in the cycle-ergometry, the indicators of the LVV of the young men increased more largely due to the increase in TV LVV than in the RR, compared with those of the younger age groups, which is explained by the completion of the morphofunctional formation of the external respiration system [3]. In our studies, during a stress test, the black hole increased by less than 70% compared to the background indicators, while the TV LVV increased almost 3.5 times. When comparing the 2nd and 3rd minutes of the load, this picture only increased, and the growth of the RR practically ceased.

It can also be seen that, during the sample, individuals with normal tolerance to the load, as well as the background, were significantly higher than the oxygen utilization factor. Considering the practically identical fan supply of the organism (LVV) in persons of both groups, this may indicate an increase in the diffusion of oxygen between the alveolar air and blood and the improvement of the oxygen transport function in the body of the boys from the 2nd group.

Since the important function of blood circulation during muscular activity is thermoregulation, it is likely that an increase in temperature in the idle parts of the body is associated with an intensification of heat transfer during physical exertion. These data are confirmed in the studies of other authors [12, 13].

Analysis of the record of erythrocyte movement showed that a statistically significant change in the rate of blood flow occurred only in a group with a normal level of resistance. Apparently, the decrease in the blood flow velocity in the skin of the distal phalanges of the fingers observed at the peak of the sample is due to the outflow of blood to the actively working muscles. This redistribution of blood flow is necessary to meet the metabolic needs of the body [18]. The groups under comparison were also characterized by a more pronounced degree of dilatation of the capillary among boys with a normal level of resistance. Apparently, the observed changes are associated with an increase in the mass transfer of erythrocytes in the capillary bed. The lack of blood flow dynamics in the group with a low tolerance to physical activity indicates the rigidity of the vascular bed, which may be a factor in reducing resistance to physical stress.

Conclusion. Given that the specific task of our research was the selection and justification of the most informative indicators reflecting the degree of tolerance to the load, we can say the following: the most important indicator reflecting the degree of resistance to the cycle-ergometric test is the HR index both at rest and during execution cycle-ergometry.

Analysis of the HRV parameters allowed us to conclude that the cardiac rhythm parameters at rest, with the exception of the heart rate, cannot be the criteria for assessing the degree of resistance to physical activity, whereas the pattern of changes in the characteristics of the heart rate variability in the course of the sample is already at the 2nd minute of the load can give an estimate of the degree of resistance to the load. The most informative criterion will be the MxDMn index in relation to the heart rate, reflecting the degree of decrease in parasympathetic activation in response to the submaximal power load. The pronounced dynamics of the characteristics described above in the two groups examined reflects a decrease in the activity of the parasympathetic link in the regulation of the heart rhythm, which is more pronounced in the group of persons with low resistance to exercise.

When considering the gas exchange parameters, it can be concluded that the marker values can be the values of the concentration of carbon dioxide in the exhaled air and the oxygen utilization factor (Ox. Util. Fact) at rest, which are higher in persons with normal tolerance to the load.

During the test, oxygen consumption (OC) can serve as such a criterion, the values of which in individuals with normal resistance continue to increase, while those with low tolerance go to the "plateau" and do not change by the 3rd minute of the load.

The noted changes in microcirculation indices indicate a different degree of reactivity of the vascular bed, depending on the level of tolerance to physical activity. It is shown that the rate of capillary blood flow can be considered as one of the indicators characterizing the functional state of the organism as a whole and determining the level of efficiency.

Thus, the degree of decrease in activity of the parasympathetic link in response to a functional test, the magnitude of background and exercise heart rate, the concentration of carbon dioxide in the exhaled air and the oxygen utilization factor at rest, the dynamics of oxygen consumption, and the rate of capillary blood flow can be considered as prognostic criteria for assessing the level of physical working capacity.

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ENDOGENOUS RETROVIRUS HERV - E *λ 4-1* INFLUENCE ON IMMUNE CELLS FUNCTIONAL ACTIVITY IN MULTIPLE SCLEROSIS PATIENTS

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Purpose: a comparative study of the blood immune cells functional activity in multiple sclerosis patients associated with the human endogenous retrovirus HERV - E *λ 4-1* activation, as well as the immunomodulating properties of the homologous to a conservative region of hydrophobic transmembrane protein p15E 17 - amino acid synthetic oligopeptide.

Materials and methods. Human endogenous retrovirus HERV - E *λ 4-1env* gene expression was determined by the method of reverse transcriptase polymerase chain reaction. The spontaneous and mitogen-induced blood mononuclear cells proliferative activity of patients with a progredient course of disease, as well as blood mononuclear cells of central and peripheral organs of the immune system cells and of experimental animals when exposed to retroviral oligopeptide in culture was evaluated by the of tritium-labeled thymidine incorporation.

Results and discussion. We found that multiple sclerosis patients with activated retrovirus HERV - E *λ 4-1* are characterized by a higher blood immune cells functional activity compared with healthy donors, as well as in multiple sclerosis patients, in whose blood mononuclear cells the expression of this retrovirus was not detected. Synthetic 17 - amino acid oligopeptide, homologous to the conservative region of the hydrophobic transmembrane protein p15E of the HERV retrovirus - E *λ 4-1*, increased the functional activity of blood mononuclear cells of multiple sclerosis patients, as well as the immune system central and peripheral organs cells and blood mononuclear cells of experimental animals *in vivo*. This oligopeptide's effect was not genetically restricted.

Conclusion. Human endogenous retrovirus HERV - E *λ 4-1* sequence - specifically increases the immune cells functional activity in multiple sclerosis patients, which determines its role in the disease pathogenesis.

Keywords: multiple sclerosis, progredient course, human endogenous retrovirus HERV - E *λ 4-1*, retroviral oligopeptide, thymocytes, splenocytes, blood mononuclear cells, functional activity, genetic restriction.

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Introduction. Multiple sclerosis (MS) is a socially significant polyetiological autoimmune disease of the nervous system with immune-mediated damage to the brain gray and white matter as a result of the inflammatory foci with fibrosis and **gliosis** of the subarachnoid and intracortical regions and secondary neurodegeneration formation [5,7]. Clinically, MS is characterized by progressive neurological dysfunction, cognitive insufficiency and affective disorders [16]. The MS incidence is characterized by a unique geographic distribution, reflecting the significance in the etiology of genetic susceptibility, disturbances of the epigenetic mechanisms of the gene expression regulation, as well as extragenetic factors, in particular, the latitude gradient, with the disease prevalence in the regions near the North and South Poles [1,9,14].

Among the autoimmune inflammation triggers in the nervous system in MS, endogenous retroviruses (ER) are considered to be one of the most significant that can induce polyclonal activation of T lymphocytes [8]. These retroviruses are an integrated as a provirus form of exogenous and are a type of mobile genome elements - RNA retrotransposons, DNA sequences that make up to 8% of the human genome, distributed in more than 700,000 discrete loci [6].

In according to the modern classification, ERs are combined into 3 classes, represented by 50 families of 3173

sequences with a single genomic organization: they consist of the 4 retroviral genes, limited with 2 long terminal repeats that regulate their expression [15]. As often as not, the activity of retroelements in the human genome is repressed by both genetic and epigenetic mechanisms [12]. However, during the process of evolution, as a result of mutations and recombinations, some of them acquired pathogenic properties and the ability to replicate, to form the virion structure and to produce the viral proteins [11]. Some of the ERs are associated with the development of autoimmunity [1,10], as they are able to produce proteins with immunomodulating properties and to act as superantigens - to form antigenic epitopes by the molecular mimicry mechanism recognized by the immune system cells [4,10,13]. Inflammation and activation of the immune system are some of the factors that modulate ER transcription, since their promoter regions contain the binding sites for transcription factors involved in the oxidative stress response formation that inhibits deacetylase activity, stimulating histone acetylation and activation of ER expression [8]. ER RNA can be recognized by Toll-like receptors as pathogen-associated, which induces of type I interferon production involved in the formation of the pathological process in autoimmune diseases [17]. Considering the previously obtained data about the association of the class I HERV – E *λ 4–1* subgroup retrovirus (ER *λ 4–1*) with the course of MS, as well as its ability to replicate and produce proteins [10,18], the purpose of this study was a comparative investigation of the blood immune cells functional activity in patients with multiple sclerosis associated with ER*λ 4–1* activation, as well as the synthetic 17-amino acid oligopeptide homologous to the conserved region of its hydrophobic transmembrane *env* protein p15E immunomodulating properties.

Materials and methods. 32 patients with an established diagnosis of MS, with a progredient course of the disease and 16 conditionally healthy donors were included in the study. The study protocol was developed in accordance with the Helsinki Declaration of the World Medical Association "Ethical principles of the medical research with human participation conducting" with amendments in 2013, and the "Rules of Good Clinical Practice", approved by the Order of the Russian Federation Ministry of Health No. 200n, dated in 04/01/2016. The *env* gene expression of ER *λ 4-1* was determined by the reverse transcriptase polymerase chain reaction method, in accordance with the method described by us earlier in the paper [2]. The patient's blood mononuclear cells (MNCs) proliferative activity was assessed by the standard method of incorporating of H^3labeledthymidine into a 72 - hours cell culture, as we described in the paper [3]. The 17-amino acid retroviral or control (with reverse amino acid sequence) oligopeptides were introduced into the cell culture in 24 hours after the start of cultivation with the suboptimal concentrations of mitogens, also at suboptimal concentrations (50 μg/ml) determined in the preliminary experiments series [4].

The study of the immune cells functional activity *in vivo* was performed in healthy adult mice - male (CBAxC57Bl /6) F1, at 12 weeks of age, weighing of 18-20 g, obtained from the Scientific and E.D. Goldberg Research Institute of Physical and Radiotherapy Experimental Biological Clinic of Laboratory Animals, , TSRMC RAS, Tomsk. Experiments with animals were carried out in accordance with the order of the Russian Federation Ministry of Health and the Social Development No. 708n dated in August 23, 2010, "On approval of laboratory practice rules" and "Guidelines for experimental (preclinical) of new pharmacological substances researches" (Moscow, 2005). All manipulations complied in accordance with the rules adopted by the "European Convention for the Protection of Vertebrate Animals used in experiments or for other scientific purposes" (Strasbourg, 1986). Oligopeptides at a dose of 300 μg/mouse were administered intravenously for three times, with an interval of 48 hours. In 24 hours after the oligopeptides, third injection, the MNC, thymus and spleen proliferative activity was determined, as described above.

Statistical data processing. was performed with the using of descriptive statistics, comparative analysis methods, mediating the non-parametric Kruskal-Wallis H-test, Mann-Whitney U-test, using the Statistica 10.0 (StatSoft, USA) commercial software package. Results were presented as medians and intervals between the 1 and 4 quartiles (Me (25%; 75%). Differences were considered as statistically significant at $p < 0.05$.

Results and discussion. To assess the of ER *λ 4-1* effect on the of MS patients blood immune cells functional activity, in a series of preliminary experiments the presence of its activation in patients' MNC on the base of the assessment of its *env* gene expression responsible for the virus envelope synthesis and its exit out of the cell was investigated. For the further research, per the 16 samples of MNCs both groups were selected each with the presence or absence of this retrovirus activation in them. The results of the MS patients MNC proliferative activity evaluation in the presence or absence of ER *λ 4-1env*gene expression in them, as well as under the retroviral oligopeptide in vitro exposure are presented in the Table 1.

Table 1

Effect of retroviral oligopeptide on the blood mononuclear cells proliferative activity in multiple sclerosis patients (Me (25%; 75%))

Groups, impact	0.9% NaCl	Control oligopeptide	Retroviral oligopeptide
Donors intact	1425 (871; 2110)	1625 (920; 2120)	2787 (2355; 3441)*
Donors, ConA	20722 (19111; 23914)	20485 (16240; 23560)	32227 (29998; 33683)*
Donors, PWM	7973 (6460; 9105)	8259 (7542; 9980)	10124 (8347; 12647)
MS patients ER(-), intact	1847 (1121; 2324)	1971 (967; 2490)	3567 (2945; 3876)*
MS patients ER(-), ConA	18396 (15811; 23501)	19920(17831; 22911)	30772 (28859; 33267)*
MS patients ER(-), PWM	8218 (5638; 9456)	9631 (7623; 10118)	9265 (7719; 9967)
MS patients ER(+), intact	2421 (2125; 3230)#	2704 (2520; 3307)	4395 (3998; 4775)*.#
MS patients ER(+), ConA	15873(13923; 20657)#	16004 (15645; 21007)	26034 (19892; 29076)*.#
MS patients ER(+), PWM	5197 (4887; 6345)#	7857 (6378; 8935)	7527 (6365; 7841)#

Note: ER (-) – the lack of the ER λ 4-1env expression; ER (+) - the presence of the λ 4–1 env expression; ConA - concanavalin A; PWM - pokweed mitogen; n = 16 in each group;
* - $p<0.05$ (Kruskal-Wallis H-criterion) between the corresponding parameters under the influence of the control and retroviral oligopeptides;
# - $p<0.05$ (Kruskal-Wallis H-criterion) between the corresponding parameters in the donors and MS patients groups.

It was found that in patients whose MNC were not expressing the ER *λ 4-1 env*, the spontaneous lymphocyte proliferation level, as well as the response to B and T cell mitogens stimulation, did not differ from the conditionally healthy volunteers corresponding parameters. At the same time, there was initially a higher level of spontaneous MNC mitotic activity, but a lower response to B and T cell mitogens stimulation in the MNC of patients with ER *λ 4-1 env* gene expression, in comparison with the appropriate parameters in healthy volunteers or MS patients with the lack of ER λ*4-1 env* gene expression.

The control oligopeptide did not change the cell cultures proliferative activity. In healthy volunteers and in patients with the lack of ER *λ 4-1 env* gene expression, the effect of the retroviral oligopeptide infers in increasing of the spontaneous and ConA-stimulated proliferation level; the effect of retroviral oligopeptide in MS patients with activated ER *λ 4-1* resulted in an even greater increase in spontaneous proliferation and had a co-stimulatory effect on the enriched with T - lymphocytes as a result of mitogenic stimulation cell cultures mitotic activity, which is probably one of the aspects of the MS pathogenesis .

In order to study the retroviral oligopeptide immunomodulating properties at the whole organism level, as well as the presence of its action genetic restriction, we evaluated the peripheral blood immune cells, as well as the cells of immune system central and peripheral organs functional activity in experimental animals when the oligopeptide was administered in vivo. It was found that the level of spontaneous and ConA-stimulated proliferation of thymocytes, splenocytes and MNCs under the retroviral oligopeptide action exceeded that level in the control groups of animals, which indicates that this oligopeptide stimulates the various degrees of maturity T-lymphocytes mitotic activity and the absence of its action genetic restriction (Table 2).

At the same time, the studied oligopeptide did not affect the cell cultures enriched with B lymphocytes proliferation as a result of the pokeweed mitogen stimulation.

Conclusion. Thus, the MS patients with activated ER *λ 4-1* are characterized by higher blood immune cells functional activity compared with those of the healthy volunteers and MS patients, with the lack of ER *λ 4-1env* gene expression. The synthetic 17 - amino acid oligopeptide homologous to the human endogenous retrovirus *λ 4-1* hydrophobic transmembrane protein p15E conserved region, associated with the multiple sclerosis course, increases the of blood mononuclear cells functional activity of patients in vitro, as well as the proliferation of experimental animal's blood immune cells and the cells of central and peripheral organs of immune system *in vivo*. Therefore, the ER λ 4-1 has a sequence - specific, genetically unrestricted immunomodulating properties that determine the role of this endogenous retrovirus in the pathogenesis of multiple sclerosis.

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Table 2

The effect of retroviral oligopeptide on the of blood mononuclear cells, cells of the immune system central and peripheral organs proliferative activity in mice (CBA´C57BL / 6) F1 (Me (25%; 75%))

Groups, impact	Spontaneous proliferation (imp/min)	ConA – stimulated proliferation (imp/min)	PWM- – stimulated proliferation (imp/min)
1.Thymocytes			
0.9% NaCl	852 (556; 1271)	24647 (19881; 28993)	945(718; 1044)
Control oligopeptide	1043 (678; 1364)	25564 (20765; 29144)	1180(754; 1250)
Retroviral oligopeptide	1975 (1302;2483)*	33105 (27675; 36165)*	1263(843; 1911)
2.Splenocytes			
0.9% NaCl	2899 (2282; 3154)	45981(30845; 53850)	31928(22184; 36543)
Control oligopeptide	2995 (2751; 3598)	42428 (32967; 51278)	29771(20567; 33852)
Retroviral oligopeptide	4066 (3256;4328)*	74246 (68977;77034)*	32470(19160; 35767)
3.Blood mononuclear cells			
0.9% NaCl	3547 (2159; 3465)	50661(33283; 53887)	29548(18276; 34547)
Control oligopeptide	3633 (2918; 3912)	42014 (32545; 51338)	27453(20657; 34278)
Retroviral oligopeptide	49554 (3176;5134)*	61324 (58116;73491)*	26541(19947; 34595)

Note: ConA - concanavalin A; PWM - pokweed mitogen; n = 9 in each group;
* - p<0.05 (Mann-Whitney U-criterion)

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BIODEGRADABLE VASCULAR PATCHES: A COMPARATIVE DESCRIPTION OF PHYSICOMECHANICAL AND HEMOCOMPATIBLE PROPERTIES

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RGD-modification is a promising approach to improve biocompatibility of biodegradable vascular patches, potentially suitable for arteriotomy. Vascular patches are electrospun from the blend of polycaprolactone and polyhydroxybutyrate/valerate and modified with RGDK, AhRGD and c[RGDFK] peptides using 1.6-hexamethylene diamine or 4.7.10-trioxa-1.13-tridecanediamine linkers. Their mechanical properties and hemocompatibility are assessed. As the benchmark samples we used human internal mammary artery and xenopericardial KemPeriplas-Neo patches that are routinely used for carotid endarterectomy. Tensile properties of both polymer and biological samples differ from that of native human internal mammary artery. Tensile strength and Fmax of KemPeriplas-Neo patches are 4- and 16.7-times higher ($p < 0.05$). Both, RGD-modified and unmodified PHBV/PCL, demonstrate results similar to human internal mammary artery. Young's modulus of KemPeriplas-Neo patches corresponds to that of native vessels, whereas in polymer patches it exceeds 9 times that of the last ($p < 0.05$). RGD-modified PHBV/PCL patches and original PHBV/PCL patches demonstrate few lysed red blood cells and mild platelet aggregation than KemPeriplas-Neo patches, indicating a high biocompatibility of polymers and modifying agents used to make vascular patches.

Keywords: tissue engineering, biodegradable polymers, vascular patches, surface modification, RGD-peptides.

Introduction. High prevalence of internal carotid artery atherosclerosis and advanced diagnosis have resulted in an increase in the number of carotid endarterectomy performed annually [10]. Carotid stenosis is commonly treated with medical therapy, carotid endarterectomy (CEA), and stenting [13]. Despite recent advances and emergence of minimally invasive techniques, CEA remains the preferred method for treating patients with carotid stenosis.

Randomized controlled trials on the effectiveness of PTFE, Dacron and bovine pericardial patches have shown a similar rate of complications in the long-term period [3]. Thus, patches used in the routine clinical practice does not fully correspond to all needs of vascular surgery, that necessitates the development of new materials and approaches to the design of advanced vascular patches.

The emergence of regenerative medicine has opened new horizons for tissue engineering approaches in the development of bioresorbable materials activating the regenerative potential of the body to restore the damaged vessel walls [15]. Synthetic biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolatone (PCL) are widely used for this purpose [2, 11].

Synthetic polymers may be combined with the natural ones to increase the biocompatibility of the resultant product. Several studies reported the development of tissue-engineered vascular patch made from PGA and coated with poly-4-hydroxybutyrate (poly-4-hydroxybutyrate, P-4-HB). Tissue-engineered pulmonary artery augmentation patches derived from autologous circulating EPC and bone marrow–derived MSC functioned in vivo for up to 6 weeks in the ovine model grossly resembled the structure of the native pulmonary artery [12].

Although cell seeding on a matrix increases its in situ remodeling rate, this approach is generally considered as time-consuming and expensive. Therefore, it seems relevant to develop a self-assembling biodegradable material able to independently populate cells in situ. Moreover, the rapid formation of endothelial monolayers on the inner surface of the patches requires options for its stimulation. Both physical and chemical modifications of the tissue-engineered matrix surfaces are known. They produce proangiogenic effects and contribute to the endothelial cell seeding from the blood flow and surrounding tissues [1, 5, 8]. Thus, new functional biocompatible patches ensuring the regeneration of the damaged vessel wall are of paramount importance.

The **aim** of our study was to develop biodegradable vascular patches modified by various RGD peptides, and to compare their mechanical properties and hemocompatibility with xenopericardial patches, routinely used in the clinical practice.

Material and Methods. Polymer matrices were electrospun from a polymer

blend contained 5% w/v PHBV (Sigma, St. Louis, MO, USA) and 10% w/v PCL (Sigma) dissolved in trichloromethane using a Nanon-01A setup (MECC CO) at a voltage of 20 kV, a solution feeding rate of 0.5 ml/h, a collector rotation speed of 200 rpm, and a tip-to-collector distance of 150 mm. A metal pin with a diameter of 8.0 mm was used as a collector. The matrix was cut lengthwise and peeled off when removing from the pin.

The surface of patches was primary modified with 1.6-hexamethylenediamine (labelled Amin1, Sigma-Aldrich, USA), or 4.7.10-trioxa-1.13-tridecanediamine (labelled Amin2, Sigma-Aldrich, USA) using the technique previously described in [6].

PHBV/PCL patches were modified by the following RGD-containing peptides: linear peptide RGDK (alanine-glycine-aspartic acid-lysine) referred as Pep1; linear peptide AhRGD (aminocaproic acid-alanine-glycine-aspartic acid) referred as Pep2; cyclic peptide c[RGDFK] (alanine-glycine-aspartic acid-phenylalanine-lysine) referred as Pep3. Modification and polymer bonding to the surface were evaluated as previously described in [6].

Mechanical properties of samples were evaluated under uniaxial tension with the universal testing machine series Z (Zwick/Roell, Germany) in accordance with the editorial rules of the ISO 270-75. The tensile strength was measured with the maximum tensile stress (MPa) at break and the maximally applied force, which represented the breaking load (Fmax, N). Elastic deformation was estimated with the relative elongation adjusted to the elongation at break (%) and Young's modulus (MPa) determined in the range of physiological loading (80-120 mmHg).

Commercially available xenopericardial KemPeriplas-Neo patches (NeoCor, LLC, RU) were used as the reference sample, since they are routinely used for CEA. Unmodified PHBV/PCL patches as well as the segments of human internal mammary artery excised during coronary artery bypass grafting were used as the benchmark samples. All patients provided written informed consent prior to surgery. Internal mammary artery samples were cut in the longitudinal axis.

The proportion of lysed blood cells was measured using fresh citrated blood. Positive and negative controls were saline and distilled water, respectively. The absorbance of the obtained supernatants was measured using the GENESYS 6 spectrophotometer (Thermo, Waltham, MA, USA) at the wavelength of 545 nm [9].

Platelet-rich plasma (PRP) was used to evaluate platelet aggregation. Platelet-poor plasma (PPP) was used for the calibration. Intact pure PRP was used as a positive control Samples were exposed to PRP for 3 min [4, 7, 14]. Spontaneous platelet activation was measured without any aggregation inducers. 0.025M CaCl2 was added to 250 μL PRP to restore the level of Ca2+ in citrated blood. Platelet aggregation was assessed using platelet aggregation analyser APACT 4004 (LA-BiTec, Germany).

Platelet adhesion and their deformation after contacting with polymeric patches as well as the surface structure was assessed using a S-3400N scanning electron microscope (Hitachi, Chiyoda, Japan) under high vacuum. "KemPeriplas-Neo" xenopericardial patches were assessed as the benchmark samples. Samples were produced according to the methodology previously described in [6]. Platelet adhesion was calculated using the platelet deformation index [7, 14]:

Deformation index = (number of type I platelets × 1 + number of type II platelets × 2 + number of type III platelets × 3 + number of type IV platelets × 4 + number of type V platelets × 5)/total platelet count. Types of platelets were assigned according to description presented in Table 1.

The normal distribution was estimated using the Kolmogorov–Smirnov test. The data are presented as a median and interquartile range [25th and 75th percentiles]. The Kruskal-Wallis test (ANNOVA) was used to compare three or more independent groups. A p value of <0.05 was considered statistically significant.

Results and Discussion. The presence of peptides on the polymer surface was confirmed using the Sakaguchi test [17, 18]. Covalent bonded RGD peptides were shown in light-yellow color even after the PHBV/PCL +RGD samples were washed. Light-yellow color of unmodified PHBV/PCL samples disappeared upon washing. Obtained data proved the efficiency of RGD peptide modification of of PHBV/PCL patches.

Scanning electron microscopy images confirmed the absence of the endothelial lining on the serosal surface of KemPeriplas-Neo patches. Though, native architectonics was preserved, including original relief with closely located tortuous collagen fibers resulting in the absence of pores (Fig. 1).

PHBV/PCL patches had highly porous structure with randomly arranged polymer fibers with a diameter of 350 nm to 4.0 μm. Pores of 5.1 up to 27.6 μm were formed due to fibers' chaotic interweaving (Fig. 1). The modification did not affect the architectonics of the PHBV/PCL + RGD patches that was similar to the original polymer patches (Fig. 1).

Biodegradable patches modified either with amines (Amin1 or Amin2) or RGD-containing peptides (Pep1, Pep2 or Pep3) demonstrated similar tensile properties. The differences were considered insignificant (p>0.05). Therefore, all patches modified with RGD peptides were assigned into the PHBCV /PCL + RGD group to compare them with the benchmark samples (xenopericardial patch, internal mammary artery, unmodified polymer patches).

Biological patches differed from human internal mammary artery (IMA) in tensile strength (Table 2). Tensile strength of the KemPeriplas-Neo patch and Fmax exceeded IMA by 4 and 16.7 times, respectively (p <0.05). However, RGD-modified patches and original PHBV/PCL patches demonstrated tensile strength and Fmax similar to human internal mammary artery (Table 2).

Young's modulus of KemPeriplas-Neo patches corresponded to that obtained for IMA, whereas polymer patches exceeded the last by 9 times (p <0.05). (Table 2, Fig. 2).

RGD modification resulted in a 3.25-fold decreased tensile strength and a 2-fold decreased Fmax exposed to the samples with similar thickness (p<0.05). None of the differences were found

Table 1

Platelet Deformation

Type	
I	Disc-shaped (no deformation)
II	Dendritic platelets with early pseudopodia sticking out
III	Spread dendritic platelets with intermediate pseudopodia sticking out; congregating
IV	Flat platelets with cytoplasm expanding among pseudopodia
V	Cytoplasm fully spreads; the shape of Pseudopodia cannot be seen clearly

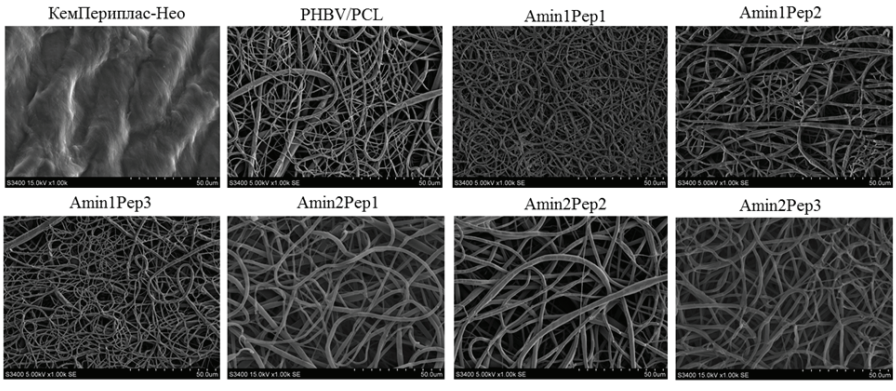

Fig. 1. Typical scanning electron microscopy images of biodegradable patches before and after RGD-peptides modification compared with KemPeriplas-Neo patches, ×1000 magnification

Table 2

Physical and mechanical properties of PHBV/PCL patches before and after RGD-peptide modification as compared to KemPeriplas-Neo xenopericardial patches and internal mammary artery, M (25-75%)

	Tensile Strength, MPa	Fmax, H	Elongation at Break, %	Young's modulus, MPa	Sample thickness, mm
PHBV/PCL	3.9 (2.88-4.5)	3.0 (2.59-3.3)	102.7 (79.37-106.3)*	21.8 (19.2-25.2)*•	0.4 (0.35-0.5)*
PHBV/PCL +RGD	1.2 (1.12-1.3)#•	1.3 (1.2-1.4)#•	102.6 (80.38-144.1)*	21.8 (20.15-23.9)*•	0.5 (0.49-0.5)*
Internal mammary artery	2.48 (1.36-3.25)	0.92 (0.59-1.72)	29.72 (23.51-39.62)	2.42 (1.87-3.19)	0.27 (0.24-0.3)
KemPeriplas-Neo	10.06 (9.12-21.38)*	15.4 (12.6-26.2)*	64.96 (61.08-72.6)*	1.11 (1.02-1.34)	0.69 (0.63-0.7)*

* – p<0.05 compared to IMA
# – p<0.05 compared to unmodified grafts
• – p<0.05 compared to KemPeriplas-Neo

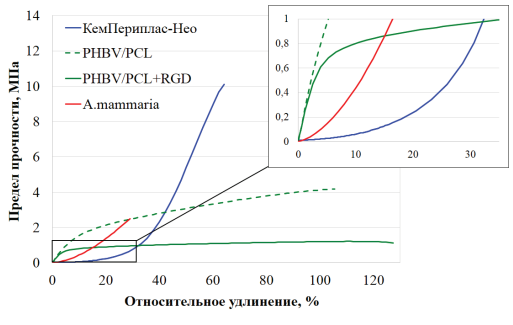

Fig. 2. Stress-strain curve of the study samples

between the elongation at break and Young's Modulus (Table 2, Fig. 2). Thus, RGD-modification resulted in decreased tensile strength, while its elongation properties remain the same.

The proportion of lysed red blood cells after contact with modified (Amin1 and Amin2) and unmodified PHBV/PCL patches was 0.36%; 0.72% and 0%, respectively (Table 3). Obtained data suggested high hemocompatibility of the study material [4]. Xenopericardial patches demonstrated a 2.12% red blood cell lysis that is generally considered acceptable [4]. However, the proportion the lysed RBCs was higher than that after the contact with modified patches (p <0.05). Significant differences were also observed between polymer patches modified with Amin1 and without modification. There were no statistically significant differences between patches modified with Amin2 and unmodified (p = 0.14). None significant differences were found between Amin1- and Amin2-modified PHBV/PCL patches (p=0.7).

The platelet aggregation maximum reliably increased after contacting with PHBV/PCL patches modified with Amin1 or Amin2 as compared to intact PRP with platelet aggregation activity of 15.02 (14.98; 17.72)%. (p <0.05). Unmodified patches and pure platelet-rich plasma demonstrated similar platelet aggregation (p=1.0), (Table 3).

KemPeriplas-Neo demonstrated the highest platelet aggregation (46.66% (21.06; 48.21), therewith a reliable increase in platelet aggregation was observed with respect to unmodified PHBV/PCL patches (p <0.05). Amin1- and Amin2-modified patches and xenopericardial patches did not differ in terms of platelet aggregation (p=0.05).

No doubt, RGD-modified PHBV/PCL and original PHBV/PCL patches had lower proportion of lysed red blood cells and superior platelet aggregation than KemPeriplas-Neo patches.

SEM images of nonwoven PHBV/PCL matrices after contact with platelets reported the presence of fibrin on their surfaces. Its presence complicated the assessment of platelet deformation (Fig. 3). Amin1Pep2- and Amin1Pep3-modified polymer patches had 1.2- and 1.4-times higher platelet deformation index than that of original PHBV/PCL patches (p<0.05). These patches had a higher number of adherent platelets mainly of type III-IV as compared to the other samples (Fig. 3). Upon contact with blood or being the result of modification, the modified and unmodified polymer patches demonstrated rather massive accumulations of adhered blood proteins. Platelet deformation indices of

Table 3

Platelet aggregation and platelet deformation after contacting with PHBV/PCL patches before and after RGD-modification in comparison with KemPeriplas-Neo xenopericardial patches

Sample	Proportion of lysed RBCs, %	Maximum Platelet Aggregation, %
	M (25-75%)	M (25-75%)
PHBV/PCL	0 (0-0)	17,06 (16,89-17,96) *
PHBV/PCL/Amin 1(RGD)	0,36 (0,36-0,36) *	23,74 (22,54-24,09)
PHBV/PCL/Amin 2(RGD)	0,72 (0-0,72) *	23,59 (21,44-24,35)
KemPeriplas-Neo	2,12 (0,9 -3,95)	46,66 (21,06-48,21)

* – p<0.05 compared to KemPeriplas-Neo

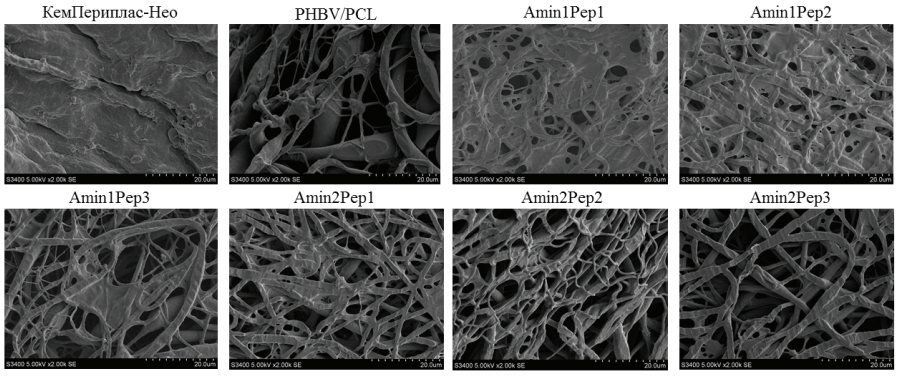

Fig. 3. Platelet adhesion on the surfaces of KemPeriplas-Neo patches and biodegradable PHBV/PCL patches with and without RGD modification, ×2000 magnification

Table 4

Platelet deformation index and the proportion of platelet types

Sample	Platelet Deformation Index. M (25-75%)
PHBV/PCL	2.7 (1.0-3.0)
PHBV/PCL/Amin1Pep1	2.5 (2.0-3.0)
PHBV/PCL/Amin1Pep2	3.31 (3.0-3.7)*
PHBV/PCL/Amin1Pep3	3.7 (3.4-4.5)*
PHBV/PCL/Amin2Pep1	2.6 (1.0-3.7)
PHBV/PCL/Amin2Pep2	1.3 (0.0-2.2)
PHBV/PCL/Amin2Pep3	2.9 (2.5-4.0)
KemPeriplas-Neo	2.33 (2.04; 3.13)

* – $p<0.05$ compared to unmodified PHBV/PCL patches

KemPeriplas-Neo and unmodified PHBV/PCL patches were almost similar. Amin2- and Amin1Pep1-modified polymer patches did not also differ significantly from them.

Conclusion. Biodegradable vascular patches have a highly porous surface that seems to be beneficial for vascular neotissue formation. RGD-modification of PHBV/PCL patches reduces their strength without affecting elongation at break. Nevertheless, RGD-modified and unmodified PHBV/PCL patches demonstrated tensile strength and Fmax similar to human internal mammary artery. However, Young's modulus of the polymer patches 9-times exceeded that of internal mammary artery.

RGD-modified and unmodified PHBV/PCL patches had few lysed red blood cells and mild platelet aggregation as compared to Kemperiplas-Neo patches. Obtained data suggested their high biocompatibility. The platelet deformation index increased greatly if 1.6-hexamethylenediamine was used for primary modification. Thus, the use of 4.7.10-trioxa-1.13-tridecanediamine as a linker for subsequent RGD-peptide modification of PHBV/PCL patches increased the biocompatibility of the implant.

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REMOTE RESULTS OF SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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УДК 616.441-089-06

The article is devoted to the problem of surgical treatment of primary hyperparathyroidism. The paper presents a comparison of the results of surgical treatment performed from a standard access with a mandatory revision of 4 parathyroid glands and a gentle method of small access with the removal of the affected parathyroid glands.

The obtained results showed the promise of sparing approach to the treatment of PGPT caused by adenoma of the parathyroid glands was.

Keywords: primary hyperparathyroidism, parathyroidism, hyperplasia, adenoma, low access, quality of life assessment.

Relevance. Primary hyperparathyroidism (PGPT) - primary pathology parathyroid glands, characterized by excessive secretion of parathyroid hormone. Since the latter is a regulator of mineral exchange in the pathological process involved almost all organs and systems, in turn, generates the clinical picture diverse and difficulties in the differential diagnosis of the disease. With scant clinical symptoms in the early stages and the presence of asymptomatic forms of the course, PGPT in most cases detected by chance, proving the importance of minimum endocrinological vigilance in respect of non-specific complaints of patients: to fatigue, weakness, depression, etc. With the development of studies and laboratory methods in routine practice introduction biochemical screening tests on blood ionized calcium levels as the primary marker of the disease, there is a jump increase PGPT initially diagnosed cases [1].

Today, surgery with the classic traditional access by Kocher is the "gold standard" treatment for patients with PGPT [2], which provides a full audit of all parathyroid glands.

Along with this, there are reports about the possibility of using a small access by removing adenomas parathyroid glands without revision others [3,4]. But among modern writers there are opponents who report high relapse rate.

Purpose. To evaluate the effectiveness of surgical treatment PGPT based on the analysis results of the nearest and remotest from the standard and parathyroidectomy small accesses.

Materials and methods. From 2009 to 2017 Burdenko Clinic of Surgery №1 based of the First Moscow State Medical University named after I.M. Sechenov. has been on the treatment of 418 patients PGPT. The selection criteria in this paper is a must histological confirmation of adenoma parathyroid glands. The current study included 370 patients with adenomas parathyroid glands. Patients with hyperplasia (n = 37) and parathyroid glands cancer (n = 11) were excluded.

The study consisted of a study of disease histories, history and primary examination data, laboratory-instrumental examination methods data, operation protocols and histological study results, and postoperative course data.

To study the long-term results of surgical treatment, 370 patients with PGPT were divided into 2 groups:

- Group 1 (GR1) - Patients who received surgical treatment until 2012, op-

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erated from the access by Kocher with a mandatory audit of all parathyroid glands 4 (n = 176)

- Group 2 (GR2) - Patients who received surgical treatment from 2013 to 2017., who have surgery performed, generally smaller incisions and was modified to remove parathyroid glands (n = 159). In the same period it was in the treatment of patients who underwent surgery of Standard Access due to discordance of results of diagnostic studies (mismatch of conclusions of ultrasound and scintigraphy) (n = 35). We also looked at these patients within group 2 (GR2) to make the groups uniform and comparable.

The average age of patients at the time of diagnosis PGPT: 56,588 ± 1,32, the distribution by age: 20-40 years - 5,7%, 41-60 years - 48.4%, and over 60 years old - 45.9% (Fig.1).

Based on the presented data, it can be concluded that PGTP affects mainly women at the age of 40-60 (Fig.2), and the peak of morbidity correlates with the onset of menopause (47 ± 1.5 years) - such patients in our work the vast majority - 47.7% (Fig.3).

Clinical diagnostics. PGPT, being a chronic endocrine, metabolic disease, often has a long period of latent course.

Clinical manifestations were detected in 35% patients (n = 129) included in the study, and 65% (n = 241) did not have clinical manifestations and PGPT was suspected at the outpatient stage as an "accidental finding," during routine dispensation, preventive examination, or under the supervision of an endocrinologist for thyroid gland disease.

The analysis of the obtained data revealed the following forms of disease: renal (visceropathic) (6%), bone (20%), mixed (9%) and subclinical forms (65%) (Fig.4).

Laboratory diagnostics. Determination of total and ionized blood serum calcium remains the simplest, most accessible and most effective method for diagnosis of PGPT.

Levels of total and ionized calcium were raised in all patients prior to starting treatment (Fig.5).

*Instrumental diagnostics.*As the main pre-operative diagnostic method for all patients in the groups under study, ultrasound of thyroid gland and parathyroid gland was carried out on stationary and portable ultrasound diagnostic devices with a frequency of radiated Uz of 3.5 MHz, thanks to which concomitant diseases of thyroid gland were also detected, as a result of which the volume of the operation was expanded to subtotal resection of thyroid gland, hemithyroidectomy or thyroidectomy with removal of affected parathyroid glands.

Scintigraphy with technetryl was also performed for topical diagnosis to 357 patients. Due to objective circumstances, 13 patients were not examined: in 8 patients it happened for technical reasons, 5 patients were operated on urgently, due to extremely high level of Ca and threat of hypercalcemic crisis development. On the basis of these two methods, it was possible to determine the percentage of matches of conclusions at the pre-operational stage of patient examination in the formation of a preliminary diagnosis.

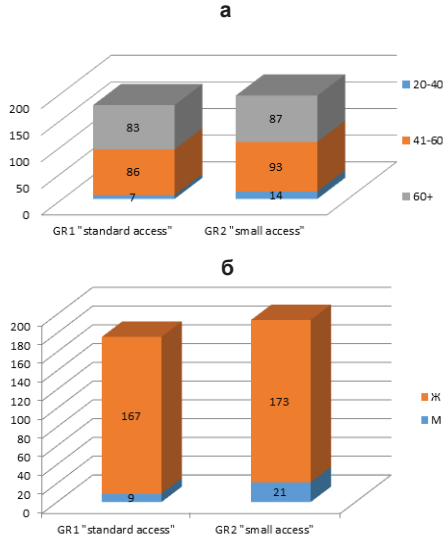

Fig. 1. Distribution of patients with PGPT by age

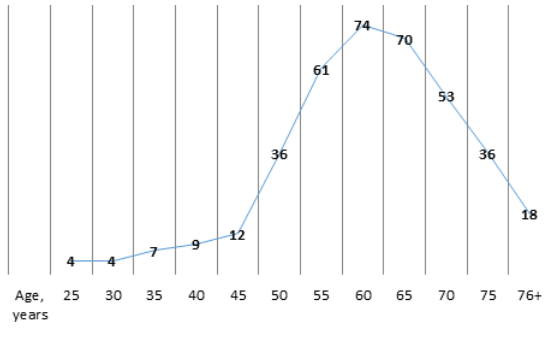

Fig.2. First-time PGPT in women according to age

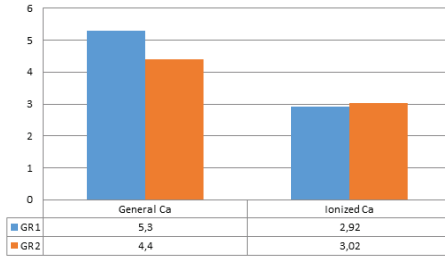

Fig. 3. Median of pre-operative Ca level distribution in patients with PGPT

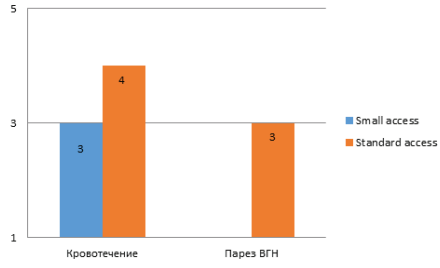

Fig. 4. Early postoperative complications

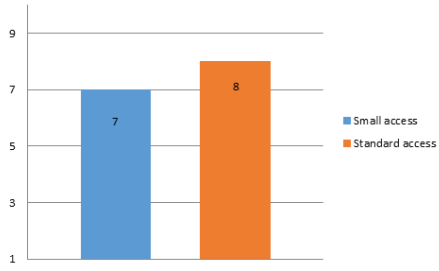

Fig. 5. Relapses of PGPT after operative treatment

The percentage of matching ultrasound and scintigraphy data was 84%, of which:

-1GR. 152 patients (86.3%),

-2GR. 159 patients (81.9%);

- 18.1% patients in 2 group, the data did not match (n = 35), so they were operated from the traditional "big" access by Koher.

Data discordance in general was identified in 59 patients (15.9%) involved in the study and was due to:

- Different location of adenoma according to ultrasound and scintigraphy - 31% (n = 18);

- Impossibility to visualize adenoma by ultrasound - 69% (n = 41).

Thus, 59 patients performed a neck Multislice computed tomography on a 320-helix computed tomograph ToshibaAquilionONE to refine the localization of the process.

Intraoperative ultrasound was performed to all patients operated since 2007. To 2012, and patients operated from 2013 to 2017 - only if the results of ultrasound and scintigraphy differ at the pre-medical stage. The data obtained were compared with the intraoperative pattern in the test groups of patients (n = 35). In the surgical treatment of 159 patients, the technique of low access was used, with complete matching of the data obtained at the pre- and intraoperative stages, which indicates the high importance of clinical data collected during the pre-hospital period.

Results of treatment. The length of the operation averaged 80 ± 15 minutes in the 1 group, and was significantly reduced to 40 ± 10 minutes in the 2 group. The development of early postoperative complications was in 1 group: 4 bleeding and 3 nervus laryngeus recurrens paresis, in 2 group - 3 bleeding (Fig.6).

Postoperative treatment results were comparable in both groups: 83% (n = 307) showed a sharp decrease in Ca to normal values and sometimes significantly lower than normal. In 11% (n = 34) patients observed clinical manifestations of hypocalcemia in the form of neuromuscular irritability - convulsions of back and leg muscles, against the background of conservative treatment, Ca level normalized.

17% patients (n = 63) showed persistent hypercalcemia, predominantly associated with hypovitaminosis D.

It was possible to analyze the distant results of treatment in 295 patients.

We observed recurrent hypercalcemia in 15 patients, which was caused by:

- "Unsuccessful" attempt to detect adenoma in the first operation - 4 cases (26.7%);

- Presence of the second "silent" adenoma in the gland, which initially did not accumulate radiopharmaceutical and could not be visualized in scintigraphy - 6 cases (40%);

- Obtaining histological conclusion indicating lymphoid tissue removal - 5 cases (33.3%).

The total recurrence rate in 1 group was 8 cases, in 2 groups - 7 cases, which is statistically unreliable and this gives grounds for parathyroidectomy from low access due to adenoma (Fig.7).

Histological examination of remote parathyroid glands was carried out in the pathologic department of First Moscow State Medical University named after I.M. Sechenov. All patients involved in the study had histologically confirmed parathyroid glands adenoma.

Discussion of results: According to many authors, the mandatory revision of all 4 parathyroid glands is a necessary measure of surgery, regardless of the results of pre-operative instrumental diagnostics, and traditional parathyroidectomy through cross-access by Koher - the "gold" standard of surgical treatment [2].

On the other hand, Sleptsov I. V. et al., (2012) consider that bilateral neck revision can be shown only in the following situations: in case of discordant or negative results of ultrasound and scintigraphy, lack of possibility to detect adenoma of parathyroid gland during intervention from small access, in case of history of operations on thyroid gland or parathyroid gland, in patients with persisting or recurrent [3, 4, 5].

The results of our work reflect modern trends towards organ-preserving surgical interventions and correspond to the results of domestic and foreign authors [6, 7].

Taking into account current trends in surgery and improvement of methods of topical diagnostics, it is more appropriate to use sparing, less traumatic technologies of treatment of PGPT - from small access, but only if there is histologically confirmed adenoma and concordance of diagnostic research.

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DIAGNOSTIC AND TREATMENT METHODS

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INTERRELATION BETWEEN THE CONCENTRATIONS OF BONE REMODELING MARKERS, OSTEOPOROSIS AND THE RISK OF PATHOLOGICAL BONE FRACTURES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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УДК 616.72-002-031.13

The aim of the study: to study the possibility of predicting bone fractures by determining the concentration of bone remodeling markers in patients with rheumatoid arthritis (RA).

Materials and methods. A prospective study was conducted in which 88 female RA patients aged 21 to 81 were under observation. The inclusion criterion was that patients had a reliable diagnosis of RA according to the ACR / EULAR 2010 criteria. When analyzing the age composition, it was found that the majority of patients are aged (from 41 to 55 years).

Results. Patients with RA, suffering from OP, had a significantly higher level of C-terminal type 1 telopeptide (p = 0.009), P1NP (p = 0.001) serum, urine calcium / creatinine (p = 0.02) than patients without OP. Patients with RA suffering from OP were found to have significantly lower levels of 25-OH vitamin D than in patients without OP. Significant changes in the concentration of blood calcium, alkaline phosphatase when comparing these two groups was not observed. A significant increase in the C-terminal telopeptide type 1 (p = 0.002), P1NP (p = 0.002), urine calcium / creatinine (p = 0.02) was also detected, as well as a significant decrease in 25-OH vitamin D (p = 0.006) in patients with a history of fractures. When comparing the level of alkaline phosphatase, blood calcium in groups of RA patients with osteoporotic fractures and without fractures in history, no significant change in the concentration of laboratory data was found.

Findings. At RA, complicated by OP, as well as in the presence of pathological bone fractures in patients with RA, an increase in C-telopeptide type I collagen, serum P1NP, urine calcium / creatinine, and a decrease in serum 25-OH vitamin D are observed.

Keywords: rheumatoid arthritis, osteoporosis, markers of bone remodeling.

