ISSN 1813-1905 (print)
ISSN 2312-1017 (online)

3(79) `2022

YAKUT MEDICAL JOURNAL

YAKUT MEDICAL JOURNAL

SCIENTIFIC - PRACTICAL JOURNAL
OF THE YAKUT SCIENCE CENTRE OF COMPLEX
MEDICAL PROBLEMS

Published since 2003

Quarterly

Registered by the Office of the Federal Service on supervision in the field of communications, information technologies and mass communications in the Republic Sakha (Yakutia) December 13/2016

Registration number PI No.TU 14-00475

Subscription index: 78781
Free price

«Yakut Medical Journal» is included in:

the approved by the Higher Attestation Commission of the Russian Federation List of leading peer-reviewed scientific journals and publications, in which the main scientific results of dissertations for the acquisition of scientific degrees of Doctor and Candidate of science on biological sciences and medicine should be published

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Yu.R. Akhverdyan, B.V. Zavodovsky, E.V. Papichev, Yu.V. Polyakova, L.E. Sivordova

SEASONAL VITAMIN D VARIATIONS IN OSTEOPOROSIS PATIENTS

DOI 10.25789/YMJ.2022.79.01

УДК 616.72

Objective: To study the seasonal variations of 25(OH) vit D in patients with osteoporosis.

Materials and methods. We observed 396 patients diagnosed with osteoporosis/osteopenia aged 24 to 93 years. The diagnosis of OP was based on the clinical recommendations of Osteoporosis-2021 approved by the Ministry of Health of the Russian Federation. All patients underwent dual-energy X-ray absorptiometry using the Lunar DPX apparatus. Vitamin 25(OH)D3 levels were determined using the commercial 25-OH Vitamin D ELISA kit. For statistical data processing, the software packages "STATISTICA 10.0 for Windows" were used.

Results. We have found that during the year most patients have significant seasonal changes in the 25(OH) vit D level. The minimum value was recorded in January and December (respectively, 50.85 and 55.83 nmol/l). We found significant differences in the concentration of 25(OH) vit D between patients who were observed in June and patients who were examined in the remaining months ($p<0.001$); as well as between patients examined in August and patients observed in the spring months ($p<0.05$). Similar significance was observed between July and April ($p=0.037$). It was found that the highest percentage of patients with vitamin D deficiency was observed in April and reached 16.67%. In the period from June to September, the frequency of hypovitaminosis was significantly lower and amounted to 1.92–3.7%. It was found that with increasing age of patients there is a gradual decrease in the level of 25(OH) vit D blood ($r = - 0.099$, $p = 0.049$).

Findings. Based on the data obtained, it is recommended to carry out the prevention of vitamin D deficiency for the population of the Volgograd region. Prevention should be carried out from September to May, in accordance with international recommendations. These recommendations are especially relevant for older people.

Keywords: vitamin D, osteoporosis, cholecalciferol, vitamin D.

Introduction. Currently, there are many publications in the scientific medical literature on the possible role of vitamin D metabolic disorders in various human pathologies [1, 2, 3, 5, 9]. Vitamin D3 (cholecalciferol) is a key player in human bone metabolism [7]. It is generally accepted that the required amount of the vitamin is synthesized by skin cells under the influence of UV rays. Later, cholecalciferol is hydroxylated in the liver, followed by the formation of 25(OH) D3 - calcidiol, which is a deposited and transport form of the vitamin. The tendency to study only one metabolite, 25(OH) vit D, is due to the fact that it is associated with indicators that reflect the state of the bone tissue. An analysis of the associations of serum vitamin D metabolites with bone mineral density (BMD) showed that only 25(OH) vit D was associated with higher BMD [6].

In many countries of the world, vitamin D deficiency is widespread, determined by the level of 25(OH) vit D less than 75 nmol/l, sometimes reaching values below 50 nmol/l [7]. This problem also exists in Russia, which is confirmed by various studies that have been carried out throughout the country. Worldwide, there is vitamin D deficiency in all age groups.

Osteoporosis (OP) is a metabolic disease of the skeleton, which is characterized by a decrease in bone mass, a violation of the microarchitectonics of bone tissue, which can lead to an increase in bone fragility, and, as a result, fractures with minor injuries [4]. All over the world there is a trend towards an increase in the incidence of fractures associated with osteoporosis, this is especially true for older people [4, 8, 10].

Considering the important protective role of vitamin D, it is important to study seasonal fluctuations in the level of vitamin D in blood serum in order to optimize schemes for the prevention of deficiency of this factor.

Objective: study the seasonal fluctuation of 25(OH) vit D in patients with osteoporosis.

Materials and methods. We observed 396 patients diagnosed with OP/osteopenia aged 24 to 93 years, of which 376 (94.95%) women and 20 (5.05%) men. The study lasted from January to December 2017 inclusive. The patients were examined at the Research Institute of Clinical and Experimental Rheumatology named after A.B. Zborowski". All patients lived in the Volgograd region. The diagnosis of OP was based on the clinical recommendations of Osteoporosis-2021 approved by the Ministry of Health of the Russian Federation. There were 245 patients with a history of fractures, 151 without fractures. All patients underwent dual-energy x-ray absorptiometry using the Lunar DPX apparatus. Vitamin 25(OH)D3 levels were determined using the commercial 25-OH Vitamin D ELISA kit. Statistical data processing was carried out using software packages "STATISTICA 10.0 for Windows." Using the standard deviation (σ), we determined how much the 25(OH) vit D values deviated on average from the average in each month. Significance of differences between groups were compared by methods of variation statistics (ANOVA). The results were considered statistically significant at $p<0.05$.

Results. We have found that most patients have significant seasonal changes in 25(OH) vit D during the year. The maximum average values of the level of 25(OH) vit D were observed in residents of the Volgograd region in June (90.38 nmol/l), and the minimum value was recorded in January and December (respectively, 50.85 and 55.83 nmol/l). The results are shown in table 1.

We compared the significance of differences in the level of 25(OH) vit D depending on the month in which the patients were examined. The results are presented in table 2.

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Table 1

Variation in 25(OH) vit D depending on the month

Month	Number of observations	Mean 25(OH) vit D (μ)	Standard deviation 25(OH) vit D (σ)
January	10	50.85	10.56
February	16	65.55	32.25
March	54	57.02	27.67
April	36	53.51	37.18
May	49	57.71	34.18
June	43	90.38	56.65
July	48	69.71	30.93
August	52	73.89	37.97
September	27	70.53	24.97
October	19	65.94	18.95
November	34	67.59	34.18
December	8	55.83	16.3
Total	396	66.58	36.44

From the data presented in Table 2, it can be seen that there were significant differences in the concentration of 25(OH) vit D between patients who were observed in June and patients who were examined in the remaining months ($p<0.001$); as well as between patients examined in August and patients observed in the spring months ($p<0.05$). Similar significance was observed between July and April ($p=0.037$).

In order to identify the number of patients in need of drug prevention of hypovitaminosis D, we calculated the number of patients with vitamin D deficiency.

Although January and December have the lowest mean 25(OH) vit D values, there were no patients deficient in that month (table 3).

From the data presented in Table 2, it can be seen that the highest percentage of patients with vitamin D deficiency was observed in April and reached 16.67%. In the period from June to September, the frequency of hypovitaminosis was significantly lower and amounted to 1.92–3.7%.

We also studied the relationship of 25(OH) vit D with gender and age of patients. We found that with increasing age of patients, there is a gradual decrease in the level of 25(OH) vit D in the blood ($r = - 0.099$, $p = 0.049$), see Figure 1.

We did not find significant differences between the sex of patients and the value of vitamin D (the level of 25(OH) vit D in men 62.1 ± σ, in women 66.8 ± σ).

We have studied the relationship between the level of 25(OH) vit D and the presence of bone fractures. The results are presented in table 4.

Table 4 shows that there are no significant differences in the level of 25(OH)

Table 2

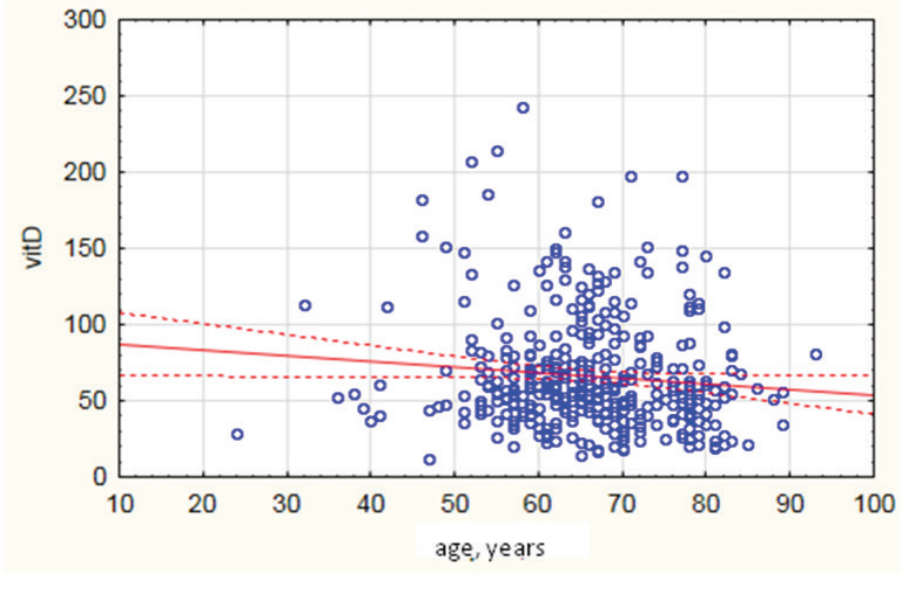
Reliability of differences in the level of 25(OH) vit D among residents of the Volgograd region, depending on the month of the survey

Month	January	Febrjuary	March	April	May	June	July	August	September	October	November	December
January (n=10)		0.302	0.611	0.833	0.575	**0.001**	0.124	0.059	0.132	0.274	0.187	0.766
Febrjuary (n=16)	0.302		0.396	0.256	0.440	**0.016**	0.682	0.409	0.654	0.974	0.848	0.525
March (n=54)	0.611	0.396		0.643	0.921	**<0.001**	0.070	**0.014**	0.105	0.344	0.171	0.928
April (n=36)	0.833	0.256	0.643		0.587	**<0.001**	**0.037**	**0.008**	0.058	0.214	0.095	0.866
May (n=49)	0.575	0.440	0.921	0.587		**<0.001**	0.094	**0.021**	0.130	0.388	0.210	0.889
June (n=43)	**0.001**	**0.016**	**<0.001**	**<0.001**	**<0.001**		**0.005**	**0.023**	**0.022**	**0.012**	**0.005**	**0.011**
July (n=48)	0.124	0.682	0.070	**0.037**	0.094	**0.005**		0.555	0.923	0.693	0.788	0.303
August (n=52)	0.059	0.409	**0.014**	**0.008**	**0.021**	**0.023**	0.555		0.688	0.401	0.419	0.178
September (n=27)	0.132	0.654	0.105	0.058	0.130	**0.022**	0.923	0.688		0.664	0.746	0.301
October (n=19)	0.274	0.974	0.344	0.214	0.388	**0.012**	0.693	0.401	0.664		0.869	0.497
November (n=34)	0.187	0.848	0.171	0.095	0.210	**0.005**	0.788	0.419	0.746	0.869		0.396
December (n=8)	0.766	0.525	0.928	0.866	0.889	**0.011**	0.303	0.178	0.301	0.497	0.396	

Table 3

The number of patients with vitamin D deficiency depending on the month of observation

Month	Total Patients	Number of patients with vitamin D deficiency	Percentage of patients with vitamin D deficiency
January	10	0	0.00
February	16	2	12.50
March	54	3	5.56
April	36	6	16.67
May	49	6	12.24
June	43	1	2.33
July	48	1	2.08
August	52	1	1.92
September	27	1	3.70
October	19	1	5.26
November	34	1	2.94
December	8	0	0.00
Total	396	23	



Correlation between patient age and 25(OH) vit D levels

Table 4

Significance of differences between patients with a history of fractures and vitamin D levels

In patients with a history of	n	25(OH) vit D (nmol/l)		Reliability
		M	σ	
Persons with a history of fracture	245	67.85	39.39	F=0.043 p= 0.834
No fracture history	151	65.80	34.55	

vit D depending on the presence of bone fractures. These results may be explained by the fact that some patients received medical treatment, including calcium and vitamin D supplements.

Findings. According to the literature, 25(OH) vit D deficiency is currently a pandemic that affects virtually all age groups. We have identified significant seasonal fluctuations in 25(OH) vit D in the examined group of patients. With the help of statistical methods of analysis, the influence of the seasonal factor on the level of 25(OH) vit D was proved. Despite the southern geographic location and the high level of insolation in the summer months, according to the data obtained, we can conclude that there is a lack of vitamin D among residents who live in the Volgograd region.

Note that there were no statistically significant differences between the average values of vitamin D levels in the summer months, accompanied by high solar activity (July-August) and the average values in the autumn months (September-November). Perhaps this fact is explained by the short time spent outdoors on hot summer days, which does not contribute to sufficient production of endogenous 25(OH)D3.

In our opinion, when choosing how aggressive and preventive therapy tactics should be in patients with OP in order to compensate for a possible vitamin D deficiency, several facts should be taken into account. Firstly, practitioners do not in all cases have the opportunity to examine the level of cholecalciferol, and even more so to track it in dynamics (for example, due to financial reasons). Secondly, patients with OP are, for the most part, elderly patients, which means they have a high comorbidity. Given the huge role of vitamin D deficiency in the development and progression of a number of cardiological, rheumatological, bronchopulmonary and other diseases, in our opinion, patients with OP need earlier preventive therapy. Without laboratory confirmation of the normal content of vitamin D, relying only on the presence of sufficient insolation (summer months), it is unacceptable to draw conclusions about the sufficient level of vitamin D in patients with OP.

Based on the results, it is recommended to carry out the prevention of vitamin D deficiency for the population of the Volgograd region. Prevention should be carried out from September to May, in accordance with international recommendations. These recommendations are especially relevant for older people.

Reference

1. Dorofeikov V.V., Zazerskaya I.V., Khazova E.L. Vitamin D i reproduktivnoe zdorov'e zhenshchiny [Vitamin D and women's reproductive health. Saint Petersburg: Jeko-Vektor; 2017. 151 p. (In Russ.).]
2. Gromova O.A., Torshin I.Y., Tomilova I.K. [et al.]. Metabolity vitamina D: rol' v diagnostiki i terapii vitamin D-zavisimoj patologii [Vitamin D metabolites: a role in the diagnosis and therapy of vitamin D-dependent pathology. Practical Medicine. 2017;5 (106): 4-10. (In Russ.).]
3. Nacional'naya programma «Nedostatochnost' vitamina D u detej i podrostkov Rossijskoj Federacii: sovremennye podhody k korrekcii» [National program 'Vitamin D Deficiency in children and adolescents of the Russian Federation: modern approaches to correction'. Pediatricians' union of Russia. Moscow: 'Pediatr' Publ., 2018; 96 p. (In Russ.).]
4. Lesnyak O.M., Yershova O.B., Belova K.Y. [et al.]. Epidemiologiya osteoporoticheskih perelomov v Rossijskoj Federacii i rossijskaya model' FRAX [Epidemiology of osteoporotic fractures in the Russian Federation and the FRAX Russian model. Osteoporosis and osteopathy. 2014;3:3-8. (InRuss.).]
5. Bae S.C., Lee Y.H. Association between Vitamin D level and/or deficiency, and systemic lupus erythematosus: a meta-analysis. Cell Mol Biol (Noisy-le-grand). 2018;64(1):7-13. DOI: 10.14715/cmb/2018.64.1.2.
6. Clinician's Guide to Prevention and Treatment of Osteoporosis. F. Cosman, S. de Beur, M. LeBoff [et al.]. Osteoporos Int. 2014 Oct;25(10):2359-81. doi: 10.1007/s00198-014-2794-2.
7. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Kanis J.A., Cooper C., Rizzoli R. [et al.]. Osteoporos Int. 2019 Jan;30(1):3-44. doi: 10.1007/s00198-018-4704-5.
8. Pavic R., Hnatesen D., Margetic P. Epidemiology of Adult Fractures in Eastern Croatia by Cause of Injury, Fracture Location and Type of Treatment. Acta Clin Croat. 2017;56(3):494-504.
9. Vitamin D levels in systemic sclerosis patients: a meta-analysis. L. An, M.H. Sun, F. Chen [et al.]. Drug Des Devel Ther. 2017;11:3119-25. DOI: 10.2147/DDDT. S144860.
10. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Rizzoli R., Boonen S., Brandi M.-L. Current Medical Research & Opinion 2013;29(4):1–9.

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DIFFERENTIAL INFORMATIVENESS OF SERUM ONCOMARKERS FOR DETECTION OF RARE FORMS OF UTERINE BODY CANCER

DOI 10.25789/YMJ.2022.79.02

УДК 618.14-006.6

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Aim. The aim of the study was to conduct a comparative analysis of the preoperative level of the concentration of tumor markers CA-125, HE4 and DJ-1 in the blood serum in endometrial and non-endometrial cancer of the uterine body.

Materials and methods. 249 patients with endometrial carcinoma (EC), 33 patients with serous (SC) and 24 patients with clear cell carcinoma (CCC) of the uterine body of stages II-IV according to FIGO were examined. Prior to the start of specialized antitumor treatment, the concentration of CA-125, HE4 and DJ-1 proteins was determined in blood serum by enzyme immunoassay.

Results. In patients with EC, SC and CCC the blood levels of CA-125 and HE4 tumor markers were elevated relative to the reference normal range, but did not differ significantly between the groups (p>0,05). A comparative analysis showed that a statistically significant difference between the groups was found only for the DJ-1 marker. In patients with EC, the mean blood level of DJ-1 corresponded to 521,4±12,8 pg/ml and in rare forms of uterine body cancer it was higher. With CCC the concentration DJ-1 was 984,2±19,2 pg/ml and in SC – 998,5±23,7 pg/ml.

Conclusion. For the differential diagnosis of endometrial and non-endometrial cancer of the body of the uterus, preoperative measurement of the concentration of DJ-1 in the blood is informative.

Key words: uterine body cancer, endometrial carcinoma, serous uterine body cancer, clear cell uterine body cancer, tumor markers.

Introduction. In the practice of oncologists, the determination of serum levels of tumor markers CA-125 (Cancer Antigen-125) and HE4 is used in the screening and prognosis of uterine cancer. An elevated level of CA-125 before surgery is accompanied by a poor prognosis for patients with endometrial carcinoma, which requires a higher frequency of postoperative examination of patients [6]. The HE4 (Human epididymis protein 4) marker is highly sensitive and specific in detecting early forms of endometrial cancer; its level has been correlated with the lethality of patients with poorly differentiated RTM [5]. In recent years, there has been encouraging information about the promise of protein deglycase DJ-1, also known as PARK7 (Parkinson's disease-associated protein 7), for the diagnosis of uterine cancer. DJ-1 is a multifunctional protein that activates proliferative cell processes and plays an important role in the pathogenesis and progression of cancer by modulating the tumor suppressor PTEN. The association of the level of DJ-1 in the blood with the course of the disease is associated by the authors with an increase in the expression of genes encoding this

protein in cells of poorly differentiated uterine body cancer and in non-endometrial carcinomas [3,7]. As is known, type II uterine cancer has a poor prognosis due to the high degree of malignancy [1]. Information about the degree of differentiation and the histological type of EC is mainly obtained from the morphological study of endometrial biopsy specimens before surgery. However, the results of histological examination of preoperative biopsy specimens of the endometrium and surgical specimens of uterine cancer in patients at high risk (G3 or non-endometrial forms of uterine cancer) do not match in a third of cases [4,8]. This mismatch can lead to incorrect surgical tactics. In this regard, oncologists need laboratory preoperative support in assessing the risk of progression of uterine cancer by determining the concentration of molecular markers in the blood. This will expand the possibilities of identifying patients with an unfavorable prognosis regarding the course of the disease. The aim of the study was to conduct a comparative analysis of the preoperative level of the concentration of tumor markers CA-125, HE4 and DJ-1 in the blood serum in endometrial and non-endometrial cancer of the uterine body.

Materials and methods. 249 patients with endometrial carcinoma (EC), 33 patients with serous (SC) and 24 patients with clear cell carcinoma (CCC) of the uterine body of stages II-IV according to FIGO were examined. The stages of uterine body cancer were determined based on the results of the revision of the organs during the operation and the results of the histological examination of surgical tissue samples according to the FIGO classification. The inclusion criteria for the study were: a histologically confirmed diagnosis of endometrial adenocarcinoma, clear cell or serous uterine body cancer; lack of specialized anticancer treatment before surgery. Exclusion criteria: decompensation of concomitant somatic diseases, oncological diseases of other localization, hormonal treatment before hysterectomy. All patients signed a voluntary informed consent to participate in the study. The study was approved by the Local Ethics Committee of the National Medical Research Center for Oncology of the Russian Ministry of Health.

All patients underwent extirpation of the uterus with appendages. Pelvic and lumbar lymph node dissection, omentectomy were performed according to indications.

Blood samples were collected the day before surgery by venipuncture of the cubital vein on an empty stomach. Blood was placed into test tubes with S-Monovette® Serum Gel (Sarstedt). Blood coagulation occurred at room temperature, samples were centrifuged at 3000 g for 10 minutes. Next, three aliquots of 300 µl were taken from the serum from each patient and stored at -80°C until the laboratory step.

Determination of DJ-1 concentration was carried out using enzyme immunoassay using specific test systems CircuLex Human DJ-1/PARK7 ELISA Kit (CycLex Co., Ltd. Japan) on an iMARK apparatus (Bio-Rad Laboratories, USA). Serum levels of CA-125 and HE4 were measured using electrochemiluminescence immunoassay using UniCel DxI 800 (Beckman Coulter, USA) and Roche Cobas e411 (Roche Group Ltd, Switzerland), respectively. The ARCHITECT Ca125 II diagnostic kit (CN 2K45-24, Abbott) was used to measure CA-125, and the ARCHITECT HE4 test system (CN 2P51-25, Abbott) was used to determine HE4.

Immunohistochemical evaluation of DJ-1 protein expression in the tissue of tumor samples was performed on paraffin sections 5 µm thick using standard technology. Anti-DJ-1 antibodies (Anti-DJ-1 antibody, 1:500, Cell Signaling Technology, Danvers, USA, 5933) were used for protein identification. Nuclear and nuclear/cytoplasmic staining was assessed using ranks 0,1,2,3: 0 - no staining, 1 point - the number of stained cells less than 10%, 2 points - 10-50%, 3 points - ≥50%.

Statistical data analysis was performed using Statistica 12.0 software (StatSoft, USA). We used descriptive statistics, analysis of variance, ROC analysis, comparison of shares using Pearson's test with a nonparametric correction.

Results and discussion. General characteristics of patient clinical groups are presented in Table 1.

The mean age of patients with EC corresponded to 64,5±1,9 years, with a diagnosis of CCC – 63,4±2,4 years and SC – 65,7±2,1 years. The diagnosis of uterine body cancer in most patients, regardless of the histological type, was first made in the postmenopausal period. Groups of patients were formed with a similar distribution of stages of the disease, mainly included patients with stages II-III according to FIGO. Obesity was a common comorbidity and occurred in EC in 87,1% (n=217), CCC – 83,3% (n=20) and SC – 78,8% (n=26), which affected the high values of the index body weight. In the majority of observations in the three groups of patients, a moderate degree of differentiation of tumor cells was noted. However, in rare forms of uterine body cancer, low differentiation of tumor cells was more common (CCC –

Table 1

General characteristics of patients with uterine body cancer

Indicator	EC (n=249)	SC (n=24)	CCC (n=33)	p
Menopausal status, abs.(%): pre-/perimenopausa postmenopausa	31 (12.4) 218 (87.6)	1 (4.2) 23 (95.8)	2 (6.1) 31 (93.9)	0.29
Body mass index, kg/m^2 (M±m)	31.4±1.8	29.7±1.5	29.4±1.9	0.83
Stage FIGO, abs.(%): II III IV	134 (53.8) 75 (30.1) 40 (16.1)	9 (37.5) 10 (41.7) 5 (20.8)	16 (48.5) 12 (36.4) 5 (15.1)	0.61
Degree of differentiation, abs.(%): G1 G2 G3	40 (16.1) 173 (69.5) 36 (14.4)	1 (4.2) 16 (66.6) 7 (29.2)	1 (3.1) 21 (63.6) 11 (33.3)	0.01
Myometrial invasion, abs.(%): <50% ≥50%	65 (26.1) 184 (73.9)	4 (16.7) 20 (83.3)	2 (6.1) 31 (93.9)	0.027
Metastases to lymph nodes, abs.(%): -yes -no	96 (38.6) 153 (61.4)	15 (62.5) 9 (37.5)	17 (51.5) 16 (48.5)	0.037

Note: Confidence probability p was determined by comparing three shares according to the Pearson test with Yates correction for continuity, quantitative indicators - according to the Kruskal-Wallis test.

Table 2

Concentration of tumor markers in blood serum before surgery in patients with uterine body cancer

Disease	Statistic	CA-125, U/ml	HE4, pmol/ml	DJ-1, pg/ml
EC (n=249)	M±m	37.9±1.2	77.8±2.6	521.4±12.8
	Me	36	79	513
	[25-75]	33-41	74-83	451-592
CCC (n=24)	M±m	40.9±1.5	87.4±2.9	984.2±19.2
	Me	41	88	985
	[25-75]	37-43	84-92	897-1124
SC (n=33)	M±m	42.5±1.6	88.3±3.3	998.5±23.7
	Me	44	90	1005
	[25-75]	39-47	86-95	864-1207
p_{EC-CCC}		0.24	0.10	<0.001
p_{EC-SC}		0.09	0.08	<0.001
p_{CCC-SC}		0.82	0.91	0.87
p_{all}		0.27	0.31	0.004

Note: M - the mean sample value, m - the error of the mean, Me - the median, [25-75] - the interquartile range, the confidence probability in multiple comparison between groups (p min) was determined using the Kruskal-Wallis test, pairwise comparison between groups were performed according to the Mann-Whitney test, adjusted for the number of compared pairs.

Table 3

Evaluation of DJ-1 expression in surgical tumor specimens taking into account the histological type of uterine body cancer

Tumor expression DJ-1, points	EC (n=249) abs.(%)	CCC (n=24) abs.(%)	SC (n=33) abs.(%)	p
0	81 (32.5)	4 (16.7)	4 (12.1)	p<0.001 ($\chi2$=51.3)
1	56 (22.5)	1 (4.2)	1 (3.0)	
2	75 (30.1)	9 (37.5)	7 (21.2)	
3	37 (14.9)	10 (41.6)	21 (63.7)	

Note: Confidence probability p was determined by comparing three shares of Pearson's test with Yates' correction for continuity.

29,2%, SR – 33,3%) compared with EC (14,4%). This circumstance affected the formation of statistically significant differences (p=0,01) depending on the degree of tumor differentiation. In rare forms of uterine body cancer, the tumor was more invasive compared to endometrial cancer (p=0,027). Metastases to the lymph nodes in CCC (62,5%) and SC (51,5%) were more common (p=0,037) compared with patients with EC (38,6%).

The values of the initial concentration of oncomarkers in the blood serum of patients with cancer of the uterine body are presented in Table 2.

The concentration of CA-125 and HE4 did not differ significantly in patients depending on the histological type of uterine cancer (p>0,05). Comparative analysis showed that the difference between the groups was found only in relation to the marker DJ-1 (p=0,004). In patients with EC, the mean blood level of DJ-1 corresponded to 521,4±12,8 pg/ml, and in rare forms of uterine body cancer it was higher. With CCC, the concentration of DJ-1 was 984,2±19,2 pg/ml, and with SC – 998,5±23,7 pg/ml.

The use of ROC analysis made it possible to clarify that before surgery, if the concentration of DJ-1 in the blood of patients with cancer of the uterine body exceeded the differential separation level of 852 pg/ml, the risk of detecting a rare form of cancer in the histological examination of surgical samples of the endometrium was high (diagnostic sensitivity 86,7 %, diagnostic specificity 81,3%, p=0,001).

Differences in the content of DJ-1 in the blood in endometrial and non-endometrial carcinoma may be due to different intensity of protein expression in the tumor tissue. Immunohistochemical study revealed that the nuclear expression of DJ-1 in tumor cells was observed more often (p=0,003) in EC (n=141, 56,6%) compared with patients with CCC (n=8, 33,3%) and SC (n=10, 30,3%). On the contrary, cytoplasmic localization of the DJ-1 protein was more common (p=0,02) in SC (n=29, 87,9%) and CCC (n=20, 83,3%) in contrast to patients with EC (n= 168, 67,5%). Overexpression of the DJ-1 protein in surgical tumor samples was more often observed in SC (63,7%), CCC (41,6%) compared with patients diagnosed with EC (14,9%) (Table 3).

DJ-1 activates the PI3K/Akt/mTOR signaling pathway, promoting tumor growth, metabolism activation, cancer cell proliferation, enhancing their viability, increasing metastatic potential, and avoiding cancer cells from apoptosis [2]. In rare forms of cancer of the body of the uterus, which differ from endometrial carcinoma in high metastatic potential and poor prognosis, the concentration of DJ-1 in the blood was higher. The difference in serum DJ-1 concentration in patients depending on the histological type of tumor is associated with different intensity of protein expression in the tumor tissue. The differential informativeness of the preoperative assessment of the level of DJ-1 in the blood before surgery in relation to the detection of forms of uterine body cancer with a high degree of malignancy complements the diagnostic capabilities of endometrial biopsy before the start of specialized treatment and makes it possible to rationally determine the tactics of surgical intervention until a final conclusion about the histological type of tumor is obtained.

Conclusions

1. For the differential diagnosis of endometrial and non-endometrial types of uterine body cancer, it is informative to measure the concentration of DJ-1 protein deglycase in the blood serum.

2. In patients with an excess of DJ-1 concentration in the blood above 852 pg/ml, the risk of detecting a rare form of uterine body cancer with a high malignant potential is increased, which requires surgical treatment in specialized centers by a multidisciplinary team of qualified oncogynecologists and morphologists to develop the correct surgical tactics.

Reference

1. Braun M.M., Overbeek-Wager E.A., Grumbo R.J. Diagnosis and Management of Endometrial Cancer. Am. Fam. Physician. 2016; 93: 468–474.

2. Wang W, Wang H, Xiang L, et al. DJ-1 is a new prognostic marker and predicts chemot-

herapy efficacy in colorectal cancer. Oncol. Rep. 2020; 44: 77–90. doi: 10.3892/or.2020.7593.
3. Di Cello A, Di Sanzo M, Perrone F.M., et al. DJ-1 is a reliable serum biomarker for discriminating high-risk endometrial cancer. Tumor Biol. 2017; 39(6): 1010428317705746. doi: 10.1177/1010428317705746.
4. Di Cello A, Rania E, Zuccala V, et al. Failure to recognize preoperatively high-risk endometrial carcinoma is associated with a poor outcome. Eur J Obstet Gynecol Reprod Biol. 2015; 194: 153–160. doi: 10.1016/j.ejogrb.2015.09.004.
5. Abbink K, Zusterzeel PL, Geurts-Moespot AJ, et al. HE4 is superior to CA125 in the detection of recurrent disease in high-risk endometrial cancer patients. Tumor Biol. 2018; 40(2): 1010428318757103. doi: 10.1177/1010428318757103.
6. Reijnen C, Visser NC, Kasius JC, et al. Improved preoperative risk stratification with CA-125 in low-grade endometrial cancer: A multicenter prospective cohort study. J. Gynecol. Oncol. 2019; 30: e70. doi: 10.3802/jgo.2019.30.e70.
7. Benati M, Montagnana M, Danese E, et al. The clinical significance of DJ-1 and HE4 in patients with endometrial cancer. J. Clin. Lab. Anal. 2018; 32: e22223. doi: 10.1002/jcla.22223
8. Matsuo K, Opper NR, Ciccone MA, et al. Time interval between endometrial biopsy and surgical staging for type I endometrial cancer: association between tumor characteristics and survival outcome. Obstet Gynecol. 2015; 125: 424–433. doi: 10.1097/AOG.0000000000000636.

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DNA COPY NUMBER VARIATIONS (14 CANCER-ASSOCIATED GENES) IN NON-SMALL CELL LUNG CANCER

DOI 10.25789/YMJ.2022.79.03

УДК 616-006.04

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, 15-30% of which is squamous cell carcinoma, 54% is adenocarcinoma. The copy number variations (CNVs) as one of the factors affecting gene transcription activity is necessary to assess the role of genetic variation in pathological processes. The purpose of our study was to research the relative number of copies of 14 onco-associated genes: *APC, AURCA, CCND1, GKN1, PIK3CA, NKX2-1, ERBB2, SOX2, EGFR1, BRCA1, BRCA2, TP63, CDKN2A, MDM2,* in lung tissue samples as tumor markers of lung cancer. The study included 72 patients with Slavic and Crimean Tatar (Crimean) population, aged 46-78 (median 64) years with a diagnosis of lung cancer T1-1aN0-2M0-1 (stage I-IV). The relative copy number variation of genetic loci was assessed by the RT-qPCR method. In our study, statistically significant CNV change events ($p<0.05$) were recorded for the *CCND1*, *GKN1*, *PIK3CA*, *EGFR1*, *SOX2*, *BRCA2*, *TP63*, *MDM2* genes in squamous cell carcinoma samples and NKX2-1 in lung adenocarcinoma samples. Thus, these genes can be used as differentiating and diagnostic biomarkers in NSCLC.

Keywords: lung cancer, copy number variations, squamous cell lung cancer, lung adenocarcinoma, biomarkers.

Introduction. Lung cancer is associated with poor prognosis and is the leading cause of cancer death [4]. Non-small cell lung cancer (NSCLC) accounts for 85% of all types of lung cancer, 15-30% of which is squamous cell lung cancer, 54% is lung adenocarcinoma [16]. Despite studies of various treatment options, patients diagnosed with NSCLC (all stages) have a mortality rate of over 50% at 1 year and an overall 5-year survival rate of less than 18% [20].

The molecular basis of lung cancer is the gradual accumulation of genetic and epigenetic changes in the cell nucleus. These changes lead to a weakening of the DNA structure and its greater susceptibility to subsequent mutations. Due to the tumor process in the cells, the mechanisms that control their division and location are violated. This is caused by disturbances in the regulation of the cell cycle (mutations of proto-oncogenes and suppressor genes) and disturbances in the processes of repair of damaged DNA. Further changes, such as increased expression of growth factors, sustained angiogenesis, avoidance of apoptosis (mutations of anti-apoptotic and pro-apoptotic genes), limitless replicative potential and tissue invasion and metastasis, affect tumor progression [14].

Among other changes, lung cancer is characterized by genomic instability leading to a high frequency of somatic mutations and extensive genomic changes in individual genomes [9]. Change in the number of copies (English copy number variations, CNV) means a change in genomic DNA, characterized by a change in the DNA sequence numbers in the normal (diploid) genome. These DNA changes can affect individual genes, chromosomal regions, or entire chromosomes. CNVs have been shown to be associated with lung cancer as well as a number of other malignancies [7]. Generally, in cancer, a decrease or increase in DNA copy number can affect tumor suppressor genes and oncogenes, respectively. CNVs play an important role in the etiology of the disease. Understanding the association of CNV with diseases will help in the early detection and prognosis of the outcome of these diseases, and will also determine the most effective treatment strategies for patients.

Purpose of the study. To study the copy number of 14 cancer-associated genes APC, *AURCA*, *CCND1*, *GKN1*, *PIK3CA*, *NKX2-1*, *ERBB2*, *SOX2*, *EGFR1*, *BRCA1*, *BRCA2*, *TP63*, *CDKN2A*, *MDM2* in lung tumor tissue relative to conditionally healthy tissue as potential lung cancer tumor markers.

Materials and methods. The study included 72 Caucasoid patients living in the Republic of Crimea, aged 46-78 years (median 64) diagnosed with lung cancer T1-1aN0-2M0-1 (stage I-IV), who underwent planned treatment at the Medical Academy named after S.I. . Georgievsky, Federal State Autonomous Educational Institution of Higher Education "KFU named after W.I. Vernadsky" in 2015-2020 (Table 1). All patients voluntarily signed an informed consent to the processing of personal data and the transfer of information constituting a medical secret, as well as to the transfer of biological material. The study was carried out in accordance with the ethical principles of biomedical research, reflect-

S.I. Georgievsky Medical Academy FSAI HE V.I. Vernadsky Crimea Federal Uniersity: **ALNSOUR Rashed D.** – postgraduate student of the Department of Oncology, xitrilis@mail.ru, **OLEKSEENKO Victor V.** – MD, Associate Professor, Head of the Departmen, FSBI NMRC of oncology, Ministry of Health of the Russian Federation, Rostov-on-Don: **PETRUSENKO Natalya Alexandrovna** – junior researcher; **MAKSIMOV Alexey Yurievich** – MD, Prof. Deputy Gen. Director, **STATESHNY Oleg Nikolayevich** – oncologist.

ed in the Declaration of Helsinki of the World Medical Association.

Extraction of total DNA from paraffin blocks of tumor and apparently healthy tissue (tissue samples fixed in 10% buffered formalin) was performed using the DNA-sorb-B kit (AmpliSens) [1]. The relative copy number variation of 14 genetic loci: *APC, AURCA, CCND1, GKN1, PIK-3CA, NKX2-1, ERBB2, SOX2, EGFR1, BRCA1, BRCA2, TP63, CDKN2A,* and *MDM2* was assessed by RT-qPCR. Each 25 µl PCR mixture contained 10 ng of genomic DNA, 0.2 mM dNTP's, 600 nM forward and reverse primers, 2.5 mM MgCl2, 1x PCR buffer, 0.05 u/µl Thermus aquaticus DNA polymerase (Synthol ", Russia). EvaGreen (Biotium, USA) was used as a dye. Amplification of each of the samples was carried out in triplicate using a CFX96 thermal cycler (Bio-Rad, USA) according to the following program: 95°C for 3 min, and 40 cycles at 95°C for 10 s, 60°C for 30 s (reading the FAM optical signal for EvaGreen) and 72°C for 15 s. Analysis of primary RT-qPCR data was performed using Bio-Rad CFX Manager (ver. 2.1) software [2]. GAPDH and B2M genetic loci were used as reference ones. Primer sequences for all genetic loci were designed using the NCBI GenBank database in the Primer-BLAST program (Table 2).

The relative copy number variation of the genetic locus (RCQ) was calculated using the formula 2-ΔCt. The dose of the studied locus was considered equal to the diploid set (2n) if the tumor/normal RCQ ratio was ~1. If the RCQ tumor/normal ratio was >1.5 or <0.5, the locus dose was considered increased (>3n) or decreased (<1n), respectively. Statistical analysis and assessment of the significance of differences were performed using the Mann-Whitney test, chi-square test, OR with an indication of the confidence interval (95% CI) and the upper and lower limits, using the Statistica v.10 program. The results of the analysis were considered statistically significant for the Mann-Whitney test and chi-square at $p<0.05$.

Results and discussion. The results obtained in this study are illustrated in Table 3 and Figure 1.

In our study, both an increase in the relative copy number and a loss for genes in lung tumor tissues relative to conditionally healthy ones were noted. Thus, for lung adenocarcinoma, a statistically significant increase in the dose of genes was observed: *NKX2-1* (p=0.049), *SOX2* (p=0.041), *BRCA1* (p=0.032), and losses for the *TP63* gene (p=0.043). In squamous cell lung cancer, amplification of genetic loci was noted: *CCND1* (p=0.007), *PIK3CA* (p=0.005), *NKX2-1* (p=0.006), *ERBB2* (p=0.045), *SOX2* (p=0.039), *TP63* (p= 0.005) (table 3, figure 1).

According to the obtained data on the relative copy number variation of genes, squamous cell carcinoma is characterized by a significant increase in the relative copy number for the *CCND1, GKN1, PIK3CA, EGFR1, SOX2, BRCA2, TP63, MDM2* genes, occurring respectively in 5.2; 5; 7.2; 3.4; 13.1; 4.8; 4.2; 4.8 times more often than with adenocarcinoma. And for adenocarcinoma of the lung, a characteristic increase in the relative copy number of the *NKX2-1* gene is 3.3 times more frequent than in squamous cell carcinoma (Table 4).

The *PIK3CA, SOX2,* and *TP63* genes located in the chromosomal region 3q were amplified more frequently in squamous cell carcinoma than in lung adenocarcinoma in this study. It is known that the most significant events in the course of carcinogenesis of squamous cell carcinoma include amplification of 3q and losses in the 3p and 9p chromosomal regions. 3q amplification is also associated with tumor progression [15].

The frequency of *SOX2* amplification in our study was 59.6% of cases of squamous cell carcinoma, 10% of cases of adenocarcinomas. In their work, Erdem et al also showed that *SOX2* amplification was predominantly observed in squamous cell carcinoma with mutations in the *TP53* gene, in addition, there was a correlation between *SOX2* and T53 mRNA levels in different samples [5]. SOX2, as a transcription factor, mainly manifests its oncogenic activity by changing gene expression. In this context, the study by Fukazawa et al. showed that SOX2 suppresses the expression of CDKN1A (a cell cycle inhibitor) and, through this mechanism, supports the growth of squamous lung tumor cells [6]. There is also evidence that high levels of SOX2 amplification are associated with a better prognosis in squamous cell lung cancer [12].

In the present study, amplification of the *PIK3CA* gene was more often observed in squamous cell lung cancer (64.3%). *PIK3CA* encodes the catalytic subunit p110 α of phosphatidylinositol 3'-kinase (PI3K). PI3K is a protein kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to form phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 is the second messenger that activates protein kinase B (Akt), which is a serine/threonine-specific protein kinase. Akt inhibits apoptosis and promotes cell proliferation. The PIK3CA gene is oncogenic and its aberrant changes have

Table 1

Clinical characteristics of groups of patients with lung cancer

Characteristic	Variables	Lung adenocarcinoma (n=30), абс.(%)	Squamous cell lung cancer (n=42), абс.(%)
Age of patients (years)	<50	3 (10)	3 (7.1)
	51-60	4 (13.3)	12 (28.6)
	61-70	16 (53.3)	23 (54.8)
	>70	7 (23.3)	4 (9.5)
Sex	men	19 (63.3)	33 (78.6)
	women	11 (36.7)	9 (21.4)
TNM	T1-1aN0-2M0	4 (13.3)	3 (7.1)
	T2-2bN0-2M1	18 (63.3)	34 (81)
	T3N0-2M0	5 (16.7)	4 (9.5)
	T4N0-2M0	2 (6.7)	1 (2.4)
The degree of tumor differentiation	G1	2 (6.7)	2 (4.8)
	G2	18 (60)	26 (61.9)
	G3	10 (33.3)	14 (33.3)

Table 2

A panel of primers for identification the relative copy number of genes

№	Gene	Chromosomal location	F (forward)	R (reverse)
1	*APC*	5q22	ATTCCCGGGGCAGTAAAGAG	TGCCTCTCTTGTCATCAGGC
2	*AURCA*	20q13.2	TGAAATTGGTCGCCCTCTGG	CTGAGCTGATGCTCCACTCC
3	*CCND1*	11q13.3	GGTGAACAAGCTCAAGTGGAAC	CCGGCCAGGGTCACCTAA
4	*GKN1*	2p13.3	CAACAATGCTGGAAGTGGGC	CAGGAGTCCCATCCGTTGTT
5	*PIK3CA*	3q26.3	GCTTGGGAGGATGCCCAAT	GCTGTGGAAATGCGTCTGGA
6	*NKX2-1*	14q13.3	ACCAAGCGCATCCAATCTCA	CCCTAGCGTGGAAAACCCAT
7	*ERBB2*	7p11.2	CAAGGACCACTCTTCTGCGT	CTTGAATGGCAACGCTCCTC
8	*SOX2*	17q12	TTTGTCGGAGACGGAGAAGC	CCGGGCAGCGTGTACTTAT
9	*EGFR1*	3q26.3-q27	GCCAAGTAAGGGCGTGTCT	GGCCGAAGAACGAAACGTC
10	*BRCA1*	17q21.31	GTAGCCCCTTGGTTTCCGTG	CCCTTTCCCGGGACTCTACT
11	*BRCA2*	13q13.1	TGCATCCCTGTGTAAGTGCAT	ACGTACTGGGTTTTTAGCAAGC
12	*TP63*	3q28	GCACAAGGTTGATGTAAAGTGGC	GGGATGCCTTTTGTAGCTCTTG
13	*CDKN2A*	9p21.3	GCCACATTCGCTAAGTGCTC	CAAATCCTCTGGAGGGACCG
14	*MDM2*	12q15	TCTTTGGGACCCATCTACCCT	AGAATGCTTTAGTCCACCTAACCTT
15	*GAPDH*		GCTGAACGGGAAGCTCACT	GCAGGTTTTTCTAGACGGCAG
16	*B2M*		TGAGTGCTGTCTCCATGTTTGA	ATTCTCTGCTCCCCACCTCT

been noted in many types of cancer. For example, taking into account the mutational status of PIK3CA with the CNV status is important in predicting the outcome in patients with cervical cancer [13].

In our study, the TP63 gene was amplified in 64.3% of squamous cell carcinoma tumors, the RCQ level (RCQ=1.96, p=0.005) was 3.6 times higher than in adenocarcinoma. Thus, losses in the TP63 gene were observed in lung adenocarcinoma (RCQ=0.54, p=0.043). The TP63 gene may be a differentiating marker for squamous cell lung cancer and lung adenocarcinoma. It has been noted that the TP63 gene is often amplified or overexpressed in primary squamous cell carcinomas of the head and neck [11].