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Introduction. Rheumatoid arthritis (RA) is an autoimmune rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and a wide range of extraarticular manifestations. The prevalence of this disease in the population reaches 1% [3, 6]. In recent years, the role of markers of bone remodeling in the pathogenesis of rheumatic diseases (RH) has been actively studied [1, 8]. In RA, the study of osteoporosis (OP) is of particular interest [2], which refers to secondary metabolic osteopathies due to a violation of bone remodeling processes, which leads to a progressive decrease in bone mineral density. Until now, the question of the relationship between markers of bone remodeling and the risk of developing bone fractures in patients with RA remains poorly understood [5, 7, 10]. In the process of remodeling, osteoblasts synthesize and secrete a number of compounds, markers of bone formation and bone resorption, into circulating blood [9, 4]. The first include the N-terminal propeptide of type I procollagen (P1NP), alkaline phosphatase, etc., the change in concentration of which reflects the rate of bone formation. The second category includes collagen C-telopeptides of type I collagen, acid phosphatase, etc. It can be assumed that the measurement of all of the above indicators, indicators of phosphorus-calcium metabolism, as well as the serum concentration of vitamin D involved in bone mineralization and in maintaining calcium homeostasis, can be used to assess the activity of osteoblasts and osteoclasts and balance bone remodeling processes. Based on the foregoing, the study of the relationship between concentrations of bone remodeling markers and the state of bone tissue is an urgent task of modern rheumatology, and can be useful for predicting the risk of pathological fractures in patients with RA.

Objective: to study the possibility of predicting bone fractures by determining the concentration of markers of bone remodeling in patients with RA.

Materials and methods. The work was carried out on the basis of the Federal State Budget Scientific Institution Scientific Research Institute of Clinical and Experimental Rheumatology named after A.B. Zborovsky, Volgograd. A prospective study was conducted, in which 88 female RA patients aged 21 to 81 years were monitored for 3 years. All patients lived in the Volgograd region.

Inclusion criteria:

1. The patient has a reliable diagnosis of RA in accordance with the criteria of ACR / EULAR 2010;

2. Patients who voluntarily gave written informed consent to participate in the study.

When analyzing the age composition, it was revealed that the majority of patients are aged (from 41 to 55 years). Assessment of the activity of the pathological process was determined by calculating the DAS28 index using a visual online calculator. According to the degree of RA activity, the patients were divided as follows: with the activity of 0 (DAS28 <2.6) patients, there were 19 patients in the study (21.59%), with a low degree of activity I (2.6 <DAS28 <3.2) –10 people (11.36%), with an average degree of activity II (DAS28≥3.2 - 5.1) – 52 people (59.09%), with a high degree of activity III (DAS28> 5.1) there were 7 patients (7.96%).

Depending on the presence of osteoporetic fractures identified by collecting medical history data, patients were divided into groups: 1st – RA patients with osteoporetic fractures (n = 11), 2nd – patients with RA without a history of fractures (n = 77).

Also, patients were divided into groups depending on the diagnosis of OP, which was exhibited by measuring BMD during dual-energy x-ray absorptiometry: 1st – patients with RA having OP (n = 22), 2nd - patients with RA who do not have OP (n = 66).

Bone remodeling marker levels were determined in all patients: C-terminal telopeptide of type I collagen, N-terminal pro-peptide of type I collagen, 25-OH vitamin D, alkaline phosphatase, blood calcium, urine calcium / creatinine using commercial kits.

Statistical processing of clinical examination data was carried out using STATISTICA 10.0 for Windows software packages. The significance of differences between the groups was compared using variation statistics (ANOVA) methods. The results were considered statistically significant at p <0.05.

Results and discussion. In order to identify the relationship between the concentrations of bone remodeling markers in patients with RA and the presence of OP, the mean value and standard deviation (M ± σ) of bone remodeling markers were calculated in the group of patients suffering from OP and in the group of patients without OP. The results of the study are presented in Table 1.

From the data presented in the table it can be seen that in patients with RA suffering from OP, a significantly higher level of C-terminal telopeptide type 1 (p = 0.009), P1NP (p = 0.001) of blood serum, calcium / urine creatinine (p = 0.02) than in patients without OP. In patients with RA suffering from OP, a significantly lower level of 25-OH vitamin D was detected than in patients without OP. A significant change in the concentration of blood calcium, alkaline phosphatase when comparing these two groups was not observed.

The relationship between the concentrations of markers of bone remodeling and the presence of pathological bone fractures in patients with RA was also studied. The data are presented in Table 2.

When studying the relationship between the concentrations of the studied parameters and the presence of low-energy bone fractures, a significant increase in the level of the C-terminal telopeptide of type 1 (p = 0.002), P1NP (p = 0.002), calcium / urine creatinine (p = 0.02), and a significant decrease in 25-OH vitamin D (p = 0.006) in patients with a history of fractures. When comparing the level of alkaline phosphatase, blood calcium in both groups, no significant change in the concentration of these laboratory parameters was found.

Findings. In RA, complicated by OP, and in the presence of pathological bone fractures patients have an increase in the concentration of type I collagen C-telopeptide, serum P1NP, urine calcium / creatinine, and a decrease in serum 25-OH vitamin D.

Table 1

Biochemical parameters of bone remodeling depending on the presence or absence of OP

Laboratory indicator	The presence of OP, n=22	The absence of OP, n=66	Reliability F, p
C-terminal telopeptide of collagen type 1, ng / ml	0.85±0.54	0.62±0.27	F=6.95. p=0.009
P1NP, ng / ml	88±84.35	49.8±24.29	F=11.02. p=0.001
25-OH Vitamin D, ng / ml	41.47±13.7	52.9±17.77	F=7.58. p=0.007
Urine Calcium / Creatinine, mmol	0.21±0.10	0.15±0.10	F=4.93. p=0.02
Blood Calcium, mmol / L	2.39±0.13	2.45±0.23	F=0.69. p=0.41
Alkaline phosphatase, units / l	85.39±77.58	67.48±27.51	F=1.19. p=0.28

Table 2

Biochemical parameters of bone remodeling depending on the presence or absence of pathological fractures

Laboratory indicator	There are fractures, n=11	No fractures, n=77	Reliability
C-terminal telopeptide of collagen type 1	0.99±0.52	0.63±0.32	F=9.64. p=0.002
P1NP	100.36±108.86	53.49±30.81	F=9.53. p=0.002
25-OH Vitamin D	36.81±16.66	51.93±16.87	F=7.75. p=0.006
Urine Calcium / Creatinine	0.23±0.12	0.15±0.10	F=5.16. p=0.02
Blood Calcium	2.34±0.15	2.45±0.21	F=0.95. p=0.33
Alkaline phosphatase	78.98±78.98	71.46±44.99	F=0.11. p=0.73

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METHOD OF DETERMINING THE DEGREE OF IMPAIRMENT OF THE GASTRIC EVACUATION FUNCTION IN PATIENTS WITH CICATRICIAL-ULCERATIVE STENOSIS OF THE DUODENUM

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УДК 615.471.03:616.33-008.821.1-074]: 519.24

Aim. To develop the method of determining the degree of impairment of gastric evacuation function in patients with cicatricial-ulcerative stenosis of the duodenum based on the data of standard daily pH-monitoring.

Materials and methods. There were examined 45 patients with with cicatricial-ulcerative stenosis of the duodenum. All patients underwent a comprehensive endoscopic and X-ray examination of the gastric evacuation function. Gastric secretory function was assessed by intragastric daily pH monitoring.

Results. A method for determining the degree of impaired gastric evacuation function is proposed, including intragastric pH monitoring, which determines the number of duodenogastric refluxes and the values of the parameters: "ratio of pH in the body of the stomach to the pH in the antrum of the stomach," "pH range in the cardiac part of the stomach."

Using the obtained data, the formulas are used to determine values of prognostic coefficients d1, d2 и d3, compare their numerical characteristics, which are what is used to evaluate degree of disorder of gastric evacuation function. With the value of d1 is greater than d2 and d3, the I degree is established, with d2 is greater than d1 and d3 - II degree and with d3 greater than d1 and d2, the III degree of impaired gastric evacuation functionis established.

Conclusion. The proposed method allows establishing the degree of impaired gastric evacuation function during standard intragastric pH monitoring.

The proposed method can be used for automated computerized, remote, screening diagnostics according to the values of daily intragastric pH monitoring.

Keywords: duodenal ulcerative stenosis, evacuation function of the stomach, intragastric pH monitoring.

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Introduction. Intragastric pH monitoring is a widely accepted standard method for the study of acid and reflux values of the stomach in acid-related diseases, one of which is duodenal (DD) ulcer (UD) [1, 2, 5, 7].

It is known that cicatricial-ulcerative stenosis (CUS) of the duodenum is one of the most frequent complications of ulcer and occurs in 10.0–56.3% of patients [1, 3, 6, 8]. Its main manifestation is a impairment of the gastric evacuation function (GEF), the assessment of the degree of which is crucial for determining indications for surgical treatment, the nature and extent of preoperative preparation [3, 6, 7].

A method has already been proposed for determining GEF impairment according to intragastric pH monitoring after various surgeries for duodenal ulcer [2]. However, a prerequisite for the use of this method is to restore the patency of the pylorus section of the stomach.

Authors performed a postoperative indirect comparative assessment of the evacuation time from the stomach to restore the initial indices of intragastric pH during evacuation to the duodenum of mixed standard food load. In this case, the degree of its preoperative disorder was not assessed using the claimed method.

The disadvantages of this method are the need to use a mixed standard food load, the patient must be in an upright position for 1.5 hours. In the absence of restoration of the initial value of intragastric pH, the need arises to conduct a repeated study.

The objective of our study was to develop the method of determining the degree of violation of the evacuation function of the stomach in patients with

cicatricial-ulcerative stenosis of the duodenum based on the data of standard daily pH-monitoring.

Technical result of the claimed method is the increased precision and simplification of degree of GEF impairment in patients with duodenal CUS.

Materials and methods. There were examined 45 patients with with cicatricial-ulcerative stenosis of the duodenum. They included 36 men and 9 women. Mean age of patients was 50.5±19.1 years.

All patients underwent endoscopic examination, intragastric pH monitoring (Table 1) and X-ray examination of GEF with determination of the extent of its impairment using classification by M.I. Kuzin et al. (1985) [3].

Radiographically, a first-degree GEF impairment was detected in 24 (53.3%) patients, II degree in 13 (28.9%) patients, and III degree in 8 (17.8) patients.

by stepwise incorporation of signs into the model with a final assessment of the contribution of each indicator to the probability share correct classification. DA was performed by the method of step-by-step inclusion of values of daily intragastric pH monitoring into the model according to Tolerance criteria and F-statistics [4]. The grouping parameter was the degree of GEF impairment.

Results. When comparing the values of intragastric pH in patients with the CUS of the duodenum, a relationship was found between the degree of GEF impairment and the intragastric pH values (Table 2).

Taking into account the obtained data, we created a mathematical model for predicting the degree of GEF impairment based on intragastric pH data in patients with duodenal CUS with a patient distribution accuracy of 92 and 100%, which was determined by the number

subjected to standard daily intragastric pH monitoring with a 3-channel pH-metric probe with sensors located in the cardia section, stomach body and antral sections of the stomach.

The use of 3-channel pH-metric probe and the location of the sensors in the sections of the stomach due to the need for simultaneous recording of the pH values of all parts of the stomach and DGR values.

After the end of study in order to determine the degree of GEF impairment with 92% precision, three parameters are evaluated: number of duodenogastric refluxes, "ratio of pH in the body of the stomach to the pH in the antrum of the stomach," "pH range in the cardiac part of the stomach."

Using the resulting numerical values of said pH-monitoring parameters, there are calculated prognostic coefficients d1, d2 and d3 using the formulas:

Table 1

Values of intragastric daily pH monitoring in patients with duodenal CUS

pH metry indicators		Healthy people (n=22)	Patients with ulcerative stenosis				p1	p2
			degree GEF impairment					
			I (n=24)	II (n=13)	p1	III (n=8)		
Aggres-sion index (pH)	Antrum	5.1±0.9	3.46±0.55*	2.32±0.75*	p<0.05	2.8±1.18*	p<0.05	p>0.05
	Body	2.13±0.28	3.68±1.44*	3.2±0.81*	p>0.05	4.1±0.92*	p<0.05	p<0.05
	Cardial part	4.38±0.51	3.54±1.5*	3.6±1.34*	p>0.05	4.0±1.64*	p<0.05	p>0.05
% of time with pH <2 in the antrum		17.16±2.13	38.7±11.7*	54.1±12.5*	p<0.05	66.7±31.2*	p<0.05	p<0.05
Duodenogastric reflux		47.4±9.5	8.3±2.21*	3.6±2.1*	p<0.05	0	p>0.05	p>0.05
The number of gastroesophageal reflux duration more than 5 min.		2.5±1.5	11.3±6.1*	16.1±2.7*	p<0.05	21.4±2.7*	p<0.05	p<0.05

To compare the values of daily intragastric pH monitoring, we determined the arithmetic average value (M) and standard deviation (s). To assess the normality of the distribution Shapiro-Wilk criterion was used. Comparison of groups by quantitative characteristics was performed using the Mann-Whitney test [4].

To create mathematical models of motor-evacuation disorders in patients with duodenal CUS, we used the discriminant analysis method (DA) based on the values of daily intragastric pH monitoring, which was carried out

of intragastral pH monitoring values included in the model (Table 3).

In clinical practice, the most convenient is the use of a smaller number of values taken into account with an accuracy of 92%. For scientific research, it is recommended to use a mathematical model with a predictive accuracy of 100% with an increased number of intragastric pH monitoring values taken into account (Table 3).

In accordance with our proposed method for indirect determination of the degree of GEF impairment according to intragastric pH monitoring, patients are

Table 2

The correlation coefficients (R) indices of intragastric pH and the degree of GEF impairment in patients with the duodenal CUS

Indicator	pH Antrum	% of time with pH <2 in the antrum	pH Cardial part	The number of duodeno-gastric reflux	The number of gastroesophageal reflux
Degree of GEF	-0.76 (p<0.05)	0.83 (p<0.05)	0.42 (p<0.05)	-0.83 (p<0.05)	0.36 (p<0.05)

d1 = -24.1293 + 1.4127 x A1 + 4.0021 x A2 + 6.3209 x A3;

d2 = -7.78924 + 0.51564 x A1 + 4.42335 x A2 + 4.25367 x A3;

d3 = -11.0768 + 0.0464 x A1 + 7.8569 x A2 + 5.3359 x A3,,

where:

"-24.1293"; "-7.78924"; "-11.0768" - constants;

"1.4127", "4.0021", "6.3209" - values of the coefficients of the discriminant function for d1;

"0.51564", "4.42335", "4.25367" - values of the coefficients of the discriminant function for d2;

"0.0464", "7.8569", "5.3359" - values of the coefficients of the discriminant function for d3;

A1, 2, 3 - numerical values of paramerers of intragastric pH-monitoring:

A1 – "number ofduodenogastral refluxes";

A2 – "ratio of pH in gastric body to pH in antral section of the stomach";

A3 – "range of pH in cardia section of stomach".

Table 3

The list of discriminating signs and the values of the coefficient "b" to determine the degree of GEF impairment in patients with the duodenal CUS

Mathematical Model Accuracy (%)	Discriminating Indicators	Coefficient values «b» Degree of GEF		
		I	II	III
92	The number of duodeno-gastric reflux	1.4127	0.51564	0.0464
	body/antrum ratio	4.0021	4.42335	7.8569
	pH range in cardiac	6.3209	4.25367	5.3359
	Constant (a)	-24.1293	-7.78924	-11.0768
100	Max pH in the antrum	-2.6941	9.6565	16.237
	pH in the antrum	21.3092	-3.6820	-23.712
	% of time with pH <2 in the antrum	0.5422	1.1849	1.612
	The number of duodeno-gastric reflux	-0.6771	1.6063	4.081
	Max pH in the body	7.9097	-4.5311	-14.416
	pH in the body	1.8949	-37.6802	-72.754
	pH range in the body of the stomach	-27.9093	34.5131	86.754
	body/antrum ratio	12.5848	-26.0493	-58.277
	Min pH in cardial part	-19.4664	23.3211	58.401
	cardia/body ratio	7.5721	-3.3728	-11.221
	Constant (a)	-66.1773	-81.3965	-126.543

With the value of d1 is greater than d2 and d3, the I degree is established, with d2 is greater than d1 and d3 - II degree and with d3 greater than d1 and d2, the III degree of impaired evacuation function of the stomach is established.

Discussion The use of the proposed method, in comparison with the analogue [2], is much simpler, due to the absence of the need to use a standard food load and the possibility of arbitrary patient behavior. In particular, it is possible to use it in weakened, bedridden patients.

With an increase in the number of discriminatory indicators included in the mathematical model, up to 10, the predictive accuracy of the proposed method for determining the degree of impairment of evacuation function of the stomach reaches 100%.

To simplify the implementation of calculations by the proposed method, we, together with the laboratory of informatization of applied research of NArFU n.a. M.V. Lomonosov (head. Ph.D. Tech, associate professor Popov A.I.) developed a computer program DiaSten-pH, which presents the results of automatic calculation in numerical and graphical form (Figure 1).

Fig. 1. An example of using the program DiaSten-pH to determine the degree of impairment of evacuation function of the stomach in a patient with cicatrical-ulcerative stenosis of duodenum.

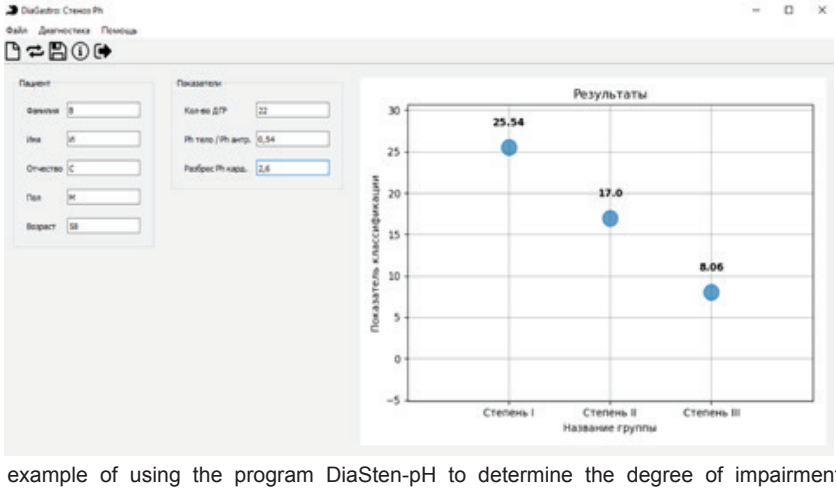
When performing intragastric pH monitoring with the Gastroskan-GEM machine, the DiaSten-pH computer program can be considered an addition to it.

DiaSten software is lightweight and cross-platform. It was tested on Windows 7 and Ubuntu 14.04 operating systems. Only free tools were used for software development.

Conclusions. A correlation was established between the degree of impairment of evacuation function of the stomach and the values of acid and reflux indices of intragastric pH monitoring.

On the basis of discriminant analysis of intragastric pH monitoring indicators, mathematical models were created that allow determining the degree of EFS impairment with an accuracy of 92% and 100%.

The use of the computer program DiaSten-pH greatly simplifies the determination of the degree of EFS impairment in patients with duodenal CUS, allows to expand the diagnostic capabilities of intragastric pH-monitoring, and carry out the remote diagnostics of patients.



An example of using the program DiaSten-pH to determine the degree of impairment of evacuation function of the stomach in a patient with cicatrical-ulcerative stenosis of duodenum.

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EPIDEMIOLOGY OF KNEE OSTEOARTHRITIS AMONG RURAL RESIDENTS OF YAKUTIA

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Knee osteoarthritis is one of the most common rheumatologic problems. A population study was performed to study the epidemiology of osteoarthritis of the knee joints (gonarthrosis) among the rural indigenous people of Yakutia.

Material and methods: we performed a population study of the adult indigenous population (Yakuts) of 7 villages in central Yakutia. A total of 3.401 people took part in the screening study. The diagnosis of gonarthrosis was made using Altman et al. criteria (1991).

Results: the prevalence of gonarthrosis among the rural population of Yakutia was 12.8% (95% CI: 11.7-14.0) and depended on the age of the examined. Knee osteoarthritis was 2 times more often observed in women. Prevalence rates were 16.9% (95% CI: 15.3-18.7) in women and 7.8% (95% CI: 6.6-9.3) in men, respectively. The mean age of patients with gonarthrosis among the rural population was 56 years. Mechanical overload of the joint in the cold was proved to be the main risk factor for knee osteoarthritis for the rural population.

Conclusions: the high prevalence of gonarthrosis among the indigenous rural residents of Yakutia is due to the features of the population life in the region with extreme climate.

Keywords: epidemiology, gonarthrosis, Yakuts, rural population, Sakha (Yakutia) Republic.

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Introduction. Osteoarthritis (OA) is one of the most common chronic diseases, reducing the life quality of patients. The disease occupies a leading position in the structure of rheumatic diseases (RD). These diseases often lead to physical disability, and their treatment is the most expensive in the world. Analysis of statistical indicators for Russia in 2015-2016 showed that the main share among the class of diseases of the musculoskeletal system (MSSD) is made up of degenerative joint diseases (the incidence of OA is 4 350 465 cases in 2015; with a slight decrease in 2016 to 4 285 464 cases). Annually in the Russian Federation more than 600 OA new cases are recorded per 100 000 adults. More complete information on the prevalence of chronic RD in the population can be obtained in the course of large-scale epidemiological studies. The first studies of the RD epidemiology were conducted in the early 70s and 80s and differed in approaches to diagnosing the disease, and therefore, the prevalence rate varied widely from 4 to 64% [2, 7, 8, 9]. Epidemiological studies using common methods and diagnostic criteria began to be carried out only in the 90s. These researches indicate the OA widespread prevalence among workers in industrial enterprises and agriculture and range from 18 to 41% depending on the region [2, 8, 9]. The last large-scale study was initiated by the Institute of Rheumatology of the Russian Academy of Medical Sciences in the mid-2000s as part of the World Decade of Bones and Joints [3, 4]. The research program developed by the Institute of Rheumatology of the Russian Academy of Medical Sciences together with the Association of Rheumatologists of Russia included the study of the epidemiology and economic burden of rheumatic diseases in various regions of the country among different social groups. The project was implemented in 15 regions of the Russian Federation, including the Sakha (Yakutia) Republic.

The Sakha (Yakutia) Republic is located in the permafrost zone, 40% of the republic's territory lies beyond the Arctic Circle. The region is characterized by a long period of below zero temperatures, the absolute value of the minimum temperature and a significant difference in temperatures in the cold and warm periods of the year. As of January 1, 2018 964.3 thousand people live in the Republic (population density - 0.31 people / km2), including the rural population - 331.5 thousand (34.4%), urban - 632.9 (65.6%). According to 2010 census, the national composition of the population is represented by Yakuts (45.5%), Russians (41.2%), Ukrainians (3.6%), Evenks (1.9%), Evens (1.2%), and other nationalities (6.6%). The territory of the

Republic can be conditionally divided into three climatic and geographical zones, each of which has its own natural, socio-economic and demographic features: polar, central and southern [10]. The polar zone includes areas mainly inhabited by the peoples of the North: Evenks, Evens, Chukchi, Yukagirs. The population is engaged in reindeer husbandry, fur trade. The central zone includes relatively densely populated areas with developed livestock. The main population of this zone is the Yakuts (Sakha). The southern zone includes areas of industrial development, populated mainly by the non-indigenous.

The objective of the research was to study the prevalence, clinical manifestations and risk factors for gonarthrosis among rural residents of the Sakha (Yakutia) Republic.

Materials and research methods. A population study was carried out in 7 rural settlements of the central zone of the Republic and 3 randomized administrative districts of Yakutsk. The article presents the study results among the rural population.

For screening among the rural population, complete lists of residents over 18 years of age were obtained in the local administrations of the villages. The number of persons meeting the inclusion criteria was 4.128. The paramedical personnel and doctors filled out a screening questionnaire for each resident individually during door-to-door survey and in organized groups. A total of 3401 villagers were surveyed, which accounted for 82.4% of the initial list of adult residents (1867 women and 1534 men). Subsequently, a random sample of 695 people was formed from the number of respondents who answered positively to the question about the presence of pain in the knee and/or hip joints during current year. Of these, 687 (98.8%) took part in the study. All study participants underwent an in-depth clinical examination in order to verify the diagnosis. The examination program included the collection of anamnestic data, a physical examination of the joints by a rheumatologist, laboratory and instrumental methods of research (radiography of the affected joints, determination of ESR, CRP, rheumatoid factor). Imaging of the joints was carried out on a portable x-ray device on-site, ESR was determined in the laboratory of local hospital, titers of CRP and rheumatoid factor (RF) were determined later on the basis of the immunological laboratory of the Institute of Health. The diagnosis of gonarthrosis was based on the clinical and radiological criteria of Altman et al. [12].

Statistical processing of the material was carried out using the IBM SPSS Statistics 22 package. The Pearson criterion $\chi 2$ was used to compare the groups. The critical value of the level of statistical significance of differences (p) was taken to be 5%. To assess the risk, the prevalence ratio was calculated at 95% confidence intervals (CI).

Results and discussion. The diagnosis of OA was verified in 687 people (468 women and 219 men) who complained of pain in the knee and/or hip joints. According to Altman et al. criteria (1991) gonarthrosis was established in 436 of examined. Thus, the prevalence of gonarthrosis among rural residents of Yakutia (n = 3401) was 12.8% (95% CI: 11.7-14.0) (Table 1). The prevalence of gonarthrosis depends on the studied population and the epidemiological method used. Comparable prevalence rates were obtained in an epidemiological study conducted in the USA in 1971-1975 (First National Health and Nutrition Examination Survey (NHANES-1). In this study, which is similar in methodology, a clinical diagnosis of the knee OA was made in 12% of 6913 subjects, aged 25-74 years [1]. According to the data of L.I. Benevolenskaya, among 2659 identified patients, gonarthrosis was diagnosed in 76.8% of men and 68% of women [2].

The modern concept of the gonarthrosis etiology connects the development of the disease with the combined influence of both endo- and exogenous factors, i.e. the disease has a multifactorial origin. Among endogenous factors, gender and age play a role. According to domestic and foreign studies, gonarthrosis is more common in women aged 50 to 80 years [1, 2, 11, 12, 13].

In our study, gonarthrosis was also two times more likely to be present in women. Prevalence rates were 16.9% (95% CI: 15.3-18.7) in women and 7.8% (95% CI: 6.6-9.3) in men. The mean age of gonarthrosis patients among the rural population was 56 years. The disease more often began at the age of 40-49 years and reached a maximum frequency at 60-69 years.

In the Republic Sakha (Yakutia), such a factor as the vast permafrost zone leaves its mark on economic, sanitary-hygienic living conditions of people [5, 6, 7]. This is especially reflected in the life of rural residents.

When analyzing the influence of risk factors on the frequency of OA, the prevalence ratio was used as an effect measure (Table 2). The prevalence of gonarthrosis was 4.1 (2.3-7.2) times higher among respondents working at low temperatures than in people without a history of this factor. Significant risk factors for the development of OA were also long walking, the need to exert great efforts during work, lifting and carrying weights, stereotypical movements, prolonged forced position of the body, load on the knee

Table 1

Prevalence of gonarthrosis among the rural population of Yakutia (%) with 95% CI

Age, yrs	Male	Female	Both
18-29	0.8 (0-3.3)	0.0 (0-2.2)	0.4 (0-1.7)
30-39	1.2 (0.2-3.4)	2.5 (1.2-4.7)	1.9 (1.8-6.0)
40-49	6.7 (4.7-9.5)	17.1 (14.2-20.4)	12.4 (10.5-14.6)
50-29	10.3 (6.9-14.8)	27.7 (23.3-32.6)	20.5 (17.5-24.0)
60-69	25.8 (18.5-34.6)	52.4 (44.0-60.7)	40.1 (34.4-46.2)
70 and elder	26.4 (17.8-36.9)	26.2 (18.8-35.1)	26.3 (20.7-32.8)
18 and elder	7.8 (6.6-9.3)	16.9 (15.3-18.7)	12.8 (11.7-14.0)

Table 2

OA prevalence ratio in relation to the risk factors with 95% CI

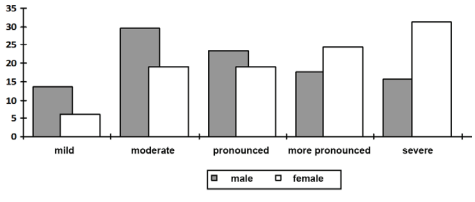
Risk factor	Prevalence ratio	p
Working at low temperature	4.1 (2.3-7.2)	<0.001
Forced position of the body	2.0 (1.5-2.6)	<0.001
Other statistical loads	2.2 (1.7-2.9)	<0.001
Long walking	2.0 (1.4-3.0)	<0.001
Squats	2.1 (1.5-2.7)	<0.001
Stereotypical movements	2.3 (1.8-2.9)	<0.001
Need to exert great efforts	2.1 (1.6-2.8)	<0.001
Lifting and carrying weights	1.3 (1.0-1.7)	0.044

joints associated with frequent squats.

Analysis of the severity of gonarthrosis according to the algo-functional index of Leken in relation to gender is presented in Fig. In men, gonarthrosis was more common with mild, moderate (29.5%) and severe (23.5%) severity, and in women - significantly pronounced (24.4%) and sharply expressed (31.3%) severity.

At analyzing research data from NHES and NHANES-1 Lawrence et al. it was found that the prevalence of mild, moderate and severe OA in the age groups of 35-44 and 45-54 years was 1.6 and 3.0% respectively, the prevalence of moderate and severe OA was 0.3 and 0.4%, respectively [1]. Thus, in the Yakut rural population, gonarthrosis of severe degrees of functional insufficiency is most common (Fig.).

The leading clinical symptom that reduces the quality of life of gonarthrosis



Leken's functional index by sex.

patients is pain. Table 3 presents the characteristics of the pain syndrome at knee OA according to the results of the questionnaire. Pain syndrome was most often manifested in the form of pain and discomfort at standing up from a sitting position (78.4%). Also, most of gonarthrosis patients (70.5%) noted morning stiffness for about 15 minutes or pain after getting out of bed. The next most characteristic sign was pain, aggravated after standing for 30 minutes (60.8%). More than half of patients noted night pain in the knee joints (65.0%).

Pain in 56.6% of patients was accompanied by a history of swelling of the knee joints. The joint swelling was most often noted by patients with a pronounced severity of gonarthrosis by Leken (32%).

Assessment of maximum distance without pain in the knee joints revealed that 60.2% of patients could walk more than 1 km without pain in the knee joints, but with limitations. A smaller proportion of patients noted a distance of 100 m to 1 km. 6.1% of respondents could walk less than 100 m only without pain. 15.6% of patients had to use a stick or crutch when walking.

Among the signs characterizing the existence of limitations in everyday life, the most common symptom was the inability to kneel due to pain in the knee joint (80.1%) and a sudden feeling of loss of support on the affected limb (54.8%).

Thus, gonarthrosis in the rural population of Yakutia has a pronounced degree of functional insufficiency, accompanied by a significant restriction of movement and pain.

Conclusion. The results of our study can serve as the basis for the planning of preventive and therapeutic care, taking into account working and life conditions of rural residents, timely diagnosis of the disease at the early stages of its development, adequate treatment, dispensary observation and rehabilitation treatment with the involvement of local hospitals.

Table 3

Characteristics of the pain syndrome at knee OA

Pain character	Definite OA		Probable OA		Manifesting OA	
	n	%	n	%	n	%
Night pain: only when moving or in a certain position	9	10.5	2	2.5	11	6.6
even without movement	51	59.3	57	71.2	108	65.0
morning stiffness for about 15 minutes or pain after getting out of bed: less than 15 min	58	67.4	59	73.7	117	70.5
more than 15 min	16	18.6	8	10.0	24	14.4
Pain. aggravated after standing for 30 minutes	55	63.9	46	57.5	101	60.8
Pain occurs when walking: only after passing a certain distance	56	65.1	51	63.7	107	92.2
from the outset. and then it is aggravated	16	18.6	21	26.3	37	22.3
Pain or discomfort when standing up	64	74.4	66	82.5	130	78.3

The study was carried out as basic part of the state task of the Ministry of Education and Science of the Russian Federation on the topic "Clinical and genetic aspects of diseases characteristic of the indigenous people of Yakutia in modern conditions" (state registration number 17.6344.2017 / 8.9).

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POSSIBILITIES OF PREDICTION OF NEUROTIC, STRESS-RELATED DISORDERS COURSE IN TERMS OF HORMONAL PARAMETERS

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One of the most common and universal disorders of mental adaptation are non-psychotic mental disorders, in which development a large role plays various endocrine and biochemical mechanisms of response to stress. The purpose of the study is to determine the contribution of the endocrine system to the formation of neurotic, stress-related disorders in order to identify the criteria for predicting their protracted course. Material and Methods. A comprehensive clinical-psychopathological and hormonal examination of 43 women (mean age 39.43±7.23 years) inpatient at the first clinical psychiatric unit of the clinic of Mental Health Research Institute of Tomsk NRMC with various types of the course of neurotic, stress-related disorders was performed. According to the criteria ICD-10 all patients were divided to clinical groups: adjustment disorders (F 43.2) and enduring personality change after psychiatric illness (F 62.1). Investigation of hormonal status included determination of concentrations of cortisol, prolactin and thyroid-stimulating hormone (TSH) in serum by the method Enzyme Immunoassay (EIA). The hormonal status of 32 healthy women was taken as a control. Results. A psychopathological investigation of patients showed that overexertion of protective mental mechanisms associated with the impact of a stressful situation can lead to a breakdown in adaptation, disturbances of normal functioning and the emergence of various neurotic symptoms that fall into the diagnostic category F 43.2 (adjustment disorders). As the damaging effects of unfavorable factors and stressful co-existence accumulated, the “health resources” decreased, which was a starting point in the formation of persistent personality changes and transition to another diagnostic category F 62.1 Persistent personality change after a mental disorder. The characteristics of the hormonal status of patients with a protracted neurotic, stress-related disorders were: high concentrations of cortisol, prolactin and low serum levels of thyrotropic hormone, which allows considering them as predictors of persistent personality change at early stage of the diseases. Conclusion We determined the hormonal criteria for predicting a protracted course of neurotic, stress-related disorders with the formation of a persistent personality changes at an early stage of the disease - at the stage of disorder of adaptive reactions.

Keywords: neurotic, stress-related disorders, adjustment disorders, enduring personality change, cortisol, prolactin, thyrotrophic hormone.

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Introduction. One of the most common and universal disorders of mental adaptation are non-psychotic mental disorders, in which development a large role is played by various endocrine and biochemical mechanisms of response to stress [1, 4]. These mechanisms are usually not the cause of the breakdown of adaptation, but its effect, since they are not specific to one or another stress factor and are aimed at achieving early compensation. [18]. Various adverse factors that can lead to maladjustment, accompany a person throughout life. However, in some individuals, adjustment disorders are acute, while others develop chronic forms of neurotic states. The question of why this is happening remains open, despite numerous studies in this field. The relevance of the problem of differentiated prediction of the course of such disorders has been dictated recently by the increasing prevalence of neurotic, stress-related disorders and the need to improve the quality of life, preserve and develop the labor potential of the population, taking into account the tasks and forecasts of the economic, social and psychological development of the country. Highlighting the criteria for distinguishing between initial and protracted forms of non-psychotic mental disorders helps to identify those suffering from these disorders at the early stages of the disease that helps to prevent an unfavorable trend in the dynamics of neurotic states. Under stress, an increase in the level of hormones is observed, which in physiological quantities are necessary for the normal functioning of all systems of the organism. But if an organism synthesizes an excessive amount of stress hormones for a long time, then undesirable reactions emerge in it, leading to the occurrence of pathological states and the development of various diseases. By additional assessment of the hormonal parameters to the general medical ones, which characterize the adaptation of the organism to the constantly changing environmental conditions, including the mobilization of the organism under the action of stress factors, a differentiated prediction of the course of non-psychotic mental disorders of the neurotic rank is carried out.

The purpose of the study is to determine the contribution of the endocrine system to the formation of neurotic, stress-related disorders in order to iden-

tify the criteria for predicting their protracted course.

Material and Methods. A comprehensive clinical-psychopathological and hormonal examination of 43 women (mean age 39.43±7.23 years) with various types of the course of neurotic, stress-related disorders being under inpatient treatment at the first clinical psychiatric unit of the clinic of Mental Health Research Institute of Tomsk NRMC was carried out. All patients were examined with use of developed at the Borderline States Department of Mental Health Research Institute "Clinical Record Book of Examination of a Patient" adjusted to tasks of the present study. The diagnostic assessment and clinical qualification of neurotic disorders were carried out by psychiatrists of the Borderline States Department in accordance with the International Classification of Diseases of the 10th revision (ICD-10). The diagnosis of neuroses was carried out with regard to accepted criteria, which include a causal relationship with a psychotraumatic situation, neurotic traits of the personality, and neurotic symptoms. 23 patients (group 1) were diagnosed as having adjustment disorders (F 43.2), 20 patients (group 2) – enduring personality change after psychiatric illness (F 62.1). The leading clinical syndrome in both groups was anxiety-depressive one. The study on human subjects was conducted in accordance with Declaration of Helsinki of World Medical Association. All patients upon admission to the clinic gave informed consent for the research.

The study of hormonal parameters - determination of concentrations of cortisol, prolactin and thyroid-stimulating hormone (TSH) in serum was carried out in accordance with the instructions for the use of reagent kits for the immunoenzymatic determination of hormones in serum (JSC "Vector-Best", s. Koltsovo, Novosibirsk Region, Russia).

As a control, data of the hormonal status of 32 practically healthy women were taken, who did not have endocrine diseases at the time of the survey and leading a normal life style.

When performing statistical analysis, STATISTICA version 12.0 for Windows (StatSoft., Inc, USA) was used, the median (Me) and interquartile interval [Q1 — Q3] were calculated. To test the equality of the medians of several samples, Kruskal-Wallis H test was used. The comparison of the studied samples was performed using the Mann-Whitney U test. The critical level of significance was assumed to be 0.05.

Results and Discussion. A psychopathological investigation of patients showed that overexertion of protective mental mechanisms associated with the impact of a stressful situation can lead to a breakdown in adaptation, disturbances of normal functioning and the emergence of various neurotic symptoms that fall into the diagnostic category F 43.2 (adjustment disorders). According to the ideas of many researchers, the general scheme for the development of neurotic disorders is as follows: in the first years of the development, in the future patient a personality structure is formed that makes contacts in the social environment difficult and leads to emotional tension; further, against this background, disturbances in the somatovegetative domain are added and the adaptive mechanisms overexertion occurs, at the same time the behavior is determined not so much by the requirements of the situation, as by the mechanisms of psychological defense. After the psychotrauma, the system of psychological defense, somatovegetative support and adaptive mechanisms was disrupted. The cause of neurotic disorders was the so-called neurotic conflict - a violation of a person's significant life relationships that go back to childhood and are activated in a psychoinjuring situation. As the damaging effects of infectious and/or existing somatic diseases, various surgical interventions, stressful events, unhealthy habits and unhealthy lifestyles accumulated, the "health resources" decreased that was a trigger link in the formation of persistent personality changes and transition to another diagnostic category - F 62.1 (enduring personality change after psychiatric illness). With a protracted course of neurotic disorder, "flight into illness" deepened and the connection between clinical dynamics and psychogenic influences gradually weakened [11]. With a protracted course of neurosis, the spectrum of neurotic symptoms expanded, the intervals between exacerbations were reduced, the wave-like course disappeared, the psychopathological symptoms stabilized and were hardly reversible.

The outcome of the disease depends on the timeliness and quality of care provided: either full recovery with a transition to a new level of adaptation, or chronicity of the pathological process and the formation of a more serious mental disease, such as panic disorder, depression or enduring personality change.

The scientific literature describes social and biological predictors of the favorable and unfavorable course of neuroses. The criteria for unfavorable dynamics of neurotic disorders are as follows: mother's toxicosis, early childhood psychological trauma, age of onset of the disease (over 40), family history (psychopathological personality traits of parents and alcoholism), presence of accentuated character traits in the patient, presence of a permanent psychoinjuring situation in the family, interpersonal conflicts in the work sphere, mixed psychogenias and other factors [10]. A method for predicting the course of neurotic disorders based on hormonal parameters is proposed. By determining the serum levels of cortisol, dehydroepiandrosterone sulfate (DHEAS), total triiodothyronine (T3), free thyroxine (T4), the authors predict the development in the patient of either an adjustment disorder with the predominance of depressive reactions, or the formation of dissociative (conversion, hysterical) disorder [6]. By calculating the ratio between the immunological and biochemical indicators of homeostasis, a method has been developed for the early diagnosis of an unfavorable course of the psychopathological state in patients with neurotic, somatoform and neurosis-like disorders [8]. We have previously developed a method for predicting a protracted course of neurotic disorders with the transition of an adjustment disorder into an enduring personality change, based on the identification of clinical syndromes of secondary immune deficiency and immunity indicators (level of circulating immune complexes, content of cytotoxic T-lymphocytes and lymphocytes-markers of late activation) [7].

We have proposed a new method that expands the arsenal of well-known methods for predicting the protracted course of neurotic disorders and provides an option in view of the laboratory equipment available at the medical institution. The task was solved by determining the serum levels of hormonal parameters in patients with adjustment disorder. Table presents the results of a hormonal investigation of healthy individuals and patients with adjustment disorder and with enduring personality change after psychiatric illness.

A comparative analysis of the findings revealed differences between all the examined groups (Table). The most significant features in the group of patients with enduring personality change in comparison with patients with adjustment disorders are higher values of concentrations of cortisol (771.23 [506.59–867.18] nmol/L and 547.77 [485.18–657.44] nmol/L, respectively; p=0.0422), prolactin (767.01 [440.20–1115.92] mIU/L and 322.74 [166.99–615.92] mIU/L, respectively; p=0.0151) and lower value of concentration of the thyroid-stimulating hormone - TSH (0.93 [0.60–1.57] mcIU/mL

Hormonal parameters of the examined groups of patients and healthy persons

Parameters	The examined groups (Me [Q1—Q3])			P_2
	Healthy individuals (n=32)	Patients with adjustment disorders (n=23)	Patients with enduring personality change	
Cortisol, nmol/L	(n=20)	547.77 [485.18–657.44] p_1=0.0016	771.23 [506.59–867.18] p_1=0.0001	0.0422
Prolactin, mIU/L	250.46 [186.63–373.50]	322.74 [166.99–615.92] p_1=0.1918	767.01 [440.20–1115.92] p_1=0.0003	0.0151
TSH, mcIU/mL	1.91 [1.63–2.69]	2.63 [1.59–3.18] p_1=1.8403	0.93 [0.60–1.57] p_1=0.0001	0.0001

Note: p1 – reliability of differences vs. healthy individuals;
p2 – reliability of differences between groups of patients.

and 2.63 [1.59–3.18] mcIU/mL, respectively; p=0.0001).

The statistical significance of the differences between the hormonal parameters presented in the table is confirmed by Kruskal-Wallis H test for cortisol [H=23.45232; p=0.0000], prolactin [H=9.28387; p=0.0096] and TSH [H=27.25318; p=0.0000].

The choice of hormones cortisol, prolactin and TSH as predictive criteria for the protracted course of neurotic, stress-related disorders at the initial stage of the disease is caused by the following factors. Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid systems under the control of higher brain regions are the main systems that implement all changes in the body under stress [17]. One of the main stress hormones is undoubtedly cortisol. Its action causes various physiological, cognitive and behavioral changes in the human body that are crucial for successful adaptation to stress [2, 14]. Prolactin is actively involved in the formation of adaptive reactions that occur when various extreme factors act on the body. By regulating mental functions, prolactin influences the body's behavioral responses [15, 16]. The question remains open about the production of thyroid-stimulating hormone of the pituitary gland and the functional activity of the thyroid gland during stress. Most authors believe that under stress, thyroid function is inhibited, and this is attributed to the action of the hypothalamic-pituitary system, namely the suppression of TSH secretion under the influence of high concentrations of adrenocorticotropic hormone [5, 12]. According to other researchers, during the formation of the response to stress the increase in the secretion of thyroid-stimulating hormone and increase in the function of the thyroid gland occur according to the following scheme: cortex - hypothalamus - secretion of thyroliberin - anterior pituitary gland - release of thyroid-stimulating hormone - thyroid gland - secretion of thyroid hormones of the thyroid gland [3, 13].

On the basis of the data obtained, we have proposed a method for predicting at the early stage of the neurotic, stress-related disorders their protracted course with the formation of an enduring personality change by determining serum levels of hormonal parameters in patients with adjustment disorders. In the group with adjustment disorders, the initial neurotization of the foundation took place in the conditions of everyday family troubles and prepared the conditions for the subsequent development of neurosis. Hormonal parameters in this group differed slightly from those in the group of healthy individuals. Under the influence of the improvement of the micro-social environment, intensive psychotherapeutic work, there was a complete regredient dynamics of neurotic symptoms and a distinct harmonization of personality response.

Earlier, the complex interaction of psychogenic and endocrine links in the development of protracted forms of neurotic states was established. Long-term psychogenic trauma often led to organic changes in somatic functions, i.e., functional changes passed into organic ones. With a massive impact of psychogenic factors, a transformation of the main neurotic symptoms was observed, mixed symptoms appeared: asthenic-depressive, asthenic-hypochondriac, obsessive-phobic. With a protracted course of neurosis, an enduring personality change was gradually formed, a deepening of the “flight into illness”, the links between clinical dynamics and psychogenic influences gradually weakened. This dynamic was accompanied by pronounced deviations from the norm in hormone status. With a simultaneous high concentration of cortisol and prolactin and a low concentration of thyroid-stimulating hormone, it is possible to predict the possibility of a protracted course of the disease with the formation of an enduring personality change. A patent for invention has been obtained for this method [9]. The proposed method was tested on 16 patients, is simple to implement and can be implemented in health care and medicine.

Conclusion. Along with general clinical indicators, the determination of the concentration of cortisol, prolactin and thyroid-stimulating hormone allows us to predict a protracted course of neurotic, stress-related disorders with the formation of enduring personality change at an early stage of the disease - at the stage of adjustment disorders. The obtained data expand the arsenal of biomarkers for predicting the course of neurotic disorders at earlier stages of the disease, help develop complex treatment methods, strengthen the impaired system of adaptation and influence all components of neurotic disorder. The advantage of the developed method lies in the fact that it allows reducing the number of days of disability spent by the patient in the hospital by providing adequate timely medical care based on the identification in addition to the clinical laboratory parameters that are objective.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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FEATURES OF IMMUNOGENETIC STATUS IN CHILDREN RESIDING IN NITRATE GEOCHEMICAL PROVINCE

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The authors assessed immunological health of children under excessive intake of nitrates with drinking water, formation of its immunological and genetic status being determined by living conditions in a particular biogeochemical province of the Perm Krai (Region).

This work aims to study the features of the immunogenic status in children living in a nitrate geochemical province.

Materials and methods. The cell differentiation markers (CD3+CD95+) were determined with flow cytometer. The level of protein expression controlling apoptosis processes – Bcl-2, p53 and surface expression of receptor to tumor necrosis factor TNRF were determined with an appropriate MCAT and simultaneous negative isotypic control procedure. The genetic features were determined using a real-time polymerase chain reaction and allele discrimination based on the diagnosis of single-nucleotide polymorphisms.

Results. The changes in cellular component of the immune system (inhibition of T-cell receptors CD95+, and intracellular proteins Bcl2), TSH deficiency, the increased expression of tumor markers associated with the growth in N-nitrosodimethylamine concentration in the blood, significant both in relation to the reference level and the comparison group, were found. An increase in specific IgG to N-nitrosodimethylamine ($p<0.05$) was detected. The study results of the gene polymorphism frequency revealed its features in children of nitrate province according to the criterion of minor allele of genes: MTHFR, PPARA, CPOX, CYP1A2, BRCA1, which characterizes the eventual violations of detoxification and cancer proliferation functions.

Conclusions. Revealed disorders of immune reactivity and genetic polymorphism indicate the immunogenic status peculiarities in population living in the nitrate technogenic chemical province of Perm region, and might be used as markers of pathological health disorders associated with tumor processes and cellular immunodeficiency inducing the identified imbalance of cellular and humoral immunity (deficiency of proapoptotic factors and hyperproduction of IgG to N-nitrosoamines).

Keywords: cell-mediated immunity, a genetic polymorphism, *BRCA1* gene rs3950989, N-nitrosamines.

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Introduction. Under long-term exposure to various toxic substances in concentrations that do not cause an externally detectable effect there can still be hidden changes in a number of physiological, neurohumoral, immunological and biochemical parameters of individual organs and systems. These substances include nitrates and their metabolites – N-nitrosamines. N-nitrosodiethylamine (NDMA) belongs to the super mutagen class and has a high toxicity, teratogenic and embryotropic action, as well as an immunosuppressive effect. What is more, it leads to malignant tumors growth and is a weak allergen [1]. Nitrates may lead to endogenous nitrotyrosine and the formation of N–nitrosamines that are very likely to be a carcinogenic factor for humans (group 2A) [3, 5]. N–nitrosamines metabolism through microsomal oxidation system using cytochrome P-450 leads to the formation of methyldiazonium ion (direct carcinogen), which can methylate the DNA cell, inducing malignant tumors of the lung, stomach, esophagus, liver and kidneys. The choice of indicators/markers for assessing the relationship between the biological system and potentially hazardous chemical factors is relevant [1, 4].