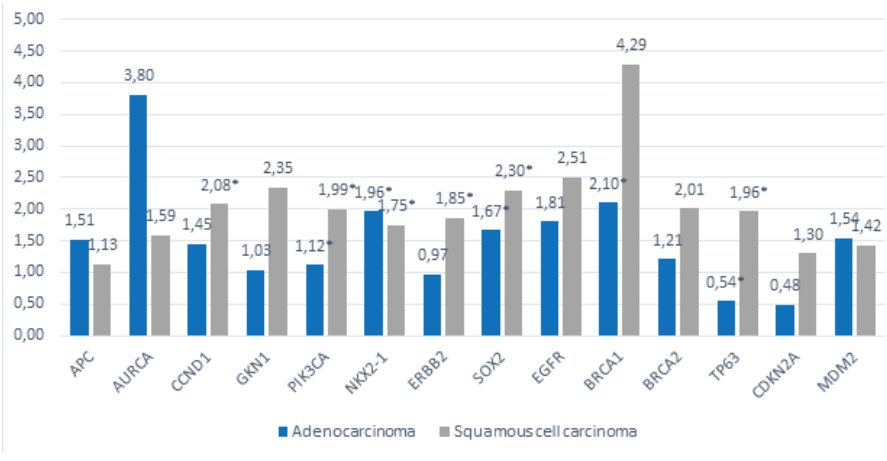
We observed a statistically significant increase in the dose of the BRCA1 gene (60%) in lung adenocarcinoma. The identification of inherited mutations in BRCA1 and BRCA2 has led to the successful use of PARP inhibitory therapy in breast and ovarian cancer. Detection of germline mutations in lung cancer may also be useful, similar to the benefit obtained from screening for pathogenic mutations in *BRCA1* and *BRCA2* [17].

In the present study, *CCND1* gene was amplified in 69% of squamous cell tumors and its RCQ level was 1.4 times higher than in lung adenocarcinoma (p=0.007). CCND1 regulates over 35 different transcription factors. The oncogenic role of CCND1 has been demonstrated in various studies, with overexpression of *CCND1* noted in numerous human cancers, including thyroid cancer, adenocarcinoma of the lung, liver, colon, and prostate [19]. CCND1 activates the MAPK/PI3K-AKT signaling pathway, and overexpression of the corresponding gene neutralizes the FGFR1 effect on MAPK/PI3K-AKT signaling, suggesting that FGFR1 partially inhibits the MAPK/PI3K-AKT signaling pathway by down-

Table 3

Frequency of amplifications and gene losses in a group of patients with non-small cell lung cancer

Gene	Adenocarcinoma (n=30)		Squamous cell carcinoma (n=42)	
	RCQ>1,5 абс. (%)	RCQ<0,5 абс. (%)	RCQ>1,5 абс. (%)	RCQ<0,5 абс. (%)
APC	12 (40)	3 (10)	10 (23.8)	2 (4.8)
AURCA	15 (50)	6 (20)	13 (31)	4 (9.5)
CCND1	9 (30)	3 (10)	29 (69)	0
GKN1	3 (10)	6 (20)	15 (35.7)	4 (9.5)
PIK3CA	6 (20)	3 (10)	27 (64.3)	4 (9.5)
NKX2-1	18 (60)	3 (10)	13 (31)	4 (9.5)
EGFR1	9 (30)	0	25 (59.6)	4 (9.5)
ERBB2	6 (20)	3 (10)	15 (35.7)	4 (9.5)
SOX2	3 (10)	3 (10)	25 (59.6)	0
BRCA1	18 (60)	3 (10)	15 (35.7)	8 (19.)
BRCA2	6 (20)	9 (30)	23 (54.8)	6 (14.3)
TP63	9 (30)	3 (10)	27 (64.3)	4 (9.5)
CDKN2A	15 (50)	3 (10)	23 (54.8)	4 (9.5)
MDM2	6 (20)	3 (10)	23 (54.8)	2 (4.8)



Показатели относительной копийности генов при немелкоклеточном раке легкого. * Статистически значимые различия от условно нормальной ткани с использованием критерия Манна-Уитни (p<0,05).

regulating CCND1. Yang et al showed that expression of the nuclear proteins CCND1 and FGFR1 is correlated and unregulated in squamous cell lung cancer. Also, CCND1 was not associated with overall survival in lung adenocarcinoma, but was associated with poor prognosis in squamous cell lung cancer [19].

In our study, the RCQ level of the *ERBB2* gene was statistically significantly higher by 1.9 times in squamous cell lung cancer. *ERBB2* has been extensively studied in breast cancer. Its amplification or overexpression of the encoded protein has become a biomarker for anti-ERBB2 targeted therapy in breast cancer. However, mutations in this gene are also common in lung cancer. ERBB2 consists of an extracellular domain that contains two -L receptor domains and a furin-like cysteine-rich domain, a trans-

Table 4

Results of the statistical analysis of the search for associations between the relative copy number variation of genes in adenocarcinoma and squamous cell lung cancer

	RCQ>1,5			RCQ<0,5		
	OR	CI 95% (lower - upper limit)	χ 2, p	OR	CI 95% (lower - upper limit)	χ 2 , p
APC	2.133	0.770-5.909	2.162. p=0.142	2.222	0.348- 14.199	0.743. p=0.389
AURCA	2.231	0.846-5.882	2.672. p= 0.103	2.375	0.607- 9.295	1.606. p= 0.206
CCND1	**0.192**	0.069-0.532	**10.706.** p= 0.002	н/р	н/р	4.383. p= 0.037
GKN1	**0.200**	0.052- 0.771	**6.171.** p= 0.013	2.478	0.632- 9.724	1.606. p=0.206
PIK3CA	**0.139**	0.046- 0.415	**13.825.** p<0.001	1.056	0.218- 5.105	0.005. p= 0.947
NKX2-1	**3.346**	1.255- 8.921	**6.023.** p= 0.015	1.056	0.218- 5.105	0.005. p= 0.947
EGFR1	**0.291**	0.108- 0.788	**6.120.** p= 0.014	н/р	н/р	3.025. p= 0.082
ERBB2	0.450	0.151- 1.345	2.818. p= 0.094	1.056	0.218- 5.105	0.005. p=0.947
SOX2	**0.076**	0.020- 0.289	**18.060.** p<0.001	н/р	н/р	4.383. p=0.037
BRCA1	1.700	0.621-4.657	**4.157.** P=0.042	0.472	0.114-1.953	1.107. p=0.293
BRCA2	**0.207**	0.070-0.609	**8.243.** p=0.005	2.571	0.802-8.242	2.620. p=0.106
TP63	**0.238**	0.087-0.650	**8.229.** P=0.005	1.056	0.218-5.105	0.005. p=0.947
CDKN2A	0.826	0.323-2.112	0.159. P=0.690	1.056	0.218-5.105	0.005. p=0.947
MDM2	**0.207**	0.070-0.609	**8.791.** p=0.004	2.222	0.348-14.199	0.743. p=0.389

Note: statistically significant differences are highlighted in bold; n/r - not calculated, because there was no group with the studied trait for a certain gene in the sample.

membrane domain (TMD) and an intracellular structure that contains a tyrosine kinase domain (TKD) and a carboxy-terminal tail. Wei et al showed that a non-TKD mutation accounted for more than half of the *ERBB2* mutations, a significant proportion of which were oncogenic. A mutation in the *ERBB2* gene was a poor prognostic factor in non-small cell lung cancer. A mutation in the *ERBB2* gene that is not associated with TKD can also be used as a therapeutic target in ERBB2-targeted therapy [18].

A statistically significant increase in the relative copy number variation of the *MDM2* gene occurred 4.8 times more often in squamous cell lung cancer than in adenocarcinoma. The *MDM2* gene is an oncogene that promotes cell growth, survival, invasion, and therapeutic resistance. MDM2 is a protein with multiple functions, of which the most widely studied function is E3 ubiquitin ligase. The main function of MDM2 is the regulation of p53. Clinical studies have shown that *MDM2* gene amplification occurs in several tumor types and tends to correlate with the presence of wild-type p53 [10].

The *NKX2-1* gene in our study was amplified 3.3 times more often (60%) in lung adenocarcinoma. The *NKX2-1* (*TTF-1*) gene encodes thyroid transcription factor 1 (TTF-1), a homeodomain-containing transcription factor for lung morphogenesis and lung epitheliocyte differentiation. Hokari S. et al. in their study also showed that *TTF-1* is expressed in 75-80% of cases of lung adenocarcinoma [8]. Thus, the NKX2-1 gene may be a marker that differentiates lung adenocarcinoma from squamous cell lung cancer.

Conclusions. The treatment of NSCLC has evolved over the past 10 years as a result of a better understanding of the heterogeneity of lung cancer and the molecular abnormalities that underlie this heterogeneity, with the consequent development of targeted therapies and immunotherapies that ushered in the era of personalized medicine [3]. Our study demonstrated statistically significant CNV (RCQ) change events for nine of the 14 studied genes that differentiated squamous cell carcinoma (*CCND1, GKN1, PIK3CA, EGFR1, SOX2, BRCA2, TP63, MDM2*) and lung adenocarcinoma (*NKX2-1*). Accordingly, these genes can be used as NSCLC biomarkers and promising targets for targeted therapy.

Reference

1. Petrusenko N.A., Verenikina E.V., Yakubova D.Yu., Timoshkina N.N. Biomarkery dlya immunoterapii nemelkokletochnogo raka legkogo [Mutations in the BRCA1 / 2 genes in patients in the south of Russia with malignant neoplasms of the ovaries. Yakut Medical Journal. 2020: 4 (72); 87-89 (In Russ.).] DOI 10.25789 / YMJ.2020.72.21.

2. Petrusenko N.A., Nikitina V.P., Spiridonova D.A., Kecheryukova M.M. Mutacii v genah BRCA1/2 u pacientok yuga Rossii s zlokachestvennymi novoobrazovaniyami yaichnikov [Changes in the copy number of genes in malignant tumors of the cervix with endophytic and exophytic forms of growth. Modern problems of science and education. 2019. No. 3 (In Russ.).] URL: http://www.science-education.ru/ru/article/view?id=28981 (date of access: 04/26/2021).

3. Kharagezov D.A., Lazutin Yu.N., Zlatnik E.Yu., Sagakyants A.B., Mirzoyan E.A., Milakin A.G., Stateshny O.N., Chubaryan A.V., Leyman I.A. Biomarkers for non-small cell lung cancer immunotherapy. South Russian Journal of Cancer. 2021;2(3):31-41 https://doi.org/10.37748/2686-9039-2021-2-3-4/

4. Duruisseaux M, Esteller M. Lung cancer epigenetics: From knowledge to applications. Semin Cancer Biol. 2018 Aug;51:116-128. doi: 10.1016/j.semcancer.2017.09.005.

5. Erdem J.S., Skuag V., Bakke P., Gulsvik A., Haugen A., Zienolddiny S. Mutations in TP53 increase the risk of SOX2 copy number alterations and silencing of TP53 reduces SOX2 expression in non-small cell lung cancer. *BMC Cancer.* 2016;16:28. https://doi.org/10.1186/s12885-016-2061-3 .

6. Fukazawa T., Guo M., Ishida N., Yamatsuji T., Takaoka M., Yokota E., Haisa M., Miyake N., Ikeda T., Okui T., et al. SOX2 suppresses CDKN1A to sustain growth of lung squamous cell carcinoma. *Sci. Rep.* 2016;6:20113. doi: 10.1038/srep20113.

7. Gamazon E.R., Stranger B.E. The Impact of Human Copy Number Variation on Gene Expression. Brief. Funct. Genom. 2015;14:352–357. doi: 10.1093/bfgp/elv017.

8. Hokari S, Tamura Y, Kaneda A, et al. Comparative analysis of TTF-1 binding DNA regions in small-cell lung cancer and non-small-cell lung cancer. *Mol Oncol*. 2020;14(2):277-293. doi:10.1002/1878-0261.12608.

10. Jabs V, Edlund K, König H, Grinberg M, Madjar K, Rahnenführer J, Ekman S, Bergkvist M, Holmberg L, Ickstadt K, Botling J, Hengstler JG, Micke P. Integrative analysis of genome-wide gene copy number changes and gene expression in non-small cell lung cancer. PLoS One. 2017 Nov 7;12(11):e0187246. doi: 10.1371/journal.pone.0187246.

11. Klein AM, de Queiroz RM, Venkatesh D, Prives C. The roles and regulation of MDM2 and MDMX: it is not just about p53. Genes Dev. 2021;35(9-10):575-601. doi:10.1101/gad.347872.120.

12. Lakshmanachetty S, Balaiya V, High WA, Koster MI. Loss of TP63 Promotes the Metastasis of Head and Neck Squamous Cell Carcinoma by Activating MAPK and STAT3 Signaling. *Mol Cancer Res*. 2019;17(6):1279-1293. doi:10.1158/1541-7786.MCR-18-1355.

13. Li Q., Liu F., Zhang Y., Fu L., Wang C., Chen X., Guan S., Meng X. Association of SOX2 and Nestin DNA amplification and protein expression with clinical features and overall survival in non-small cell lung cancer: A systematic review and meta-analysis. *Oncotarget.* 2016;7:34520–3ENca. *Onkol. Prak. Klin.* 2014;10:199–211.

Rooney M., Devarakonda S., Govindan R. Genomics of squamous cell lung cancer. Oncologist. 2013;18:707–716. doi: 10.1634/theoncologist.2013-0063.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7–30.

Turnbull C, Sud A, Houlston RS. Cancer genetics, precision prevention and a call to action. *Nat. Genet.* 2018;50:1212–1218. doi: 10.1038/s41588-018-0202-0.

Wei XW, Gao X, Zhang XC, Yang JJ, Chen ZH, Wu YL, Zhou Q. Mutational landscape and characteristics of ERBB2 in non-small cell lung cancer. *Thorac Cancer*. 2020;11(6):1512-1521. doi:10.1111/1759-7714.13419.

Yang Y, Lu T, Li Z, Lu S. FGFR1 regulates proliferation and metastasis by targeting CCND1 in FGFR1 amplified lung cancer. *Cell Adh Migr*. 2020;14(1):82-95. doi:10.1080/19336918.2020.1766308.

Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016 Jun;5(3):288-300. doi: 10.21037/tlcr.2016.06.07.

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THE EFFECT OF OBESITY ON SEXUAL DIMORPHISM OF IRISIN LEVELS

DOI 10.25789/YMJ.2022.79.04

УДК 577.17

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The aim of this study is to conduct a comparative analysis of average irisin levels between female and male (with normal weight and obese) to assess sexual dimorphism. Circulating levels of irisin in the blood of 279 Yakuts (185 female, 94 male, average age 19.8 ± 2.03 years) were determined. A comparative analysis of irisin levels between male and female in three BMI groups (underweight, normal weight, overweight/obesity) was carried out. The average level of irisin in the blood plasma in female was 8.33 ± 2.74 mcg/mL, and in male 7.76 ± 1.86 mcg/mL. Sexual dimorphism (p = 0.02) was detected in Yakuts with normal weight, where the level of irisin was higher in women (8.42 = 2.92 mcg/mL) compared to men (7.51 = 1.61 mcg/mL). Conducted a comparative analysis of irisin levels between male and female based on global data, were including this analysis are 2132 people. The age of the participants ranged from 18 to 61 years old. The meta-analysis was carried out for two different BMI groups: the first group included people with normal weight (18.5-24.9 kg/m^2), the second group included people with varying degrees of obesity (>30 kg/m^2). Comparative analysis of irisin levels in a large sample revealed statistically significant sexual dimorphism, where irisin levels were also higher in female compared to male, only in a sample of obese people (p = 0.02), in a sample of people with normal weight, no sexual differences were found (p = 0.09). Thus, the influence of obesity on sexual dimorphism was revealed.

Keywords: irisin, obesity, adipose tissue, Yakut population.

Introduction. During the previous decade, adipose tissue and skeletal muscles were recognized as endocrine organs secreting hormones adipokines and myokines, respectively. It is believed that there is a certain relationship between muscles and adipose tissue [24], which may be crucial for the regulation of body weight and metabolism, but specific metabolic pathways and mediators remain unclear [12]. Irisin is a short-lived myokine and is produced by proteolytic cleavage of fibronectin type III domain-containing protein (FNDC5) in response to the activation of gamma coactivator 1 of the alpha receptor activated by the proliferator peroxisome (PGC-1 α) [1]. Although irisin is primarily known as a myokine, it can also be an adipomyokine, since it is produced in adipocytes [1]. There are several factors known to affect the levels of irisin circulating in the blood, such as physical activity and diseases such as obesity and type 2 diabetes mellitus (DM2).

Irisin is mainly produced by skeletal muscles during aerobic exercises (running, swimming and treadmill workouts) [19-23, 33]. With intense physical exertion, an increase in the concentration of irisin occurs after 30-60 minutes [23], but after 90 minutes of training, irisin levels no longer increase [2]. In addition, prolonged training leads to a general decrease in the level of circulating irisin, so athletes have rather low levels compared to people who lead a sedentary lifestyle [5].

On the other hand, irisin can be produced by adipocytes, and numerous studies show that the levels of irisin circulating in the blood are significantly higher in obesity and in a prediabetic state [13, 15, 16, 18, 25, 31]. It is believed that in obesity and in a prediabetic state, irisin may be involved in general cycles of compensatory mechanisms, in which the recorded increased amount of irisin is explained by its increased secretion in an attempt to increase energy consumption due to browning of white adipose tissue or other, as yet unidentified effects in skeletal muscles [4, 23, 28]. Sesti et al., [27] suggested that in obesity, an increased level of irisin is an adaptive mechanism for preserving beta cells from overload, and can compensate for impaired insulin sensitivity. However, in T2D, irisin levels begin to decrease over time and become significantly lower in the decompensation stage than in people without diabetes [4, 14, 34]. This pattern is probably related to the dysfunction of β-cells, due to the depletion of their adaptive abilities to insulin resistance [3, 9].

Sexual dimorphism of irisin levels remains an open question, as there are many contradictory results. Some studies do not find differences in irisin levels between male and female [4, 5, 10-13,

21, 34]. However, in some studies, the authors observed a slight sexual dimorphism, where female had elevated levels of irisin, unlike male [2, 6-8, 30, 32].

In this regard, the purpose of this study is to conduct a comparative analysis of average irisin levels between female and male (normal weight and obesity) to assess sexual dimorphism.

Materials and research methods. *Sample.* The research sample comprised 279 people: 185 females and 94 males (with a mean age of 19.8±2.03 years). They presented no health issues at the time of the study and had completed a questionnaire in which they specified their sex, ethnicity, and age. All participants gave written informed consent for participation in the study. This study was approved by the local Biomedical Ethics Committee at the Yakut Scientific Center of Complex Medical Problems, Siberian Branch of the Russian Academy Scientific of Medical Sciences, Yakutsk, Russia (Yakutsk, Protocol No. 16, and 13 December 2014).

Anthropometric measurements. Anthropometric parameters (body weight in kilograms, height in centimeters) were measured for all participants by standardized methods. Body mass index (BMI) was calculated by dividing body mass by the square of the body height. The sample was divided into three groups by BMI [29]: underweight (≤18.49 kg/m^2), normal weight (18.5–24.99 kg/m^2), and overweight/obese (≥25 kg/m^2).

Irisin levels test. Fasting plasma irisin levels (mcg/mL) were determined with the human irisin sandwich enzyme-linked immunoassay (ELISA) "Irisin ELISA BioVendor" (BioVendor – Laboratorni medicina A.S., Czech Republic). The concentration of irisin in the samples was measured at the wavelength of 450 nm on a VICTOR X5 Multilabel Plate Reader (Perkin Elmer Inc., Waltham, MA, USA).

Search criteria for publications for comparative analysis. For this analysis, they carried the main search for suitable studies out in the electronic databases PubMed-Medline. The following search strings were used: "irisin AND obesity OR body mass index OR BMI AND sex differences". The last search was carried out on 04/06/2022. Details of each study included were collected in a pre-designed form. Thus, data were collected: first author, publication date, serum or plasma, age of participants, unit of measurement (mcg/mL or ng/mL), manufacturer of the ELISA kit, study location, sample size, irisin levels (mean average ± standard deviation). Comparative analysis was performed using The RevMan 5.3 software (The Cochrane Collaboration, UK). The difference in blood irisin levels between female and male was assessed using the total inverse variance. Heterogeneity was assessed using the Q-test based on the χ-square analysis and the I^2 test ($p<0.10$ denoted significance). The criteria for inclusion of studies in this analysis were as follows: studies should have been controlled, cross-sectional, prospective or clinical, studies should have studied serum/plasma levels of irisin in male and female aged 18 years and older with normal weight (18.5-24.9 kg/m^2) and/or obesity (>30 kg/m^2). The exclusion criteria were as follows: studies with participants under the age of 18, studies with sick individuals, in vivo and in vitro studies, review publications, studies on laboratory animals, lack of sufficient information on irisin concentrations, lack of BMI data, duplicate study.

Literature search and relevant research. A literature search in electronic databases revealed 622 publications. After applying different filters (sample age, and unit of measurement of irisin in the blood) 325 articles were excluded. The full texts of 297 articles were reviewed, and this resulted in the exclusion of 292 articles. As a result, 5 publications [4, 8, 10, 17, 34] met the inclusion criteria and were included in the final analysis (Figure 1).

Statistical analysis. The obtained data were analyzed using Statistica 13.5, a statistical software program (TIBCO Software Inc., Palo Alto, CA, USA). Values of $p \leq 0.05$ were considered statistically significant. Quantitative results are reported as the mean ± standard deviation. The Kolmogorov–Smirnov test was performed to test the normal distribution and homogeneity of the data was examined. The association of BMI with irisin levels was assessed with the correlation analysis. Comparative analysis of the three BMI groups between males and females was performed with the Mann–Whitney U test for the underweight and overweight/obese groups and with the Student's t-test for the individuals with normal weight.

Results and discussion. The plasma irisin concentration was 8.33 ± 2.74 mcg/mL in females and 7.76 ± 1.86 mcg/mL in males. Table 1 presents characteristics

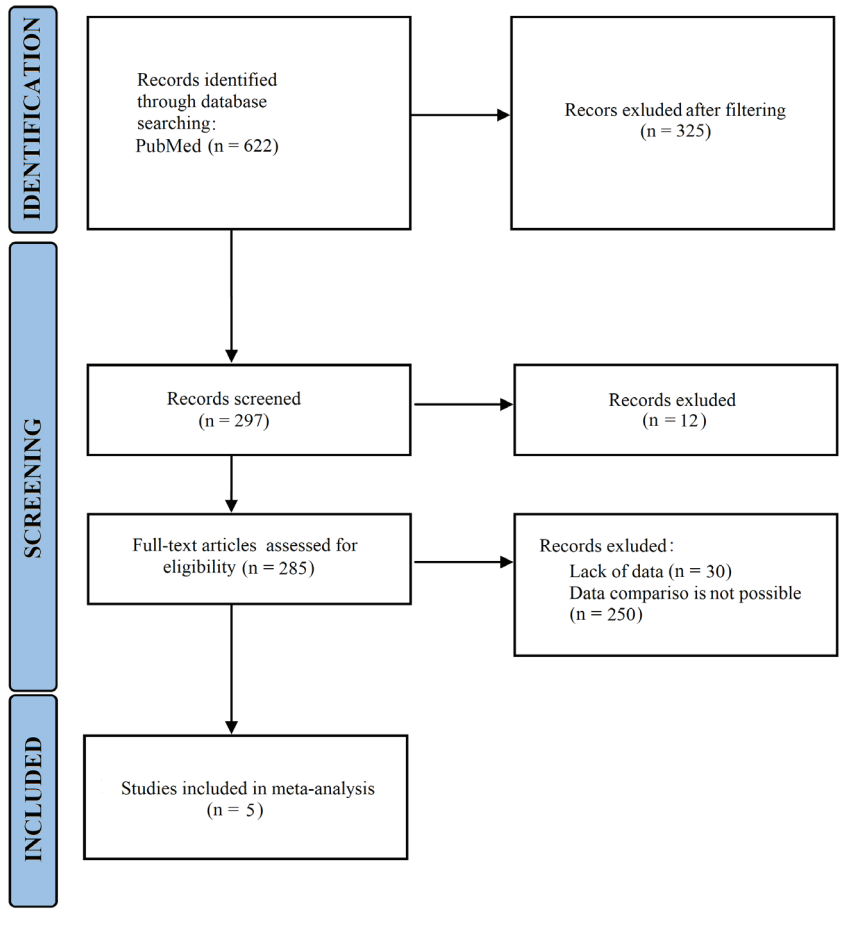

Fig. 1. Block diagram of the selection of publications for comparative analysis.
Note: Representation of the process by which relevant studies were retrieved from databases, selected, or excluded (PRISMA) [35]

of the sample (n = 279), stratified by BMI into three groups – underweight, normal weight and overweight/obese. Men showed significantly higher indicators of weight and height than women (p=0.01) in all three groups. Males with a normal weight displayed a significantly higher BMI than females (p = 0.03). The level of circulating irisin in the "normal weight" group was significantly higher in women (8.42 ± 2.92 mcg/mL) compared to men (7.51 ± 1.61 mcg/mL; p=0.02).

To verify the insignificant sexual dimorphism found by us in irisin levels, we conducted a comparative analysis using literature data. A total of 2132 individuals were included in the comparative analysis, the sample sizes varied from 7 to 537 in individual studies. All the studies were published between 2014 and 2022. The age of the participants ranged from 18 to 61 years. The meta-analysis was carried out for two different BMI groups: the first group included people with normal weight (18.5-24.9 kg/m^2), the second group included people with varying degrees of obesity (>30 kg/m^2). Detailed characteristics of these studies are given in Table 2.

Comparative analysis of normal weight individuals showed that there is a tendency of elevated irisin levels in women (p=0.09) (Figure 2A), heterogeneity in this group was average (I^2=53%). Stronger (p=0.02) sex differences were found in the group of people with obesity of 1 and 2 degrees, where the average levels of irisin were significantly higher in women than in men, the degree of heterogeneity was also average (I^2=54%) (Figure 2B).

The results obtained in an expanded sample of individuals with normal weight probably indicate the presence of minor sexual dimorphism in irisin levels at normal weight. With obesity of varying severity, this sexual dimorphism deepens, which indicates the role of irisin as an adipomyokine, since it is the adipokines secreted by adipose tissue that have a clear sexual dimorphism. For example, women, unlike men, have higher levels of adiponectin, leptin and visfatin [26]. The sexual dimorphism we found in irisin levels in Yakuts with normal weight may be associated with a high content of adipose tissue at normal BMI, but this requires further research.

Conclusion: In the Yakut population, among the group of people with normal weight, sexual differences in irisin levels were found, in female irisin was significantly higher (8.42±2.92 mcg/ml) compared with male (7.51±1.61 mcg/ml; p=0.02). The analysis of irisin levels in 2132 people revealed statistically sig-

Table 1

Characteristics of study subjects by BMI and sex

Characteristics	Underweight (n = 36)		p[1]	Normal Weight (n = 214)		p[2]	Overweight/Obese (n = 29)		p[1]
	F (n = 25)	M (n = 11)		F (n = 144)	M (n = 70)		F (n = 16)	M (n = 13)	
Weight (kg)	44.88 ± 3.71	50.45 ± 3.42	**0.01**	55.53 ± 5.8	66.19 ± 7.44	**0.01**	72.75 ± 11.13	81.46 ± 8.3	**0.01**
Height (cm)	160.24 ± 5.14	170.36 ± 5.89	**0.01**	160.92 ± 6.03	173.33 ± 5.98	**0.01**	162.19 ± 4.96	174.69 ± 6.64	**0.01**
BMI (kg/m2)	17.45 ± 0.73	17.39 ± 0.91	0.868	21.42 ± 1.62	22 ± 1.89	**0.03**	27.56 ± 2.88	26.64 ± 1.49	0.539
Irisin (mcg/mL)	7.88 ± 1.96	8.52 ± 2.64	0.904	**8.42 ± 2.92**	**7.51 ± 1.61**	**0.02**	8.27 ± 1.96	8.48 ± 2.16	0.965

Note: [1] Mann–Whitney U test; [2] Student's t-test; F–females; M–males. Data represent the mean±std.dev.

Table 2

Characteristics of publications included in the comparative analysis

№	Authors of the article and year of publication	Serum or plasma	Age, years	Unit of measurement	ELISA kit	Country	n	Female, mcg/mL	n	Male, mcg/mL
GROUP I										
1	This work	Plasma	19-30	mcg/mL	BioVendor, Czech Republic	Russia	142	8.43±2.94	60	7.65±1.66
2	Jameel et al., 2014 [34]	Plasma	34-39	mcg/mL	AdipoGenen, Switzerland	Australia	21	6.6±1.83	28	7.1±2.12
3	Oelmann et al., 2016 [10]	Plasma	40-61	mcg/mL	AdipoGenen, Switzerland	Germany	537	1.97±1.19	430	1.89±1.12
4	Choi et al., 2019 [4]	Serum	51-66	mcg/mL	BioVendor, Czech Republic	S.Korea	187	4.6±3.8	213	4.2±2.3
Всего							**N=887**		**N=731**	
GROUP II										
5	D'Amuri et al., 2022 [8]	Plasma	37.2 ± 9.1	mcg/mL	AdipoGenen, Switzerland	Italy	7	6.48 ±1.96	9	4.76 ±1.25
6	Klangjareonchai et al., 2014 [17]	Serum	58-64	mcg/mL	AdipoGenen, Switzerland	Thailand	73	3.08+1.03	25	2.67±0.6
7	Choi et al., 2019 [4]	Serum	51-66	mcg/mL	BioVendor, Czech Republic	Germany	200	4.4 ±2	200	4.3 ±1.8
Total							**N=280**		**N=234**	

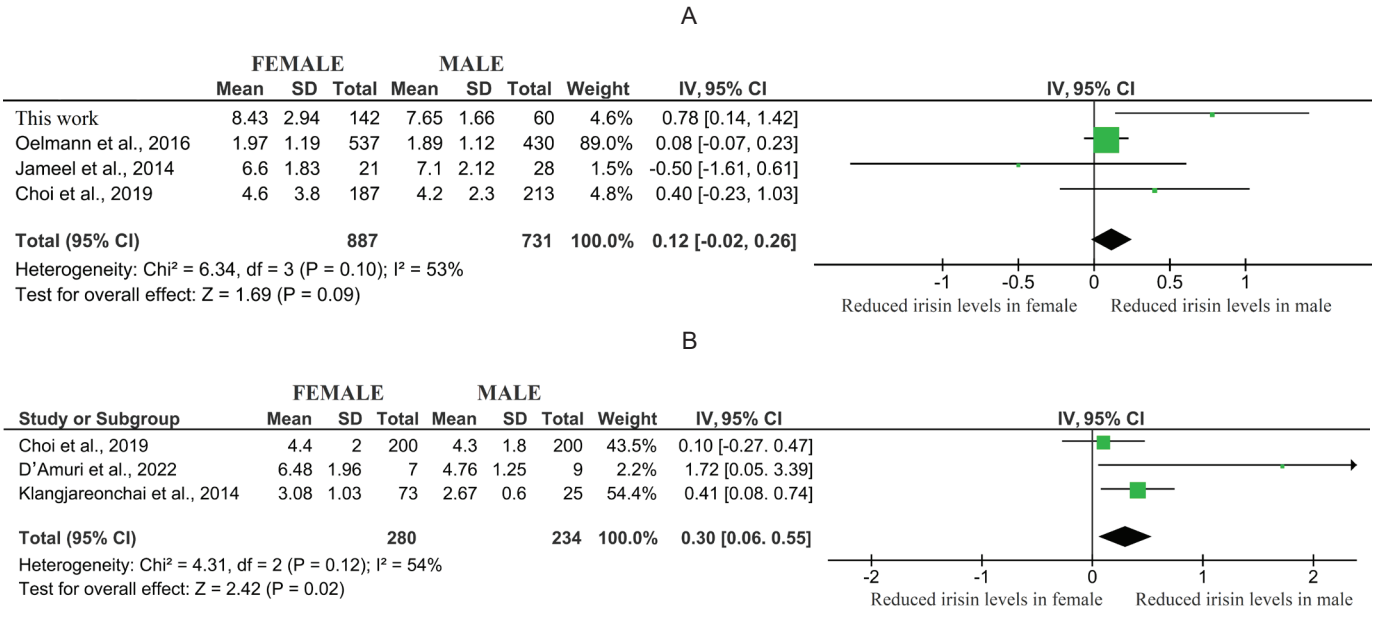

Fig. 2. Comparative analysis of average irisin levels between female and male. Note: A – group I, B – group II.

nificant sexual dimorphism: irisin levels were higher in women compared to men, in a sample of obese individuals (p=0.02). No sexual differences were found in the sample of persons with normal weight (p=0.09). Thus, it was revealed that sexual dimorphism in irisin levels manifests itself with obesity.

The work was done within Yakutsk scientific center for complex medical problems "Study of the genetic structure and burden of hereditary pathology of populations of the Republic of Sakha (Yakutia)", the base part of a state assignment of the Ministry of Science and Higher Education of the Russian Federation (FSRG-2020-0016).

Reference

1. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012: 7382(481): 463-468. doi:10.1038/nature10777

2. Kraemer RR, Shockett P, Webb ND, et al. A transient elevated irisin blood concentration in response to prolonged, moderate aerobic exercise in young men and female. Hormone and metabolic research. 2014. 46(2): 150-154.

3. Biondi G, Marrano N, Borrelli A, et al. Adipose Tissue Secretion Pattern Influences β-Cell Wellness in the Transition from Obesity to Type 2 Diabetes. International Journal of Molecular Sciences. 2022. 23(10): 5522.

4. Choi ES, Kim MK, Song MK, et al. Association between serum irisin levels and non-alcoholic fatty liver disease in health screen examinees. PloS one. 2014. 9(10): e110680.

5. Kerstholt N, Ewert R, Nauck M, et al. Association of circulating irisin and cardiopulmonary exercise capacity in healthy volunteers: results of the Study of Health in Pomerania. BMC pulmonary medicine. 2015. 15(1): 1-9.

6. Wu LF, Zhu DC, Tang CH, et al. Association of plasma irisin with bone mineral density in a large Chinese population using an extreme sampling design. Calcified tissue international. 2018. 103(3): 246-251.

7. Yan B, Shi X, Zhang H, et al. Association of serum irisin with metabolic syndrome in obese Chinese adults. PloS one. 2014. 9(4): e94235.

8. D'Amuri A, Raparelli V, Sanz JM, et al. Biological Response of Irisin Induced by Different Types of Exercise in Obese Subjects: A Non-Inferiority Controlled Randomized Study. Biology. 2022. 11(3): 392.

9. Christensen AA, Gannon M. The beta cell in type 2 diabetes. Current diabetes reports. 2019. 19(9): 1-8.

10. Oelmann S, Nauck M, Völzke H, et al. Circulating irisin concentrations are associated with a favourable lipid profile in the general population. PloS one. 2016. 11(4): e0154319.

11. Lagzdina R, Rumaka M, Gersone G, et al. Circulating irisin in healthy adults: Changes after acute exercise, correlation with body composition, and energy expenditure parameters in cross-sectional study. Medicina. 2020. 56(6): 274.

12. Anastasilakis AD, Polyzos SA, Saridakis ZG, et al. Circulating irisin in healthy, young individuals: day-night rhythm, effects of food intake and exercise, and associations with gender, physical activity, diet, and body composition. The Journal of Clinical Endocrinology & Metabolism. 2014: 99(9): 3247-3255. doi:10.1210/jc.2014-1367

13. Park K, Zaichenko L, Brinkoetter M, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. The journal of clinical endocrinology & metabolism. 2013. 98(12): 4899-4907.

14. Dozio E, Passeri E, Cardani R, et al. Circulating irisin is reduced in male patients with type 1 and type 2 myotonic dystrophies. Frontiers in endocrinology. 2017. 8: 320.

15. Winn NC, Liu Y, Heden TD, et al. Circulating irisin levels in response to acute and chronic exercise in obese adults. International Journal of Exercise Science: Conference Proceedings. 2013. 11(1): 42.

16. Stengel A, Hofmann T, Goebel-Stengel M, et al. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity-Correlation with body mass index. Peptides. 2013. 39: 125-130.

17. Klangjareonchai T, Nimitphong H, Saetung S, et al. Circulating sclerostin and irisin are related and interact with gender to influence adiposity in adults with prediabetes. International Journal of Endocrinology. 2014. 2014.

18. Shoukry A, Shalaby SM, El-Arabi Bdeer S, et al. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. IUBMB life. 2016. 68(7): 544-556.

19. Kurdiova T, Balaz M, Vician M, et al. Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: In vivo and in vitro studies. J. Physiol. 2014. 592: 1091–1107. doi: 10.1113/jphysiol.2013.264655.

20. Kang YS, Kim JC, Kim JS, et al. Effects of swimming exercise on serum irisin and bone FNDC5 in rat models of high-fat diet-induced osteoporosis. Journal of sports science & medicine. 2019. 18(4): 596.

21. Espes D, Lau J, Carlsson PO. Increased levels of irisin in people with long-standing Type 1 diabetes. Diabetic medicine. 2015. 32(9): 1172-1176.

22. Lecker SH, Zavin A, Cao P, et al. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure. Circulation: Heart Failure. 2012. 5(6): 812-818.

23. Huh JY, Panagiotou G, Mougios V, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 2012: 61(12): 1725-1738. doi:10.1016/j.metabol.2012.09.002

24. Roca-Rivada A, Castelao C, Senin LL, et al. FNDC5/irisin is not only a myokine but also an adipokine. PloS one. 2013: 8(4): e60563. doi:10.1371/journal.pone.0060563

25. Cao RY, Zheng H, Redfearn D, et al. FNDC5: a novel player in metabolism and metabolic syndrome. Biochimie. 2019. 158: 111-116.

26. Geer E.B., Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gender medicine. 2009. 6: 60-75.

27. High circulating irisin levels are associated with insulin resistance and vascular atherosclerosis in a cohort of nondiabetic adult subjects / Sesti G, Andreozzi F, Fiorentino TV, et al. Acta diabetologica. 2014. 51(5): 705-713.
28. Guilford BL, Parson JC, Grote CW, et al. Increased FNDC 5 is associated with insulin resistance in high fat-fed mice. Physiological reports. 2017. 5(13): e13319.
29. International Obesity Task Force. Obesity: Managing the Global Epidemic: Report of the World Health Organization (WHO) Consultation; World Health Organization: Geneva, Switzerland, 1997.
30. Hecksteden A, Wegmann M, Steffen A, et al. Irisin and exercise training in humans–results from a randomized controlled training trial. BMC medicine. 2013. 11(1): 1-8.
31. Sahin-Efe A, Upadhyay J, Ko BJ, et al. Irisin and leptin concentrations in relation to obesity, and developing type 2 diabetes: a cross sectional and a prospective case-control study nested in the Normative Aging Study. Metabolism. 2018. 79: C. 24-32.
32. Campolo J, Corradi E, Rizzardi A, et al. Irisin and markers of metabolic derangement in non-diabetic Caucasian subjects with stage I-II obesity during early aging. PloS one. 2020. 15(2): e0229152.
33. Brenmoehl J, Albrecht E, Komolka K, et al. Irisin is elevated in skeletal muscle and serum of mice immediately after acute exercise. International journal of biological sciences. 2014. 10(3): 338.
34. Jameel F, Thota RN, Wood LG, et al. Sex-Dependent Association between Circulating Irisin Levels and Insulin Resistance in Healthy Adults. Journal of Nutrition & Intermediary Metabolism. 2015. 2(3): 86–92. https://doi.org/10.1016/j.jnim.2015.10.001.
35. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Systematic reviews. 2021. 10(1): 1-11.

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THE ROLE OF HUMORAL IMMUNITY IN THE COMPLEX DIAGNOSIS OF DESTRUCTIVE FORMS OF ACUTE CHOLECYSTITIS

DOI 10.25789/YMJ.2022.79.05

УДК 616.366-089

The incidence of acute cholecystitis, to date, remains at the same level and amounts to 1.6 cases per 100,000 people. Mortality in this pathology ranges from 4 to 26%. There is no doubt that changes occur in any pathology, both in the local and in the general link of immunity, acute cholecystitis is no exception. The most significant deviations are observed in humoral immunity. Based on this, these criteria can be used to improve the diagnosis of acute destructive cholecystitis. The aim. To evaluate changes in the humoral link of immunity in patients with acute destructive cholecystitis. Materials and methods: A single-stage study of 105 patients with various clinical and morphological variants of acute calculous cholecystitis (acute catarrhal cholecystitis (n=35); acute phlegmonous cholecystitis (n=35); acute gangrenous cholecystitis (n=35)), comparable in age, gender and concomitant pathology and time of surgical intervention, was conducted. When patients were admitted to the hospital with suspected acute cholecystitis, the activity of the following immunogram parameters was determined in the first 2 hours: IgA, IgG, IgM and total immunoglobulin. Statistical processing of the obtained results was carried out using the SPSS Statistics 10.0 program in compliance with the principles of statistical analysis adopted for research in biology and medicine. The results. As a result of the study, an increase in the level of IgA in a subgroup of patients with acute gangrenous cholecystitis (subgroup № 3) to 139.5 IU/ml was found, which is 1,3 times higher than the reference level (p<0,05), 1.1 times less (p<0,05) than the values of the clinical comparison group, and 1.1 times higher (p≤0.05) values obtained in subgroups with catarrhal (subgroup № 1) and phlegmonous (subgroup № 2) acute cholecystitis. It was revealed that the concentration of IgG in subgroup № 3 reaches 196,6 IU/ml, which exceeds the indicators in other groups, relative to the norm values by 1,4 times (p≤0,05), comparison group by 1,4 times (p≤0,05), subgroup № 1 by 1,6 times (p≤0,05), subgroup № 2 1,2 times (p≤0,05). In the subgroup with acute gangrenous cholecystitis, it was found that the concentration of IgM is 190,4 IU/ml, which is higher than in other groups: the clinical comparison group by 1,6 times (p≤0,05), subgroup № 1 by 1,5 times (p≤0,05), subgroup № 2 by 1,2 times (p≤0,05). Conclusions. The study found that in destructive forms of acute cholecystitis, an increase in IgG was recorded by 1,6 times in comparison with the group of patients with non-destructive cholecystitis (p<0,05), as well as IgM by 1,3 times in comparison with the group of patients with non-destructive cholecystitis.

Keywords: cholelithiasis, acute cholecystitis, prognosis, destructive forms, cholelithiasis, diagnosis, humoral immunity, IgA, IgM, IgG.

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Acute cholecystitis still remains an important and still unresolved issue of emergency surgery. The continuing high incidence of this nosology (1,6 cases per 100 thousand) and postoperative mortality (0,9-1%) explain the need to search for new prognostic criteria that will increase the sensitivity and specificity of known and publicly available diagnostic methods for acute destructive cholecystitis [9].

Undoubtedly, changes in local and general immunity accompany the pathology of the organs of the hepato-pancreato-duodenal zone, affecting the cellular and humoral link [1,2,3]. At the same time, a number of both domestic and foreign authors indicate that in patients with calculous cholecystitis, which is accompanied by stagnation and thickening of bile, there is an increase in the concentration of immunoglobulins [2, 5]. In her study, N.M. Kozlova points out that the pathology of the biliary system is characterized by an increase in all classes of immunoglobulins [4]. The liver serves as the main source of utilization of serum IgA, which is captured by hepatocytes and secreted into bile, which explains the increase in this immunoglobulin in bile "sludge" [6,8,10]. In the works of L.G. Levkoeva, G.A. Eliseeva, devoted to the study of the level of CEC in blood plasma in patients with chronic cholecystitis, no significant changes were found [6]. At the same time, there are no data in the literature that reliably show changes in humoral immunity in acute destructive cholecystitis.

The aim. To evaluate changes in the humoral link of immunity in patients with acute destructive cholecystitis

Materials and methods. A simultaneous study of 105 patients with various clinical and morphological variants of acute calculous cholecystitis (acute catarrhal cholecystitis (n=35); acute phlegmonous cholecystitis (n=35); acute gangrenous cholecystitis (n=35)), comparable in age, gender and concomitant pathology and time of surgical intervention (Tab.1.). The study group included patients operated on (laparoscopic cholecystectomy) about acute calculous cholecystitis at the age of 30 to 70 years. Exclusion criteria from the study group: patients suffering from cholelithiasis complicated by mechanical jaundice, aged <30 years and > 70 years. The clinical comparison group consisted of 35 patients suffering from chronic calculous cholecystitis aged 30 to 70 years, whose examination revealed no pathology of the stomach, duodenum, operated by the standard method of laparoscopic cholecystectomy. Exclusion criteria from the clinical comparison group: patients suffering from chronic calculous cholecystitis, acute calculous cholecystitis, aged <30 and >70 years, whose examination revealed pathology of the stomach, duodenum.

During admission to the hospital with suspected acute cholecystitis, the activity of the following immunogram parameters was determined in the first 2 hours: IgA, IgG, IgM. The immunoglobulin content was assessed using a set of reagents "Diagnostic monospecific sera against IgG (H+L), IgA (H), Ig M(H) human, dry".

Statistical processing of the obtained results was carried out using the SPSS Statistics 10.0 program in compliance with the principles of statistical analysis adopted for research in biology and medicine. The results are given in an average value with an average quadratic error (M ± m). To study the relationships between the studied parameters, a paired Pearson correlation analysis was performed. The distribution of degrees of freedom was evaluated by the chi-square criterion for evaluating qualitative data in three or more independent groups. When comparing the average values of a quantitative trait in three or more independent groups, with a normal distribution of data in all groups, a one-factor analysis of variance (ANOVA) was performed. The Friedman criterion was used to compare three or more related samples, the data in which do not obey the law of normal distribution. The Mann–Whitney criterion was used for paired comparison of independent samples [7].