Materials and methods. The study focused on children aged 4-8 years (n=111): 57 people (monitoring group) living in conditions of high nitrate content (exceeding hygienic standard by 1.1 times) in water used for drinking purposes, and 54 people (comparison group) living in the area of relative sanitary-epidemiological well-being (water with standard content of nitrates). Children attended pre-school educational institutions for children in the Perm Territory.

The N-nitrosodimethylamine content in drinking water samples was evaluated via gas chromatography with a thermionic detector. The technique enables determining N-nitrosodimethylamine in drinking water in the concentration range of 0.005 - 0.1 mg/dm^3 with an error of ± 20 % when a confidence level amounts to 0.95. The blood tests on the N-nitrosamines content were carried out with gas chromatography-mass spectrometry method. The N-nitrosamines concentrations ranged from 0.002 to 0.1 mg/dm^3 with an error of ±27 % at a confidence level of 0.95.

The examination of 95 children involved studying cell differentiation markers (CD3+CD95+). The level of proteins expression controlling apoptosis – p53 and surface expression of the receptor to tumor necrosis factor (TNFR) was determined by flow cytometer FACSCalibur using appropriate MCAT ("BD", USA) and simultaneous negative isotypic control procedure. The mediator of intercellular immune regulation of tumor necrosis factor (TNF) and indicators of

proliferative reactions of carcinoembryonic antigen (CEA) and CA199 were analyzed with ELISA test on the "Elx808IU" analyzer.

The polymorphism (SNP) of genes CYP1A1_3, MTHFR, CPOX, SULT1A1, SOD, system piroxicam genes PPAR, FAS, FOXP3, VEGF, APO-E, NO-synthase, MMP9, p53, NR3C1 was studied in all examined persons. The genetic material was isolated from peripheral blood using a DNA extraction kit from the clinical material "DNA-Sorb-B" (NextBio, Russia). The polymorphism was genotyped using "SNP-screen" kit (Synthol, Russia) on CFX96 Real Time System. The frequencies of gene polymorphisms for correspondence are estimated according to the Hardy-Weinberg equilibrium. The analysis of the mean values relative to normal levels is presented in diagrams as x±SE. The results with p<0.05 were considered as significant. The Bonferoni correction was also used for paired comparisons. It sets the significance level at p<0.008 (less than 1%).

Results and discussion. Increased levels of nitrates and N-nitrosodimethylamine in water (4.7 times and 2.5 times respectively) towards the comparison territory were determined (Table 1). It was found that long-term exposure to nitrates and N-nitrosodimethylamine in drinking water within concentrations range of 45-51.7 mg/dm^3 and 0.01-0.016 mg/dm^3 respectively leads to the fact that N-nitrosodimethylamine concentrations in the blood of children in the observation group is 1.5 times more (0.0045±0.0014 mg/dm^3) relative to the comparison group (0.003±0.0009 mg/dm^3) (table 1). The chemical analysis enables to determine nitrates in the urine of children from the observation group at the level of 66.6 mg/dm^3, which is 1.5 times more than in the comparison group (43.7 mg/dm^3).

The level of membrane activation marker CD3+CD95+ (in 100% of children), transcription factor p53 (in 87% of children) and TNFR receptor (in 100.0% of children) responsible for apoptosis (p<0.05) was significantly reduced in relation to the norm (Tab. 2). The methodological technique of estimating the odds ratio changes of immunological tests while increasing contaminant concentrations in biological media enabled to determine significant (p<0.05) reduction of CD3+CD95+ when the N-nitrosodimethylamine concentration in the blood (R2=0.91 by p<0.05) went up. The tumor necrosis factor content was significantly reduced by 3 times in relation to the control group. The elevated level of fetal protein CA 199 was recorded in the serum in 2 % of children living in the observation area. There was a significant (p<0.05) increase in the concentration of CA 199, CEA with growth in the N-nitrosodimethylamine concentration in the blood (R2=0.74 at p<0.05). A high level of specific sensitization to N-nitrosodimethylamine by the IgG criterion (93% of the examined persons in the observation group, p<0.05) was found with a significant difference towards the comparison group (excess 2.2-times, p<0.05).

The results of genetic analysis revealed key genes whose polymorphism frequency differed significantly from the regional average prevalence of polymorphic deviations (Table 3). The polymorphism of detoxification and oxygenation genes changed: methylenetetrahydrofolate reductase gene MTHFR, and piroxicam proliferator genes (*PPARA, PPARG, PPARGC1A*) associated with the 2nd phase of the detoxification of xenobiotics – conjugation (the frequency of the mutant allele was 1.5 times higher than in the control group).

Increase of the T allele frequency of the methylenetetrahydrofolate reductase gene (*MTHFR* rs1801133) and the A allele frequency of the oncoproliferation gene *BRCA1* rs3950989, as well as increased by 1.5-2,0 times the frequency of occurrence of variant alleles of metalloproteinase 9 (*MMP9* rs17576), cytochrome (*CYP1A2* rs2069522), and coproporphyrinogenoxidase (*CPOX* rs1131857) genes in the group of children, that consume water with a high content of nitrates are characterized as a risk group for the development of processes associated with the folate cycle, homocysteine and collagen metabolism (violation of vascular endothelium function), detoxification and metabolism of haptens, cancer processes.

An increased frequency of the minor allele of the BRCA1 gene enzyme rs3950989 is significantly associated with a deficit in the level of tumor necrosis factor (TNFR) which indicates the formation of additional risk factors of carcinogenesis under geochemical provinces (Table 3).

Table 1

The results of the nitrate content in water and urine, N-nitrosodimethylamine in blood of children in the comparison and observation groups (one-time concentration of nitrate and N-nitrosodimethylamine in drinking water for the spring-summer period n=95)

Drinking water, mg/dm3 (R ≤0.005)			
Nitrate concentration		N-nitrosodimethylamine concentration	
MAC=45 mg/dm^3		MAC=0.01 mg/dm^3	
Arithmetic mean			
Comparison group	Observation group	Comparison group	Observation group
10.9±2.7	51.7±12.92	0.0065±0.001	0.016±0.003
Biological media, mg/dm^3			
Nitrate concentration in urine		N-nitrosodimethylamine concentration in blood	
Median		Arithmetic mean	
Comparison group	Observation group	Comparison group	Observation group
43.7	66.6	0.003±0.0009	0.0045±0.0014

Table 2

Parameters of immunity in children under exposure to nitrates (Perm krai)

Parameter	Norm	*Observation group, M±m*	*Comparison group,*
M±m	15-25	7,65±1,07*/**	12,833±2,28
CD3+CD95+-lymphocytes, relative., %	15-25	7.65±1.07*/**	12.833±2.28
p53, %	1.2-1.8	0.324±0.11*	0.522±0.10
TNFR, %	1-1.5	0.514±0.187**	1.418±0.301
CA-19-9, units/cm^3	0-35	18.07±2.2**	10.06±3.20
CEA (carcinoma embryonic antigen), ng/cm^3	0-2.9	6.35±0.08**	1.001±0.17
Tumor necrosis factor, pg/cm3	0-6	2.824±1.43**	8.199±3.85
Specific IgG to NDMA, c.u.	0-0.1	0.176±0.033**	0.115±0.022

* – the difference is significant relative to the reference level (p<0.05)
** – the difference is significant relative to the comparison group (p<0.05)

Table 3

Features of genetic polymorphism under human impact - BRCA1 gene associated with the expression of TNFR

Ген *BRCA1*/ ответ TNFR				
Genotype	Group	n	X (s.e)	OR (CI 95%)
G/G	Control	10	0.97(0.31)	0.00
G/A		12	0.77(0.16)	-0.17(-1.22-0.87)
A/A		6	1.61(0.35)	0.60(-066-1.86)
G/G	Study group	14	2.34(0.29)	0.00
G/A		30	1.20(0.28)	-1.16(-1.96-0.37)
A/A		8	0.98(0.49)	-1.38(-2.46-0.30)

According to the study results, it might be assumed that the hidden changes in immunological and biochemical parameters associated with the polymorphic genetic background are revealed under chronic exposure to nitrates in concentrations that do not cause acute effects. The studies carried out on the example of Perm region have confirmed that the excess concentrations of nitrates in water are metabolized to N-nitrosamines against the altered genetic background and lead to the immune-mediated mechanism of proliferative shifts in homeostasis which are characterized by an imbalance of membrane and transcription factors of apoptosis.

Conclusion. It was found out that the long-term exposure to nitrate with drinking water in a concentration range of 45-51.7 mg/dm^3 and N - NDMA at 0.01-0.016 mg/dm^3 creates an increased N-NDMA concentration in the blood of the children in the exposed group (0.0045±0.0014 mg/dm^3) relative to the comparison group (0.003±0.0009 mg/dm^3) by 1.5 times. There was a significant hyperproduction of specific IgG to N - NDMA ($p<0.05$) both in relation to the reference value and the comparison group. The following changes in the cellular component of immune system are revealed: inhibition of T-cell receptors CD3CD95+ of transcription factor p53 and TNFR receptor, an increased expression of tumor markers associated with elevated N-NDMA concentration in the blood, accurate in relation to the reference level and the comparison group. The results of gene polymorphism analysis revealed an excessive frequency of minor allele of *MTHFR* gene (*MTHFR*), the piroxicam proliferator genes and the first phase of detoxification of coproporphyrinogen oxidase (*CPOX*) and cytochrome (*CYP1A2*), cancer proliferation (*BRCA1*), characterizing genetic polymorphic variants of imbalance in metabolic processes. An increased frequency of the minor allele of the BRCA1 gene enzyme rs3950989 in children contaminated with N-NDMA is significantly ($p=0.016$) associated with a deficit in the level of tumor necrosis factor (*TNFR*), which indicates the formation of additional risk factors of carcinogenesis under nitrate geochemical province. The hidden changes in immunological and biochemical parameters associated with the polymorphic genetic background are revealed under chronic exposure to nitrates in concentrations that do not cause acute effects.

Conflict of interest. The authors state that there is no conflict of interest.

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FEATURES OF TRACE ELEMENT STATUS AT ANEMIA IN PREGNANT WOMEN

A comprehensive clinical and laboratory research of 408 women from the Amur region during and after their pregnancy was carried on. The environment in the Amur region is characterized by low level of I, Se, high content of Mn, Fe, Zn and an imbalance of other trace elements. Research showed an increased amount of Cu in serum and decreased amount of Cu in blood cells. In anemia, regardless of the level of Fe, there was a decrease in Co, Se in serum and an increase in Mn in blood cells. The distinctive features of microelement status for iron deficiency anemia – an increased Mn in blood serum; for iron-saturated anemia – increased Li in serum, increased Li and Co in blood cells were determined.

Keywords: pregnant women, trace elements, anemia.

Introduction. Due to the rapid growth of the fetus and placenta in a pregnant woman's body there are numerous metabolic changes that are more apparent than in any other period of a woman's life. The mechanisms of adaptive adjustment during pregnancy naturally relate to the microelement homeostasis. The most "ancient" microelementosis is iron deficiency [2]. The main function of iron is oxygen transfer and participation in many oxidation-reduction processes. One of the consequences of Fe homeostasis disorders is iron deficiency anemia (IDA). About 41.8% of pregnant women worldwide are anaemic, half of which are iron-deficient [11]. However, anemia is a manifestation of the lack and imbalance of many micro - and macronutrients in the body, and other causes (genetic, biogeochemical, etc.) that affect the health of a mother before pregnancy, during pregnancy and full child bearing. Disorders in micronutrient status during pregnancy have long-term consequences [1, 3, 4, 6 - 9]. Despite a large number of studies on pathogenetic mechanisms, diagnosis and treatment of anemia, many questions remain unclear [10], especially the group of conditions with reduced hemoglobin and normal iron parameters. The objective of the work is to assess the trace element status in pregnant women of the Amur region depending on iron content at early stages of gestation to justify additional correction of imbalance disorders.

Materials and methods. The work is based on the results of a comprehensive clinical and laboratory research of 377 pregnant women at early gestation and 31 non pregnant women of reproductive age living in the territory (Amur region), in accordance with the current medical and economic standards [5] with informed consent to diagnostic studies.

The indicators of the content of Fe-one of the main microelementosis (ferritin and serum iron) and the level of hemoglobin (Hb), which includes the element for oxygen transport were taken as the basis of women groups formation.

Thus four groups were formed: non-pregnant women (n=31); pregnant women with normal amount of Hb (n=177) or comparison group; pregnant women with reduced amount of Hb and without Fe deficiency (n=102) – iron-saturated anemia (ISA); pregnant women with reduced amount of Hb and Fe deficiency (n=98) – iron deficiency anemia (IDA).

Determination of Hb, ferritin and serum iron was carried out by standard hardware methods. Trace element status of patients was estimated by the method of atomic-absorption analysis of serum and blood cells (Cu, Co, Mn, Se, Li) following sample preparation for spectrophotometer Hitachi Z900. Statistical processing and evaluation of the data were carried out using the software package "Statistica" (version 10), the calculation of the main descriptive characteristics, the reliability of differences and correlation relationships in groups with an accuracy of $p<0.05$.

Results and discussion. A comparative analysis of the research results of pregnant women is presented in the Table.

The content of copper (Cu) in blood serum in non-pregnant women from the Amur region was within the accepted norm (11-24 μmol/l), in blood cells with statistical fluctuations (14-24 μmol/l) 2-3 times lower. In pregnant women of the comparison group, amount of Cu in serum corresponded to the upper limit of the norm (23.49±0.62 μmol/l), but in comparison with the indicators of not pregnant women (16.43±1.71 μmol/l) the results were significantly higher ($p<0.001$). In anemic conditions of both ISA (26.27±0.755 μmol/l, $p<0.01$) and IDA (27.12±0.758 μmol/l, $p<0.001$), Cu content in serum remained 1.6-1.7 times higher. A decrease in Cu in blood cells in almost all women, including pregnant and non-pregnant, and all forms of anaemic conditions, were detected, which is a compensatory reaction of the body, first, to the implementation of increased needs associated with gestation, and secondly, the output of the element from the tissue depot, associated with low content in blood cells.

The content of cobalt (Co) involved in hematopoiesis in serum of pregnant women in the comparison group did not differ from that of non-pregnant women. A significant decrease ($p<0.001$) was detected in patients with anemia regardless of the nature of ferrodynamic at ISA – 0.17±0.021 μmol/l (1.6 times), IDA – 0.13±0.018 μmol/l (2.1 times). Blood cells showed a tendency towards increasing levels of Co in pregnant women, both in a comparison group (1.03±0.047 μmol/l) and IDA (1.12±0.091 μmol/l), and significant ($p<0.001$) increase in ISA – 1.5 times (1.45±0.128 μmol/l), which indicates a change in the relationship between the content of Co in serum and blood cells directly with anemia, especially in ISA.

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The content of trace elements in blood of pregnant women of the Amur region (s – serum, bc – blood cells)

Trace elements, (µmol/l)	Normal amount of Fe			Fe deficiency
	Non-pregnant	Pregnant		
	(n=31)	Comparison group (n=177)	ISA (n=102)	IDA (n=98)
	M ± m	M ± m	M ± m	M ± m
Cu s	16.43±1.71	23.49±0.62***	26.27±0.755**/o	27.12±0.758***/o
Cu bc	6.78±0.57	6.67±0.288	7.40±0.483	6.56±0.287
Co s	0.27±0.02	0.27±0.013	0.17±0.021***/ooo	0.13±0.018***/ooo
Co bc	0.97±0.05	1.03±0.047	1.45±0.128***/ooo	1.12±0.091
Mn s	0.26±0.02	0.30±0.018	0.37±0.045	0.43±0.073*/o
Mn bc	1.14±0.08	1.12±0.05	1.57±0.142***/ooo	1.70±0.139***/ooo
Se s	0.99±0.12	0.92±0.078	1.02±0.099	1.0±0.1
Se bc	1.52±0.19	1.66±0.22	0.55±0.081***/ooo	0.51±0.066***/ooo
Li s	0.17±0.06	0.22±0.038	0.47±0.099**/o	0.16±0.035
Li bc	1.61±0.06	1.45±0.04	1.82±0.18**/o	1.52±0.068

Note. Difference in indexes with the group of non-pregnant women* and control group o:
* - p<0.05; ** - p<0.01; *** - p<0.001; o - p<0.05; oo - p<0.01; ooo - p<0.001

The need to determine the manganese (Mn) in the blood is due to several reasons. The element stimulates hematopoietic processes; is an activator or part of the centers of a number of enzymes, including those involved in the catalytic cycle of radical oxidation; region of residence of the researched women, is characterized by a high content of Mn in the environment (in water, soil, plants). In this regard, we should expect an increased content of this element in the blood, which was confirmed by the results. The tendency to increase of Mn in serum was observed in the examined pregnant comparison group and in ISA. IDA was characterized by a significant increase in the content of the trace element by 1.7 times (0.43±0.073 µmol/l, p<0.05). In blood cells a sharp rise in the level of Mn (1.4-1.5 times) (p<0.001) was revealed both in ISA (1.57±0.142 µmol/l) and in IDA (1.70±0.139 µmol/l).

During the studies it was found that during pregnancy, the average content of essential trace element selenium (Se) in serum in all groups did not differ significantly (0.81-1.01 µmol/l) and corresponded to the lower limit of norm. It is important to determine trace elements in blood cells. The study revealed significantly low (p<0.001) Se content in ISA (0.55±0.081 µmol/l) and IDA (0.51±0.066 µmol/l) directly in blood cells relative to the comparison group (1.52±0.19 µmol/l). A clearer picture of the Se content in pregnant women (1.66±0.22 µmol/l) was due to an analysis of the percentage in each group.

There was Se deficiency in serum in 65.9% of women of the comparison group, in blood cells of 33.3% of the examined. Se deficiency in serum in ISA was found in 51.4% of pregnant women, while the deficiency in the blood cells increased to 90.3% of the examined. The same tendency continued in IDA, the number of pregnant women with Se deficiency in serum reached 59.1%, in blood cells – 90.6%.

Considering the functional characteristics of lithium (Li) in the body, it is logical to assess its status in pregnant women. A peculiarity of blood cells in women during gestation was a significant increase in Li in ISA in serum 0.47±0.099 µmol/l, (p<0.01) and in blood cells 1.82±0.18 µmol/l, (p<0.01). IDA was accompanied by unchanged status in comparison with groups of non-pregnant and comparison group during pregnancy.

The correlation of blood microelement status and ferrodynamic parameters in pregnant women was confirmed by the correlation analysis. Multidirectional bonds of Hb, ferritin and the studied elements in serum (Cu, Co, Mn, Se, Li), blood cells (Co, Mn, Se, Li) were revealed in anemic states.

Conclusion. The obtained data revealed the peculiarity of the blood trace elements level in pregnant women of the Amur region, which consisted in increasing Cu in serum and decreasing in blood corpuscles in both pregnant and non-pregnant women. Anemia, regardless of Fe level, is characterized by a decrease in Co, Se in serum and an increase in Mn in blood cells. A distinctive feature of ISA was an increase of Li in serum, of Li and Co in blood cells. A distinctive feature of DDA was an increase of Mn in serum.

The conducted studies have convincingly shown and confirmed that the anaemic states cannot be regarded as a violation of the metabolism of only iron, but the imbalance of other trace elements as consistent changes. Accommodation of pregnant women in biogeochemical province with deficiency of I, Se, excess of Mn, Fe and imbalance of other elements in the environment contributed to the development of a certain trace element status, similar to environmental features. This can be attributed to anemic state to poly/microelementosis and justify the correction of violations.

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INDICATORS OF LIPID PEROXIDATION OF NON-NATIVE RESIDENTS OF THE REPUBLIC SAKHA (YAKUTIA)

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In the article lipid peroxidation of native people and non-natives in Yakutia was compared. The obtained data clearly indicate existence of lengthening of the adaptation phase under modern socio-economic conditions of life of the population of Yakutia compared to similar studies of the several decades before. It is likely that adaptation to the harsh conditions of the North is associated with the activation of an antioxidant-responsive element that induces the expression of proteins responsible for maintaining internal homeostasis.

Materials and methods. Samples of blood were collected in biomedical expeditions during simultaneous examination of the population of Yakutia in the spring. 357 people were examined.

The intensity of free radical lipid oxidation was determined by the content of TBARS, the antioxidant defense was determined by the total content of low molecular weight antioxidants in serum, also ascorbic acid and catalase activity were studied. The activity of alanine aminotransferase and aspartate aminotransferase enzymes was studied.

Results. The level of TBARS and indicators of antioxidant protection (LWMAO, ascorbic acid and catalase) of people who moved to reside to studied area were higher, compared to indigenous people. There is an increase in the level of TBARS, catalase activity, AST / ALT coefficient in the first 5 years after relocation to Yakutia from other regions. The stabilization period of the biochemical parameters occurred in the period from 5 to 10 years.

Conclusion. Obtained data indicate a lengthening of the adaptation phase in modern socio-economic conditions of life of the population of Yakutia in comparison with scientific studies of previous years. It is likely that adaptation to the harsh conditions of the North is associated with the activation of an antioxidant-responsive element, which increases the expression of proteins responsible for maintaining internal homeostasis.

Keywords: adaptation, TBA-active products, TBARS, total content of low molecular weight antioxidants, ascorbic acid, catalase, Nrf2, antioxidant-responsive element.

Introduction. The modern geopolitical strategy of the state is aimed to develop Northern regions of the country, therefore one of the most important tasks of medical science at the present time is to help to maintain health and working capacity of the population living under extreme conditions of the North. In this regard, close attention is paid to research and activities aimed at shaping the quality of life of the population in the context of globalization and increasing population mobility.

As an integral criterion of health, the adaptive capabilities of organism, which reflect the degree of its dynamic equilibrium with the environment, are increasingly being considered. Adaptation is directly related to the background, which ultimately determines the risk of developing diseases, and therefore the level of health. Consequently, the approach to quantifying the adaptive capabilities of people can be a key point on which the gradual assessment of health depends.

The Republic Sakha (Yakutia), with its inherent set of climatic and geographical conditions, belongs to the regions of the Far North, which defines the impact of a number of adverse health factors of residing people.

According to the results of previous decades studies, it was found that the populations of the Northern people, living for thousands of years in the North, were formed by natural selection as a result of centuries of evolution [18]. They have developed a number of adaptations, that are genetically fixed and accordingly inherited. However, recent decades have been characterized by socio-economic transformations, urbanization of the indigenous population and change of the traditional way of life, all of which affect their health [13, 21].

Currently, study of nonspecific reactions of human organism that underlie adaptive-compensatory mechanisms in healthy people, such as changes in pro-oxidant-antioxidant balance, is of great interest [17].

The **objective** of the research was to study the indicators of lipid peroxidation of non-native residents depending on the duration of their residence in the Republic Sakha (Yakutia).

Material and methods of the research

This work was carried out at the Yakut Science Centre of Complex Medical Problems in Research: "Regional features of normal and pathological biochemical and immunological indicators in the indigenous and non-indigenous population of the Republic of Sakha (Yakutia)".

Samples of blood were collected in biomedical expeditions in the course of a cross-sectional study of the population of Yakutia in spring. 357 people between the ages of 18 and 77 were examined, including 253 native and 102 non-native residents. The native inhabitants in this work are people who were born and permanently reside in the territory of Yakutia, and non-native residents are people who, for one reason or another, came to Yakutia for permanent residence from other regions of Central Russia and living in Yakutia for at least a year. The ethnicity of the residents of both groups was heterogeneous and not taken into account.

Serum was used for all analysis. The intensity of free radical lipid peroxidation was determined by the contents of TBA-reactive substances (TBARS) [20], indicators of antioxidant protection of people were determined by the total content of low molecular weight antioxidants (LMWAO) [8], ascorbic acid level [16], catalase activity (CAT) [5] using the SPECORD 40 "AnalytikJena" (Germany) spectrophotometer. Transaminase activity: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined on a "Labio" automated

biochemical analyzer using "Analyticon" reagents (Germany). The level of interleukin-6 (IL6) and interleukin-18 (IL18) cytokines was assessed on a "Multiscan" analyzer (USA) using the enzyme-linked immunosorbent assay utilizing "Vector-Best" CJSC (Russia) kits.

Statistical analysis of data was made using IBM SPSS Statistics. The significance of differences between the medians was evaluated using the Mann-Whitney U test. The data in the tables are presented as M±m, where M is the mean, m is the error of the mean. The differences were considered statistically significant at p <0,05.

Results and discussion. Indicators of lipid peroxidation in the population of the Republic of Sakha (Yakutia) were as follows: the TBARS level was equal to 3,572±0,122 μMol/l, the total content of LMWAO was 91,471±1,956 nmol/l, the activity of the antioxidant enzyme CAT was 0,490±0,010 μKat/l, the concentration of ascorbic acid was 0.255 ± 0.009 mg/dl (Table 1).

There is a strong opinion that the indigenous population of the Far North evolutionally adapted under extreme factors conditions, and people have formed a certain lifestyle that can inhibit reactions of lipid peroxidation [4, 9, 10]. The above statement is confirmed in our work. The level of end products of lipid peroxidation - TBARS and indicators of antioxidant protection (LMWAO, vitamin C and CAT) of non-indigenous people were higher compared to indigenous people (Table 2).

The staged nature of adaptation processes was described in study of researchers led by V. Yu. Kulikov et al. (16) and V.P. Kaznacheev (3). The first phase lasts on average up to six months and is characterized by destabilization of many physiological parameters. The second phase comes in 3-4 years. During this period, the normalization and synchronization of vegetative and somatic functions takes place in the conditions of physiological rest and moderate physical and psycho-emotional stress. After 8 - 10 years, the body's condition is relatively stabilized.

Data on the terms of adaptation of the non-native population in the 90s in Yakutia are given in the paper by A.S. Popova [7]. Comparison of physiological parameters was studied by dynamics of glucose and cholesterol in blood of non-native and native Yakutians. In this work, three phases of adaptation were distinguished among non-native residents. In the residing period up to 5 years, the level of cholesterol in blood was higher than that of native people (p <0.05). After 5 years of living in the North, content of these indicators decreased, after 10 years of living it increased. Thus, the first phase of adaptation took place before 5 years, the second phase - in the interval of 5-10 years, and the third after residing for more than 10 years [7].

In our study, we noted the intensification of free radical peroxidation of lipids of non-native residents for 5 years. Moreover, the peak increase of the level of the final product of lipid peroxidation occurred in the period of 2 to 5 years, as evidenced by the high content of TBARS (1.47 times (p=0.02) above the average value). At the same time, an increase in exogenous antioxidant - ascorbic acid, was observed. The concentration of ascorbic acid was 1.69 times higher than the average value (p = 0.01). At the same time, the total content of LMWAO and the activity of catalase did not change.

Subsequently, with an increase in the time spent in the North, the levels of TBARS and the antioxidant defense indices shifted to values close to the average biochemical indices of indigenous people (Table 2).

According to the concept of stress-limiting systems founded in the 1980s by F.Z. Meerson [6] a general stress response leads to the formation of an organism short-term adaptation, which, in turn, acts as a basis for a long-term adaptation formation. Moreover, the initiators of lipid peroxidation, reactive oxygen species, are linked to the development of short-term and long-term adaptation [1]. Long-term adaptation occurs gradually, as a result of prolonged or repeated action of environmental factors on the organism. It arises not on the basis of pre-existing physiological mechanisms, but on newly formed regulatory programs.

Modern data support the concept of stress-limiting systems, clarifying the mechanisms of regulatory processes controlled by reactive oxygen species [23]. The mechanisms for protecting human from the negative effects of extreme factors of the North depend on the expression of transcription factors that are responsible for the functional state of protective systems [2]. Exposure to extreme factors can activate the redox-sensitive signaling system of the antioxidant-responsive element Keap1/Nrf2/ARE, which includes the transcription factor Nrf2, which is constantly monitored by the Keap1 repressor protein [2, 14]. Nrf2 regulates the expression of many protective

Table 1

Indicators of lipid peroxidation of indigenous and non-indigenous people of the Republic of Sakha (Yakutia)

Indicators	native	M+m	P
TBARS (nmol/l)	non-native residents	3.089±0.153	0.551
	native	3.920±0.213	
LMWAO (mEq/mg)	non-native residents	90.090±2.288	0.032
	native	101.94±3.886	
CAT (μKat/l)	non-native residents	0.444±0.018	0.551
	native	0.496±0.032	
Ascorbic acid (mg/dl)	non-native residents	0.151±0.013	0.151
	Приезжие	0.246±0.025	

Table 2

Indicators of lipid peroxidation of non-indigenous people of the Republic of Sakha (Yakutia) depending on the duration of residence

Duration of residence in the Republic of Sakha (Yakutia)	TBARS (nmol/l)	LMWAO (mEq/mg)	CAT (μKat/l)	Ascorbic acid (mg/dl)
less than 2 years	4.28±0.75	83.29±2.16	0.55±0.07	0.43±0.11
from 2 to 5 years	5.78±0.98	87.82±4.18	0.52±0.06	0.41±0.11
from 5 to 10 years	3.75±0.77	100.00±8.56	0.50±0.03	0.13±0.04
from 10 to 20 years	3.86±0.41	103.10±1.00	0.47±0.05	0.23±0.05
20 and more years	3.57±0.28	99.22±0.40	0.53±0.06	0.29±0.03
P	p_{1-5}=0.05 p_{2-5}=0.04	-	p_{2-4}=0.04	p_{1-3}=0.03 p_{3-5}=0.04

Table 3

Serum activity of alanine aminotransferase and aspartate aminotransferase levels among residents of Yakutia

Indicators		ALT (U/l)	AST (U/l)	AST/ALT ratio
Duration of residence in the Republic of Sakha (Yakutia)	less than 2 years	17.85±1.47	26.78±1.90	1.54±0.08
	from 2 to 5 years	15.65±1.03	25.13±1.58	1.65±0.06
	from 5 to 10 years	18.05±1.95	26.64±2.14	1.53±0.04
	from 10 to 20 years	20.75±2.46	27.93±2.44	1.38±0.08
	20 and more years	18.21±1.14	23.26±0.90	1.27±0.11
	Native	19.08±0.51	25.52±0.42	1.36±0.02
p		-	-	p_{1-5}=0.03 p_{2-5}=0.04 p_{2-6}=0.05 p_{3-5}=0.03

systems genes: antioxidant and immune defenses [24], detoxification of xenobiotics [24], molecules controlling DNA repair [15]. According to scarce publications other Nrf2 functions were mentioned as: the effect on ATP production and cellular respiration; removal of damaged or improperly folded proteins by regulating the expression of proteasomes; regulation of NADPH content in the cell by activation of transcription factor-4 (ATF4), which stimulates the expression of phosphoglycerate dehydrogenase; affects the transcriptional vibrations of circadian genes in human cells and mouse tissues, etc. [22].

According to published data, the intensification of free radical processes activates the redox-sensitive signaling system of the antioxidant-responsive element [26]. Reactive oxygen species and lipid peroxidation metabolites are capable of modifying the sensitive thiol groups of Kear1 protein, which hinders its ability to inhibit the transcription factor Nrf2 of the antioxidant-responsive element [19].

In addition, there is evidence that reactive oxygen species and lipid peroxidation products are capable of activating other redox-sensitive transcription factors NF-kB (nuclear factor kappa-light-chain-enhancerofactivated B cells), AP-1 (Activator protein 1) and P53 [22].

Our results have confirmed those defined in the literature. We noted an increase in the coefficient showing the AST/ALT ratio (de Ritis ratio) indicating the predominance of anabolic processes over catabolic of non-native residents in the first 5 years of their stay in Yakutia. The optimal ratio of kata and anabolic processes of non-native residents is established in the period from 5 to 10 years. Moreover, the de Ritis coefficient has a positive correlation r = 0.32 (p = 0.03) with the content of TBARS, which, in our opinion, is evidence of the influence of the antioxidant-responsive element on the adaptation of non-native residents to the extreme conditions of Yakutia.

Thus, the level of TBARS and indicators of antioxidant protection (NMAO, ascorbic acid and catalase) of non-native residents were higher compared to native people. There is an increase in the level of TBA-AP, catalase activity, AST / ALT coefficient in the first 5 years of people after relocation. The stabilization period of the biochemical parameters occurred in the period from 5 to 10 years. The results indicate lengthening of the adaptation phase in modern socio-economic conditions of life of the population of Yakutia in comparison with scientific studies of previous years. It is likely that adaptation to the harsh conditions of the North is associated with the activation of an antioxidant-responsive element, which increases the expression of proteins responsible for maintaining internal homeostasis.

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A RISK FOR CONGENITAL HEART DEFECTS DEVELOPMENT ASSOCIATED WITH INFECTIOUS FACTORS IN NEONATES OF THE REPUBLIC SAKHA(YAKUTIA)

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The article represents the results of retrospective investigation of pathogenic infectious factors role in possible development of congenital heart defects (CHD) in neonates of the Republic Sakha(Yakutia).

The objective is to investigate the effect of the pathogenic infectious factors on the possible development of CHD in neonates of the Republic Sakha(Yakutia).

Materials and methods: There were 1824 cases with CHD selected from the period of 2001-2003 and 2013-2015. We conducted retrospective evaluation of a number of the maternal anamnestic data, including: 1) results of immunological tests for a variety of infections (toxoplasmosis, chlamydia, herpex simplex virus and cytomegalovirus IgM and IgG); 2) various harmful factors of infectious genesis (recorded cases of acute viral respiratory infections at various terms of pregnancy, viral hepatitis, tuberculosis etc.)

Results: It has been determined that cytomegalovirus, herpes virus and acute viral respiratory infections at early pregnancy are risk factors for CHD development.

Keywords: congenital malformations, risk factors, herpes virus, viral infection, cytomegalovirus infection, Yakutia, Russia.

Introduction. Nowadays, congenital malformations significantly result in the structure of childhood morbidity, disability and neonatal mortality. It occurs in 4.0-6.0% of neonates, thus resulting in 20.0% of all childhood mortalities in the first year of life. In the structure of congenital malformations, congenital heart defects (CHDs) and congenital defects of great vessels are most common and prevalence of their rate is 8-14 cases in 1000 neonates.

The importance of risk factors analysis is in possibility of initial prevention of CHD development. Thus, significant risk factors for congenital malformations are pathological pregnancy, obstetric anamnestic record, peculiarities of the current pregnancy and birth.

Some investigators constitute that the presence of persistent intracellular infection, which results in permanent decrease of immune reaction, is one of the reasons for CHD [2, 3]. A retrospective cohort investigation of correlation between the present viral infection (influenza, rubella, measles, chicken-pox and hepatitis) for the period from 6 months before pregnancy to the moment of prenatal examination revealed statistically significant discrepancies in cohort of children with CHD and cohort of healthy children in respect of influenza virus [4]. Statistic survey showed that maternal viral infection of the first term of pregnancy increases the risk of non-chromosomal congenital malformations. At the same time, the prevalence of clinically confirmed cases of TORCH-infection among neonates with clinical manifestations, characteristic to intrauterine infection, amount to 18.9% [1]. Thus, the investigations of the role of the intrauterine infection in the development of CHD in neonates are greatly significant.

Objectives: The objective is to investigate effect of the pathogenic infectious factors on the possible development of CHD in neonates of the Republic Sakha (Yakutia).

Materials and methods: There were 1824 cases with CHD selected from the period of 2001-2003 and 2013-2015. According our data, for the period A (2001-2003) 697 cases were recorded, and for the period B (2013-2015) there were 1127 cases of CHD in neonates born alive and hospitalized in profile departments.

CHD group 1: low-probability CHD. Isolated low-probability interatrial septal defect, low-probability interatrial septal defect in association with patent ductus arteriosus (PDA) with less than 0.2 cm defect size are included in the group.

CHD group 2: probable CHD. Isolated probable interatrial septal defect, probable interatrial defect with PDA less than 0.2 cm are included here.

CHD group 3: The group includes neonates with confirmed CHD, who are diagnosed with: 1) simple CHD: a defect of interatrial septum is highly probable, a defect of interventricular septum is with / without combined PDA, 2) complex CHD with / without PDA. The diagnosis of all patients of the 3-rd group with complex CHD, are confirmed not only by ECG methods but also X-Ray examinations.

Thus, CHD group 1 composed 55.5% (n=1013), CHD group 2 constituted 10.1% (n=184), and CHD group 3 revealed 34.4% (n=627) of all the selected cases of CHD (n=1824). We assessed maternal anamnestic factors retrospectively: 1) results of immune analysis (IgM and IgG) to toxoplasmosis, chlamydia, herpes simplex virus, and cytomegalovirus; 2) different harmful factors of infectious genesis (recorded cases of respiratory viral infection at different terms of pregnancy, viral hepatitis, tuberculosis etc.)

Results and discussion. To assess the influence of infectious factors to CHD development we have analysed the re-

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sults of serologic tests. Serologic tests to *Chlamidia trachomatis, Chlamidia pneumonia, Toxoplasma gondii,* cytomegalovirus and herpes simplex (IgM, IgG) in mothers were detected.

In whole selection of CHD with serologic test to *Chlamidia trachomatis* (*Chl. Trach*), (n=643, 34%) immunoglobulin of class G (IgG) (27.1%) was most common. The analysis shows statistically significant results of IgG prevalence to *Chl. Trach* in all three groups of CHDs – 26.5%, 42.2%, 25.7% respectively (p=0.067). The second group shows the highest case detection of IgG to Chl. Trach – 42.2% (Table 1).

The analysis of serologic investigation to *Chlamidia pneumonia* in children with CHD is represented in a table 2. In whole selection of CHD (n=648, 37.8%) with serologic test to *Chlamidia pneumonia* (Chl. pneum.) immunoglobulin of class G (IgG) (26.7%) was most common. In all groups the level of IgG was significantly high - 28.7%, 22.0%, 23.6% respectively.

When analyzing serologic tests to *Toxoplasma gondii* (*T. gondii*) immunoglobulin of G class (IgG) most common among mothers (6.0%). The analysis shows the prevalence of IgG to T. gondii in all three CHD groups – 5.5%, 9.8%, 5.7% respectively (table 3).

Table 1

Antibodies to *Chlamidia trachomatis* and CHD groups

CHD groups	Antibodies to *Chlamidia trachomatis* (p=0.067)			
	No antibodies. %	High level of IgM. %	High level of IgG. %	High level of Ig class M+G. %
1) (n=407)	66.6	5.2	26.5	1.7
2) (n=64)	56.2	1.6	42.2	0.0
3) (n=172)	68.6	5.8	22.7	2.9
Total (n=643)	66.1	5.0	27.1	1.9

Table 2

Antibodies to *Chlamidia pneumonia* and CHD groups

CHD groups	Antibodies to *Chlamidia pneumoniae* (p=0.261)			
	No antibodies. %	High level of IgM. %	High level of IgG. %	High level of Ig class M+G. %
1) (n=415)	58.6	9.4	28.7	3.4
2) (n=59)	67.8	8.5	22.0	1.7
3) (n=174)	69.0	5.2	23.6	2.3
Total (n=648)	62.2	8.2	26.7	2.9

Table 3

Antibodies to *Toxoplasma gondii* and CHD groups

CHD groups	Antibodies to *T. gondii* (p=0.553)		
	No antibodies. %	High level of IgM. %	High level of IgG. %
1) (n=362)	93.1	1.4	5.5
2) (n=61)	90.2	0.0	9.8
3) (n=159)	93.7	0.6	5.7
Total (n=582)	93.0	1.0	6.0

Таблица 4

Antibodies to cytomegalovirus CMV and CHD groups

CHD groups	Antibodies to CMV (p=0.343)			
	No antibodies, %	High level of IgM, %	High level of IgG, %	High level of Ig class M+G, %
1) (n=380)	12.4	15.3	69.2	3.2
2) (n=63)	9.5	9.5	79.4	1.6
3) (n=172)	14.0	8.7	74.4	2.9
Total (n=615)	12.5	12.8	71.7	2.9

The analysis of serologic tests to cytomegalovirus (CMV) revealed high prevalence of cytomegalovirus in mothers. In whole selection of CHD with serologic test to CMV 87.4% cases were revealed, immunoglobulin of class G (IgG – 71.7%) was most common. When analyzing the initial CHD groups the prevalence of IgG to CMV in all three groups was noticed - 69.2%, 79.4%, 74.4% respectively (table 4).

When analyzing serologic test to herpes simplex we revealed high prevalence of herpes simplex infection in mothers of CHD children. In whole selection of CHD with serologic test to *Herpes simplex* 87.5% cases were revealed, the most significant level was G class of immunoglobulin (IgG – 70.3%). When analyzing the initial CHD groups the prevalence of IgG to *Herpes simplex* in all three groups was noticed - 66.9%, 89.9%, 75.6% respectively (table 5).

Thus, we have obtained the following results as high prevalence of cytomegalovirus infection (n=615, 87.4%), herpes simplex virus (n=489, 87.5%), mean prevalence of *Chlamidia pneumonia* infection (n=648, 37.8%), *Chlamidia trachomatis* (n=643, 34.0%), and low prevalence of Toxoplasma gondii infection (n=582, 7.0%), among neonates born with CHD.

Old acute respiratory viral infections turned to be most common among exogenous infectious factors. Total specific weight resulted in 16.4%. It is acute respiratory viral infection at early terms of pregnancy (before the 12th week), at the 28th week and later, including all terms of pregnancy, that resulted in CHD.

According to the results of the research, the structure of exogenous infectious factors in all selection of CHD (n=1824) was the following: acute respiratory viral infection before 12th week of pregnancy – 11%, acute respiratory viral infection at the 28th week and later – 4.4%, other infectious factors 2.0%, chronic viral hepatitis B – 1.6%, acute respiratory viral infection at all terms of pregnancy – 1.0%, chronic viral hepatitis C – 0.7%.

According to the table 6, in a group with confirmed CHD 13.7% cases are caused by acute respiratory viral infection, in 4.7% at the 28th week of pregnancy and later, 1.8% caused by viral hepatitis B, 2.9% of cases result from other infectious factors as: old syphilis, herpes infection before the 12th week of pregnancy, parental tuberculosis, rubella contact, helminthic invasion, diphyllobothriasis, maternal brucellosis, chicken pox before the 12th week of pregnancy, recurrent syphilis.

Table 5

Antibodies to Herpes simplex and CHD groups

CHD groups	Antibodies to Herpes simplex (p=0.123)		
	No antibodies. %	High level of IgM. %	High level of IgG. %
1) (n=323)	13.0	20.1	66.9
2) (n=47)	8.5	10.6	80.9
3) (n=119)	12.6	11.8	75.6
Total (n=489)	12.5	17.2	70.3

Table 6

Exogenous infectious factors and CHD groups

Factors	CHD groups (p=0.342)			
	1) (n=1013) %	2) (n=184) %	3) (n=627) %	4) (n=1824) %
0	79.5	85.3	75.4	79.3
1	9.4	10.3	13.7	11.0
2	4.7	2.2	4.5	4.4
3	1.1	0.0	1.1	1.0
4	1.6	1.1	1.8	1.6
5	0.8	0.5	0.6	0.7
6-15	2.9	0.6	2.9	2.0

Note. 0 – absence of exogenous infectious factors; 1 – acute respiratory viral infection before the 12th week of pregnancy; 2 - acute respiratory viral infection from the 28th week of pregnancy and later; 3 - acute respiratory viral infection at all terms of pregnancy; 4 – chronic viral hepatitis B; 5 – chronic viral hepatitis C; Other infectious factors: 6 – old syphilis; 7 – herpes infection before the 12th week of pregnancy; 8 – parental tuberculosis; 9 – rubella contact; 10 – chronic bronchitis; 11 – helminthic invasion, diphyllobothriasis; 12 - maternal brucellosis, 13 - chicken pox before the 12th week of pregnancy, 14 – paternal tuberculosis; 15 - recurrent syphilis.

Conclusion. A research of the role of pathogenic exogenous factors at all terms of pregnancy and their possible association with CHD development in neonates of the Republic Sakha(Yakutia) revealed high prevalence of cytomegalovirus infection (n=615, 87.4%), herpes simplex virus (n=489, 87.5%) in CHD neonates. Moreover, there is a high risk for CHD development in a case of acute respiratory viral infection at early terms of pregnancy noticed in a group of possible CHD occurrence (13.7%). Thus, the research of risk factors for CHD development becomes fundamental for pregravid preparation.

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FEATURES OF NORTHERN LONGEVITY: LONG LIVERS OF YAKUTSK

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The social portrait of the Yakutsk long-livers is compiled based on the primary data analysis. Long-livers, who spent their childhood and youth in the war years, are still not clearly defined as a separate group in many scientifical areas. An interdisciplinary approach revealed the history of life, gender and psychological differences of people 90 years of age and older in order to identify common and stable characteristics of the portrayed group.

It has been established that most of the long-livers of Yakutsk are not indigenous, while a significant part of the respondents had a family life of more than 30 years, and labor character in adulthood was associated with mental work or light physical labor. The majority of the old people continued to take care of themselves on their own, with every third leading the household alone. Sexual life in women ceased at 59.4 ± 2.0 years, in men - 72.1 ± 2.1 years. Compared with the long-lived people of the previous generation, the number of smokers has significantly decreased, and the proportion of people performing active lifestyle has increased. Nevertheless, arterial hypertension was detected in almost all examined patients, whereas in earlier studies this indicator was significantly lower.

Keywords: somatometric indicators, anamnesis vital, non-indigenous and indigenous population, social portrait of long-livers.

Introduction. In Yakutia, the population has always been "rejuvenated" due to migrants arriving at working age. In 1989, the population aged 60 and over was 4.9%, then by 2012 this indicator reached 12.7%, most possibly due to the emigration peak in the 1990s. In the last decade, the number of 90 years old and more has grown markedly. So, in 2010 there were 316 people, and at 01.01.2019, 951 people were registered, including 404 people in outpatient clinics in Yakutsk. We considered it inappropriate to compare with the data of earlier censuses (1928, 1950, 1970). In these years, due to various circumstances, significant distortions of the considered age cohorts were observed [1].

As known earlier, the growth factors in the proportion of older people is a decrease in population natural growth. An equally important contribution is made by the scientific achievements of medicine and their introduction into health care, which contribute to an increase in life expectancy. Population aging is perceived today as a risk or a challenge to society, which requires an adequate response. The possible way out from situation is increasing the age of "active old age" - the state where an elderly person will be able to independently lead a relatively full life. In this regard, it was interesting to study the family history, lifestyle, health, gender and ethnic differences of Yakutsk long-livers with the aim of compiling their social portrait. We assumed the obtained data will allow to perform comparative analysis with the centenarians of subsequent generations.

Materials and methods. In order to achieve this goal, empirical data are analyzed in the framework of the pilot research team of the Federal State Budgetary Scientific Institution "YSC CMP": "Factors of active longevity in the permafrost zone: socio-medical parameters" (2019-2021). As a toolkit, a questionnaire of 76 questions which divided into 6 blocks that reflect anthropometric data, a history of life, family and work history, vital interests, some aspects of the social sphere of the long-lived, etc.

The collection of primary material was carried out in Yakutsk from February to March 2019, both on the basis of the Republican Hospital No. 3 GBU RS(Ya) and the place of residence of long-livers. A socio-medical examination of 65 people at the age of 90 years and older (91.4 ± 0.3 years) was conducted, including 33 women and 32 men. The psychodiagnostic examination included a brief mental status assessment scale (MMSE) and an anxiety and depression scale (HADS). The obtained results were processed in Microsoft Excel and "IBM SPSS Statistics 23" software applications.

Results and discussion. The maximum age of centenarians in the female group is 94 years, in the male group - 97 years. Distribution of respondents by ethnicity: Yakuts (72.3%), Russians (24.6%), Evens (3.1%).

The average height of women is 152 ± 0.1 cm, body weight 53.9 ± 0.9 kg, of men -162.0 ± 0.1 cm and 63.0 ± 0.8 kg (Table 1). Moreover, as a rule, the considered indicators in Russians are higher than among representatives of the indigenous population. In all groups, the body mass index (BMI) is normal, but all respondents had the abdominal type of obesity (waist / hip index >0.9). It should be noted that in both young and adulthood, none of the long-livers surveyed were overweight.

Regardless of ethnicity, the majority (98.3%) of the centenarians, Yakutsk is not their birthplace. More than half (53.3%) of the indigenous respondents and every fourth Russian (26.7%) moved in the capital after 50 years. 50 people lived in Yakutia, including 2 Russians. 15 long-lived respondents arrived from various regions of Russia (mainly from Siberia) at 36.9 ± 4.0 years.

According to the level of education: 39.4% of women and 43,7% of men have higher education, 21.2% of women and 43.7% of men had secondary education, and one respondent had no education . After retirement, women continued to work until 61.7 ± 1.7 years, men until 71.8 ± 2.0 years.

According to the labor activity (in terms of physical activity) almost every second centenarian (55.4%) had a occupation mainly related to mental work. More than one third of centenarians (38.4%) were engaged in low and moderate physical labor. A smaller share of respondents (6.2%) performed heavy physical labor, but long-livers whose professions were associated with especially hard physical labor were not found in our sample. However, it should be noted that most of the respondents started to work in agriculture as early as primary school age (7-12 years), while the majority of centenarians (92.3%) noted that during this period of their life (late 1930s and early 1940s) they were very hungry or malnourished.

Table 2 compares the level of education, occupation character, and the activity of respondents in everyday life at the time of inspection with similar indicators of Yakut centenarians born at the very beginning of the 20th century. That information was received in 1994-1995. by O.V. Tatarinova [2]. As can be seen from the data above, less than a quarter of a century ago the number of centenarians with higher and middle special education who were employed in the field of intellectual work has increased significantly. Of course, we cannot ignore the general level of education growth during the industrialization. In addition, most of the centenarians are able to take care of themselves and do small homework. At the time of the survey the majority of centenarians (66.2%) lived with their relatives, and 33.8% of respondents conducted their own households. 89.2% of centenarians took care of themselves on their own. The list of their daily activities includes: watching TV (75.4%), reading (66.2%), performing small household work, including dry cleaning, washing, cooking (63.1%), listening of radio (24.6%). At the same time, almost half of long-livers did not go outside in the winter till 87.8 ± 0.9 years. Assistance in housekeeping for lonely living respondents was provided by relatives or social workers.

After retirement, the majority of long-livers (69.2%), were engaged in amateur vegetable growing up to 78.1 ± 1.5 years, part of the respondents (16.9%) were

Table 1

Main somatometric indicators of long-livers

Indicator	Women			Men		
	A group (n = 22)	B group (n = 11)	Mean (n = 33)	A group (n = 27)	B group (n = 5)	Mean (n = 32)
Height, cm	150±0.01	157.0±0.02	152±0.1	161.0±0.01	167.0±0.03	162.0±0.1
Weight, kg	50.1±1.8	61.5±3.5	53.9±0.9	61.4±1.8	71.6±4.0	63.0±0.8
BMI	22.2±0.7	25.1±1.3	23.2±0.7	23.4±0.6	26.0±1.9	24.1±0.6
Waist-hip index	0.90±0.01	0.92±0.02	0.91±0.01	0.94±0.01	0.97±0.03	0.94±0.01

Table 2

Education level and household activity of the long-livers born at 1900-1920

Category	Education level			Mental labor	Active lifestyle
	Higher	Secondary special	No education		
Born in the beginning of XX century.	8.9	16.1	32.1	19.6	60.7
Born in the beginning of 1920s.	40.0	33.8	1.5	55.4	86.2

engaged in domestic cattle breeding, and, accordingly, took part in the procurement of feed as far as possible. It can be concluded that most centenarians, up to old age, not only spent more time outdoors doing physical labor, but also consumed natural fresh products from their garden and farms.

The diet of most centenarians includes meat and sour-milk products, various cereals, vegetables and fruits; confectionery consume - daily (32.3%), several times a week (20%), rarely or not at all (47.7%). Most respondents prefer to drink tea (83.1%) and instant coffee in the morning (13.8%).

As for marital status, the sample consisted of: married women (12.1%), two women were never married, 75.7% are widows: the average age at the time of the death of the spouse was 80.2 ± 2.1 years; and married men (40.6%), widowers (59.4%) who were widowed at the age of 71.9 ± 2.5 years. Most of the respondents (84.6%) have more than 30 years of overall family life duration, and 81.8% of women and 75% of men had only one marriage. 9.1% of women and 21.9% of men entered into family-marriage relations twice. One man and one woman got married three times. This means that most centenarians had a stable family and marriage experience and a socio-psychological comfort in private life, which can contribute to the formation of family values.

According to the number of child: 29.2% had 1-2 children, 61,5% had 3 or more children, 9.2% - childless Yakuts. The age at birth of the first child in mothers was 27.7 ± 0.7 years, the last child - 35.0 ± 0.9 years. However, in large Yakut families, the average number of children exceeded the same indicator in Russian families - 4.5 ± 0.3 people against 3.4 ± 0.3 people.

At the same time cases of pregnancy of 4.9 ± 0.5 are the same in Russians and Sakha. Sexual life in women faded away at 59.4 ± 2.0 years, in men - 72.1 ± 2.1 years, while in some cases the male part of the respondents noted that the termination of sexual relations was not due to their state of health, but illness or death of the spouse. The average age of menopause is 48.3 ± 2.1 years.

It is necessary to indicate that the majority of centenarians (78.5%) were born in large families. Currently, one in three of the long-livers surveyed have well and alive siblings. As for the longevity of the parents of the respondents, only 1/5 of them had a biological father or mother who lived to be 90 years old, while the rest of the parents died of illness or external causes under the age of 50 years. Unfortunately, in some cases, respondents were unable to recall the cause and exact date of death of their parents.

Attitude of centenarians to bad habits amid the promotion of a healthy lifestyle are interesting. As they admitted, at the age of 40-50 years, only men abused alcohol (9.2%); 11 women and 7 men among women who never consumed alcohol (27.7%), the majority (63.1%) drank alcohol in limited quantities only on holidays.

As for smoking, 1 woman and 9 men (15.4%) smoked between the ages of 20 and 75, the length of tobacco dependence in some cases reached 40 years, the number of cigarettes smoked was up to 1 pack/day, but currently no one of the centenarians does not smoke. For comparison, according to O.V. Tatarinova [2], in the group of long-livers born at the beginning of the 20th century, during their lives were tobacco addicts (37.5%) with smoking experience from 50 to 81 years old, continued to smoke (7%).

Now when the issue of balance between physical inactivity and hyperactivity, the violation of which leads to illness, is interesting how long-livers behave. Despite the fact that a significant part of the respondents in adulthood did not go in for sports, 67.7% of long-livers performed physical exercises as well as breathing exercises daily. A small part of the examined (6.2%) conducted more intensive classes. For example, an hour-long workout of a 92-year-old P. includes 20 push-ups, squats, etc.

Arterial hypertension (AH) was detected in almost all examined patients (95.4%), except of one man and two women. By the way, in the group of long-livers born at the beginning of the 20th century, hypertension was in 68% of the examined [2]. According to the respondents or their relatives, women (48.4%) developed hypertension before the age of 60, while in all men it began to be observed only after reaching old age (Table 3). But it is possible that this fact can only be an additional confirmation of a less attentive attitude of men to their health [3, 4]. At least, to the question of what respondents did in adulthood when they were unwell, the answer "visit to the doctor" was chosen by the half of men, while in 72.2% of the women choose this option. It is also worth noting that at the time of the examination, most women (67.7%) and only 41.9% of men (41.9%) took antihypertensive drugs daily. By the way, 6.2% of men only after our examination first learned that they had a 2nd degree of hypertension, although they previously considered themselves healthy. In the women's group, this was not noted.

Since hypertension is currently considered as a leading risk factor for the development of cognitive impairment [5, 6, 7], a survey of centenarians was conducted on a short MMSE scale. According to our data, mild cognitive impairment was diagnosed in the majority (63.1%), moderate cognitive impairment was noted in almost one in five surveyed long-livers (27.7%), severe cognitive impairment in a small proportion (9.2%) of respondents. It should be noted that moderate cognitive impairment was 2 times more often diagnosed in women (66.6% versus 33.4% in men). However, a pronounced relationship between the degree of cognitive deficit and indicators of BP of long-livers was not noted: for SBP r = -0.14, for DBP r = -0.13.

Analysis of the HADS scale showed statistically significant differences in the anxiety index: in women, 8.09 ± 2.1 points (corresponds to the level of subclinically expressed anxiety), in men - 5.74 ± 1.8 points (corresponds to the norm). The average value on the depression scale for women was also higher than for men

Table 3

Blood pressure and antihypertensive drug intake regularity

Sex	Blood pressure at the examination moment, mmHg		Share of long-livers (%), with hypertension				Antihypertensive drugs intake, %		
	SBP	DBP	<59	60-69	70-79	>80	everyday	episodically	Do not take
Women	148±3.9	76±1.7	48.4	12.9	19.4	19.4	67.7	32.3	-
Men	147±4.1	76±1.9	-	12.9	25.8	61.3	41.9	48.4	9.7

- 7.3 ± 2.6 points and 5.8 ± 2.2 points, respectively. At the same time, a direct relationship was established between the level of anxiety and the level of depression (r = +0.58), there was also an insignificant relationship between the above indicators and the experience of hypertension (r = + 0.23 ... + 0.28).

Conclusion. Today's centenarians, this generation, whose childhood and youth came into contact with wartime, they passed the test of hunger, cold, loss of parents. The average social portrait of the long-lived city of Yakutsk today: these are men and women who were born and raised in rural areas in a large family, graduated, and, accordingly, were engaged in intellectual types of labor. They have the only marriage in which three or more children were born. This large family had a farm, consumed fresh natural products, in adulthood they changed their place of residence and moved to Yakutsk.

Comparison of relevant data with the previous generation showed that the number of smokers has significantly decreased, and the proportion of people who keep active lifestyle has increased. A medical examination showed that the proportion of hypertensive patients increased (from 68% to 95.4%). Unfortunately, at the same time, a significant part of centenarians, especially men, do not follow the antihypertensive drug regimens or do not consume them at all.

On the MMSE scale, severe cognitive impairment was recorded in 9.2% of respondents; on the HADS scale, anxiety and depression rates were higher in women than in men, but in general, pronounced deviations were not observed in long-livers.

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ACTUAL TOPIC

M. P. Kirillina, I. V. Kononova, S. I. Sofronova, A. K. Ivanova, E. L. Lushnikova

ANALYSIS OF PRECANCEROUS CERVICAL DISEASES IN WOMEN OF POST-PRODUCTIVE AGE IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2019.68.19

УДК 618.146-006.6-084(571.56)

Cytological studies of biomaterial from the cervix and cervical canal were analyzed for the incidence of precancerous diseases and cervical cancer in women of post-productive age. The incidence of CIN 1, CIN 2, CIN 3 and CC in CC and cervical canal smears is inversely dependent on the degree of dysplasia in examined women from 2016 to 2018. The incidence of CIN 1 had been increasing from 2016 to 2018, while CIN 2, CIN 3 and CC were decreasing rates. Analysis of the incidence characteristics of CIN 1, CIN 2, CIN 3 and CC depending on age revealed that women of 46-55 years had the highest incidence of CIN 1 and CIN 3. Women of 56 years and older are more frequent to have CIN 2 and CC.

Keywords: screening, oncocytology, diagnosis, dysplasia, cervical cancer.

Relevance: In modern society, the interest in the problems of health and social adaptation of postmenopausal women is growing steadily due to the increased number of women who have crossed the line of menopausal age. One of the complications of the physiologic course of postmenopause is the development of metabolic disorders of an involutional nature in the reproductive system, as in the cervix uteri, vagina and vulva. Such changes are caused by natural processes of aging, metabolic reactions at all levels, and microscopically expressed by changes in the cellular composition of the epithelial lining and connective tissue components of stroma [2]. The age is known to be a universal factor and the most important determinant of the malignant neoplasm risk [1]. Literature data indicate that for each cancer site has its own age peak, which falls on different periods of human life [3]. The pathogenesis basis of atrophic and dystrophic processes in perimenopause is estrogen deficiency. The lack of estrogens in this period leads to the loss of the main protective properties of the stratified squamous epithelium, glycogen-and pyroxin-binding functions. As a result, the number of lactobacilli is decreasing, up to complete disappearance, and, as a consequence, potentially pathogenic flora is intensively increasing. The change of vaginal biocenosis against the background of atrophic changes of the mucus barrier in the cervical and vaginal mucosa, as a rule, causes the development of nonspecific, often recurrent, slow inflammatory processes. It doesn't have a clinical effect of anti-inflammatory therapy and progressing with the increasing duration of postmenopause. The significant violation of blood supply to the vaginal walls and the exocervix is also a contributing factor. As a result of blood supply disorders, the amount of vaginal transudate sharply decreases, which is clinically appears by dryness and dyspareunia, and a tendency to microtrauma of the vaginal mucosa and vulva, which also, in turn, increases the appearance of infectious and inflammatory processes. There are gradual changes in the tissues of the vulva and vagina with the onset of menopause. The epithelium atrophies and becomes thinner, there may be signs of cytological dysplastic changes. Therefore, diagnosis and differential diagnosis of vagina and cervix uteri age-related atrophy, and dystrophic processes of the vulva should be aimed primarily at excluding, not only inflammatory changes caused by a specific infection process but also oncological disorder [2].

Purpose of the research: To study the dynamics of the incidence of precancerous diseases and cervical cancer in women of post-productive (perimenopausal and menopausal) age.

Materials and methods of research: The analysis of cytological studies of biomaterial from the cervix and cervical canal was carried out in 353 women aged 46 years and older who applied independently for various medical care in the period from 2016 to 2018 inclusive. Cytological diagnosis was carried out by the Romanovskiy-Gimza staining glasses method. Staining of the biomaterial and cytological diagnostics were carried out in the laboratory of pathomorphology, histology, and cytology based on the NEFU Medical Institute Clinic. Cytological diagnosis, degree of CIN and CC, was determined in accordance with the clinical and morphological classification of Bokhman (1976). The incidence of CIN1, CIN2, CIN3, CC in smears were calculated separately and expressed as a percentage of the total number of examined women.

Results and discussion. The total number of examined women was 46 women in 2016, 117 women in 2017 and 190 women in 2018, who had cervix dysplastic changes of varying severity. In terms of age groups were as follows: women of 46-55 years -192 (54.4%), women of 56 years and over - 161 (45.5%).

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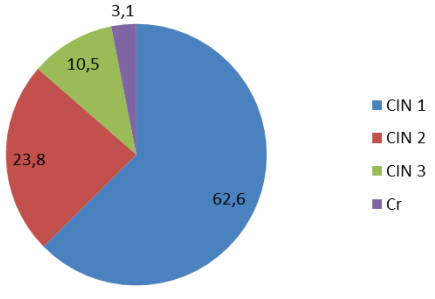
According to the results of cytological analysis of the incidence of cervical dysplasia for the period 2016-2018, it can be seen that the highest frequency falls on CIN 1, which was registered in 221 women and amounted to 62.6% of the total number of examined women, CIN 2 was detected in 84 women (23.8%), CIN 3 was diagnosed in 37 women, which amounted to 10.5% of all cervical dysplasia in the examined group (Fig.1). Cervical cancer was detected in 11 cases and was 3.1%.

Depending on the year of the survey,



Pic. 1. The dysplasia occurrence of different degrees for the period 2016-2018

the analysis of CIN 1, CIN 2, CIN 3 and CC incidence for a three-year period showed an increase of CIN 1 with a decrease of CIN 2 and CIN 3 (pic.2). The incidence of CIN 1 in 2018 increased by 1.7 times compared to 2016, while CIN 2 did not show significant dynamics at the same time, and the incidence of CIN 3 decreased by 3.5 times. The frequency of CC detection decreased by 4.1 times in the examined smears. In general, such multi directionality of indicators shows positive dynamics in the development of dysplasia. Decreasing of CIN 2, CIN 3 and CC can be explained by constant monitoring of patients, constant monitoring of the dysplasia development in the dynamics and effectiveness of the treatment. The growth of CIN1 can be explained by the fact that despite the treatment, colpitis often develops on the background of already existing age-related The cause of colpitis can be both specific infections and opportunistic flora. There are gradual changes in the tissues of the vulva and vagina with the onset of menopause. The epithelium atrophies and becomes thinner, there may be signs of cytological dysplastic changes.

When studying the incidence of cervical dysplasia depending on age, the analysis showed that the most frequently diagnosed cervical pathology in all age groups was CIN 1 (pic.3). The maximum frequency of occurrence of CIN 1 (66.1%) was observed in women aged 46-55 years. The highest incidence of CIN 2 (30.4%) was observed in the age group of 56 years and older. The highest incidence of CIN3 was observed in women aged 46-55 years and was 13%. The maximum incidence of CC was observed in the age group of 56 years and older – 6 cases (3.7%). It should be noted that the incidence of CC increases depending on the age of patients. This is confirmed by studies, according to which the progression of the severity of dysplasia goes for many decades [4].

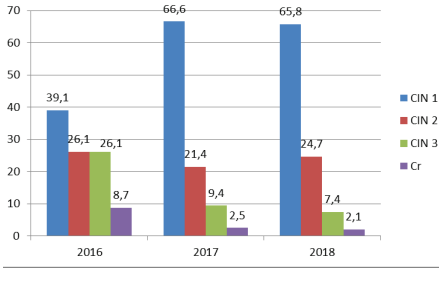
There is an interesting fact, that CIN 3 in the group of women 56 years and older has a lower incidence than in the group 46-55 years. Given the age of the older women's group, CIN 3 should have a more incidence rate, as well as established rates of CIN 2 and CC. It can be explained that in women older than 56 years, the transition of moderate and severe dysplasia to CC is more rapid.

Conclusion. The incidence of CIN 1, CIN 2, CIN 3 and CC in CC and cervical canal smears is inversely dependent on the degree of dysplasia in examined women from 2016 to 2018. The incidence of CIN 1 had been increasing from 2016 to 2018, while CIN 2, CIN 3 and CC were decreasing rates. Analysis of the incidence characteristics of CIN 1, CIN 2, CIN 3 and CC depending on age revealed that women of 46-55 years had the highest incidence of CIN 1 and CIN 3. Women of 56 years and older are more frequent to have CIN 2 and CC.

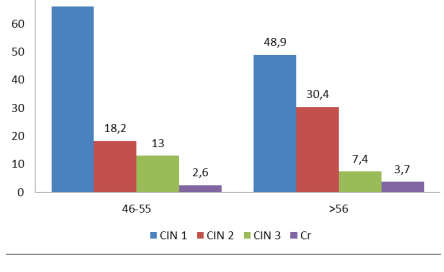
Our analysis of cytological material indicates the growth of gynecologic oncology disease rate with increasing age, and it is approved by the literature data. The increased risk and peak incidence of CC occur at the age of 56 years and older.

Prevention, early detection and adequate treatment of malignant tumors are the most important tasks of modern medicine. According to the results of the data analysis, it needs to improve the preventive examinations of women with a mandatory cytological examination, clinical examination, and treatment of patients with background diseases of the cervix uteri. This problem takes special research aimed at developing scientifically based solutions for the main problems associated with the CC findings on the initial stage.

The paper was written as part of R&D "The epidemiological aspects of cancer on the Far North living environment, development of modern early detection methods, and prevention methods with high-informative fundamental research. (M06;01;01)" (№ 0556-2014-0006).



Pic.2. Dynamics of dysplasia occurrence of different degrees for the period 2016-2018



Pic.3. Incidence of cervical dysplasia in women of post-productive age

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CONCOMITANT DISEASES AND RISK FACTORS OF GASTRODUODENAL EROSION IN THE CONDITIONS OF YAKUTIA

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The **purpose** of this study was to study concomitant diseases and risk factors for gastroduodenal erosion (GDE).

Materials and methods. A retrospective analysis of the medical history of 64 patients was carried out, including 36 women and 38 men, aged 26 to 82 years, average age 58 years. All patients undergoing inpatient treatment underwent a history of the disease, a complete clinical examination and laboratory and instrumental diagnostics. According to the time of their stay in the Far North, patients were divided into 2 groups - indigenous and alien.

Results and discussion. Among those examined with erosive lesions of gastric CO, males predominate. Of the age groups, GDE is often found in people over 50 years old, mainly in the indigenous population. Clinical symptoms are dominated by epigastric pain, heartburn, belching, and flatulence. More often chronic erosion is detected in the antrum and prepiloric stomach. According to a biopsy, in patients with gastric CO erosion, an inflammatory-hyperplastic type is detected in 51.2% of the indigenous and 43.4% of the newcomers, which indicates chronic erosion. Among the examined social groups, employees are more often found in 37.5% of cases and the predominance of urban residents is 74.2%, this is mainly due to the fact that people engaged in mental work are more often subjected to various psycho-emotional stresses, stresses, and mental breakdowns. The seasonality of revealing GDE in the autumn-spring period is noted. HDE is accompanied by diseases of the stomach: chronic gastritis, peptic ulcer, duodenogastric reflux and diseases of the hepatobiliary system: chronic cholecystitis, chronic pancreatitis, and cardiovascular diseases, which must be taken into account in the diagnosis and treatment of erosion. Risk factors for GDE are smoking, alcohol abuse, and psycho-emotional overload.

Keywords: gastroduodenal erosion, concomitant diseases, risk factors, hepatobiliary system, cardiovascular diseases.

According to modern data, erosion is the second most common pathology of the stomach and duodenum. Clinicians' attention to the problem of erosive and ulcerative injuries is due to the fact that erosion and acute ulcers of the stomach and duodenum are the cause of gastrointestinal bleeding and take second place after peptic ulcer. Thanks to esophagogastroduodenoscopy (EGD) with biopsy, our ideas about erosion of the stomach and duodenum have been enriched. Erosions differ from ulcers in etiology, healing processes and rates, and clinical manifestations. Erosions are often detected in patients with ulcer, with chronic active diffuse liver damage, tumors of the gastrointestinal tract, diseases of the cardiovascular and respiratory system, with kidney damage, etc., which raises the question of a complete examination of patients with gastroduodenal erosion (GDE) [1-3].

GDE is detected at autopsy in 6% of cases, and at endoscopy in 2-20%, including with ulcer - in 33 - 50%; with gastritis - in 14 -22%. And besides, they are found in cirrhosis of the liver, occurring with portal hypertension (in 10-40%); with heart defects, arterial hypertension (AH), coronary heart disease (CHD), especially with heart failure complications; with atherosclerosis of the abdominal part of the aorta and its branches (in 10-40%); in chronic non-specific diseases of the lungs and pulmonary heart disease (in 30%). These are secondary (symptomatic) GDE. An increase in the frequency of detection of GDE with age is noted; up to 60-90% after 50 years [2, 5].

GDE is found more often in men than in women (in a ratio of 1.5 - 2.8: 1), and gastric localization of erosion over duodenal prevails significantly: 75/25%, of which 95% is in the prepiloric zone and only 5% in the fundal department of gastric CO, the hemorrhagic complications of HDE are second only to gastric ulcer and duodenal ulcer.

Sometimes the erosive process in the stomach proceeds "under the mask" of other diseases: chronic cholecystitis, pneumonia, an infectious or tumor process. In such situations, it is almost impossible to assume the presence of GDE, they are detected by chance with EGD.

When analyzing complaints of patients with erosive gastritis, it was found that the predominant part of acute erosion is characterized by the scarcity of the symptoms of diseases: more often - heartburn, belching with acid and air; very rarely - fasting and fasting pains in the epigastric region of low intensity.

Acute erosion (OE) most often develops a second time as a complication of various diseases, and not only gastroenterological ones, while chronic erosion (CE) often proceeds in isolation, as the primary pathological process that affects the mucous membrane (CO) of the stomach and duodenum. ChE in 50% gives moderate pain on an empty stomach and early pain after eating. Flatulence and burping prevail. Over time, dull, aching pains are increasingly combined cramping. The severity in the abdomen increases, nausea, instability of the stool with a tendency to constipation are more often noted. Nausea is often combined with vomiting, and flatulence - with bitterness in the mouth [2, 4].

There are 2 groups of risk factors for GDE - exogenous and endogenous. Among the exogenous factors are called: Helicobacter pylori infection (HP), HP - the infection is not the main pathogenic factor of GDE and does not have any effect on their clinical manifestations, but it may contribute to the chronicity of the erosive process and its progression; local and systemic microcirculatory disorders, stressful effects; toxic-chemical, including medicinal (NSAIDs; GCS - glucocorticoid, potassium chloride, etc.), professional (vibration, vapors of fatty acids, alkalis, fluorine compounds, etc.) and alimentary (alcohol and its surrogates, spicy seasonings and spices , untreated coffee, etc.). Among the endogenous factors there are identified - acid peptic aggression; action of "detergents" (toxic bile acids and lysolecithin); with duodenogastric reflux (DGR); local immune disorders that lead to a decrease in the cytoprotective properties of CO stomach

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and duodenum; symptomatic GDE in various diseases of the internal organs; with extensive surgical interventions on the organs of the abdominal cavity, etc. With often recurrent GDR in the antrum of the stomach, erosion is detected in 70% of the examined [4, 5].

The purpose of this study is to study concomitant diseases and risk factors for HDE among indigenous and alien residents of Yakutia.

Materials and methods. A retrospective analysis of the medical history of 64 patients was carried out, including 36 women and 38 men, aged 26 to 82 years, average age 58 years. All patients who were hospitalized in the treatment department underwent a history of the disease, a complete clinical examination and laboratory and instrumental diagnostics. According to their stay in the Far North, patients were divided into 2 groups. 1 group of indigenous people permanently residing in the North, total 41 people, of which 26 are men and 15 women and 2 are newcomers who have arrived in Yakutia from other regions of Russia for 15 years, only 23 people, including 12 men and 11 women, as well as patients were distributed by social groups and place of residence. A prerequisite was to obtain informed consent from patients to participate in the study. Processing of research data was carried out according to the program "Office Microsoft Excel 2010". The results were considered reliable when the student value p less than 0.05 (p <0.05).

Results and discussion. The clinical symptoms of HDE are presented in Fig. 1. Regardless of the group, the pain symptom in the epigastric region prevails in 85.9%, heartburn in 70.3%, belching in 57.8% of patients. In the first group, in the vast majority of cases, periodic dull, aching pain in 54.3% of patients and heartburn in 83.5% (p <0.05) are disturbing. In the second group, paroxysmal, acute, stitching pains prevail in 60% of patients (p <0.05), belching with acid or air in 73.9% of patients (p <0.05).

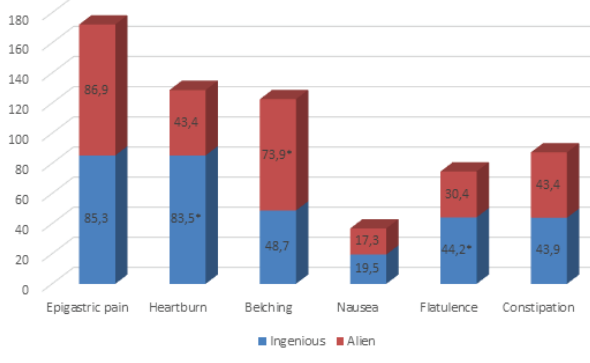

Fig. 1. Clinical symptoms in patients with HDE (%).
Note: * - p <0.05, significance of differences between indigenous and non- indigenous patients

According to endoscopy, the most typical localization of HDE, regardless of the group, is the antrum in 76.5% of cases, followed by the prepyloric department - 56.2% (Fig. 2).

According to a biopsy, in patients with gastric CO erosion, an inflammatory-hyperplastic type is detected in 51.2% of the indigenous and 43.4% of the newcomers, which indicates chronic erosion. This is followed by erosion, located on the polyposis fold in 29.2% in the indigenous and 39.6% in the newcomers, a hemorrhagic-necrotic type in 8.6% and erosion with fibrin plaque in 13% are detected less frequently (Fig. 3).

The ratio between acute and chronic erosion is 1: 4, the low percentage of detection of acute erosion is explained by the low number of people with this disease. Since acute erosion of gastric CO in the stomach in 60% of cases is not very symptomatic, and in 30% it is characterized by the absence of any manifestations. By the size of erosion in 68.7% of cases they do not exceed 0.5 cm in diameter, by the amount of 68.7% there are multiple erosions.

In the dynamics of observation of erosive defects of the coolant, examined during or after the course of treatment, there is a positive trend in 75.1%, a weakly positive trend in 20.3% and negative in 4.6% of patients.

All 64 examined patients have concomitant diseases, of which the leading place is occupied by diseases of the gastrointestinal tract (GIT). Gastritis predominates in 96.8%, with indigenous atrophic gastritis, and in newcomers mixed gastritis in 39.1%. In 90.6% of patients, chronic cholecystitis was detected, in 62.5% of patients with chronic pancreatitis. Of the diseases of other organs and systems, cardiovascular diseases are in the first place, in primary IHD - in 58.5% and in newcomers - hypertension - in 60.8% (Table 1).

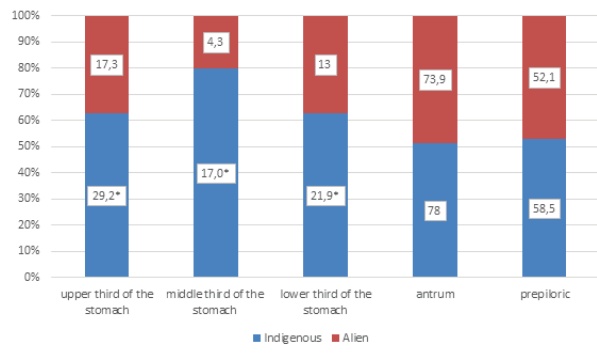

Fig. 2. Localization of erosion in the stomach (%)

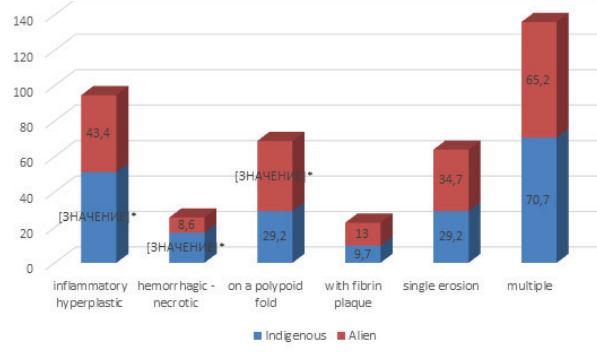

Fig.3. The results of the endoscopic examination of GDE with biopsy (%)

Among the examined groups, erosive lesions prevailed among the indigenous in 64.0%, in men in 59.4% more often than in women in 40.6%. The main contingent of patients is people older than 50 years, which is probably associated with a weakening of the body's defenses, the duration of exposure to gastric CO, adverse factors like smoking - in 35.9%, often in the newcomer population, violation of the diet - in 18.7 %, psychoemotional overload in 9.3% and alcohol abuse - in 9.3% of cases (Table 2).

Among the examined social groups, employees are more often found in 37.5% of cases and the predominance of urban residents is 74.2%, this is mainly due to the fact that people engaged in mental work are more often subjected to various psycho-emotional stresses, stresses, and mental breakdowns. According to the literature, it is known that people with dyspepsia report a greater level of stress at work and in the family and more problems associated with financial situation than people in the control group. Various studies have identified a relationship between depression, on the one hand, and chronic abdominal pain, female gender, single marital status and low income, on the other [4].

Seasonal exacerbations are more often observed in the autumn-spring

Table 1

Concomitant diseases in patients with HDE

pathology	indigenous		Non-indigenous		total	
	abs.	%	abs.	%	abs.	%
A. Gastrointestinal pathology						
1. Gastritis: atrophic	16	39.0*	8	34.7	24	37.5
mixed	12	29.2	9	39.1*	21	32.8
surface	11	26.8	6	26.0	17	26.5
2. Reflux - esophagitis	7	17.0	6	26.0	13	20.3
3. Peptic ulcer	3	7.3	4	17.3	7	10.9
4.Duodeno-gastric reflux	12	29.2	9	39.1*	21	32.8
5.Chronic cholecystitis	39	95.1*	19	82.6	58	90.6
6.Chronic pancreatitis	28	62.2*	12	52.1	40	62.5
7. Gallstone disease	1	2.4	2	8.6	3	4.6
8. Chronic colitis	7	17.0*	3	15.0	10	15.6
9. Colonoptosis	1	2.4	1	4.3	2	3.1
B. Diseases of other organs and systems						
1. Atherosclerosis	8	19.5	6	26.0	14	21.8
2.Arterial hypertension	20	48.7	14	60.8*	34	53.1
3. IHD	24	58.5*	12	52.1	34	53.1
4.Discirculatory encephalopathy	7	17.0	5	21.7	12	18.7
5.Osteochondrosis of the spine	16	39.0	9	39.1	25	39.0
6. Bronchial asthma	1	2.4	-	-	1	1.5
7. Diabetes	1	2.4	-	-	1	1.5
8.Chronic pyelonephritis	2	4.8	3	15.0	5	7.8

Table 2

GDD Risk Factors

Factors	indigenous		non-indigenous		total	
	abs.	%	abs.	%	abs	%
violation of diet	7	17	5	22	12	18.7
psycho-emotional stress	2	5	4	17	6	9.3
smoking	9	22	14	61*	23	35.9
alcohol abuse	3	7	3	13	6	9.3

period, which coincides with the data of various authors. In autumn, 30.1% of patients turned to and in the spring - 26.7%. The peak of exacerbations occurs in the month of October, at 16% and in May, at 12%. The smallest number of patients is observed in August - at 4.6%.

When studying the hereditary predisposition, convincing data were obtained on the relationship of dyspepsia with family burden for diseases of the gastroduodenal zone in 61.2% of patients. These indicators coincide with hereditary burden in patients with gastric ulcer and duodenal ulcer.

Conclusion. Among those examined with erosive lesions of gastric CO, males predominate. Of the age groups, GDE is often found in people over 50 years old, mainly in the indigenous population. Periodic, aching, dull epigastric pains and belching predominate in clinical symptoms in indigenous people, and paroxysmal sharp, stitching pains and heartburn in newcomers. Chronic erosion in the antrum of the stomach is more often detected.

GDE is accompanied by diseases of the stomach: chronic gastritis, ulcer, duodenogastric reflux and diseases of the hepatobiliary system: chronic cholecystitis, chronic pancreatitis, cardiovascular diseases: IHD and arterial hypertension, which must be taken into account in the diagnosis and treatment of erosion. Risk factors for HDE are smoking, alcohol abuse and neuropsychic overload, as well as eating disorders and comorbid conditions.

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DIET IN THE NORTH

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SOURCES OF VITAMINS B_1 AND B_2 IN FOOD

This article presents the content of vitamins B1 and B2 in the most used foods: cereals, legumes, meat and lactic acid. The aim of the work was to determine the level of vitamins in the most consumed products, taking into account the heat treatment. The level of vitamins was determined by fluorimetric methods on a fluorimeter.

The results of the study showed that heat treatment affects the content of these vitamins. Moreover, the greatest losses of thiamine in the preparation of products are from 20% to 71.5%, and riboflavin from 16.3% to 71.5%. The results of our studies indicate that the intake of vitamins B1 and B2 with food does not fully satisfy the daily requirement of the body.

Keywords: thiamine, riboflavin, food, heat treatment, vitamins, Yakutia, human health.

Introduction. Human health is closely linked to good nutrition. Nutrition provides the most important function of the human body, supplying it with the energy necessary to cover the costs of vital processes. Cell and tissue renewal also occurs due to the ingestion of “plastic” substances – proteins, fats, carbohydrates, vitamins and mineral salts – into the body with food.

As is known, a feature of vitamins is that they are either not synthesized at all in the human body, or are synthesized in the human body in very small quantities that do not satisfy the human need. Therefore, the body's supply of vitamins is directly dependent on their content in food and the degree of digestibility of these vitamins in the gastrointestinal tract. Pathological disorders can be caused by both vitamin deficiency and hypervitaminosis. Long-term deficiency of certain vitamins can cause severe pathologies leading to disability, and long-term vitamin deficiency can be life-threatening [1, 10].

It is known that the need for vitamins of the inhabitants of the Far North is increased in comparison with those who live in the European part of Russia - in more favorable climatic conditions. Studies on the provision of vitamins to the inhabitants of Yakutia are insufficient. There are only a few publications regarding ascorbic acid, retinoids and tocopherol. It should be noted that the actual content of vitamins in food products of residents of the Far North (Yakutia) has not been studied.

The aim of this work is to determine the level of vitamins B1 and B2 in the most used products, taking into account the heat treatment.

Materials and methods. The research materials were food products: cereals - buckwheat kernel and barley; legumes - peas and beans; meat products - beef fillet, boiled liver and sausage, lactic acid product - hard cheese and chicken egg. Food products were analyzed before and after heat treatment. Heat treatment of cereals and legumes by boiling in water until crumbly.

The level of vitamins was determined by fluorimetric methods on a fluorate "Fluorate 02- ABLF" at the wavelengths of thiamine -320-390 nm, riboflavin - 360-480 nm [8,9]. Statistical data processing was performed using standard methods of mathematical statistics using the STATISTICA program.

Results and discussion. Since vitamins are destroyed during the heat treatment of second courses, we determined the content of thiamine and riboflavin before and after heat treatment. The data we obtained are presented in tables 1 and 2.

An analysis of our data showed that before heat treatment, most of all vitamin B1 is contained in buckwheat, from legumes - peas, and from products of animal origin - beef liver. The smallest thiamine content was found in chicken eggs and cheese (Table 1).

The highest level of vitamin B2 before heat treatment was noted in buckwheat. The content of riboflavin in beans and peas is virtually the same: 0,18 μg / 100 g and 0,19 μg / 100 g, respectively. In chicken eggs and in beef liver, the level of riboflavin was also kept in the same range. The smallest B2 content was noted in barley groats (Table 2).

According to the results of our research, buckwheat, beef liver and legumes are the most valuable food products for the content of thiamine and riboflavin before heat treatment. Our data do not contradict the literary information. So, according to the data presented in the tables of the content of basic chemicals in food products of the Institute of Nutrition RAMS in buckwheat groats, the thiamine content ranges from 0,40 – 0,45 mg / 100 g. However, in beef meat and, especially, in beef liver according to our data, thiamine contains more. Probably, this fact can be explained by a richer content of biologically active substances in pasture plants [12]. As for riboflavin, its actual content in the products we studied does not differ from the literature [1, 2, 3].

The daily requirement of the human body for thiamine is 1.5-2.0 mg, and in riboflavin 2,0-2,5 mg. In [4, 5, 7, 10], there is evidence that the daily diet of the inhabitants of Yakutia does not provide a daily need for water-soluble vitamins.

Thiamine is found in animal and plant cells in a free, esterified and bound form. The main form of thiamine in living cells is its coenzyme form - thiamine diphosphate (TDP). The thiamine content in food is relatively small (from 0.2-0.5 mg per 100 g). Thiamine is not deposited in the human body, and the renewal of existing stocks in most organs and tissues is characterized by high speed. The biochemical mechanism of thiamine utilization is due to the fact that it, in the form of a coenzyme of thiamine diphosphate, is involved in the decarboxylation of pyruvate. Decarboxylation of pyruvate is associated with the complete oxidation of glucose, which provides a high level of functional activity of muscles and the heart. In addition, vitamin B1 normalizes the nervous and emotional state, since it is involved in the synthesis of the neurotransmitter acetylcholine, a deficiency of which leads to the formation of polyneuropathy [5, 6, 14].

Riboflavin is widely distributed in nature and occurs in three forms: free riboflavin, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Riboflavin is found in almost all foods.

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Vitamin B1 in foods before and after heat treatment

Food	Thiamin. mcg/100 g		Riboflavin. mcg/100 g	
	Before heat treatment	After heat treatment	Before heat treatment	After heat treatment
Buckwheat	0.42±0.02	0.12±0.04	0.21±0.06	0.06±0.01
Barley groats	0.27±0.01	0.21±0.06	0.08±0.02	0.03±0.01
Beans	0.50±0.10	0.40±0.10	0.18±0.05	0.11±0.07
Peas	0.80±0.30	0.30±0.10	0.19±0.05	0.15±0.04
Beef meat	0.11±0.01	0.06±0.01	0.15±0.04	0.09±0.05
Beef liver	0.90±0.50	0.30±0.10	2.11±0.70	1.19±0.11
Chicken egg	0.07±0.03	0.04±0.02	0.43±0.03	0.36±0.15
Hard cheese	0.04±0.01	-	0.44±0.04	-
Cooked sausage	0.12±0.04	-	0.15±0.04	-

The human body does not synthesize riboflavin unlike plants, a number of bacteria, molds and yeasts. Therefore, riboflavin enters the body only with food. Riboflavin is a precursor to the coenzymes of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which are involved in redox reactions of the respiratory chain, in the Krebs cycle, in the oxidation of fatty acids, in detoxification and detoxification of carcinogens in the liver [1,13].

As you know, the technology of cooking affects the content of vitamins. During heat treatment, the level of vitamins decreases as a result of the destruction of their chemical structure. The data presented in tables 1 and 2 indicate that heat treatment several times reduces the level of vitamins in food. In the process of heat treatment of cereals and legumes, a number of physico-chemical changes occur in the substances contained in these products. During cooking, the water level in them increases significantly as a result of its absorption by gelatinizing starch.

According to our data, the content of vitamin B1 in buckwheat as a result of heat treatment decreased 3,5 times, which corresponds to a loss of this vitamin by 71,5%. And in barley groats the thiamine level decreased by 22% (1.2 times) (Fig. 1).

The level of vitamin B2 in buckwheat and barley groats after heat treatment decreased by 71.5% (3.5 times) and by 62.5% (2.6 times) (Fig. 2).

The same pattern was observed for legumes - peas and beans. Thus, heat treatment reduced the content of vitamin B1 in peas by 62.5% (2,6 times) and in beans by 20% (1.2 times) (Fig. 3).

The level of vitamin B2 in peas after heat treatment decreased by 21, 1% (1,2 times), and in bean 38,9% (1,6 times) (Fig. 4).

The loss of vitamin B1 during heat treatment of a chicken egg (6 minutes) decreased by 42,9% (1,7 times), and vitamin B2 by 16,3% (1,1 times) (Tables 1 and 2).

In the literature, there is evidence that when cooking buckwheat, 22,4% of vitamin B1 is destroyed. Loss of thiamine up to 60% (Table. 1) is probably due to a longer heat treatment time.

We analyzed the change in the level of these vitamins in beef and beef liver before and after heat treatment.

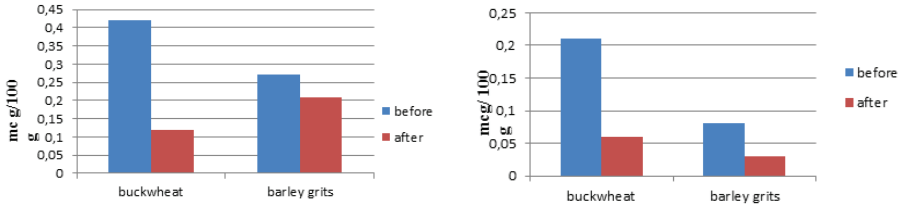

Fig 1. The content of vitamin B1 and B2 in buckwheat and barley groats before and after heat treatment

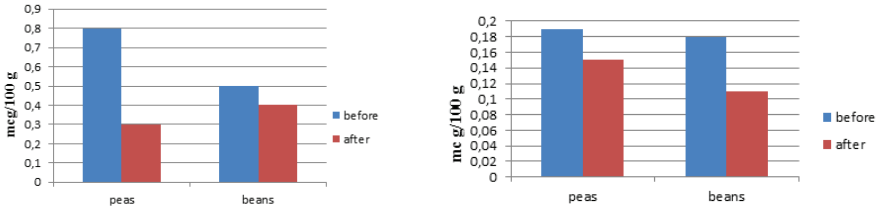

Fig 3. The content of vitamin B1 and B2 in peas and beans before and after heat treatment

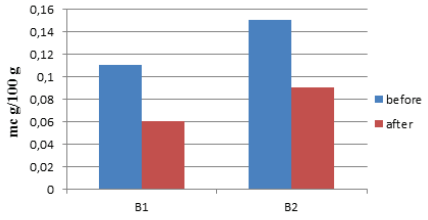

Fig 5. The content of vitamins B1 and B2 in beef meat before and after heat treatment

The level of vitamin B1 of boiled beef decreased by 45,5% (1,8 times), and in boiled beef liver – 66,7% (3 times) (Fig. 5).

The content of vitamin B2 after heat treatment decreased in beef meat by 40% (1,6 times), and beef liver by 43,7% (1,7 times). During the heat treatment of meat products, a significant loss of vitamins occurs, both due to the transition to a solution, and due to thermal decomposition. According to published data, heat treat-ment leads to the loss of thiamine by 25-45%, and riboflavin by 8-40%. It should be noted that when cooking vitamins more is lost than when frying.

Conclusion. Vitamins B1 and B2 are involved in the synthesis of the main energy substrates in the human body, which is very important for people living in the extreme conditions of the Far North. Therefore, adequate intake of vitamins with foodstuffs most frequently consumed by residents is of great importance in maintaining health.

The richest vitamin B1 of the foodstuffs we have studied is buckwheat, beef liver, beans and peas, the least is found in cheese and chicken eggs. Vitamin B2 was most found in beef liver, chicken egg and cheese, least in barley, cooked sausage and beef. Their entry into the human body depends on heat treatment. Thermal processing of food products on the one hand promotes assimilation, and on the other hand leads to significant loss of vitamins.

The results of our studies indicate that the intake of vitamins B1 and B2 with food does not completely satisfy the daily requirement of the body. Further study of the intake of vitamins with food into the body, as well as the technology of their preparation are of great importance in maintaining human health.

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DIETARY HABITS OF SCHOOL CHILDREN IN RURAL AREAS OF THE REPUBLIC SAKHA (YAKUTIA)

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The results of dietary habits and preference of certain products in school children of Kysyl-Syr, Namsky region of the Republic of Sakha (Yakutia) are represented in the article. We have assessed nutrition and health status of 64 adolescents, aged from 12 to 16.

The result of data analysis shows that children in Namsky region consume more meat rather than fish, unlike the children in the Arctic regions of the Republic of Sakha (Yakutia). Fish is consumed rarely, only several times a month – 48.4%, or even less than once a month – 37.5%. Beef is more consumed out of the other meat products. In the Arctic regions poultry and game products are eaten more. It is revealed that dairy products are daily consumed by a less than a half of the survey group – 39%, the rest 37.5% consume several times a week. A lack of vegetables and fruit in the diet results in significant drawback. Only 15.6% ate vegetables daily, and 12.5% ate fruit. Children prefer bakery and confectionary products. Food preferences of most of them are sweets, fizzy drinks and excessive amount of salt.

We have examined and revealed the structure of morbidity in children of the Namsky region.

Dental pathology was most commonly revealed (53.1%). In Namsky region people use water from the river Lena, where the fluoride level is low. The diseases of the respiratory system were present in 37.5%, mostly ENT disorders, which were possibly associated with unfavourable environmental conditions, chronic infections, incorrect dietary habits and stress. Muscular skeletal system diseases were present in 26.6%. Commonly it was associated with the deficiency of vitamin D, lack of exposure to sunlight, as there are few sunny days, and insufficient amount of vitamin D in the diet (fish, eggs, milk).

The obtained results revealed food habits in school children of the Central regions of the Republic of Sakha (Yakutia).

The results of the survey require improved organization of the children dietary habits.

Keywords: dietary habits, school children, the Republic Sakha (Yakutia).

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Introduction. The epidemiological surveys, performed in different regions of Russia, show considerable disturbances in dietary habits and health in school children. These disturbances result from misbalance of main food substances, insufficient amount of polyunsaturated fatty acids, vitamins, macro and microelements (calcium, iron, iodine etc.), and dietary fibers. Excessive amount of bakery, confectionary products, salt and additional sugar is common for all surveys all over. This dietary misbalance results in decreased health index in children and adolescents.

Dietary habits of children and teenagers of the Republic of Sakha (Yakutia) have their regional peculiarities, characterized by low energy value, deficiency of main food components, unbalanced nutritive density, and poor formation of traditional value and food culture. Diet is restricted it is characterized by insufficient amount of dairy products, meat, fish, veg-

etables, fruit and berries. It is noticed the traditional dietary habits of indigenous peoples of the North are changing, 10% of these children rarely consume traditional products on average. Such irrational dietary habit results in health disorders and disturbance of the development at early life and afterwards [7]. Due to disturbances of principles of the rational dietary habits, health index as well as anthropometric characteristic decrease in children and adolescents population [2, 3, 6, 8]. To reduce the risk of overeating in children, resulting in overweight, it is necessary to counsel the parents informing them about amount and dietary intake at educational institutions [5].

Objectives: The objective of the research is to analyze the dietary intake of school children in Kysyl-Syr, Namsky region of the Republic of Sakha (Yakutia).

Materials and methods. To analyze the attitude to the rational dietary pattern, schoolchildren were questioned. The children from the 6th grade to 10th grade (aged from 12 to 16) of the secondary school of Kysyl-Syr, Namsky region of the Republic of Sakha (Yakutia) were totally selected. Total selection included 64 schoolchildren (the parents agreed their children to participate in the survey). The research was performed in 2017-2018. The parents filled in the form: 'Information on food and dietary behavior' to investigate regular diet and affordability of food. The research is performed within the 'Monitoring the children health status in the Republic of Sakha (Yakutia)'. Actual dietary habits were investigated by the methods of analysis of the frequency of dietary intake (Martinchik A.N. et al, 1998). The questionnaire contained 55 kinds of products. Dietary pattern and dietary behavior were defined additionally. Database was entered by EXCEL program. Statistica for Windows (ver.6) helped analyze statistical data.

Results and discussion. As a result of analysis it was determined that meat products (beef) were present in a daily dietary intake of the rural schoolchildren (60.9%), fish was rarely consumed only once a month (48.4%) or even less than once a month (37.5%) (Table 1). Daily intake of dairy products was only in 39%, the others (37.5%) take it several times a week. Significant negative factors are highly neglected fruit and vegetables. Only 15.6% had vegetables in their dietary intake, and 12.5% fruit.

Most of the respondents (75%) had one glass of milk or dairy products 2 or 3 times a week. 25% of them ate sweets and chocolate, among them 39% had 3 or 4 sweets, 11% had a lot of them; 32.8% had 3 or 4 chocolates, and 17.2% ate a lot, the results show that a daily intake of sweets and chocolate goes beyond the recommended amount. The data shows (Table 1) eggs are daily consumed only by 20.3%, 2 or 3 times a week (46.9%), and 37.5% have eggs only several times a month. Commonly they eat 1 or 2 eggs (54.7%), and 31.2% have 3 or 4 eggs monthly. Bakery products (pancakes, patties) are daily consumed (9.4%), several times a week (42.2%); quantitatively 40.6% eat 3 or 4 pieces, and 43.8% eat a lot. Fizzy drinks are taken several times a week (28.1%), several times a month (50.0%); 45.3% have 1 or 2 glasses, and 29.7% have 2 or 3 glasses (Tables 2-3). As to the salt, the consumption of salt was excessive, 60.1% of the respondents like salty food. Only 21.9% of the respondents do not like salty food.