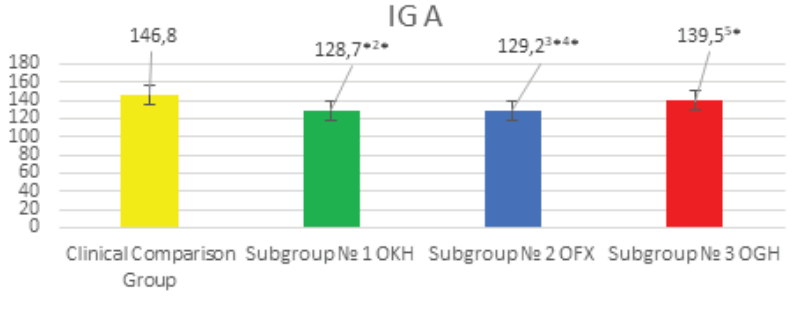
Distribution of patients depending on age and gender / Distribution of patients depending on age and gender

Patient subgroups	Quantity people, %					
	Up to 30 years old		30 to 50 years old		Over 50	
	M	AND	M	AND	M	AND
Acute catarrhal cholecystitis (n=35)	3 (8,6)	5 (14,3)	4 (11,4)	16 (45,7)	1 (2,9)	6 (17,1)
Acute phlegmonous cholecystitis (n=35)	2 (5,7)	7 (20)	5 (14,3)	14 (40)	3 (8,6)	4 (11,4)
Acute gangrenous cholecystitis (n=35)	4 (11,4)	3 (8,6)	7 (20)	13 (37,1)	1 (2,9)	7 (20)
Chronic calculous cholecystitis (clinical comparison group) (n=35)	2 (5,7)	4 (11,4)	4 (11,4)	17 (48,6)	3 (8,6)	5 (14,3)
Total (n=140)	11 (7,9)	19 (13,5)	20 (14,3)	60 (42,9)	8 (5,7)	23 (15,7)

The results. As a result of the study, there was no pronounced increase in Ig A indicators in subgroups of patients with destructive forms of acute cholecystitis. In patients of the clinical comparison group, the average concentration of Ig A reached the level of 146,8 IU/ml, which exceeds the average reference value by 1,4 times (p<0,05). At the same time, in the subgroup of patients with acute catarrhal cholecystitis, the IgA index in blood plasma was 128,7 IU/ml, which is 1,2 times higher (p<0,05) than the average value of the norm and 1,2 times lower (p<0,05) than the level of this immunoglobulin in the clinical comparison group. In the subgroup with acute phlegmonous cholecystitis, the average concentration of IgA was 129,2 IU/ml, which corresponds to the concentration in patients with acute catarrhal cholecystitis, but at the same time, it is 1,2 times lower than similar indicators in the clinical comparison group (p<0,05) and 1,2 times higher than the average reference index (p<0,05). In the subgroup of patients with acute gangrenous cholecystitis, the IgA index was 139,5 IU/ml, which is 1,3 times higher than the reference level (p<0,05), 1,1 times less (p<0,05) than the values of the clinical comparison group, and 1,1 times higher (p<0,05) than the values obtained in the subgroups with catarrhal and phlegmonous acute cholecystitis (Figure 1).

When assessing the sensitivity of this criterion, it was revealed that the highest sensitivity and specificity in the diagnosis of: acute catarrhal cholecystitis has an Ig A index of <130 IU/ml (Sensitivity 71,4% [CI 66,1 -76,7]; Specificity 97,1% [CI 94,4-99,8]); acute phlegmonous cholecystitis – <130 IU/ml (Sensitivity 65,7% [CI 58,8 -72,6]; Specificity 97,1% [CI 94,4-99,8]); acute gangrenous cholecystitis - >150 IU/ml (Sensitivity 40% [CI 27,7-53,3]; Specificity 68,6% [CI 62,2-75]) (Figure 2).

It was revealed that when a destructive process appears in the gallbladder, IgG indicators increase. In the clinical comparison group, the indicator was 138,4 IU/ml, which does not exceed the



* p≤0,05 chi-square criterion in subgroup №. 1 and subgroup №. 3,
2* p≤0,05 chi-square criterion in subgroup №. 1 and clinical comparison group,
3* p≤0,05 chi-square criterion in subgroup №.2 and clinical comparison group,
4* p≤0,05 chi-square criterion in subgroup № 2 and subgroup № 3,
5* p≤0,05 criterion chi-squared in subgroup № 3 and clinical comparison group,

Fig. 1. Ig A index in the study group (IU/ml)

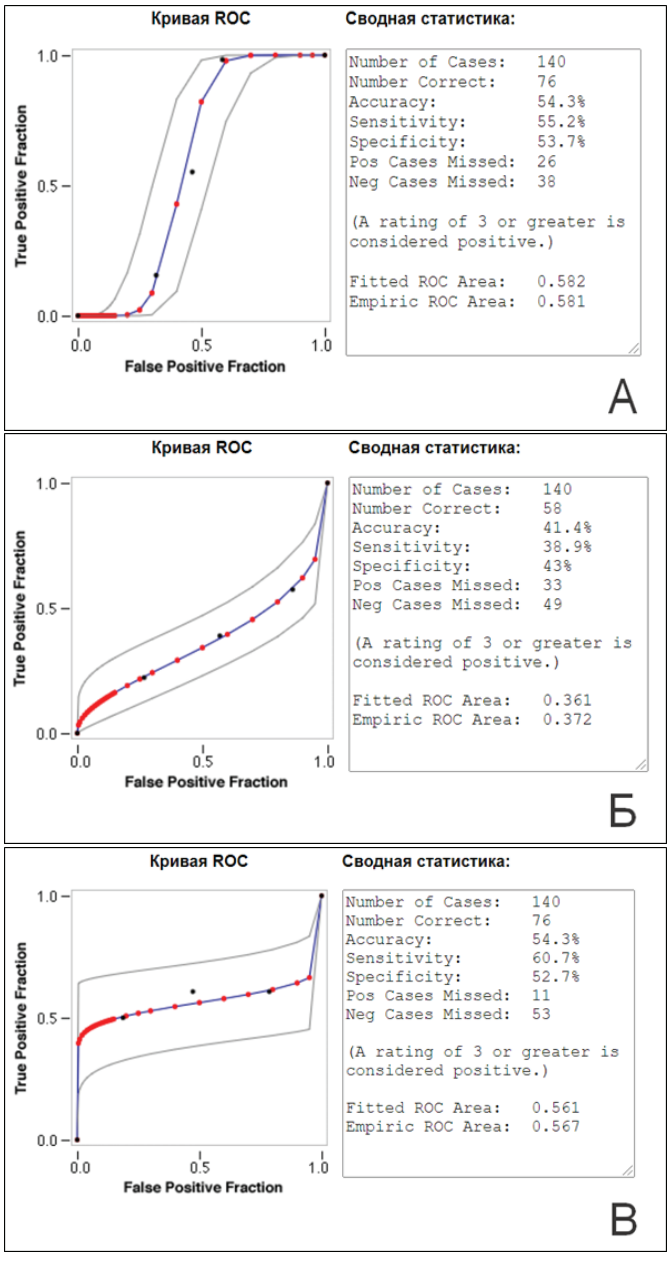


Fig. 2. ROC curve of Ig A indices obtained in patients with acute calculous cholecystitis: A - <130 IU/ml; B- 130-150 IU/ml; C->150 IU/ml

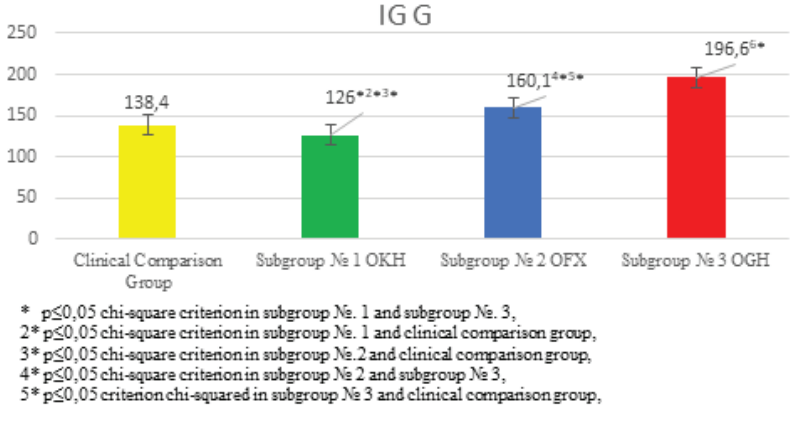


Fig. 3. Ig G index in the study group (IU/ml)

norm. At the same time, in a subgroup of patients with acute catarrhal cholecystitis, the IgG concentration corresponds to 126 IU/ml, which does not exceed the norm. In patients with acute phlegmonous cholecystitis, this indicator is 160,1 IU/ml, which is 1,1 times higher (p<0,05) than the reference value, 1,2 times higher (p<0,05) than the indicators in the clinical comparison group and 1,3 times higher (p<0,05) than the values obtained in the subgroup of acute catarrhal cholecystitis. In subgroup № 3, the IgG concentration reaches 196,6 IU/ml, which exceeds the indicators in other groups, relative to the norm values by 1,4 times (p≤0,05), the comparison group by 1,4 times (p≤0,05), group № 1 by 1,6 times (p≤0,05), group № 2 by 1,2 times (p≤0,05) (Figure 3).

It was found that the highest sensitivity and specificity in the diagnosis of acute catarrhal cholecystitis is IgG - 100-130 IU/ml (Sensitivity 65,7% [CI 58,8 -72,6]; Specificity 68,6% [CI 62,2-75]); acute phlegmonous cholecystitis – 160-200 IU/ml (Sensitivity 45,7% [CI 38,8-52,6]; Specificity 91,4% [CI 86,1-96,7]); acute gangrenous cholecystitis - 160-200 IU/ml (Sensitivity 62,9% [CI 55,1-70,7]; Specificity 91,4% [CI 86,1-96,7]) (Figure 4).

As a result of the study, it was found that when destruction occurs in the gallbladder, Ig M indicators also increase. In patients in the clinical comparison group, the indicator was 117,5 IU/ml, and in subgroup No. 1 -131 IU/ml, which is within the normal range. At the same time, in the subgroup with acute phlegmonous cholecystitis, this indicator was 161,3 IU/ml, which is 1,2 times higher (p<0,05) than the average norm, 1,4 times higher (p<0,05) than in the clinical comparison group and 1,2 times higher (p<0,05) than the concentration of this immunoglobulin in a subgroup with acute catarrhal cholecystitis. In the subgroup with acute gangrenous cholecystitis, the concentration of IgM is 190,4 IU/ml, which is higher than in other groups: the clinical comparison group by 1,6 times (p≤0,05), subgroup №. 1 by 1,5 times (p≤0,05), subgroup № 2 by 1,2 times (p≤0,05) (Figure 5).

Sensitivity and specificity in the diagnosis: acute catarrhal cholecystitis has an IgM index from 100-130 g/l (Sensitivity 54,3% [CI 49,7 – 58,9]; Specificity 5,7% [CI 0-12,6]); acute phlegmonous cholecystitis – 160-200 g/l (Sensitivity 54,3% [CI 49,7 – 58,9]; Specificity 97,1% [CI 94,4-99,8]); acute gangrenous cholecystitis - 160-200 g/l (Sensitivity 71,4% [CI 66,1-76,7]; Specificity 97,1% [CI 94,4-99,8]) (Figure 6).

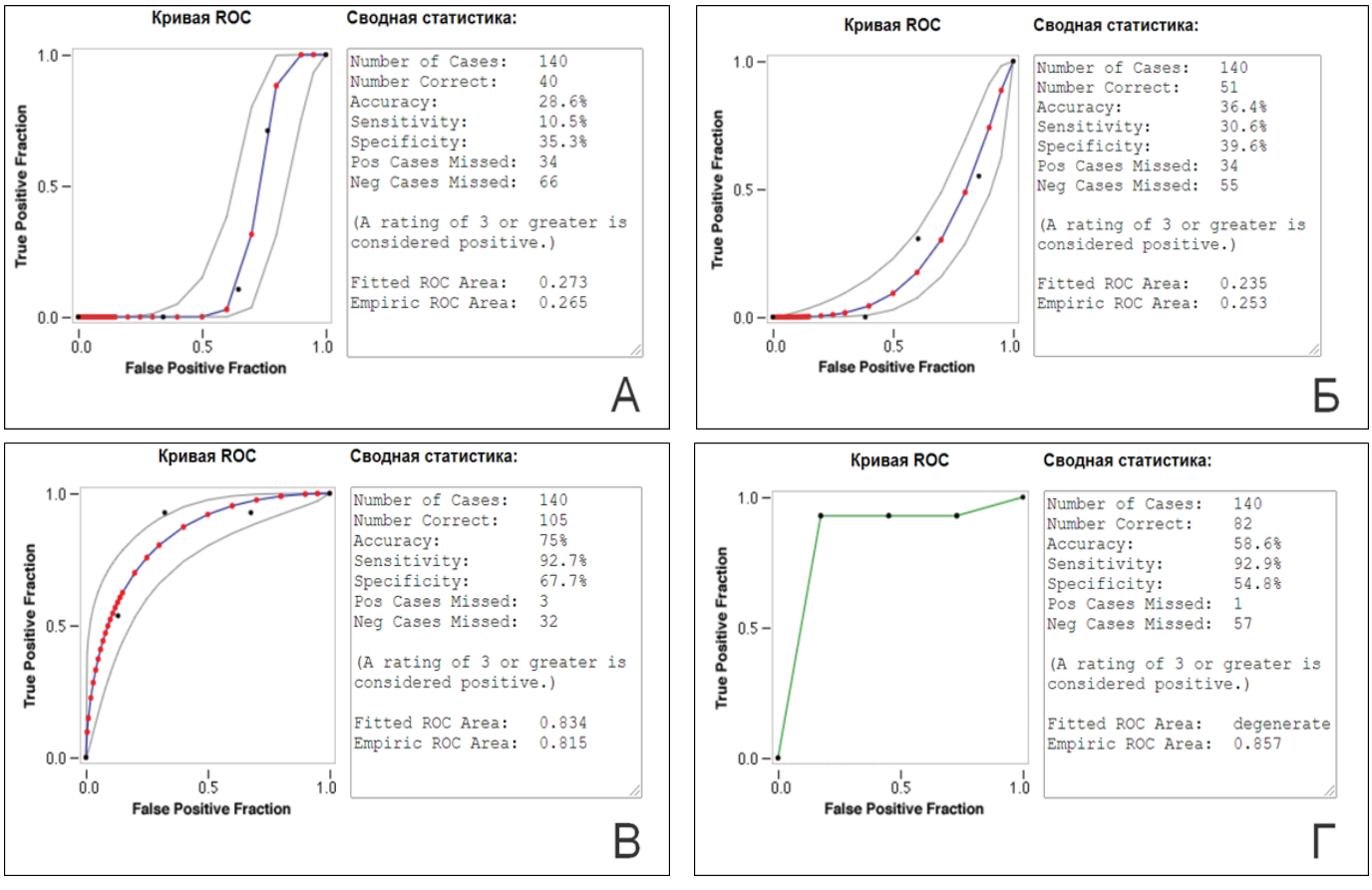


Fig. 4. Sensitivity and specificity of IgG indicators obtained in patients with acute calculous cholecystitis: A- 100-130 IU/ml; B- 130-160 IU/ml; C-160-200 IU/ml; D- >200 IU/ml

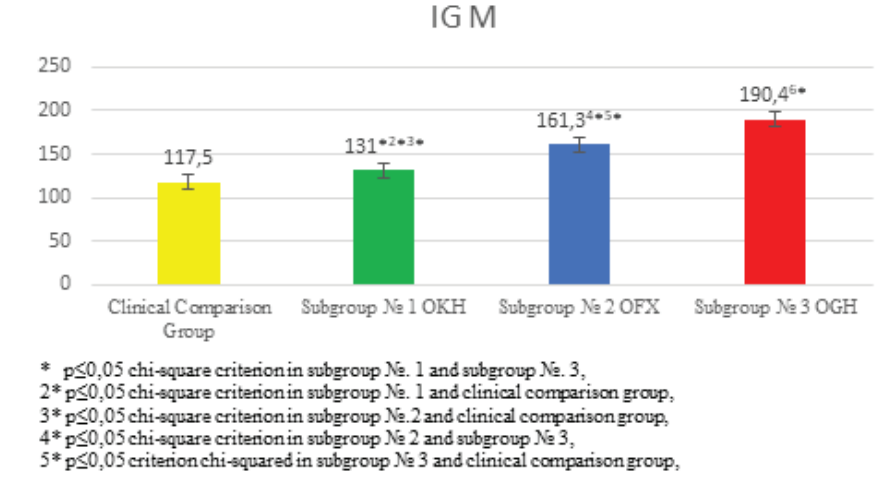


Fig. 5. Ig M index in the study group (IU/ml)

Conclusions: The study found that in destructive forms of acute cholecystitis, there is an increase in IgG by 1,6 times in comparison with the group of patients with non-destructive cholecystitis (p<0,05), as well as an increase in the level of Ig M by 1,3 times in comparison with the group of patients with non-destructive cholecystitis. There was no change in IgA indicators in patients with destructive cholecystitis in the study.

Reference

1. Entsova LL. Znachenie pokazatelej nespecificheskoj immunologicheskoj reaktivnosti organizma v ocenke sostoyaniya bol'nyh holecistitom do i posle operacii [Importance of non-specific immunological reactivity of the organism with assessment of cholecystitis patients up to and after the surgery: diss. ... cand. med. sciences: 03.00.07. Moscow, 1973. 123 p. (In Russ.).]

2. Ilchenko AA, Vikhrova TV, Zotova MM. Sostoyanie mestnogo i obshchego gumoral'nogo immuniteta pri holecistolitiaze i biliarnom «sladzhe» [The state of local and general humoral immunity in cholecystolithiasis and biliary "sludge. Russ. gastroenterol. Journal. 2001; 1: 10-14 (In Russ.).]

3. Kalygina TA, Bolotova ND. Fagotsitarnaya aktivnost' leikotsitov i test vosstanovleniya nitrosinego tetrazoliya u bol'nykh khronicheskim kolitom i kholetsistitom Immunologicheskie narusheniya pri zabolevaniyakh organov pishchevareniya [Phagocytic activity of leukocytes and the nitrosine tetrazolium recovery test in patients with chronic colitis and cholecystitis: coll. scientific. works. Immunological disorders in diseases of the digestive system: collection of scientific tr.; edited by A.M. Nogaller. Ryazan, 1981; 74: 59-62 (In Russ.).]

4. Kozlova N.M. Sostoyanie gumoral'nogo immuniteta pri zabolevaniyakh zhelchevyvodyashchikh putei [The state of humoral immunity in diseases of the biliary tract. Bulletin of the All-Russian Scientific Research Center of the Russian Academy of Medical Sciences. 2006; 5(51): 93-96 (In Russ.).]

5. Kotelnikova LP, Burenkova LK. Diagnosticheskaya znachimost' immunoglobulinov syvorotki krovi i pechenochnoi zhelchi [Diagnostic significance of serum immunoglobulins and hepatic bile. The first Moscow International. Congress of Surgeons: materials of conf. M., 1995. P. 325-326 (In Russ.).]

6. Levkoeva LG, Eliseeva GA. Izuchenie tsirkuliruyushchikh immunnykh kompleksov pri khronicheskikh zabolevaniyakh pishchevaritel'nogo trakta [The study of circulating immune complexes in chronic diseases of the digestive

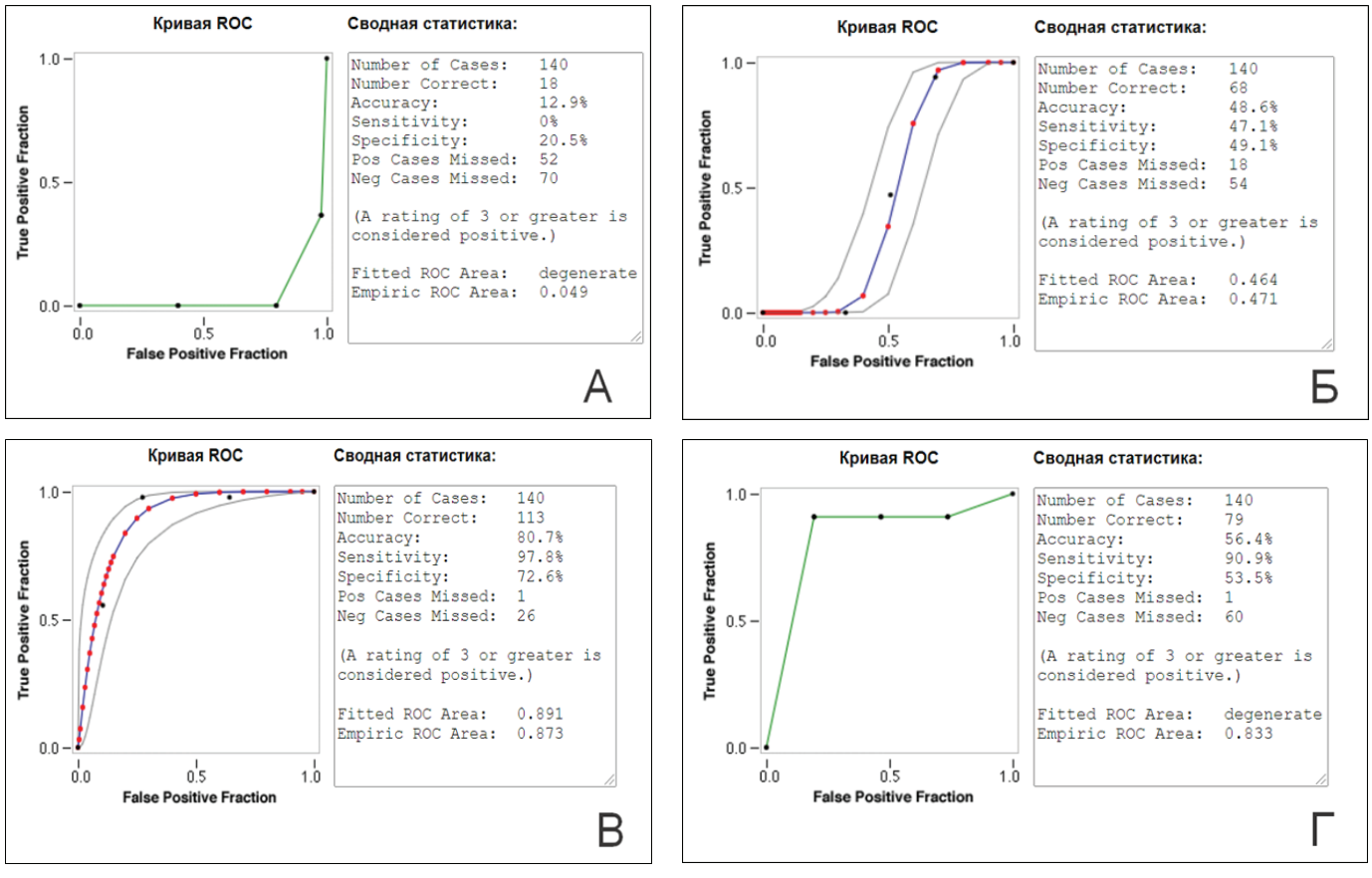


Fig. 6. Sensitivity and specificity of IgM indicators obtained in patients with acute calculous cholecystitis: A- 100-130 IU/ml; B- 130-160 IU/ml; C- 160-200 IU/ml; D- >200 IU/ml

tract. Immunological disorders in diseases of the digestive organs: Collection of scientific works.; Edited by A.M. Nogaller. Ryazan, 1981; 74: 22-24 (In Russ.).]

7. Mudrov V.A. Algoritmy statisticheskogo analiza kachestvennykh priznakov v biomeditsinskikh issledovaniyakh s pomoshch'yu paketa programm spss [Algorithms for statistical analysis of qualitative features in biomedical research using the spss software package]. Zabaikalsky meditsinicheskiy vestnik [Trans-Baikal Medical Journal]. 2020: 1; 151-163 (In Russ.).] https://doi.org /10.52485/19986173_2020_1_140]

8. Paltsev MA, Anichkov NM. Patologicheskaya anatomiya [Pathological anatomy. M.: Meditsina, 2000. 528 p. (In Russ.).]

9. Revishvili ASh, Olovyanny VE, Sazhin VP, Anishchenko MM. Khirurgicheskaya pomoshch' v Rossiiskoi Federatsii v period pandemii – osnovnye itogi 2020 goda [Surgical care in the Russian Federation during the pandemic – the main results of 2020. Surgery. N.I. Pirogov journal. 2021; 12:5-14] https://doi.org /10.17116/hirurgia20211215

10. Kerr M.A. Function of immunoglobulin A in immunity. Gut. 2000; 47: 751–752.

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DOI 10.25789/YMJ.2022.79.06

УДК 616-002.5:615.281

ASSOCIATION OF DELETION POLYMORPHISMS *GSTT1* AND *GSTM1* WITH INCREASED ACTIVITY OF HEPATIC TRANSAMINASES IN THE BLOOD OF PATIENTS RECEIVING ANTI-TUBERCULOSIS DRUG THERAPY

Tuberculosis is one of the most common infectious diseases worldwide. According to the approved clinical recommendations, combined anti-tuberculosis therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Isoniazid is one of the most effective anti-tuberculosis drugs for the treatment of drug–sensitive tuberculosis, however, it has a wide range of undesirable side effects, including drug-induced liver injury. The enzyme glutathione S-transferase is involved in the detoxification of toxic metabolites of isoniazid. There are a number of studies in which the role of deletion genotypes GSTM1 and GSTT1 of the enzyme glutathione S-transferase has been investigated and established, both individually and in combination to increase the frequency of undesirable adverse reactions when using drugs. However, the data obtained are ambiguous and contradictory. In this regard, we have presented an article aimed at studying the effect of polymorphic genes *GSTM1* and *GSTT1* on the activity of alanine aminotransferase and aspartate aminotransferase in blood serum in patients with newly diagnosed tuberculosis of the respiratory system.

Preliminary results of our study showed that carrying a combination of deletion genotypes in the *GSTM1* and *GSTT1* genes statistically significantly increases the activity of ALT and AST in tuberculosis therapy in patients of Yakut nationality. An increase in ALT and AST levels in the blood indicates the likelihood of hepatocellular liver damage during anti-tuberculosis therapy in carriers of a combination of deletion genotypes (*GSTM1(del)/GSTT1(del)*) of the enzyme glutathione-S transferase.

Keywords: Glutathione-S transferase, alanine aminotransferase, aspartate aminotransferase, deletion polymorphism, tuberculosis, isoniazid.

Introduction. Tuberculosis is one of the most common infectious diseases worldwide. According to the World Health Organization, about 10 million people in the world get tuberculosis every year, about 1.4 million of them die, the mortality rate from this disease is about 14% [21]. Despite this, in the Russian Federation there is a stabilization and a persistent trend towards a decrease in morbidity and mortality from tuberculosis. In Russia in 2020, the incidence of tuberculosis was 32.4 cases per 100,000 population [10]. Among patients diagnosed with active tuberculosis, the majority are patients with tuberculosis of the respiratory system. According to Vasilyeva et al., in 2022, the pandemic of a new coronavirus infection made its negative contribution to the clinical structure of tuberculosis. There was an increase in the proportion of newly diagnosed tuberculosis patients with destruction of lung tissue, massive bacterial excretion and fibrous-cavernous tuberculosis [3]. Therefore, at present, along with anti-epidemic and preventive measures, effective anti-tuberculosis drug therapy plays an important role in the fight against the tuberculosis epidemic.

According to approved clinical recommendations, combined anti-tuberculosis therapy with isoniazid, rifampicin, pyrazinamide and ethambutol is prescribed for the treatment of patients with newly diagnosed tuberculosis with established sensitivity of mycobacterium tuberculosis to isoniazid and rifampicin, as well as patients without bacterial excretion and the risk of developing multidrug resistance of the pathogen [6]. Anti-tuberculosis therapy with these drugs can cause a number of undesirable side effects, which can worsen the results of treatment. According to literature data, in the treatment of tuberculosis, undesirable adverse reactions occur in 7 to 69% of cases [42], the proportion of serious adverse reactions reaches 22.2%, complete withdrawal of drug therapy is required in 7.4% of cases [16]. Hepatotoxic reaction (drug-induced liver damage) is the main adverse reaction to anti-tuberculosis therapy [5] and the reason for drug withdrawal [4]. Most often, in 10-20% of cases, the hepatotoxic reaction is manifested by a transient increase in the activity of aminotransferases in blood plasma [29]. There are many factors leading to the development and progression of the hepatotoxic effect of anti-tuberculosis drugs: age, gender, pre-existing liver diseases, ethnicity, chronic intoxication, etc. [37, 38, 40, 41, 50].

Currently, the role of genes controlling the synthesis and operation of drug metabolism enzymes, in particular cytochrome P450 isoenzymes (*CYP2D6, CYP2C9, CYP2C19*) and biotransformation phase II enzymes (N-acetyltransferase (*NAT2*), UDP-glucuronyltransferase (*UGT*), thiopurine methyltransferase (*TPMT*), glutathione S-transferase (*GST*), etc.). In recent years, the effect of

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polymorphism of drug transporter genes on drug pharmacokinetics has been studied: organic anion transporters (*SLCO1B1, OAT-1, OAT-3*), organic cation transporters (*OST-1*) and glycoprotein-P (*ABCB1*). It is the polymorphism of genes that determines the individual pharmacological response – resistance (low efficacy or lack thereof at all) or the development of an adverse side reaction when using drugs, including anti-tuberculosis drugs [1].

Isoniazid is one of the most effective anti-tuberculosis drugs for the treatment of drug–sensitive tuberculosis, however, it has a wide range of undesirable side effects, including drug-induced liver injury. The hepatotoxicity of isoniazid is due to the high toxicity of the drug, whose chemical structure contains the hydrazide group -C(O)-NHNH and its metabolites – hydrazine and acetylhydrazine [11].

In the body, isoniazid is metabolized by acetylation with the participation of the enzyme NAT2. Studies evaluating the metabolism of isoniazid in patients with tuberculosis have shown the presence of many single-nucleotide substitutions in the structural region of the *NAT2* gene causing genetic changes in enzyme activity [8], leading to a decrease or, conversely, an increase in the metabolic rate of isoniazid.

Currently, the effect of polymorphisms of genes of enzymes of the *CYP2E1* and *GST* biotransformation system on the frequency of hepatotoxic reactions when using isoniazid is being established [11].

GST is an enzyme involved in the detoxification process. GST conjugates the sulfhydryl group of glutathione with xenobiotics or their metabolites formed in the first phase of biotransformation. Xenobiotics with different chemical structures, including isoniazid, undergo conjugation with glutathione. GST exist in several isoforms differing in tissue-specific expression. GSTT1 and GSTM1 are the most important enzymes of the GST family [1]. There are a number of studies in which the role of deletion genotypes *GSTM1* and *GSTT1*, both individually and in combination, has been investigated and established to increase the frequency of undesirable adverse reactions when using drugs [7]. However, the data obtained on the effect of carrying homozygous null genotypes *GSTM1 and GSTT1* on the risk of hepatotoxic reactions induced by anti-tuberculosis drugs [14] are ambiguous and contradictory.

The aim of the study was to research the effect of polymorphic genes *GSTM1* and *GSTT1* on the activity of alanine aminotransferase and aspartate aminotransferase in serum in patients with newly diagnosed respiratory tuberculosis.

Material and methods of research. A retrospective comparative single-center cohort study was conducted on a clinical site in Yakutsk (hereinafter SBI RS(Y) SPC "Phthisiology"). The protocol of the study was reviewed and approved by the Ethics Committee at the SBI RS(Y) SPC "Phthisiology".

53 patients of Yakut nationality with newly diagnosed respiratory tuberculosis, hospitalized in the therapeutic department of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Science and Practical Center "Phthisiology" named after E.N. Andreev" (group 1) participated in the study. Among them were 23 (44%) women and 30 (56%) men aged 41.4±4.2 years. Inclusion criteria: 1) respiratory tuberculosis detected for the first time; 2) age of 18 years and older; 3) intensive phase of anti-tuberculosis chemotherapy with mandatory inclusion of isoniazid; 4) signed informed consent of the patient. Exclusion criteria: generalized tuberculosis, HIV infection, the presence of malignant neoplasms, pregnancy, duration of the intensive phase less than 60 days. In accordance with clinical recommendations, all patients in the intensive phase of tuberculosis treatment received izoniazid at a dose of 5-10 mg/ kg/ day (no more than 600 mg/ day); ethambutol at a dose of 15-25 mg/ kg/ day (no more than 2000 mg/day); rifampicin at a dose of 10 mg/kg/day (no more than 600 mg / day); pyrazinamide at a dose of 25-30 mg / kg / day (more than 2500 mg / day) [6].

The control group (group 2) consisted of 74 conditionally healthy volunteers of Yakut nationality aged 41.7±3.2 years, 41 (55%) men and 33 (45%) women who signed informed consent.

For genotyping, DNA was isolated from whole blood by the standard two-stage method of phenol-chloroform extraction. DNA samples were sampled by deletion polymorphisms of the biotransformation genes: *GSTT1* and *GSTM1*, which encode the glutathione S-transferase enzymes θ1 and μ1, respectively. Typing of samples by the *GSTT1* and *GSTM1* genes was carried out using polymerase chain reaction (PCR) according to the method described in the work of Zehra et al. (2018).

The results were visualized electrophoretically in 3% agarose gel, with the addition of ethidium bromide. The PCR results were viewed in transmitted UV light on a transilluminator. The presence of deletion polymorphisms of the *GSTM1* and *GSTT1* genes was determined by the absence of the corresponding fragments: 219 bp for GSTM1 and 459 bp for GSTT1. The presence of these fragments indicates the presence of at least one normal (without deletion) copy of the genes. β-globulin with a 268 bp fragment was used as an internal control. Evidence of successful PCR analysis was the presence of an amplification of 268 bp, the *β-globulin* gene.

The activity of ALT and AST in blood serum was determined once on an XL-640 automatic biochemical analyzer (Erba Lachema, Czech Republic) using XL System Pack® reagents (ERBA Mannheim, Czech Republic). 8-9 ml of blood was taken from the ulnar vein in the morning on an empty stomach from all participants of the study and transfered into vacuum tubes without filler (Zhejiang Gongdong Medical Technology Co., Ltd, China)

Statistical processing was carried out using the software package SPSS 11.5 for Windows and Microsoft Excel. The data of the descriptive analysis are presented in the form of M ± m, where M is the average value, m is the standard error of the average value. The significance of the differences was assessed using the Mann-Whitney criterion. Comparison of genotype frequencies in groups of sick and healthy individuals was carried out using the Pearson chi-squared criterion. The differences were considered statistically significant at $p < 0.05$.

Results. Patients (group 1) and conditionally healthy volunteers (group 2) were comparable in age (U=97.0; p=0.65) and gender ($\chi 2 = 0.45$; p=0.2).

Analysis of the association of deletion polymorphisms of the GSTM1 and GSTT1 genes with tuberculosis showed that there were no differences in the frequencies of the *GSTM1* and *GSTT1* genotypes, as well as between their combinations, between the study groups, patients and healthy ones (Table 1).

In patients carrying the double deletion genotype *GSTM1(del)/GSTT1(del)*, the ALT level in the blood serum was significantly higher than in healthy volunteers with the same genotype. For other genotypes of the *GST* gene and its combinations, no significant differences were found among the 1st and 2nd groups (Table 2).

When comparing the activity levels of ALT and AST enzymes among patients, we found a significant increase in transaminase activity (**p=0.038 and p=0.047**, respectively) in carriers of the double deletion genotype of the *GSTM1* and *GSTT1 genes,* compared with carriers

of genotypes without deletions in these genes (Table 2). We have not established a comparison of ALT and AST activity in carriers of other variants of deletion genotypes and their combinations in the group of patients.

Discussion. The main pathways of isoniazid metabolism include the reaction of acetylation by the enzyme NAT2 to form N-acetylisoniazid, as well as hydrolysis by the enzyme amidase to form hydrazine and concomitant formation of isonicotinic acid. N-acetylisoniazide is hydrolyzed by amidase to the toxic metabolite acetylhydrazine and isonicotinic acid. Acetylhydrazine can be further hydrolyzed by amidase to hydrazine and acetylated by NAT2 to diacetylhydrazine. The low activity of the enzyme NAT2 leads to the accumulation of acetylhydrazine, which is oxidized with the participation of the cytochrome P450 CYP2E1 isoenzyme into toxic reactive metabolites [8]. Potentially dangerous electrophilic metabolites of isoniazid formed with the participation of the CYP2E1 enzyme can be neutralized by the GST enzyme by conjugation of the sulfhydryl group of glutathione with metabolites [12] Conjugation with glutathione of dangerous metabolites facilitates their excretion from the body and, thus, reduces the likelihood of toxicity.

In the human body, there are 7 classes of cytosolic GST enzymes (α, μ, π, θ, σ, ω, ζ), which include 17 isoforms of the enzyme, each encoded by a separate gene or a group of genes located on different chromosomes. GST isoenzymes are characterized by a wide substrate specificity, often their specificity overlaps. For example, GSTA-class isoenzymes are mainly bound to cumene hydroperoxide, GSTM-class – epoxides, GSTP-class – ethacric acid [19], etc.

The most studied genes are *GSTM1* and *GSTT1*, since their extensive deletion polymorphisms of 16kb and 54-kb, respectively, are known, which lead to the complete absence of protein products. Deficiency of GST enzyme activity due to homozygous null mutations at the *GSTM1* and *GSTT1* loci modulates susceptibility to hepatotoxicity caused by drugs and xenobiotics.

Each organ has a unique set of GST isoenzymes. Thus, the *GSTM1* gene is expressed in 116 tissues and cells, and the expression of the *GSTT1* gene is found only in 9 human tissues, according to the database of the UniProt consortium [https://www.uniprot.org]. Basically, both genes are expressed mainly in the liver, occupying a key position in the detoxification and metabolism of a large number of xenobiotics.

Some researchers have presented evidence that homozygous deletion mutations of these genes increase the risk of liver damage caused by drugs such as troglitazone [22; 48], takrin [39], carbamazepine [46], etc. However, it is still unclear whether the null genotypes of *GSTM1* and *GSTT1* are genetic predictors of liver damage when using anti-tuberculosis drugs.

The available research on this problem is very contradictory. Thus, it has been established that homozygous zero polymorphism *GSTT1* may be a risk factor for hepatotoxicity caused by anti-tuberculosis drugs in representatives of the Caucasian race [25]. At the same time, the presence of at least one functional allele of *GSTM1* was significantly more common among groups with a higher degree of hepatotoxicity of anti-tuberculosis drugs in Brazilians [32]. In contrast, *GSTT1* and *GSTM1* were not associated with increased liver damage caused by anti-tuberculosis drugs in the populations of India, Korea [15; 24] and China [44]. It has been shown that the null genotype of the *GSTT1* gene increases the risk of drug damage to the liver, in particular, due to the use of isoniazid [34].

It is likely that the contradictory data are associated with a high degree of heterogeneity in the frequencies of deletion genotypes of the *GSTM1* and *GSTT1* genes among different ethnic populations in the world [35]. Deletion of *GSTT1* was found in 20% of Caucasians and 80% of Asians. While the zero genotype of *GSTM1* is detected in 38-67% of representatives of the Caucasian race, in 33-63% of East Asians and in 22-35% of Africans and African Americans [36].

Table 1

Frequencies of polymorphic deletion genotypes *GSTM1* and *GSTT1* in patients with respiratory tuberculosis and conditionally healthy volunteers

Polymorphic variants	Group 1, (n=53), n (%)	Group 2, (n=74), n (%)	χ^2	Significance level
GSTM1 (del)	22 (41)	29 (39)	0.07	0.79
GSTT1 (del)	27 (51)	32 (43)	0.73	0.39
GSTM1(del) / GSTT1 (del)	11 (21)	13 (17)	0.20	0.65
GSTM1(+) / GSTT1 (+)	15 (28)	26 (35)	0.20	0.65
GSTM1(+) / GSTT1 (del)	16 (30)	19 (26)	0.31	0.57
GSTM1(del) / GSTT1 (+)	11 (21)	16 (22)	0.01	0.90

Table 2

ALT and AST activity in blood serum of patients receiving anti-tuberculosis therapy and healthy volunteers according to deletion genotypes *GSTM1* and *GSTT1*

Polymorphic variants	Group 1 (n=53)		Group 2 (n=74)		ALT	AST
	ALT, units/l	AST, units/l	ALT, units/l	AST, units/l	Significance level	Significance level
GSTM1 (del)	69.22±33.29	38.04±6.97	27.88±2.79	29.69±4.52	0.18	0.52
GSTT1 (del)	60.61±23.87	41.74±10.28	31.41±4.37	31.91±5.09	0.51	0.51
GSTM1(del)/GSTT1 (del)	92.45±52.64*	42.86±10.35	24.83±4.56	23.83±1.84	**0.04**	0.54
GSTM1(+)/GSTT1 (+)	19.95±2.52	21.66±2.10	29.38±3.88	27.25±2.09	0.65	0.13
GSTM1(+)/GSTT1 (del)	36.12±11.64	40.89±16.76	34.42±6.50	29.28±3.31	0.68	0.21
GSTM1(del)/GSTT1 (+)	30.50±8.70	30.00±6.89	28.65±3.60	26.04±1.24	1.00	0.98

*p <0.05.

Finally, a meta-analysis conducted by Li et al. (2013) showed that *GSTM1* polymorphism is associated with an increased risk of hepatotoxicity associated with taking anti-tuberculosis drugs in the entire population, especially among East Asians. At the same time, there was no statistically significant association between *GSTT1* polymorphism and the risk of hepatotoxicity. The authors of this work suggested that detoxification of antitubercular drugs takes place to a greater extent with the participation of the *GSTM1* enzyme, and the *GSTT1* enzyme is only able to partially compensate for the absence of *GSTM1*. Researchers Tang et al. (2013), Yang et al. (2019) in their works came to similar conclusions.

Unlike previous studies, our work has not established a clear relationship between the increase in ALT and AST levels in carriers of the deletion genotype *GSTM1* and/or *GSTT1*. However, in the group of patients with a recent diagnosis of pulmonary tuberculosis, the carrier of the double deletion genotype *GSTM1(del)/GSTT1(del)* led to a significant increase in the activity of ALT and AST against the background of anti-tuberculosis therapy, compared with carriers of genotypes without deletions.

Probably, in the Yakut population, the *GSTM1 and GSTT1* genes are equally capable of participating in the detoxification of drugs used in the treatment of tuberculosis. That is, in the absence of one enzyme, the other is fully capable of compensating for its absence. Since our study is preliminary, performed on a small set and needs further research.

In addition, the results obtained in a group of healthy volunteers were interesting. We observed a tendency to increase the levels of transaminases in the body of carriers of the deletion genotype of the *GSTT1* gene, as well as in combination with *GSTM1(+)/GSTT1(del)*. This is probably evidence that the *GSTT1* gene has a greater affinity in detoxification of endogenous metabolites in contrast to the *GSTM1* gene.

Thus, the preliminary results of our study showed that the carriage of a combination of deletion genotypes in the *GSTM1* and *GSTT1* genes statistically significantly increases the activity of ALT and AST in tuberculosis therapy in patients of Yakut nationality. An increase in ALT and AST levels in the blood indicates the likelihood of hepatocellular liver damage during anti-tuberculosis therapy in carriers of a combination of deletion genotypes (*GSTM1(del)/GSTT1(del)*) of the enzyme glutathione-S transferase.

Reference

1. Abdullaev ShP, Sychev DA, Ametov AS, Boyarko AV, Denisenko NP, et.al. Prikladnaya farmakogenetika: monografiya [Applied pharmacogenetics: monograph / Ed. coll.: under the editorship of Doctor of Medicine, professor, corresponding member. RAS, head of the Department of Clinical Pharmacology and Therapy. Academician B.E. Votchala, RMANPO Rector D.A. Sychev. Moscow: Triada, 2021. - 496 p. (In Russ.).]

2. Babushkina, AA, Okhotina IN, Cherkasova SP. Nekotorye parametry funkcional'nogo sostoyaniya pecheni v intensivnoj faze protivotuberkuleznoj himioterapii u pacientov Tyumenskogo OPTD [Some parameters of the functional state of the liver in the intensive phase of anti-tuberculosis chemotherapy in patients of the Tyumen OPTD]. Ural Medical Science and Education. – 2020; 21. No. 1 (101): 107-110. – EDN TVOYPH (In Russ.).]

3. Vasilyeva IA, Testov VV, Sterlikov SA. Epidemicheskaya situaciya po tuberkulezu v gody pandemii COVID-19 – 2020-2021 gg [Epidemiological situation in tuberculosis during the years of the COVID-19 pandemic - 2020-2021. Tuberculosis and lung diseases. – 2022; 100 (3): 6-12. http://doi.org/10.21292/2075-1 230-2022-100-3-6-12 (In Russ.).]

4. Krasnova NM, Evdokimova NE, Egorova AA, et.al. Vliyanie tipa acetilirovaniya na chastotu gepatotoksichnosti izoniazida u pacientov s vpervye vyyavlennym tuberkulyozom organov dyhaniya [Influence of the type of acetylation on the frequency of isoniazid hepatotoxicity in patients with newly diagnosed respiratory. Antibiotics and chemotherapy. 2020; 65 (7-8): 31-36 (In Russ.).]

5. [Ivanova DA. Nezhelatel'nye pobochnye reakcii pri lechenii bol'nyh tuberkulezom [Undesirable adverse reactions in the treatment of patients with tuberculosis]. Tuberkulez i bolezni legkih [Tuberculosis and Lung Diseases. 2011; 6: 60–9. (In Russ).]

6. Klinicheskie rekomendacii [Clinical guidelines]. Tuberkulez u vzroslyh [Tuberculosis in adults]. 2020 (In Russ.).]

7. Kondratyeva EI, Novoselova OG, Petrova N,. et.al. Vozmozhnosti klinicheskoj farmakogenetiki v personalizipovannom primenenii antibakterial'nyh lekarstvennyh sredstv [Possibilities of clinical pharmacogenetics in the personalized use of antibacterial drugs]. Medicinskaya genetika [*Medical genetics]*. 2015; No. 14. 12 (162): 11-20 (In Russ.).]

8. Krasnova NM, Nikolaev VM. Izoniazid-inducirovannoe porazhenie pecheni: farmakogeneticheskie aspekty [Isoniazid-induced liver injury: pharmacogenetic aspects]. Rossijskij zhurnal personalizirovannoj mediciny [Russian Journal of Personalized Medicine. 22022;2(3):38-46 (In Russ.).] DOI: 10.18705/2782-3806-2022-2-3-38-46

9. Prikaz Minzdrava RF ot 05.04.2019 № 199 «Ob utverzhdenii vedomstvennoj celevoj programmy «Preduprezhdenie i bor'ba s social'no znachimymi infekcionnymi zabolevaniyami» [Order of the Ministry of Health of the Russian Federation of April 5, 2019 No. 199 “On approval of the departmental target program “Prevention and control of socially significant infectious diseases” (In Russ.).]