60.1% of schoolchildren prefer salty food, 17.2% like spicy hot food, and 21.9% do not like salty products.

As a part of the research the schoolchildren of Kysyl-Syr, Namsky region of the Republic of Sakha (Yakutia) were examined and the structure of morbidity was determined (Table 4). Dental disorders (53.1%) are in the leading position, according to the results of the research; they are represented by multiple caries (39%) (Table 4). One of the factors for caries development is low concentration of fluoride in the drinking water. The mineral components of the main sources of drinking water were analyzed, according to The Federal Service for Supervision of Consumer Rights Protection and Human Well-Being "Center for hygiene and epidemiology in the Republic of Sakha (Yakutia) for the period of 2009-2010 (in the rivers Lena, Aldan, Kolyma, Indigirka, Yana, Viluy and underground source of the drinking water in Neryungry). In these water sources the level of fluoride was extremely low (from 0.04 to 0.3 mg/l, together with the other factors it can certainly result in caries [1]. In winter time people use ice water (melted water), where the level of fluoride is even a lot less than in water itself. In Namsky region people drink water of the river Lena. Active ions of fluoride, taken from the drinking water, are of great importance in structural resistance of the hard tissues of the teeth.

Moreover, sweets are considered to be one of the factors for caries development. Many respondents take excessive amount of sweets.

The diseases of the respiratory organs (37.5%) are in the second position, being represented by ENT disorders as hypertrophic and hyperplastic changes of pharyngeal lymphoid ring or Waldeyer's lymphatic ring, chronic tonsillitis, nasal septum deviation without respiratory disturbances. Immune deficiency is likely to be associated with unfavorable conditions of the environment, chronic infections, unhealthy diet and stress.

The diseases of muscular skeletal system are in 26.6% of respondents, mostly there are cases of spinal curvature 18.8%. In the North it is mostly associated

Table 1

Dietary intake of schoolchildren in Kysyl-Syr. Namsky region of the Republic of Sakha (Yakutia)

Food	Percentage of schoolchildren consuming the product. %				
	Several times a day	Daily	Several times a week	Several times a month	Less than once a month
Meat products	9.3	60.9	25	1.6	3.1
Milk and dairy products	9.3	39	37.5	9.3	4.7
Vegetables	0	15.6	67.1	10.9	6.2
Fish and fish products	3.1	1.6	9.4	48.4	37.5
Eggs	1.6	20.3	46.9	37.5	3.1
Fruit	0	12.5	51.6	31.3	4.7
Butter	14.1	57.8	17.2	7.8	3.1
Pasta (macaroni products)	4.7	21.9	68.8	4.7	0
Porridge	3.1	23.4	35.9	23.4	14
Sausages	3.1	6.3	56.2	26.6	7.8
Sweet. chocolate	3.1	25	56.3	15.6	0
Fizzy drinks	6.3	3.1	28.1	50	12.5
Packaged natural juice	4.7	4.7	18.7	48.4	23.4
Fried food	1.6	12.5	48.4	29.7	7.8
Bakery products	3.1	9.4	42.2	37.5	7.8

Table 2

A distribution of the respondents according to the consumed product, %

Drinks	1-2 glasses	2-3 glasses	3 glasses	Do not consume
Milk and dairy products	75	12.5	12.5	0
Fizzy drinks	45.3	29.7	25	0
Packaged natural juices	54.7	40.6	4.7	0

Table 3

A distribution of the respondents according to the consumed product, %

Food	1 or 2 pieces	3 or 4 pieces	A lot	Do not eat
Sweets	50	39	11	0
Chocolate	50	32.8	17.2	0
Eggs	54.7	31.2	14	0
Bread	28.1	53.1	18.8	0
Cookies	15.6	43.8	40.6	0
Sugar	26.6	32.8	40.6	0
Pancakes, patties	15.6	40.6	43.8	0

Table 4

Prevalence of pathology in children of Kysyl-Syr, Namsky region

Morbidity	Amount of the schoolchildren	
	Absolute number	%
Disorders of endocrine system	9	14.1
Disorders of respiratory organs	24	37.5
Disorders of digestive system	7	10.9
Disorders of muscular skeletal system and connective tissue	17	26.6
Disorders of the nervous system	8	12.5
Eye disorders	12	18.8
Disorders of cardiovascular system	7	10.9
Dental disorders	34	53.1

with the deficiency of vitamin D, as there are few sunny days and, as we can see from the questionnaire, it may also be connected with insufficiency of vitamin D containing products (fish, egg, and milk).

Conclusion. Thus, the questionnaire revealed insufficient amount of fish, dairy products, eggs, vegetables and fruit in the diet, while sugar and salt were in excess. Moreover, the results show that the quality of the food does not correspond to the standards and recommendations. Children sometimes prefer to eat sweets (candies, chocolate, fizzy drinks) when they are hungry; they eat pasta with meat and bakeries (pancakes and patties) at home, sometimes it can be associated with familial dietary habits. The situation is aggravated by the fact that most of the children did not realize possible negative consequences of such dietary pattern for their health.

As for the type of morbidity the situation is the following: 53.1% of respondents suffer from dental disorders; 37.5% from the diseases of the respiratory system; and 26.6% from disorders of muscular skeletal system. On a whole both the questionnaire data and type of morbidity reveal grave dietary breakdown in schoolchildren of Namsky region and require complex measures, aimed at dietary optimization.

It is necessary to update and improve the organization of the diet at home and school meal according to the modern guidelines and standards. Schoolchildren meals are organized according to the out-of-date management, financing and producing programs and rules. Changes in school meal organization and dietary habits at home should pass more actively together with the development of modern food technologies.

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THE TRANSFORMATION OF FOOD CULTURE IN RURAL AREAS AND ITS IMPACT ON THE MEDICAL AND SOCIAL SITUATION IN THE REGION

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The article presents the results of a study to identify the ongoing transformation of the daily food culture of the rural population, which allows us to talk about changes in the daily food culture in two conventionally divided aspects: material and spiritual, understood as traditions, taboos, proverbs and sayings related to food or specific dishes.

The purpose of the study is to identify changes in the traditional food culture in rural areas and compare with the actual nutritional value and incidence to determine indicative medical and social situations in the region. An analysis of the data shows that women are mainly involved in the preparation of everyday food. Respondents try to follow traditional cooking techniques of national dishes and use special dishes (25%). The modern daily rhythm of life requires saving time in cooking, so most (61%) of the villagers noted that instant food meets their needs to save time. The desire for diversity in food is so significant that 73% of the villagers said that it was customary in their family to cook dishes of other nations. Every second respondent likes national traditional dishes, 46% do not have special preferences, but love meat dishes. In conditions of intense diffusion of individual constituent cultures of peoples and the globalization of food culture, the cuisine of the peoples living in the North-East of the Russian Federation is mixed, not only in urban, but also in rural conditions.

During the transformation of the food culture in the actual nutrition of the population, there was a shift towards an increase in the diet of the share of simple carbohydrates and saturated fats with a deficiency of almost all the vitamins and minerals examined. These factors affect the health status of the population. A comprehensive assessment of the actual nutrition and analysis of the incidence of the adult population of the Republic of Sakha (Yakutia) over the past 20 years by the main classes of diseases should highlight a significant increase in oncological diseases. Cancer pathology increased in 2017 to the 1998 level by 2.6 times. However, the incidence rate of the circulatory system diseases in the republic in 2015-2017 was lower than the national average, while in previous years it significantly exceeded the national average.

Keywords: everyday food culture, fast food, world cuisines, actual nutrition, health, morbidity.

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Introduction. In the complex of life support systems of any ethnic group, the main role belongs to food as one of the components of a person's daily vital need. Since ancient times, a traditional nutritional model based on the consumption of meat, fish, and gathering products has played an important role in the livelihoods of the indigenous peoples of the North, which is most clearly reflected in the vocabulary associated with traditional food. But, during the XX century, Russia went through a period of dramatic economic, social and political transformations, which could not but affect the development of the indigenous peoples of the North, their traditional economic activities, which primarily led to the transformation of ethnic cultures of these peoples, including food culture [6].

The massive spread of urban lifestyles, the intensity of the modern rhythm of life, the development of the global market for goods and services, the increased availability in the countryside of a variety of «cookery» information, techniques and technologies for preparing everyday food cannot but lead to a mixture of peoples' cuisines at the global level. The influence of public opinion and the media circulating information on «harmful» and «wholesome» food, the expansion of the range of various nutritional services, the appearance of various diets, and the medicalization of the nutritional sector correct the taste preferences of the villagers [8]. All these factors encourage rural residents to consume food products of large-scale industrial production, also because these products are cheaper in cost than natural ones. Borrowing a variety of dishes of other nations, adapting them to local cuisine with the change of ingredients from local raw materials and using other cooking technologies can be called kitchen meshes, because from dishes of other nationalities, in fact, only their names can remain. Moreover, during the survey, the villagers indicate the names of dishes of other nations with their national dishes [3]. Therefore, the scientific view of intercultural interaction is based on global and local approaches [2].

Food provides the entry into the human body of substances that form the basis of the processes of anabolism - the synthesis of individual body substances for the formation and renewal of cells and tissues, reimbursement of the body's energy consumption, normalization of the physical and neuropsychic development of the body, and improvement of working capacity. Therefore, from an early age, a person should have knowledge and sustainable skills based on scientific achievements in culture and food hygiene. One of these skills is that food should be varied and contains all the necessary components: proteins, fats, carbohydrates, mineral salts, vitamins and water [4].

Numerous publications and research results show that the actual nutrition of certain groups of the population of Russia is characterized by a decrease in the consumption of meat, dairy, fish products, vegetable oil, fresh vegetables and fruits in recent years. As an unfavorable fact, a decrease in energy intake with food (91%) should be considered, especially due to animal proteins. This creates the prerequisites for the formation of individual, especially low-income and living in extreme conditions of the Far North, categories of the population, and signs of protein-energy deficiency. The content of vitamins in the diets of certain population groups is 55-60% of the recommended level. In fact, the majority of the population revealed a malnutrition, due to both an energy imbalance and insufficient consumption of nutrients, primarily vitamins, macro- and micronutrients, essential amino acids, polyunsaturated fatty acids, with their irrational ratio [14-16]. In the nutritional structure, there are fewer protein products, therefore, essential amino acids, and the nutrition of the population has become pronounced carbohydrate-lipid nature with a reduced content of vitamins, minerals, dietary fiber and other vital nutrients and a large consumption of refined products [1; 8]. All this, along with a negative impact on the processes of acclimatization and immunity, is reflected in the prevalence of risk factors for noncommunicable diseases and alimentary-dependent pathologies [5; 12].

On average, an increase in the incidence rate is observed in the Russian Federation, the Far Eastern Federal District and the Republic of Sakha (Yakutia) (at the same time, higher rates are recorded in the republic). Thus, the incidence rate in 2017 compared to 1998 in the Republic of Sakha (Yakutia) increased by 41.1% (amounting to 1021.1 cases per 1000 population), on average in the Russian Federation - by 16.2%, and the Far Eastern Federal District - by 21 , 8% (778.9 and 796.1 cases per 1000 population).

The purpose of the study is to identify changes in the traditional food culture in rural areas.

Materials and methods. A sociological study was carried out using a selective method-questioning of residents of rural settlements in Mirny, Namsky, Verkhny-Vilyui, Oymyakonsky, Suntarsky, Tomponsky and Ust-Aldan districts, with the exception of Mirny. Students who came from rural settlements were also interviewed. The survey was conducted in July-August 2017 on the quota sample (n = 1648), the confidence interval was ± 5%. The selective method was compiled by taking into account the structure of the general population by the remoteness of the places of residence of respondents from district centers. The questionnaire questions concerned the daily nutritional culture of the entire family of respondents. Data processing and analysis was performed in the SPSSStatistics 22.0 software application.

Although quota selection is most common among nonrandom sample types and competes in accuracy with probabilistic types, interviewers select those that are most accessible to them for filling quotas. Accessibility also refers to the «coverage» of settlements, i.e. opportunities for traveling to certain settlements. In the sample, the proportions of only one of the indicated trait (place of residence) were observed; therefore, the quantitative characteristics of the remaining traits may not coincide with the structure of the general population.

Evaluation of actual nutrition was carried out by individual interviewing of respondents in accordance with the standards of the WHO international program on integrated prevention of noncommunicable diseases - CINDI. In the work, a special questionnaire was used by the Federal State Budgetary Institution “State Scientific Research Center for Preventive Medicine” of the Ministry of Health of Russia and the Federal State Budgetary Institution of Nutrition, Biotechnology and Food Safety, adapted for the surveyed population in accordance with the local living conditions of Yakutia. The analysis of daily diaries of nutrition respondents. Evaluation of the amount of food consumed was carried out in accordance with the «Album of servings of foods and dishes», 1995 [10].

The coding of dishes was carried out in accordance with the reference book «The chemical composition of Russian food products» [14].

When analyzing the incidence of the population by the main classes of diseases, the data of the Ministry of Health of Russia for 1998-2017 were used. [7].

Results and discussion. In the study, we divided the everyday home meal of the family into its components: cooking, which is associated with the distribution of responsibilities between family members, cooking technology, its speed, knowledge and observance of some national traditions, rituals, the desire to diversify the menu, sources of information for new recipes etc. In this sequence, we followed how modern cuisine meshes of the surveyed villagers occur. An analysis of the data shows that women are engaged in preparing everyday food; however, other members of the respondent's families are not «aloof» (Table 1). Today, social reality is becoming more complicated due to the development of post-industrialism and sociocultural communications, and the rhythm of life is accelerating not only in cities, but also the countryside. To the questions «how is the traditional technology of preparing national dishes preserved in such conditions?» And «how much new technologies in cooking are in demand?». The respondents answered that they are trying to comply with traditional technologies for preparing national dishes. 25.4% of respondents said that they use special dishes, "22.5% - modern technologies and household appliances to speed up cooking, although they believe that the taste of the dish is changing. 16.8% of respondents do not see a big difference in cooking technology, so they use modern technology and equipment. 14.7% think that life is developing, and therefore the technology of cooking is changing. An insignificant part (7.0%) of the villagers surveyed admits that they do not know traditional technologies, therefore they use modern technologies.

As noted above, the modern daily rhythm of life requires saving time on household needs, including when cooking. As can be seen from the data (Table 2), the majority of the villagers surveyed (61.4%) noted that such types of food meet their needs to save time, in addition, 27.9% of respondents also save on food costs. As you know, not only the rhythm of life forces you to consume factory semi-finished products, fast food, but their prices are not comparable to natural foods that are currently not available to everyone [13].

Apparently, the desire for diversity in food is so significant that the villagers prepare dishes of other nations for their families. So, 72.9% of respondents answered that it is customary in their family to cook dishes of other nations. Almost a quarter of respondents (24.1%) gave a negative answer. However, given how deeply the cuisines of the peoples of the USSR mixed up, these data may indicate that dishes of other peoples that were «mastered» back in Soviet times are no longer perceived by respondents as «strangers». Respondents called many popular dishes of the peoples of the former USSR, as well as European,

Table 1

Who usually cooks everyday food in the family of surveyed villagers, %

Usually cooking	Всего	District (ulus)					
		Mirninsky	Namsky	Oymyakonsky	Suntar	Tomponsky	Ust-Aldansky
I usually (myself) cook for the family	42.3	23.1	51.5	39.8	55.4	29.6	38.6
I have no time, so my spouse is more involved in this	6.3	2.8	7.0	8.2	7.4	1.9	15.9
We have a grandmother (grandfather), usually she (he) cooks for our family	8.0	6.0	10.5	10.2	5.8	14.8	6.8
We have a priority set in our family and we follow it all	4.1	7.4	4.5	4.1	1.9	1.9	2.3
Children have more time, so they cook for the family when we are at work	2.1	2.3	0.5	4.1	1.6	3.7	2.3
Who comes home before the rest, he begins to cook	27.9	30.6	23.0	31.6	24.8	42.6	29.5
Mother/father	5.7	19.9	2.0	-	0.4	1.9	2.3
Sister/brother	0.7	2.3	-	-	0.4	-	-
No answer	2.9	5.6	1.0	2.0	2.3	3.7	2.3

Table 2

Evaluation of the distribution factors of fast food (fast foods). convenience foods. %

Factor spreading	Total	District (ulus)					
		Mirninsky	Namsky	Oymyakonsky	Suntar	Tomponsky	Ust-Aldansky
These products are cheaper	27.9	39.8	21.0	30.6	22.1	31.5	25.0
They are comfortable. can be cooked quickly. a lot of time is required	61.4	62.0	60.5	50.0	64.3	63.0	68.2
Such dishes are tastier than our traditional food	7.9	12.5	8.0	10.2	5.0	-	6.8
Everyone today eats such food. I do not want to lag behind life	5.2	4.2	9.5	9.2	2.7	1.9	-
My daily food is boring. why not eat something new from time to time	11.7	10.2	20.0	4.1	10.5	7.4	11.4
Such food is good for health. low-calorie. does not allow to gain excess weight	0.8	0.9	-	3.1	0.8	-	-
Other	7.7	6.0	4.0	11.2	11.6	1.9	9.1
No answer	27.9	39.8	21.0	30.6	22.1	31.5	25.0

oriental cuisines, asking them to indicate the name of their favorite dishes in the questionnaire.

Every second respondent likes national traditional dishes, 46.3% do not have special preferences, but prefer meat dishes. Almost a third of respondents (37.0%) admitted that they like flour products, pastries, and a quarter of respondents prefer fish dishes. When asked whether respondents know ritual dishes and ritual food, the majority (77.4%) answered that they know, and 17.0% of respondents admitted that they did not know.

Table 3 shows the opinions of the villagers surveyed what exactly is being lost in the food culture today, dividing it conditionally into everyday practices of the actions taken and spiritual components, i.e. the use of proverbs and sayings related generally to nutrition. Respondents noted the same proportion of the loss of traditions and rituals in the culture of everyday nutrition, a little less indicated restrictions (taboos) in food. We attribute this to everyday practice, i.e. the commission of certain actions that are given certain meanings and ideas.

According to the results of studies conducted by employees of the Center for Nutrition Research Institute of Health NEFU named after M.K. Ammosov, there are differences in the daily calorie intake among respondents depending on gender and ethnicity. The daily energy consumption in men was 2308, in women 1801.3 kcal ($p < 0.05$). The caloric value of the diet of the rural population was statistically significantly higher (1787.1 and 2129.2 kcal, respectively, $p < 0.05$). The highest calorie diet was observed from the surveyed areas in Suntar ulus (women average 1983 kcal / day, in men

Table 3

Respondents' assessment of the loss of traditions and rituals in the culture of everyday nutrition, %

Loss	Total	District (ulus)					
		Mirninsky	Namsky	Oymyakonsky	Suntar	Tomponsky	Ust-Aldansky
	778 people	32 pax	229 people	175 pax	20 pax	277 people	45 pax
Eating traditions	29.2	31.3	29.3	22.9	35.0	31.0	37.8
Food related rituals	28.9	18.8	27.5	29.7	60.0	30.3	17.8
Bans on eating certain foods	22.9	25.0	23.1	20.6	35.0	24.2	15.6
Proverbial heritage about food (proverbs, sayings)	15.7	18.8	14.4	18.3	55.0	13.4	6.7
Traditional food storage systems	13.5	15.6	13.1	12.6	30.0	14.4	4.4
Other	0.4	-	0.9	-	-	0.4	-
I believe that some traditions are preserved, and not which are forgotten	12.0	15.6	15.7	14.9	-	8.3	6.7
No, I believe that traditions are preserved	11.2	6.3	12.7	8.6	-	12.3	15.6
No answer	17.5	18.8	16.2	15.4	10.0	19.1	24.4

- 2777 kcal / day.). The lowest calorific value is observed in the Mirny district (for women, on average, 1566 kcal / day, for men - 1730 kcal / day).

The study also examined the intake of minerals and vitamins. So, in terms of iron consumption, there is a deficit in all uluses, a total of 11.8 against 18 mg per day. Calcium consumption in all uluses is also significantly lower than normal (1000 mg), in some uluses 2 or more times. On phosphorus, the average consumption in the republic was 893.9 mg per day (normal 800 mg). For potassium, 2039.3 mg versus 2500 mg (normal). Magnesium intake was also lower than the recommended figures (220.5 versus 400 mg per day).

There is also a significant deficit in the consumption of vitamins for all major species, since the deficiency in vitamin C is more than 37%. For vitamins B1 - B2, the deficiency is about 50%. There is also a significant deficiency in vitamin PP and retinol (52–70% of the recommended norm).

In the Republic of Sakha (Yakutia), an increase in the incidence rate in recent years has been noted for many classes of reasons, but a significant increase in oncological diseases should be highlighted. Cancer pathology has grown 2.6 times in 2017 compared to the 1998 level (reaching 10.5 cases per 1000 population), while the national average growth was 148.1%, in the Far Eastern Federal District - 163.2% (11.4 and 11.1 cases per 1000 population, respectively).

Circulatory system diseases are the main cause of premature death of the population. If on average in the country there is an increase in circulatory system diseases (in 2017 compared to 1998 - 2.1 times, amounting to 32.1 cases per 1000 people), then in MS (Y), on the contrary, from 2014 there has been a decrease in the incidence of for this reason (in 2017 compared to the level of 2013 by 46.3%, by 1998 - by 12.6%, amounting to 20.2 cases per 1000 people). On average, in the Far Eastern Federal District, after a marked decrease in the incidence rate in 2014, its growth was again recorded, in 2017 reaching 24 cases per 1000 people. The incidence rate of the circulatory system diseases in the republic in 2015-2017 was lower than the average for the Russian Federation, while in previous years it significantly exceeded the average Russian values.

The decrease in mortality from diseases of the digestive system in the republic to a certain extent is due to a decrease in the incidence rate for this class of diseases. The number of registered relevant diseases in patients diagnosed for the first time in their life decreased in 2017 compared to 2013 (the highest value in the reporting period was noted) by 39.2% and amounted to 58.3 cases per 1000 population (however, this is significant higher than the 1998 level - by 72.5%). It should be noted that if the dynamics of this indicator on average across the country and the Far Eastern Federal District was relatively stable, then in the Republic of Sakha (Yakutia) it tended to noticeably increase in the period 2000-2013 with its subsequent significant decrease. The indicator for the republic significantly exceeds the average data of the Russian Federation and the Far Eastern Federal District (in 2017 - by 71.5% and 43.6%).

Conclusion. In conditions of intense diffusion of individual constituent cultures of peoples and the globalization of food culture, the cuisine of the peoples living in the North-East of the Russian Federation is mixed, and not only in urban, but also in rural conditions. Metisation is accompanied not only by a change of products by local components, but also by technology.

As follows from the data obtained, there are changes in the distribution of responsibilities in cooking for respondent families. In traditional culture, the woman was responsible for cooking. Among 42.3% of the respondents engaged in cooking for the family, only half were women. An even more “flexible” form of adaptation to modern conditions is the answer "who comes home earlier than the others, he begins to cook" (27.9%). A shift in the metisation of the cuisine of different peoples is evidenced by the list of names of favorite dishes (respondents entered the names themselves), among which are not only their national dishes, but also other peoples. When asked at what rate the components of food culture are being lost according to the surveyed villagers, less than a third of the villagers said that today they forget traditions and rituals, taboos in everyday food and out of turn into proverbs, sayings related to food. Perhaps, these phenomena are associated with insufficient consumption by the villagers of basic food products,

such as meat, fish, and dairy products. They are characterized by excessive consumption of bread and bread products (pasta, cereals, flour). Due to the last group of products, caloric intake is replenished.

Thus, during the transformation of the food culture in the actual nutrition of the population, there was a shift towards an increase in the proportion of simple carbohydrates and saturated fats in the diet with a deficiency of almost all of the examined vitamins (C, B1, B2, PP, retinol (microgram ret. Equiv.) And mineral substances (iron, calcium, potassium, magnesium). These factors, of course, affect the health status of the population and the high increase in the incidence. In this connection, the transformation of food culture cannot but affect the medical and social situation and does not affect the sustainable development of the region.

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ARCTIC MEDICINE

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CEREBRAL ENERGY METABOLISM IN CHILDREN WITH HIGH LEVEL OF ANXIETY

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People living in the conditions of the Arctic latitudes become the cause of more intensive use of the body's adaptation reserves. The children's body reacts heavily to the effects of climatic factors because it has the immaturity of the functional systems. Currently, it is important to study the specifics of the functional state of the central nervous system in children living in the Arctic region. Chronic psycho-emotional stress is a significant characteristic of distress in the Arctic region. This is one of the manifestations of readiness to respond in an alarming manner. A child with high anxiety will be at high risk of sensitivity to the action of adverse environmental factors. The body requires the use of more effort to process incoming information and the formation of responses. The purpose of this study is to determine the characteristics of the distribution of the level of DC potential of the brain in children with a high level of anxiety living in the Arctic region. We conducted a cross-sectional study with the participation of 105 children aged 9-10 years. The level of personal anxiety in children was assessed using the “Multidimensional Evaluation of Child Anxiety” test. A DC potential was recorded using a 5-channel hardware-software complex for topographic mapping of brain electrical activity, NEURO-KM (Russia). We have revealed an increase in the absolute values of the constant DC potential of high-anxious children living in the Arctic region. The absolute values of the DC potential show an increase in all leads, the shift in the distribution of DC potentials is changed to the occipital region of the brain. The results of the study indicate a higher energy consumption of the brain in children living in the Arctic region. An increase in total DC potentials indicators was recorded. In children with high anxiety, these indicators show even greater DC potentials. The reduction of energy consumption in the frontal regions relative to other brain areas in children of the North can be regarded as a manifestation of the functional tension of the central nervous system when living in the Arctic region.

Keywords: children, anxiety, DC potential, North, Arctic region.

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Introduction. It is known that living in the Northern latitudes has a negative impact on human health and causes more intensive use and rapid depletion of adaptive reserves of the body [4, 7]. Children react more intensively to external influences, because they are in the process of forming functional systems. Therefore, the study of the specifics of the functional state of the Central nervous system in children living in the Arctic region is very important. The age of 9-10 years is a period of structural and functional rearrangements of the Central nervous system, which requires large energy expenditure and is characterized by high sensitivity to external influences, including adverse climatic factors of high latitudes [1, 11]. In this regard, the study of brain energy exchange, as an indicator of the functional co-existence of the Central nervous system, using the method of recording the level of constant potential is important [2, 3]. The registration is based on the assessment of the intensity of cerebral metabolism and is a method of its biochemical neuroimaging. High readiness to react according to the alarm type is one of the significant characteristics of distress in the North [8]. A child with high anxiety will be at increased risk of vulnerability to adverse environmental factors, due to the need for the body to spend more effort on processing incoming information and responses [5, 10, 12]. At the same time, studies of the relationship of children's anxiety with the peculiarities of the functional state of the Central nervous system of northerners are not numerous, and the study of the peculiarities of cerebral energy processes with high anxiety in children is not given due attention. the purpose of our study is to determine the features of the distribution of the level of permanent brain potential in children with high anxiety levels living in the Arctic region.

Materials and methods of research. The cross-sectional study involved 105 children aged 9-10 years. All children were trained in the third classes of comprehensive schools of the city of Arkhangelsk. The study was carried out in accordance with the standards of good Clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study was approved by the Ethical Committee of the Northern Arctic Federal University named after M. V. Lomonosov. The examination of children was carried out with the written informed consent of the parents. The level of personal anxiety in children was assessed using the test "Multivariate assessment of children's anxiety (MACA)."

We used a 5-channel hardware-software complex "NEURO-KM" (Russia) to record and analyze the intensity of cerebral energy metabolism. The level of permanent potential was recorded monopolarly in the frontal (Fz), Central (Cz), occipital (Oz), right temporal (Td) and left temporal (Ts) leads according to the international scheme 10-20. The values of the constant potential were recorded 5-6 minutes after the electrodes were

applied to the lead points and then the recording was carried out continuously. Analysis of constant potential was done by mapping the unipolar values and calculate the Transconductance of the difference. Local values of the constant potential in each of the departments were measured, excluding the influence of the reference electrode. Deviations of the constant potential level from the average in each of the leads were calculated for all areas of the cerebral cortex. The obtained characteristics of the distribution of the level of constant potential were compared with the average normative values allocated for the corresponding age groups of the middle latitudes of Russia.

There were no statistically significant differences between the groups of boys and girls according to the studied indicators. schoolchildren living in the Arctic region were divided into two groups: with a high level of personal anxiety (40 people) and with a normal level of anxiety (65 people). The control group included the results of mapping children from Central Russia, built into the software hardware and software complex "NEURO-KM".

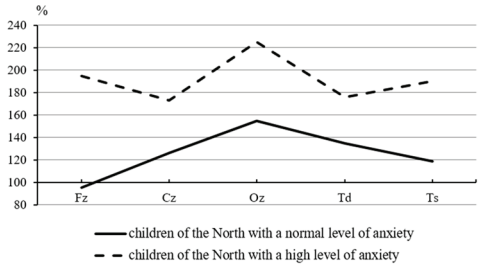
Data processing was carried out using the statistical software package "SPSS 17 for Windows". The distribution of signs to normality was evaluated using the criteria of Shapiro-Wilk and Kolmogorov-Smirnov. student's t-test was used to identify differences between the compared groups. The critical level of significance (p) when testing statistical hypotheses was taken to be 0.05.

Results and discussion. We obtained results that characterize the flow of cerebral energy metabolism in children-northerners. The results indicate that for the inhabitants of the Far North there is a tension of physiological systems of the body. At the same time, we recorded a change in brain energy consumption in northerners with high levels of anxiety (Fig.).

We have shown that the intensity of cerebral metabolism in children decreases after the age of 9 [2]. However, our results also indicate that in children living in the Arctic region, indicators of the intensity of cerebral energy exchange have increased values. Thus, the total cerebral energy consumption of children from the North, both in the group with a normal level of anxiety and in the group of children with high anxiety exceeds the normative values by 37% and 85%, respectively. The absolute values of the constant potential of the children of the North of both groups exceed the indicators of the control group for all leads. The exception is the indicators of frontal abduction in the group of children of the North. In the group of children of the North with a normal level of anxiety – they are identical to the indicators of children of Central Russia (Fz 8.1 mV and 8.5 mV, respectively), while in high-anxiety children of the North it is increased twice compared to the other two groups.

The relative values of the constant potential of the children of the North have confirmed the assumption of a slower rate of maturation of some structures and functions of the brain in children of the Arctic region compared to their peers from Central Russia. The decrease in energy consumption in the frontal lobes relative to other parts of the brain in children of the North of 9-10 years speaks of the relative immaturity of the frontal structures of the brain. According to the normative values of this difference is -2,4 mV, and in the group of children of the North of 5.7 mV in children with normal levels of anxiety and 4.2 mV in children with a high level of anxiety.

The high value of the index characterizing the energy consumption in the left temporal region (Ts 20.1 mV; p≤0.001) is recorded in the group of highly anxious children of the North, which is almost twice the same value in the other two groups. In addition, the absolute values of the constant potential in this group are significantly higher than the other two groups in all leads almost twice. The cortex of the human brain can inhibit the underlying centers, which allows the body to mitigate the manifestations or regulate the intensity of anxiety in normal conditions [6]. This type of control is possible at the optimal level only with the functional maturity of the neocortex. Functional systems of the brain are actively maturing and improving throughout the period of primary school age [3, 9]. Probably, high anxiety aged 9-10 years, actively affects the dynamics of these processes, which is confirmed by the highest increase in the level of constant potential in children with anxiety in the frontal and left temporal regions of the brain.



Distribution of constant potential indicators. Comment. normative values of the control group are accepted for 100%

The values of constant potential in Northern children in the Central parts of the brain exceed the values in other leads. However, the relative distribution of their constant potential does not correspond to the dome-shaped distribution: there is practically no difference in energy consumption between the Central and occipital parts of the brain (0.8 mV), while in children of the middle band when comparing the indicators for these leads it is the maximum (3.1 mV). At the same time, in terms of deviation from the average level of constant potential in the Central parts of the brain, groups of children do not have statistically significant differences (p = 0.616), and in terms of deviation from the average value of the constant potential in the occipital sections, the difference between children of the North and their peers from the Central strip of Russia is significant (p = 0.014).

In children of the North with high anxiety, the maximum values of constant potential in the occipital lead were registered. There is no difference in energy consumption between the Central and occipital parts of the brain. At the same time, according to the indicators of deviation from the average value of constant potentials in the occipital sections, the difference is established between highly anxious younger students and their peers with a normal level of anxiety (p = 0.034). Therefore, a violation of the principle of Cuprobraze distribution neuroenergetic in the group of children of the North with a high level of anxiety due to the increase of constant potential in the occipital parts of the brain. It is known that the local constant potential in the occipital region reflects changes in energy metabolism in the stem structures involved in the regulation of emotions. At the same time, it was found that the structures of the hypothalamic-pituitary system and the stem reticular formation are activated under stress. Obviously, the shift in the distribution of constant potential in the occipital region of the brain in anxious children may also be associated with increased functional activity of non-specific reticular-limbic-cortical neural connections with high anxiety.

Thus, the violation of the principle of dome-like distribution of neuro-energy in the group of children living in the Far North is due to a significant increase in the constant potential in

the occipital parts of the brain. In this case, a high level of anxiety affects the increase in energy exchange in the occipital areas of the brain.

Conclusion. We have shown that children living in the Arctic region have increased the total indicators of the level of permanent potential. Potential values in each area of the brain are increasing in children of the North and, also, indicators of constant potential with a high level of anxiety in children of the North are increased. The principle of "dome-shaped" distribution of neuroenergosatrats is broken, which is due to the shift of the distribution of constant potential in the occipital region of the brain, and may be associated with both the impact of adverse climatic and environmental living conditions, and with increased functional activity of non-specific reticulo-limbic-cortical neural connections with high anxiety. Energy consumption in the frontal lobes relative to other parts of the brain are reduced in children of the North compared to their peers from the Central regions of Russia, which can be regarded as a manifestation of the functional tension of the Central nervous system when living in the Arctic region.

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EPIDEMIOLOGICAL EVOLUTION OF SKIN MELANOMA IN THE POPULATION OF CIRCUMPOLAR REGION (ON THE EXAMPLE OF ARKHANGELSK REGION)

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The deterioration of the epidemic situation with the incidence of skin neoplasms (including melanoma) actualizes the task of identifying the sex and age characteristics of the population at risk of cancer, intra-and intergenerational features of the evolution of its incidence. Aim: to establish the features of primary incidence of melanoma evolution in the population of circumpolar region of the Russian Federation (on the example of the Arkhangelsk Oblast) in 2007 – 2017. Materials and methods. A retrospective observational register-based study was performed. The data from the Arkhangelsk Regional Cancer Register were used to calculate the actual and standardized (direct method) values of indicators of incidence rates of melanoma. Age-Cohort-Period analysis was used to determine intra-and intergenerational features of the dynamics (evolution) of incidence rate coefficients. Results. In 2007-2017, incidence rate of a skin melanoma in the male population of the Arkhangelsk Oblast increased by 103.1% (from 3.2 to 6.5 cases per 100.000 population); in the female population – by 33.3% (from 8.7 to 11.6 cases per 100.000 population). Women were in the gender group at risk of developing this kind of neoplasms; older and elderly people were in the age group at risk. Cohort (intra-generational) and period (inter-generational) effects in the dynamic of age-specific indicators of the incidence rate of skin melanoma were revealed. Conclusion. Further evolution of the "cohort" and "period" effects in the dynamics of age-specific indicators of incidence rate of skin melanoma in the Arkhangelsk Oblast will lead to a dramatic changes in the characteristics of the gender and age group at risk of this neoplasm: an outstripping increase of the incidence rates among men; citizens of working age (30-49 years).

Keywords: melanoma, primary morbidity, circumpolar regions, Arkhangelsk Oblast, cohort effect, period effect.

Background. Skin melanoma (C43.0-9) is a malignant neoplasm of neuroectodermal origin, coming from melanocytes; the skin accounts for up to 95% of all localizations of this type of tumor. The incidence of the condition on a global scale tends to increase; in the group of special risk (up to 80% of all new cases) – representatives of the European race living in Northern Europe, North America, Australia and New Zealand [16].

The highest primary incidence of skin melanoma was noted among the descendants of European migrants of Oceania (62.7 cases per 100 thousand population in 2015), the United States (up to 40-50 cases per 100 thousand population) [15]. In the Russian Federation, at the beginning of the XXI century, the incidence of neoplasm also tends to increase; in the period from 2006 to 2015, the value of the indicator increased by 34.6% (from 5.2 to 7.0 per 100 thousand population). According to experts, by 2020 the primary incidence of melanoma of the skin will increase by 20-25% [1,4].

The etiological factor in the formation of melanoma is not installed. Experts of the world health organization (WHO) argue that up to 80% of all new cases of tumors are the result of damage to sensitive areas of the skin by ultraviolet radiation [16]. The risk of the latter is especially high among the representatives of the European race, constantly living in the Northern (including polar) regions, but periodically resting in the South. Taking into account the fact that the number of Russians, including residents of the Northern (circumpolar) regions, making trips to the countries of the "far" abroad, is constantly growing (in 2017 compared to 2016 – by 31.6%) [3], the probability of deterioration of the epidemic situation with the incidence of skin tumors, including melanoma, is quite high [7,8,9]. In this regard, it seems appropriate to solve the problem of identification of sex and age characteristics of the population risk group of cancer pathology, which requires to establish intra-and intergenerational features of the evolution of its incidence.

Aim of the study: to characterize the evolution of primary morbidity of population of the circumpolar region of the Russian Federation (on the example of Arkhangelsk region) melanoma of skin (C43.0-9) in 2007 – 2017.

Materials and methods. A complete retrospective observational register-based study was performed. Anonymous information on all cases of primary diagnosis of skin melanoma (C43) has been extracted from the database of the Arkhangelsk regional cancer registry (ARKR) on all cases of primary diagnosis of skin melanoma (C43.0-9) medical workers of the Arkhangelsk region in 2007-2017 (n = 1044) [2]. The formed database contained the following variables: sex of the patient, date of diagnosis, age (years) at the time of diagnosis, place of residence (urban / rural settlements), clinical diagnosis (with ICD-10 code). Repeated records on the treatment of relapses and progression of

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the disease (n = 223) were excluded from the subsequent analysis. Data on the population dynamics of the Arkhangelsk region in 2007-2017 were provided by the Territorial Body of the Federal State Statistics Service (Archangelskstat); on the age and gender structure of the population of the Russian Federation in 2017 - by the Federal state statistics service (Rosstat) [5].

Based on the data obtained, the actual values of the indicators of primary morbidity of the population of skin melanoma (including in the age and sex groups) were calculated. The corresponding standardized values were calculated by the direct method (according to W. Oglu) taking into account the age structure of the male and female population of Russia on 01.01.2017. The Age-Period-Cohort (APC) analysis [17] was used to determine the intra-and intergenerational features of the dynamics (evolution) of indicators of primary morbidity in the region of melanoma of the skin. The STATA 12.0 application package was used for statistical data processing. The calculation of the limits of the 95% confidence interval (95% CI) of rates by Fisher's method was performed using the WinPepi program.

Results. In 2007-2017, 1044 new cases of skin melanoma were registered in the Arkhangelsk region, including 323 cases among men (30.9%) and 721 cases among women (69.1%). The incidence of neoplasm among the male and female population of the Arkhangelsk region increased significantly during the study period (the growth rate of the indicator values was +103.1% and +33.3%, respectively) (Fig. 1).

The primary incidence of melanoma in the rural population of the region was 1.4 – 1.8 times lower than in the urban population until 2015 (Fig. 2). In 2015, the indicator values in the population groups were equalized.

For the analysis of intra-and intergenerational dynamics of indicators of primary morbidity of the population of the Arkhangelsk region, skin melanoma data for 2007 and 2017 were used. The gender risk group for the development of tumors in the study period were women; age - the elderly population, as evidenced by the pronounced age (age effect, change in the frequency of occurrence of the condition, correlated with the age of the respondents at the time of the study) effect in the dynamics of the values of the incidence of the state in 2017 compared with 2007 (table 1).

Attention is drawn to the positive intra-generational (cohort, birth cohort effect) effect in the dynamics of the values of age-related indicators of primary morbidity in the region of melanoma of the skin (for example, the rate of increase in the values of the indicator in the group of women who in 2007 were 40-49 years old, and in 2017 – 50-59 years, was [per decade] +107.7%). Among the younger generations of northerners cohort effect was more pronounced.

The positive intergenerational (period, period effect) effect (increase in the frequency of occurrence of the condition to a certain age in representatives of subsequent generations of citizens) in the dynamics of the incidence of melanoma of the skin also indicates the aggravation of the epidemic situation with neoplasm in the Arkhangelsk region. Thus, in the generation of women born in the 1980s, by the time they reached the age of 20-29 (in 2007), the incidence of the condition was 2.9 cases per 100,000 of us.; in the next generation of women born in the 1990s, by the time they reach the age of 20-29 years (in 2017) - already 6.5 cases per 100,000 of us. (growth rate: + 124.1%). In General, the positive intergenerational effect in the group of men in the study period was more pronounced than in the group of women.

Discussion. The high level of morbidity of the Russian population with malignant neoplasms is recognized as one of the leading risk factors for public health, a threat to the national security of the country at the beginning of the XXI century [10, 12]. Search conditions accompanying increase in the cancer burden, development of measures aimed at reducing its size, has acquired a high relevance in connection with the approval of decrees of the President of the Russian Federation No. 598 dated 07.05.2012 "On improving state policy in the sphere of health protection" and No. 214 dated 07.05.2018 "On national goals and strategic objectives of the development of the Russian Federation for the period up to 2024", the beginning of the implementation of the new national project "Health" from 2019, an important element of which is the Federal project "Fight against cancer" [11,13].

The epidemic situation with malignant neoplasms in the Northern regions of the country, including the Arkhangelsk region, remains quite complex. Indicators of primary disease of the population of the region melanoma of the skin in 2007-2017 years, the rate of increase of their values was higher than in the whole country (in the Arkhangelsk region of 6.2 in 2007 and 9.2 per 100 thousand population in 2017 growth rate: +48,4% per decade; in the Russian Federation: 5.2, 2007 and 7.0 per 100 thousand population in 2016, the growth rate: +34,6% per decade). It should be noted that the beginning of the program of clinical examination of the adult population in 2013 had almost no impact on the detection of malignant tumors, which indirectly indicates a low level of cancer care of medical workers in the region.

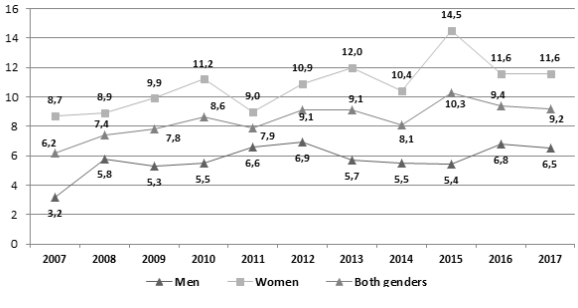

Fig. 1. Standardized values of the coefficient of primary morbidity of the population of the Arkhangelsk region of skin melanoma in 2007-2017 (per 100 000. population)

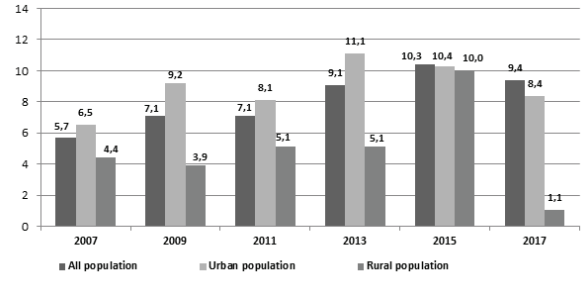

Fig. 2. Actual values of incidence rates of the skin melanoma in urban and rural populations of the Arkhangelsk region in 2007-2017 (per 100,000 population)

Globally, the incidence of neoplasms in the group of men and women is almost identical [1]. In the Russian Federation, by contrast, the gender structure of patients is significantly dominated by women (for example, in 2016 – they accounted for 61.0% of the total number of newly diagnosed cases) [6]. In the Arkhangelsk region in 2007-2017 the primary incidence of melanoma in the group of women was 1.6–1.8 times higher than in the group of men. The causes of these features

of the epidemic process are not reliably established. Experts determine the use of cosmetic services (including solarium) as an additional risk factor, causing a higher probability of developing tumors in women [1].

The incidence of malignancy among residents of rural settlements in the region was significantly lower than among residents of cities until 2015 (Fig. 2). We believe that this is due to the varying degree of exposure to the influence of the leading risk factor - excessive insolation (due to the higher solvency of citizens often use cosmetic services, spend holidays abroad in tropical, sub-Equatorial countries), the effectiveness of diagnostic work (cancer) of health workers [2,4,9,14]. At the same time, the degree of influence of each of these factors on the dynamics of the indicators of the identified primary incidence of melanoma remains unknown.

At the national level, the highest incidence of neoplasm is traditionally recorded in the group of elderly and senile citizens [15]. A similar situation is noted in male and female populations of the Arkhangelsk region (Table 1). However, this feature is not sufficient evidence of the etiological role of age in the pathogenesis of tumors. It should be taken into account the low value of the indicator of active detection of patients with melanoma in the Russian Federation (estimated N.P.Malishevskaya et all.: +25.8% in 2016), as well as the unsatisfactory quality of self-preservation behavior of citizens [6,7,9].

Reliable evidence of the influence of the age factor on the incidence of tumors are the results of APC-analysis, in particular, - a positive intra-generational (cohort) effect in the dynamics of values of age-specific indicators (table. 1). To a greater extent, it was expressed among the younger generations of northerners (born in the 1980s – 1990s) - exposed to excessive exposure to leading risk factors for the disease. The reasons for the reduction of the registered primary incidence of melanoma in the generation of men born in the 1980s should be studied in subsequent studies, but, according to the authors, there is a hypodiagnosis of the condition due to the above circumstances.

The progressive deterioration of the epidemic situation with the incidence of skin melanoma in the population of the Arkhangelsk region is evidenced by the positive intergenerational effect in the dynamics of age-specific indicators of its incidence (Table 1, 2). In the study period (2007-2017) it was more pronounced in the group of men. In the world population, the same trend was noted, which is explained by the experts of the progressive gender unification of risk factors for the development of neoplasm [15].

Summing up the revealed sex and age features of dynamics of primary incidence of melanoma of the population of the Arkhangelsk region, the authors determine the following vectors of its evolution in the next decade:

1. Further steady increase in the incidence of gender and age groups in the region;

2. Changes in the gender structure of the incidence of the condition, - gradual equalization of the values of the primary incidence of neoplasm among women and men;

3. Changing the characteristics of the age group at risk of neoplasm, - outstripping the growth of incidence in the group of citizens of working age (30-49 years).

Conclusion. 1. The primary incidence of male and female population of the Arkhangelsk region with melanoma of the skin in 2007-2017 had a tendency to increase; the rate of increase in the incidence of the condition in the group of men was +103.1%; in the group of women +33.3%. Women were the gender risk group for the development of neoplasm; the age group was the elderly population.

2. Positive intra-generational (cohort) effect in the dynamics of values of indicators of the primary morbidity of male and female population of the Arkhangelsk region melanoma of the skin proves the influence of age factor on the risk of developing the disease.

3. The positive intergenerational (periodic) effect in the dynamics of skin melanoma incidence rates, more pronounced in the group of men, allows us to expect in the near future changes in the gender structure of the incidence of the condition, an outstripping increase in the incidence of the condition in the group of citizens of working age (30-49 years).

Intra-and intergenerational effects in the dynamics of the actual values of the incidence rates of the skin melanoma in male and female sub-populations of the Arkhangelsk region in 2007 and 2017 (per 100.000 of the respective population)

Age group. in years	Пол	Incidence rate in 2007 (95% CI)		Growth rate (cohort effect). %
		2007 г.	2017 г.	
0-19	муж.	0.7 (0.0 – 3.8)	0.0 (0.0 – 2.9)	
	жен.	0.7 (0.0 – 4.0)	0.8 (0.0 – 4.6)	
20-29	муж.	1.8 (0.2 – 6.7)	2.8 (0.3 – 10.3)	+300.0
	жен.	2.9 (0.6 – 8.5)	6.5 (1.8 – 16.5)	+828.6
30-39	муж.	2.3 (0.3 – 8.4)	1.1 (0.0 – 6.0)	-38.9
	жен.	4.7 (1.3 – 12.1)	5.8 (1.9 – 13.4)	+100.0
40-49	муж.	0.0 (0.0 – 3.9)	4.1 (0.8 – 12.0)	+78.3
	жен.	13.0 (6.9 – 22.2)	16.8 (8.9 – 28.7)	+257.4
50-59	муж.	7.4 (2.7 – 16.2)	17.2 (9.2 – 29.4)	+ ∞
	жен.	9.8 (4.7 – 18.0)	14.4 (7.7 – 24.7)	+107.7
60-69	муж.	5.6 (0.7 – 20.0)	15.8 (7.2 – 30.0)	+113.5
	жен.	16.8 (8.0 – 30.8)	27.2 (17.1 – 39.7)	+177.6
> 70	муж.	11.4 (2.4 – 33.4)	22.5 (8.3 – 49.0)	+301.8
	жен.	18.2 (9.7 – 31.1)	16.6 (8.6 – 29.0)	-1.2

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MINERAL DENSITY OF BONE TISSUE OF THE AXIAL SKELETON IN POSTMENOPAUSAL WOMEN WITH OVERWEIGHT

The study evaluated the relationship between obesity and mineral bone density (BMD) of the axial skeleton in postmenopausal period of women living in the conditions of Yakutia. It was revealed that the body mass index statistically significantly affects the mineral density of bone tissue, while the ratio of muscle tissue to adipose tissue is very important. The increased mineralization of the bone tissue of the axial skeleton in postmenopausal women directly depends on the degree of obesity.

Keywords: bone density, obesity, composite body composition.

Introduction. The postmenopausal period is characterized by a decrease in female sex hormones, leading to a change in metabolic processes in the body, which in further causes the occurrence of metabolic disorders and may become the basis of metabolic diseases, such as osteoporosis, obesity [3]. Both diseases can be present simultaneously in one patient, repeatedly enhancing its pathological effect, which is one of the reasons for the highlevel morbidity and mortality [8].

Osteoporosis (OD) refers to multifactorial metabolic diseases. a skeleton characterized by a decrease in bone mineral density (BMD) and violation of its microarchitectonics, causing deterioration of bone strength and high risk of fractures [5]. Currently, OP is one of the main reasons of disability, reduced quality of life and premature mortality of the elderly people [1]. The main risk factors and causes of metabolic disorders in the bone tissues are: a decrease in the level of sex hormones, female gender, insufficient body weight, fractures in parents, insufficient or excessive physical activity, the presence of concomitant diseases and the use of drugs that affect bone the cloth. Female gender is one of the risk factors for osteoporosis, since onset of menopause, they lose bone mass from 0.86 to 1.21% per year, unlikemales from 0.04 to 0.90% [5]. Adipose tissue consists of adipocytes, is a variety of connective tissue and performs heat-insulating in the body, energy, endocrine function [4]. With obesity, excessive accumulation of subcutaneous and visceral fat. In the postmenopausal period, more than 50% of women begin to develop obesity or it progresses [7,9,22]. After menopause, as a result of decrease in female sex hormones becomes most noticeable accumulation of visceral fat (abdominal obesity). Also during this period 25–40% of women develop OP [9.27]. Adipose tissue performing endocrine function, may affect bone tissue alone or through adipokine production [9]. Using the dual-energy X-ray method absorptiometry has made it possible to selectively measure the amount of mineral, fat and lean mass and explore the relationship between body componentsin recent years [2].

Results of studies on the relationship between fat and bone fabrics are quite controversial. According to a number of studies, obesity can lead to an increase in bone mineral density (BMD) due to a higher level of estradiol and increased mechanical stress [10,11, 18,19, 24]. Other studies show that excess fat mass cannot protect a person from osteoporosis, and an increase in adipose tissue leads to a decrease in BMD, since an increase in visceral fat is associated with higher levels of pro-inflammatory cytokines, which increase the activation of osteoclasts, which, in turn, in turn, leads to an increase in bone resorption and, consequently, to a decrease in BMD [13,14,16,17,25]. Premaor M. et al. In their study showed a significant increase in the risk of hip fracture in postmenopausal women with obesity [20]. Today there is growing evidence that with visceral obesity and metabolic syndrome, bone tissue becomes even more fragile, causing an increased risk of low-energy fractures [19]. The results of biochemical studies reveal lower rates of bone formation in obese women [11]. It is believed that increased body fat inhibits the formation of new collagen structures. With the discovery of bone marrow obesity, researchers focused on the role of adipocytes in the bone marrow and their effect on bone formation and the development of osteoporosis [8]. To date, the question of the effect of adipose tissue on bone mineral density remains ambiguous and requires further study.

The purpose of this study is to study the relationship between the degree of obesity and bone mineral density (BMD) in women in postmenopausal period living in Yakutia.

Materials and methods: In a one-shot observational study, a simple random sample involved 147 women in postmenopausal period living in Yakutsk with a body mass index (BMI)> 25, which corresponded to overweight (World Health Organization, 1997). The average age of the subjects was 61 ± 6.6 years, the period in menopause was 14 ± 6.8 years. All patients were divided into 4 groups by type of obesity: group I - pre-obesity (BMI = 27.39 ± 1.3; n = 64); Group II - obesity I Art. (BMI = 32.21 ± 1.5; n = 52); Group III - obesity II tbsp. (BMI = 36.71 ± 1.2; n = 24); Group IV - obesity III tbsp. (BMI = 43.67 ± 1.8; n=7). Research was carried out in compliance with ethical standards (opinion of the ethics committee, protocol No.7 of September 12, 2016). All subjects received voluntary written consent to participate in the survey. Exclusion criteria were refusal to participate in the examination, all clinical manifestations of atherosclerosis, endocrine diseases accompanied by overweight, diseases that cause secondary osteoporosis, malignant diseases, taking drugs that affect bone and fat metabolism.

The examination was performed on a GE Lunar iDXA X-ray axial densitometer (USA). We had analyzed (AP Spine) BMD for L1–4 (g/cm2), (Dual Femur) femoral neck, evaluated the T-criterion (comparison with normal peak bone mass) and the total amount of minerals (g). To determine the composite composition of the body (the absolute and relative amount of fat, muscle and bone tissue), the program (Body Composition) was used.

To process the research data, we used the package of statistical processing of experimental data on MS Excel and the statistical program Stat Soft STATISTICA Automated Neural Networks 10 for Windows Ru. Verification of the laws of normal distribution was done using the Kolmogorov-Smirnov criterion. To identify the relationship between the studied parameters, a Pearson correlation analysis (r) was performed. Comparison of two independent groups in quantitative terms with a normal distribution of values was carried out using the modified Student criterion. Statistically significant results are recognized at p<0.05.

The results of the study. BMD in the lumbar vertebrae (segments L1-L4) in women with obesity in the postmenopausal period was higher than in women with obesity (Pic. 1). A direct correlation was obtained (r = 0.60) between BMD and body mass index (BMI). The highest BMD was found in women of group IV (p <0.001).

The study of the composite composition of the body of women was carried out in all groups, where fat and muscle mass were separately considered (Pic.2). The results obtained indicate that with obesity of I and II degree, the ratio of adipose tissue to muscle, equal to 0.86, is the same as in women with obesity (group I). In group IV, with III degree obesity, the proportion of adipose tissue exceeds muscle tissue and their ratio becomes more than unity (1.04). A statistically significant decrease in muscle mass in group IV, compared with other groups, is not an isolated process, but occurs with the simultaneous accumulation of fat mass (Pic. 2). The proportion of adipose tissue in total body weight in women with grade III obesity (group IV) was significantly higher than in women in all other groups (p<0.001).

In women with grade III obesity, a statistically significant positive relationship was found between BMI, BMD of the lumbar spine and adipose tissue mass (r = 0.61), and a negative correlation between BMI and muscle mass (r = - 0.57) (Pic.3).

Examination of women revealed asymmetry of the BMD in the left and right femoral neck (Pic. 4). BMD in the left femoral neck in all groups of examined

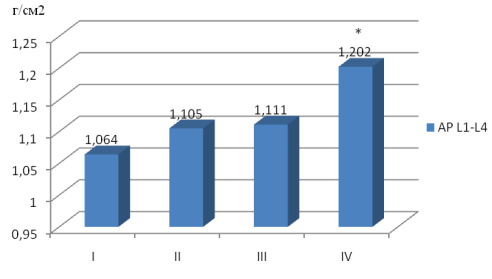

Fig. 1. Mineral bone density (BMD; g/cm 2) in the lumbar spine (segments L1-L4) in postmenopausal women in groups with different body mass index (BMI)
* significance of differences with group I - p < 0,0001; with group II - p = 0.0039; with group III - p <0,042

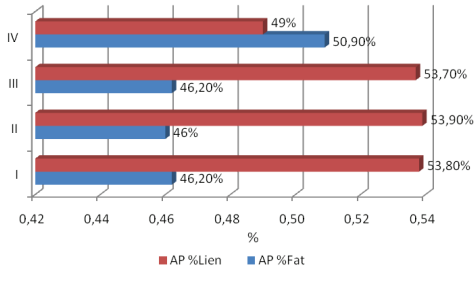

Fig. 2. The ratio of fat (Fat) and muscle mass (Lien) (%) depending on the degree of body mass index

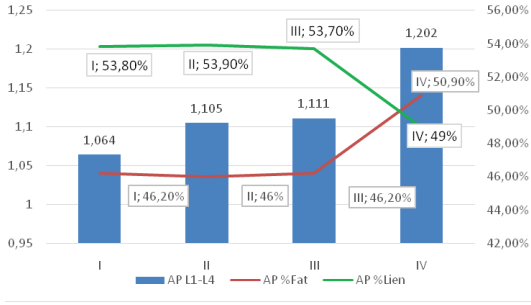

Fig. 3. The ratio of fat (Fat), muscle mass (Lien) (%) and bone mineral density (AR L1-L4) in the lumbar spine in groups

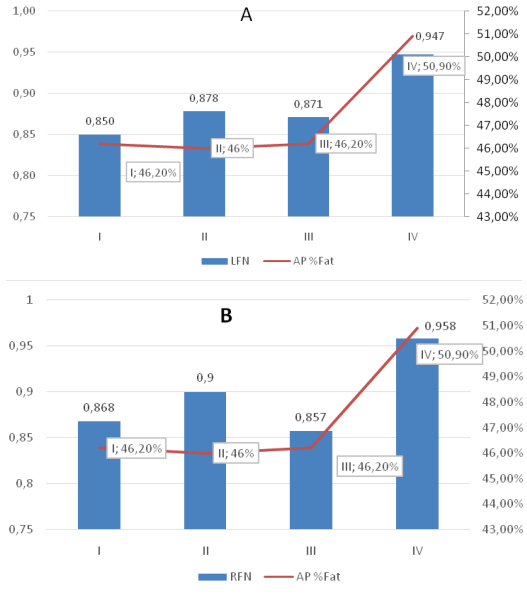

Fig. 4. Bone mineral density of the left (LFN; A), right (RFN; B) neck of the femur and% ratio of fat mass (Fat) in the lumbar spine of women in the postmenopausal period

obese women was higher than in group I (Pic. 4A). In group III, BMD of the right femoral neck was lower than in women with obesity (Pic. 4B).

Women with obesity from group II to group IV is detectedan uneven growth in BMD. In group III, bone mineralization in the femoral neck both on the left (LFN) and on the right (RFN) was lower than in group II. When studying BMD in the area of the femoral neck in group IV, a direct statistically significant moderate relationship was found with the mass of adipose tissue (r = 0.449) (Pic. 4). With an increase in the body above 50% of the mass of adipose tissue, the BMD increases.

The discussion of the results. The study of the relationship between the degree of obesity and BMD in postmenopausal women living in the conditions of Yakutia is of particular interest due to the fact that people living in extreme climatic conditions of the North show a high level of psycho-emotional stress, high morbidity and rapid progression of chronic non-infectious diseases, acceleration aging processes, the earlier onset of menopause and a reduction in life expectancy [5].

As a result of studying the relationship between BMI and BMD of the axial skeleton in women in the postmenopausal period living in Yakutia, a direct significant correlation between these indicators was revealed (r = 0.60). In the modern literature, information about the relationship between obesity and osteoporosis in women in the postmenopausal period is quite contradictory [15,16,20-23,25]. This is probably due to the fact that the researchers did not divide the subjects into groups according to the degree of obesity and the results of the study depended on the proportion of individuals with varying degrees of obesity in the sample. Since BMI is associated with obesity, we tried to analyze the relationship between BMD and the degree of obesity. The study of composite body composition in women with abdominal obesity of the first and second degree indicates that the ratio of muscle and adipose tissue does not significantly change in these groups. The highest BMD values were found in women with III degree of obesity ($p<0.001$), in whom an increase in the proportion of adipose tissue (more than 50%) with a decrease in the proportion of muscle tissue leads to an increase in the mineral density of the spongy bone tissue of the axial skeleton (spine, femoral neck), which can be considered as an adaptive protective reaction of the body.

Since ovaries no longer secrete estrogen in postmenopausal women, extragonadal synthesis of estrogen in adipose tissue becomes the dominant hormone, therefore, during this period, the role of adipocytes as estrogen producers can become quite important for bone metabolism [28]. It is possible that in women with III degree obesity, the revealed positive relationship between adipose tissue and BMD is associated with increased estrogen synthesis in adipose tissue, which may also be one of the potential mechanisms of the body's adaptive protective reaction.

Conclusion. The body mass index statistically significantly affects the mineral density of bone tissue, while the ratio of muscle tissue to adipose tissue is very important. The increased mineralization of the bone tissue of the axial skeleton in postmenopausal women directly depends on the degree of obesity.

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SCIENTIFIC REVIEWS AND LECTURES

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FEATURES OF THE COURSE AND MODERN DIAGNOSIS OF CHRONIC HEART FAILURE ON THE BACKGROUND OF COMORBID ASSOCIATIONS

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The review presents current information on the course of chronic heart failure on the background of comorbid associations. Special attention is paid to the peculiarities of the course of heart failure on the background of rheumatological diseases.

The authors evaluate epidemiological indicators, as well as the most relevant studies and meta-analyses devoted to this topic. Modern methods of diagnostics of myocardial morphofunctional parameters in this group of patients are presented, in particular, the possibilities of two-dimensional spectral-tracking echocardiography are presented.

The data of actual researches concerning the use of such immunological markers as galectin-3, pentraxin-3, adiponectin and cystatin-C are presented.

Keywords: chronic heart failure, comorbidity, modern diagnosis of CHF, prognosis.

Chronic heart failure is one of the most common cardiovascular diseases (CVD), and belongs to the category of so-called chronic noncommunicable diseases (CVD). The prevalence of CHF continues to grow steadily, naturally prompting new questions of diagnosis and therapy tactics. Due to the active development of pharmacological approaches in the treatment of CHF, including CHF, the life expectancy of patients is increasing. In this regard, practitioners have to deal with an increasing number of cases of associations of various diseases in one patient. This phenomenon inevitably leads to difficulties in the management of such a patient, as there is a significant number of factors and relationships leading to undesirable consequences, worsening the course of both the underlying disease and concomitant, increasing the number of re-hospitalizations. It is also worth noting the impact of this phenomenon on the health care system as a whole, as the combination of several diseases in one patient leads to an increase in the cost of its treatment.

This relationship is described in the literature as comorbidity. By this term, experts mean the coexistence of two or more diseases in one patient, pathogenetically and genetically interrelated. It is necessary to emphasize that the term multimiorbidity, used as a synonym, is often found. However, multimorbidity is a combination of several chronic diseases of various origins in one patient. In this case, no causal relationship is implied. Therefore, when describing this problem, it is logical to use the term comorbidity [5].

Comorbidity and chronic heart failure. Among the chronic noncommunicable diseases having significant relevance in this matter it is necessary to highlight the cardiovascular disease. Cardiovascular diseases (CVD), despite the enormous advances in medicine and pharmacy, remain the most common pathology throughout the world, and are the first cause of death in developed countries. The classic ending of the most common CVD is chronic heart failure, the prevalence of which in Western countries reaches from 1 to 2% in the general population, reaching 10% in people over 70 years of age [19]. The absolute number of people with CHF has doubled in the last 20 years: from 7.18 to 12.35 million people [8]. This phenomenon is due, according to experts, oddly enough, modern advances in medicine in this area. However, an increase in the life expectancy of patients with CHF does not lead to an increase in the number of cases of repeated hospitalization, an increase in the financial burden on patient households and on the health care system as a whole. According to WHO, the global cost of treatment of CVDs is about 863 billion US dollars annually. Approximately 10% of this amount is due to heart failure. Experts predict a further increase in the financial burden due to continued urbanization, increased life expectancy and population aging [24].

Cardiovascular comorbidity in the context of heart failure is a phenomenon with a high prevalence. For patients with CHF, this phenomenon is of particular relevance. It is quite difficult to specify specific numbers of the prevalence of certain comorbid conditions against a background of insufficiency, since it depends on many different factors: the level of medical care of a particular region or country, incomes of the population, the quality of tracking patients with these conditions. It is also necessary to take into account unregistered patients with asymptomatic heart failure [14].

The most complete and objective information on this issue is provided by experts from central Europe and the USA. According to the European register EHFSII which includes 3580 patients with CHF of all functional classes with an average age of 70 ± 13 years, the most common comorbid associations in CHF are atrial fibrillation (AF) - 39%, type II diabetes mellitus - 33% and chronic kidney disease (CKD) III and IV stages - 17% [18].

However, compared with the ADHERE registry (USA) in patients with heart failure, the most common associated condition is anemia - 53%, then type II diabetes - 44%, AF and chronic obstructive pulmonary disease - 31% and CKD stage III and IV - 30% [12]. The high frequency of occurrence of anemia is associated with manifestations of cardiorenal syndrome.

It has been proven that the above-described conditions are the leading causes of worsening of the course of CHF, regardless of its etiology and stage,

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which inevitably leads to an increase in the number of repeated hospitalizations and a worsening prognosis. The described data demonstrate the dominance of diabetes among these states.

According to the meta-analyzes of randomized clinical trials, SOLVD, RESOLVD, BEST, ALLHAT and others showed a significantly high frequency of repeated hospitalizations with CHF decompensation and renal function compared with patients without diabetes [15]. According to DIABHYCAR, the annual mortality rate of patients with CHF on the background of diabetes is 12 times higher [14].

A special topic of active research in recent years has been the peculiarities of the course of CHF against the background of liver pathology, oncological diseases, in particular, issues of chemotherapy. For example, cardiotoxicity problems are actively discussed when using drugs of the anthracycline series [16].

According to experts, the systemic inflammatory process should be singled out among the actual mechanisms of development of CVD, in particular, CHF, as well as the causes of its decompensation. The relevance is CHF in combination with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), osteoarthritis (OA).

It has been shown that it affects the progression of heart failure. Interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and C - reactive protein (CRP). Patients with this association have an increased risk of developing cardiovascular events [7,20].

There are a number of specific mechanisms that significantly aggravate the course of heart failure. First of all, it is worth noting the decline in quality of life. For various numerous studies, the most informative questionnaires in this aspect are the SF-36 and Charlson questionnaires. There is a significant deterioration in the indices of physical activity, psychoemotional state, vital activity, and general health [2, 1].

Current diagnostics of heart failure. When analyzing the problems of diagnosing heart failure associated with various clinical conditions, the issue of timely diagnosis of CHF, as well as the identification of the morphological and functional features of the myocardium in this group of patients is relevant. Especially worth noting patients with intact of LVEF. In this category, basic diagnostic criteria do not provide a complete picture of clinical features. It is also necessary to understand that the detailed estimated specific morphofunctional parameters can be used in models, according to the forecast for this category of patients.

Regarding echocardiography, it is worth noting two-dimensional spectral-tracking technology with the definition of global longitudinal strain. This indicator is a non-Doppler indicator, and, therefore, angle-independent, which allows increasing the objectivity of the results. In contrast to the pulse-wave mode, this technology allows you to determine the systolic longitudinal function, regional longitudinal systolic deformation of 17 segments at three levels (basal, medial and apical) with automatic formation of a map. According to experts, the value of systolic dysfunction with the definition of its depth and comparison with other morphofunctional parameters on the background of intact LV EF can be significant parameters for the formation of cardiac risk groups at the preclinical stage of disease development [22].

Absolutely absolute criterion for the diagnosis of heart failure today is the use of natriuretic peptides. To date, it has been established that an increase in these markers in the blood is associated with decompensation of CHF and a worsening prognosis for the disease. Also, the use of this marker allows for a detailed differential diagnosis [13].

Among the most common clinical associations with CHF is a link with metabolic syndrome and diabetes. In this regard, markers that regulate energy homeostasis, fibrosis and myocardial hypertrophy are of interest. These include adiponectin. It is believed that the development of diabetes mellitus type 2 and insulin resistance are associated with impaired secretion of adiponectin. The prognostic significance of adiponectin in patients with CHF is currently not well understood. However, according to some studies, it has been found that in patients with heart failure with CHD, a low level of adiponectin is associated with diastolic dysfunction [23].

Progressive deterioration of renal function is the most important prognostic factor for the adverse outcome of chronic heart failure [3, 5]. In this relationship, against the background of studying the dynamics of the natriuretic peptide, it is worth highlighting the role of cystatin C as a marker of the predictor of the development of chronic kidney disease and target organ damage [10].

The last few years have been actively discussing the mechanisms of the influence of chronic inflammation on the development, course and prognosis of heart failure. This relationship is particularly relevant for patients with heart failure in the background of inflammatory diseases of the joints. In this aspect, it is worth highlighting such markers as galectin-3 and pentraxin-3. There is an opinion of experts about the possibility of using galectin-3 as a marker of the effectiveness of treatment of RA [16]. Observations of an increase in the level of galectin-3 in the presence of a positive antibody titer to cyclic citrulline peptide are described: 4.2 μg / ml (3.6; 6.1) versus 3.8 μg / ml (3.0; 4.8); p <0.01 in the control group [17]. In relation to pentaxin-3, data on the use of this protein in patients with autoimmune diseases have been published. In particular, in a meta-analysis (China) in 20 studies in patients with RA, systemic lupus erythematosus, ankylosing spondyloarthritis, and multiple sclerosis, a significant increase in pentaraxin-3 was observed compared with healthy individuals (p <0.001) [11]. There are no studies on the significance of this marker in patients with comorbid status in heart failure, however, given the high prevalence of the above diseases in CHF and the relevance of the subject of inflammation in CVD, this marker is likely to have significant interest in the future.

Among modern markers that are currently undergoing active research, it is worth highlighting the growth factor of differentiation (RDS-15), osteopontin, kopetin. Studies on these cytokines are local and do not have broad evidence. However, already now there is evidence that these markers have significantly greater specificity with respect to the myocardium compared to standard acute phase proteins, as well as inverse correlation with the parameters of myocardial contractility [21,25,26].

Conclusion. Today we can confidently assert that CHF is a pathology that needs a multidisciplinary approach from different specialists. Patients with the above clinical associated conditions should be examined not only within the framework of a clinical standard. Especially it concerns the assessment of morphofunctional parameters of the myocardium and prognosis of heart failure. In general, the problem described requires further research and development.

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BIOMARKERS OF EPILEPSY

More than 50 million people worldwide suffer from epilepsy. Almost in 30% of cases it is not possible to achieve control over attacks, despite the use of a wide range of antiepileptic drugs, and surgical treatment. To date, there are no methods of treatment and prevention of the development of epilepsy in people at risk. All this indicates the need for a search for biomarkers of epileptogenesis, diagnosis, disease progression, drug response and treatment safety.

As biomarkers of epilepsy, the following are considered: electrophysiological changes, the presence of a clinical attack, genetic changes, micro ribonucleic acid (microRNA) of plasma / serum / cerebrospinal fluid; protein biomarkers, plasma exosome biomarkers, cerebral cortex microRNAs; biomarkers, strain gauge images / diffusion-weighted images of magnetic resonance imaging (MRI).

The authors review the literature on modern studies of various biomarkers of epilepsy, which allow a personalized approach to assessing the diagnosis, treatment and response to epilepsy therapy.

Keywords: epilepsy, epileptic seizures, biomarkers, microRNA.

Introduction. According to epidemiological studies, today there are more than 50 million people diagnosed with epilepsy in the world, of which control over epileptic seizures is achieved only in 70% of cases, despite the use of various combinations of antiepileptic drugs (AED). The remaining group consists of patients with uncontrolled epileptic seizures, the search for control over which is an important and urgent problem that requires the development of new approaches, both in the diagnosis and treatment of epilepsy [15].

The relevance of the search for new non-invasive biomarkers for the diagnosis of epilepsy is high due to the fact that there are no diagnostic approaches and therapeutic methods to timely identify, suspend or weaken the process of epileptogenesis in individuals at risk for the formation of epilepsy [25]. Further research on the search for new biomarkers of epilepsy will allow the formation of informative and accessible test systems that will help in the diagnosis of the disease [12].

A biomarker is an indicator used to evaluate normal or pathogenic biological processes, as well as responses to various effects on the body, including therapeutic interventions [7].

Currently, active research is underway to search for biomarkers in cancer [26], some neurodegenerative diseases, such as Alzheimer's disease [17], the developed strategies can be applied to the search for biomarkers of epilepsy.

In this practice, the biomarker must meet the following criteria: specificity, sensitivity, predictive value, reliability and availability. Biomarkers have different characteristics: molecular, histological, radiological and physiological.

In 2015, the US National Institutes of Health, in conjunction with the Food and Drug Administration, the National Institutes of Health and the Food and Drug Administration (FDA-NIH) developed the classification of biomarkers "The BEST biomarker categories", which includes: biomarkers of risk of disease; diagnostic biomarkers; biomarkers monitoring; biomarkers prognosis (prognostic); predictive biomarkers; pharmacodynamic biomarkers (biomarkers of drug response (PM)); biomarkers of therapy safety [11].

The boundaries between different categories of biomarkers are not strict. A single biomarker can be divided into subtypes and included in several categories depending on when and how often it is measured. Development of new biomarkers takes place in the process of analytical and clinical validation with demonstration of clinical significance [17].

About 30 publications in the last 4 years are devoted to the study of different types of biomarkers in the field of epilepsy: plasma / serum / liquor microRNA; protein biomarkers, plasma exosome biomarkers, cerebral cortex microRNA; biomarkers, strain / diffusion-weighted MRI images; electrophysiological biomarkers: diagnosis of epilepsy [18, 24], temporal epilepsy [27], idiopathic generalized epilepsy [8] pharmacoresistant epilepsy [12]. None of the found biomarkers is currently used in wide practice for the diagnosis of epilepsy, and the need to search for such remains relevant [7].

Let us consider the main biomarkers of epilepsy.

Diagnostic biomarkers. Diagnostic biomarkers are used to identify or confirm the presence of a disease for which treatment can be indicated. Diagnostic biomarkers of epilepsy include markers of epileptogenesis, drug resistance, and high risk of epileptic status. Some of the biomarkers of epileptogenesis can be considered as prognostic for individuals who have suffered acute cerebrovascular accident. Also, prognostic indicators include the outcome of surgical treatment of epilepsy and prognosis of conservative treatment. The «gold» standard for diagnosing epilepsy is epileptic seizures. Epilepsy is a disease with heterogeneous etiology and, as a consequence, with different outcomes/prognoses and responses to therapy [20].

The «gold» standard for the diagnosis of epilepsy is the occurrence of a clinical

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or electrographic epileptic attack, which is used as a reference diagnosis at the stage of determining the epileptic or non-epileptic nature of the attack. However, there are many situations where an epileptic seizure occurs as a natural, acute, symptomatic or provoked event in response to a transient pathological condition [5] that does not guarantee a diagnosis of epilepsy. Many people who experience provoked or reactive epileptic seizures do not have epilepsy.

According to the WHO, up to 10% of people worldwide suffer a single epileptic attack, which does not indicate the presence of epilepsy, since the following criteria must be met for diagnosis: 1) at least two unprovoked (or reflex) epileptic attacks with an interval of more than 24 hours; 2) one unprovoked (or reflex) attack and the probability of recurrence of attacks close to the overall risk of relapse (≥60%) after two spontaneous attacks in the next 10 years; 3) diagnosis of epileptic syndrome [4,20].

A type of clinical or electrographic attack serves as a predictive biomarker for the response to antiepileptic therapy. Different genetic markers (for example, genes for epileptic encephalopathy) associated with a particular type of epileptic seizure can predict the course of the disease, that is, they are also predictive biomarkers. Thus, a diagnostic biomarker (in this case, a clinical or electrographic attack) can not only identify the disease, but also be used for diagnostic classification, and therefore serve as both a prognostic and predictive biomarker of epilepsy [7].

Prognostic biomarkers. Prognostic biomarkers are used to determine the prognosis of a disease, its relapse or progression, for example, biomarkers for assessing the development of cognitive impairment in patients with epilepsy. Prognostic biomarkers differ from disease risk biomarkers because they apply to groups of people with epilepsy who receive or do not receive therapy [7]. It is important to note that the type of AED can affect the sensitivity and specificity of prognostic biomarkers in the differential assessment of results. The response to the treatment methods used may vary. Most often and more expectedly, this is a decrease in the symptoms of the disease, with an improvement in the survival rates of patients, however, in some cases it is necessary to face the development of adverse effects [15].

Prognostic biomarkers can be used in studies to stratify patients with epilepsy into biomarker-positive and biomarker-negative treatment groups, with the main endpoint being the effect in the biomarker-positive group of patients. Studies of prognostic biomarker-positive subjects are important to demonstrate the potential for the development of research methods of treatment, for example, antiepileptic drugs. It is important to note that prognostic biomarkers for assessing the effectiveness of the treatment of epilepsy may be characteristics of a person's biological constitution or the disease process itself. For example, the type of epileptogenic brain damage (structural changes) or the patient's genetic characteristics (genetic epilepsy variants) can predict the response to a particular probe, emphasizing the relevance of a personalized approach and further research to find new prognostic biomarkers. Gallek et al. (2016) found that the carriage of a combination of genes: ZNF852, CDCP2, PRRT1, FLJ41170 with downregulation of expression in the lateral temporal cortex of the brain is a predictive biomarker of a positive outcome for the surgical treatment of epilepsy [13].

Pharmacodynamic biomarkers. Pharmacodynamic biomarker or response biomarker – used to prove the occurrence of a biological reaction in response to exposure to a medical product or environmental factor. Changes in pharmacodynamic biomarker levels in response to treatment it may provide information that it is biologically active and / or has an impact on the clinical end point, in addition, it becomes possible to determine the range of doses of the drug for further therapy, its duration, as well as to predict the risk of adverse reactions. Pharmacodynamic biomarkers require serial evaluation, as a result of which they often fall under the category of monitoring.

To date, only one of the published studies searching for markers of epilepsy has evaluated pharmacodynamic biomarkers / response biomarkers. Walker L.E. et al. (2017) on an animal model of epilepsy showed that treatment with anakinra / BoxA / ifenprodil prevents the increase in the level of amphoterin protein (high-mobility group protein B1 - HMGB1) in blood plasma in rats with epileptic status. HMGB1 is a key activator of inflammation after the development of an epileptic seizure [24]. However, the assessment of HMGB1 level was carried out only during treatment without studying the effect after treatment and the dose-dependent effect [15, 24].

Monitoring biomarkers. A biomarker of monitoring is an indicator measured sequentially to assess the state of a disease in order to prove the effect of a medical product or environmental factor. The sequential nature of the measurements allows us to record changes in the values of the biomarker as an indicator of the current state of the person. Thus, the category of monitoring biomarkers may include other groups of biomarkers represented in the classification when they are measured sequentially. As an example, the registration on the electroencephalogram of epileptic spikes, complexes «acute-slow wave» in the cortical region, corresponding to the site of brain damage (for example, with craniocerebral trauma).

Safety biomarkers. Safety biomarkers are indicators measured before or after exposure to a medical product or environmental factor to determine the likelihood, presence, and toxicity of an adverse effect. One of the tasks, in this case, is to identify the risk group among patients with epilepsy, for which should not be prescribing some AED because of the significant risk of adverse reactions [1]. Genetically determined changes in liver cytochrome P450 enzyme activity and glucuronidation are examples of safety markers for patients taking AED. Markers of drug response safety include pharmacogenetic features of pharmacokinetics, pharmacodynamics and safety of AED. For example, single-nucleotide variants (SNV) of cytochrome P450 genes, uridine-5' - diphospho-glucuronosyltransferase determine the peculiarities of metabolism of many anticonvulsants, one of which is valproic acid (VA). To date, algorithms have been developed for personalized dose selection of VA in patients with epilepsy, taking into account the carrier of the SNV gene CYP2C9*2 and CYP2C9*3, which minimizes the risks of adverse reactions [2, 3, 6].

Biomarkers susceptibility / risk biomarkers. Susceptibility/risk biomarkers indicate an increased or lower risk of epilepsy in a healthy person.

For example, an animal model showed that CD1 mice carrying the APP/PS1 gene mutation had a higher risk of epilepsy after traumatic brain injury (TBI) [29]. Thus, biomarkers of susceptibility / risk allow identifying individuals at risk of epilepsy in need of dynamic monitoring, as well as actualize the use of preventive measures.

Currently, much attention is paid to neurophysiological and neuroimaging biomarkers of epilepsy diagnosis. However, there are no screening diagnostic biomarkers of epileptogenesis [14]. The development of new methods

of treatment of epilepsy remains a priority international direction of modern research [22]. The search for new biomarkers of epileptogenesis is laborious, including because, this requires long-term EEG monitoring. The only known serum biomarker confirmed on an animal model of epilepsy is the level of amphoterin (B1 – HMGB1). The study of its concentration makes it possible to differentiate epileptogenic and non-epileptogenic zones of the rat brain after epileptic status [24]. Therefore, for the diagnosis of epilepsy, the search for non-invasive or minimally invasive, informative and cost-effective biomarkers continues.

Recently, microRNA research has been proposed as new biomarkers that meet the requirements [18].

MicroRNAs are candidates for use as biomarkers in cardiovascular, oncological diseases, acute conditions: ischemic strokes, traumatic brain injuries [10, 23].

Several microRNAs have been shown to be involved in regulating cholesterol in the brain, disorders in the metabolism of which can trigger neurodegenerative diseases such as Alzheimer's disease, Nieman-pick type C disease, Smith-Lemley-Opitz disease, Huntington's disease and Parkinson's disease [28].

In psychiatric practice, miRNAs are considered for the diagnosis of depressive disorders, schizophrenia, autism spectrum diseases [19].

A prerequisite for the use of microRNA as a possible biomarker of epilepsy is stability in serum. In addition, it is a good study of the levels of expression in brain tissues and peripheral blood circulation in animal models of epilepsy [12, 18], as well as the availability of separate data on changes in microRNA levels in both peripheral blood and brain tissues of epilepsy patients [12, 15].

Over the past 5 years, several targeted and wide-genomic studies of miRNA expression in epilepsy have been carried out. According to the obtained these changes were found in more than 100 different microRNAs in the animal model and in patients with epilepsy, which proves the relationship of microRNA expression levels with epilepsy [12, 30].

MicroRNAs are an important class of small non-coding RNAS that play a critical role in brain development and function. New studies show that the levels of several microRNAs vary as a result of convulsive activity in animal models, and also differ in those areas of the brain from which seizures occur in patients with epilepsy (for example, the hippocampus) [16].

However, most of these studies were performed using small samples and / or without a control group. The vast majority of studies do not report any limit values of biomarkers, allowing differentiating epilepsy with the control group [15]. The specificity of epilepsy biomarkers in comparison with other brain diseases important for differential diagnosis is insufficiently studied. Problem related to investigation of epilepsy biomarkers associated with the use of anticonvulsants [21] regulate microRNA expression. On the other hand, the use of other drugs may also affect the analysis of biomarkers [9].

In the future, the search for biomarkers will form test systems and improve the diagnosis of epilepsy and epileptogenesis.

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КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА СПОСОБОВ БЛОКАДЫ НИЖНЕГО ЛУНОЧКОВОГО НЕРВА

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Nowadays the improvement of health care system in long-term state policy is of great importance which is based on the development and adaptation of innovative technologies. At the same time dental help to the population is the most massive that is connected with the prevalence of pathological processes of organs and tissues of the oral cavity where methods of inferior alveolar nerve block are widely applied.

There is a set of anesthesia methods that have various technological and methodological features for inferior alveolar nerve block. At the same time, the general point for all types of anesthesia is anesthetic injection into the mandibular foramen area and the upper back quadrant of the branch of the lower jaw where a set of anatomical-topographical markers, which the dentist when performing local anesthesia, has to present accurately for himself, is used. Anatomical-topographical features of the inferior alveolar nerve allow carrying out this block by extra- and intraoral access. The extra access is submalar method through the lower jaw incisure, a submaxillary method – from bottom edge of the lower jaw and from the edge of the lower jaw branch.

Palpation, portiligature methods of mandibular anesthesia and also torus anesthesia are often used in clinical dentistry among intraoral methods of anesthesia. Vazirani-Akinosi, Laguardia and Egorov-Lapis' methods are applied for inferior alveolar nerve block in clinical situations connected with restriction opening of the mouth. Besides, the stem anesthesia at oval foramen by S.N.Waisblat's method is used for the mandibular nerve block. This technique is used when carrying out the traumatic operations demanding anesthesia in the field of tissues of the whole lower jaw. Gow-Gates's method has its peculiarity which characterizes its efficiency of anesthesia in the conditions of tissues inflammation of the lower jaw. The submalar method is used by Bershe (1922) and P.M. Egorov (1985) methods, where there is a relaxation of chewing group of muscles due to deactivating of motion branches of the mandibular nerve. It should be noted that the modified intraoral mental anesthesia, recommended by S. Malamed, is applied.

In general, methods of inferior alveolar nerve block are widely used in clinical dentistry for treatment-and-prevention. A set of anatomical-topographic points is used that demand certain experience and skills of the doctor causing some difficulties. This situation needs the improvement of mandibular anesthesia methods for maximum anesthesia technology simplification with complex clinical, laboratory and functional researches that will promote further safety and analgesic effect.

Keywords: lower jaw, anatomy and topography, inferior alveolar nerve, mandibular anesthesia, extra - and intra oral methods, maxillary artery, efficiency and safety of anesthesia.

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Nowadays the priority tasks of health care development are quality improvement of the provided medical care by introducing of the innovation technologies, having positive impact on strengthening and maintaining health of the population [2, 15, 26, 32]. In clinical dentistry, one of the key factors is adequate anesthesia which is constantly improving and searching of effective methods [1, 25].

It should be mentioned that there is a set of anesthesia methods which have various technology and methodological features for inferior alveolar nerve block [3, 4, 6, 18, 28, 29]. The general reference point for all types of anesthesia is anesthetic administration to the area of mandibular foramen and upper back quadrant of the mandible branch [3, 4]. At the same time the dentist uses a set of anatomical-topographical reference points when performing a local anesthesia. So, 11 approximate points of a needle, 6 directions of needle advance in horizontal position and 5 – in vertical position, 9 "targets-points" directly in the field of mandibular foramen and 12 – on mandible branches where the needle contacts with an internal surface of a mandible branch are applied for orientation. Such situation

causes certain difficulties in memorizing anatomy and topography of organs and tissues of the oral cavity, maxillofacial area and performance of the existing methods of inferior alveolar nerve block [3, 4, 21, 29].

It is necessary to emphasize that anatomical-topographical features of the inferior alveolar nerve allow carrying out its block with extra and intraoral accesses [3, 4]. At the same time, subjugal method refers through mandible incisure, a submaxillary method -extraoral access – from bottom edge of a mandible and from the rear edge of a mandible branch. The subjugal way is used at Bershe's (1922) and P.M. Egorov's (1985) methods where there is a relaxation of chewing group of muscles due to deactivating of motion branches of a mandibular nerve [17]. At the same time there is a relaxation of the muscles lifting a mandible, and these methods of anesthesia are used at inflammatory contracture of a mandible. Also there is Bershe-Dubov's method differing in depth of 1 cm needle injection deeper further when lower alveolar and lingual nerves are blocked as well as masticator nerve. At the same time there are difficulties with depth of needle immersion and a possibility of salpinx large vessels trauma. The submaxillary method is used at the complicated opening of the mouth and has difficulties of a needle depth injection. Access from the rear edge of a mandible branch is accompanied by passing of a needle through a parotid salivary gland where external carotid artery and branches of a facial nerve are located that causes the probability of development of complications of traumatic character [3, 4, 18].

Today mandibular anesthesia is widely applied at dental out-patient, polyclinic and in-patient departments [5, 9]. Palpation, portiligature methods of mandibular anesthesia and also torus anesthesia are often used in clinical dentistry among intraoral methods of anesthesia.

Gow-Gates method has its pecularity which characterizes its efficiency in the conditions of inflammation of mandible tissues [23, 29]. It is connected with simultaneous block of inferior alveolar, lingual, maxillary and hypoglossal, ear-temporal and buccal nerves [18, 30]. According to S.A. Rabinovich et al. (1999) adequate anesthesia when using this method is reached in 90–97% of cases, the positive aspiration sample is nearly 10 times less, than at other methods of anesthesia, and local post-injection complications arise extremely seldom [11]. It can be explained by the fact that there are no muscle and large neurovascular bunches on its way of a needle injection and the internal maxillary artery remains below needle advance at the level of mandible incisure. But, at the same time there is a probability of trauma of maxillary artery and pterygoid veniplex [10].

Despite its advantages, the greatest difficulty when performing anesthesia is caused by definition of the direction of a needle immersion into the tissue that is connected with individual intra and extraoral reference points. For elimination of this disadvantage, S.A. Rabinovich and O.N. Moskovits (1999) suggested the manual method simplifying its practical application where only specialists having certain skills and experience can perform it.

According to P.M. Egorov, it is not obligatory to find inferior alveolar nerve by a needle tip in the depth of tissues for effective blockade. High concentration of local anesthetic around the site of this nerve can be created with anesthetic injection in pterygoid and maxillary tissue plane where the nerve passes [18]. At the same time the author of the method conditionally divides an internal surface of a mandible branch into 4 quadrants with two crossed lines. The internal surface of a back upper quadrant of a mandible branch limits pterygoid and maxillary tissue plane. And also the mandibular foramen is defined in the same quadrant. Its upper edge is located in the front bottom corner of a quadrant. The least traumatic and effective for block of the lower alveolar nerve is the middle of the upper back quadrant. It should be noted that the back border of this quadrant is especially dangerous to emergence of post-injection complications. There is the end of pterygoid and maxillary tissue plane and the beginning of parotid salivary gland in which facial nerve branches are located [42]. P.M. Egorov and S.A. Rabinovich (1990) suggest the doctor to carry out orientation by finger-tips. At the same time the long fingertip is placed in the imagined upper back quadrant that will indicate a projection of pterygoid and maxillary tissue plane and a mandibular foramen which will promote adequate anesthesia [3, 4, 23, 31].

The methods of Vazirani-Akinosi, Laguardia and Egorov-Lapis are applied to block of the inferior alveolar nerve in clinical situations connected with restriction opening of the mouth [22, 27]. The efficiency of anesthesia is 80-85%. It is important to emphasize that, despite positive sides, there are certain disadvantages connected with complexity of definition of individual reference points, especially depths of needle immersion, and a high probability of post-injection complications [10, 22].

It is important to emphasize that one more type of conductive anesthesia is torus anesthesia according to M.M. Weisbrem. The anesthetizing solution is entered into the area of the mandibular torus. Anesthesia after solution injection comes in 5 minutes [11, 13, 22]. Meanwhile, the modified intraoral method of mental anesthesia recommended by S. Malamed [58] is practiced. At the same time the level of injury as there is no need, unlike classical mental anesthesia considerably decreases, there is no need of finding of a mental foramen with a needle and advances on the channel that simplifies anesthesia technology as well as increases its safety. After injection and needle removal from tissues, the pressure in soft tissues is kept within 2 more minutes for prevention of outflow of the entered solution from the foramen. Anesthesia comes in 3 minutes [18].

It should be noted that S.N. Waisblat's method for stem anesthesia at oval foramen is used for a mandibular nerve block. This technique is used when carrying out the traumatic operations demanding anesthesia in the field of all mandible tissues. The research of S.N. Waisblat showed that the simplest and available reference point at blockade of the III branch of a trifacial is the external plate of a pterygoid-shaped process of a wedge-shaped bone. The oval foramen is in one plane with an external plate of a pterygoid-shaped process and is located behind it. It is necessary to use a needle of 7-8 cm long for stem anesthesia. Anesthesia comes in 10–15 minutes. Anesthesia zone: all tissues and organs receiving an innervation from the III trifacial branch. This technique is applied extremely seldom that is connected with the probability of complications. It is possible to get to a nasal cavity or an acoustical pipe during performance of stem anesthesia with a needle, therefore, to bring infection to skull. There can be a diplopia, mechanical damage of third cranial nerves. Anesthetic can lead to temporary loss of sight. Injury of internal maxillary and palatal arteries, average artery of meninx, pterygoid-shaped veniplex is possible [40, 42]. Prevention of complications is careful technology anesthesia [7, 12, 14, 31].

It should be noted that also lingual and buccal nerves are located in pterygoid and maxillary tissue plane, in addition to inferior alveolar nerve

[22, 23]. In this regard most patients feel deactivating of the inferior alveolar nerve together with blockade of lingual, and also buccal nerves. When using torus anesthesia of the inferior alveolar nerve, most of patients, as a rule, do not feel pain [20]. Meanwhile, it is necessary to carry out additionally infiltration anesthesia with vestibular party for a total block of a buccal nerve for pain exception [18].

Thus, methods of the inferior alveolar nerve block in clinical dentistry are widely applied where a set of anatomical-topographical reference points demanding certain experience and skills from the specialist which cause certain difficulties. This situation needs the improvement of mandibular anestesia methods for maximum anesthesia technology simplification with complex clinical, laboratory and functional researches that will promote further safety and analgesic effect.

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POINT OF VIEW

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VILIUISK ENCEPHALOMYELITIS AS PRIMARY CHRONIC NEURODEGENERATIVE DISORDER

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The paper presents a new concept of the nature of Viliuisk encephalomyelitis – the unique disease of the Sakha ethnic group as primary chronic neurodegenerative disorder. It is based on an analysis of the participation of TNF superfamily members in the pathogenesis of the disease.

The ligands and receptors of TNF superfamily are key players of important biological processes, including the maintenance of tissue cell homeostasis using immunity mechanisms. It is suggested that sTRAIL ligand induce the loss of neurons in the cases of a primary chronic degenerative process. The sTNFα ligand is associated with an inflammatory complication of this disease under conditions of stress and perhaps participates in the neuronal necrosis in the acute stage. Elevated levels of sCD40L, detected in the plasma of patients, may act as a factor of the development of microvascular pathology, the cause of chronic hypoxia, inducing and supporting chronic processes of brain tissue atrophy.

Keywords: Viliuisk encephalomyelitis, Bokhooror, neurodegeneration, TNF superfamily, sTRAIL, sTNFα, sCD40L.

Introduction. "Bokhooror" is the native name for a rare primary chronic degenerative disease of the human central nervous system, observed among the Yakut population in Yakutia and known to medical science for more than 80 years. Phenotypic manifestations of this disease are associated with paresis of the muscles of the laryngeal area and motor functions caused by damage to the pyramidal, extrapyramidal tracts and the cerebellum. Patients experience difficulties in the initiation of movement, show emotional immobility and loss of socially significant features of the relationship in combination with the problems of reproductive memory. The disease is endemic and sporadic. Group cases of the disease is not observed, but can be traced generic ties [9, 14, 17].

One of the main features of the pathology is brain atrophy (in 83% of patients) and significant decrease of a brain mass, which correlates with the duration of the disease [1, 8]. Pathological findings indicate diffuse atrophy, predominantly of the cerebral cortex, cerebellum, and upper spinal cord, associated with loss of neurons. On the other hand, patients may have an inflammatory episode (about 30% of patients experienced acute encephalitis), which clinically manifests itself as neuroinfectious diseases. The clinic of inflammation that gave the name of the disease - Viliuisk encephalomyelitis (VE), is described and studied in detail by P.A. Petrov, A.P. Shapoval, L.G. Goldfarb, R.S. Tazlova and A.I. Vladimirtsev [2, 3, 6, 7, 9]. In the pathological picture of these patients, on the background of neuronal loss, scattered necrosis foci with an inflammatory reaction in the form of infiltrate in the fibrous membrane of small vessels in the brain parenchyma are added [33]. The infectious nature of this inflammation, despite many years of attempts, did not receive its confirmation, which suggests the idea of its aseptic nature associated with congenital abnormalities of the immune system in patients.

The potential possibility of self-limiting the inflammatory process (indicating a controlled process) and the transition to the chronic degenerative form is a characteristic feature of the acute forms of VE. In recent years, with the improvement of social and living conditions, the inflammatory episodes in patients gradually disappear and the primary chronic form of the disease is widespread. This form develops gradually with age and has the character of a neurodegenerative disease of the brain and spinal cord with a clinical picture according definition "Bokhooror". Another feature of the chronic form of this disease is immunosuppression (immune tolerance) of the pathogenic brain. Patients show pronounced and sustained suppression of the immune system [2, 4].

The causes and mechanisms of atrophy of the brain tissue and induction of a controlled inflammatory process (encephalitis) are main issues, which will allow reveal the pathogenesis and develop the treatment of the disease. The article presents a review of clinical, pathological data, as well as our own research on the immunology of Viliuisk encephalomyelitis, on the basis of which the hypothesis of the pathogenesis of the disease is proposed.

The primary chronic brain degeneration is the basis of the VE disease. In this section, we consider a typical clinical picture and pathological changes in the brain tissue in patients with primary chronic disease, which is more consistent with the native definition of the disease "Bokhooror". It is assumed that this state of encephalopathy is the basis of the disease, which may be complicated by an acute inflammatory episode.

The initial symptoms of encephalopathy manifest as stem symptoms. The most frequent complaints are headaches, fatigue and body aches. This state occurs, when the balance of functions of the excitatory and inhibitory neural

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pathways fails, excitement disinhibited and control of the spinal cord reflexes by the cortical structures is disturbed. The chronic disinhibition of excitability of the neurons leads to the depletion of this neural circuit (dystrophy of neurons) and irreversible organic neurological changes. The first researcher of this disease, A.N. Shapoval notes the same complaints and their resistance in patients with a developed clinical picture, which indicates the general nature of encephalopathy and the chronic form of the disease [9]. Astheno-depressive conditions are characteristic of these patients. Early disability of patients is associated with the aggravation of the symptoms of spastic paresis and speech disorder. Neuroimaging of the patient's brain reveals diffuse atrophy, more pronounced in the upper and temporal lobes and spongiosis of the cerebral cortex.