10. Rossijskij statisticheskij ezhegodnik [Russian statistical yearbook. 2021: Stat. /Rosstat. - P76. M. 2021: 692 (In Russ.).] https://rosstat.gov.ru/folder/210/document/12994.

11. Snalina NE, Sychev DA. Geneticheskie prediktory gepatotoksichnosti izoniazida [Genetic predictors of isoniazid hepatotoxicity]. Molekulyarnaya medicina [Molecular Medicine]. 2018; (2) (In Russ.).] https://doi.org/10.29296/24999490-2018-02-04]

12. Stepanova NA, Galimzyanov KhM, Kantemirova BI. Sindrom intoksikacii u bol'nyh tuberkulezom legkih v zavisimosti ot polimorfizma genov sistemy glutationtransferaz [Syndrome of intoxication in patients with pulmonary tuberculosis depending on the polymorphism of the genes of the glutathione transferase system]. ZHurnal infektologii [Journal of Infectology]. 2017; 9 (2): 13-16 (In Russ.).] DOI:10.22625/2072-6732-2017-9-2-13-16

13. Antituberculosis Agents. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. *Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases*; September 22, 2017.

14. Chanhom N, Wattanapokayakit S, Satproedprai N, et al. CYP2E1, GSTM1, and GSTT1 genetic polymorphisms and their associations with susceptibility to antituberculosis drug-induced liver injury in Thai tuberculosis patients. *Heliyon*. 2021;7(4):e06852. Published 2021 Apr 20. doi:10.1016/j.heliyon.2021.e06852

15. Chatterjee S, Lyle N, Mandal A, Kundu S. GSTT1 and GSTM1 gene deletions are not associated with hepatotoxicity caused by antitubercular drugs. *J Clin Pharm Ther*. 2010;35(4):465-470. doi:10.1111/j.1365-2710.2009.01101.x

16. Borisov S.E. et al. Effectiveness and safety of the bedaquiline-containing six-month chemotherapy regimens in pulmonary tuberculosis patients. // *Tuberculosis and socio-important diseases*. – 2015. – № 3. – P. 30-49.

17. Ginsberg G, Smolenski S, Hattis D, Guyton KZ, Johns DO, Sonawane B. Genetic Polymorphism in Glutathione Transferases (GST): Population distribution of GSTM1, T1, and P1 conjugating activity. *J Toxicol Environ Health B Crit Rev*. 2009;12(5-6):389-439. doi:10.1080/10937400903158375

18. Hassan HM, Guo HL, Yousef BA, Luyong Z, Zhenzhou J. Hepatotoxicity mechanisms of isoniazid: A mini-review. *J Appl Toxicol*. 2015;35(12):1427-1432. doi:10.1002/jat.3175

19. Hayes JD, McLellan LI. 1999. Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. *Free Radic. Res*. 31:273–300

20. Huang YS. Genetic polymorphisms of drug-metabolizing enzymes and the susceptibility to antituberculosis drug-induced liver injury. *Expert Opin Drug Metab Toxicol*. 2007;3(1):1-8. doi:10.1517/17425255.3.1.1

21. https://www.who.int/ru/news-room/fact-sheets/detail/tuberculosis

22. Ikeda T. Drug-induced idiosyncratic hepatotoxicity: prevention strategy developed after the troglitazone case. *Drug Metab Pharmacokinet*. 2011;26(1):60-70. doi:10.2133/dmpk.dmpk-10-rv-090

23. Jokhadze T, Buadze T, Gaiozishvili M, Kiria N, Khujadze I, Lezhava T. *Georgian Med News*. 2019;(296):111-116.

24. Kim SH, Yoon HJ, et al. GSTT1 and GSTM1 null mutations and adverse reactions induced by antituberculosis drugs in Koreans. *Tuberculosis (Edinb)*. 2010;90(1):39-43. doi:10.1016/j.tube.2009.12.001

25. Leiro V, Fernández-Villar A, Valverde D, et al. Influence of glutathione S-transferase M1 and T1 homozygous null mutations on the risk of antituberculosis drug-induced hepatotoxicity in a Caucasian population. *Liver Int*. 2008;28(6):835-839. doi:10.1111/j.1478-3231.2008.01700.x

26. Li C, Long J, Hu X, Zhou Y. GSTM1 and GSTT1 genetic polymorphisms and risk of an-

ti-tuberculosis drug-induced hepatotoxicity: an updated meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2013;32(7):859-868. doi:10.1007/s10096-013-1831-y

27. Liu F, Jiao AX, Wu XR, et al. Impact of glutathione S-transferase M1 and T1 on anti-tuberculosis drug-induced hepatotoxicity in Chinese pediatric patients. *PLoS One*. 2014;9(12):e115410. Published 2014 Dec 19. doi:10.1371/journal.pone.0115410

28. Meng X, Maggs JL, Usui T, et al. Auto-oxidation of Isoniazid Leads to Isonicotinic-Lysine Adducts on Human Serum Albumin. *Chem Res Toxicol*. 2015;28(1):51-58. doi:10.1021/tx500285k

29. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. *Br J Clin Pharmacol*. 2016;81(6):1030-1036. DOI: 10.1111/bcp.12885

30. Metushi IG, Cai P, Zhu X, Nakagawa T, Uetrecht JP. A fresh look at the mechanism of isoniazid-induced hepatotoxicity. *Clin Pharmacol Ther*. 2011;89(6):911-914. doi:10.1038/clpt.2010.355

31. Metushi IG, Hayes MA, Uetrecht J. Treatment of PD-1(-/-) mice with amodiaquine and anti-CTLA4 leads to liver injury similar to idiosyncratic liver injury in patients. *Hepatology*. 2015;61(4):1332-1342. doi:10.1002/hep.27549

32. Monteiro TP, El-Jaick KB, Jeovanio-Silva AL, et al. The roles of GSTM1 and GSTT1 null genotypes and other predictors in anti-tuberculosis drug-induced liver injury. *J Clin Pharm Ther*. 2012;37(6):712-718. doi:10.1111/j.1365-2710.2012.01368.x

33. O'Connor C, Brady MF. Isoniazid. In: StatPearls. *Treasure Island (FL)*: StatPearls Publishing; April 8, 2022.

34. Perwitasari DA, Atthobari J, Wilffert B. Pharmacogenetics of isoniazid-induced hepatotoxicity. *Drug Metab Rev*. 2015;47(2):222-228. doi:10.3109/03602532.2014.984070

35. Pourkeramati A, Zare Mehrjardi E, Dehghan Tezerjani M, Seifati SM. Association of GSTP1, GSTT1 and GSTM1 Gene Variants with Coronary Artery Disease in Iranian Population: A Case-Control Study. *Int J Gen Med*. 2020;13:249-259. Published 2020 May 28. doi:10.2147/IJGM.S252552

36. Prysyazhnyuk V, Sydorchuk L, Sydorchuk R, et al. Glutathione-S-transferases genes-promising predictors of hepatic dysfunction. *World J Hepatol*. 2021;13(6):620-633. doi:10.4254/wjh.v13.i6.620

37. Sharifzadeh M, Rasoulinejad M, Valipour F, Nouraie M, Vaziri S. Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during antituberculosis [correction of antituberclosis] treatment. *Pharmacol Res*. 2005;51(4):353-358. doi:10.1016/j.phrs.2004.10.009

38. Sharma SK. Antituberculosis drugs and hepatotoxicity. *Infect Genet Evol*. 2004;4(2):167-170. doi:10.1016/j.meegid.2003.01.001

39. Simon T, Becquemont L, Mary-Krause M, et al. Combined glutathione-S-transferase M1 and T1 genetic polymorphism and tacrine hepatotoxicity. *Clin Pharmacol Ther*. 2000;67(4):432-437. doi:10.1067/mcp.2000.104944

40. Singh J, Arora A, Garg PK, Thakur VS, Pande JN, Tandon RK. Antituberculosis treatment-induced hepatotoxicity: role of predictive factors. *Postgrad Med J*. 1995;71(836):359-362. doi:10.1136/pgmj.71.836.359

41. Sun HY, Chen YJ, Gau CS, Chang SC, Luh KT. A prospective study of hepatitis during antituberculous treatment in Taiwanese patients and a review of the literature [published correction appears in J Formos Med Assoc. 2009 Mar;108(3):265. Chen, In-Lon [corrected to Chen, Ying-Jung]]. J *Formos Med Assoc*. 2009;108(2):102-111. doi:10.1016/s0929-6646(09)60040-1

42. Sysoev P.G. Alexandrov A.Y., Miftahova E.G. Adverse events of chemotherapy of tuberculosis // *Synergy sciences*. – 2018. – № 20. – P. 593-598

43. Tang N, Deng R, Wang Y, et al. GSTM1 and GSTT1 null polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2013;17(1):17-25. doi:10.5588/ijtld.12.0447

44. Tang SW, Lv XZ, Zhang Y, et al. CYP2E1, GSTM1 and GSTT1 genetic polymorphisms and susceptibility to antituberculosis drug-induced hepatotoxicity: a nested case-control study. *J Clin Pharm Ther*. 2012;37(5):588-593. doi:10.1111/j.1365-2710.2012.01334.x

45. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepato*l. 2008;23(2):192-202. doi:10.1111/j.1440-1746.2007.05207.x

46. Ueda K, Ishitsu T, Seo T, et al. Glutathione S-transferase M1 null genotype as a risk factor for carbamazepine-induced mild hepatotoxicity. *Pharmacogenomics*. 2007;8(5):435-442. doi:10.2217/14622416.8.5.435

47. van Beek JH, de Moor MH, de Geus EJ, et al. The genetic architecture of liver enzyme levels: GGT, ALT and AST. *Behav Genet*. 2013;43(4):329-339. doi:10.1007/s10519-013-9593-y

48. Watanabe I, Tomita A, Shimizu M, et al. A study to survey susceptible genetic factors responsible for troglitazone-associated hepatotoxicity in Japanese patients with type 2 diabetes mellitus. *Clin Pharmacol Ther*. 2003;73(5):435-455. doi:10.1016/s0009-9236(03)00014-6

49. Yang S, Hwang SJ, Park JY, Chung EK, Lee JI. Association of genetic polymorphisms of CYP2E1, NAT2, GST and SLCO1B1 with the risk of anti-tuberculosis drug-induced liver injury: a systematic review and meta-analysis. *BMJ Open*. 2019;9(8):e027940. Published 2019 Aug 1. doi:10.1136/bmjopen-2018-027940

50. Yimer G, Aderaye G, Amogne W, et al. Anti-tuberculosis therapy-induced hepatotoxicity among Ethiopian HIV-positive and negative patients. *PLoS One*. 2008;3(3):e1809. Published 2008 Mar 19. doi:10.1371/journal.pone.0001809

51. Zehra A, Zehra S, Ismail M, Azhar A. Glutathione S-Transferase M1 and T1 Gene Deletions and Susceptibility to Acute Lymphoblastic Leukemia (ALL) in adults. *Pak J Med Sci*. 2018;34(3):666-670. doi:10.12669/pjms.343.14911

DIAGNOSTIC AND TREATMENT METHODS

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NEW POSSIBILITIES FOR THE TREATMENT OF NEOVASCULAR AMD. THE REAL CLINICAL PRACTICE

DOI 10.25789/YMJ.2022.79.07

УДК 617.736 (571.56)

The results of treatment of patients with neovascular age-related macular degeneration with a modern anti-angiogenic drug registered in Russia in November 2020 were analyzed. After three intravitreal injections in the recommended Treat&Extend regimen, the patients showed positive dynamics in both anatomical and functional parameters during the examination.

Keywords: age-related macular degeneration, retinal pigment epithelium detachment, subretinal fluid, anti-angiogenic therapy, intravitreal injection.

Age-related macular degeneration (AMD) is one of the leading causes of vision loss in people over 50 years of age in the economically developed countries of the world, characterized by irreversible progressive damage to the central zone of the retina. The predicted number of people with age-related macular degeneration in the world by 2040 will increase up to 288 million [20].

In Russia, in 25% of cases, visual disability develops due to diseases of the fundus, AMD being one of the leading causes among them [12] .

In the Republic of Sakha (Yakutia) the incidence of AMD according to 2019 was 195.9 per 100 thousand of the population. Despite the preservation of restrictive measures in connection with the prevention of the spread of a new coronovirus infection, in 2021 the incidence of this pathology increased by 26 %, which is associated with an increase in the availability of a diagnostic option - optical coherence tomography due to an increase in the number of tomographs in the RS (Yakutia) and specialists who own this research technique.

The neovascular form (“wet”) of age-related macular degeneration (nAMD) is characterized by the appearance of pathological choroidal neovascularization caused by the germination of newly formed blood vessels through defects in the Bruch's membrane under the retinal pigment epithelium or neuroepithelium. In the future, it is possible to accumulate intraretinal fluid (IRF), fluid under the retinal pigment epithelium (RPE), subretinal fluid (SRF) - between the neurosensory part of the retina and RPE. This can lead to rapidly progressive significant impairment of central vision and a pronounced decrease in the quality of life in general [5].

Modern advances in the treatment of nAMD are due to the active use of drugs that suppress neoangiogenesis [7, 10, 13, 17]. Antiangiogenic therapy can significantly improve the anatomical and functional parameters of patients with nAMD. Since this disease is chronic and requires long-term treatment, which creates a burden for the patient and for medical institutions, the selection of the optimal dosing regimen, which would reduce the number of necessary injections without loss of therapeutic effect, remains relevant [1, 4, 8], as well as the introduction of new modern drugs with these functions [2, 3].

In RS(Ya), angiogenesis inhibitors for the treatment of nAMD have been introduced since 2012. In dynamics over the past three years, the number of intravitreal injections of angiogenesis inhibitors (IVIs) has almost doubled by 49.3%, from 659 in 2019 to up to 1300 in 2021, of which about 50% were performed in patients with nAMD.

In 2021 Brolucizumab (Vizkyu), a new molecule registered by Novartis in Russia in November 2020, was introduced to treat patients with nAMD at the State Autonomous Institution of the Yakut Republican Ophthalmological Clinic (SAI RS (Ya) YROC). This is the next generation of anti - VEGF drugs , the variable domain of a monoclonal antibody. Its effect is based on the unique properties of the molecule: low molecular weight and high molar concentration contribute to the achievement of a therapeutic effect expressed in terms of speed and duration. Currently, the drug has been approved for use in more than 60 countries around the world [6,11,15,16,19].

Aim: to analyze the results of nAMD treatment in 17 patients of YROC RS(Y) who received three loading IVIs with Brolucizumab in real clinical practice in 2021.

Material and methods: In 2021 190 intravitreal injections of Brolucizumab were performed in 129 patients in the hospital of the State Agrarian University of the Republic of Sakha (Yakutia) of the Yaroslavl Regional Clinic. Of these: 20% of patients previously not treated with angiogenesis inhibitors and 80% switched from another previously performed angiogenic drug. During the study period, out of 129 patients: 17 received three injections, 27 - two injections, 85 - one injection.

In the group of patients who received three injections, 41% were already treated with other angiogenesis inhibitors and intravitreal administration of Brolucizumab was carried out in the Treat & Extend “treat and extend the interval” mode after 3-4 months [9,14].

The functional response to the treatment was assessed by the change in the maximum correctable visual acuity (MCVA), the anatomical response according to the dynamics of the pathological fluid in the retina: intraretinal fluid (IRF), subretinal fluid (SFR) and detachment of the retinal pigment epithelium (RPE) [5,18].

The results of treatment on the example of two of our own clinical observations are presented:

Case report No.1. The patient M., 72 years old, in February 2019 addressed to the YROC with complaints of decreased

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vision, the appearance of a dark "spot" in front of the left eye.

Visit No.1 (02/23/2019) OS: BCVA OS = 0.06 n/c; IOP OS - 29 mm Hg. Art. according to Maklakov.

Fig. 1 a) OCT of the macular area of the left eye of the patient M.

b) OCT-angiography at the level of the outer retina; c) OCTA at the level of choriocapillaries (Fig. 1a) revealed: SRF, intraretinal inclusions, subretinal neovascular membrane (SNM), in the OCT angiography mode (Fig. 1b, 1c) - an extensive loop-like vasculature in a coral-like shape in the outer retina.

Diagnosis: OS - AMD, type I choroidal neovascularization; OUG III "c", incomplete complicated cataract.

Since 2019 the patient underwent 11 IVI Aflibercept in the left eye, then operations: phacoemulsification (PE) with implantation of an intraocular lens (IOL) and non-penetrating deep sclerectomy (NPDS).

Visit No. 11 (24.07.2020) OS: BCVA OS = 0.3 n/c; IOP - 18 mm Hg. Art.

Fig. 2 a) OCT of the macular area of the left eye of the patient M.

b) OCTA at the level of the outer retina; c) OCTA at the level of choriocapillaries

As a result of the treatment, according to OCT data (Fig. 2a), the following was observed: a decrease in the height of the neuroepithelium (NE), a decrease in intraretinal inclusions, a decrease in the height of the SNM , however, a thin layer of SRF ≤200 μm of subfoveal localization was preserved , according to OCT angiography (Fig. 2b, 2c) "mature vessels" were traced in the outer retina and the layer of choriocapillaries. The patient constantly saw a translucent "spot" in front of the left eye.

From April 2021 the patient received 3 IVI Brolucizumab in the Treat & Extend mode once every three months. A month after the third injection at the control examination, a positive trend was revealed.

Visit No.15 (11/14/2021) OS: BCVA OS = 0.5 n/c; IOP - 17 mm Hg. Art.

Fig. 3 OCT of the macular area of the left eye of the patient M.

No SRF was detected on OCT (Fig. 3). The patient noted an improvement in vision, increased clarity, and the absence of a translucent “spot” in front of the left eye.

Case report No. 2. Patient K., 67 years old. Complaints about the deformation of the lines, a reading disability

Visit No.1 (26.07.2021) OS: BCVA OS = 0.3 n/c.

Fig. 4. OCT of the macular area of the left eye of the patient K.

OCT (Fig. 4): The foveolar profile is

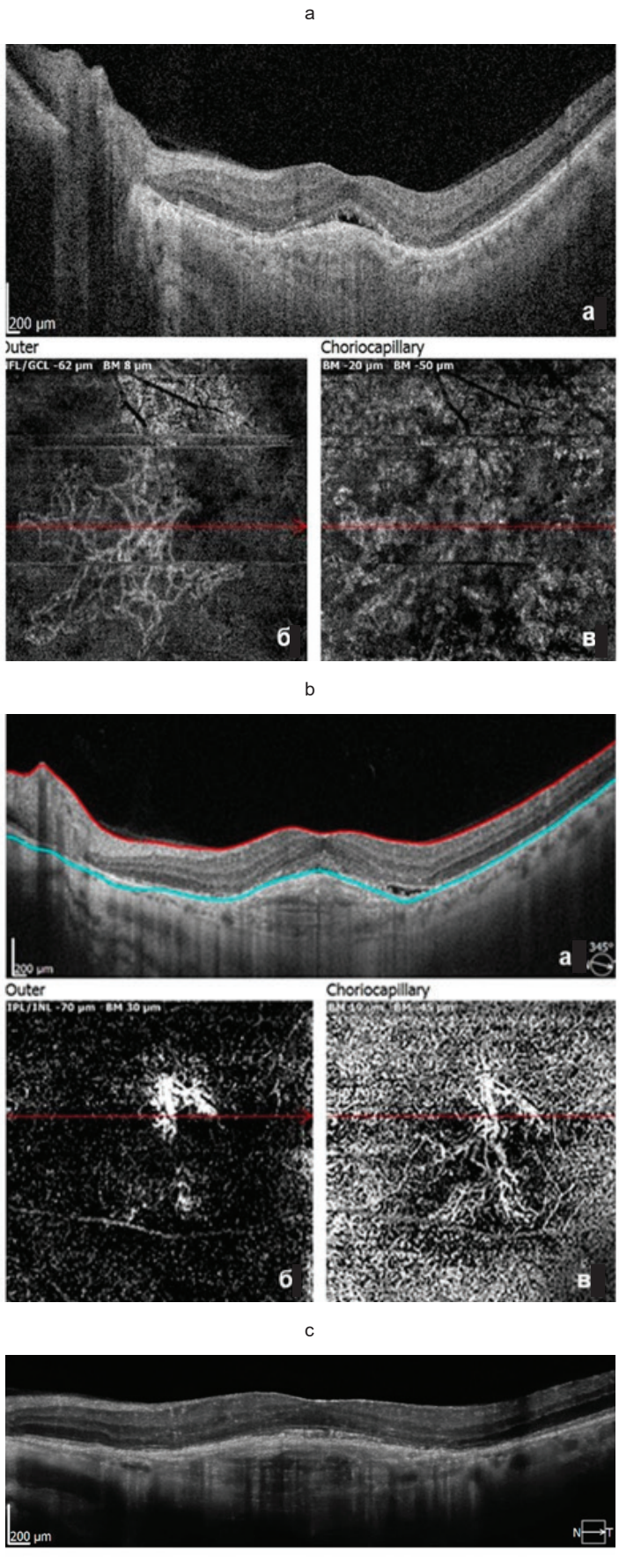


Fig 1. Patient M., A - 23.02.2019, B - 24.07.2020, C - 14.11.2021. a - OCT of the left eye macular area, b - OCTA at the outer retina level, c - OCTA at the level of choriocapillaries

deformed. The thickness of the retina is increased, NE detachment, detachment of the retinal pigment epithelium (RPE) with mixed reflectivity content, SNM is determined subfoveolarly, the RPE contour is heterogeneous, intermittent.

Diagnosis: OS AMD, type I choroidal neovascularization.

3 bootstrap IVI Brolucezumab were conducted. At the control examination 1 month after the third injection, a positive trend was revealed.

Visit No. 3 (24.09.2021) OS: BCVA OS = 0.5n/c.

Fig. 5 OCT of the macular area of the left eye of patient K.

On OCT (Fig. 5), the deformation of the foveolar profile is significantly less, a flat detachment of the RPE with medium reflectivity content is preserved, the contour of the RPE is inhomogeneous, and a discontinuous layer of photoreceptor articulation is traced.

Results and discussion: After 3 IVI Brolucizumab, all 17 patients noted a subjective improvement in vision: a decrease in line distortion, the disappearance of the “spot” in front of the eye, or the “spot” became more transparent.

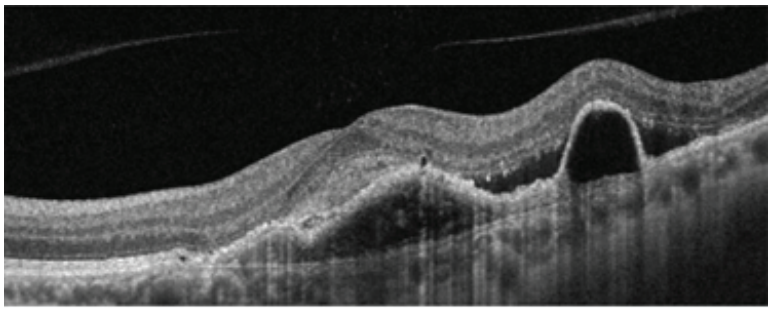
1. Improvement of the best correctable visual acuity (BCVA) by 1-2 lines, in 75% of cases.
2. According to OCT data, 100% showed positive dynamics: the absence or a significant decrease in pathological fluid in the retina: IRF, SRF, and OPES.
3. When switching patients from injections of other angiogenic drugs, loading doses were not required, therapy was continued in the "treat and increase the interval" mode.
4. Of the 96 patients who received from 1 to 2 IVI Brolucizumab, according to the results of the diagnostic study after 1 month, conducted in 62 patients, 64% showed a positive trend according to OCT.
5. During the therapy of 190 IVI Brolucizumab, 129 patients did not experience any manifestations of local adverse events in any case.

Conclusion: In all 17 patients who received 3 IVI Brolucezumab, there was a positive trend in anatomical and functional parameters.

Taking into account the peculiarities of the region of the RS (Y): a vast territory, with an area of 3.1 million square km., low population density of 0.3 people per 1 sq. km, which leads to non-compliance with the dosing regimen due to the large distance of patients from the clinic, the therapy with Brolucizumab allows switching to regimens with fewer visits, which will increase patient adherence to treatment and preserve the visual functions of patients.

In the ongoing conditions of restrictive measures in connection with the prevention of the spread of the new coronovirus infection COVID -19, the treatment of patients with Brolucizumab can reduce the burden on the patient and the healthcare system.

a



b

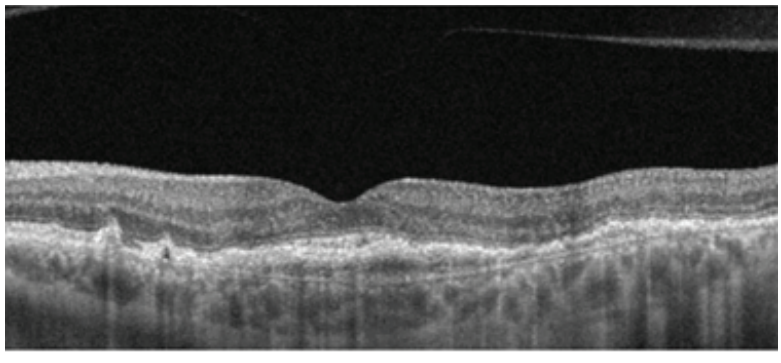


Fig. 2. Patient K. OCT of macular area of the left eye: a - 26.07.2021, b - 24.09.2021

Reference

1. Astakhov YuS, Nechiporenko PA. Rezhimy naznacheniya ingibitorov angiogeneza pri lechenii pacientov s neovaskulyarnoĭ vozrastnoĭ makulyarnoĭ degeneracieĭ [Modes of administration of angiogenesis inhibitors in the treatment of patients with neovascular age-related macular degeneration]. Oftal'mologicheskie vedomosti [Ophthalmological vedomosti]. 2019; 12 (2): 47-56. URL: https://cyberleninka.ru/article/n/rezhimy-naznacheniya-ingibitorov-angiogeneza-pri-lechenii-patsientov-s-neovaskulyarnoi-vozrastnoi-makulyarnoi-degeneratsiei
2. Bobykin EV. Lechenie zabolevanij makuly: vzglyad v budushchee (obzor literatury) [Treatment of macular diseases: a look into the future (literature review)]. Otrazhenie [Reflection]. 2020; 10 (1): 61-72. URL: https://eyepress.ru/article.aspx?44251
3. Bobykin EV. Rezhimy primeneniya antiangiogennoj terapii dlya lecheniya zabolevanij makuly v oftal'mologii. Obzor literatury [Modes of application of antiangiogenic therapy for the treatment of macular diseases in ophthalmology. Literature review]. Prakticheskaya medicina [Practical medicine]. 2018; 16 (5): 104-111. URL: https://cyberleninka.ru/article/n/rezhimy-primeneniya-antiangiogennoy-terapii-dlya-lecheniya-zabolevaniy-makuly-v-oftalmologii-obzor-literatury
4. Bobykin EV, Korotkih SA, Nerus IA, Morozova OV. Udovletvorennost' lecheniem pacientov s neovaskulyarnoj vozrastnoj makulyarnoj degeneraciej, poluchayushchih antiangiogennuyu terapiyu [Satisfaction with the treatment of patients with neovascular age-related macular degeneration receiving antiangiogenic therapy]. Tihookeanskij medicinskij zhurnal [Pacific Medical Journal]. 2019; 2(76): 14-18. URL: https://cyberleninka.ru/article/n/udovletvorennost-lecheniem-patsientov-s-neovaskulyarnoy-vozrastnoy-makulyarnoy-degeneratsiey-poluchayuschih-antiangiogennuyu
5. Budzinskaya MV, Plyukhova AA. Novye kachestvennye metody ocenki «zhidkosti» v setchatke pri vozrastnoj makulyarnoj degeneracii [New qualitative methods for assessing the "fluid" in the retina in age-related macular degeneration]. Ophthalmology. 2021; 18 (2): 222-227. URL: https://www.ophthalmojournal.com/opht/article/view/1536
6. Budzinskaya MV, Plyukhova AA. Perspektivy antiangiogennoj terapii pri zabolevaniyah setchatki [Prospects of antiangiogenic therapy in retinal diseases]. Ophthalmology. 2021; 18 (3S): 638-645. URL: https://www.ophthalmojournal.com/opht/article/view/1634
7. Gavrilova NA, Gadzhieva NS, Tishchenko OE, Zinovieva AV. Analiz rezul'tatov provedeniya klinicheskih issledovanij pri neovaskulyarnoj vozrastnoj makulyarnoj degeneracii za 2005–2020 gg. Obzor literatury [Analysis of the results of clinical studies in neovascular age-related macular degeneration for 2005-2020. Literature review]. Ophthalmology. 2022; 19 (1): 22-32. URL: https://www.ophthalmojournal.com/opht/article/view/1766/930
8. Durasov AB. Terapiya neovaskulyarnoj vozrastnoj makulyarnoj degeneracii: obosnovannye ozhidaniya vracha i pacienta [Therapy of neovascular age-related macular degeneration: reasonable expectations of a doctor and a patient]. Klinicheskaya oftal'mologiya [Breast cancer. Clinical ophthalmology]. 2021; 21 (3):

169-174. URL: https://cyberleninka.ru/article/n/terapiya-neovaskulyarnoy-vozrastnoy-makulyarnoy-degeneratsii-vobosnovannye-ozhidaniya-vracha-i-patsienta

9. Ioshin IE, Anoprieva TA. Podhody k naznacheniyu antiangiogennyh preparatov pri terapii pacientov s neovaskulyarnoj vozrastnoj makulyarnoj degeneraciej [Approaches to the appointment of antiangiogenic drugs in the treatment of patients with neovascular age-related macular degeneration]. Russian Ophthalmological Journal. 2019; 12(3): 102-112. URL: https://roj.igb.ru/jour/article/view/307

10. Koroleva IA, Gvetadze AA, Romanova TB. Farmakoterapiya VMD: obzor novyh tendencij [Pharmacotherapy of AMD: an overview of new trends]. RMJ. Clinical ophthalmology. 2019; 19 (2): 105-109. URL: https://cyberleninka.ru/article/n/farmakoterapiya-vmd-obzor-novyh-tendentsiy

11. Medvedeva LM. Nekotorye aspekty patogeneza i lecheniya vozrastnoj makulyarnoj degeneracii [Some aspects of pathogenesis and treatment of age-related macular degeneration]. Vestnik Vitebskogo gosudarstvennogo medicinskogo universiteta [Bulletin of the Vitebsk State Medical University]. 2021; 20 (5): 7-14. URL: https://cyberleninka.ru/article/n/nekotorye-aspekty-patogeneza-i-lecheniya-vozrastnoy-makulyarnoy-degeneratsii-1

12. Neroev VV. Invalidnost' po zreniyu v Rossijskoj Federacii [Visual disability in the Russian Federation]. 'Belye nochi' [White Nights]. 2017. organum-visus.com , eye-portal.ru , glaucoma-eye-portal.ru

13. Zhayvoronok N. S., Egorov V. V., Smolyakova G. P. [et al.] Pervyj klinicheskij opyt primeneniya aflibercepta v lechenii pacientov s neovaskulyarnoj vozrastnoj makulyarnoj degeneraciej, rezistentnoj k ranibizumabu [The first clinical experience of using aflibercept in the treatment of patients with neovascular age-related macular degeneration resistant to ranibizumab]. Sovremennye tekhnologii v oftal'mologii [Modern technologies in ophthalmology]. 2018; 2: 144-147. URL:https://khvmntk.ru/assets/files /conf2018/sbornik2018.pdf#page=144

14. Fayzrakhmanov RR. Anti-VEGF terapiya neovaskulyarnoj vozrastnoj makulyarnoj degeneracii: ot randomizirovannyh issledovanij k real'noj klinicheskoj praktike [Anti-VEGF therapy of neovascular age-related macular degeneration: from randomized trials to real clinical practice]. Rossijskij oftal'mologicheskij zhurnal [Russian Ophthalmological Journal]. 2019;12 (2): 97-105. URL: https://roj.igb.ru/jour/article/view/279/236

15. Fursova AZh, Zabanova VE, Gamza YuA [et al.] Profil' oftal'mologicheskoj bezopasnosti antiangiogennoj terapii [Vestnik oftal'mologii Profile of ophthalmological safety of antiangiogenic therapy]. Bulletin of Ophthalmology. 2021; 137 (2): 114-122.

16. Dugel P. U., Koh A., Ogura Y. [et al.] HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration//Ophthalmology.2020.Vol.127.N.1.URL: https://www.aaojournal.org/article/S0161-6420(18)33018-5/fulltext

17. Garca-Quintanilla L., Luaces-Rodrguez A., Gil-Martnez M. [et al.] Pharmacokinetics of Intravitreal Anti-VEGF Drugs in Age-Related Macular Degeneration // Pharmaceutics. 2019. Vol. 11. N. 8. P. 365. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723750/

18. Schmidt-Erfurth U., Vogl W. D., Jampol L. M., Bogunović H. Application of Automated Quantification of Fluid Volumes to Anti-VEGF Therapy of Neovascular Age-Related Macular Degeneration // Ophthalmology. 2020. Vol. 127. N. 9. P. 1211-1219. URL: https://www.sciencedirect.com/science/article/pii/S0161642020302682

19. Tadayoni R., Sararols L., Weissgerber G. [et al.] Brolucizumab: A Newly Developed Anti-VEGF Molecule for the Treatment of Neovascular Age-Related Macular Degeneration // Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde. 2021. Vol. 244. N. 2. P. 93-101. URL: https://www.karger.com/Article/FullText/513048

20. Wong W. L. et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2: e106–e116.

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SURGICAL TREATMENT OF PRIMARY NON-PIGMENTED COLON MELANOMA: A CASE REPORT

DOI 10.25789/YMJ.2022.79.08

УДК 616.345-006.81-089

Primary colonic melanoma is a rare malignant tumor with an aggressive course and a poor prognosis. The extremely low incidence of this pathology is due to the fact that there are no melanocytes in the mucosa of the gastrointestinal tract, from which the tumor develops. The development of non-pigmented melanoma are even rarer. Due to the lack of clinical guidelines for the treatment of primary colonic melanoma, therapy is mainly carried out empirically. The article describes a clinical case that demonstrates the possibilities of surgical treatment of primary non-pigmented melanoma of the colon with satisfactory oncological results.

Keywords: primary non-pigment melanoma, colon, surgical treatment.

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Introduction. Melanoma is an aggressive tumor that develops as a result of malignant transformation of melanocytes. The main localization of melanoma is the skin, but there are reports of primary melanoma of various organs [1]. According to the American College of Surgeons and the American Society of Oncology, during the period from 1985 to 1994, out of 84836 cases of melanoma, the most common lesions were skin - 91.2%, eyes - 5.2%, mucous membrane of the gastrointestinal tract (GIT) - 1.3%, in some cases, the primary localization of the tumor was not verified - 2.2% [2].

Primary melanoma of the gastrointestinal tract is an extremely rare malignant disease [3], for the reason that normally in the mucous of the digestive tract there are no melanocytes and they appear only when ontogenesis is disturbed. Currently, there are several theories about the appearance of melanocytes in the colon: some authors believe that primary intestinal melanomas arises from melanoblastic cells of the neural crests, which migrate to the distal ileum through the omphalomesenteric canal [4], according to the others, these tumors develops from cells of the APUD system [5], either from neuroblastic Schwann cells of the enteric autonomic nervous system [6]. At the same time, a number of researchers believe that primary colon melanoma does not exist, and all founded cases are only metastatic foci from primary skin melanoma, which is asymptomatic or in remission [7, 8]. In this regard, the question of the primary or metastatic origin of melanomas of the gastrointestinal tract is still open.

According to the world literature, 36 cases of primary colon melanoma were described in 2018 [3]. Cases of non-pigmented melanoma of the gastrointestinal tract are even rarer [9], which makes it more relevant for studying. In the presented article, we will consider a clinical case about surgical treatment of a patient with primary non-pigmented melanoma of the transverse colon.

Patient T., aged 60, applied to the Oncology Research Institute of the Tomsk National Research Medical Center in July 2021 with complaints of recurrent pain in the mesogastric region. Examination during videocolonoscopy (July 08, 2021) revealed an exophytic tumor in the lumen of the transverse colon, narrowing the lumen of the intestine to a slit-like one (Fig. 1). Histological examination revealed an undifferentiated tumor of the epithelioid cell type with solid structure.

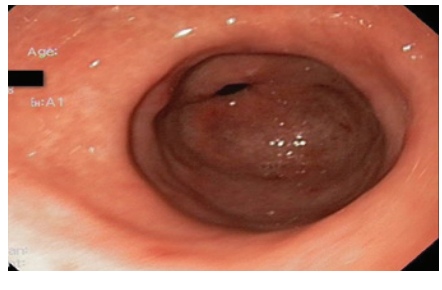

Fig. 1. Colonoscopy finding. Exophytic tumor in transverse colon

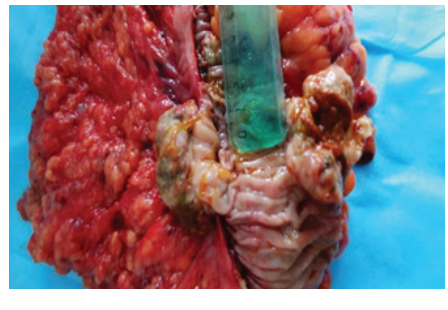

Fig. 2. Gross photograph. Tumor of the transverse colon

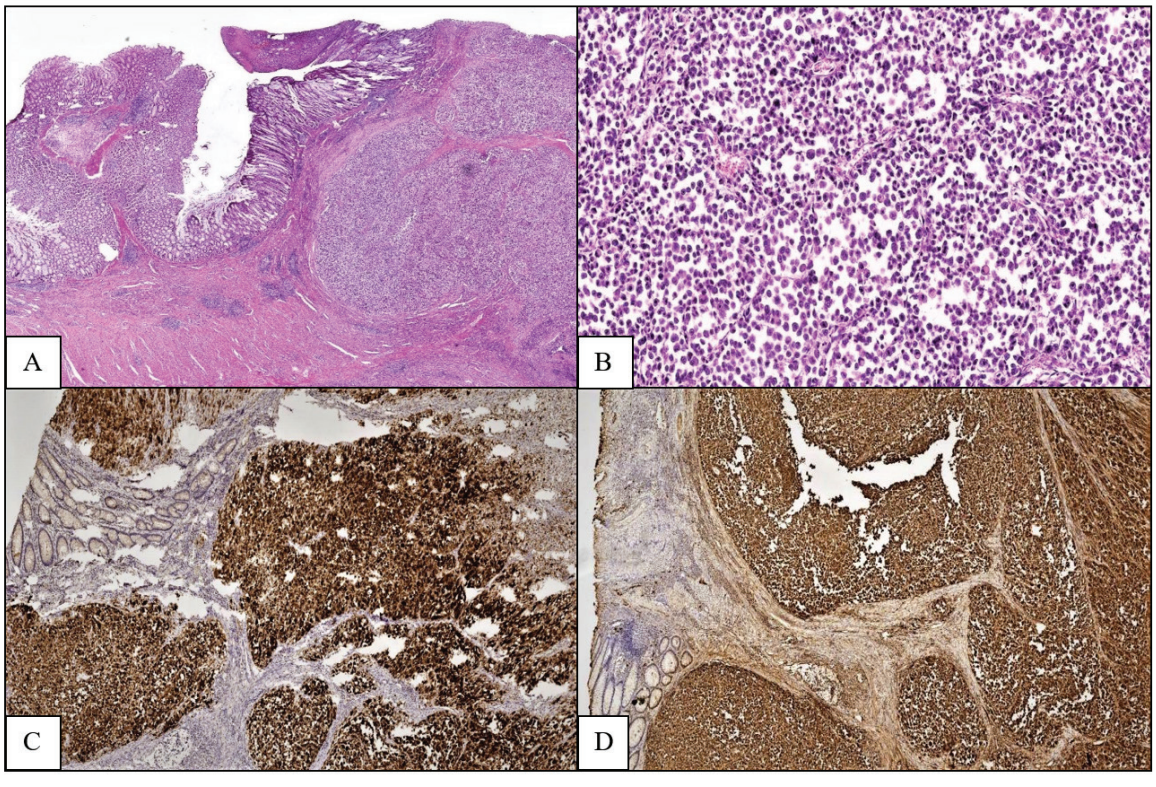

Fig. 3. Microscopy. A) The growth of a tumor of a solid structure in the intestinal wall (Magnification × 20, hematoxylin-eosin) B) Medium-sized tumor cells with a clear even cytoplasmic membrane, sparse homogeneous eosinophilic cytoplasm and large moderately polymorphic nuclei with unevenly distributed clumpy and pulverized chromatin. (Magnification × 80, hematoxylin-eosin). An IHC study in tumor cells revealed an active diffuse expression of Melan A (C) and S100 (D)

On August 24, 2021, after the standard preoperative preparation, the patient underwent video-assisted resection of the transverse colon with D3 lymph node dissection. Pathological examination of the colon resection specimen revealed exophytic component up to 5 cm in diameter, obturating the intestinal lumen with lymph nodes in the mesentery of the intestine up to 1.5–2 cm in diameter (Fig. 2). In the postoperative period there were signs of dynamic intestinal obstruction, that were treated by conservative therapy.

According to postoperative histological and immunohistochemical (IHC) studies (Fig. 3) we found out malignant non-pigmented melanoma of the transverse colon with ulceration of the mucous membrane and spread to 1/3 of the muscular plate. Tumor emboli in the lumen of the vessels and signs of neural invasion were not found. There were no tumor cells along the resection borders and in 25 examined lymph nodes.

In the postoperative period, a detailed clinical examination and a comprehensive examination showed no signs of tumor lesions of the skin and eyes, as well as the brain, skeleton and parenchymal organs. Thus, based on the results obtained, the final clinical diagnosis was formed: Pigmentless melanoma of the transverse colon, subcompensated stenosis. Stage I, T2N0M0. Condition after video-assisted resection of the transverse colon (August 24, 2021). Considering the stage of the tumor process and the radical nature of the operation performed, adjuvant treatment was not performed. On the 7th day after surgery, the patient was discharged from the hospital. At the control examination after 6 months (February 2022), there were no signs of disease progression.

Discussion. Nowdays, the diagnosis and treatment of melanoma of the colon present definite difficulties, which is caused with the low cases of incidence and underexplored of this pathology. The leading role in the diagnosis of primary melanoma of the colon is assigned to the IHC study (positive result for protein S100, melan-A, HMB-45 and vimentin), if there are no specific lesion of the skin or eyes in patients history or in present, which account for up to 96.4% of all cases of melanoma [2].

Currently, there are no clinical guidelines for the treatment of primary colonic melanoma. The main method of treatment is surgical, which, in addition to removing the tumor, allows for adequate staging and to develop further treatment tactics. Radiotherapy in some cases can provide good local control, but does not lead to an improvement in patient survival. [1].

It is known that patients with primary colonic melanoma with a widespread primary tumor and lymph node involvement have a poor prognosis [2]. This situation requires an interdisciplinary approach to treatment, including surgery, chemotherapy and possibly immunotherapy using modern anticancer drugs. [3, 10].

Conclusion. This clinical observation demonstrates the possibilities of surgical treatment in a patient with primary non-pigmented melanoma of the transverse colon (T2N0M0).

Due to the fact that primary melanoma of the colon is a rare pathology, the diagnosis is established on the basis of the IHC study, as well as the results of a comprehensive examination aimed at excluding the metastatic nature of the gastrointestinal tract (lack of data on melanoma of the skin and organs of vision). In the case of a localized tumor process, radical resections are performed, however, with locally advanced melanoma of the colon, especially with regional lymph nodes involved, a combination of surgical treatment with chemotherapy and/or immunotherapy is indicated.

Reference

1. Mihajlovic M., Vlajkovic S., Jovanovic P., Stefanovic V. Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol. 2012;5(8):739-53. PMID: 23071856; PMCID: PMC3466987.
2. Chang A.E., Karnell L.H., Menck H.R. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998 Oct 15;83(8):1664-78. doi: 10.1002/(sici)1097-0142(19981015)83:8<1664::aid-cncr23>3.0.co;2-g. PMID: 9781962.
3. Miliaras S., Ziogas I.A., Mylonas K.S., Papadopoulos V.N. Primary malignant melanoma of the ascending colon. BMJ Case Rep. 2018 Mar 9;2018:bcr2017223282. doi: 10.1136/bcr-2017-223282. PMID: 29523612; PMCID: PMC5847959.
4. Amar A., Jougon J., Edouard A., Laban P., Marry J.P., Hillion G. Mélanome malin primitif de l'intestin grêle [Primary malignant melanoma of the small intestine]. Gastroenterol Clin Biol. 1992;16(4):365-7. French. PMID: 1397858.
5. Krausz M.M., Ariel I., Behar A.J. Primary malignant melanoma of the small intestine and the APUD cell concept. J Surg Oncol. 1978;10(4):283-8. doi: 10.1002/jso.2930100402. PMID: 29168.
6. Mishima Y. Melanocytic and nevocytic malignant melanomas. Cellular and subcellular differentiation. Cancer. 1967 May;20(5):632-49. doi: 10.1002/1097-0142(1967)20:5<632::aid-cncr2820200510>3.0.co;2-7. PMID: 6024276.
7. Schuchter L.M., Green R., Fraker D. Primary and metastatic diseases in malignant melanoma of the gastrointestinal tract. Curr Opin Oncol. 2000 Mar;12(2):181-5. doi: 10.1097/00001622-200003000-00014. PMID: 10750731.
8. Manouras A., Genetzakis M., Lagoudianakis E., Markogiannakis H., Papadima A., Kafiri G., Filis K., Kekis P.B., Katergiannakis V. Malignant gastrointestinal melanomas of unknown origin: should it be considered primary? World J Gastroenterol. 2007 Aug 7;13(29):4027-9. doi: 10.3748/wjg.v13.i29.4027. PMID: 17663525; PMCID: PMC4171183.
9. Yi N.H., Lee S.H., Lee S.H., Kim J.H., Jee S.R., Seol S.Y. Primary malignant melanoma without melanosis of the colon. Intest Res. 2019 Oct;17(4):561-564. doi: 10.5217/ir.2019.00020. Epub 2019 Aug 5. PMID: 31302994; PMCID: PMC6821945.
10. Raja J., Hegde R., Srodon M., Katoch A., Kurtzman S., Zhang Z. A Case of Primary Melanoma of the Transverse Colon. Cureus. 2017 Oct 26;9(10):e1803. doi: 10.7759/cureus.1803. PMID: 29308331; PMCID: PMC5749940.