The pathology of the brain after a patient's lethal outcome shows far-gone morphological changes in the brain tissue — the result of secondary destructive processes, and therefore the analysis of these changes has no informational value for identifying the initial causes of pathogenesis. The primary morphological signs of damage to the brain tissue, adopted by the consensus of researchers, are neuron death by apoptosis without inflammation and neuron necrosis (destruction and release of cell contents), inducing an acute immune response toxic to neighboring healthy cells.

In patients with the chronic form, without acute inflammatory onset, it is registered mainly dystrophic changes of cortical neurons and their lysis. Despite the absence of pronounced inflammation of the brain tissue, isolated foci of micronecrosis are found surrounded by hypertrophic astrocytes, which subsequently initiate cortical foci of spongiosis [2, 20, 33]. The inflammation of the nervous parenchyma in these patients occurs in a subclinical form. In these cases unstable state of the brain is stabilized by the protective mechanisms of the brain.

In contrast, the patients with acute inflammatory onset (encephalitis) show a pronounced rash of numerous micronecrosis, mainly in the gray matter of the cerebral cortex with an active immune response. At the same time, the degenerative processes of the brain parenchyma outside the inflammatory focus are very pronounced and occur in the form of severe dystrophic changes of neurons, their lysis and the formation of cavities in the brain tissue. The extreme stress in the patients with an astheno-depressive state may cause acute encephalitis, which exacerbates the primary degenerative course of the disease.

The pathophysiological role of the superfamily of TNF receptors and ligands. The superfamily of TNF receptors and their ligands is one of the important systems in maintaining homeostasis of healthy tissue and the formation of a protective immune response [10, 15, 18]. The members of the TNF family are mainly expressed on the immune cells that monitor tissue cells and specifically detect pathogenic cells (immune and other non-hematopoietic tissue cells). The implementation of the three phenotypic manifestations of the target cell: cell survival, apoptosis or necroptosis is the result of the induction of biochemical signals by the interaction of the ligand and the receptor [12]. Survival of the target cell is supported by the expression of apoptosis protection and anti-inflammatory cytokines genes. The mechanism of cell destruction is initiated by the interaction of receptors (R) and ligands (L) of the TNF family. The most well-known L-R systems from the TNF family involved in these processes are TNFα, Fas, TRAIL, CD40.

The protein receptors of the members of TNF family, besides CD40, have a domain inducing activation of the cell apoptosis mechanism. The CD40 receptor is able to activate the generation of toxic T cells (CD8 +) and also induce apoptosis [13]. If the target cell has irreversible destructive changes, the TNFα ligand induces the formation of a toxic protein complex in the cytoplasm that performs apoptosis. The shock stress induces the intracellular activation of an alternative mechanism of cell destruction — programmed necroptosis. The triggering of these mechanisms depends on the state of another important system, including the p53 gene protein, which controls the health of tissue cells and its genome [25]. Numerous signaling pathways (outside and intracellular) monitor the state of the cells, and in the event of a pathophysiological cell crisis (genomic instability or dangerous metabolic changes occurring under stress), activate p53 protein, which induces the activity of the described cell death mechanisms.

Membrane-bound ligands or their receptors can split off and, in a soluble form, participate in nonspecific immune response reactions [32] with the development of the pathophysiological process of the body. Elevated concentrations in the circulating blood of soluble forms of L, R (sTNFα, sFas, sTRAIL, sCD40L, sCD40) can be an indicator of the development of this process.

Laboratory studies of sTNFα, sFas, sTRAIL, CD40L in the VE patients. In our study the levels of sTNFα, sFas, sTRAIL in peripheral blood of patients with chronic VE did not differ from healthy controls. The involvement of sTNFα in the development of an inflammatory episode (encephalitis) among patients (the indicator is an intrathecal synthesis of IgG) was revealed. Patients without inflammation show a twofold low level of sTNFα in the blood, which indicates their lack of an immune response with the participation of sTNFα. It is shown, that after immunosuppression of inflammation, the level of sTNFα in the blood decreases with the duration of the chronic course of the disease. Residual activity of sTNFα can also be traced in the cerebrospinal fluid (CSF).

In contrast to the above ligands, the level of sCD40 and sCD40L increased in peripheral blood of the patients with the chronic form. At the same time, the sCD40L ligand is several orders higher than the content of the sCD40 receptor of both blood and CSF. A high level of sCD40L, unbalanced with soluble CD40 receptor in the circulating blood, is able to induce pathophysiological processes.

The content of sTNFα, sFas in CSF samples of the patients was low. In contrast, the level of sTRAIL in patients CSF can be increased. Analysis of the role of these ligands in the pathogenesis reveals the participation of only the sTNFα and sTRAIL. As shown, the sTNFα ligand is a factor of the induction of neuron necrosis with the development of inflammation (encephalitis) and a participant in an inflammatory episode. The sTRAIL ligand seems to be considered as a factor inducing apoptosis of neurons in the primary chronic degenerative process [16, 31].

The self-limiting nature of inflammation in a disease indicates the immunosuppression and mechanism of regulated necrosis. What is this mechanism? One possible explanation is based on the involvement of the sCD40L ligand. The involvement of sCD40L in immunosuppression of circulating peripheral blood immune cells was shown. The sCD40L ligand induces proliferation of suppressor cells (Treg) and myeloid-derived cells (MDSC), and inhibition of the activation of monocyte and T-cells [27]. Perhaps the sCD40L ligand is a factor inducing the self-limiting

process of an inflammatory episode. In episodes of acute inflammation of the brain, the activity of immune T cells can also be blocked by an inflammatory reflex through the hypothalamic-pituitary-adrenal axis by glucocorticoid secretion [30]. These facts explain the immune tolerance of the pathogenic brain of a patient with disease chronic form, described previously.

It is known that platelet cells are the main producer of sCD40L in peripheral blood [22, 28]. Platelets control intravascular immunity, being active participants of the immune response. The secretion of sCD40L and inflammatory cytokines by platelets induces the expression of membrane receptors (integrins) of immune and endothelial cells, binding of the immunoactive cells with extracellular matrix and endothelial cells and provoke microvascular pathology. It has been shown that the blood of patients with chronic VE is characterized by a high content of platelets [5], which can be a source of high levels of sCD40L. The involvement of sCD40L in the blood-brain barrier disruption has been shown [24]. The small size of the sCD40 molecule contributes to their infiltration into the brain parenchyma, induction of astrocyte hypertrophy, which limits the necrotic focus of inflammation, gliolysis and, in general, disruption of trophic function. Developing microvascular pathology can be the cause of chronic hypoxia, inducing and supporting chronic apoptosis of brain tissue. It is possible that platelets chronically secreting sCD40L into the circulating blood may be a major factor in the pathogenesis of primary chronic VE.

Other diseases with high levels of sCD40L in blood are atherosclerosis, type 2 diabetes, metabolic syndrome, lupus erythematosus and others [19, 26]. It is known neurological diseases with elevated levels of sCD40L (multiple sclerosis, Alzheimer's) [24, 29]. Different nosologies can be associated with different sensitivity of organs to circulating sCD40L. In our case, the congenital high sensitivity of the microcirculatory system of the brain parenchyma to elevated levels of sCD40L may predispose to the brain pathology. The role of heredity in this disease is indicated by the tracing of generic connections, its endemicity and the sporadic nature of the onset of the disease. Sensitivity to sCD40L in VE may be associated with selective constant expression and / or higher receptor density in the endothelial cells of the brain microvascular system of the patients. The molecular nature of this sensitivity of the brain parenchyma in this disease remains uncovered.

Therapy issues. The ligands of the TNFα superfamily are currently the subject of much attention as promising tools for the destruction of pathogenic and toxic cells, including oncogenic ones. The innovative methods of therapy using these ligands are being developed. For example, the ways to reduce or block the action of sCD40L ligand in circulating blood in animal models at atherosclerosis, systemic lupus erythematosus and other diseases [11, 21, 23]. The use of these methods in the pharmacotherapy of this disease can be one of the promising approaches to the treatment of the disease.

Conclusion. The analysis of the participation of members of the TNF superfamily in the VE pathogenesis allow to us to re-examine the nature of this unique disease of the Sakha ethnos. Members of this family are key players in important biological processes of cell life, including maintaining homeostasis of tissue cells through immune mechanisms. In our case, brain tissue atrophy processes are associated with the participation of the sTRAIL and sTNFα ligands. In the case of a primary chronic degenerative process that occurs most often in a subclinical form, the loss of neurons appears to be induced with the participation of the sTRAIL ligand. In conditions of stress (severe hypothermia, excessive physical and psychological stress), patients with primary chronic degeneration may undergo acute inflammation, clinically manifested as an acute form of Viliuisk encephalomyelitis with prolonged fever, severe headache, impaired consciousness, inflammatory manifestations in the liquor. In this case, the ligand sTNFα is involved in the development of inflammation in the brain and induce neuron necrosis. In patients with a chronic form who survived after an acute period, the level of this ligand decreases over time.

The level of sCD40L is statistically significantly increased in the blood of patients. It is assumed that it can be a factor in the development of microvascular pathology, the cause of chronic hypoxia, inducing and supporting chronic processes of brain tissue atrophy. Earlier, researchers A.N. Shapoval [9], A.P. Savinov [8], S.A. McLean [33] adhered to the hypothesis of the primacy of neuronal damage based on the absence of inflammation of the brain parenchyma in primary chronic patients, as well as topographic dissociation of necrosis foci and infiltrates of the vascular fibrosis of patients with inflammatory episodes of the brain. Other authors A.P. Avtsyn and A.A. Zhavoronkov pointed out the important role of angiopathy in the slowly developing reduction of the microcirculatory bed in the chronic form of the disease [1]. Based on his own research on the pathology of the disease, F. Ikuta considered primacy of angiopathy [20]. The results of recent studies are most consistent with the last position.

Further study of the molecular mechanisms of the immunological disturbances in the brain can help in disclosing the etiology and pathogenesis of this unique disease, as well as in developing new approaches to the treatment of neurodegenerative diseases.

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THE INFLUENCE OF THE LOW TEMPERATURE OF THE FAR NORTH ON THE BODY TEMPERATURE OF PIGS IN THE EXPERIMENT

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Today it can be considered established that the thermal scheme of the human body consists of a "nucleus" comprising the brain, internal organs of the thoracic and abdominal cavities, and a "shell" consisting of skin, subcutaneous base and superficial muscles. We have carried out experimental studies of the temperature of the pig under natural hypothermia under conditions of a full-scale experiment. Graphs of temperature changes in various parts of the body over time are presented. The permission of the bioethical commission of the YSC CMP is available.

Key words: pig, hypothermia, thermometry, low temperatures, cold injury, frostbite.

Introduction. I.M. Sechenov, a Russian physiologist and enlightener, wrote: "An organism without an external environment that supports its existence is impossible; therefore, the environment influencing it must also be included in the scientific definition of an organism. One of the factors of the external world that affects the human body is the low ambient temperature. Russia, by virtue of its geographical location, is the coldest country in the world. Yakutia in Russia is the most extremely cold region. There is almost no summer in the Far North of Russia - nine months of the year are snowstorms. The average temperature of the coldest month is –50 ° C Oymyakon.

The relatively high prevalence of deaths from the effects of cold in Yakutia has long ceased to be a purely forensic problem, now acquiring an important socio-economic component. Serves as a measure of social well-being of our citizens.

In the world medical literature there is no source from which to borrow the epidemiological characteristics of cold death. We in Russia do not have an in-depth analysis of death from exposure to cold. In Yakutia, 180–200 people die every year from exposure to cold, of which 80–90 are in Yakutsk. In the UK, about 300 people die from cold injuries every year. In the United States of America, averages of 754 people die every year. In the Russian Federation, averages of 1241 people die a year. In Moscow, the lowest death toll from cold injury was 48 (1991), the highest death toll was 1261 in (2002). From the analysis it is clear that the idea that the accidental death of people from the action of low temperature is encountered exclusively in the cold season is wrong. It is also not true, the statement that only socially unadapted individuals are victims of the cold. The body temperature of a person at which death occurs, it is not constant, and depends on age, the presence of concomitant diseases and many other factors [1].

The idea of a uniform response of the whole body to thermal stimuli was shaken by I.P. Pavlov in his article on the innervation of the pancreas in 1888, expressing the idea of a difference in a single organism of higher mammals, homotermic and poikilothermic components. He wrote: "It is possible with the right to divide the organs of a warm-blooded animal into two groups: organs with a constant temperature and organs with varying temperature, sometimes descending far below the internal level. There can be no physiological difference between the tissues of the internal cavities, which represent the daily temperature fluctuation at the most 1 degree, and the tissues and organs of the skin, whose temperature can vary with impunity between 10 and 20 degrees or more. Consequently, a warm-blooded animal can be imagined as if consisting of two halves: a warm-blooded animal and a cold-blooded one "[2].

Today it can be considered established that the thermal scheme of the human body consists of a "nucleus" ("homothermal core"), which includes the brain, internal organs of the thoracic and abdominal cavities, and a "shell" ("poikilothermic surface layer") consisting of skin, subcutaneous basement and superficial muscles.

The "deadly" temperature can be different for different people. As a general scheme, you can take the following: a decrease in temperature to 25 ºC is very dangerous; up to 20 ºC - causes almost irreversible consequences; body temperature in the rectum, equal to 17-20 ºC, can be considered absolutely deadly. According to some information, the mortal rate of hypothermia for a person is 22-25 ºC. It is believed that at 24 ºC the body temperature of a person is still possible revival and that death from general cooling becomes inevitable at a temperature of about 20 ºC. According to our data, at a temperature inside the stomach of 27 ºC, a specially hardened swimmer was able to swim across the Bering Strait. A decrease in body temperature is one of the main characteristic signs of a consistent development of cold injury [4].

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Purpose. Investigation of temperature changes in the "core" and "shell" of pigs when receiving hypothermia under conditions of a full-scale experiment.

Materials and research methods. The work was performed in 2019 from January to February on the basis of the faculty of veterinary medicine of the YSAA. We have modeled the conditions for obtaining natural deep hypothermia on animals at temperatures of about – 40 °C.

The experiments were carried out on clinically healthy pigs obtained from the “Khatassky pig complex” at the age of 2-3 months, weighing from 15 to 20 kg. In the first model of a pig, in order to limit the mobility and fixation of animals, neuroplegia was performed at the beginning of the experiment (neuroleptic - Xyla 0.2% 0.5 ml and Droperidol 0.5 ml). Then it was used to simulate the state of alcohol intoxication - ethyl alcohol orally at a dose of 5-6 ml / kg of live weight. The animals were fixed and placed on the street at an ambient temperature of - 40 ° C ... - 43 °C.

Experimental work was carried out in accordance with the ethical standards governing animal experiments, in accordance with the European Convention for the Protection of Vertebrate Animals used for experiments or for other scientific purposes No. 123 of March 18, 1986, Strasbourg, and the order of the Ministry of Health of Russia of 01.04. 2016 № 199n "On approval of the rules of good laboratory practice." The permission of the bioethical commission of the YPC KMP is available.

The following measuring devices were used for this study:

1. To characterize temperature changes, especially muscular, needle thermocouples of chromel-alumel type K were used. The temperature range is from -40 to 200 °C, which are introduced to a depth of 0.5 to 1 cm in the region of five and the wrist of a pig.

2. Rectal thermocouple chromel-alumel type K was used to determine the temperature in the large intestine.

3. External surface temperature thermocouple chromel-alumel type K was used.

For visualization of temperature readings from thermocouples, a precision Tercon signal converter was used as a controller.

The precision signal converter of thermometers of resistance and thermocouple "Tercon" produced by LLC "Termeks" is used for temperature measurements. The device has two input channels on which it measures the resistance of a connected resistance thermometer or EMF of a connected thermocouple, and then calculates the temperature from a given conversion function.

The Tercon-K switchboard supplied with the converter allows you to expand the number of input channels to 16.

Measurement of voltage signals from thermocouples is performed by comparing with the reference voltage built into the device. Measurement of resistance of thermistors is made by the method of comparison with the reference resistance connected in series with the sensor. An integrated analog-to-digital converter converts the comparison result into a digital code. Next, the microprocessor converts the digital code into a temperature value. The result obtained is displayed on a digital scoreboard and sent to a personal computer via the RS-232 interface in the form of a string in which the channel, measured value and unit of measure are sequentially indicated. Complete with the converter the software application for work in the environment of Windows is delivered. The program receives the data sent by the converter via the RS-232 interface to a computer, and outputs the data in the form of graphs and a table.

Results. The figures show the temperature of pigs with hypothermia in the “cooling – warming” cycle. We performed a selective antegrade cerebral perfusion technique using an artificial blood circulation apparatus (AIC) with a perfusion rate of 8 ml / min / body weight with a gradual warming of the perfusate (maintaining a temperature gradient of less than 5 °C). After the sternotomy, aortic cannula was inserted into the aortic root and the venous cannula into the cranial vena cava for perfusion. Heparinization was carried out at the rate of 3 mg / kg. Warming of the perfusate through AIC was performed with maintaining the temperature gradient less than 5 °C [5].

Conclusion. As a result of our experiments, it is possible to establish that the temperature in the “shell” is minus, and the core region is positive. A very characteristic picture of the protection of the "core" from the damaging effects of cold. The decrease in internal temperature depends on the ambient temperature.

Experiments with animals made it possible to establish a number of factors that impede the process of restoring the vital functions of the brain. These include prolonged exposure to low temperatures. Further warming of the heart, did not give the results of warming the brain in a small circle. The impossibility of establishing the time when you can "start" the reverse mechanism for restoring the work of the brain. Research on this issue of "revitalization" will continue. The given

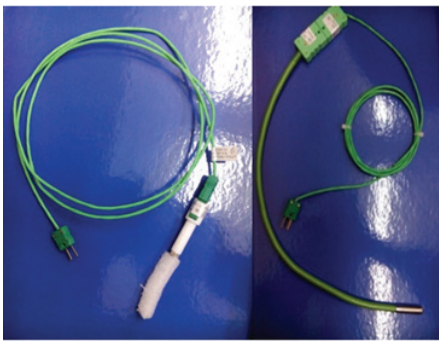

Fig. 1. From left to right: 1. Needle thermocouple to establish intramuscular temperature. 2. Rectal thermocouple to establish temperature in the large intestine

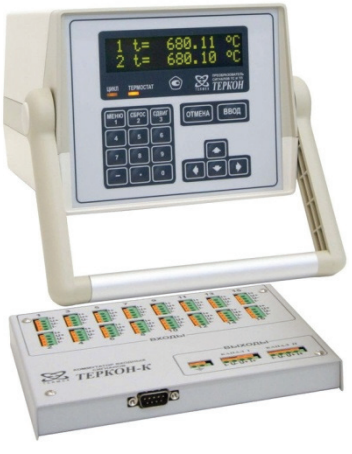

Fig. 2. “Tercon” signal converter

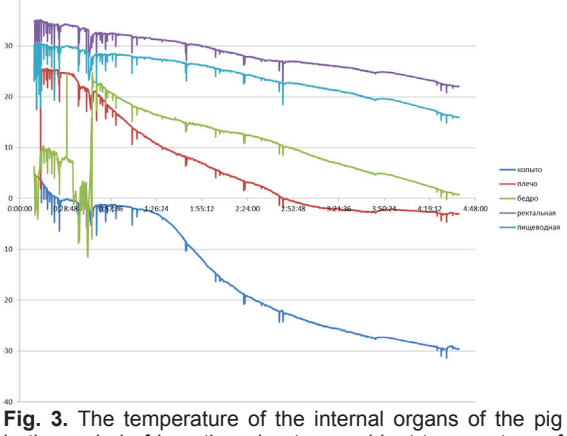

Fig. 3. The temperature of the internal organs of the pig in the period of hypothermia at an ambient temperature of -42 °C.

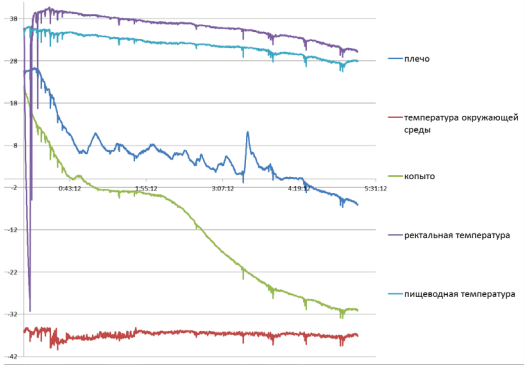

Fig. 4. The temperature of the internal organs of the pig in the period of hypothermia

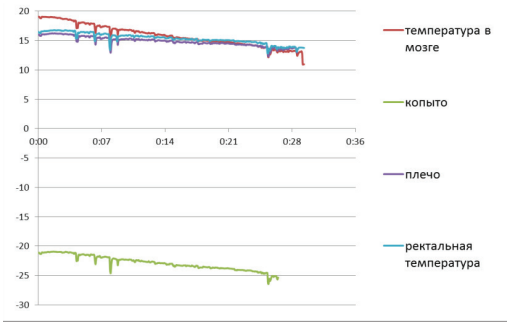

Fig. 6. Monitoring body temperature after cardiac arrest

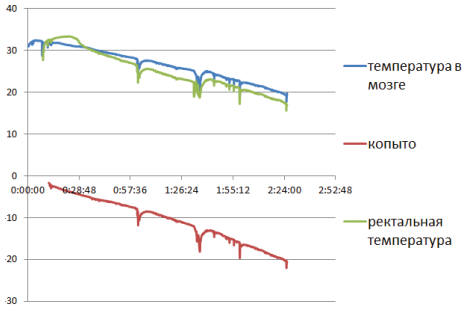

Fig. 5. The temperature of the internal organs of the pig in the period of hypothermia at an ambient temperature of -37 °C

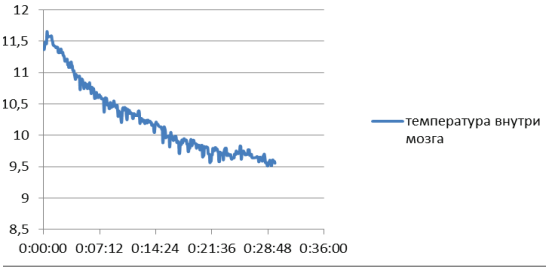

Fig. 7. Measuring the temperature around the pig's brain after bringing the body into a warm room

experimental materials show that the mechanisms of the brain work during cold injury have not yet been elucidated and there are still enormous and complex tasks to further study this problem.

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THE ROLE OF NEUROENDOCRINE FACTORS IN THE FORMATION OF ALCOHOL DEPENDENCE AND HUMAN ECOLOGY IN VARIOUS ETHNIC POPULATIONS, NEW APPROACHES TO THERAPY

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Given the biological vulnerability of indigenous peoples to the effects of alcohol and the significant impact of environmental and ethnocultural factors on the clinical and dynamic characteristics of alcohol dependence in people of indigenous nationalities, integrated approaches were used - clinical and clinical-biological in conducting studies to study the disorders caused by alcohol use in people of various ethnicity, which is important for determining effective treatment strategies. The study examined the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity - representatives of the indigenous population of Siberia, especially neuroendocrine metabolism in these patients in comparison with patients of Russian nationality. The therapeutic efficacy of the original anticonvulsant halodif was assessed for the severity of the symptom of alcohol withdrawal syndrome (AAS) and the levels of neuroactive hormones: cortisol and progesterone in the blood of the examined patients. It has been established that the course of alcohol dependence among representatives of the Tuvan ethnic group acquires a highly prodigious character, which indicates a greater vulnerability of representatives of the native Tuvan ethnic group to the effects of alcohol. The index of the ratio of cortisol/progesterone of examined patients with alcoholism of Russian nationality is almost double the index of healthy donors, in patients of Tuvan ethnicity it is almost five times higher than the index of healthy examined persons. The revealed change in the levels of neuroactive hormones and the index of their ratios serves as a prognostic marker in the treatment and rehabilitation of patients, which seems significant in relation to the therapy and rehabilitation of patients of Tuvan nationality, in which hormone levels and their balance largely reflect the severity of the disease compared with Russian patients nationality. The use of the anticonvulsant halodif in basic therapy leads to a dynamic decrease in the total number of points on the Hamilton scale, significantly reduces the level of cortisol and stimulates an increase in progesterone levels, changing the balance of the ratio of hormone levels, closer to that in healthy donors. The ongoing psychopharmacotherapy is pathogenetically directed and increases the effectiveness of treatment, prevents the development of relapse and the progressive dynamics of alcohol dependence, which is especially important for human ecology in the Tuvan ethnic group and, possibly, other populations of the indigenous peoples of the North, Siberia and the Far East.

Keywords: ecology, ethnos, alcohol, addiction, pharmacotherapy, endocrine factors, hormone.

Introduction. In recent decades, considerable attention has been paid to the problem of alcohol consumption and the formation of alcohol dependence among the indigenous ethnic populations of the peoples of the North, Siberia and the Far East. Traditional communities of indigenous northerners in their history of existence have developed specific forms of practice of psychotherapeutic correction - holidays and rituals associated w ith shamanism. The desire for alcohol in people in ethnic populations is often due to the desire to get rid of mental discomfort, to relieve emotional stress caused by the stressful situation associated with a change in the original lifestyle. It is known that representatives of indigenous peoples face the most detrimental consequences of drinking alcohol and have an increased rate of formation of dependence [1, 5, 6]. The individual sensitivity of a person to psychoactive substances includes the effects of ethanol, defined as the possibility of adequate adaptive reactions that are controlled by genetic, social and sociocultural factors in general, reflecting collectively the common features of the human ecology in this population.

Human ecology is “a comprehensive science designed to study the laws of interaction between people and the environment, issues of population development, preservation and development of human health, improving the physical and mental capabilities of a person”, as defined by V.P. Kaznacheeva (1998) [3]. This science has a completely independent value, although it is based on biomedical research. Modern research indicates the biological vulnerability of indigenous populations to the effects of alcohol. In addition, the results of the studies indicate a significant effect of ethnocultural factors on the clinical and dynamic characteristics of alcohol dependence - people of indigenous nationalities have a certain peculiarity of the clinic and the course of alcoholism [1, 2, 4-6].

Integrated approaches - clinical and clinical-biological in conducting studies to study the disorders caused by alcohol consumption in people of different ethnic backgrounds, are important for determining effective treatment strategies. In this regard, additional studies are needed to identify the clinical and biological features and molecular targets that underlie alcohol-induced dependence. One of the predispositions of the formation of alcohol addiction is a violation of the balance of the processes of excitation and inhibition in the brain, leading to hyper-excitability of the central nervous system, which increases the risk of alcoholism [8,14,18]. Patients with alcoholism are distinguished by impulsivity, extravagant behavior and other disorders associated with this condition [2,9,12]. The effects caused by alcohol associated with changes in the nuclei of the thalamus and limbic regions of the brain lead to disruption of the synchronization processes in the thalamus, a change in the relationship of the functional parameters of the brain and individual differences in behavioral characteristics. An increase in the high-frequency β-activity recorded on the EEG in the deep layers of the frontal cortex of the brain causes the development of relapse in patients with alcoholism [7,8]. The descendants, whose parents were patients with alcoholism, revealed an increase in the fluctuations of beta and gamma frequencies [8]. Sleep disturbance associated with increased excitability due to a decrease in inhibition

processes in the brain caused by chronic alcoholization can play a role in the progression of alcoholism and can be a factor in relapse in these patients.

Alcohol addiction has a similar etiology to other neuropsychiatric disorders, often including dysfunction of the same brain neuronal networks and neurotransmitter systems [14]. The GABAA receptor (GABAAP), as the main mediator of the fast inhibitory effect in the central nervous system [13,16], is modulated by many exogenous compounds, including benzodiazepines (BDZ), barbiturates, alcohol, and endogenous steroids such as progesterone and its metabolites. This non-genomic interaction of neuroactive steroids with GABAAP causes anxiolytic and anticonvulsant effects [13,16,18]. Chronic alcohol consumption and alcohol withdrawal increase levels of cortisol, an anxiogenic neuroactive hormone associated with increased stress function. Dysfunction of GABAR in the brain underlies the pathogenesis of some neurological and mental disorders of a person: epilepsy, insomnia, anxiety, alcoholism and is associated with altered levels of some neuroactive steroids, such as progesterone and cortisol [7,12,15,17,18,21]. The homeostasis control system and the neuroendocrine system are closely connected with such a phenomenon as individual tolerance to alcohol and the level of alcohol dependence of a person, especially from some ethnic groups. Optimization of impaired homeostasis during (or after) acute or chronic ethanol consumption is provided by a specific modulation mechanism of endogenous neurosteroids, which may be a useful pharmacotherapeutic strategy in the fight against alcohol and alcohol abuse [2,10,11,20].

The general basis of the pathogenic mechanisms of epileptic paroxysms and disorders of β-oscillations in the brain associated with hyperactivity of the hypothalamic-pituitary-adrenal axis, causing compulsive craving for alcohol, were prerequisites for a clinical study of the therapeutic efficacy of the original drug galodif1 (a new, highly effective anticonvulsant meta-chloro- benzhydrylurea) and levels of steroid hormones progesterone and cortisol in the treatment of patients with alcoholism.

Purpose: to study the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity, to determine the role of neuroendocrine factors in the formation of alcohol dependence in various ethnic populations: Russians and Tuvans with the aim of further developing effective pathogenetically based therapy.

Materials and methods. During the study, the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity — representatives of the indigenous population of Siberia2, the features of neuroendocrine metabolism in these patients compared with patients of Russian nationality were studied. The therapeutic efficacy of the original anticonvulsant drug, galodif, was evaluated for the severity of the symptom of alcohol withdrawal syndrome (AAS) and the levels of the neuroactive hormones cortisol and progesterone in the blood of the examined patients. Clinical and biochemical studies in patients with alcoholism in withdrawal and postabstinence conditions were carried out in the addictive conditions department of clinics of the Scientific Research Institute of Mental Health of the Tomsk Scientific Research Center and in the Republican Tuberculosis Drug Dispensary, Republic of Tyva, Kyzyl. 68 patients with alcoholism from the Russian ethnic population living in the Tomsk Region and 67 patients from the Tuvan ethnic group were monitored; only men from 24 to 53 years old (mean age: 38.3 ± 8.9 years) with different levels were included in the survey alcohol consumption. The diagnosis of examined patients with alcoholism according to ICD-10 - code F10.201 and F10.202 - mental and behavioral disorders due to alcohol consumption, addiction syndrome, currently - abstinence. The type of course of alcoholism in the examined patients was progressive in nature. The control group included 20 healthy male volunteers (according to the standard set of clinical and laboratory tests). Clinical assessment of the condition of patients was carried out with the traditional clinical description, using clinical, psychopathological, clinical and dynamic methods at different stages of the therapy. Anticonvulsant galodif1 was used in accordance with the recommendations at a dose of 300 mg per day (100 mg x 3) during the course of therapy - 21 days in the post-withdrawal period with varying severity of affective disorders. Quantitative characteristics were evaluated according to Russian versions of HARS - Hamilton's: Anxiety scale and HDRS - Hamilton depression scale. Enzyme-linked immunosorbent assay kits were used to determine serum hormone levels in patients and volunteers. All patients and volunteers examined had no serious liver disease. Blood for the study was taken from the subjects in the morning on an empty stomach. The subjects were informed of the planned studies and agreed. Collected blood serum samples were immediately frozen and stored until analysis at –700 C in a freezer. To determine the levels of hormones (cortisol and progesterone), appropriate kits for enzyme-linked immunosorbent assay of hormones were used; in this work, kits from Bio-Rad were used. The principle of the method is universal; used to determine cortisol, progesterone. Statistical data processing was performed using the standard software "Statistika 10.0" for "Windows", using parametric and non-parametric criteria.

Research and discussion. In the course of the study, we established the clinical and dynamic features of the formation and course of alcohol dependence in persons of Tuvan ethnicity - representatives of the indigenous population of Siberia2. Alcohol dependence in patients of Tuvan nationality differs from alcohol dependence in patients of Russian nationality in a number of clinical and biomedical signs: the first sample of alcohol in Tuvans occurs on average at 18 years old (17.9 ± 2.0), which is much later than in Russians who are familiar with the effects of alcohol from adolescence (15.2 ± 3.0). The systematic consumption of alcoholic beverages develops among Tuvans in adulthood (35.1 ± 9.8), in contrast to Russian men who begin to drink systematically young (24.6 ± 5.9). Accordingly, signs of alcohol dependence in people of Tuvan nationality are formed several years (7-8) later than in Russians: a symptom of loss of quantitative control over use was detected in Tuvans at 36.9 ± 9.9 years, in Russian patients at 29 8 ± 7.5 years; the formation of withdrawal syndrome in Tuvans occurs at the age of 37.7 ± 8.4 years, unlike Russians, in whom the withdrawal syndrome develops on average at the age of 29.6 ± 6.0 years (the level of confidence in all respects is $p = 0.00002$ - $p = 0.00004$). This is due to the ethno-cultural characteristics of the living environment of the indigenous population of Tuva, as well as family and religious relations.

According to the results of the study, we noted that the symptoms of alcohol addiction in Tuvans are formed progressively - on average for 2-2.5 years of systematic drinking, which is on average twice as fast as in people of Russian nationality, and indicates a malignant type of formation of alcoholism. The formation of dependence among Tuvans during the development of psychotic alcoholism has a different dynamics. The onset of systematic alcohol consumption in this case occurs earlier in comparison with the nonpsychotic form (27.9 ± 6.9

years and 35.1 ± 9.8 years, respectively, at p = 0.0007), the main symptoms of the disease are the age of loss of quantitative control over consumption (31.6 ± 6.4), age of manifestation of amnestic forms of intoxication (32.5 ± 6.9), age of withdrawal syndrome (32.4 ± 6.7 and 37.7 ± 8.4 at p = 0.006) - are formed on average five years earlier (differences are significant at the level of p = 0.033; 0.045). According to the clinical and dynamic parameters, Tuvans with a psychotic form of alcoholism are approaching Russians with nonpsychotic alcoholism. Consequently, Tuvans, signs of the formation of alcoholism in which are similar to the age dynamics of the development of alcoholism in Russians (non-psychotic form), have an unfavorable prognosis of the development of the disease - a manifestation of psychotic disorders of 37.4 ± 7.8 years (psychotic alcoholism). Thus, Tuvans reliably later than the Russians first try, and also begin to drink alcohol systematically (35.1 ± 9.8 and 24.6 ± 5.9 years, respectively; p = 0.000007), addiction syndrome forms on average in 2- 2.5 years of systematic drinking, i.e. the course of alcohol dependence among representatives of the Tuvan ethnic group acquires a highly prodigious character, which indicates a greater vulnerability of representatives of the native Tuvan ethnic group to the effects of alcohol.

As you know, alcohol abuse and the formation of alcohol dependence is associated with the development of alcohol withdrawal syndrome (AAS) when alcohol is stopped. The development of AAS in patients with alcoholism is accompanied by an increase in anxiety, the occurrence of paroxysms, a compulsive state, increased convulsive activity, developed autonomic symptoms, and a stress reaction. According to the results of modern research, an "epileptogenic concept" of the occurrence of an unmotivated paroxysmal-compulsive craving for ethanol during the period of alcohol withdrawal was formed. Previously repeated "auras" and paroxysmally arising violent memories of pro-alcoholic content are designated as "flashbacks" - a paroxysmal burst of memories. This process can "ignite" and reach a generalized form of attraction with strong excitement, when the craving for alcohol is realized. The process of fomenting a limbic psychotic trigger reaction - a persistent change in the functional state (excitability) of certain areas of the brain - has been defined as "kindling". The Kindling model is considered in the structure of alcoholism as a chronic epileptiform activity, manifested at the behavioral level. With this course of the disease, the use of anticonvulsants is indicated in complex therapy; anticonvulsants pregabalin and carbamazepine are widely used, which are well tolerated by patients, but are imported pharmaceuticals.

The indications for prescribing the anticonvulsant galodif1 in the complex treatment of patients with alcoholism were the clinical manifestations of a pathological craving for alcohol with a distinctly periodic character, richly affective color and signs of paroxysmality. Galodif was prescribed at a dosage of 300 mg per day (100 mg x 3) in the withdrawal and post-withdrawal periods with varying degrees of severity of affective symptoms (compulsive, paroxysmal, dysthymic and dysphoric disorders), the duration of the course was 21 days. The clinical dynamics of the neurotropic toxic effects of ethanol in the structure of alcohol withdrawal syndrome (asthenia, cranialgia, cardialgia, dissomnia, autonomic-vascular and discoordinate-atactic disorders) were analyzed as a symptom-target complex for the pharmacotherapeutic effect of galodif: sedative, timoleptive and timoleptic effects were studied, as well as the effect of galodif on the primary pathological craving for alcohol. The study used the clinical and psychopathological method, the Hamilton anxiety and depression scale.

Our studies have shown that the therapeutic effect of the anticonvulsant galodif was associated with a decrease in the intensity of the ideator component of the pathological craving for alcohol in AAS, a weakening and / or disappearance of craving in the post-withdrawal state. The use of halodif (300 mg / day) in the basic therapy of patients in the withdrawal and post-withdrawal conditions had a normotoleptic effect on the dysphoric component of affective disorders (72.2%), on anxiety-phobic manifestations (50.0%), pronounced effect in sleep disturbance, "psycho-vestibular" dreams (85.7%); with local muscle-tonic hyperkinesis of the "krampi" type (60%); vegetative stabilizing effect in cardiovascular disorders with normalization of heart rate (66.7%) and relief of cardialgia (63.6%); marked effect on cephalgic and diencephalic disorders - a weakening of the intensity of the senestopathic and algic components of cephalgia (71.4%), relief of diencephalic paroxysms (57.1%); a decrease in the pathological craving for alcohol during withdrawal symptoms (88%) and post-withdrawal symptoms (57%); which was expressed in a 5-fold decrease in the total score on the Hamilton Depression Scale (HDRS), and a 6-fold decrease in the Hamilton anxiety scale (HARS) [Fig. one]. The greatest effect of the drug was expressed in patients with a compulsive spontaneous manifestation of a pathological craving for alcohol. The drug did not aggravate discoordinate-atactic manifestations in the structure of AAS and did not cause unwanted adverse reactions.

When conducting a comparative analysis of the levels of steroid hormones in patients with alcoholism and volunteers from the control group, it was found that the level of cortisol was significantly higher than the level of this hormone in the blood of patients with alcoholism, and these changes were significantly more pronounced in patients of the Tuvan ethnic group [Table 1, Fig. 2]. Affective disorders and alcoholism are associated with impaired hormonal metabolism and regulation of the negative feedback mechanism, according to which cortisol released from the adrenal glands inhibits the production of corticotropin-releasing hormone, as a result of which the content of adrenocorticotropic hormone and cortisol increases abnormally. In contrast, the progesterone (PG) content in the blood was significantly lower in

Fig. 1. Therapeutic efficacy of halodif, reduction in the severity of symptoms in% of cases

Table 1. Levels of the neuroactive hormones cortisol and progesterone in patients with alcoholism in various ethnic groups

Type of hormone/marker	Alcoholics Russian nat. (before treatment)	Alcoholics Russian nat. (21 days of therapy galodif)	The control group of the Russian nat. (healthy donors)	Alcoholics Tuvinian nat.
Cortisol (nmol/l)	661.32±108.12*	478.36±97.32	492.07±68.24y	875.00 ±79.54*
Progesterone (nmol/l)	2.66 ± 0.32*	4.28±0.63	4.00 ± 0.54	1.78 ± 0.23*
Index (IR) Cortisol / Progesterone	253.06*	114.44	126.05	499.02*
	n=68	n=66	n=20	n=67

*Уровень значимых различий P <0.005.

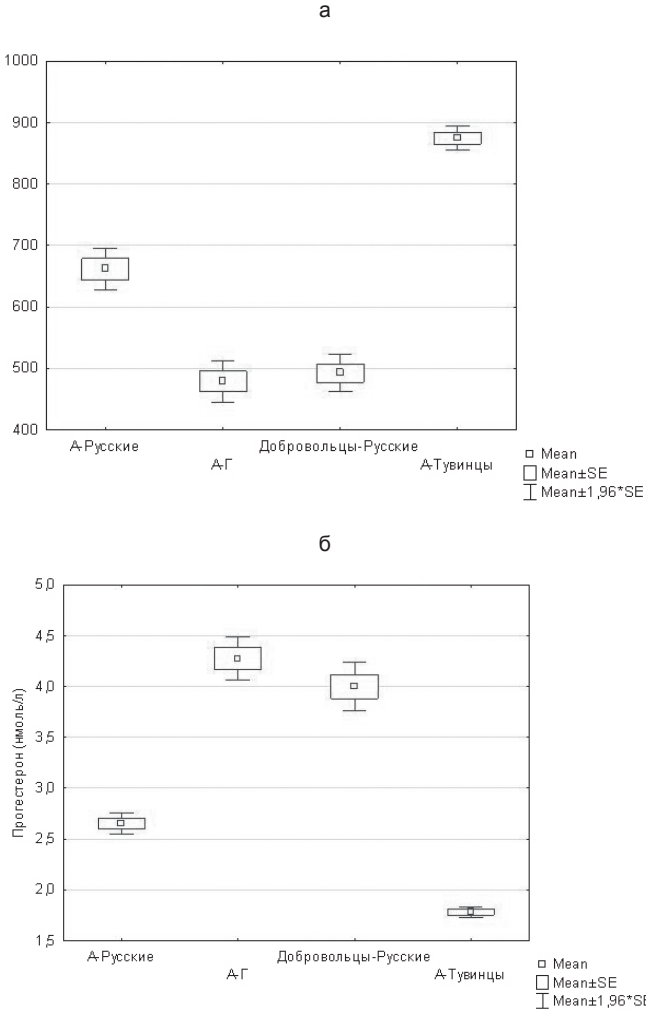

Fig. 2. Statistical analysis of cortisol hormone levels in patients with alcoholism in various ethnic groups
Groups:
A-Rus – Russian patients with alcoholism before treatment;
A+G – Russian patients with alcoholism after treatment with galodif
Volunters –Rus – healthy volunteers
A-Tuv – Tuvan alcoholics

patients compared with the concentration of this hormone in the control group, lower levels of PG were detected in Tuvinian patients [Table 1, Fig. 3]. PG is a precursor in the biosynthesis chain of pregnan, a neurosteroid that modulates GABAergic function in the nuclei of the thalamus and limbic system. PG and its metabolites have an antiglucocorticoid and neuroprotective effect, activates the recovery of myelin, which is especially important for neurotoxic and neurodegenerative lesions of the central nervous system [10,11]. A decrease in the level of PG and its metabolites leads to impaired neuroprotection. Our data indicate that alcohol abuse causes a change in the levels of cortisol and PG, as well as their balance - indices of the ratio of the concentrations of these hormones. The index of the ratio Cortisol / Progesterone (Index Ratio - IR) in the blood of examined patients with alcoholism of Russian nationality is almost twice as high as the IR index in the blood of examined healthy donors; in patients of Tuvan ethnicity, IR is almost five times higher than the IR index of healthy examined individuals [Table 1, Fig. 4]. This fact indicates an imbalance in the ratio of these hormones that regulate the human stress system, as a result of increased levels of cortisol and a decreased level of progesterone, a positive modulator of GABAA, the receptor neurotransmitter system. Moreover, patients of Tuvan ethnicity revealed significantly deeper shifts in the balance of the National Assembly, which are associated with a high risk of developing alcohol dependence and a highly progressive course of the disease.

The use of the original anticonvulsant Galodif (meta-chloro-benzhydrylurea) for 21 days at a dose of 300 mg per day in patients with alcoholism caused an induced decrease in symptoms characteristic of AAS. Galodif is safe for use in people with a relatively small number of side effects compared to other anticonvulsants, it has a detoxifying effect, stimulating the monooxygenase system of the liver [20], which is important in case of chronic alcohol intoxication. A dynamic decrease in the total Hamilton score (anxiety and depressive disorder) was faster in the studied patients. Halodif significantly reduced the level of cortisol and stimulated an increase in PG levels, changing the balance of the ratio of hormone levels, bringing the IR index closer to that in healthy donors [Table 1, Fig. 4].

Neuroactive steroid hormones are able to specifically modulate the function of the GABAergic neurotransmitter system of the brain. NS (progesterone and its metabolites) and drugs that have a positive modulating effect on GABAA - receptors that enhance the inhibitory function in the central nervous system, have anxiolytic, analgesic, anticonvulsant, sedative, hypnotic and anesthetic effects, reducing the severity of symptoms in AAS and the primary pathological attraction to ethanol.

In the light of the data obtained, the balance of the NS is considered by us as one of the factors of the pathogenetic mechanism of the development of alcoholism, and the use of galodif in the treatment of patients with alcoholism allows us to correct the levels of NS and their ratio. This leads to positive clinical dynamics, faster and more stable remission, and may be a prospect for the development of new approaches in the treatment of patients with alcoholism.

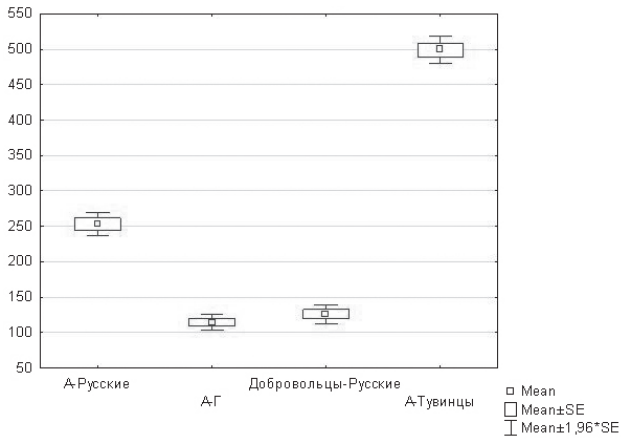

Fig. 4. Statistical analysis of Index Ratio (IR) cortisol/ progesterone in patients with alcoholism in various ethnic groups

Pharmacological drugs that modulate neurosteroid activity can exert clinical effects through their effect on the balance of neuroactive hormones. The development of new pharmaceuticals that affect the metabolism of endogenous NS, taking into account individual ethnic characteristics associated with deeper shifts in the balance of NS and creating a high risk of development and progressive dynamics of alcohol dependence, is one of the significant strategies in the treatment of mental disorders and alcoholism in patients in various ethnic populations.

Conclusion. Thus, based on the results of our work, it can be assumed that the detected change in the levels of NS and the index of their ratios serves as a prognostic marker in the treatment and rehabilitation of patients, which seems significant in relation to the treatment and rehabilitation of patients of Tuvan nationality, whose NS levels and their balance to a large extent reflect the severity of the course of the disease in comparison with patients of Russian nationality.

A study in the Addictive Clinic of the Mental Health Research Institute of Tomsk Scientific Research Center of the Russian Academy of Sciences allows recommending the use of the anticonvulsant galodif as a therapeutic and prophylactic agent in patients with alcoholism with compulsive and paroxysmal disorders associated with impaired levels of neuroactive hormones in various ethnic groups, especially those with sharp changes hormonal balance. Psychopharmacotherapy that corrects this condition is pathogenetically directed and increases the effectiveness of the treatment, prevents the recurrence of the disease and the progressive dynamics of alcohol dependence, which is especially important for human ecology in the Tuva ethnic group and, possibly, other populations of the indigenous peoples of the North, Siberia and the Far East.

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CLINICAL CASE

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CLINICAL CASE OF SEX CORD-STROMAL TUMOR OF THE FALLOPIAN TUBE

The article presents a case of sex cord-stromal tumor of the fallopian tube in a 18-year-old female patient. Single cases of extra-ovarian localization of sex cord-stromal tumor have been described in the literature, however the primary lesion of fallopian tube still hasn`t been reported.

Keywords: fallopian tube, sex cord-stromal tumor.

Introduction. Sex cord-stromal tumors (SCST) is a heterogeneous group of tumors with a predominantly low malignant potential that contain sex-cord cells and/or stromal cells, such as granulosa cells, theca cells, Sertoli and Leydig cells and fibroblasts of stromal origin. According to the WHO 2014 classification [5,8] SCST includes 3 groups of tumors: pure stromal tumors, pure sex cord tumors and mixed sex cord-stromal tumors, which include sex cord-stromal tumours, NOS; besides, there are mixed germ-cell tumors and sex cord-stromal tumors. Not otherwise specified SCST include tumors in which it is impossible to determine the differentiation of the predominant component, clinically the tumor may be hormone-active and inactive, the clinical course and prognosis of such tumors are uncertain [2].

Malignant neoplasms of the fallopian tube are very rare - the frequency of occurrence in the world is from 0.11 to 1.18 % [3], more than 95% of cases are carcinomas [7]. There are no SCST known cases in the fallopian tube described in the literature. The available statistics on morbidity and mortality from the fallopian tubes malignancies, unfortunately, needs to be clarified and updated, as these indicators for fallopian tubes malignancies are usually grouped with other localizations of the female genital organs (i.e ovary, uterus malignancies). According to the American Cancer Society [12] in 2017 in the United States, 4,810 cases of morbidity and 1,240 deaths from female genital organs (excluding breast, uterus, ovaries and vulva) were reported. In Russia in 2017 there were 1679 lethal cases from the malignancies of female genital organs (with the exception of the breast, uterus and ovaries) [1].