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DETERMINATION OF NASAL SEPTUM DEVELOPMENT PATTERNS IN INDIGENOUS CHILDREN AGED 0 TO 4 IN THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.09

УДК617.723.2:616.31.002

Dynamics in the development of otorhinolaryngological pathologies among Sakha Republic's population has a positive upward trend, and one of the main reasons is the deformity of the nasal septum, which, according to some authors, makes up 56 to 95% of all treatment cases. Congenital deformities or developmental anomalies leading to deviation of the nasal septum in children with untimely diagnosis can lead to chronic inflammatory processes in the mucous membrane of the cavity and paranasal sinuses. This causes a violation of the airway function of the upper respiratory tract and increased probability of infectious diseases. Diagnosis of these conditions in children under 6 years of age will prevent these consequences, as well as reduce the need for surgical treatment of septoplasty. This article discusses a method for describing the developmental patterns of the nasal septum as one of the practical methods for early diagnosis of children. The method uses computed tomography data of children of the indigenous population of the Sakha (Yakutia) Republic. We have analyzed the results of studies of multislice CT of the head in multiplanar mode for children aged 0 to 4 with a total of 48 patients. At the same time, the grouping of research subjects was based on gender (boys, girls) and age (by years). While analyzing the images, we used the linear dimensions of the nasal septum, including the length and height of the septum, as well as its angle of deviation. According to the results of the analysis, we found statistically significant correlations, which made it possible to conclude that there is a linear relationship between age groups and each of the indicators, as well as a decrease in the deviation angle of the nasal septum with age.

Keywords: developmental patterns; nasal septum; CT scan; anatomy; indigenous people; deviated nasal septum.

Introduction. The nasal septum is located on the facial region of the head in the middle part of the nasal cavity. It separates the two nasal passages and forms a scaffold to support the external nose. This structure has a mosaic developmental pattern and consists of bony structures, such as the perpendicular plate of the ethmoid bone above, the vomer below, and the tetrahedral cartilage in front. It develops from three main embryological sources: ectoderm, neural crest and mesoderm, which, by the end of the fourth week of gestation, form paired thickenings of the ectoderm in the embryo, forming the nasal cavity and its structures. [1, 2, 3, 4, 9, 11].

Deviations in the development of the nasal septum in the embryonic and postembryonic periods entail an increased risk of otorhinolaryngological pathologies and cause a violation of the nasal airway function [2, 7, 8, 9, 11, 13]. Conditions arise where the biomechanical aspects of air going through the nasal passages worsen. This leads to — in children in particular — chronic hypoxic conditions, an increase in the development of infectious diseases of the upper respiratory tract, impaired olfactory function, and speech problems. These also include the common pathology of deviation, or curvature, of the nasal septum. With untimely diagnosis of this disorder, there may be violation in the circulation of the nasal discharge from the paranasal sinuses, which leads to a favorable environment for infectious agents and the development of sinuses inflammation (e.g., sinusitis, ethmoiditis, frontal sinusitis). Inflammation of the nasal mucosa can also cause chronic rhinitis, the development of polyps, and sleep apnea [4, 11].

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To solve the problems described above, otorhinolaryngologists resort to surgical treatment of septoplasty [1, 2, 4, 5]. The surgery aims to correct parts of the nasal septum under conditions as part of endoscopic intervention and to restore adequate air flow through the nasal passages in the postoperative period. In the preoperative period, the doctor needs to study in detail the structure and form of the nasal passages and the septa, assess the degree of deviation and determine the appropriate surgical strategy. To do this, surgeons use the results of computed tomography, which allows visualizing problematic areas of the nasal septum in detail, as well as examining the anatomical zone in three planes (axial, frontal and sagittal) and using three-dimensional reconstruction of the nasal structures [10, 14].

As mentioned above, computed tomography is one of the main methods for diagnosing deviated nasal septum. Meanwhile, patients seek medical help for symptoms that are the result of a chronic inflammatory process occurring in the nasal cavity. While being examined by an otolaryngologist, patients learn for the first time that they have a deviated nasal septum. These data may indicate insufficient measures related to preventing nasal cavity pathologies among the population and raises the issue of increasing the effectiveness of the measures to prevent them.

It is also worth noting that deviated nasal septum often occurs even in the embryonic period of the child's development, which may indicate congenital deviations or prerequisites for their occurrence. Considering that the growth and development of human bone and cartilage structures occurs rapidly in the early period, we infer that the risk group for deviated nasal septum includes children, newborn to preschool age [6, 15].

In connection with the problems described above, this article aims to study the developmental patterns of nasal septum structures in the indigenous inhabitants of the Far North living in the Sakha Republic aged 0 to 4, to identify these patterns and to also identify the minimum necessary criteria for predicting and determining nasal septum deviation in children.

Materials and Methods. The study was conducted on the basis of the Department of Radiation Diagnostics at the M.K. Ammosov Republican Hospital. We have studied skull from tomograms obtained using multispiral computed tomography with GE Optima CT660. In the course of a retrospective cohort study, we selected intravital tomograms of the facial skull of indigenous children aged 0 to 4 in various gender samples. A total of 48 children were studied, of which 16 were girls (30.7%) and 32 were boys (69.3%). The distribution by age was carried out with a breakdown by one year (Table 1). Within the group of boys, there were 13 children less than one year of age (40.6% or 27.1% of the total), aged one to two years old — 7 children (21.9% or 14.6% of the total), aged two to three — 3 children (9.4% or 6.3% of the total), from three to four — 9 children (28.1% or 18.8% of the total). Among girls, the distribution went as follows: less than one year of age — 3 children (18.75% or 6.3% of the total), aged one to two — 3 children (18.75% or 6.3% of the total), aged two to three — 4 children (25% or 8.3% of the total) and aged three to four — 6 people (37.5% or 12.5% of the total).

The study included 48 results of multispiral CT scans of the brain and paranasal sinuses in standard mode and standard positions in patients undergoing routine examination or suspected head injury. The selection criteria included patients where, according to the results of computed tomography of the brain, there were no traumatic changes in the bones of the skull and nasal septum detected. The exclusion criteria had children with an anomaly in the development of the maxillofacial region, traumatic fractures of the bones of the nose and septum, as well as after surgery to correct deviated nasal septum. Image processing was carried out in DICOM (Digital Imaging and Communications in Medicine) based on the ArchiMed Radiological Information System (commercial license) using linear measurements in multiplanar two-dimensional mode. All results were anonymized with the preservation of relevant information, such as age and gender.

The measurement of the linear dimensions of the nasal septum was carried out according to the following craniometric reference points [10, 12]: total length of the nasal septum between the piriform opening and the vomer edge (length of septum or LS); maximum length of the septum between the most anterior part of the nasal septum and the edge of the vomer (maximal length of septum or MLS); height of the nasal septum at the level of the intersection of its bone and cartilaginous parts or at the level of the middle third of the total length between the hard palate and the maximum upper point of the perpendicular plate of the ethmoid bone (septum height or SH); angle of deviation of the nasal septum relative to the vertical line at the level in the middle third of the total length (septum deviation angle or SDA).

Further statistical processing was carried out using Microsoft Office Excel (shareware license), as well as using the Python programming language with NumPy and pandas libraries for static analysis. We assessed the correspondence of the empirical distribution of the studied variables to the normal distribution law using the Shapiro–Wilk test. During the analysis, it turned out that the results of the MLS parameter do not correspond to the normal distribution, and we therefore decided to use the nonparametric Kruskal–Wallis test. We also assessed the homogeneity of the variance using Levene's test. We used nonparametric analysis of variance (ANOVA) to assess the differences between the studied age groups. To conclude on the presence or absence of statistical significance, we used the criterion of $P \le 0.05$.

Results and Discussions. When measuring the craniometric parameters of the subjects' nasal septum, we revealed a statistically significant relationship between the age groups (Table 1).

Considering the results without gender differentiation in the total sample, we noticed a significant correlation between the age of the child and the following parameters: length of the nasal septum (0.69; $p < 0.05$), maximum length of the nasal septum (0.78; $p < 0.05$) and its height (0.83; $p < 0.05$). This may be because during this period of a child's life that the structures that form parts of the facial skull and nasal cavity are actively developing, tending to threshold values of these areas' parametric indicator ratios. With the child's active growth in the first years of life, the biomechanical aspects of the nasal cavity's structure, which form with the help of its septum, ensure adequate air passage through the upper respiratory tract.

We have also noticed a slight difference in linear measurements of LS, MLS and SH between boys and girls of the total sample in different age groups,

Table 1

Pearson Linear Correlation Values (rx. y) for Nasal Septum Depending on Patient's Age at P<0.05 (N=48)

Parameter	$r_{x.y}$
LS	0.691319
MLS	0.779506
SH	0.828580
SDA	-0.186490

Table 2

Results of Nasal Septum Measurements

		LS (mm)		MLS (mm)		SH (mm)		SDA (degrees)	
Age, years	Gender	m±SD	95% CI	m±SD	95% CI	m±SD	95% CI	m±SD	95% CI
0-1	Combined	35.0±4.04	31.17-35.48	42.25±2.87	40.53-43.59	22.35±1.67	21.01-22.79	10.80±2.68	8.73-11.59
	Boys	33.70±4.38	30.22-35.51	42.80±3.19	40.15-44.01	22.30±1.77	20.62-22.76	11.80±2.77	8.81-12.16
	Girls	35.00±0.58	33.9-36.77	41.70±0.83	39.89-44.04	23.10±0.70	21.06-24.54	7.90±2.08	3.57-13.89
1-2	Combined	40.6±6.44	33.73-42.95	46.60±5.63	43.69-51.75	26.3±2.74	23.93-27.85	7.45±3.57	5.56-10.68
	Boys	41.60±5.92	35.16-46.1	51.10±5.31	44.86-54.68	26.10±2.10	23.53-27.42	7.10±4.21	4.22-12.00
	Girls	31.50±4.54	21.72-44.28	41.80±2.97	35.56-50.30	26.60±4.31	16.17-37.56	8.80±2.08	2.96-13.30
2-3	Combined	42.1±3.03	39.21-44.82	54.10±2.57	51.15-55.9	27.3±3.29	25.13-31.21	5.90±0.94	5.59-7.34
	Boys	44.70±4.48	32.1-54.37	56.10±3.73	44.84-63.36	27.30±3.87	19.18-38.42	5.90±0.74	4.34-7.99
	Girls	41.10±1.54	38.65-43.56	53.80±1.84	50.17-56.03	27.75±3.31	22.44-32.96	6.50±1.12	4.92-8.48
3-4	Combined	44.1±2.55	42.32-45.15	55.20±3.54	52.44-56.35	31.1±3.64	29.42-33.44	6.80±3.03	6.38-9.73
	Boys	44.10±3.11	41.21-45.99	55.50±4.09	51.03-57.31	32.65±3.28	30.65-35.7	6.70±2.16	5.59-8.92
	Girls	43.80±1.66	42.19-45.68	54.65±2.84	51.76-57.72	28.35±2.48	26.22-31.42	9.30±3.91	5.15-13.35

Note: m is median line; SD is standard deviation; CI is confidence interval.

which is confirmed by the data in Table 2. When considering the results of the study of the length of the nasal septum (LS) among boys, we can note that the most pronounced values are at the ages of 3-4 (44.7 ± 4.48 mm at $p < 0.05$ and 44.1±3.11 mm at $p < 0.05$, respectively). In the group of girls, a similar situation is observed, while the length of the nasal septum (LS) tends to lengthen from the ages of 2 (31.5±4.54 mm, $p < 0.05$) to 3 (41.1 ± 1.54 mm, $p<0.05$), respectively.

Analysis of the maximum length of the nasal septum (MLS) and its height (SH) showed an identical picture by 3-4 years of age, due to an increase in the size of not so much the bone component of the septum as its cartilaginous part. At the same time, if the difference between the craniometric lengths of LS and MLS in the first year is about 6-7 mm, then between the second and third years it reaches about 11-12 mm. This may be caused by the active development of the tetrahedral cartilage of the nasal septum, which forms the framework of the anterior nasal cavity, as well as maintaining the components of the external nose, and providing more effective inhaling and air going through the nasal passages.

According to W. Likus et al. [10], length dimensions of the bone and cartilage parts of the nose develop similarly. At the same time, we have recorded the size growth in indicators between age groups between the second and third years of life. When comparing our results of the study of nasal septum's linear parameters in indigenous children aged 0 to 4 with the results of W. Likus et al., who have studied Caucasian children of the same age group, we can trace longer linear dimensions of nasal septum in the second year of life in Sakha children (40.6 ± 6.44 mm) over those in Caucasian children (31.90 ± 3.24 mm).

Conclusions. The correlation between the children's age and the craniometric data of the nasal septum has a statically significant linear relationship, where there is a positive trend in nasal septum size, especially by ages 3-4. Simultaneously with the growth of these dimensions, we can observe the decrease in nasal septum deviation angle, as evidenced by the negative Pearson correlation values. This trend indicates an adequate and comprehensive development of the nasal cavity, facial skull and nasal septum in children. Also noteworthy is the rapid growth of the cartilaginous part of the nasal septum by age 3, which is confirmed by the difference between indicators, such as LS and MLS. This data demonstrates how this method of studying the nasal septum based on CT results can be applied when detecting deviations in the septum's development and using it to prevent naval cavity diseases.

Reference

1. Oganesyan SS, Yanov YuK, Naumenko NN, Iliin SN, Mishkorez MV. Morfometricheskie varianty stroeniya naruzhnogo nosa i vnutrinosovyh struktur pri rinoskalioze: komp'yuterno-tomograficheskoe issledovanie [In Russian]. лMorphometric Variants of the Structure of the External Nose and Intranasal Structures in Rhinoscaliasis: Computer Topographic Study. RO. 2009. No. 6 (In Russ.).]

2. Markeeva MV, et al. Osobennosti izmenchivosti kostnoj chasti peregorodki nosa v detskom vozraste [Features of the Variability of the Bone Part of the Nasal Septum in Childhood]. Izvestiya vuzov. Povolzhsky region. Medicinskie nauki [News of Universities. Volga Region. Medical Sciences. 2020; 2 (54) (In Russ.).]

3. Lutsay ED, et al. Sovremennye predstavleniya o razvitii i stroenii nosovoj polosti cheloveka [Modern Ideas About the Development and Structure of the Human Nasal Cavity]. Medicinskij vestnik Bashkortostan [Medical Bulletin of Bashkortostan. 2021. No. 1 (91) (In Russ.).]

4. Subbotina M.V., Kokhanov V.S. Vliyanie narusheniya arhitektoniki polosti nosa i nosoglotki na razvitie okolonosovyh pazuh i formirovanie v nih vospalitel'nyh processov [Influence of Violations of the Architectonics of the Nasal Cavity and Nasopharynx on the Development of the Paranasal Sinuses and the Formation of Inflammatory Processes]. RO. 2020; No. 5 (108) (In Russ.).]

5. Chistyakova V.R. Klinicheskoe znachenie anatomii i fiziologii LOR-organov u novorozhdennykh i grudnykh detey: natsional'noe rukovodstvo [Clinical Significance of the Anatomy and Physiology of the Ent Organs in Newborns and Infants: National Guidelines]. Ed. by M.R. Bogomilsky, V.R. Chistyakova. Moscow: GEOTAR-Media, 2008: 736 (In Russ.).]

6. Lee S.H., Yang T.Y., Han G.S., Kim Y.H., Jang T.Y. Analysis of the Nasal Bone and Nasal Pyramid by Three-Dimensional Computed Tomography. Eur. Arch. Otorhinolaryngol. 2008: 265.

7. Ruano-Gil D, et al. Deformities of the Nasal Septum in Human Fetuses. Rhinology. 1980 Vol. 18, No. 2.

8. Devareddy M.M., Devakar S. Evaluation of Anatomical Variations in Nose and Paranasal Sinuses by Using Multidetector Computed Tomography. International Journal of Contemporary Medicine, Surgery and Radiology. 2019 Vol. 4, No. 3.

9. Cellina M. et al. Nasal Cavities and the Nasal Septum: Anatomical Variants and Assessment of Features with Computed Tomography. Neuroradiology Journal. 2020 Vol. 33, No. 4.

10. Likus W. et al. Nasal Region Dimensions in Children: A CT Study and Clinical Implications.

Experimental and Therapeutics Medicine. 2017; 14 (2): 1519-1525.
11. Janovic N. et al. Relationship Between Nasal Septum Morphology and Nasal Obstruction Symptom Severity: Computed Tomography Study. Brazilian Journal of Otorhinolaryngology. 2020.
12. Serifoglu I. et al. Relationship Between the Degree and Direction of Nasal Septum Deviation and Nasal Bone Morphology. Head and Face Medicine. 2017 Vol. 13.
13. Radulesco T. et al. Geometric Morphometric Contribution to Septal Deviation Analysis. Surgical and Radiological Anatomy. 2019; 41 (7).
14. Som P.M., Naidich T.P. Illustrated Review of the Embryology and Development of the Facial Region, Part 2: Late Development of the Fetal Face and Changes in the Face from the Newborn to Adulthood. American Journal of Neuroradiology. 2014; 35(1): 10-18
15. Wozniak J., Kedzia A., Dudek K. Mathematical Assessment of Fetal Facial Skeleton Development. Archives of Perinatal Medicine. 2010;16 (4): 211-217.

HEALTHY LIFESTYLE. PREVENTION

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THE ROLE OF PREVENTIVE MEASURES IN REDUCING THE CONSUMPTION OF TOBACCO AND ALCOHOL AMONG YOUTH STUDENTS IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.10

УДК 616.31-08-039.71

The article presents the results of a sociological study of the impact of preventive activity in the form of information and educational lectures on the attitude of students to the consumption of tobacco, alcohol and other drugs. Monitoring studies conducted from 2010 to 2017 demonstrate significant reduction in smoking and alcohol consumption among students of both sexes.

Keywords: prevention of substance use, Shichko's method, tobacco, alcohol, students, sober healthy lifestyle.

Purpose of the study is examination the effectiveness of preventive measures carried out in the form of lectures among young students in the Republic of Sakha (Yakutia).

Materials and research methods. The study used data from sociological surveys, in which representatives of young people took part (high school students of general education schools and students of vocational and higher educational institutions). The sociological study "The effectiveness of lectures on the dangers of tobacco and alcohol consumption" (n=648) consisted of two waves, stages. The first questionnaire survey recorded the situation with the consumption of alcohol, tobacco and other psychoactive substances in the social environment of students. The second survey was conducted after the course of lectures and revealed the assessment of the lectures by the target audience, and also determined what attitudes were established in relation to the consumption of tobacco and alcohol. The study "Monitoring the consumption of psychoactive substances among young students" (n=1213) recorded the dynamics of the use of psychoactive substances from 2010 to 2017.

Results and discussion. According to the results of surveys conducted after the course of lectures on the Shichko method among the first-year students of NEFU in 2015, the majority of students highly appreciated the work of lecturers, the average rating in almost all educational units corresponds to 4 ("good") on a 5-point scale. According to the results of the study, it was revealed that the proportion of students who decided to give up alcohol after the courses turned out to be 19.9% more than those who had not previously consumed alcohol.

Table 1

Оценки качества прослушанных лекций студентами СВФУ им. М.К. Аммосова (n=648)

Факультет/институт	ФЛФ	ИЗФИР	ИЕН	ИП	АДФ	ФЭИ	МИ
Средний балл оценки курса лекций	**4,2**	**4,2**	**4,6**	**4,2**	**4,3**	**4,3**	**4,4**
Слушатели, принявшие решение отказаться от потребления алкоголя, %	**67,1**	**69,7**	**81,3**	**75,0**	**61,5**	**76,5**	**63,9**

Table 2

Эффективность курса лекций по методу Шичко среди студентов-первокурсников СВФУ им. М.К. Аммосова (n=648)

Данные опроса до проведения курсов		Данные опроса после проведения курсов	
Доля потребителей алкоголя, %	Доля не потребляющих алкоголь, %	Доля студентов, принявших решение отказаться от алкоголя, %	Эффективность курса, %
49,3	50,7	**70,6**	**+19,9**

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Monitoring studies show that the number of students who use tobacco and alcohol from 2010 to 2017 decreased significantly. This indicates that psychological and pedagogical methods aimed at preventing the use of psychoactive substances help to reduce the proportion of young people with bad habits. Thus, the number of smoking students during this period among women decreased by more than half, and among men by 20.5%. With regard to alcohol consumption, the number of non-drinking students among both sexes increased by 3.9 times. The number of those who consume alcohol “once a week and more often” in the female population decreased by 4.6 times, in the male population by 5.8 times.

Conclusion. Thus, the preventive measures carried out in general education schools, colleges and universities over the course of several years have shown good results. The state policy to promote a healthy lifestyle in the region, the support of NGOs, and the accumulated experience of sobriety lecturers contributed to improving the situation with tobacco and alcohol consumption among young students. In order to maintain and develop the results achieved, further activation of the work of the authorities and the public on the prevention of the use of psychoactive substances is needed. It is also necessary to purposefully train lecturers - specialists in preventology, which will improve the quality and effectiveness of preventive measures.

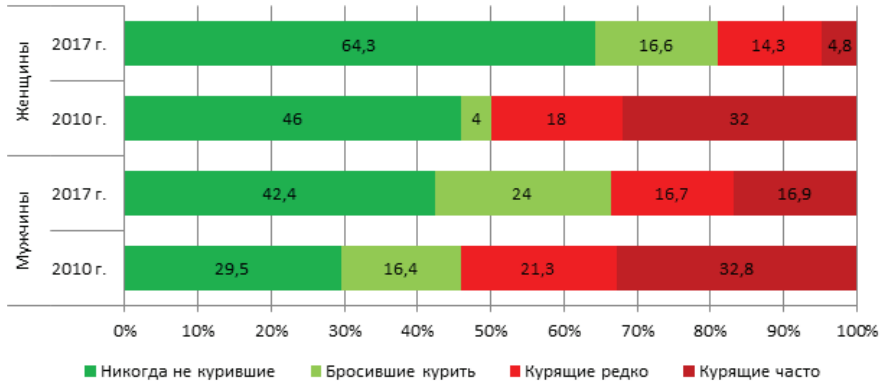

Рис. 1. Изменение количества курящих и некурящих студентов с 2010 по 2017 г. (n=1213)

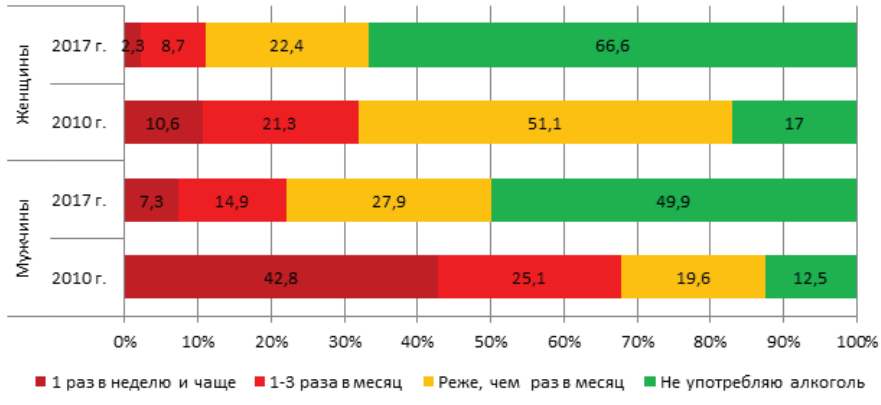

Рис. 2. Изменение количества потребителей алкоголя среди студентов с 2010 по 2017 г. (n=1213)

Reference

1. Matveeva N.P., Hoyutanova N.V., Afonskaya M.I., Borisova V.I. Realizaciya gosudarstvennoj politiki formirovaniya zdorovogo obraza zhizni v Respublike Saha (YAkutiya): analiz, rezul'taty, prognoz [Implementation of the state policy for the formation of healthy lifestyle in the Republic of Sakha (Yakutia): analysis, results, forecast. 2015; 2 (87): 31-38 (In Russ.).]

2. Lebedeva A. M., Lebedeva L. M. Mediko-pravovye osnovy politiki zdorovogo obraza zhizni v Respublike Saha (YAkutiya) [Medical and legal foundations of healthy lifestyle policy in the Republic of Sakha (Yakutia)]. Arktika XXI vek. Gumanitarnye nauki [Arctic of XXI century. Humanitarian sciences. 2018; 2 (16): 48-59 (In Russ.).]

3. Lukina G.A., Efimova N.N. Sovershenstvovanie raboty po propagande zdorovogo obraza zhizni v municipal'nom obrazovanii (na primere MR «Suntarskij rajon» Respubliki Saha (YAkutiya)) [Improving work to promote a healthy lifestyle in the municipality (on the example of the municipality "Suntarsky district" of the Republic of Sakha (Yakutia)]. Gosudarstvennoe i municipal'noe upravlenie v XXI veke: teoriya, metodologiya, praktika [State and municipal management in the XXI century: theory, methodology, practice. 2015: 16. URL: https://cyberleninka.ru/article/n/sovershenstvovanie-raboty-po-propagande-zdorovogo-obraza-zhizni-v-munitsipalnom-obrazovanii-na-primere-mr-suntarskiy-rayon-respubliki (data obrashcheniya: 17.01.2022) (In Russ.).]

ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

T.K. Davydova, A.N. Romanova, N.V. Savvina, N.A. Schneider

IMPLEMENTATION STAGES OF THE COMPLEX PROGRAM OF THE YAKUT SCIENTIFIC CENTER FOR COMPLEX MEDICAL PROBLEMS ON IMPROVING THE MODEL OF SPECIALIZED MEDICAL CARE FOR PATIENTS WITH NEURODEGENERATIVE DISEASES IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.11

УДК 614.2

Neurodegenerative diseases (NDD) are one of the most important medical and social problems of modern society, as they are characterized by a continuously progressive course, severe disability of patients and the absence, in the vast majority of cases, of etiotropic methods of treatment. A significant part of the diseases in this group is age-dependent and develops mainly in the elderly and senile age. The absence in the Republic of Sakha (Yakutia) (RS (Y) of a round-the-clock specialized hospital for the provision of medical care (MC) for patients with NDD is an urgent problem of regional healthcare. To date, the epidemiological situation of NDD in the RS (Y) remains insufficiently studied, despite The fact that the list of NDD under the code ICD-10 "G10-G37" is very wide and, according to annual reports, accounts for 75% of primary diseases of the nervous system. The article presents a comprehensive scientific program developed at the Federal State Budgetary Scientific Institution "Yakutsk Scientific Center for Complex Medical Problems" (FBSI YSC CMP). The program is aimed at improving and improving the existing model for providing specialized medical care to patients with neurodegenerative diseases (NDD) in the Republic of Sakha (Yakutia) (RS (Y). The comprehensive program included 5 consecutive stages that made it possible to open on the basis of the Clinic of YSC KMP Center for Neurodegeneration diseases (CNDZ), in which patients can receive both outpatient and inpatient care. This improved organizational model for the provision of specialized medical care to patients with NDD in the Republic of Sakha (Yakutia) was created as a result of the integration of a medical research institution and regional health authorities.

Keywords: neurodegenerative diseases (NDD), Parkinson's disease (PD), Alzheimer's disease (AD), spinocerebellar ataxia (SCA), specialized medical care.

Introduction. Currently, one of the urgent problems of healthcare and social protection in Russia and the Republic of Sakha (Yakutia) is the issue of providing medical and social assistance to patients with NDDs at the outpatient hospital stage. Due to the severity of their condition, patients with NDDs belong to the group of the most difficult patients who are limited in receiving adequate medical care. The provision of high-quality medical and social care to patients with NDDs has its own defining features and requires the improvement of specialized care. It is known that neurodegenerative diseases (NDDs) are age-dependent and affect people of the older age group. For most of these diseases, the etiology and pathogenesis remain unclear, despite many years of scientific research in the world [2,3, 8]. According to the UN, the population aged 60 years and older in 1960-2000 increased by more than 2 times and amounted to 900 million people, and by 2025 it will reach 2 billion and make up 20-30% of the total

population. According to these forecasts, by 2050, persons of older age groups will amount to 5-6 billion people, or 50% of the total population [5]. In Fig. 1 and Fig. 2 it can be seen that life expectancy continues to increase (Rosstat 2021), despite the decline in life expectancy in 2020, associated with an increase in mortality among the elderly due to the COVID-19 pandemic. This suggests that the incidence of age-dependent diseases, including NDDs, will grow both in Russia as a whole and in the Republic in particular. Thus, the provision of specialized care at the outpatient and hospital stages will be one of the most important healthcare tasks.

Features of the organization of specialized medical care (SMC). In the Republic, the percentage of NDDs is relatively high among all diseases of the nervous system [7]. The most studied are spinocerebellar ataxia (SCA) type 1, oculopharyngeal myodystrophy (OPMD) [4], Charcot-Marie-Toute disease (CMT) [6], Parkinson's disease (PD) [8], amyotrophic lateral sclerosis (ALS) [1]. Yakutia is the territory with the highest prevalence of type 1 SCA in the world - 34.4 cases per 100 thousand population [10]. The situation of Alzheimer's disease remains unresearched, which ranks 1st in the world among NDDs [9], as well as various genetic and inherited diseases of the nervous system common in Yakutia.

Patients with NDDs are practically deprived of medical care at the outpatient stage due to social maladaptation because they have problems with motor and speech activity, as well as impaired cognitive functions. The lack of specialized round-the-clock hospitals for patients with NDDs makes inpatient medical care impossible for this category of patients. In addition, this problem is interdisciplinary in nature, since NDDs cause not only nervous system disorders, but also disorders from other body systems, entailing violations of vital functions. All of the above requires the organization of a set of mea-

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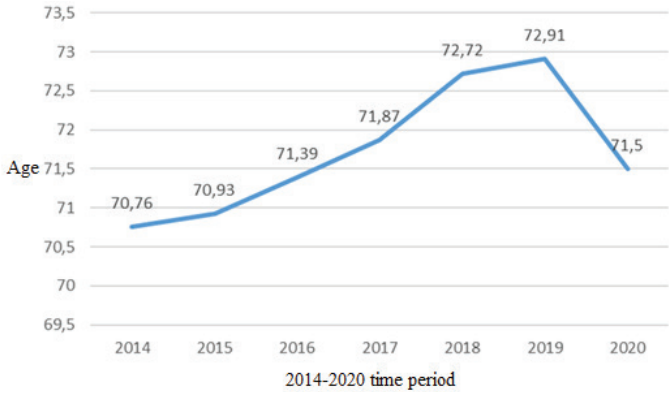

Fig.1. Life expectancy in the Russian Federation (Rosstat 2021)

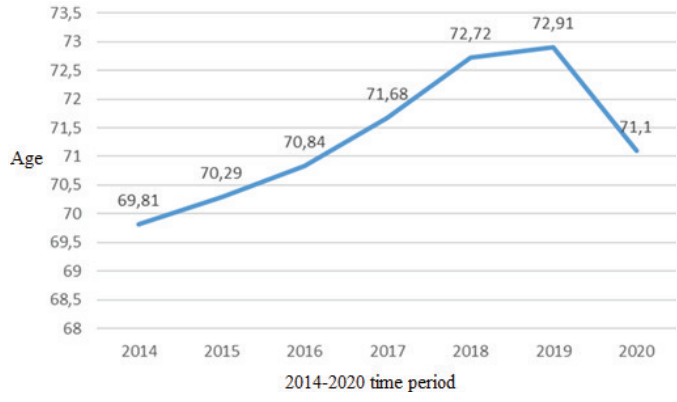

Fig.2. Life expectancy in the Republic of Sakha (Yakutia) (Rosstat 2021)

sures in the field of practical health care and social services for citizens.

Ways to solve the provision of specialized medical care. In Russia, there are examples of the opening of centers for the provision of specialized medical care to patients with NDDs in the system of the Ministry of Science and Higher Education, namely in scientific institutions that have medical clinics in which both medical care at the outpatient hospital stage and scientific research are carried out in parallel.

For example, specialized and high-tech medical care for patients with neurodegenerative diseases in Russia is provided by the Scientific Center of Neurology (SCN), Moscow [11], the N.P. Bekhtereva Institute of the Human Brain (IHB RAS), St. Petersburg [1 2]. In this article, we want to present a joint solution to this problem by the forces of a federal scientific institution - the Yakut Scientific Center for Complex Medical Problems (YSC CMP) and the Ministry of Health (MOH) of the Republic of Sakha (Yakutia). Consolidation of medical science and regional healthcare will allow solving existing problems both in the organization of SMC for patients with NDDs in the Republic and in scientific research of NDDs.

Materials and methods of research. For the organization of the Center for Neurodegenerative Diseases (CND) in the Clinic of the YSC CMP, a comprehensive program was prepared, which consisted of the following stages:

1. Analysis of the initial organizational model of neurological care for patients with neurodegenerative diseases in the Republic;
2. Studying the database of the YSC CMP Clinic to determine the potential possibilities of opening a CND;
3. Definition of the structure of the CND;
4. To propose an improved model for the organization of specialized medical care for patients with neurodegenerative diseases at the Board of the Ministry of Health of the Republic;
5. To coordinate the opening of the CND with the Ministry of Health of the Republic and to prepare an order on the procedure for routing patients with NDDs according to the "neurology" profile at the outpatient hospital stage in the CND;

The materials for this study were the register of patients with SCA 1 and ALS, report data of district neurologists from 2016-2018, regulatory documents of the Ministry of Health of the Russian Federation and the Republic.

Clinical, comparative analysis and organizational modeling methods were used for the study. The clinical method included the study of the register of patients with SCA 1 and ALS, reports of district neurologists of the republic on other NDDs, and this method was also used to determine the list of diseases and criteria for selecting patients for hospitalization in the newly created neurological department of the CND. The method of comparative analysis and organizational modeling included the study of the initial organizational structure of the provision of MP to patients with NDZ and the proposed improved model, as well as the study of the base of the YANC KMP Clinic, on which it was planned to organize the NDZ Center, as a new organizational model for the provision of specialized care to patients with NDZ.

Results and discussion. At the *first stage* of the program, the initial organizational structure of providing medical care to patients with NDDs was studied, which revealed a number of shortcomings of both outpatient and inpatient specialized medical care.

Outpatient specialized medical care. In the Republic, for outpatient specialized care, patients can apply to municipal clinics and the Medical and Genetic Center (MGC) of the Republican Hospital

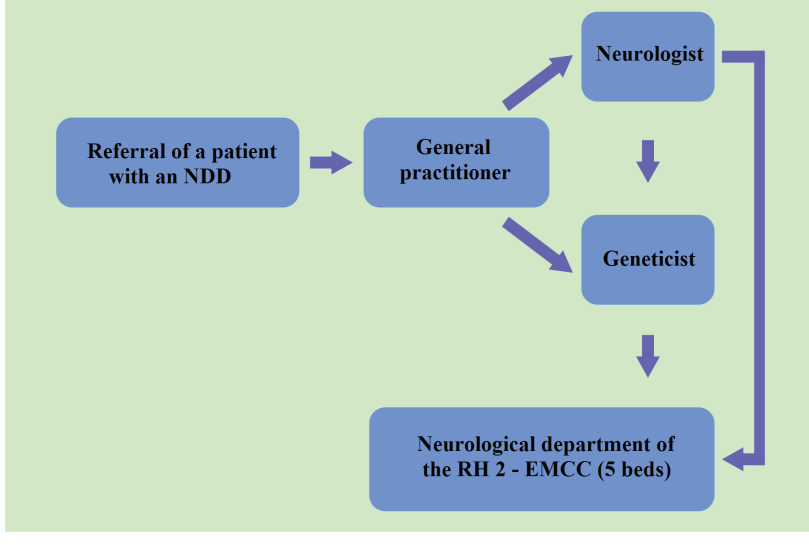

Fig.3. The scheme of organization of specialized medical care for patients with neurodegenerative pathology before the opening of the CND in the Clinic of the YSC CMP

Num. 1. Patients are referred to the neurologist of the clinic through their GP and specialists in the order of the general queue, repeat referrals and those who are on the register of patients with NDDs can apply immediately, bypassing these specialists. In the MGC, patients with NDDs are referred by a neurologist or GP. But due to specific neurodegenerative processes leading to motor and cognitive disorders, disorders of the psycho-emotional sphere, this category of patients cannot receive sufficient assistance at the outpatient stage, since they require a long examination by a neurologist at reception and to receive the prescribed treatment on an outpatient basis is a difficult task for many patients. Despite the fact that by the order of the Ministry of Health of the Russian Federation in 2015, the time for outpatient admission by a neurologist of one patient was increased to 22 minutes, still this time is not enough to process a patient with NDDs, which affects the quality of the patient's examination by a neurologist and the establishment of a preliminary diagnosis [1].

Inpatient specialized medical care. In the Republic, there are 2 neurological hospitals in the healthcare system for round–the-clock stay, which are based in the Republican Hospital Num. 2 - Emergency Medical Care Center (RH No. 2-EMCC):

1. Neurological department for patients with acute disorders of cerebral circulation in the Regional Vascular Center (RCC) with 50 beds;

2. Department of General Neurology with 30 beds for emergency care of neurological patients, of which 5 beds are allocated for patients with NDDs for the entire Republic.

Patients with severe pain syndromes, seizures, acute inflammatory diseases of the nervous system, exacerbations of demyelinating diseases and other urgent conditions. The available 5 beds in the neurological department of RH No. 2-EMCC for patients with NDDs cannot cover the needs for inpatient care throughout the Republic.

The study of annual reports of neurologists showed not only the lack of data on the primary incidence of such diseases as Alzheimer's disease and other dementias, many hereditary diseases, including SCA1, myotonic dystrophy, OPMD, hereditary spastic paraplegia, dystonia, ALS and other diseases. There is no data on the amount of assistance provided (the number of requests per year, treatment in a hospital or at home, data on hospitalization). The severity of the condition of patients with NDDs is an undoubted obstacle to visiting outpatient clinics.

Thus, in the Republic, if patients with NDDs have the opportunity to receive medical care at the outpatient stage, although not in full, then the absence of round-the-clock hospitals for rehabilitation or rehabilitation treatment deprives them of receiving medical care at the hospital stage. Taking into account the current situation, it became clear that there was a need to improve the existing organizational model for providing neurological care to patients with NDDs.

At the *second stage* of the comprehensive program, the base of the YSC CMP Clinic was investigated in order to identify the real possibilities of creating a CND. Not only the material and technical base was studied, but also personnel issues and issues of financing this category of patients from the funds of the Territorial Compulsory Medical Insurance Fund (TCMIF) were considered. It is known that medical organizations have single-channel funding from TCMIF funds. The YSC CMP clinic occupies the 1st and 2nd floors of a 4-storey building of a typical dormitory. The 1st floor is reserved for the clinic, and the 2nd floor is occupied by a round-the-clock hospital with 110 beds, including (at the time of the study) a therapeutic department with 40 beds, of which 10 are neurological, a gynecological department with 25 beds, a cardiology department with 35 beds. The Clinic has a physiotherapy department, a clinical diagnostic laboratory that serves the clinic and the hospital. In addition, the structure of the YSC CMP includes the department of medical genetics, which includes a laboratory of hereditary pathology. MRI and radiation diagnostics in the Clinic are carried out through the bilateral agreements with medical organizations that have this equipment. In general, if there is space to accommodate the proposed center for patients with NDDs, this issue could be successfully solved.

When analyzing the amount of funding for the Clinic from the funds of the TCMIF, the administration of the YSC CMP found effective ways to solve the release of funds and direct them to solving strategic tasks for the further development of the YSC CMP Clinic. Firstly, it was decided to shut down the hospital's kitchen and turn to outsourcing services for catering for patients. Secondly, the unprofitable bed fund of gynecological and cardiological departments was revealed. This was due to the fact that in the Republic in 2011, within the framework of the National Project "Health", a Regional Vascular Center (RVC) was opened on the basis of the RH No.2-EMCC equipped with the most modern equipment, designed to provide specialized high-tech round-the-clock medical care to patients with acute disorders of cerebral circulation (ADCC) and acute coronary syndrome (ACS). Thus, patients with chronic ischemic heart disease, hypertension and other diseases of the heart and blood vessels, which belong to the "therapy" profile during hospitalization, began to enter the cardiology department of the YSC CMP Clinic, excluding patients with ACS. In addition, in Yakutsk, in March 2018, the Republican Perinatal Center (RPC) opened with a 130-bed hospital (department of pregnancy pathology, obstetric physiology department, maternity department, department of pathology of newborns and premature babies), a consultative and diagnostic department for 150 visits per shift, a department of intensive care and intensive care for women and newborns, as well as the department of catamnesis for young children, etc. The opening of the RPC also affected the unprofitability of the beds of the gynecological department of the YSC CMP Clinic. Meanwhile, the main part of the group of orphan diseases of the nervous system consists of hereditary diseases leading to neurodegeneration of the nervous system, which, due to the severity of the course, expensive treatment and examination, are among the highly paid clinical and statistical groups (CSG) in the CHI system. At the same time, due to the lack of a round-the-clock hospital for patients with NDDs, this category of patients was deprived of specialized medical care.

The above objective reasons led to the decision to reduce the gynecological department and 25 beds of the cardiology department due to their unprofitability and placement of the CND in their place.

The third stage of the comprehensive program was to determine the structure of the Central Hospital as a module that would include both outpatient and inpatient care. Therefore, it was decided to allocate a separate block on one floor for the CND. The structure of the Central Clinical Hospital includes a cognitive disorders room, a bioethics and medical and social care room and a round-the-clock hospital of the neurological department. An essential role is played by the location of these offices and the hospital on the same floor, which is important for patients with limited mobility. As a result of such an arrangement, the CND would be an integral section, isolated from other Clinic premises.

The CND is the main link in our pro-

posed improved organizational model of specialized medical care (IOMSMC) for patients with NDDs and represents a single unit of specialized care, where all stages of the provision of medical care are interconnected.

[1] Order of the Ministry of Health of the Russian Federation of June 2, 2015 N 290n

At the fourth and fifth stages of the program, joint work was carried out with the Ministry of Health of the Republic and the Republican TCMIF to clarify the amount of funding for neurological beds. The functional structure of the CND was presented by us at the Board of the Ministry of Health of the Republic in December 2018. Considering that the neurological department will serve patients from all over the Republic and for its full functioning, at the Board of the Ministry of Health of the Republic, it was recommended to draft an order on the routing of patients suffering from NDDs. Thus, based on the Decree of the Head of the Republic of 27.12.2016 [2]. "On approval of the regulations of the Ministry of Health and its Board" and pursuant to the order of the Ministry of Health of the Russian Federation [3], the order of the Ministry of Health of the Republic "On the procedure for routing neurological patients suffering from neurodegenerative diseases at the outpatient and hospital stages"[4] was drawn up and approved, in which 15 beds out of 30 are provided for general neurological patients profile who need planned restorative treatment. The above-issued order of the Ministry of Health of the RS (Ya) makes it possible to gradually concentrate data on patients with neurodegenerative pathology in one medical organization, which makes it possible to create a single database of NDDs, track new cases, consult patients and maintain direct communication with neurologists of central district hospitals using modern gadgets and telemedicine advisory assistance. The data of the created hospital registers will also allow providing rehabilitation to patients in need, monitoring their condition in dynamics, identifying the features of the clinical picture, tracking families with genetic diseases. Based on this knowledge, an assessment of the current state of the epidemiological situation of NDDs in the regions of the Republic and prospects for the development of early (preclinical) diagnostics will be given, approaches to personalized treatment of NDDs, primarily Parkinson's disease, Alzheimer's disease and type 1 SCA will be developed.

The moral and ethical side of this problem is also an important factor, since the introduction into the practice of healthcare of this order on the routing procedure and the creation of the CND, in fact shows that there is a search in solving the tasks of providing SMC to this category of patients, which will make them feel like full-fledged members of society, improving their quality of life.

Fig.5 Model of the organization of specialized medical care for patients with neurodegenerative pathology after the opening of the CND in the Clinic of the YSC CMP

Conclusion. Thus, the opening of a specialized center for patients with NDDs is an example of the consolidated interaction of a federal scientific medical institution and regional healthcare in solving a medical and social problem.

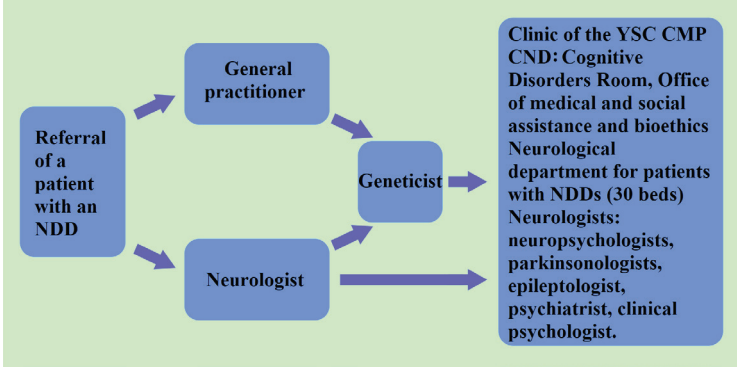

Fig.4. Structure of the Center for Neurodegenerative Diseases of the YSC CMP Clinic

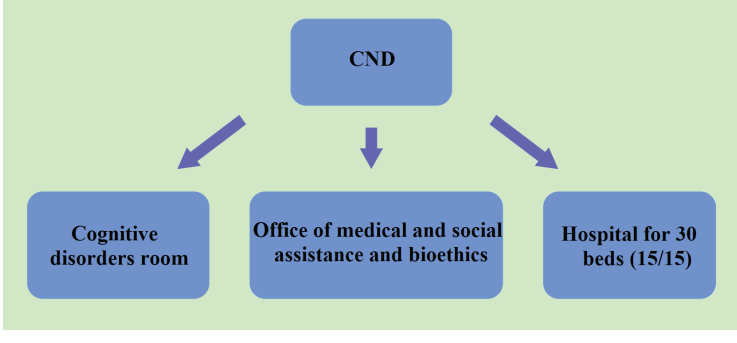

Fig.5. Model of the organization of specialized medical care for patients with neurodegenerative pathology after the opening of the CND in the Clinic of the YSC CMP

[2] Decree of the Head of the Republic of 27.12.2016. "On approval of the Regulations of the Ministry of Health and its Board" (Appendix 1, paragraphs 3.11, 3.19, 3.20)

[3] Order of the Ministry of Health of the Russian Federation3 dated 15.11.2011 No. 926n "On approval of the Procedure for providing medical care to adults with diseases of the nervous system"

[4] Order of the Ministry of Health of the Republic No. 01-07/184 dated 02/14/2019. "On the procedure for routing neurological patients suffering from neurodegenerative diseases at the outpatient and inpatient stages"

Reference

1. Davydova TK. Sporadicheskij bokovoj amiotroficheskij skleroz v Respublike Saha (YAkutiya). [Sporadic amyotrophic lateral sclerosis in the Republic of Sakha (Yakutia)]. Vestnik SVFU [Bulletin of NEFU. 2015; 2 (12): 119-123 (In Russ.).]

2. Illarioshkin SN, Vlasenko AG, Fedotova E.Yu. Sovremennye vozmozhnosti identifikacii latentnoj stadii nejrodegenerativnogo processa [Modern possibilities of identifying the latent stage of the neurodegenerative process]. Annaly klinicheskoj i eksperimental'noj nevrologii [Annals of Clinical and Experimental Neurology]. 2013; 2 (7): 39–50 (In Russ.).]

3. Levin OS, Dokadina LV. Epidemiologiya parkinsonizma i bolezni Parkinsona [Epidemiology of parkinsonism and Parkinson's disease]. Nevrologicheskij zhurnal [Neurological journal. 2005. No. 5. P. 41–49 (In Russ.).]

4. Sukhomyasova A.L. Autosomno-dominantnaya miotonicheskaya distrofiya v Respublike Saha (YAkutiya): avtoref. dis.kand.med.nauk [Autosomal dominant myotonic dystrophy in the Republic of Sakha (Yakutia): diss. abst. candidate of Med. Science. Tomsk; 2005. 22 p (In Russ.).]

5. Gitinova Z.A., Magomedov R.G., Aliev A.K., Shamsudinov R.S. K ocenke ambulatorno-poliklinicheskoj pomoshchi licam pozhilogo i starcheskogo vozrasta [To the assessment of outpatient care for the elderly and senile age]. Problemy social'noj gigieny, zdravoohraneniya i istorii mediciny [Problems of social hygiene, public health and the history of medicine]. 2017; 25(2): 101-103 (In Russ.).] DOI 10.18821/0869-866X-2017-25-2-101-103]

6. Guryeva PI, Maksimova NR, Nikolaeva TYa, Gurinova EE, Korotov MN, Stepanova SK, Sukhomyasova AL, Okoneshnikova LT.

Kliniko-geneticheskaya harakteristika bolezni SHarko-Mari-Tuta 1A tipa v Respublike Saha (YAkutiya) [Clinical and genetic characteristics of Charcot-Marie-Tut disease type 1A in the Republic of Sakha (Yakutia)]. Yakut Medical Journal. 2013; 3 (43): 26-29.

7. Nikolaeva IA, Korotov M.N., Gurinova E.E., Stepanova S.K. et al. Nasledstvennye bolezni nervnoj sistemy v RS (YA) [Hereditary diseases of the nervous system in the Republic of Sakha (Yakutia)]. Yakut Medical Journal. 2009; 2 (26): 52-54.

8. Popova TE, Tappakhov AA, Nikolaeva TYa, Okoneshnikova LT, et al. Epidemiologiya bolezni Parkinsona v Respublike Saha (YAkutiya) [Epidemiology of Parkinson's disease in the Republic of Sakha (Yakutia)] Yakut Medical Journal. 2017; 3 (59): 98-101

9. Platonov F.A. Tyryshkin K, Tikhonov D.G. [et al.] Genetic fitness and selection intensity in a population affected with high-incidence spinocerebellar ataxia type 1. Neurogenetics. 2016; 17(3): 179-185. doi: 10.1007/s10048-016-0481-5.

10. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol Review. 2018; 25 (1): 59-70. DOI: 10.1111 / ene.13439. Epub 2017 Oct 19.

11.https://www.neurology.ru/

12.https://ihb.spb.ru/

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CHARACTERISTICS AND RESULTS OF THE SPECIALIZED ANESTHESIOLOGY AND INTENSIVE CARE FOR PATIENTS WITH COVID-19 IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.12

УДК 615:616.9 (571.56)

Aim: To analyze the work in the specialized anesthesiology and intensive care unit in the Republic of Sakha (Yakutia) for patients with COVID-19 in the context of the pandemic.

Materials and methods: A retrospective observational study was conducted based on work perfomed by anesthesiology and intensive care unit (AICU) in the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital" (YRCH) for the period since March, 2020, to December, 2021.

Results and discussion: YRCH have repurposed the hospital beds and enhanced the material and technical equipment supply of the AICU. Given the epidemiological situation, the bed capacity and the staff schedule of the unit were in the scope of regulation. The medical staff level was 76.5 % in 2020 and 80 % in 2021. The level of nursing and medical attendant staff for the entire period was 100 %.

During the study period 1,796 patients were admitted (488 patients in 2020, 1,308 patients in 2021). The bed turnover was 24.4 and 28.2 patients per bed, the average rate of bed occupancy was 136 and 244.6 days, the average length of stay of patients was 5.5 and 6.0 days in 2020 and 2021, respectively. In total, 1,015 patients have died (mortality rate – 56.5 %), with 281 patients to have died in 2020 (mortality rate — 58.0 %) and 734 in 2021 (mortality rate — 56.2 %). The mortality rate of patients significantly increases with age and amounted to 71.2 % in patients older than 81 years.

The main cause for admission in AICU was acute respiratory failure (ARF), the treatment has used is stepwise respiratory therapy. Standard oxygen therapy (15-20 l/min) was effective in 64 (3.6 %) patients, high-flow oxygen therapy (HFOT) was used in 1,732 (96.4 %) patients, non-invasive mechanical ventilation (NIV) was used in 717 (39.9 %), invasive mechanical ventilation was used in 1,015 (56.5 %) patients.

Conclusion: The complex of measures for the deployment of specialized anesthesiology and intensive care for adults with COVID-19 in the YRCH has allowed to succeed with an overflow of patients suffering a severe course of the disease. The characteristics of the unit indicated the difficulties in managing patients with COVID-19 complicated by viral pneumonia with severe ARF.

Keywords: COVID-19, specialized anesthesiology and intensive care, Republic of Sakha (Yakutia).

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Introduction. The rapid spread of the novel coronavirus infection (NCVI) COVID-19, the severe course of the disease and the high mortality rate of patients led to the mobilization of all levels o health care.

In the Republic of Sakha (Yakutia) a plan for organizing medical care for patients with COVID-19 was developed and a three-level medical care system was deployed [4]. The main role for the organization and provision of specialized care for patients with COVID-19 was assigned to the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital" (YRCH) which included an infectious disease department.

The high level of extremely severe and complicated forms of the disease, the rapid progression of acute respiratory failure (ARF) demanding the use of active respiratory therapy required the anesthesiology and intensive care services of medical organizations to carry out a complex of organizational and therapeutic-tactical measures.

Purpose of the study: Analyze of the work of the specialized anesthesiology and intensive care unit in the Republic of Sakha (Yakutia) for patients with COVID-19 in the context of the pandemic.

Materials and Methods: A retrospective observational study was conducted based on work performed by anesthe-

siology and intensive care unit (AICU) in the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital" (YRCH) for the period since March, 2020 to December, 2021. The following medical documents were studied — annual reports of AICU, register of admitted, discharged, transferred patients and inpatient medical records. Analysis of the main indicators of the AICU activities (staffing level, bed occupancy, bed turnover and mortality rate) and methods of respiratory therapy used in the treatment of patients was conducted.

Study Results and Discussion: The timely and adequate treatment for patients with severe and extremely severe forms of COVID-19 has required a set of measures in the following areas:

1. Deployment of additional beds for intensive care and formation of a temporary staff schedule. Based on the orders of the Ministry of Health of the Russian Federation [4,5] and the Ministry of Health of the Republic of Sakha (Yakutia) [6] in the YRCH, the hospital beds were repurposed and the relevant material and technical equipment supply of the AICU was enhanced (increase of the number of beds and addition of the staff schedule). The unit was additionally equipped during March-April 2020 with equipment, principally with ventilators and bedside monitors at the rate of 1 device per bed, as well as an uninterrupted provision of medical oxygen was arranged.

2. Training of employees on diagnosis, clinical course, treatment and infection safety of COVID-19 which was carried out continuously taking into account the updated clinical recommendations. At the time of preparation of this article the Ministry of Health of the Russian Federation submitted the 15th version of the Temporary Recommendations [9] and the 6th version of the Methodological Recommendations of the Federation of Anesthesiologists and Reanimatologists (FAR) [1].

3. Providing of operational assistance on the treatment of patients with COVID-19 in form of telemedicine consultations by the Federal Remote Consulting Centers of Anesthesiology and Intensive Care (FRCC) which were created by the order of the Ministry of Health of the Russian Federation [7]. So, 126 consultations in 2020 and 317 consultations in 2021 were held in the FDCC for adults on the basis of the Federal State Autonomous Educational Institution of Higher Education First Moscow State Medical University named after Sechenov I.M. of the Ministry of Health of the Russian Federation; in regard to the admission of pregnant women in 2021, 89 consultations were held in the FRCC for pregnant women on the basis of the federal state budget institution "National Medical Research Center of Obstetrics, Gynecology and Perinatology named after V.I. Kulakov" of the Ministry of Health of the Russian Federation. According to the results of consultations, the treatment was assessed as adequate, in cases of pregnant women consultations, a correction of pregnancy management and the timing of delivery was carried out.

The key work indicators of AICU are presented in Table 1.

The medical staffing level was 76.5 % in 2020 and 80 % in 2021, i.e., the shortage of medical staff was 23.5 and 20 %, respectively. The level of nursing and medical attendant staff in the unit for the entire period was 100 %. To the note, bed capacity and the staff schedule of AICU were regulated, given the epidemiological situation and depending on the number of patients in need of intensive care. Thus, during the period of the peak of morbidity the number of beds in AICU was increased to 36 and the staff of doctors was increased to 32 rates, along with a decrease in the number of admissions the number of beds was reduced to 30 and the medical rates were reduced to 24. Anesthesiologists-intensive care specialists of other medical organizations which were sent or employed during the vacation on their main job were involved for work on temporary rates. The contribution was also made by medical institute residents specializing in the anesthesiology and intensive care, which, according to the order of the Ministry of Health of the Russian Federation [8], were registered as interns after completion of a 36-hour training course on COVID-19.

In total, the period under study saw 1,796 patients admitted (488 patients in 2020 and 1308 patients in 2021). There were no re-admissions to AICU in 2020, but 23 (1.8 %) patients were re-hospitalized in 2021. When analyzing the quality of medical care provided there were no cases of underestimation of the severe patients' condition at the time of their transfer to the pulmonology department. Rehospitalization of patients in AICU occurred due to the increase of ARF on the 2nd-5th day and the ineffective standard oxygen therapy.

An increase in the incidence rate of COVID-19 among pregnant women was characteristic of 2021. Thus, 17 pregnant women and new mothers were transferred to AICU from the Perinatal Center of this hospital during May-December 2021. There were five (29.4 %) women died among those who were admitted to AICU postoperative caesarean section for invariable indications due to severe viral pneumonia and increased fetal hypoxia.

Analysis of the main indicators of the use of bed capacity reflecting the intensity of invariable indications activities showed the following. In 2020-2021 the number of patients increased from 488 to 1,308, the bed turnover was 24.4 and 28.2 patients per bed, the average period of bed occupancy was 136 and 244.6 days, and the average length of stay of patients was 5.5 and 6.0 days. Interestingly, the average bed occupancy and bed turnover are significantly different from the standards. According to Nedashkovsky, E.V., the average bed occupancy in the general profile units of intensive

Table 1

The key work indicators of AICU (2020-2021 years)

Index	Year	
	2020	2021
Medical staff level (%) Doctors Nurses Medical attendant staff	 76.5 100 100	 80 100 100
Trainee doctor (resident) (No.)	5	5
ICU admission (No.)	488	1308
Readmission (No. and %)	-	23
Total days after admission	2701	7826
Bed turnover	24.4	28.2
Average rate of bed occupancy	136	244.6
Average length of stay	5.5	6.0
Death (%)	58.0	56.2

care is within 280-320 days, the average length of stay of patients is 3.5-5.5 days [3]. Sure, these indicators of the bed capacity may vary depending on the department profile and, in fact, are formed by the clinical circumstances and the medical capabilities of the medical organization's department. Please, note that the calculation of 2020 indicators included only 10 months of the year (from March to December), the number of beds in the department changed from 30 to 36, which affected the estimated average bed occupancy and the average length of stay of patients in the department. In addition, respiratory support for up to 14 days or more is recommended for COVID-19 treatment even with positive lung function dynamics, since a recurrent deterioration in the course of interstitial pneumonia is often observed [1], which implies an extension of the period of stay of the patient in AICU.

A detailed study of the duration of patients' stay in the department shows that 70.3 % of patients stayed for 4-20 days — 38.2 % of patients stayed for 4-10 days, 32.1 % stayed for 11-20 days (Fig. 1).

In total, 1,015 patients died (mortality rate – 56.5 %) of which 281 patients died in 2020 (mortality rate — 58.0 %) and 734 in 2021 (mortality rate — 56.2 %).

The monthly dynamics in admission of patients and deceased for the period under study is shown in Fig. 2.

The presented chart shows an increase in admissions of patients in AICU in October 2020, in May and October 2021. The same months accounted for the largest number of deaths.

The mortality rate of patients increases with age and amounted to 71.2 % in the age group of 61-80 and 71,2 % (Fig. 3) in patients older than 81.

Treatment of patients in AICU was carried out in accordance with the recommendations of the Ministry of Health of the Russian Federation and the recommendations of the Federation of Anesthesiologists and Reanimatologists and included etiotropic, pathogenetic and symptomatic treatment [1,8]. The prevailing syndrome and the main indication for admission of patients in AICU was ARF, the treatment whereof has used a stepwise approach among the methods of respiratory therapy (Table 2).

Standard oxygen therapy (15-20 L/min) was effective only in 64 (3.6 %) patients. High-flow oxygen therapy (HFOT) was used in 1,732 (96.4 %) patients. Subsequently, 717 (39.9 %) patients underwent the non-invasive ventilation along with an increase in ARF. Increase in hypoxemia despite HFOT, non-invasive ventilation with prone position in 1,015 (56.5 %) patients served as an indication for tracheal intubation and switching to invasive ventilation in protective modes.

To increase the efficiency of ventilation and adequate sanitation of the tracheobronchial tree, 113 (11.1 %), patients with invasive ventilation on day 2-3 underwent tracheostomy. The proportion of respiratory therapies in 2020 and 2021 did not differ significantly.

These results are consistent with foreign and domestic studies. Thus, in the international study "UNITE-COVID", which included 240 centers from 46 countries and 5 continents, it was indicated the beginning of the COVID-19 pandemic led to an emergency increase in the bed stock of intensive care units of medical organizations by an average of 155% [12]. The FRCC of Anesthesiology and Intensive Care for

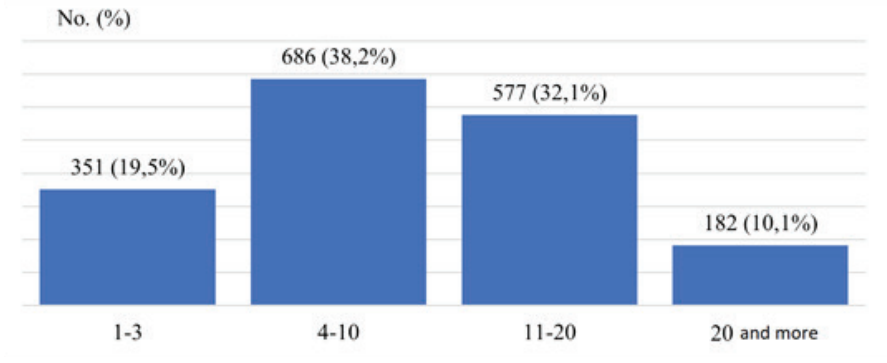

Fig. 1. Days after admission in ICU

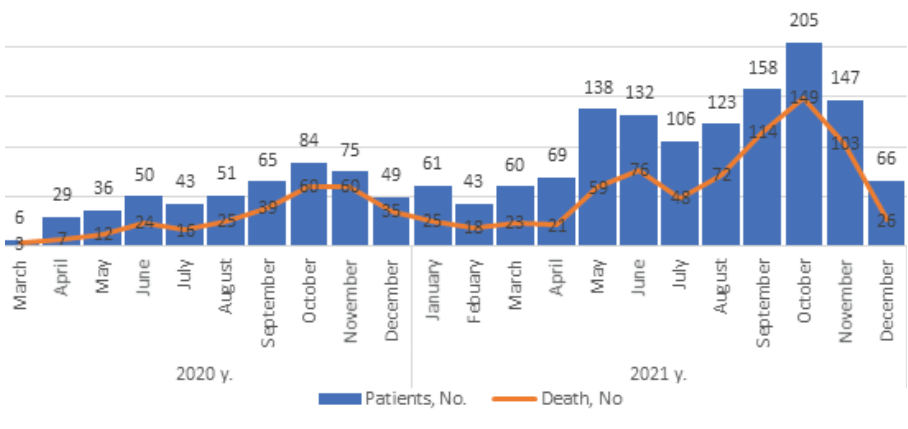

Fig. 2. ICU admission in 2020-2021 years

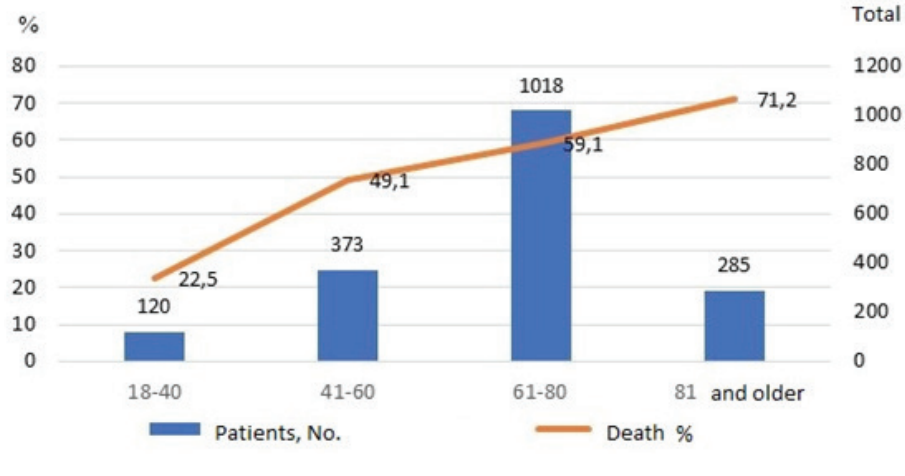

Fig. 3. Inhospital mortality in age groups

Table 2

Respiratory support

Method of respiratory support	Patients. No. (%)		Total
	2020 г.	2021 г.	No. (%)
Standard oxygen supplementation	19 (3.9)	45 (3.4)	64 (3.6)
High-flow oxygen therapy	469 (96.1)	1263 (96.5)	1732 (96.4)
Non-invasive mechanical ventilation	188 (38.5)	529 (40.5)	717 (39.9)
Invasive mechanical ventilation	281 (57.6)	734 (56.1)	1015 (56.5)
Total	488 (100)	1308 (100)	1796 (100)

Adult patients with COVID-19 analyzed treatment of 1,522 patients with severe COVID-19 in the ICU of hospitals in Moscow, the Moscow region and 70 regions of the Russian Federation and indicated that 80% of patients needed a mechanical ventilation [2]. Two large studies – COVID-ICU and UNITE-COVID, covering more than 8000 ICU patients, identified that the need for mechanical ventilation increased to 80-85,8% [11, 12].

High mortality in COVID-19, its association with age and comorbidity is confirmed in all studies. One of the first studies with COVID-19, presented by Chaomin Wu et al., was demonstrated a high mortality rate in patients with severe pneumonia, which was 52.4% [13]. According to the FDCC of Anesthesiology and Intensive Care for Adult the mortality rate of patients with severe COVID-19 was 65.4% and its main cause was acute respiratory distress syndrome - 93.2%. The mortality rate of patients undergoing oxygen therapy was 10.1%, noninvasive mechanical ventilation – 36.8%, invasive mechanical ventilation – 76.5%, with signs of septic shock – 86.6% [2].

Conclusion. Therefore, the complex of well-timed measures for the deployment of specialized anesthesiology and intensive care for adult patients with NCVI COVID-19 in the YRCH has made it possible to cope with a large flow of patients with a severe course of the disease. It took a short time to repurpose the hospital beds, enhance the material and technical equipment supply of AICU, implement a system of continuous training of doctors in diagnostics, clinical course, treatment and infectious safety, as well as consultations with the Federal Centers for Anesthesiology and Intensive Care. The indicators of the department demonstrate evidence of difficulties in managing patients with COVID-19 complicated by bilateral multisegmented viral pneumonia with severe ARF.

Reference

1. Anestesiologo-reanimacionnoe obespechenie pacientov c novoi koronovirusnoi infekciei Kovid-19: Metodicheskie rekomendacii, versia 6, ot 02.12.2021g. [Anesthesiological and intensive care support for patients with a new coronavirus infection COVID-19: Methodological Recommendations of the FAR, version 6, December 02, 2021] https://faronline.ru/api/static/cms-files/7e17aba2-57d5-40da-8553-f164ebe2f2dd/ %D0 %9C %D0 %A0_ %D0 %A4 %D0 %90 %D0 %A0_covid-19_ver6_v07_for_website.pdf.

2. Glybochko PV, Fomin VV, Moiseev SV, et al. Iskhody u bol'nyh s tyazhelym techeniem kovid-19, gospitalizirovannyh dlya respiratornoj podderzhki v otdelenii reanimacii i intensivnoj terapii. [Clinical outcomes of patients with COVID-19 admitted for respiratory support to the intensive care units in Russia]. Klinicheskaya pharmakologiya I terapiya [Clinical Pharmacology and Therapy]. 2020; 29(3):25-36. DOI: 10.32756/0869-5490-2020-3-25-36.

3. Nedashkovskii E.V. Operativnoe upravlenie anestesiologo-reanimacionnoi sluzhboi mnogoprofilnoi bolnici: monografia [Operational management of the Anesthesiological and Intensive Care Service of a multidisciplinary hospital: monograph]. Arhangelsk: Izdatelstvo Severnogo gosudarstvennogo medicinskogo universiteta [Arkhangelsk: Publishing House of the Northern State Medical University]. 2009; 200.

4. Prikaz Ministerstva Zdravoohraneniya Rossiiskoi Federacii ot 19 marta 2020 g. №198-n «O vremennom porydke organizacii raboti medecinskoi organizacii v celyah realizacii mer po prophilaktike I snizheniu riskov rasprostraneniya novoi koronovirusnoi infekcii COVID-19» [Order of the Ministry of Health of the Russian Federation No. 198-n dated March 19, 2020 “On the temporary procedure for organizing the work of medical organizations in order to implement measures to prevent and reduce the risks of the spread of a new coronavirus infection COVID-19”]. https://base.garant.ru/7376969.

5. Prikaz Ministerstva zdravoohraneniya Rossiiskoi Federacii ot 27.03.2020 № 246n "O vnesenii izmenenii v prikaz" ot 19 marta 2020 g. №198-n « O vremennom porydke organizacii raboti medecinskoi organizacii v celyah realizacii mer po prophilaktike i snizheniu riskov rasprostranenii novoi koronovirusnoi infekcii COVID-19» [Order of the Ministry of Health of the Russian Federation No. 246n dated March 27, 2020 “On amendments being made to the Order No. 198-n dated March 19, 2020 "On the temporary procedure for organizing the work of medical organizations in order to implement measures to prevent and reduce the risks of the spread of a new coronavirus infection COVID-19”]. https://cdnimg.rg.ru/pril/185/28/84/57860.pdf.

6. Prikaz Ministerstva zdravoohraneniya Respubliki Saha (Yakutiya) №01-07/496 ot 17 aprelya 2020 g «O sovershenstvovanii shemi marshrutizacii pacientov v period deistviy vremennogo pereprofelirovaniya stacionarov pri okazanii medicinskoi pomoshi bolnim s vnebolnichnimi pnevmoniymi, podozreniem na koronovirusnuu infekciu Covid - 19» [Order of the Ministry of Health of the Republic of Sakha (Yakutia) No. 01-07/496 dated April 17, 2020. “On improving the patient routing scheme during the period of temporary hospital conversion in providing medical care to patients with community-acquired pneumonia suspected of Covid-19 coronavirus infection”].

7. Prikaz Ministerstva zdravoohraneniya Respubliki Saha (Yakutiya) №01-07/437 ot 8 aprelay 2020 g. “O distancionnih konsultativnih centrah anesteziologii i reanimatologii po voprosam diagnostiki i lecheniya infekcionnogo zabolevaniya, vizvannogo koronovirusom shtamma COVID-19, i pnevmonii” [Order of the Ministry of Health of the Republic of Sakha (Yakutia) No. 01-07/437 dated April 8, 2020 “On distant advisory centers of anesthesiology and intensive care for the diagnosis and treatment of infectious diseases caused by the COVID-19 strain coronavirus and pneumonia”].

8. Prikaz Ministerstva zdravoohraneniya Rossiiskoi Federecii ot 14 aprely 2020 g. № 327n «Sluchai I usloviya, pri kotorih fizicheskie lica mogut bit dopusheni k osushestvleniu medecinskoi deyatelnosti i (ili) farmacevticheskoi deyatelnosti bez sertifikata specialista ili svidetelstva ob akkreditacii specialista i (ili) po specialnostyam, ne predusmotrennim sertifikatom specialista ili svidetelstvom ob akkreditacii specialista [Order of the Ministry of Health of the Russian Federation No. 327n dated April 14, 2020 “Cases and conditions under which individuals can be admitted to medical activities and (or) pharmaceutical activities without a specialist certificate or a certificate of accreditation of a specialist and (or) in specialties not provided for by a specialist certificate or a certificate of accreditation of a specialist”]. https://www.garant.ru/products/ipo/prime/doc/73801854.

9. Profilaktika, diagnostika i lechenie novoi koronovirusnoi infekcii (COVID-19): Vremennie metodicheskie rekomendacii MZ RF, versiy 15 (22.02.2022) [Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19): Temporary methodological recommendations of the Ministry of Health of the Russian Federation, version 15 (02/22/2022)].https://static0.minzdrav.gov.ru/system/attachments/ attaches/000/059/392/original/%D0%92%D0%9C%D0%A0_COVID-19_V15.pdf

10. Sleptsova SS, Borisova EA, Tarasova VE, Malinnikova EY. Opit paboti infekcionnoi slujbi Respubliki Saha (Yakutiya) v period pandemii novoi koronovirusnoi infekcii [Experience of the Infectious Diseases Service of the Republic of Sakha (Yakutia) during the pandemic of a new coronavirus infection]. Infekcionnie bolezni: Novosti, mneniy, obucheniy [Infectious diseases: news, opinions, training]; 2020; 9 (3); 30-35. doi: https://doi.org/10.33029/2305-3496-2020-9-3-30-35).

11. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med - 47, 2021. p 60-73. https://doi.org/10.1007/s00134-020-06294-x.

12. Greco M. Clinical and organizational fac-

tors associated with mortality during the peak of first COVID - 19 wave: the global UNITE - COVID study /Greco M., De Corte T., Ercole A., Antonelli M., and Azoulay E.// Intensive Care Med. 2022 Jun; 48(6): 690-705. https://doi.org/10.1007/s00134-022-06705-1.

13. Wu C. et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-943. doi:10.1001/jamainternmed.2020.0994.

HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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STUDY OF 1-HYDROXYPYRENE PAH EXPOSURE IN URINE OF WORKERS OF THE ALUMINUM SMELTER IN EASTERN SIBERIA

DOI 10.25789/YMJ.2022.79.13

УДК 612.461:[547.6:66-05]

Aim: to study the content of the biomarker of PAH exposure – 1-hydroxypyrene (1-OHPyr) in the urine of workers in modern aluminum production in Eastern Siberia.

Materials and methods. 159 workers of electrolysis workshops with the technology of self-baked and pre-baked anodes were examined. The I group included 142 workers of the main professions engaged in the servicing of electrolyzers, anodes and cranes, the group II included 17 workers of auxiliary professions for pouring metal. The control group consisted of 14 people. Determination of 1-OHPyr was carried out by chromato-mass-spectrometry on an Agilent 7890A gas chromatograph. The data was processed in the Statictica 6.1 program.

Results. Significant differences were established between the median levels of 1-OHPyr in urine among workers of the main (2.2–75.2 μg/l) and auxiliary (0.48–7.6 μg/l) occupations in comparison with the values of the control group (0.17 μg/l) and Biological Exposure Index (2.5 μg/l, AGGIH 2020). The concentrations of 1-OHPyr in anodes workers were 6.4-20.9 times higher than those of electrolyzers workers and crane operators, and 9.9-156.7 times higher than the levels of auxiliary professions. The lowest concentrations of 1-OHPyr were found in urine samples of workers - operators of workshops with the technology of pre-baked anodes.

Conclusion. The research results confirmed the increased professional impact of PAHs on aluminum production workers. The highest levels of 1-OHPyr in urine, characterizing the internal loads of PAHs and the associated high risk of health disorders, were found in operators servicing anodes of workshops with the technology of self-baked anodes.

Keywords: polycyclic aromatic hydrocarbons, 1-hydroxypyrene, aluminum production, workers.

Introduction. Polycyclic aromatic hydrocarbons (PAHs) belong to the group of persistent toxic substances, which can accumulate in the environment and in the body, have high toxicity, carcinogenic and mutagenic activity, and have a harmful effect on human health and his offspring [7, 9]. The increased content of PAHs and oncological diseases are noted in such carcinogenic industries as smelting of aluminium, cast iron and steel, coal gasification, getting coke, bitumen and asphalting of roads etc. The impact of PAHs on workers in these industries is usually due to a different chemical mixture of PAHs. They include known (group 1), probable (group 2a) and possible (group 2b) carcinogenic compounds: benz(a) pyrene, dibenz(ah)anthracene, benz(a) anthracene, chrysene, benz(h)flurentene etc. Entering the body, chemical compounds of PAHs are biotransformed mainly by the monooxygenase enzyme system of the liver, forming specific indicative hydroxylated metabolites [13].

Based on a large number of studies conducted, it has been shown that the level of PAHs metabolites in urine can be used as a biological indicator of the adverse effects of PAHs. 1-hydroxypyrene (1-OHPyr) is recognized as a particularly preferred parameter for assessing the effects of PAHs among a number of metabolites, since pyrene is the main component in PAHs mixtures, and its metabolite correlates well with the total PAHs content in the air and DNA damage in persons exposed to benz(a)pyrene [5, 10, 11, 16]. The available foreign publications provide separate information about the levels of excretion of 1-OHPyr in urine and the risk of health disorders in workers of aluminum smelters in a number of countries [8, 11, 14], however, in Russia, such studies, to date, have not been properly reflected in the literature.

In this regard, the aim of the work was to study the content of the biomarker of PAH exposure – 1-OHPyr in the urine of workers of modern aluminum production in Eastern Siberia.

Materials and methods. The present study involved 159 workers of electrolysis workshops using the traditional technology of producing aluminum with self-baked anodes (TTSBA) and modernized – with pre-baked anodes (MTPBA). All employees participating in the study were classified into professional activity groups: group I consisted of the main professions engaged in maintenance electrolyzers, anodes and lifting cranes (average age 37.4–37.5 years and average experience 6.7–9.0 years), group II included auxiliary professions working the metal pouring and ladle farming (average age 40.3 years, average experience 5.8 years). The control group consisted of 14

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a person who does not have professional contact with PAHs. The persons included in the studies received information about the purposes of the examination and signed an informed consent issued in accordance with the Helsinki Declaration of the World Medical Association (2008).

Urine samples from workers were collected during a medical examination in the polyclinic of the plant in propylene containers, which were stored at a temperature of -20°C until analysis. Determination of concentrations of 1-OHPyr in urine was carried out by chromato-mass-spectrometry on an Agilent 7890A gas chromatograph with an Agilent 5975 mass selective detector using an improved method of analyte sample preparation [2]. The results of measurements of 1-OHPyr in the urine of workers were compared with the median level of the control group (0.17 μg/l) and the limit value of the biological exposure index (BEI) in urine established by the American Conference of Governmental Industrial Hygienists (AGGIH), which is 2.5 μg/l [15].

Statistical processing of the obtained results was carried out using the Statistica 6.1 program, using the nonparametric Mann–Whitney criterion with and without Bonferroni correction. The normality of the distribution of quantitative indicators was checked using the Shapiro-Wilk criterion. The results of the conducted studies are presented in the form of median, interquartile range and concentration interval, μg/l.

Results and discussion. Analysis of the results of the conducted studies showed that the median concentrations of 1-OHPyr in the urine of workers of the main professions of workshops with TTSBA varied in a wide range from 3.6 to 75.2 μg/l and were higher ($p<0.05$) than the level of the control group and the limit value of BEI (AGGIH, 2020) by 21.2–442.3 and 1.4–30.1 times, respectively (Table). At the same time, the highest median levels of 1-OHPyr content in urine exceeding the limit parameter BEI (2.5 μg/l) were observed in anodes workers (30.1 times) and crane operators (4.7 times), while in electrolyzers workers it was the lowest – 3.6 μg/l.

Quite other levels of 1-OHPyr excretion with urine were observed in workers in workshops with MTPBA. The median values of 1-OHPyr in the urine of operators of automated maintenance process of modern electrolysis baths were 2.2–6.8 μg/l, exceeding the limit value of BEI by 1.4-2.7 times only for operators servicing electrolyzers and crane operators. In general, the observed level of 1-OHPyr in the urine of the entire cohort of workshops operators with MTPBA was 3.1 times lower than that of workshops workers with TTSBA ($p<0.05$). This may indicate higher levels of PAH exposure in workers of workshops using TTSBA.

Among workers of auxiliary professions, approximately the same parameters of the content of 1-OHPyr in urine (according to a median 0.48–7.6 μg/l) were noted as in workers of the main professions of new workshops with MTPBA. The excess of the median concentrations of 1-OHPyr in urine relative to the limiting level of BEI was observed only in metal pourers (brigade of pouring) (by 3.0 times).

The data obtained are consistent with the results of foreign studies carried out at aluminum plants in Sweden, France and Slovenia [8, 12, 14], indicating the presence of high PAH exposures and levels of 1-OHPyr in the urine of persons working near electrolyzers and anodes. Some authors have suggested that exposure to PAHs at the level of 1-OHPyr in the urine of 4.4 μg/l may correspond to a relative risk of developing lung cancer at approximately 1.3, and the content of 1-OHPyr in the urine over 7.7 μg/l should be assessed as a higher risk of lung carcinoma for workers [3, 6]. However, it should be borne in mind that the harmful effects of PAHs on the body significantly depend on the chemical structure of the hydrocarbon itself and carcinogenic properties. After absorption in the body, many PAHs are metabolized to different types of reactive compounds capable of binding to DNA and initiating a carcinogenic process. Carcinogenic metabolites act on the principle of covalent binding to DNA, cause replication error, transcription changes and subsequent mutation, which leads to suppression of apoptosis, the onset of cell malignancy and the growth of a cancerous tumor [4, 13].

As our studies have shown, the anode workers of the workshops with TTSBA, serving coal anodes in electrolyzers, the levels of 1-OHPyr in urine were the highest, significantly exceeding the limit of BEI and the parameters of 1-OHPyr in workers of other groups of professions, which, combined with an increased content of PAHs (including benz(a)pyrene) in the air of these workshops [1] indicates a serious threat to their health. At the same time, the lowest concentrations of 1-OHPyr were noted among workers of new electrolysis workshops with MTPBA. Thus, the detected high levels of 1-OHPyr content and their significant excess of the BEI value in the urine of aluminum production workers may indicate the presence of an increased occupational carcinogenic risk of their health disorders. The performed pilot study confirms the feasibility of determining the PAH

Concentrations of 1-OHPyr in urine of workers of electrolytic aluminum production

Type of technology, profession	n	Me (Q25–Q75), μg/l	Min–Max, μg/l
TTSBA. All workers	112	11.0 (2.3–39.5)*, **	0.17–267.0
Electrolyzers worker	49	3.6 (1.5–13.3)▲	0.17–98.0
Anodes worker	26	75.2 (15.0–138.6)▲, ■, ♦	0.87–267.0
Crane operator	37	11.8 (2.7–30.0)■	0.18–57.7
MTPBA. All workers	30	3.5 (1.4–7.3)*	0.61–14.7
Operator of maintenance electrolyzers	16	3.5 (1.2–8.0)	0.61–14.7
Operator of maintenance anodes	6	2.2 (1.4–3.7)♦	1.1–7.3
Operator of maintenance crane	8	6.8 (1.9–8.4)	0.81–10.9
The site of metal pouring and ladle farming. All workers	17	6.7 (0.96–9.1)**	0.21–29.8
Metal pourers:			
Brigade of pouring	10	7.6 (4.9–14.5)●	0.96–29.8
Brigade of cleaning	7	0.48 (0.37–4.8)●	0.21–9.1
Control group	14	0,17 (0,10–0,30)	0,08–0,9

Notes: *, **, ♦, ● – the differences of the compared indicators are statistically significant at $p<0.05$; ▲, ■ - the differences of the compared indicators are statistically significant at $p<0.017$.

marker 1-OHPyr in urine to assess the harmful effects of PAH on the body and related major types of health disorders in aluminum plant workers.

Conclusion. The results of the conducted studies have shown that a particular problem in modern aluminum production is the continued exposure of workers to harmful chemical compounds of PAHs. The highest levels of 1-OHPyr in urine, characterizing the internal loads of PAHs and the associated high risk of health disorders, were found in the anodes workers in the workshops with TTS-BA. It is necessary to continue research on biomonitoring of 1-OHPyr in the urine of aluminum production workers during preventive medical examinations to prevent production-related diseases.

*The work was carried out as part of a research work on a fragment of the laboratory of analytical ecotoxicology and biomonitoring of the FSBSI ESIMER "Identification of the risk of remote environmental and socially caused health disorders in areas of accumulated technogenic load (on the example of Eastern Siberia)", No state registration AAAA-A17-117021750013-2.*1.

Reference

1. Shayakhmetov SF, Meshchakova NM, Lisetskaya LG, et al. Gigienicheskie aspekty uslovij truda v sovremennom proizvodstve alyuminiya [Hygienic aspects of working conditions in the modern production of aluminum]. Gigiena i sanitariya [Hygiene and sanitary. 2018; 97(10):899–904. (In Russ.).] DOI: 10.18821/0016-9900-2018-97-10-899-904.

2. Alekseenko AN, Zhurba OM, Merinov AV, et al. Hromato-mass-spektrometricheskoe opredelenie 1-gidroksipirena v moche kak biomarkera vozdejstviya policiklicheskih aromaticheskih uglevodorodovm [Determination of 1-hydroxypyrene as a biomarker for the effects of polycyclic aromatic hydrocarbons in urine by chromatography–mass spectrometry]. Zhurnal analiticheskoy khimii [Journal of analytical chemistry. 2020; 75(1):67–73. (In Russ.).] DOI: 10.31857/S0044450220010028

3. Tuček M, Bencko V, Volný J et al. A contributionn to the health risk assessment of exposure to exhaust gases in custom officers at border crossing. Ceske Pracovni Lekarstvi. 2006; 7(2):76–83.

4. Talaska G, Thoroman J, Schuman B et al. Biomarkers of polycyclic aromatic hydrocarbon exposure in European coke oven workers. Toxicology Letters. 2014; 231(2):213–6. DOI: 10.1016/j.toxlet.2014.10.025

5. Zhang Y, Ding J, Shen G et al. Dietary and inhalation exposure to polycyclic aromatic hydrocarbons and urinary excretion of monohydroxy metabolites - A controlled case study in Beijing, China. Environmental Pollution. 2014; 184:515–22. DOI: 10.1016/j.envpol.2013.10.005

6. Buchet JP, Gennart JP, Mercado-Calderon F et al. Evaluation of exposure to polycyclic aromatic hydrocarbons in a coke production and a graphite electrode manufacturing plant: assessment of urinary excretion of 1-hydroxypyrene as a biological indicator of exposure. British Journal of Industrial Medicine. 1992; 49(11):761–8. DOI: 10.1136/oem.49.11.761

7. Yang L, Zhang H, Zhang X et al. Exposure to atmospheric particulate matter-bound polycyclic aromatic hydrocarbons and their health effects: a review. International Journal of Environmental Research and Public Health. 2021; 18(4):2177. DOI: 10.3390/ijerph18042177

8. Carstensen U, Yang K, Levin JO et al. Genotoxic exposures of potroom workers. Scandinavian Journal of Work, Environment and Health. 1999; 25(1):24–32. DOI: 10.5271/sjweh.379

9. Ifegwu OC, Anyakora C. Polycyclic aromatic hydrocarbons: part I. Exposure. Advances in Clinical Chemistry. 2015; 72:277–304. DOI: 10.1016/bs.acc.2015.08.001

10. Käfferlein HU, Marczynski B, Simon P et al. Internal exposure to carcinogenic polycyclic aromatic hydrocarbons and DNA damage: A null result in brief. Archives of Toxicology. 2021; 86(8):1317–21. DOI: 10.1007/s00204-012-0882-7

11. Jongeneelen FJ. Benchmark guideline for urinary 1-hydroxypyrene as biomarker of occupational exposure to polycyclic aromatic hydrocarbons. Annals of Occupational Hygiene. 2001; 45(1):3–13. DOI: 10.1093/annhyg/45.1.3

12. Barbeau D, Persoons R, Marques M et al. Relevance of urinary 3-hydroxybenzo(a) pyrene and 1-hydroxypyrene to assess exposure to carcinogenic polycyclic aromatic hydrocarbon mixtures in metallurgy workers. Ann. Occup. Hyg. 2014; 58(5):579–90. DOI: 10.1093/annhyg/meu004

13. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon; 2010.

14. Klöslová Z, Drímal M, Balog K et al. The relations between polycyclic aromatic hydrocarbons exposure and 1-OHP levels as a biomarker of the exposure. Central European Journal of Public Health. 2016; 24(4):302–7. DOI: 10.21101/cejph.a4179

15. TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIN. Cincinnati; 2020.

16. Yamano Y, Hara K, Ichiba M et al. Urinary 1-hydroxypyrene as a comprehensive carcinogenic biomarker of exposure to polycyclic aromatic hydrocarbons: a cross-sectional study of coke oven workers in China. International Archives of Occupational and Environmental Health. 2014; 87(7):705–13. DOI: 10.1007/s00420-013-0913-6

DOI 10.25789/YMJ.2022.79.14

УДК 615.099.036.8(571.56)

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DETECTION OF HUMAN PAPILLOMAVIRUS OF HIGH CARCINOGENIC RISK IN WOMEN WITHIN THE ONCOSEARCH PROGRAM IN YAKUTIA

The study was conducted as part of a pilot project at the Yakut Republican Oncological Dispensary titled ОНКОПОИСКСАХА.РФ (ONCO-SEARCH), which is part of the national healthcare project. In 2021, 724 women from 5 uluses (villages) of the Republic of Sakha (Yaku-tia) and the city of Yakutsk took part in the study. The overall infection rate of high carcinogenic risk human papillomavirus (HCR HPV) among women in the Zhigansky Ulus was 10.6%, the Verkhoyansky Ulus – 4.7%, the Churapchinsky Ulus – 11%, the Namsky Ulus – 8.3%, the Srednekolymsky Ulus – 10.9%, and the city of Yakutsk – 5.5%. HCR HPV genotypes 16, 18 and 45 were identified as the most aggressive forms integrated into the human genome. In the article, we present the prevalence of HPV types by districts. We also highlight differences in in-fection among women of different age groups. The largest proportion of HCR HPV carriers falls on the age groups of 20-30 years (14.6%) and over 70 years (13.9%).

Keywords: human papillomavirus, screening, integrated forms, age distribution.

Introduction. Human papillomavirus (HPV) is one of the most common infections in the world, which is divided into categories of low and high carcinogenic risk. HPV causes skin and anogenital warts, neoplasms of the oropharynx, cervix, anal canal, vulva, vagina, and penis [4, 7, 8, 10]. Harald zur Housen and his colleagues were first to demonstrate that genital warts contain the human papillomavirus genome [9, 11]. Later, the main cause of cervical cancer (CC), as well as precancerous lesions, was attributed to HPV infection (certain types), transmitted mainly through sexual contact. In 2008, German scientist Harald zur Hausen was awarded a Nobel Prize for discovering the role of HPV as a cause of cervical cancer.

According to 2020 data, cervical cancer takes fourth place (after breast, colorectal, and lung cancer) in global cancer incidence among women of all age groups. In Russia, according to data for 2018, cervical cancer accounted for 5.3% of all oncological conditions in women [1]. At the same time, in terms of prevalence related to the reproductive period in the age group of 15 to 44 years, it ranks second. Regarding geographic distribution, data are presented on the highest prevalence of HPV in developing countries in low- and middle-income regions. In Eswatini (Af-rica), this figure is 84.5 cases per 100 thousand people; Bolivia (South America) – 36.6; Mal-dives (Asia) – 24.5; Montenegro (Europe) – 26.2; Fiji (Oceania) – 29.8. In Europe, Russia ranks 13th with 14.1 cases per 100,000 people.