Primary fallopian tube tumors always need to be separated from secondary lesions according to the criteria proposed by C. Y. Hu et al. in 1950 [6]: most of the tumor mass is located in the fallopian tube with mucosal invasion and the presence of a transition between the unaffected and affected tubal epithelium.

The aim: to show the clinical and morphological observation of sex cord-stromal tumor of the fallopian tube in a patient of 18 years.

The results of observation: An 18 y.o female patient presented with nausea, single loose stools the night before admission, pain in the lower abdomen, fever up to 37.4 C in the City Clinical Hospital №31 of Moscow; these symptoms appeared a day before admission, for the first time. Gynecological history: menarche at 12 years old, moderate amount of flow, menstruation was regular and painless, lasted for 4 days, cycle length was 30 days; patient denied sexual history - Virgo intacta; last menstruation from October 1st to 5th 2018, in term, no abnormalities.

The patient was examined in the emergency room by an attending surgeon and an obstetrician-gynecologist: patient had fair condition, clear consciousness, skin and mucous membranes of normal color, no edema, the mammary glands were soft, there was no discharge, blood pressure 120/80 mm Hg, heart tones were clear, 18 breaths per minute, vesicular breath sound, tongue was dry and coated with plaque, abdomen was tense and sharply painful; gynecological status: speculum examination was not carried out, the discharge from the cervical canal was abundant and bloody. Recto-abdominal examination of the uterine body in anteflexio showed normal sized uterus with dense consistency, it was mobile, painless, with a smooth surface, fornices of the vagina were free and deep, there were no infiltrates in the pelvis. The right and left adnexa were not identified during exam, their area was sharply painful. During pelvic ultrasound 400 ml of free fluid with clots were found plus the left ovary with a yellow body up to 30 mm. Blood sample showed leukocytosis up to 17,8x109/L.

Based on the patient's complaints, clinical and anamnestic data, general and gynecological examinations, instrumental and laboratory methods of examination in the emergency room and the conclusions of medical specialists, the diagnosis of "Left ovarian apoplexy, hemorrhagic form" was made. Laparoscopy was performed on an emergency basis.

Intraoperative: Up to 150 ml of blood in the abdominal cavity. Normal-sized uterus, with pink serosa. Left fallopian tube was not visually altered, the fimbria were free and normal. The left ovary was 4x3x2cm with lobed structure and increased by the yellow body to 2cm in diameter with a rupture site up to 0.5 cm with signs of active bleeding. The right fallopian tube was thickened throughout to 3 cm, edematous, in the area of the fimbriae and twisted for 360 degrees: the fimbriae presented by a cyanotic in color spongy texture that was irregular in shape with dimensions 5x5cm. Right ovary 3x2,5x2cm with lobed structure.

Taking into account the intraoperative laparoscopic picture and the patient's age, it was decided to perform coagulation of the left ovary, tubectomy on the right and sanitation of the pelvis.

The right fallopian tube was extracted from the abdominal cavity through the left aperture in the endobag and sent for urgent intraoperative histological examination.

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Macroscopic description of surgical material: fallopian tube with a length of 7.5 cm and a diameter of 0.5 up to 1.3 cm – serosa of the tube bluish, glittering, with hemorrhages, blood clot in fimbriae margin. 1 cm away from the fimbriae - a tube wall defect with fragmentary appearance 1x1cm in size. Also with the fallopean tube pieces of loose brown cloth were sent with overall dimensions 8x6x1cm, on the incision surface with subtle layers of pink fabric. 4 tissue fragments were taken for histological examination.

During urgent pathological evaluation of the specimen in the wall of the fallopian tube separate foci of atypical glandular structures consisting of large polymorphic cells with the presence of a single mitotic figures and small clusters of tumor cells with hyperchromatic nuclei were determined. Conclusion: C57.0 - Histological picture is extremely suspicious for a tumor of uncertain malignant potential in the fallopian tube wall.

Taking into account the age of the patient, it was decided not to expand the scope of the operation and limit it to right-sided tubectomy.

In further pathological examination of the surgical material, 34 additional tissue fragments from the fallopian tube and adjacent brown tissue were taken. Microscopic description: Fallopian tube with edema, hemorrhages, foci of lymphoplasmacytic infiltration with an admixture of neutrophils, fibrin clots in the lumen of the vessels; along with the above, there are large areas of tumor tissue mainly of the nest-trabecular structure, with the presence of small areas with small glandular structures - tumor cells with weak polymorphism, hyperchromic nuclei and few mitoses. Immunohistochemical study [9] using a panel of 14 antibodies in tumor cells showed striking expression of calretinin, vimentin, CD99, WT-1, weak expression of CK8/18, PLAP and desmin, the absence of expression of EMA, S100, alpha-inhibin, mesothelin, melan A and alpha-fetoprotein; index of cell proliferation Ki-67 was 3% (Fig., a-.

On the basis of a comprehensive study the pathological diagnosis was formed: D39.7 - Unclassified sex cord-stromal tumor of the right fallopian tube with a Ki-67 proliferation index of 3%. M8590/1.

The postoperative period in the patient proceeded normally and on the 5th day after the operation she was discharged from the hospital with recommendations for follow-up in a specialized oncological institution at the place of residence.

Conclusion: The presented clinical case of the fallopian tube tumor is an extremely rare case of non-organ (extra-ovarian) localization of SCST - the literature describes only single observations with the localization of the tumor in the soft tissues of the abdominal cavity, pelvis and in the omentum [13]. Diagnosis of such tumors of the fallopian tube has significant difficulties not only for clinicians, but also for pathologists - along with traditional morphological methods of diagnosis of the surgical material, the

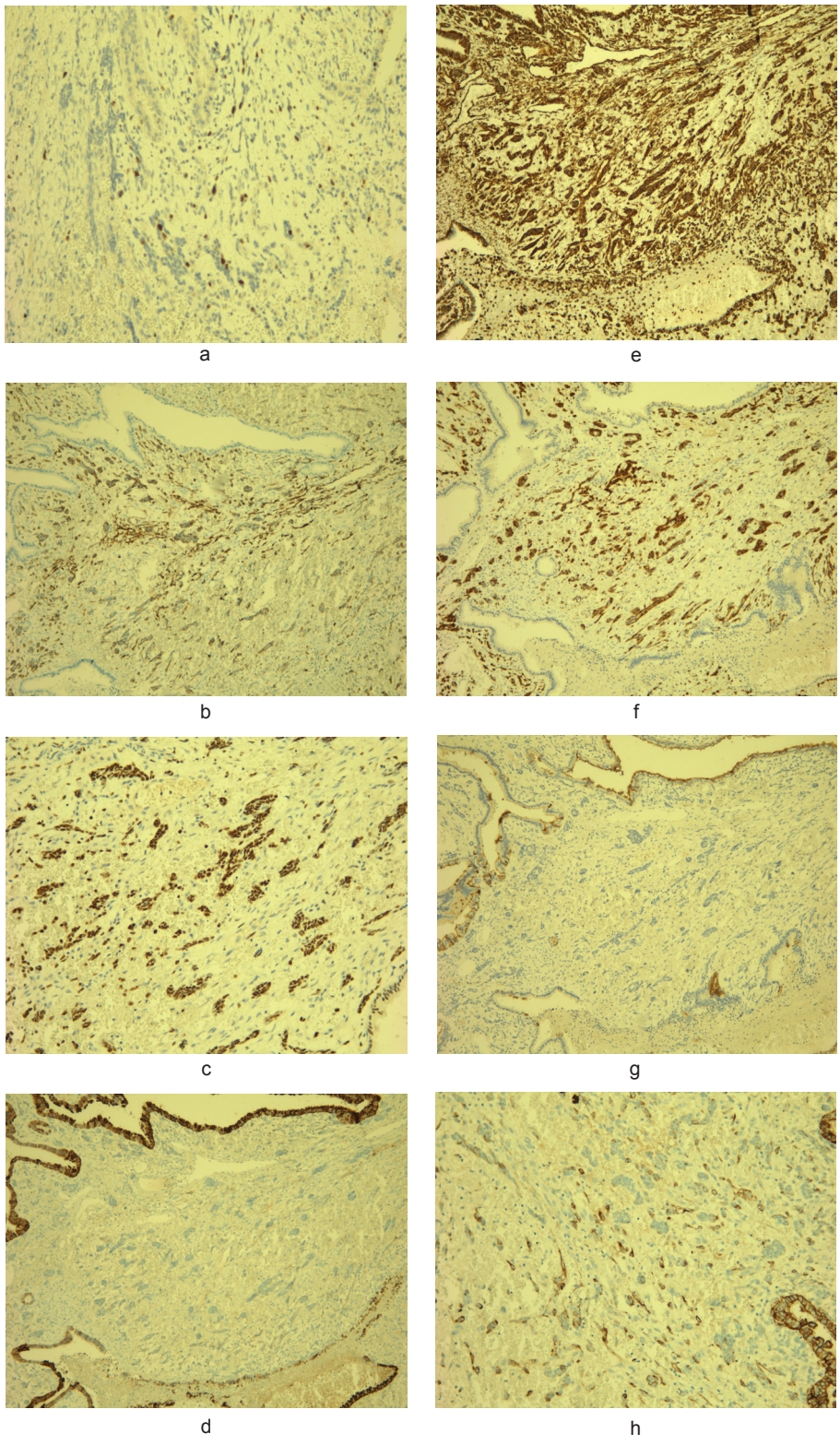

Fig.1. a-h Sex cord-stromal tumor of the fallopian tube. Immunohistochemical study with antibodies of: a) Ki-67 – proliferation in 3% in tumor cells; b) Desmin – expression in tumor cells; c) WT1 – expression in tumor cells; d) EMA – absence of expression in tumor cells; e) Vimentin – expression in tumor cells; f) Calretinin – expression in tumor cells; g) Mesotelin – absence of expression in tumor cells; h) CK8/18 – expression in some tumor cells.

use of immunohistochemical studies with a wide panel of antibodies is required, which allows to clarify the immunophenotype of the tumor. Preoperative diagnosis of uterine tube tumors is also extremely uninformative [11] - clinical symptoms are either absent or poorly specific. The diagnostic panel includes a number of clinical, laboratory and instrumental methods of research, and if SCST is suspected - the level of inhibin, estradiol, testosterone and alpha-fetoprotein (AFP) should be evaluated: elevated levels of inhibin and estradiol can be detected in granulosa-cell tumors, and tumors from Sertoli-Leydig cells are characterized by increased testosterone levels or, rarely, AFP [10].

Clinical tactics for tumors with an uncertain (or low) degree of malignancy and biological behavior is determined by the stage of TNM and FIGO systems [4]. In children, adolescents and women of reproductive age, as a rule, fertility-preserving operations are considered in patients with SCST at stage I according to FIGO [10]. Patients after surgical treatment are under dispensary supervision for the first two years to determine the level of tumor markers in the blood serum and ultrasound and CT of the pelvic organs (The National Comprehensive Cancer Network (NCCN)).

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A CLINICAL CASE OF BRUTON AGAMMAGLOBULINEMIA IN A CHILD OF THE REPUBLIC SAKHA (YAKUTIA)

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Bruton's disease is a genetic disease associated with impaired synthesis of serum immunoglobulins and B cells. The disease refers to primary immunodeficiency.

This article is devoted to the description of the clinical course of Bruton's disease in a child. The child has a history of 6 episodes of pneumonia. Primary immunodeficiency is suspected in the Pediatric center. Then the child is sent to the leading scientific institution of pediatric Oncology and immunology and the diagnosis is clarified. Clinical diagnosis: Primary immunodeficiency. Bruton's Disease. All patients with Bruton's disease require lifelong replacement therapy with intravenous immunoglobulins. Early diagnosis of primary immunodeficiency in children will avoid the risk of life-threatening conditions. Primary care pediatricians should be wary of the disease.

Keywords: immunodeficiency, immunoglobulins, patient, hereditary disease.

Introduction. Bruton agammaglobulinemia is a hereditary disease, associated with synthesis of serum immunoglobulin and B-cells. The disease is referred to the primary immunoidefficiency diseases. It was first described by Dr. Ogden Bruton, an American pediatrician, in 1952. He reported of an 8-year old boy, suffering from different infectious diseases. The boy was 14 times infected by pneumonia from the age of 4, besides he had otitis, sinusitis, sepsis and meningitis. In the blood analysis no antibodies were found out.

A molecular mechanism was first performed in 1993, when two groups of the scientists independently demonstrated that X-linked agammaglobulinemia resulted from mutation at non-receptor tyrosine kinase gene, which was later named as Bruton's tyrosine kinase [1,2].

The disease is manifested by frequent viral infectious diseases complicated by bacterial ones. Genetic defect is present on the long arm of the X-chromosome resulting in mutation of cytoplasmic protein kinase gene. Thymus gland size and structure are within the norm, the number and function of T-lymphocytes in peripheral blood are not changed. No germinal centers and plasmatic cells are present in lymph nodes. Low concentration of B-cells and immunoglobulins of all isotypes are defined [3,4].

Bruton agammaglobulinemia is transmitted by X-linked recessive inheritance; the disease is common only for males (with XY sex-determination system). Females do not develop Bruton agammaglobulinemia, even if they are heterozygous a recessive gene of an X-chromosome is compensated by normal gene homologous X-chromosome. The disease is common for males with 1:25000 of prevalence.

Objective: A clinical case of a boy with Bruton agammaglobulinemia is described in the article.

Materials and methods: We have analysed a case report of the patient made by the Consultative polyclinic, the Pediatric Center of Republican hospital #1 under National Center of medicine. The boy has been examined there for 2 years.

Clinical description of Bruton agammaglobulinemia. Anamnesis: A second pregnancy boy was born on the 40 week of gestation by operative delivery. The boy was breast-fed until he was 1 year and two months. He lives in a village. His psychomotor development was according to his age. From the very first days after delivery he suffered from the infection of the upper respiratory system once a month, by the age of 3 he developed acute pneumonia 6 times, he had chronic otitis and sinusitis. When he was 4 he developed pains in the joints, the child could not walk. In November 2018 the child was referred to the cardiorth-eumotology department of the Pediatric center of the Republican hospital #1, National health center.

On admission he complained of the pains in joints, a stuffy nose and purulent nasal discharge.

The condition was estimated as grave. Skin surface was moderately moist and swarthy. Mucous membrane of the oral cavity was rose and moist. The pharynx was not hyperemic. The tonsils were not enlarged, without coating. Nasal breathing was complicated, and there was nasal discharge of purulent origin. On auscultation the respiration was vesicular, no crackling sounds were present. There was no cough and dyspnea. Heart sounds were loud and rhythmic. The abdomen showed no pain on palpation. Stool was regular and formed. The liver was on the costal margin and painless. The spleen was impalpable. Urine was unchanged, no dysuria. No signs of meningeal and focal disorder were noticed.

Laboratory findings: tests for rheumatoid disorders were within the norm: rheumatoid factor – 10 mUn/ml, C-reactive protein – 2.1 mg/ml, antistreptolysin O 120 Un/l. Immunogram data reveal impaired humoral immunity. The immunogram shows absence of immunoglobulin A, and reduced level of immunoglobulin M and G.

On admission (12.11.2018) total blood analysis showed: hemoglobin (120 g/l); erythrocytes 4.77x1012 /l, leucocytes 10.76x109 /l, sedimentation rate 15 mm/hr.

In 13.09.2019 the electrocardiogram revealed a sinus rhythm. The electrical axis shows vertical position. The ultrasound investigation of the organs of the abdominal cavity revealed no abnormalities.

In 13.09.2019 the boy was examined by an otolaryngologist. The examination revealed chronic otitis of both ears, dry anterior rhinitis.

The child is hereditary complicated by his mother side. The patient's mother said that her brother died of acute pneumonia at the age of 5.

As a result of examination at the con-

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Indices of immune status, 12.11.2018

Index	Result	Reference interval
IgA total	0.00mg/ml	(0.7-3.00)
IgM total	0.07 mg/ml	(0.6-2.00)
IgG total	4.9 mg/ml	(8.00-16.00)
Complement C4	29.16 mg/dl	(9.00-36.00)
Complement C3	113.80 mg/dl	(75.00-135.00)
CD3+	94.00%	(62.00-69.00)
CD16+CD56+	2.17%	
CD4CD8	4.00%	
CD4+	63.00%	(30.00-40.00)
CD8+	29.00%	(25.00-32.00)
CD19+	2.00%	
CD3+HLA-DR+	6.00%	(8.00-12.00)
CD25+	6.00%	
IgE total	1.5 IU/ml	(0.00-100.0)
Circulating immune complex	35 IU	

sultative polyclinic of the Republican hospital #1, National health center, the boy was diagnosed with primary immunodeficiency, chronic otitis of the both ears, dry anterior rhinitis. In January 2019, the child was referred to the department of immunology at the National research medical center of children hematology, oncology and immunology. After profound examination he was diagnosed with primary immunodeficiency, Bruton agammaglobulinemia, chronic bilateral otitis, and dry anterior rhinitis.

There were the following recommendations:

1. Regular follow-ups at a local immunologist, pediatrician, and otolaryngologist.

2. Life-long replacement therapy with immunoglobulin – Ig Vena.

3. In a case of infectious process not less than 2-week of intravenous antibiotics of wide spectrum (like cephalosporins of the 3rd-4th generation, macrolids, and aminoglicosyds) therapy should be recommended.

4. Total blood analysis with leukogram, biochemical blood analysis and immunogram once in 3 months.

5. Preventive inoculations are not recommended as they are ineffective in that case. Mantoux test (Diaskin test) should be annual.

6. In a case of next pregnancy the mother is recommended to carry out prenatal genetic screening between 9 and 10 weeks.

7. Molecular-genetic investigation of inheritance through the female line, and immunological examination of (IgA, IgG, IgM) of males through the female line.

8. Taking into account that primary immunodeficiency is genetically determined disease with inevitable breakdown of the immune system functions and with high risk of life-threatening bacterial infections, autoimmune processes; it requires life-long replacing therapy with IV-introduced immunoglobulins; replacement therapy refuse results in life-threatening conditions with infectious and autoimmune complications. Thus, for the reasons given that the child has a severe breakdown with stable disturbance of the functions of the body resulting in limited life-style and necessity of social support (including rehabilitation), in accordance with the Government order of the Russian Federation 20.02.2006 #95 “On order and recognition of the disability of the individual” it is recommended to refer the patient to the local medical and social disability examination. In accordance with the Government order of the Russian Federation #339 29.03.2018 “On introduction of changes in the Rules of disability acknowledgement” disability is acknowledged by the age of 18 for the patients with primary immunodeficiency.

Since February 2019 the child is regularly examined by the immunologist, the otolaryngologist, and the pediatrician of the Consultative polyclinic of the Republican hospital #1, National health center.

From February 2019 to September 2019 the patient took IV immunoglobulin (Ig Vena 10 gr) 6 times. The patient is examined monthly: he is taken blood analysis, biochemical blood examination, immunogram, and immunoglobulin of peripheral blood. For the time mentioned the child suffered from acute respitatory viral infection once and there were no recurrent cases of otitis. The child is considered as disabled.

Thus, IV immunoglobulin introduction is necessary for the patients with Bruton agammaglobulinemia to prevent life-threatening complications.

Conclusions:

1. All the patients with Bruton agammaglobulinemia should have life-long IV-immunoglobulin therapy.

2. Early diagnosis of primary immunodeficiency among children can prevent life-threatening conditions afterwards.

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ОБМЕН ОПЫТОМ

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HETEROGENEITY OF METASTATIC GASTRIC NEUROENDOCRINE TUMOR

The purpose of the study was to demonstrate the effect of heterogeneity of a tumor and its metastases on the choice of treatment tactics in a clinical case. A patient with gastric neuroendocrine cancer and liver metastases was examined. According to immunohistochemical analysis, the primary neuroendocrine tumor (NET) of the stomach was highly differentiated (NET, G1). In liver metastases S1, S2, S5, S8, NETs were moderately differentiated (NET, G2), and in S7 NETs were poorly differentiated (NEC, G3), demonstrating the tumor heterogeneity which progressed as the malignant process developed. Only in the low-differentiated NETs (NEC, G3), the reaction with Chromogranin A was negative, which is typical of low-differentiated NET. The reaction with SSTR2 was moderately and sharply expressed in liver metastases S7, S5, S8 and, on the contrary, was nearly undeterminable in the primary NET of the stomach and in liver S1, S2. The clinical case demonstrates the phenomenon of tumor heterogeneity and the associated ambiguity of the results of immunohistochemical research. Therefore, testing of tumors prior to the treatment is of paramount clinical importance for the correct treatment choice and disease prognosis. The development of specific molecular markers for the diagnosis of neuroendocrine tumors remains an actual problem of oncology.

Keywords: intratumoral heterogeneity, genetic instability, gastric neuroendocrine tumor, somatostatin receptors.

Background. The problem of metastatic neuroendocrine tumors (NETs) is extremely relevant in modern clinical oncology, because most NETs, being functionally inactive, often clinically manifest only at the metastasis stage. One of the main problems also lies in the peculiarities of molecular biology of metastatic foci whose characteristics do not always coincide with that of the primary tumor. The main mistake of the "default" treatment is that it considers the response to therapy only in the primary tumor based on its differentiation, hormonal status and other indicators. Hence the obvious conclusion why therapeutic treatment cannot give positive results in every case [3].

Currently, there is no doubt that the tumor is a complex dynamic system. Starting from a genetically normal cell, the tumor process leads to the formation of a population consisting of trillions of tumor cells that have formed many different phenotypes providing more aggressive behavior [1]. Thus, over time, the tumor modifies its characteristics, which leads to a number of differences in the cells of the primary tumor and metastases, which, in essence, constitutes tumor heterogeneity [2]. This phenomenon was first described by Rudolf Virchow in the mid-19th century. "The increased instability of the genome, being a necessary reason for the formation of highly aggressive cell populations within the tumor, together with the ongoing selection, underlies the intratumoral heterogeneity" [2]. This thesis by Peter Novel started the modern era of the study of this phenomenon, extremely complex and diverse in its forms.

Numerous studies of recent years report phenotypic and genotypic differences between the cells of primary tumors and metastases, as well as heterogeneity of metastatic foci of the same tumor. These differences may apply to tumor cells at both the morphological and functional levels. Meanwhile, primary and metastatic tumors are considered to be able to develop as genetically different when metastatic spread occurs at an early stage of tumor progression [1, 3].

The intratumoral heterogeneity is based on genetic instability, including both gene and chromosomal mutations and microsatellite instability [4]. Along with genetic mechanisms, there are also epigenetic factors that enhance or weaken various damage to the cell genome and are quite reversible [4, 5, 6]. Heterogeneity also inevitably arises from "noise processes" - stochasticity in the gene expression which results in the production of genetically identical cells of different levels of specific proteins at every moment [2]. The phenotypic heterogeneity of tumor cells is a consequence of both the above mechanisms and the influence of the tumor microenvironment, which is especially significant in metastatic foci [2, 6]. This means that tumor cells adapting to a new microenvironment acquire new properties that cause an increase in heterogeneity. The oncologist has to prescribe combined targeted therapy taking into account heterogeneity of the primary tumor and metastases by a number of different signs [1, 2, 4, 5].

According to the American Association for Cancer Research (AACR), the treatment for a patient in the near future may look like this: a biopsy of metastases; DNA analysis of tumor cells in the plasma by digital PCR with determination of the molecular and genetic profile of the tumor; prescribing a universal drug active for the revealed changes; subsequent assessment of the molecular and genetic profile in patients with disease progression; the appointment of a new drug that

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suppresses the activity of newly identified changes [3, 7].

Thus, all of the above determines the high relevance of studying the problem of tumor heterogeneity in all forms of its manifestation, and the development of new approaches to the treatment of malignant neoplasms is the most important task of modern oncology.

The purpose of the study was to demonstrate the effect of heterogeneity of a tumor and its metastases on the choice of treatment tactics in a clinical case.

Material and methods. A standard immunohistochemical study was performed on sections with a thickness of 3-5 μm prepared from paraffin blocks using Autostainer (Autostainer, ThermoScientific, type 480s). Deparaffinization of sections and restoration of antigenicity was performed in a buffer with pH 9 in PT Module (ThermoScientific, UK). An immunohistochemical study included antibodies to chromogranin A, synaptophysin, and nonspecific enolase (NSE). Antibodies to Ki-67 were used to evaluate the proliferative activity of tumor cells; monoclonal antibodies, Anti-somatostatin Receptor 2, were used to detect the expression of somatostatin receptors.

Results and discussion. Patient G. was admitted to Department of Abdominal Oncology No.1, Rostov Research Institute of Oncology, with the diagnosis of gastric neuroendocrine cancer, T3NxM1, stage IV, clinical group 2, secondary (metastatic) liver cancer. A council of physicians (surgeon, chemotherapist and radiologist) recommended surgical treatment according to the clinical practice guidelines for the treatment of gastrointestinal (GI) NETs by the Association of Oncologists of Russia. The surgery involved gastrectomy with extended lymphadenectomy using laparotomy access with atypical resection of S1, S2, S5, S7, S8 of the liver. The surgery and the postoperative period proceeded without complications. Tissue samples were referred for pathohistological and immunohistochemical testing.

Pathohistological testing showed: neuroendocrine tumor, sporadic ECL-cell (type III), alveolar and pseudoglandular growth with ulceration and germination into all layers of the stomach wall, invasion of subserous fatty tissue, lymphatic and blood vessels, pT3N2M1 (hep).

Immunohistochemical analysis showed that primary gastric neuroendocrine tumor was highly differentiated (NET, G1), according to the WHO classification of GI NETs from 2010, with a Ki-67 proliferation index = 1.8%. Reactions with chromogranin A, synaptophysin, NSE were highly pronounced. These markers are included in the minimum NET diagnostic panel, and positive reactions with them reliably confirm the NET diagnosis. Reactions with specific markers of the extended diagnostic panel (gastrin, insulin, glucagon, serotonin, etc.) were negative, indicating the non-functioning nature of the tumor. NET metastases of a similar nature with Ki-67 proliferative activity index up to 9.5% (NET, G2) were detected in 3 of 12 examined lymph nodes.

5 remote metastatic foci in the liver (S1, S2, S5, S7, S8) were examined immunohistochemically. The Ki-67 proliferation index calculated at the “hot spots” manually was 12.2% (S2), 14.5% (S1), 17.1% (S8), 18.3% (S5), 27.4 % (S7). Thus, in liver metastases S1, S2, S5, S8 NETs were moderately differentiated (NET, G2), and in S7 NETs were poorly differentiated (NEC, G3), demonstrating the tumor heterogeneity which progressed as the malignant process developed. The proliferative activity assessed by the Ki-67 level is an indicator of the tumor phenotype, which determines the tumor growth rate, its course and outcome. Therefore, in our clinical case, the disease outcome was determined both by the fact of liver metastases and by an extreme biological aggressiveness of the metastatic foci themselves. Only in the low-differentiated NETs (NEC, G3), the reaction with Chromogranin A was negative, which is typical of low-differentiated NETs [2, 3]. This suggests probable differences in the results of immunohistochemical reactions between the primary NET (localized in the stomach in this case) and metastatic foci in the liver, which only confirms the phenomenon of tumor heterogeneity.

For the primary tumor and metastatic nodes, a reaction was performed to establish the expression of type 2 somatostatin receptors (SSTR2), and it gave mixed results. The reaction with SSTR2 was moderately and sharply expressed in liver metastases S7, S5, S8 and, on the contrary, was undeterminable in the primary NET of the stomach and in liver S1, S2. In our case, the expression of SSTR2 in clinically significant amounts increased as the malignant potential increased. It is impossible to reliably speak of a clear relationship between the NET differentiation and the level of SSTR2expression, since these observations are not enough and studies on a large and representative sample are necessary. In any case, we recommend determining the status of SSTR2 (as the most common type of a somatostatin receptor) before starting NET treatment in a routine morphological study. In our opinion, this will expand the possibilities of therapy. Russian specialists have already gained sufficient experience with the use of somatostatin analogues for the treatment of NETs, mainly GI and pancreatic ones [1].

Conclusions. The presented clinical case clearly demonstrates the phenomenon of tumor heterogeneity and the related ambiguity of the results of immunohistochemical studies. Therefore, the immunohistochemical testing of neuroendocrine tumors is of crucial clinical importance even before the start of treatment to select the correct treatment regimen and for the disease prognosis. The development of specific molecular markers for the diagnosis of cancer remains an actual problem of oncology.

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MORPHOMETRIC PARAMETERS OF MAMMARY GLANDS IN WOMEN OF DIFFERENT BODY TYPES IN NORMALITY AND IN BREAST CANCER

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Objective: to compare macromorphometric breast data with the constitution of women who need aesthetic breast correction in normal conditions and in breast cancer.

Material and methods. There was conducted macromorphometry of the mammary glands in 101 healthy women and 24 women with a confirmed diagnosis of breast cancer, using the Body Logic system, as well as anthropometry and somatotyping with indication of sthenic, ectomorph and endomorph body types.

Results and discussion. Among women with aesthetic problems of mammary glands, tubular breast deformity was revealed in 17.6% of sthenics, 23.5% of ectomorphs, and 58.8% of endomorphs. In breast cancer, tubular deformity was not detected. The Norwood Index, as an objective criterion of tubularity, had the largest value in endomorph women.

Conclusion. Endomorph women were more susceptible to the development of tubular breast deformity in comparison with women of other body types. In the physique of women with breast cancer, asthenomorphy predominates.

Key words: mammary gland, breast cancer, morphometry, tubularity, somatotype.

Introduction. In modern mammology, much attention is paid not only to the health of the mammary glands, but to the aesthetics as well [1- 3, 5]. High concern of women for their appearance, including breast, necessitate constant improvement in plastic surgery technologies. Breast surgical procedures performed in the modern world can be called the evolutionary achievement of medical science. At the same time, aesthetic operations with the use of silicone implants sometimes lead to adverse medical consequences - these can be both clinical complications and patient's dissatisfaction with the result.

Capsular contracture is one of the most frequent clinical complications of augmentation mammoplasty. According to the data from different authors, it occurs in about 74% of women. Furthermore, in 12% of women the formation of a dense capsule around the implant requires re-operation in the first 2 years given that this percentage increases with time and over the next 3 years it reaches 20%. The prevention of the development of capsular contracture has been worrying plastic surgeons since the introduction of mammoplasty into practice. By now, there has been identified a sufficient number of reasons causing capsular contracture. However, there is no single treatment, neither criteria have been developed to predict the development of capsular contracture nor preventive measures [5, 9]. In this regard, fundamental disciplines can help the surgeon. In particular, constitutional anatomy allows us to consider issues of breast surgery from individual perspective [6]. However, despite all the relevance of the clinical anatomy of mammary glands in terms of its practical application, studies that compare the morphometric characteristics, taking into account the constitution of the body, are not numerous.

Also of great scientific interest is breast cancer. The disease, its pathogenesis, clinical course have been the subject of many studies in oncoepidemiology. In the literature, there are works related to the nature of the course of cancer in humans, depending on the type of physique.

In connection with the importance of the problem, there was set the objective of the research: to conduct a comparative analysis of the results of breast macromorphometry and the somatotype of women who need aesthetic breast correction, as well as in breast cancer.

Material and methods. The research was carried out among 101 women of the first period of mature age (21-35) who applied to the clinic of plastic surgery for the possibility of surgical correction of mammary glands. The criterion for exclusion from the survey was the presence of childbirth in case history. Twenty-four women with a specified diagnosis of breast cancer were also examined.

Breast macromorphometry was carried out using the Body Logic system, developed specifically for the company "Mentor", a manufacturer of silicone implants [7]. The following measurements were included into the research program: the distance from jugular notch to breast crease, from jugular notch to nipples, from nipples to breast crease, from nipples to breast crease under tension, thickness of the skin-glandular fold in the upper poles of the mammary gland. The elasticity of the skin in the lower pole region was also evaluated.

After measuring the diameter and degree of protrusion of the areola, the Norwood index (IN) was calculated using the following formula: IN = areola protrusion / areola diameter. On the basis of IN value, tubular breast deformity was either established or excluded.

Somatotype was defined by Rees-Eysenk index distinguishing three body types: sthenic, ectomorph and endomorph. Body mass index (BMI) was also calculated, the values of which were in-

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terpreted in accordance with the WHO recommendations.

In the statistical processing of the retrieved data, nonparametric methods for data analysis were used in MS Office Excel 2010, as well as SPSS Statistics 22.0. Central tendencies and dispersions of quantitative characteristics were evaluated by the median, the third and the first quartiles of LQ; Uq. The significance of intergroup differences in quantitative characteristics was evaluated using the non-parametric Mann-Whitney U test, qualitative – using $\chi 2$ criterion. Correlation analysis was also used.

Results and discussion. The examined women were divided into three groups according to their somatotypes: normosthenic (sthenic) somatotype was detected in 32.7% of women, asthenic (ectomorph) - in 33.7%, and endomorph (pyknic) type - in 34.6% of women.

The median length of women's body was 164.0 [158.8; 167.2] cm, body weight - 62.8 [59.4; 64.7] kg. It should be noted that endomorphy (pyknic type) is not always associated with overweight; it can be connected with large size of the chest, defined in the frontal plane. Our research confirmed this concept. Among the examined women there were no registered persons with overweight and obesity. 80.2% of women had normal BMI values. 19.8% of women had weight deficit.

The use of individual typological approach during the initial examination of women revealed a number of significant features of the morphometric parameters of the mammary glands, depending on the body type. In women of sthenic somatotype, the distance from the jugular notch to the breast crease was 24.7 [24.1; 25.2] cm, which is significantly less than that of the representatives of asthenic somatotype (25.5 [23.6; 25.7] cm) and more than that of the pyknic somatotype (23.4 [20.5; 26.2] cm).

According to the distance from the jugular notch to the nipple, somatotypes were clearly ranged: the smallest distance was found in sthenics (17.0 [16.5; 17.1] cm), the biggest one in endomorphs (18.3 [17.9; 18.6] cm), ectomorphs occupied a middle position between the sthenics and endomorphs by the value of this parameter (17.5 [17.3; 17.6] cm). Also, women of pyknic type were characterized by minimal values of the distance from the nipple to the breast crease at rest and during tension in the absence of statistically significant differences in the indicated characteristics between the representatives of asthenic and sthenic somatotypes. The thickness of the skin-glandular folds in the upper poles of the breast and skin extensibility in the area of the lower pole of the gland revealed no typological features (table 1).

Tubular breast deformity was detected in 33.6% of women who needed aesthetic correction. At the same time, a differentiated approach to this problem, taking into account the body type, made it possible to identify a number of specific features. Thus, the Norwood index for women of sthenic type was 0.31 [0.24; 0.36], which was not significantly different from asthenic - 0.27 [0.24; 0.36], p = 0.158. At the same time, women of pyknic type were characterized by its higher values - 0.44 [0.24; 0.57]; p = 0.023.

The frequency distribution of the tubular mammary gland, depending on the somatotype, is presented in Figure 1.

It was adjusted that the aesthetic problems of women of pyknic somatotype were due to the presence of tubular breast deformity, which was registered in 58.8% of cases in our study. Among ectomorphs, the tubular mammary gland was found in 23.5% of cases, and in 17.6% of cases in sthenics.

The correlation of the tubular breast deformity with the morphometric parameters of the mammary gland and the somatotype was objectively confirmed by the results of the correlation analysis. There were established strong inverse correlations between the Norwood index and the distance from the jugular notch to the breast crease (r = -0.865), the Norwood index and the distance from the nipples to the breast crease in a free state (r = -0.879) and under tension (r = -0.885). Also, this index correlated with the thickness of the skin-glandular fold in the region of the upper pole of the mammary gland (r = 0.716) and the elasticity of the skin in the region of the lower pole of the gland (r = -0.674).

There were found direct correlations of the average force between the Norwood index and BMI (body mass index) (r = 0.523). In other words, when the BMI was higher, there was a greater risk of the formation of tubular breast deformity.

It was revealed that women suffering from breast cancer mainly belong to the asthenic type of physique. This somatotype occurred in 18 of the 24 examined. A picnic somatotype was detected in 4 patients, and only in 2 women the physique was rated as normosthenic.

Preoperative macromorphometry of the mammary glands did not reveal a single case of tubular deformation of the gland.

Conclusion. The need for anatomical justification in determining the tactics of corrective surgery of the mammary glands is out of the question. Questions of the anthropological approach during mammoplasty had already been raised earlier. In the work of V.N. Casanova et al. [4] special attention was paid to the influence of the ethnic component on the formation of various forms of mammary glands, it was recommended to consider it when selecting an implant and it was important for the development of measures to prevent adverse postoperative complications. At the same time in the available literature there was practically no information about the constitutional features of the morphometric parameters of the mammary glands in the formation of its anatomical features that require aesthetic correction. In the present work, there had been made an attempt to com-

Morphometric parameters of mammary glands depending on somatotype

Parameter	Somatotype		
	Normosthenic	Asthenic	Pyknic
Distance from the jugular notch to the submammary fold, sm	24.7 [24.1; 25.2]	25.5 [23.6; 25.7]	23.4 [20.5; 26.2]
	p_{1-2}=0.003; p_{2-3}=0.012 ; p_{1-3}=0.031		
Distance from the jugular notch to the nipple, cm	17.0 [16.5; 17.1]	17.5 [17.3; 17.6]	18.3 [17.9; 18.6]
	p_{1-2}<0.001; p_{2-3}<0.001; p_{1-3}<0.001		
Distance from the nipple to the submammary fold, sm	8.1[8.0; 8.2]	8.1 [7.8; 8.3]	4.8 [2.5; 8.1]
	p_{1-2}=0.560; p_{2-3}=0.013; p_{1-3}=0.008		
Distance from the nipple to the submammary fold in tension, sm	9.7 [9.5; 9.8]	9.7 [9.3; 9.9]	6.0 [4.0; 9.9]
	p_{1-2}=0.925; p_{2-3}=0.048; p_{1-3}=0.044		
Thickness of the skin-glandular fold in the upper poles of the breast, cm	2.8 [2.7; 3.1]	2.5 [2.1; 3.0]	3.2 [2.3; 3.4]
	p_{1-2}=0.065; p_{2-3}=0.078; p_{1-3}=0.089		
Skin extensibility in the area of the lower pole	1.6 [1.5; 1.7]	1.6 [1.4; 1.7]	1.5 [1.4; 1.8]
	p1-2 =0.905; p2-3 =0.765; p1-3=0.771		

pare the data of breast morphometry with the body type of women, which we regard as a scientific novelty. According to the results of the work, the following conclusion can be made: women of pyknic somatotype were more susceptible to the development of tubular breast deformity in comparison with women of other body types. Given the conjugation of pycnomorphy of the physique with the formation of tubular deformation of the breast and asthenomorphy with breast cancer, it can be assumed that there is no connection between the development of this disease and the presence of the tubular form of the mammary gland.

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MEDICAL AND SOCIAL CHARACTERISTICS OF PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 1 WHO RECEIVED SUPPORTIVE CARE WITHIN THE CONFINES OF THE CNDD OF THE YSC CMP

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A retrospective analysis of the data of patients with spinocerebellar ataxia type 1 who received supportive care at the Center for Neurodegenerative Diseases at the YSC CMP Hospital for the period from September 2017 to June 2019 was performed. Data on age, educational and marital status are presented, and in particular, an analysis of the change in type of professional activity and family status associated with the period of pronounced manifestation of the SCAI clinic was carried out. During the period described, 52 patients received supportive care, which confirms the demand for supportive care among patients with SCAI. Low referral of patients from SCA1 endemic regions is associated with financial and climatic transportation difficulties of affected families and low awareness of specialists on-site. Of 6 patients under 35 years of age, 5 patients had inherited the mutant gene on the paternal side, which predetermined the early onset of the disease. Of the 8 patients over 60 years of age, seven had inherited the disease through the maternal line, which explains the later onset of manifestations and the more benign course of SCAI. A woman's awareness of the presence of a mutant gene for SCAI does not change her plans for childbirth. Perhaps the disease indirectly affects the change in the marital status of patients, in particular the number of divorces in women. In order to slow down the progression of the disease, ensure medical and social rehabilitation, improve the quality of life and social status of patients with SCAI, it is necessary to organize the provision of regular supportive care, monitor timely presentation at MSE, and provide full medical, social and psychological assistance on-site.

Keywords: Neurodegenerative disease, spinocerebellar ataxia, supportive care, social characteristics.

Introduction. Hereditary spinocerebellar ataxias are heterogeneous neurodegenerative diseases, the main characteristic of which is impaired coordination of movement due to degeneration of the cerebellum, afferent and efferent neuronal systems. To date, according to the transmission mechanism in generations, hereditary ataxia is divided into autosomal dominant, autosomal recessive, X-linked forms and ataxia with a mitochondrial type of inheritance. And also sporadic forms with an unidentified or unknown mechanism of genetic transmission are distinguished [1].

One of the most common hereditary neurodegenerative diseases in Yakutia is spinocerebellar ataxia type I (SCAI) (4). The frequency of SCAI in Yakutia is 46 cases per 100 thousand of the rural population, compared to 1-2:100 thousand in the world population [2,4]. The absence of a state support program for patients with hereditary ataxia in particular, and neurodegenerative diseases in general, predominantly late manifestation, severe progredient course, incurability, shortage of medical and nursing staff, and an ever increasing load due to urgent patients in specialized neurological departments, generate a lot of medical, epidemiological, organizational, ethical, social and psychological issues.

In order to implement the Decree of the President of the Russian Federation No. 204 "On National Goals and Strategic Tasks of the Development of the Russian Federation for the period until 2024" dated 07.05.2018 - the Center for Neurodegenerative Diseases (CNDD) with the NDD laboratory was created by order of the Director of the YSC CMP No. 08-06/295A at the Federal State Budget Scientific Institution YSC CMP from November 1, 2018.

An order of the Minister of Health of the Republic of Sakha (Yakutia) No. 01-07/184 dated 14.02.2019 “On the routing procedure for neurological patients suffering from neurodegenerative diseases at the outpatient and hospital stages” was also issued in order to improve the provision of specialized neurological care for patients with neurodegenerative diseases, residents of the Republic of Sakha (Yakutia) at the outpatient and hospital stages, based on the Decree of the Head of the Republic of Sakha (Yakutia) dated 27.12.2016 No. 1637 “On approval of Statutes on the Ministry of Health of the Republic of Sakha (Yakutia) and its board, and pursuant to the order of the Ministry of Health of the Russian Federation on 15.11.2011 No. 926n “On approval of the Process of provision of medical care to adults with diseases of the nervous system” [5]

With the opening of the Center for Neurodegenerative Diseases within the confines of the YSC CMP Hospital, systematic supportive care for patients with SCAI became more accessible, which made it possible to provide better medical care and draw attention to the many diverse problems of patients with hereditary ataxia in Yakutia.

Aim of the study: medical and social analysis of patients and development of

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principles for the provision of supportive care to patients with SCA1.

Materials and methods. The study was conducted at the YSC CMP Hospital in the Department of Neurodegenerative Diseases. For retrospective analysis, medical histories, genetic maps of patients with SCAI, their survey, medical and genetic counseling results and analysis of the pedigree of patients who were on regular supportive care (SC) were used. Predominantly all patients were from known pedigrees, and most of them were previously tested for the presence of the SCA1 mutation in the MGC of the RH No. 1 - NMC. The work also used statistical and analytical research methods.

Results and discussions. During the period described, 52 patients received supportive care: 18 were men (34.6%) and 34 - women (65.4%). Out of 52 patients, 17 people (32.7%) lived in the city of Yakutsk, and 35 (67.3%) in other regions of the Republic of Sakha (Yakutia). Before the official opening of the Center for Neurodegenerative Diseases (CNDD), from September 2017 to October 2018 (14 months), 31 patients received supportive care, and for the six-month period after the opening of the CNDD, there were 51 patients, which averaged 2.2 hospitalizations one month before , and 7.3 hospitalizations of patients with SCAI after the opening of the Center of NDD. This fact confirms the demand for supportive care among patients with SCAI.

Referral of patients to SC from Yakutsk hospitals was as follows: 6 patients were referred from hospital No. 3, 5 patients from the Medical Center of Yakutsk, 4 patients from hospital No. 1, and one patient from the YSC CMP Hospital. Hospitalization of patients from regions of the Republic of Sakha (Yakutia) is presented in Fig. 1. Low referral of patients from SCA1 endemic regions is associated with financial and climatic transportation difficulties of affected families and low awareness of specialists in district hospitals, outpatient clinics and paramedic stations in the villages.

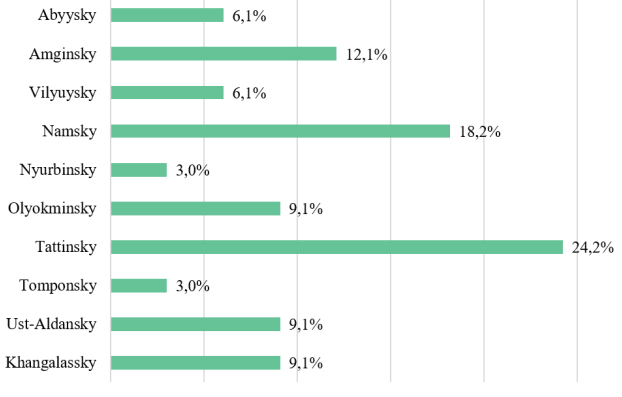

Fig. 1. Structure of referral of patients on supportive care across the Republic of Sakha (Yakutia)

Considering the late-manifesting factor of spinocerebellar ataxia type 1, an analysis of the age of the subjects is of particular interest (Fig. 2). Of 6 patients under 35 years of age, 5 patients had inherited the mutant gene on the paternal side, which predetermined the early onset of the disease. Of the 8 patients over 60 years of age, seven had inherited the disease through the maternal line, which explains the later onset of manifestations and the more benign course of SCAI.

An analysis of the educational level of patients who underwent SC showed that 27 participants in the study had higher education, which amounted to 51.9%, with secondary vocational education - 22 (42.3%) and with a secondary general education - 3 patients (5.8%). 31 (63.2%) out of 49 patients were working in a specialty relevant to their education. Since the onset of severe manifestations of the disease, 35 (68%) patients switched to light work. Seven (13%) patients had to leave work since the onset of severe manifestations of the disease. Among patients there were two researchers with a scientific degree, two physicians. Three of the patients worked in the municipal government before the onset of severe manifestations of SCAI.

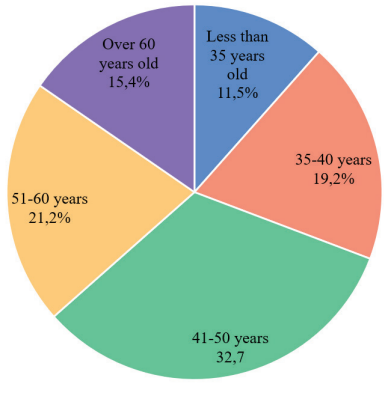

Fig. 2. Age structure of patients that have received supportive care

An analysis of marital status revealed that of the total number of divorcees, only two marriages broke up before the onset of the manifestation of the disease (Fig. 3). It is worth noting that men are more likely than women to get divorced after the onset of the manifestation of the disease in his wife. Thus, the number of divorces among male patients is 1.5 times less than among women with SCAI. The presence of children in patients was distributed as follows: did not have children - 6 patients (11.5%), one child - 10 families (19.2%), two children - 15 patients (28.8%), 3 children - 14 families (26.9%), 4 children - 4 families (7.8%) and five children were in three families (5.8%). It should be noted that 15 women from 21 families with three or more children were carriers of the mutant gene, which confirms the conclusion about extended reproduction in families with SCA1 (4).

The majority of patients who received SC repeatedly underwent the MSE examination procedure to obtain a disability class based on their spinocerebellar ataxia type I. Thus, 14 patients had a class I disability, which accounted for 26.9%, 21 patients - class II (40.4%), class III - 13 (25%) and at the time of hospitalization on SC - 4 patients had no disability class (7.7%). The results of the analysis showed that among patients with a class I disability there were 11 women (32.3% among women), and only 3 men (16.7% among men). This fact is probably due to the persistence of the female half of patients in obtaining disability classes.

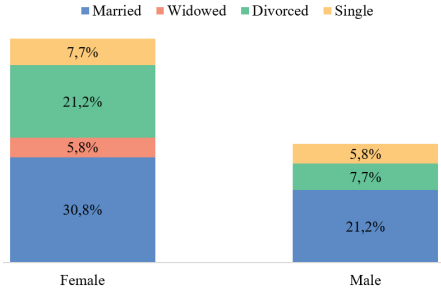

Fig. 3. Marital status of patients that have received supportive care

Conclusion. A more than a threefold increase in the frequency of hospitalizations for supportive care in the short period of time since the opening of the Center of NDD confirms the demand for SC in patients with SCAI. The analysis showed that most patients with SCA1 have higher education. A woman's awareness of the presence of a mutant gene for SCAI does not change her plans for childbirth. Perhaps the disease indirectly affects the change in the marital status of patients,

in particular the number of divorces in women. Women were more active and persistent in obtaining disability classes. In order to slow down the progression of the disease, ensure medical and social rehabilitation, improve the quality of life and social status of patients with SCAI, it is necessary to organize the provision of regular supportive care, monitor timely presentation at MSE, and provide full medical, social and psychological assistance on-site.

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