According to the WHO concept [2], the fundamental ways to combat cervical cancer in-clude vaccination, screening, diagnosis, and treatment of precancerous conditions and invasive cervical cancer. Diagnosis at an early stage of cervical cancer and immediate treatment in most cases can avoid the progression of the disease and contribute to recovery. Cervical screening pro-grams based on a cytological examination (Pap test) and/or a molecular diagnostic PCR method [6] make it possible to identify women at high risk of developing cervical cancer and prevent the disease in a timely manner. Statistics show that among all age groups, the prevalence of HPV av-erages about 20-30%. However, different studies show highly variable results between regions and social groups, which indicates the focal nature of the spread of HPV [3]. At the same time, the published data on HCR HPV in Russia and Yakutia, in particular, are based to a greater ex-tent on studies of patients seeking medical help, which does not allow an objective assessment of the overall prevalence of the virus among the population.

The Purpose of the Study: mass screening testing, and analyzing carriage and character-istics of the viral load of 14 oncogenic HPV types in women living in various uluses (villages) of the Republic of Sakha (Yakutia).

Material and Methods. Women participated in the voluntary screening study (n = 724), they were from 5 uluses (villages) of the Republic of Sakha (Yakutia) and the city of Yakutsk, aged 20 to 86 years. The mean age was 50.6±8.6 years. The study materials were epithelial cells of scrapings from the cervical canal, placed in a transport medium for liquid cytology with vol-umes of 2-5 ml. DNA extraction was carried out with the AmpliSens® DNA-sorb-D reagent kit designed for isolating total DNA from epithelial cells taken for liquid cytology. For amplification and detection of HPV DNA segments (multiplex PCR), we used the AmpliSens® HCR HPV screen-titer-14-FL test system, which makes it possible to identify the 14 most potent oncogenic types of high carcinogenic risk using one fluorescent channel with ROX dye:

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- for genotypes 16, 31, 33, 35, 52, 58 – region E1 gene
- for genotypes 18, 39, 45, 56, 59, 66, 68 – region E2 gene
- for genotype 51 – region E7 gene

Separate channels allowed us to detect the 16th (FAM), 18th (JOE), and 45th (Cy 5.5) genotypes in the E6 gene regions (Table 1). Detections of the E6 region with no detections in E1/E2 regions point to the integration of the virus into the human genome.

Additionally, we used the AmpliSens® HRC HPV genotype-titer-FL reagent kit. Ampli-fication was carried out on a 6-channel detecting amplifier with a Real-time CFX-96 Touch 96 x 0.2 ml thermal block from Bio-Rad (USA). Amplification was set up and the results were analyzed using the FRT Manager (version 3.4). Statistical data processing was carried out using Sta-tistica 6.0.

Results and Discussion. Some studies have shown that the most common HCR HPV genotypes, in descending order of occurrence, are: 16, 18, 59, 45, 31, 33, 52, 58, 35, 39, 51, 66, and 68. However, we also note variability in genotypic prevalence depending on the geographical region. Knowledge gained about the prevalence and genotype structure of HPV in a particular geographic region can be of great help in choosing a strategy to prevent HPV-associated diseases. As a result of our studies, we found that the total infection rate with HCR human papillomavirus among all examined women (n = 726) was 7.6% (n = 55; Table 2). In the structure of the studied districts of the Republic of Sakha (Yakutia), the highest infection rates were noted in: Churap-chinsky Ulus – 11.0%, Srednekolymsky Ulus – 10.9%, Zhigansky Ulus – 10.6%, and Nam-sky Ulus – 8.3%. In the city of Yakutsk and the Verkhoyansk Ulus, these figures were 5.5 and 4.7%, respectively. It should be noted that in Zhigansky and Churapchinsky Uluses, there have been cases of simultaneous carriage of two HCR HPV genotypes, and three in Srednekolymsky Ulus (Table 2). We registered combinations of genotypes 16 with 18, as well as 16 with 31 and 56, respectively. It is also noteworthy that out of the total number of screened women in the Verkhoyansk Ulus, there have been infections with only two HPV genotypes, 16 and 18.

The integration of the virus into the host cell's genome plays a special role in the devel-opment of HPV diseases; likewise, the development of cervical cancer is often associated with the integration of virus DNA into the genome [5]. Most often, HPV 16 and 18 genotypes are in-tegrated, while the E1/E2 section breaks apart while maintaining the E6/E7 oncogene.

The viral genes E6 and E7 play a key role in the process of tumor transformation. Their activity is controlled by the upstream regulatory region (URR). Oncoprotein E6 plays the role of a coactivator that interacts with transcription factors and elements of the main transcription com-plex. Thus, the E6 gene is a multifunctional protein. Its transactivating activity involves regula-tion of transcription, interaction with the p53 gene and its degradation, and violations in the cell growth control mechanism and in the process of cell differentiation. The E7 protein is able to re-verse cell arrest in the G1 phase of the cell cycle, exert a mitogenic effect, and stimulate uncon-trolled DNA synthesis [9, 12]. Thus, cervical cancer is a unique model of carcinogenesis associ-

Table 1

Distribution of Fluorophores by Detection Channels

Channel for Fluorophore	FAM	JOE	ROX	Cy5	Cy5.5
Target DNA	HCR HPV DNA Genotype 16	HCR HPV DNA Genotype 18	Genotypes **16,18,31,33,35, 39,45,51,52,56, 58,59,66,68**	Plot DNA β -Globin Gene (Internal Control Sample Glob)	HCR HPV DNA Genotype 45
Amplification Region	E6 gene	E6 gene	E1 Gene (for genotypes 16, 31, 33, 35, 52, 58)/ E2 gene (for genotypes 18, 39, 45, 56, 59, 66, 68)/ E7 gene (for genotype 51)	β-Globin Gene	E6 Gene

Table 2

Structure of HCR HPV Infection

Ulus (Village)	HPV 16[1]	HPV 18[1]	HPV 45[1]	HCR[2]	Mixed (Geno-types), Persons	Negative, Persons	Total, Persons/(%)	Infected, Per-sons/ (%)
Zhigansky	5	-	2	5	1[1] (16.18)	110	123/(17.0)	13/(10.6)
Verkhoyansk	3	1	-	-	-	81	85/(11.7)	4/(4.7)
Churapchinsky	-	1	2	5	1[1] (16.18)	73	82/(11.3)	9/(11.0)
Namsky	1	-	-	5	-	66	72/(10.0)	6/(8.3)
Srednekolymsky	1	1	-	3	1[2] (16.31.56)	49	55/(7.6)	6/(10.9)
Yakutsk	2	4	2	9	-	290	307/(42.4)	17/(5.5)
Total:	**12**	**7**	**6**	**27**	**3**	**669**	**724/(100)**	**55/(7.6)**

[1] – genotypes –region E6 gene (likely integrated into the human genome);
[2] –genotypes 16, 31, 33, 35, 52, 58 – E1 gene region, genotypes 18, 39, 45, 56, 59, 66, 68 – E2 gene region, geno-type 51 – E7 gene region.

at-ed with a viral infection, its uniqueness is due to the exogenous genetic information with trans-forming potential in tumor cells.

Figure 1 shows the distribution of HCR HPV forms integrated into the genome against the background of general infection with the virus in the uluses of the Republic of Sakha (Yaku-tia). The average value for the studied regions of the Republic was 3.9%. In the Verkhoyansk Ulus, despite the low overall infection rate (4.7%), all forms of the virus were integrated. We identified three cases of the 16th genotype and one of the 18th genotype of the E6 gene region, while other genotypes of the E1 gene/E2 gene/E7 gene regions were not identified (Table 2).

In the Zhigansky Ulus, 8 cases (6.5%) out of 13 (10.6%) infected were integrated forms of HPV 16 and HPV 45, with a predominance of the 16th genotype (n = 5). In one case, we identified the integration of two genotypes at once: 16 and 18. In Churapchinsky, we noted gen-otypes 18 and 45 (1 and 2 cases, respectively) and, just like in the Zhigansky Ilus, one case of an integrated form of two genotypes at once – HPV 16 and HPV 18. We identified only one case of carriage of the integrated form of HPV 16 in the Namsky Ulus. In the Srednekolymsky Ulus, we recorded one case of a non-integrated form of HPV 16 carriage. We detected the E6 gene region of HPV 16 and the HRC E1/E2/E7 gene region. This may indicate that the integration of the virus into the human genome has not yet occurred. In this case, a more effective response to therapeutic measures with a more favorable prognosis is likely. We also highlight one case of car-riage of integrated forms of 16 and 18 genotypes. In Yakutsk, 8 out of 17 cases had integrated forms: 2 cases each for genotypes 16 and 45, and 4 cases for HPV 18. We have not detected HCR HPV 51 genotype with the E7 gene detection region.

To identify the age characteristics of HPV distribution, the subjects were divided into 6 age groups: 20-30 years (5.7%), 31-40 (16.9%), 41-50 (27.3%), 51-60 (24.4%), 61-70 (20.6%), and older than 71 (5.1%; Fig. 2).

Analysis of the distribution of HCR HPV showed that the largest proportion of carriers were in the groups of women aged 20-30 (14.6%) and over 70 (13.9%) (Fig. 3). The lowest infec-tion was observed in the age group of 41-50 and amounted to 2.0%. It should be noted that in our study, the age samples of younger and older women were relatively small (n = 41 and n = 36, respectively).

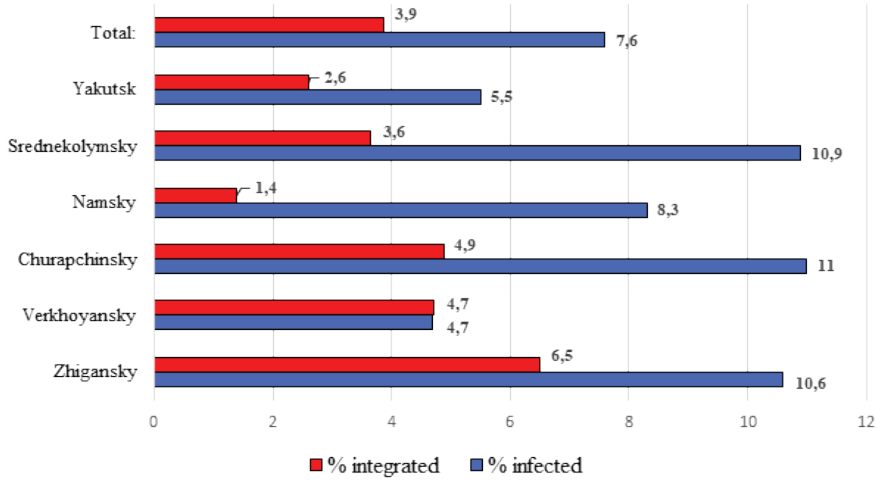

Fig. 1. Structure of the Territorial Distribution by Uluses of General Infection and HPV Forms Integrated into the Human Genome (%)

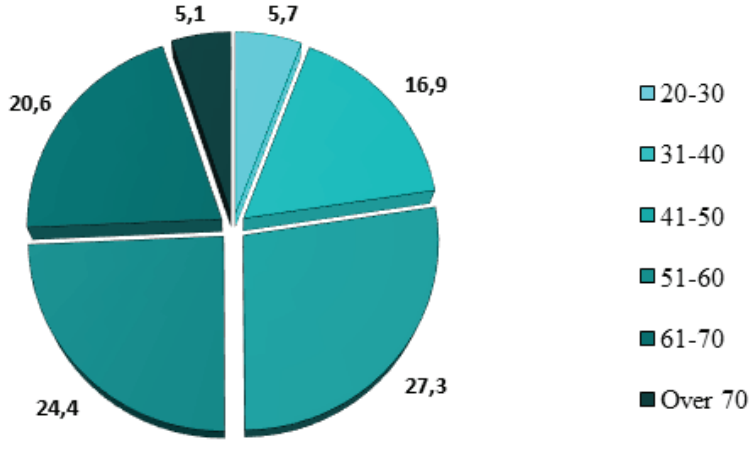

Fig. 2. Structure of the Distribution of the Studied by Age Groups (%)

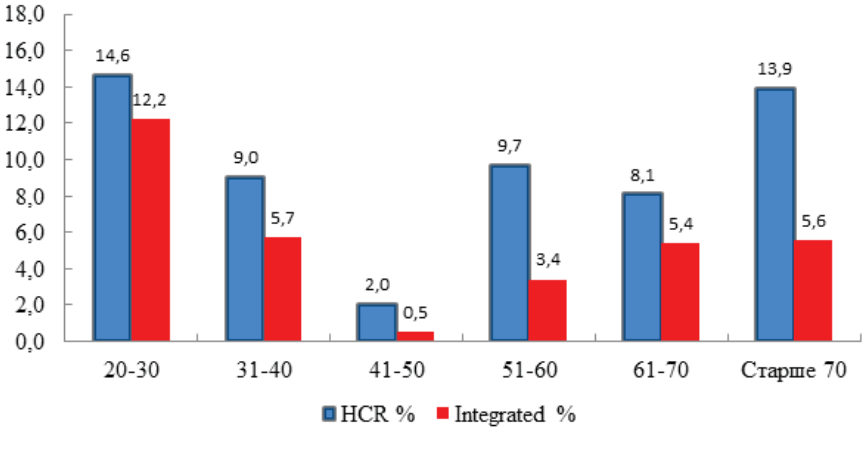

Fig. 3 Distribution of HCR HPV and Integrated Forms of the Virus by Age Groups X-Axis: Age (Years); Y-Axis: Infection (%)

Therefore, in order to obtain the most reliable statistical data on the age characteris-tics of HPV distribution in the Republic, it is necessary to involve more women of this age.

The maximum proportion of integrated forms of HCR HPV was found in the group of women aged 20-30 (12.2%) and 31-40 (5.7%). Then, in decreasing order, there were groups of: older than 70 (5.6%), 61-70 (5.4%), 51-60 (3.4%) and the smallest number of cases (0.5%) of in-tegrated forms of the virus was found in women aged 41-50.

With this study, data on the spread of HCR HPV in the regions of the Republic, and es-pecially integrated forms of the virus, have been obtained for the first time. Further research is needed to obtain more accurate statistics.

Conclusion. Thus, we have established that the overall infection rate in the Republic var-ies from 5.5% (Yakutsk) to 11% and averages 7.6%. The highest overall infection rate was found in the Zhigansky Ulus – 10.6%, the Churapchinsky Ulus – 11%, and the Srednekolymsky Ulus – 10.9%. In the same uluses, cases of infection with two or more HCR HPV genotypes were noted. We detected integrated forms of HPV were detected in 3.9% of women, and non-integrated forms in 3.7% of cases. The structure of integrated forms is dominated by the HPV 16 genotype (1.7%), followed by HPV 18 (1.0%) and HPV 45 (0.8%). The largest proportion of HCR HPV carriers falls on the age groups of 20-30 years (14.6%) and over 70 years (13.9%). The largest proportion of the forms of the virus integrated into the human genome was found in women aged 20-30 and 31-40 years – 12.2% and 5.7%, respectively. The smallest number of cases (0.5%) of integrated forms of the virus was observed in the group with a low percentage of virus carriers (2.0%) among women aged 41 to 50 years.

All detected cases of infection have HPV genotypes of high oncogenic risk and, with a high probability, can cause cervical cancer and severe dysplasia. All the patients with HCR HPV infection were registered and directed for further research (Pap test and colposcopy), in accord-ance with the cervical screening program in the conditions of the Yakut Republican Oncological Dispensary under the ОНКОПОИСКСАХА.РФ (ONCOSEARCH) pilot project.

Reference

1. Kaprin AD, Starinsky VV, Petrova GM. Zlokachestvennye novoobrazovaniya v Rossii v 2018 godu (zabolevaemost' i smertnost') [Malignant Neoplasms in Russia in 2018 (Morbidity and Mor-tality). Herzen P.A. MNIOI (In Russ.).]

2. Kompleksnaya profilaktika raka shejki matki i bor'ba s nim – zdorovoe budushchee dlya devochek i zhenshchin. Vsemirnaya organizaciya zdravoohraneniya [WHO Guidance Note: Comprehensive Cervical Cancer Prevention and Control: A Healthier Future for Girls and Wom-en. 2013 (In Russ.).]

3. Rogovskaya SI, Mikheeva IV, Shipulina OYu, et al. Rasprostranennost' papillo-mavirusnoj infekcii v Rossii [The Prevalence of Papillomavirus Infection in Russia]. Epidemi-ologiya i vakcinoprofilaktika [Epidemiology and vaccine prevention]. 2012; 1 (62): 25-33. (In Russ.).]

4. Buchanan TR, Graybill WS, Pierce JY. Morbidity and Mortality of Vulvar and Vaginal Cancers: Impact of 2-, 4-, and 9-Valent HPV Vaccines. Hum Vaccines Immunother. (2016) 12:1352–6. doi: 10.1080/21645515.2016.1147634.

5. Castle PE, et al. Performance of Carcinogenic Human Papillomavirus (HPV) Test-ing and HPV16 or HPV18 Geno-Typing for Cervical Cancer Screening of Women Aged 25 Years and Older: A Subanalysis of the ATHENA Study. Lancet Oncol. 2011 Sep;12(9): 880-90.

6. Debbie Saslow, et.al. American Society for colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. CA CANCER J CLIN 2012; 62:147-172.

7. De Martel C., Ferlay J., Franceschi S., Vignat J., Bray F., Forman D., et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet On-col. (2012) 13:607–15. doi: 10.1016/S1470-2045(12)70137-7.

8. De Martel C., Plummer M, Vignat J, Franceschi S. Worldwide Burden of Cancer Attributable to HPV by Site, Country and HPV Type. Int J Cancer. (2017) 141:664–70. doi: 10.1002/ijc.30716.

9. De Villiers EM, Gissmann L, and H. zur Hausen. 1981. Molecular Cloning of Vi-ral DNA from Human Genital Warts. J. Virol. 40:932-935.

10. Forman D., de Martel C., Lacey C.J., Soerjomataram I., Lortet-Tieulent J., Bruni L., et al. Global Burden of Human Papillomavirus and Related Diseases. Vaccine. (2012) 30:F12–23. doi: 10.1016/j.vaccine.2012.07.055.

11. Gissmann, L, and H. zur Hausen.1980. Partial Characterization of Viral DNA from Human Genital Warts (Condylomata acuminata). Int. J. Cancer 25:605-609.

12. Matlashewski G /Anticancer Res. -1989.- No. 9.- p.1447-1456.

TOPICAL ISSUE

DOI 10.25789/YMJ.2022.79.15

УДК 616 – 053. 2 (571.56)

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FEATURES OF GASTROINTESTINAL DISORDERS IN CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH COVID-19

Resume. Gastrointestinal tract damage is a part of the course of multisystem inflammatory syndrome in children (MVS-D) associated with the new COVID-19 coronavirus infection. According to the results of a retrospective study, gastrointestinal tract damage was detected in 77% of patients with MVS-D and is represented by signs such as abdominal pain, vomiting, diarrhea and peritoneal symptoms. In children with gastrointestinal tract lesions, significant differences were noted in the frequency of occurrence of the following signs: hepatomegaly, splenomegaly, hypotension/shock, as well as conjunctivitis and facial swelling. Among laboratory abnormalities, hypoalbuminemia is more characteristic, but the level of CRP and troponin is higher. The article shows that gastrointestinal tract damage is an important early predictor of the severity of MVS-D.

Keywords: multisystem inflammatory syndrome, gastrointestinal tract lesion, hepatomegaly, splenomegaly, Russia.

Introduction. According to systematic reviews, cases of COVID-19 in children were observed relatively less frequently, and, mostly, had a lighter course [14, 15, 4, 22]. The incidence in children is estimated from 1-5% to 19% of all COVID-19 cases. [14, 3]. For the first time, the suspicion of a possible link between COVID-19 and Kawasaki disease (KD) was put forward by Jones et al [12], who reported a case of Kawasaki disease in a 6-month-old girl with positive PCR result on SARS-CoV-2. Also among the first to describe this problem were groups of researchers from Italy [19] and France [17]. However, this condition occurs in older children than KD, and is also often manifested with gastrointestinal symptoms (diarrhea, abdominal pain, vomiting) and heart disorders (myocarditis, pericarditis), which often lead to myocardial damage and shock, while these clinical manifestations are less common in KD [13]. This phenomenon was later called multisystem inflammatory syndrome in children (MIS-C). The incidence of MIS-C is 1:4000 children who had COVID-19 [8]. One of the most frequent early manifestations and features that help to distinguish MIS-C from KD is the involvement of gastrointestinal tract in the pathological process, manifested by abdominal pain, diarrhea, nausea and vomiting, and in some cases with mesenteric lymphadenitis.

The aim of the study: To analyze the main clinical and laboratory characteristics of the disease course and to determine the factors associated with the gastrointestinal involvement in MIS-C.

Materials and methods: In the retrospective study were included 162 patients (96 boys, 66 girls) aged from 4 months to 17 years (median 8.2 years) with a diagnosis of "multisystem inflammatory syndrome associated with COVID-19 in children" who were on inpatient treatment in pediatric clinics of Saint Petersburg, Irkutsk, Yakutsk, and Kaliningrad. The inclusion criteria met the criteria of the World Health Organization (WHO) for the definition of MIS-C. Inclusion criteria (all items must be present):

1. Age from 0 to 18 years.
2. Fever for ≥ 3 days.
3. Clinical signs of a multisystem disorders (at least 2 of the following):

- Rash, bilateral non-purulent conjunctivitis or signs of inflammation of the skin and mucous membranes (oral cavity, hands or feet).
- Hypotension or shock.
- Cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiographic data or elevated troponin/BNP).
- Signs of coagulopathy (prolonged PT or PTT; elevated D-dimer).
- Acute gastrointestinal symptoms

(diarrhea, vomiting, or abdominal pain).

4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin).

5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes.

6. Signs of previous COVID-19: Positive PCR of SARS-CoV-2 / Positive serology / Positive antigen test / Contact with a person with confirmed COVID-19.

The fact of previous COVID-19 infection in patients was confirmed by at least one of the following methods: a positive result of PCR with reverse transcription (13%), the presence of antibodies of classes IgM (40.3%) or IgG (97.4%) to SARS-CoV-2, contact with a person with confirmed COVID-19 (65.6%).

The frequency of clinical signs and the severity of laboratory changes in patients with MIS-C were evaluated. To conduct a comparative analysis, patients with MIS-C were divided into two groups: group 1 - with gastrointestinal disorders (n=125, 77.2%) and group 2 - without signs of gastrointestinal disorders (n=37, 22.8%).

Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., Tulsa, OK, USA). The description of quantitative indicators is carried out with the indication of the median (25th; 75th percentiles). Comparison of qualitative indicators was carried out using the Pearson criterion χ2.Comparison of quantitative indicators was carried out using the Mann-Whitney criterion. For quantitative variables, cut-off values were calculated using AUC-ROC analysis (AUC – area under the curve – "area under the curve") with the determination of 95% confidence interval (CI), calculation of odds ratio (OR) without taking into account the time of development of events of interest using 2×2 tables. The multivariate regression analysis included parameters that had clinical significance and statistical reliability. The coefficient of determination (R2) was taken into account from the parameters of the multivariate regression model. Differences or connections were considered statistically significant at $p<0.05$.

The study was approved by the Ethics Committee of the St. Petersburg State Pediatric Medical University (Protocol No. 03/09 of 03/22/2021) for compliance with the provisions of the Helsinki Declaration on the Rights of the Patient.

Results and discussion: The analysis of the clinical manifestations of MIS-C revealed the most frequent clinical signs: fever (100%), conjunctivitis (84.8%), rash (78.9%), gastrointestinal symptoms (77.2%), cervical lymphadenopathy (66.9%), mucosal brightness (64%), hepatomegaly (64.4%), erythema/swelling of the hands/feet (62.4%), sore throat (56.3%), facial swelling (50.5%), respiratory symptoms (49.4%), red cracked lips (49.3%), neurological symptoms (47.8%), hypotension/shock (43.8%), splenomegaly (40.7%), peeling fingers (35.7%), arthritis/arthralgia (14.7%).

Among the laboratory parameters, most patients showed a significant increase in inflammatory markers, such as ESR, CRP, ferritin, hypoalbuminemia, hypoproteinemia, increased ALT, AST, LDH and D-dimer.

The following echocardiographic changes were noted: dilation/aneurysms of coronary arteries (16.2%), myocardial lesion (31.4%), pericardial effusion (29.5%). More than half of the patients (50.6%) were hospitalized in the intensive care unit. Glucocorticosteroids (81.5%), acetylsalicylic acid (57.1%), intravenous immunoglobulin (44.7%) were used to treat patients with MIS-C, and 4.9% of patients needed the anti-interleukin-6 biological therapy. The average length of hospital stay was 18 days.

Gastrointestinal disorders were represented by such features as abdominal pain (64.2%), vomiting (59.8%), diarrhea (69.6%) and peritoneal symptoms, which required diagnostic laparoscopy and removal of the appendix in 3 patients (1.8%). There was a predominance of boys in group 1 (64.8%) than in group 2 (40.5%,

Table 1

Comparative characteristics of patients with MIS-C, depending on the presence of symptoms of gastrointestinal tract damage

Parameters	The whole group (n=162)	1 group – with gastrointestinal involvement (n=125)	2 group - without gastrointestinal involvement (n=37)	p
Demographic indicators				
Age, months	98 (59; 134)	101 (60; 133)	96 (56; 141)	0.842
Gender, male, n (%)	96 (59.2)	81 (64.8)	15 (40.5)	0.008
Gender, female, n (%)	66 (40.8)	44 (35.2)	22 (59.5)	
Clinical and laboratory characteristics				
Neurological symptoms, %	47.5	51.6	33.3	0.053
Conjunctivitis, %	84.8	91.2	64.9	0.0001
Face swelling, %	50.5	56.5	30.8	0.022
Hepatomegaly, %	64.4	69.6	47.1	0.016
Splenomegaly, %	40.7	46	23.5	0.02
Hypotension/Shock, %	43.8	51.2	18.9	0.0005
C-reactive protein, mg/l	138 (44.0; 236.0)	157.7 (64.0; 238.0)	106.1 (31.0; 236.0)	0.077
Total protein, g/l	56.5 (49.0; 63.0)	55.6 (48.4; 62.8)	60.0 (53.0; 63.9)	0.081
Albumin, g/l	29.3 (25.8; 34.0)	28.8 (25.0; 33.2)	30.3 (28.3; 35.0)	0.034
Troponin, pg/ml	5.1 (1.0; 56.0)	7 (2; 90)	1 (0; 5)	0.065
ECHO-CG changes				
Coronary artery dilatation/CA aneurysms, %	16.2	15.3	19.4	0.551
Myocarditis, %	31.4	35	19.4	0.078
Pericarditis, %	29.5	30.8	25	0.501

Table 2

Factors associated with gastrointestinal tract damage in children with MIS-C

Parameter	*Se*	*Sp*	OR (95%CI)	p
Male gender	64.8	59.5	2.7 (1.3; 5.7)	0.008
Neurological symptoms	57.6	66.7	2.1 (0.98; 4.65)	0.053
Conjunctivitis	91.2	35.1	5.6 (2.2; 14.4)	0.0001
Face swelling	56.5	69.2	2.9 (1.1; 7.5)	0.022
Hepatomegaly	69.6	52.9	2.6 (1.2; 5.7)	0.016
Splenomegaly	45.9	76.5	2.8 (1.2; 6.6)	0.02
Shock/hypotension	51.2	81.1	4.5 (1.8; 11.0)	0.0005

Abbreviations: OR – odds ratio; CI – confidence interval; Se - sensitivity; Sp – specificity.

p=0.008). Hypotension or shock were significantly more common in patients of group 1 (51.2%) than in group 2 (18.9%, p=0.0005). There were differences in the frequency of neurological symptoms, which were more often observed in children of group 1 (51.6% vs. 33.3%, respectively, p=0.053). Among patients of the group 1 hepatomegaly (69.6% vs. 47.1%, p=0.016), splenomegaly (46% vs. 23.5%, p=0.02), conjunctivitis (91.2% vs. 64.9%, p=0.0001) and facial puffiness (56.5% vs. 30.8%, p=0.022) were observed more frequently.

Among laboratory abnormalities, patients of group 1 had a greater tendency to hypoalbuminemia (albumin - 28.8 g/l) than in group 2 (30.3 g/l, p=0.034), the level of CRP was significantly higher (157.7 mg/l vs. 106.1 mg/l, p=0.077), as well as troponin level (7 pg/ml vs. 1 pg/ml, p= 0.065). Signs of myocardial damage were more common for group 1 patients (35% vs. 19.4%, p=0.078). The comparative characteristics between the two groups are presented in Table 1.

The next stage was the identification of clinical and laboratory signs associated with gastrointestinal tract damage using sensitivity analysis, specificity and calculation of odds ratio. The transformation of quantitative variables into qualitative ones was performed using AUC-ROC analysis. The results of the one-factor analysis are presented in Table 2.

Table 3

Factors associated with gastrointestinal tract damage in patients with MIS-C

Parameter	β	SE	p
Male gender	0.18	0.076	0.018
Conjunctivitis	0.27	0.075	0.0004
Shock/ hypotension	0.27	0.075	0.0003

Characteristics with the highest sensitivity, specificity, odds ratio and clinical significance were included in the multivariate regression analysis. Of the initial 7 factors included in the model, only 3 variables were significantly associated with gastrointestinal tract damage: male gender, conjunctivitis and hypotension/ shock. The results of multivariate regression analysis are presented in Table 3.

It is important to notice that gastrointestinal involvement in the pathological process is an extremely important early predictor of the possible severity of MIS-C, associated with such characteristics of the course of MIS-C as conjunctivitis, face swelling, central nervous system damage, hepatomegaly and splenomegaly, hypotension / shock, common for the severe course of the disease.

Discussion: The data obtained are comparable with studies previously published in the literature, however, it should be noted that there are not many publications of multicenter studies. Fever is described in 100% of cases in almost all studies. Most researchers note a high frequency of mucocutaneous manifestations (rash in 45-65% of cases, conjunctivitis in 30-81%, lip lesion in 27-76%) [7, 9, 6]. Many researchers note a fairly high frequency of hypotension or shock in patients with MIS-C (32-76%) [5, 6, 7, 9, 18]. Among laboratory changes, most researchers describe an increase in inflammatory biomarkers, thrombocytopenia, hypoalbuminemia, a significant elevation of D-dimer [17, 19, 6, 20]. The gastrointestinal disorders are noted in MIS-C in 71-86% of cases on average according to different researchers [9, 2], which is comparable with our data (77.2%). Among the examined patients with gastrointestinal involvement in our sample, three had acute appendicitis in the structure of the disease, which required laparoscopic appendectomy. Similar cases are described in previously published works [10, 11, 16, 1].

Factors associated with gastrointestinal involvement (including a higher incidence of troponin levels and myocardial dysfunction) include an association with hypotension/shock and, apparently, gastrointestinal disorders can be caused by a decrease in mesenteric blood flow due to shock. However, there is also an opinion about the role of persistence of the SARS-Cov-2 virus in gastrointestinal tract, which can lead to local inflammation of the mucous membrane, increased release of zonulin and subsequent increased intestinal permeability for coronavirus antigens, including a superantigen-like motif of spike protein [21]. Face swelling in patients with MIS-C is also probably a consequence of hypoproteinemia, which is the result of shock / hypotension and, resulting from this, liver dysfunction. As for conjunctivitis, it refers to one of the signs of damage to the skin and mucous membranes due to systemic vasculopathy and is among the Kawasaki-like symptoms also characteristic of multisystem inflammatory syndrome.

Conclusion. In the conditions of still ongoing COVD-19 pandemic and, accordingly, the continuing risk of MIS-C morbidity, it is necessary to study the epidemiological history, conduct a thorough assessment of possible multiple lesions of organs and systems, paying special attention to abdominal symptoms. Gastrointestinal involvement is an extremely important early predictor of the severity of MIS-C, requiring subsequent careful clinical and laboratory monitoring and correction of therapy.

The work was carried out within the framework of the research topic "Physical development and health status of children in the Far North (on the example of Yakutia)" (state registration number: 1021062411641-9-3.2.3), within the framework of the state task of the Ministry of Science and Education of the Russian Federation (FSRG-2020-0016).

Reference

1. Kadyrkulov AZh, Nakipov RN, Nasybullin MN, Multisystem inflammatory syndrome associated with COVID-19 complicated by destructive appendicitis in a child, Medicus. 2021; 1 (37): 32-36.

2. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, Acosta S, Naqvi R, Burmeister-Morton F, Burmeister F, Tarriela A, Petershack M, Evans M, Hoang A, Rajasekaran K, Ahuja S, Moreira A. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020 Sep; 26:100527. doi: 10.1016/j.eclinm.2020.100527. Epub 2020 Sep 4. PMID: 32923992; PMCID: PMC7473262.

3. American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. (2021). Available online at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-leveldata-report/.

4. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020 Sep 1;174(9):882-889. doi: 10.1001/jamapediatrics.2020.1467. PMID: 32320004.

5. Cattalini M, Della Paolera S, Zunica F, Bracaglia C, Giangreco M, Verdoni L, Meini A, Sottile R, Caorsi R, Zuccotti G, Fabi M, Montin D, Meneghel A, Consolaro A, Dellepiane RM, Maggio MC, La Torre F, Marchesi A, Simonini G, Villani A, Cimaz R, Ravelli A, Taddio A; Rheumatology Study Group of the Italian Pediatric Society. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome-temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. PediatrRheumatol Online J. 2021 Mar 16;19(1):29. doi: 10.1186/s12969-021-00511-7. PMID: 33726806; PMCID: PMC7962084.

6. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, Soma VL, Maddux AB, Mourani PM, Bowens C, Maamari M, Hall MW, Riggs BJ, Giuliano JS Jr, Singh AR, Li S, Kong M, Schuster JE, McLaughlin GE, Schwartz SP, Walker TC, Loftis LL, Hobbs CV, Halasa NB, Doymaz S, Babbitt CJ, Hume JR, Gertz SJ, Irby K, Clouser KN, Cvijanovich NZ, Bradford TT, Smith LS, Heidemann SM, Zackai SP, Wellnitz K, Nofziger RA, Horwitz SM, Carroll RW, Rowan CM, Tarquinio KM, Mack EH, Fitzgerald JC, Coates BM, Jackson AM, Young CC, Son MBF, Patel MM, Newburger JW, Randolph AG; Overcoming COVID-19 Investigators. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021 Mar 16;325(11):1074-1087. doi: 10.1001/jama.2021.2091. PMID: 33625505; PMCID: PMC7905703.

7. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, Roguski K, Wallace B, Prezzato E, Koumans EH, Lee EH, Geevarughese A, Lash MK, Reilly KH, Pulver WP, Thomas D, Feder KA, Hsu KK, Plipat N, Richardson G, Reid H, Lim S, Schmitz A, Pierce T, Hrapcak S, Datta D, Morris SB, Clarke K, Belay E; California MIS-C Response Team. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1074-1080. doi: 10.15585/mmwr.mm6932e2. Erratum in: MMWR Morb Mortal Wkly Rep. 2020 Sep 04;69(35):1229. PMID: 32790663; PMCID: PMC7440126.

8. Holm M, Hartling UB, Schmidt LS, Glenthøj JP, Kruse A, Rytter MH, Lindhard MS, Lawaetz MC, Zaharov T, Petersen JJ, Andersen RM, Lemvik G, Marcinski P, Thaarup J, Jensen LH, Borch L, Nielsen AB, Vissing NH, Schmiegelow K, Nygaard U. Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus 2. Acta Paediatr. 2021 Sep;110(9):2581-2583. doi: 10.1111/apa.15985. Epub 2021 Jun 28. PMID: 34129731; PMCID: PMC8444758.

9. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021 Jul;180(7):2019-2034. doi: 10.1007/s00431-021-03993-5. Epub 2021 Feb 18. PMID: 33599835; PMCID: PMC7890544.

10. Hwang M, Wilson K, Wendt L, Pohlman J, Densmore E, Kaeppler C, Van Arendonk K, Yale S. The Great Gut Mimicker: A case report of MIS-C and appendicitis clinical presentation overlap in a teenage patient. BMC Pediatr. 2021 Jun 1;21(1):258. doi: 10.1186/s12887-021-02724-x. PMID: 34074244; PMCID: PMC8167300.

11. Jackson RJ, Chavarria HD, Hacking SM. A Case of Multisystem Inflammatory Syndrome in Children Mimicking Acute Appendicitis in a COVID-19 Pandemic Area. Cureus. 2020 Sep 29;12(9):e10722. doi: 10.7759/cureus.10722. PMID: 33145128; PMCID: PMC7599036.

12. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr. 2020 Jun;10(6):537-540. doi: 10.1542/hpeds.2020-0123. Epub 2020 Apr 7. PMID: 32265235.

13. Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. N Engl J Med. 2020 Jul 23;383(4):393-395. doi: 10.1056/NEJMe2023158. Epub 2020 Jun 29. PMID: 32598829; PMCID: PMC7346677.

14. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. (2020) 109:1088–95. doi: 10.1111/apa.15270

15. Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. J Clin Virol. 2020 Jul;128:104395. doi: 10.1016/j.jcv.2020.104395. Epub 2020 May 8. PMID: 32417675; PMCID: PMC7207144.

16. Olmos García JM, Pareja Marín F, Martínez Bayo Á, Silvestre Beneyto R, Escrivá Tomás P. Apendicitisagudaenniños con síndromeinflamatoriomultisistémicopediátricoasociado a SARS-CoV-2 (SIM-PedS). Una complicación a considerar [Acute appendicitis in children with multisystemic inflammatory syndrome associated to SARS-CoV-2 (MIS-C). A complication to consider]. An Pediatr (Barc). 2021 Jun 1:S1695-4033(21)00203-4. Spanish. doi: 10.1016/j.anpedi.2021.05.015. Epub ahead of print. PMID: 34183280.

17. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, Bensaid P, Pichard S, Kouider H, Morelle G, Craiu I, Pondarre C, Deho A, Maroni A, Oualha M, Amoura Z, Haroche J, Chommeloux J, Bajolle F, Beyler C, Bonacorsi S, Carcelain G, Koné-Paut I, Bader-Meunier B, Faye A, Meinzer U, Galeotti C, Melki I. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020 Aug;79(8):999-1006. doi: 10.1136/annrheumdis-2020-217960. Epub 2020 Jun 11. PMID: 32527868; PMCID: PMC7299653.

18. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021 Feb;180(2):307-322. doi: 10.1007/s00431-020-03766-6. Epub 2020 Aug 15. PMID: 32803422; PMCID: PMC7429125.

19. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020 Jun 6;395(10239):1771-1778. doi: 10.1016/S0140-6736(20)31103-X. Epub 2020 May 13. PMID: 32410760; PMCID: PMC7220177.

20. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herberg J, Burns JC, Lyall H, Levin M; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020 Jul 21;324(3):259-269. doi: 10.1001/jama.2020.10369. PMID: 32511692; PMCID: PMC7281356.

21. Yonker LM, Gilboa T, Ogata AF, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. J Clin Invest. 2021;131(14):e149633. doi:10.1172/JCI149633

22. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270-273. doi: 10.1038/s41586-020-2012-7. Epub 2020 Feb 3. PMID: 32015507; PMCID: PMC7095418.

DOI 10.25789/YMJ.2022.79.16

УДК 616.12; 578.834.1

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POSTCOVID CARDIOMETABOLIC DISORDERS IN RESIDENTS OF YAKUTSK

A pilot single-stage study of residents of Yakutsk, attached to the YSC CMP Clinic, with a history of new coronavirus infection COVID-19 in the period from March to December 2020 (1st and 2nd waves of the pandemic) was conducted. 2 groups of 80 people from 30 to 59 years old were formed, which were divided according to the time of infection with COVID-19. The 1st group included patients with a postcovid period from 3 to 6 months, in the 2nd - from 7 to 11 months. The analysis revealed a high frequency of cardiometabolic disorders, in particular hypertension, obesity and metabolic syndrome. Men had a more severe course of infection, both in the first and in the second wave of the pandemic. The relationship between blood pressure, body mass index, waist circumference and blood triglyceride levels with the severity of the disease is presented.

Keywords: COVID-19, Yakutsk residents, obesity, arterial hypertension, metabolic syndrome.

Metabolic syndrome, described in the second half of the 20th century, increases the risk of death from cardiovascular pathology and has been named by WHO experts as a "pandemic of the 21st century" [11]. Since the end of 2019, the whole world has been gripped by the protracted pandemic of the new coronavirus infection COVID-19. During the first studies of COVID-19, scientists have already proven the risk of developing more severe manifestations and deaths from it in combination with cardiovascular pathology, including metabolic syndrome [4; 7;9;10;12;17;20;23]. Our study covered the period of the first and second waves of the COVID-19 pandemic. The analysis of the epidemiological situation during the second wave of the pandemic showed a significant increase in morbidity and mortality both worldwide and in the Russian Federation [1;15;18]. During this period, the Eurasian International Registry ACTIVE noted an increase in newly detected cardiovascular pathology after 4-6 months [3]. An earlier study of cardiovascular pathology in residents of Yakutsk who had a new coronavirus infection showed a high incidence of arterial hypertension (AH) (59.6%), coronary heart disease (CHD) (16.8%), type 2 diabetes mellitus (14.3%) [2]. The state of health of people who have had COVID-19 requires detailed monitoring, because the infection, acting on the proinflammatory and prothrombotic status of patients, caused the appearance or progression of the existing pathology. The study of the state of health in the postcovid period, in particular the detection of cardiometabolic disorders, is relevant and requires detailed study and monitoring.

The aim of the research was to study cardiometabolic disorders in residents of Yakutsk who suffered a new coronavirus infection COVID-19.

Materials and methods of research. In March 2021, a pilot single-stage study of residents of Yakutsk, attached to the Clinic of the YSC CMP with a history of new coronavirus infection COVID-19 in the period from March to December 2020 (1st and 2nd waves of the pandemic) was conducted. A total of 161 people were studied. The response rate was 76%. Out of these, 2 groups of 80 people from 30 to 59 years old were formed, which were divided according to the time of infection with COVID-19. The median age was 43 [39, 55] years in men, 47 [41, 54] years in women.

The 1st group included patients with a postcovid period from 3 to 6 months - 20 men and 20 women comparable in age, that were infected during the second wave of the COVID-19 pandemic;

In the 2nd group - 20 men and 20 women comparable in age, with a postcovid period from 7 to 11 months, that were infected during the first wave of the COVID-19 pandemic;

Inclusion criteria: adult population of Yakutsk from 30 to 59 years old, attached to the Clinic of the YSC CMP, a history of COVID-19 disease, informed consent to the study.

Exclusion criteria: malignant neoplasms, acute infectious diseases, exacerbations of chronic diseases, acute myocardial infarction, acute cerebrovascular accident, type 2 diabetes mellitus.

The examination program included: a questionnaire survey to assess symptoms and quality of life, an anthropometric study measuring height, weight, waist (WC) and hips circumference, rest ECG, spirometry, blood sampling from the ulnar vein in the morning on an empty stomach for clinical, biochemical and immunological studies, clinical examination by a cardiologist and a hospitalist. The measurement of blood pressure (BP) was carried out by an automatic tonometer "OMRON M2 Basic" (Japan) twice in while sitting with the calculation of average blood pressure with a limit of permissible measurement error of ± 3 mm Hg. Informed consent was obtained from all participants of the study to conduct an examination, questionnaire, and blood collection for further analysis of the results according to the protocol of the Ethics Committee of the YSC CMP (Protocol No. 52 of 03/24/2021).

The body mass index (BMI) or Quetelet II index was calculated using the formula: BMI (kg/m2) = body weight (kg)/ height (m2). BMI values of ≥25 and <30 kg/m2 were taken as overweight, obesity was recorded at a BMI of ≥30 kg/m2 [6].

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM) ≥ 80 cm on women, ≥94 cm on (VNOK, 2009).

The blood pressure level of ≥140/90 mmHg or the use of antihypertensive drugs was taken for hypertension. According to degrees of severity, they were divided into: stage 1 AH - BP 140-159/90-99 mm Hg, stage 2 AH - BP 160-179/100/109 mmHg, stage 3 AH - BP ≥180/≥110 mmHg [4].

Laboratory methods of the research included analysis of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL Cholesterol), low-density lipoprotein cholesterol (LDL Cholesterol), very low-density lipoprotein cholesterol (VHDL Cholesterol), levels glucose.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the VII revision of Society of cardiology of Russian Federation, 2020, into account the European recommenda-

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tions, 2019. Hypercholesterolemia (HCS) is the level of TC ≥ 5,0 mmol/l (190 mg/dl) taking into account the risk of cardiovascular death on the SCORE scale, the high LDL Cholesterol level >3,0 mmol/l (115 mg/dl) with low, > 2.6 mmol/l with moderate, >1,8 mmol/l with high, > 1,4 mmol/l with very high and extreme risk, the low HDL Cholesterol level <1,0 mmol/l on men; <1,2 mmol/l on women, the hypertriglyceridemia (HTG) is the TG level is >1,7 mmol/l. A hyperglycemia (HG) on an empty stomach (a glucose in a blood plasma on an empty stomach > 5,6 mmol/l). Respondents with these disorders also included participants receiving specific medication for these conditions.

Metabolic syndrome (MS) was diagnosed according to the criteria of the RSC (second revision), 2009: the main feature: abdominal obesity (AO) (WC >80 cm in women, >94 cm in men); additional criteria: hypertension (BP >130/85 mmHg), TG level ≥1.7 mmol/l; HDL-C level <1.0 mmol/l in men; <1.2 mmol/l in women; LDL-C level >3.0 mmol/l; fasting hyperglycemia (fasting plasma glucose ≥ 6.1 mmol/L) or impaired glucose tolerance (glucose in blood plasma 2 hours after exercise glucose in the range ≥ 7.8 and ≤11.1 mmol/ l). The presence of the main feature and 2 additional criteria serves as the basis for the diagnosis of MS.

The degree of lung damage and its severity were assessed according to the results of computer tomography (CT): CT-0 – absence of viral pneumonia, CT-1 lung lesions less than 25%, CT-2 – 25-50%, CT-3 – 50-75%, CT-4 >75% lung damage in the form of "ground-glass opacities".

Statistical processing of the results was carried out using the standard SPSS package version 26.0. To characterize the features, the arithmetic mean (M) and the standard error of the mean value of the feature (m), median (Me) and the 25th and 75th quartiles (Q1, Q3) were calculated. When comparing the groups, nonparametric criteria of Mann-Whitney, Kraskel-Wallis, and Pearson were used. To assess the relative risk, the odds ratio was used with a 95% confidence interval. The correlation analysis was carried out using the Spearman coefficient. The differences were considered statistically significant at p<0.05.

Results and discussion. The severity of the new coronavirus infection was interpreted by us according to the CT of the lungs available in outpatient charts or extracts from the medical history.

Of the 80 examined persons, the largest number (41.3%) had a mild infection with CT-1 lung lesion.There were no respondents in this age group with the most severe CT picture (CT-4). Their characteristics according to the severity of the disease (CT picture) are presented in Table.

Comparing the groups by the duration of the postcovid period, a more severe course of the disease in group 1 (wave II) was noted , there was an increase in the number of patients with more severe lung damage in this group up to 30% of the total. In group 2 (wave I), the largest number of patients underwent COVID-19 in a milder form (CT-1), accounting for 52.5% of the total number of study participants in this group.

A comparative analysis of the degree of lung damage by gender showed that men had more severe lung damage in COVID-19 compared to women, mainly due to group 1, patients with a postcovid period up to 6 months, infected in the second wave of the pandemic (Fig.). The women had a relatively mild course of the disease.

Of the total number of patients with COVID-19, 26 or 32.5% were hospitalized, 54 people (67.5%) were outpatient (p=0.004). Comparing the groups of the postcovid period, we obtained the following results. In group 1, the number of hospitalized patients was 37.5% of the total, in group 2 - 27.5%, no significant differences were found (χ 2=0.912, p=0.340). The largest number of hospitalized patients in group 1 is probably due to the more severe course of infection and the more well-established work of the healthcare system during the second wave of the pandemic.

In the postcovid period up to a year, newly diagnosed cardiovascular diseases were registered in 12 study participants, which was 15%, equally often, both in the group of up to 6 months (15%) and from 7 to 11 months (15%). According to the research data of the international registry "Analysis of the dynamics of comorbid diseases in patients infected with SARS-CoV-2 (ACTIVE SARS-CoV-2)", which included 7 countries besides the Russian Federation, "new" diseases were most often detected in patients aged 49-50 years [3]. Our data explain the high percentage of disease detection by the younger average age of the study participants.

Hypertension was registered in 43.8% of the examined individuals of both groups, its highest frequency was observed in hospitalized patients, hypertension was registered in almost half of the cases - 47.2%, in outpatient patients slightly less - 42.7%, there was no statistical difference (OR 1.15 [95% CI 0.45-2.96], p=0.764). Comparing the occurrence of hypertension by groups, we found that in the 1st group of study participants, hypertension was recorded in almost half of the patients - 47.5%, in the 2nd - 40% (χ 2=0.457, p=0.499). Our data are consistent with the data of the ACTIVE registry, which included 5808 patients from the Russian Federation, the republics of Belarus, Armenia, Kazakhstan and Kyrgyzstan [5]. The study of the relationship of systolic BP (SBP) with the severity of the infection by CT of the lungs showed a direct correlation (r=0.400, p=0.000), the higher the SBP indicators, the more severe the new coronavirus infection was. The indicators are lower than in the international registry ACTIVE, where the incidence of hypertension was 58.5%, due to the examination of mostly hospitalized older patients, where the average age was 57.9 [47.67] years [3;4].

The analysis of lipid metabolism disorders in the participants of the pilot study was carried out. In more than half, HCL was detected equally often – 62.5% in group 1 and 65.0% in group 2, there was no statistical difference (p=0.816). Atherogenic HCL was equally frequently registered in both groups - 82.5% and 85.0%, respectively (p=0.762), a reduced level of HDL cholesterol was also detected in more than half of the study participants (62.5% and 67.5%, respectively), there was no significant difference (p=0.639). TG concentrations in group 1 (22.5%) were statistically slightly higher than in group 2 (17.5%) (p=0.576). Fasting HG was equally unreliably frequent in both groups – 22.0% and 28.2%, respectively (p=0.204). The average values of lipids and blood glucose had no statistical difference between the groups.

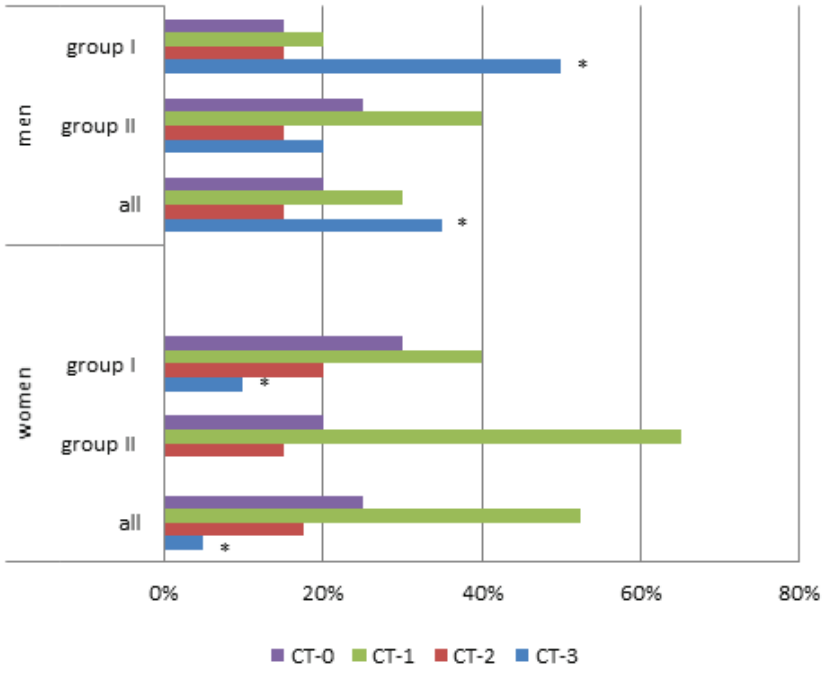
With the severity of the infection (by CT of the lungs) in the postcovid period, an average correlation was revealed only with TG (r=0.314, p=0.005), with the rest of the lipid panel, no significant correlation was found in our study.

Thus, dyslipidemia was equally often observed in both groups of the postcovid period, being one of the components of MS and a risk factor for cardiovascular diseases. This is also confirmed by other researchers [13, 19].

Weight gain after infection was noted by many survey participants: 22.5% - from group 1, 17.5% - from group 2, there was no significant difference (OR 1.36 [95% CI 0.45-4.12] p=0.576). The reason for this was probably quarantine measures during the pandemic, which led to inactivity. Studies by foreign authors also noted an increase in body weight during the pandemic of a new coronavirus infection

Characteristics of patients according to the severity of the disease

CT picture	CT-0	CT-1	CT-2	CT-3	CT-4
	n (%)				
all	18 (22.5)	33 (41.3)	13 (16.3)	16 (20.0)	0
group I	9 (22.5)	12 (30.0)	7 (17.5)	12 (30.0)	0
group II	9 (22.5)	21 (52.5)	6 (15.0)	4 (10.0)	0
P_{I-II}	нд	0.044	нд	0.0282	



Gender characteristics of patients on CT lung * - p<0,05

[14]. The correlation analysis of BMI with the severity of the infection showed a statistically significant relationship between BMI and CT picture (r=0.406, p=0.000). According to BMI , 28 people (35%) were overweight, 29 people (36.3%) were obese. Our data are consistent with the International Registry of ACTIVE SARS-CoV-2, where 35.54% of 5808 patients were obese [5], and meta-analysis also showed that obese patients had a more severe course of SARS-CoV2 (OR = 2.31; 95% CI, 1,3-4,12) [8;16;22]. A comparative analysis of overweight and obesity in groups 1 and 2 showed that the incidence of overweight and obesity was higher in the group with a postcovid period of up to 6 months (n=32 or 80% of the total number in the group), when in group 2 there were 25 people or 62.5%, respectively (OR 2.40 [95% CI 0.87-6.55] p=0.08).

AO is the main component of MS, it affects, to a certain degree, the development of hypertension and type 2 diabetes mellitus. The frequency of occurrence of AO in the total sample was 65%. Higher frequency of AO was observed in men (72.5%) rather than in women (57.5%), there were no statistically significant differences (OR 1.94 [95% CI 0.76-4.96] p=0.241). A strong correlation was found between WC and the degree of lung damage in COVID-19 (r=0.452, p= 0.000), the greater the WC, the more severe the course of the disease.

The frequency of MS according to the criteria of the RSC in the general sample was more than half - 56.3%. In gender comparison, the incidence of this syndrome in men is slightly higher compared to women (n=25 or 62.5%; n=20 or 50%, respectively), the results did not differ significantly (OR 1.66 [95%CI 0.68-4.06] p=0.260). Higher incidence of AO and MS explains the relatively severe course of COVID-19 in men compared to women. There was also no significant difference when comparing between the groups for the postcovid period. Among COVID-19 patients receiving inpatient treatment, MS occurred in 42.3% of the total number of hospitalized, in contrast to outpatients, among whom MS was registered in more than half (63.0%) (p=0.08). Higher incidence of MS in outpatient patients may be due to the high prevalence of the syndrome in the general urban population. We also did not obtain a significant correlation with MS from the degree of lung damage according to the CT picture (r=0.109, p=0.334). This is due to the fact that our pilot study included a small sample with an age limit of up to 69 years, among which there were no persons with extremely severe lung damage (CT-4). However, the results of numerous studies confirm the negative impact of MS on the severity of viral infection [7;9;10;17;20;23].

Conclusion. A survey of residents of Yakutsk who had a history of a new coronavirus infection in the first two waves of the pandemic showed a high prevalence of cardiometabolic disorders, in particular hypertension, obesity and metabolic syndrome. The most unfavorable course of COVID-19 was in the participants of the pilot study that got infected during the second wave of the pandemic. When comparing by gender, men were the most vulnerable to the disease - they had a more severe manifestation of the disease, both in the first and in the second wave of the pandemic. The relationship of blood pressure, body mass index, waist circumference and blood triglyceride levels with a more severe course of a new coronavirus infection in the anamnesis was presented.

It can be acknowledged that the pandemic has provoked a new wave of obesity and metabolic syndrome, as a consequence of stress, depression, deviant behavior and low physical activity during quarantine measures, which may soon cause a surge in the incidence of cardiovascular pathology and as a consequence of mortality from cardiovascular complications and diabetes mellitus. In the future, it is necessary to develop measures for broad medical examination, telehealth consultations, and make an emphasis on reducing modifiable risk factors for cardiovascular diseases in order to prevent premature deaths from diseases of the circulatory system.

Reference

1. Popova T.E., Tikhonova O.G., Romanova A.N., et al. Analiz epidemiologicheskoj situacii po COVID-19: vtoraya volna [Analysis of the epidemiological situation on COVID-19: the second wave]. Yakut medical journal. 2021; 1: 61-64. (In Russ.).] Doi:10/25789/YMJ.2021.73.17

2. Sofronova S.I., Nikolaev V.M., Kononova I.V., et al. Kardiovaskulyarnaya patologiya i COVID-19 u zhitelej g. YAkutska [Cardiovascular pathology and COVID-19 in residents of Yakutsk]. Yakut Medical Journal. 2022;1:90-

93. (In Russ.).] Doi:10.25789/YMJ.2022.77.23

3. Arutyunov G.P., Tarlovskaya E.I., Arutyunov A.G., et al. Klinicheskie osobennosti postkovidnogo perioda. Rezul'taty mezhdunarodnogo registra «Analiz dinamiki komorbidnyh zabolevanij u pacientov, perenesshih inficirovanie SARS-CoV-2 (AKTIV SARS-CoV-2)». Predvaritel'nye dannye (6 mesyacev nablyudeniya) [Clinical features of the post-COVID period. Results of the international registry "Analysis of the dynamics of comorbid diseases in patients who have undergone SARS-CoV-2 infection (SARS-CoV-2 ACTIVE)". Preliminary data (6 months of follow-up)]. Rossijskij kardiologicheskij zhurnal [Russian Cardiologic Journal. 2021; 10: 86-98. (In Russ.).] Doi: 10/15829/1560-4071-2021-4708

4. Arutyunov G.P., Tarlovskaya E.I., Arutyunov AG, et al. Mezhdunarodnyj registr "Analiz dinamiki komorbidnyh zabolevanij u pacientov,perenesshih inficirovanie SARS-CoV-2 (AKTIV SARS-CoV-2)": analiz 1000 pacientov [International registry "Analysis of the dynamics of comorbid diseases in patients who have undergone SARS-CoV-2 infection (SARS-CoV-2 ACTIVE)": analysis of 1000 patients]. Rossijskij kardiologicheskij zhurnal [Russian Cardiologic Journal. 2020; 11(25): 98-107. (In Russ.).] doi:10.15829/1560-4071-2020-4165

5. Arutyunov G.P., Tarlovskaya E.I., Arutyunov A.G., et al. Mezhdunarodnyj registr "Analiz dinamiki komorbidnyh zabolevanij u pacientov, perenesshih inficirovanie SARS-CoV-2" (AKTIV SARS-CoV-2): analiz prediktorov neblagopriyatnyh iskhodov ostroj stadii novoj koronavirusnoj infekcii [International register "Dynamics analysis of comorbidities in SARS-COV-2 survivors" (AKTIV SARS-COV-2): Analysis of predictors of short-term adverse outcomes in COVID-19]. Rossijskij kardiologicheskij zhurna [Russian Cardiologic Journal. l. 2021; 4(26): 116-131. (In Russ.).] doi:10.15829/1560-4071-2021-4470

6. Dedov I.I., Melnichenko G.A., Shestakova M.V. et al. Nacional'nye klinicheskie rekomendacii po lecheniyu morbidnogo ozhireniya u vzroslyh. 3-ij peresmotr [National clinical guidelines for the treatment of morbid obesity in adults. 3rd revision]. Ozhirenie i metabolism [Obesity and Metabolism. 2018; 15(1): 53-70 (In Russ.).]

7. Bae S, Kim SR, Kim M.-N, et al. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID 19 according to age: a systematic review and meta-analysis. Heart 2021; 107(5): 373–380, https://doi.org/10.1136/ heartjnl 2020–317901

8. Chu Y, Yang J, Shi J, et al. Obesity is associated with increased severity of disease in COVID-19 pneumonia: a systematic review and meta-analysis. Eur J Med Res. 2020 Dec 2;25(1):64. doi: 10.1186/s40001-020-00464-9

9. Denson JL, Gillet AS, Zu Y, et al. Metabolic Syndrome and Acute Respiratory Distress Syndrome in Hospitalized Patients With COVID-19 // JAMA Netw Open. 2021 Dec 1;4(12):e2140568. doi: 10.1001/jamanetworkopen.2021.40568

10. Giorgi AD, Fabbian F, Greco S, et al. Prediction of in-hospital mortality of patients with SARS-CoV 2 infection by comorbidity indexes: an Italian internal medicine single center study. Eur Rev Med Pharmacol Sci 2020; 24(19): 10258–10266, https://doi.org/10.26355/ eurrev_202010_23250.

11. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 2004; 89(6): 2595–600. https://doi.org/10.1210/jc.2004–0372.

12. Hidekatsu Y. Metabolic Syndrome and COVID-19 // Cardiol Res. 2020;11(6):360-365. https://doi.org/10.14740/cr1181

13. Kočar E, Rezen T, Rožman D. Cholesterol, lipoproteins, and COVID 19: basic concepts and clinical applications. Biochim Biophys Acta Mol Cell Biol Lipids 2021; 1866(2): 158849, https://doi. org/10.1016/j.bbalip.2020.158849

14. Manent JR, Jané BA, Cortés PS, et al. Impact of COVID-19 Lockdown on Anthropometric Variables, Blood Pressure, and Glucose and Lipid Profile in Healthy Adults: A before and after Pandemic Lockdown Longitudinal Study // Nutrients. 2022 Mar 15;14(6):1237. doi: 10.3390/nu14061237.

15. Petrov AN, Welford M, Golosov N.et al. The "second wave" of the COVID-19 pandemic in the Arctic: regional and temporal dynamics // Int J Circumpolar Health. 2021 Dec;80(1):1925446. doi: 10.1080/22423982.2021.1925446.

16. Pranata R, Lim MA, Yonas E, et al. Body mass index and outcome in patients with COVID-19: A dose-response meta-analysis / Diabetes Metab. 2021 Mar;47(2):101178. doi: 10.1016/j.diabet.2020.07.005

17. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID 19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol 2020; 127: 104354, https://doi.org/ 10.1016/j.jcv.2020.104354.

18. Shukla D, Bhadoria S, Bansal M, Changulani R. Evolution of the pandemic: Analysis of demographic characteristics of COVID-19-infected patients during its two waves in Gwalior district of central India // J Family Med Prim Care. 2022 Apr;11(4):1314-1321. doi: 10.4103/jfmpc.jfmpc_1189_21.

19. Surma S, Banach M, Lewek J. COVID 19 and lipids. The role of lipid disorders and statin use in the prognosis of patients with SARS-CoV 2 infection. Lipids Health Dis 2021; 20(1): 141, https://doi. org/10.1186/s12944–021–01563–0.

20. Wang J, Zhu L, Liu L, et al. Clinical features and prognosis of COVID 19 patients with metabolic syndrome: a multicenter, retrospective study. Med Clin (Barc) 2021; S0025–7753(21)00320–1, https://doi.org/10.1016/j.medcli.2021.05.014.

21. Williams B, Mancia G, Spierin W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) // European Heart Journal, Volume 39, Issue 33, 01 September 2018, Pages 3021–3104, https://doi.org/10.1093/eurheartj/ehy339

22. Yang J., Hu J., Zhu C. Obesity aggravates COVID 19: a systematic review and meta-analysis. J Med Virol 2020; 93(1): 257–261, https://doi.org/10.1002/jmv.26237.

23. Zuin M, Rigatelli G, Zuliani G, et al. Arterial hypertension and risk of death in patients with COVID 19 infection: systematic review and meta-analysis. J Infect 2020; 81(1): e84 e86, https://doi.org/10.1016/j.jinf.2020.03.059.

DOI 10.25789/YMJ.2022.79.17

УДК 159.963.2; 591.481.3

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EVALUATION OF MELATONIN LEVELS AFTER COVID-19 IN YAKUTSK RESIDENTS

The article presents the results of assessing the level of melatonin after Covid-19 in residents of Yakutsk. It was found that after the coronavirus infection, there is a decrease in the level of melatonin. Coronavirus infection affects the production of melatonin, which subsequently leads to disruption of vital rhythms.

Keywords: melatonin, Covid-19, anxiety, depression, insomnia.

Introduction. The COVID-19 pandemic has increased the number of patients suffering from insomnia. Sleep disturbance is an unfavorable prognostic factor in infections [9, 12]. The quality and duration of sleep play a key role in maintaining a person's physical and mental health. In turn, lack of sleep and psychoemotional disorders are risk factors and contribute to the emergence of serious diseases, including depression, stroke, chronic inflammation, cancer, as well as insufficient immune defense and individual predisposition to infectious diseases with an unfavorable outcome [13]. Sleep disturbance is directly related to a decrease in the production of melatonin (MT) in the human body.

Melatonin is a multifunctional hormone with diverse biological effects, such as immunomodulatory, antioxidant, geroprotective, anti-inflammatory, synchronization of circadian and seasonal rhythms [1].

Melatonin is a molecule that reduces overreaction of the innate immune response and excess inflammation, promoting adaptive immune activity. In addition, melatonin is an endogenous molecule produced in small amounts, the synthesis of which decreases with age. Anderson G., Reiter R.[4] and Zhang R. et al. [18] data from their studies confirm the positive use of melatonin preparations in patients with COVID-19.

Zambrelli E. et al. noted that melatonin at doses up to 10 mg is safe in patients in intensive care units, and it should be used for the prevention and treatment of sleep and psychoemotional disorders in COVID-19 [17]. It may also play a role in the treatment of "long-term COVID-19" patients experiencing similar conditions [11].

Some studies also mention the benefits of melatonin in the treatment of COVID-19. MT can reduce pulmonary fibrosis, which is a serious complication of COVID-19 [18, 15].

The aim of the study was to assess the level of melatonin in the urine of patients who recovered from COVID-19 in Yakutsk.

Material and research methods. The study involved 80 residents of Yakutsk aged 20 to 72 who had recovered from COVID-19. Of these, 40 women, 40 men. The mean age was 51.07±0.97 years. To determine melatonin, a urine test was taken once.

Informed consent for the study was obtained from all study participants (protocol of the local ethical committee of the Yakut Scientific Center for Complex Medical Problems No. 52 dated March 24, 2021). All examined persons had extracts with the data of biochemical, morphological blood analysis and computed tomography. An oral survey was conducted with all the examined, and a questionnaire was filled out on the state of health, sleep, and a test on the HADS anxiety and depression scale was also taken.

The determination of melatonin concentration in urine was carried out using the Melatonin-SulfateUrine ELISA kit (IBL international, Germany), by the method of three-phase enzyme immunoassay on a Uniplan photometer (Russia) at the Laboratory of Immunology and Biochemistry of the YSC KMP. Reference values

Table 1

Concentration of melatonin in urine depending on the statute of limitations of COVID-19 and computed tomography of the lungs

CT degree/term. months	Melatonin. average values	p
1/ 6	46.64± 8.86	<0.010
1/ 9	19.49± 3.17	
1 /6	46.64±8.86	<0.025
3 /6	22.95±4.15	

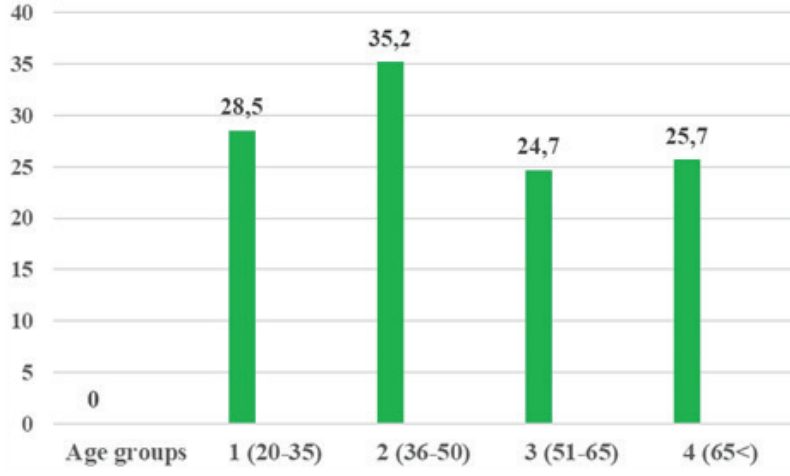

Fig. 1. Melatonin levels depending on age in recovered COVID-19 patients

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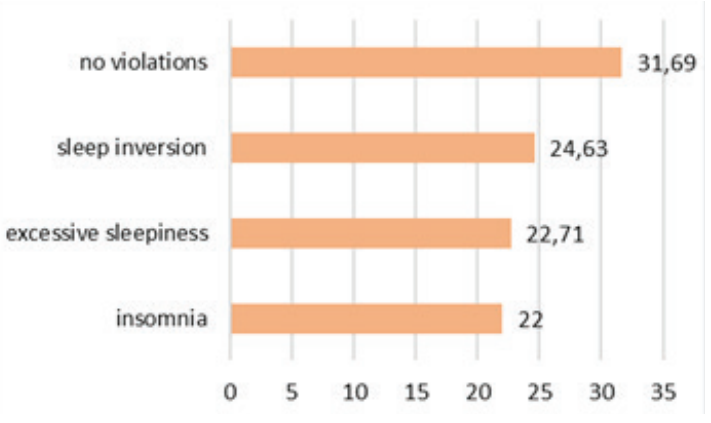

Fig. 2. Level of melatonin depending on the disturbance of vital activity rhythms, (ng/ml)

Table 2

Melatonin concentration depending on gender

	Gender	
	Men	Woman
Normal (n/%)	20/52,6	19/46,3
Above normal (n/%)	10/26,3	9/22,0
Below normal (n/%)	8/21,1	13/31,7
$\chi 2$ Pearson =1,166, p< 0,558		

Note. CT - computed tomography, 2 - after 6 months, 3 - after 9 months. transferred COVID-19.

for melatonin in human urine are in the range of 7.5-58.1 ng/ml.

Statistical processing of our own research results was carried out using the Microsoft Excel application package and the IBM SPSS Statistics 24 statistical program. The initial quantitative variables are presented as a median with an interquartile range (25-75%). Statistical significance of differences determined by Student's t-test and ANOVA for independent groups. The critical value of the level of statistical significance of differences (p) was taken equal to 5%.

Results and discussion. In our study, we assessed the effect of the level of lung damage and recovery time on the concentration of melatonin in the urine of people who recovered from coronavirus infection. According to our data, the average value of melatonin in the urine, depending on the timing of computed tomography, shows that people who have recovered from coronavirus infection begin to experience a decrease in melatonin concentration after 9 months. from the beginning of the disease (Table 1). We also observe that the degree of lung damage significantly affects the production of melatonin in Covid-19: the higher the degree of lung damage (CT grade 3) ($p<0.025$), the less melatonin is produced in the body. The data obtained can probably be explained by the duration of the effect of the virus on the body. There are studies that have shown that coronavirus infection has a long recovery period after recovery [11].

It is known that melatonin levels decrease with age, so older people are more likely to suffer from insufficient melatonin production [7]. According to our data, the level of melatonin in residents of Yakutsk, regardless of age, was within the normal range. The highest concentration of melatonin was in the age group of 36-50 years, the lowest in the group of 51-65 years (Fig. 1). The trend of decreasing levels of melatonin in the body with age in older people continues.

We also examined the content of melatonin depending on gender. Table 2 shows that there is a tendency for an increase in the concentration of MT in the urine in men - 52.6% and a decrease in women - 42.3%. We can explain this fact by the fact that women are more sensitive at the psycho-emotional level than men.

The relationship of rhythm disturbances with anxiety disorders is noted when the onset of an anxiety disorder precedes the onset of sleep disorders. From the data obtained, we found that in residents who had a coronavirus infection and noted in the questionnaire a complaint about a violation of the rhythms of life - insomnia, the concentration of melatonin decreased by 1.4 times, with excessive drowsiness and sleep inversion by 1.2

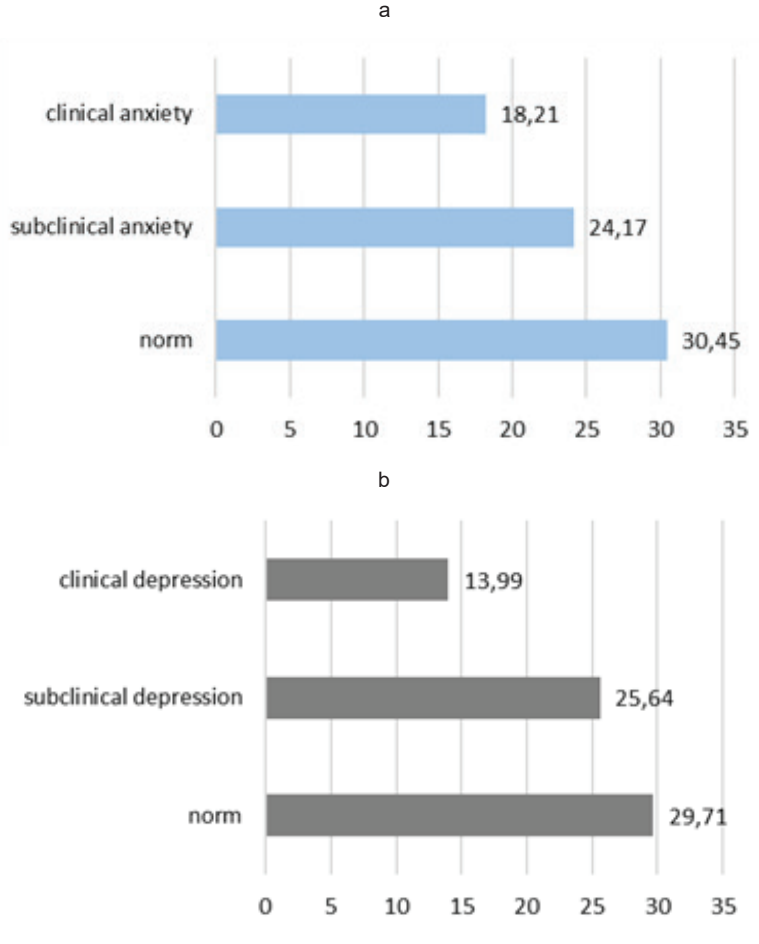

Fig. 3. Melatonin concentration on the HADS scale depending on: a - state of anxiety, b - state of depression, ng/ml

and 1.3 times, respectively, in comparison with the group - without sleep disturbance (Fig. 2). The results obtained showed that when the body is exposed to Covid-19, the level of melatonin decreases, which can lead to some changes in the functioning of the central nervous system (CNS) [11].

The main sleep disorders in people with coronavirus are insomnia (presomnic disorders) and restless legs syndrome. This may be directly related to infection, hypoxia and mental state [5]. According to E. Ibarra-Soronado et al., changes in sleep during illness are a component of the acute phase response that promotes recovery through mechanisms including cytokines and interleukins. The virus can reach the central nervous system through the nasal as well as hematogenous routes. The subsequent secretion of these immunological mediators is accompanied by reactions from the nervous and endocrine systems [6,10]. Also, the cytokine storm, which is an immune response in COVID-19, leads to inflammation and damage to the central nervous system. The SARS-CoV-2 virus mainly affects the prefrontal cortex, basal ganglia, and hypothalamus, i.e., those areas that are involved in sleep regulation [8].

Anxiety disorders are a predisposition to serious consequences in the human body. When interviewing the subjects, it was revealed that during the coronavirus infection, many experienced a sense of anxiety. From the responses to the test on the HADS scale, we obtained the following values: in the normal state, melatonin is 30.45 ng / ml, in patients with subclinical anxiety - 24.17 ng / ml and with clinically expressed anxiety - 18.21 ng / ml. From the data obtained, it can be revealed that there was a tendency for a decrease in the level of melatonin in anxiety disorders of the nervous system during coronavirus infection (Fig. 3).

A decrease in melatonin secretion may be involved in the mechanism of insomnia. Such serious disturbances in the psycho-emotional state of a person can lead to more serious consequences, such as high anxiety and depression. Anxiety spectrum disorders are among the most common consequences of coronavirus on the human psyche. People who are not prone to excessive worries and worries notice that they have begun to take everything to heart, fear for themselves and their loved ones, as well as a second illness. All this leads to a general increase in the anxiety background among the population. Due to constant fear and anxiety, habitual life, a person's sleep are disturbed, which is already reflected in the physical condition [2].

On the HADS scale, the section associated with depression revealed that the level of melatonin was lower in patients with clinically severe and amounted to - 13.99 ng / ml, in subclinically expressed - 25.64 ng / ml, and was equal to 29.71 ng / ml in the norm. (Fig. 4). A number of studies have noted that decreased melatonin levels in patients have been associated with depressive disorders. Melatonin phasic changes are a major feature of most depressive disorders, and low melatonin levels have been described as a "characteristic" of depression [3, 14].

Conclusion. Melatonin is one of the important hormones for regulating the vital activity of the body. When exposed to coronavirus infection on the body, a significant decrease in the secretion of melatonin occurs. The content of melatonin in residents of the city of Yakutsk did not depend on age and was within the reference values. The concentration of melatonin in relation to sex showed that there is a tendency for men to have more MT in the urine than women. Insufficient synthesis of melatonin during Covid-19 leads to disturbances in the rhythms of human life.

Reference

1. Berezova DT. Melatonin: svojstva, bioritmy i vozmozhnosti ispol'zovaniya v medicine [Melatonin: properties, biorhythms and possibilities of use in medicine]. Vladikavkazskij mediko-biologicheskij vestnik [Vladikavkaz Medical and Biological Bulletin. 2012; 23: 127-133. (In Russ.).]

2. Tardov MV, Poluektov MG. Bessonnica pri covid-19 [Insomnia at Covid-19]. Effektivnaya farmakoterapiya [Effective pharmacotherapy]. 2021; 17 (33): 36-41 doi: 10.33978/2307-3586-2021-17-33-36-41 (In Russ.).]

3. Danilov AB, Kurganov Yu.M. Melatonin – unikal'naya molekula? [Melatonin is a unique molecule?] Effektivnaya farmakoterapiya. Nevrologiya i psihiatriya [Effective pharmacotherapy. Neurology and psychiatry. 2013; 1: 26-30. (In Russ.).]

4. Anderson G, Reiter RG. Melatonin: roles in influenza, Covid-19, and other viral infections. Rev Med Virol. (2020) May;30(3):e2109. doi: 10.1002/rmv.2109.

5. Abdelhady A. COVID-19-associated sleep disorders: A case report. Neurobiol Sleep Circadian Rhythms. 2020. Vol. 9, no. 2. P. 3–5. DOI: 10.1016/j.nbscr.2020.100057.

6. Asmundson GJ, Taylor S. Coronaphobia: Fear and the 2019-nCoV outbreak. Journal of Anxiety Disorders. 2020. Vol. 70. P. 10–21. DOI: 10.1016/j.janxdis.2020.102196.

7. Xie Z, Chen F, Li William A, et al. A review of sleep disorders and melatonin. A Journal of Progress in Neurosurgery, Neurology and Neurosciences Volume 39, 2017 - Issue Pages 559-565 doi.org/10.1080/01616412.2017.1315864

8. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. Physiol. Rev. 2019. Vol. 99, No. 10. P. 1325–1380. DOI: 10.1152/physrev.00010.

9. Kolokolov OV, Salina EA, Yudina VV, et al. Infections, pandemics and sleep disorders. S.S. Korsakov J. Neurol Psych. 2021; 121 (4. Iss. 2): 68-74. doi: 10.17116/jnevro202112104268

10. Ibarra-Coronado EG, Pantaleón-Martínez AM. The Bidirectional Relationship between Sleep and Immunity against Infections. J. Immunol Res. 2015; 3 (1): 67–75. DOI: 10.1155/2015/678164

11. Jarrott B, Head R, Pringle KG, et al. "LONG COVID"—A hypothesis forunderstanding the biological basis and pharmacological treatment strategy. Pharmacol Res Perspect. 2022;10:e00911. doi:10.1002/prp2.911

12. Mousavi SA, Heydari K, Mehravaran H, et al. Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial. J Med Virol. 2022 Jan; 94(1): p. 263-271. doi: 10.1002/jmv.27312.

13. Richter K, Kellner S, Hillemacher T, et al. Sleep quality and COVID-19 outcomes: the evidence-based lessons in the framework of predictive, preventive and personalised (3P) medicine EPMA. J. 2021 Jun 8;12(2): p.221-241. doi: 10.1007/s13167-021-00245-2

14. Rubin RT, Heist EK, McGeoy SS, et al. Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. Arch. Gen. Psychiatry. 1992; 49(7): 558–567. DOI: 10.1001/archpsyc.1992.01820070052008

15. Shneider A, Kudriavtsev A, Vakhrusheva A. Can melatonin reduce the severity of COVID-19 pandemic? Int Rev Immunol. 2020; Apr 29: 1-10. doi.org/10.1080/08830185.2020.1756284

16. Zhang R, Zhang R, Wang X, Ni L, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. (2020) 250:11758. doi: 10.1016/j.lfs.2020.117583

17. Zambrelli E, Canevini M, Gambini O, et al. Delirium and sleep disturbances in COVID-19: a possible role for melatonin in hospitalized patients? Sleep Med, 70 (2020 Apr 17), p. 111. doi. org/10.1016/j.sleep.2020.04.006

18. Zhang R, Zhang R, Wang X, Ni L, et al. COVID-19: melatonin as a potential adjuvant treatment. Life Sci, 250 (2020 Jun 1): 1-6. DOI: 10.1016/j.lfs.2020.117583

ARCTIC MEDICINE

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CORRELATION OF BLOOD SERUM TRANSPORT PROTEIN CONTENT OF IMMUNOGLOBULINS OF M, G, A AND E CLASS WITH THE LEVEL OF IMMUNE RESPONSE IN INHABITANTS OF THE ARCTIC ZONE OF THE RUSSIAN FEDERATION

DOI 10.25789/YMJ.2022.79.18
УДК 612.017.1 (470.1)

The paper presents the results of studying of the relationship of serum immunoglobulins (Ig) content of classes M, G, A and E with the level of immune response in residents of the Arctic zone of the Russian Federation. It was found that the average concentration of IgM, IgA and IgE in the peripheral venous blood of the Arctic residents was higher by 1.5-2 times, the registration frequency of elevated levels was higher by 2.4-8.6 times than of the people living in more favorable climatic conditions. Activation of autosensitization processes in Arctic residents is accompanied by a high frequency of recording of increased concentrations of autoantibodies to leukocytes, erythrocytes, ds-DNA, RNP, cardiolipin, oLDL at 10.41-57.14%. In the conditions of the Arctic a significant excessthe concentrations of CIC with IgM and IgA than the complexes with IgG, which indirectly confirms the activation of preventive inflammation responses and the more significant binding ability of secretory antibodies. The increase concentrations of IgM and IgA of the Arctic residents are associated with a decrease in cell-mediated cytotoxicity and with the increase in the level of IFN-γ, sCD71, which increases the efficiency clearance of waste product in hypoxic conditions.

Keywords: immunoglobulins, autoantibodies, immune complexes, neutrophilic granulocytes, cell-mediated cytotoxicity, sCD71, IFN-γ, Arctic.

Introduction. Eating disorders are one of the factors associated with the risk of diseases of the cardiovascular system and digestive organs. As a result of excessive consumption of food, the threat of incompatible foods and loss of tolerance to food antigens increases in humans. The inhabitants of the North have a predominant carbohydrate-lipid type of diet with insufficient intake of vitamins, minerals, dietary fiber, which has a manifestation in the level of disease. Functional nutrition enriched with biological substances that are insufficient in high latitude conditions ensures the normal course of physiological processes in the body and the prevention of diseases [10]. In the conditions of northern latitudes, there is a high risk of developing of non-carcinogenic effects of the development of diseases when using drinking water and local food products containing pollutants from industrial enterprises [8,14]. In modern nutrition, the food of the inhabitants of the North may contain a large number of substances that the body cannot dispose of. Thus, the transport and disposal of exchange products is of the greatest importance.

Immunoglobulins (Ig) are transport structures with enhanced properties for specific interaction with a variety of ligands [18]. IgM, due to its polyreactivity, provides antibacterial, antiviral protection and immunological tolerance, a very small part of them stands out with secrets [12]. Antigenic protection, enhancement of the humoral response, removal of immune complexes in the vascular bed are performed by IgG, while more than 70% of them are in tissues [3,13]. The greatest variety of specific recognition of antigen is characteristic of IgA [19]. The effectiveness of the protection of the mucous membranes of the body is ensured by the presence of several antigen-binding centers and the polyreactivity of sIgA [12]. IgA deficiency is compensated by IgE, which are typical secretory immunoglobulins and appear with prolonged antigenic effects and hypersensitivity [4]. Concentrations of IgA and IgE are concentrated mainly in mucous membranes, secretions and excreta, exudates and transudates [2,17].

The main function of antibodies is the ability to bind cellular antigens and transport a certain substance, substrate, decomposition and metabolism products [3]. The efficiency of transport provision largely depends on the concentration and the total number of transport units. Based on the regulatory levels of immunoglobulins in the blood serum, the concentration of IgG is the highest (74.9%), the content of IgA is 17.4%, the level of IgM is noticeably less and does not usually exceed 10% (7.7%). IgE concentrations are usually quite insignificant (0.001%), but sharply increase with IgA deficiency. It must be assumed that IgG is of primary importance in the transport of waste products, although if we take into account that binding occurs primarily in of areas of inflammation, a significant role in that process is assigned to secretory immunoglobulins.

Most of the population of the Arkhangelsk region lives in the cities of Arkhangelsk, Severodvinsk, Novodvinsk, whose territories are located in the Arctic zone of the Russian Federation (AZRF) and are characterized as an unfavorable zone for living according to the degree of influence of natural conditions. The village of Revda of the Murmansk region (67°56'13" s.w.) belongs to an extremely uncomfortable zone of residence [1] with the functioning of the city-forming Lovozersky mining and processing plant (Lovozersky GOK), whose activities exert an anthropogenic load due pollutionings of drinking water sources and soil [8]. Elevated concentrations of Ni, Cu, Co, Cd and Pb were found in the liver and kidneys of residents of Monchegorsk, Apatity, Olenegorsk, Alakurtti and Lovozero [15].

It was of interest to study the relationship between the content of serum trans-

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port proteins (IgM, IgG, IgA, IgE) and the level of immune reactions in people living in the Arctic zone of the Russian Federation with different natural and climatic living conditions.

Material and methods. The paper presents the results of studying the immunological parameters of 236 people who were practically healthy at the time of the survey, of which 99 people (84.85% of women and 15.15% of men whose age was 48.19 ± 1.66 years) living in the village Revda of the Murmansk region and 137 residents (80.81% of women and 19.19% of men whose age made 48.56 ± 2.68 years) of the Arkhangelsk region. All research was conducted with the consent of the volunteers and in accordance with the requirements of the "World Medical Association's Declaration of Helsinki on the Ethical Principles of Medical Research with the participation of a person as a subject" (1964 with amendments and additions from 2013). The inclusion criteria were residence of the examined persons in the Arctic zone of the Russian Federation: Arkhangelsk and Murmansk regions, voluntary consent to the examination. The type of study is retrospective; the samples are random. For residents of the Arctic (Murmansk Region) comparison groups were subsequently formed: 1) persons with simultaneous IgM and IgA content within the normal range and 2) persons with simultaneously elevated IgM and IgA concentrations (above reference values).

The complex of immunological parameters was including the study of a hemogram, the phagocytic activity of neutrophil of peripheral blood. The number and ratio of hemogram cells were counted in blood smears stained according to the Romanovsky–Giemsa method. The phagocytic activity of neutrophils was determined using the Reacomplex test kit (Russia). Lymphocyte phenotypes (CD3+, CD4+, CD8+, CD10+, CD16+, CD19+, CD25+, CD71+, CD95+, HLADR II) were studied by indirect immunoperoxidase reaction using monoclonal antibodies (Sorbent, Moscow) and flow cytometry using the Epics XL apparatus of Beckman Coulter (USA) reagents "Immunotech a Beckman Coulter Company" (France). The content of IgM, IgG, IgA, IgE ("Seramun Diagnostica GmbH"), free receptor of transferrin sCD71 ("AccBind Elisa Microwells"), intercellular adhesion molecule sCD62L, apoptosis protein sApo-1/Fas, ligand to Fas sFasL, cytokine IFN-γ ("Bender MedSystems"), antibodies to double-stranded DNA (AT to ds-DNA), antinuclear antibodies (AT to RNP), antibodies to cardiolipin and antibodies to oxidized low-density lipoproteins (AT to oLPNP) («Biomedica Gruppe») were studied by enzyme immunoassay. The concentration of circulating immune complexes (CIC) was determined by precipitation using 3.5; 4.0; 7.5% PEG-6000. Reactions were evaluated using an automatic enzyme immunoassay "Evolis" from Bio-RAD (Germany) and a Multiskan MS photometer (Labsystems, Finland). Serum autoantibodies to leukocytes and erythrocytes with registration of titers in log2 were determined in the reactions of leuko- and hemagglutination in preparations of the "thick drop" type at dilution 1/5, 1/20, 1/40, 1/80, 1/60, etc.

The mathematical analysis of the research results was carried out using «Statistica 21.0» software package («StatSoft», USA). The results are presented as the arithmetic mean and the error of the mean (M±m). For comparison between groups, the t-test of independent sampling or the nonparametric Mann-Whitney U-test were used, depending on the condition of subordination or non-subordination of data to the law of normal distribution. The relationship between the content of IgM, IgA and the parameters of the immunological study was analyzed using correlation analysis with determination of Pearson linear correlation coefficients and Spearman rank correlation. The critical significance level (p) was considered to be 0.05.

Results and discussion. The inhabitants of the Arctic, showed the average concentration of IgM, IgA and IgE in peripheral venous blood which was 1.5-2 times higher compared to the persons living in the areas with more favorable climatic conditions (p<0.001) (*figure 1*). The registration frequency of elevated concentrations of IgM (> 1.9 g/l), IgA (> 5.4 g/l), IgE (> 100 MU/ml) was also significantly higher by 2.4-8.6 times, on the contrary, IgG concentrations in 72.3% were below the reference limit. In addition, the residents of the Arkhangelsk region have an IgA deficiency (<1.2 g/l) in 55.6% (p<0.001) (*figure 2*). The concentrations of immune complexes among the inhabitants of the Murmansk region were 1.2-2.2 times higher than among the individuals living in the Arkhangelsk region (p <0.05-0.001) (*figure 3*). Attention is drawn to the significant excess of CIC concentrations with IgA and IgM in Arctic residents, compared with complexes including IgG which indirectly confirms the connection of activation of systemic reactions of the production of secretory classes of immunoglobulins (p<0.001) (*figure 4*).

These results indicate the need for immunoglobulin transport in the blood system. In unfavorable climatic conditions, an increase in the synthesis of antibodies and/or autoantibodies is aimed at specific binding with subsequent transportation of antigenic structures, waste products, even in small concentrations [3]. IgG are of primary importance in the transport of metabolic products and vital activity, although given that the binding occurs primarily in the tissues of trouble areas, secretory, polyreactive immunoglobulins (IgM, IgA) play a significant role in this process. IgM participates in the clearance of cellular antigen, have a much greater activity in 100-1000 times than IgG in the tests of cytolysis and bacteriolysis. The greatest variety of specific antigen recognition of IgA are causes of the variety of molecular forms of IgA and IgA-binding receptors on cells of different histogenesis [6]. An increase in the concentrations of IgM and IgA in the blood of residents of the Arctic is associated with an increase in the content of INF-γ above the refer-

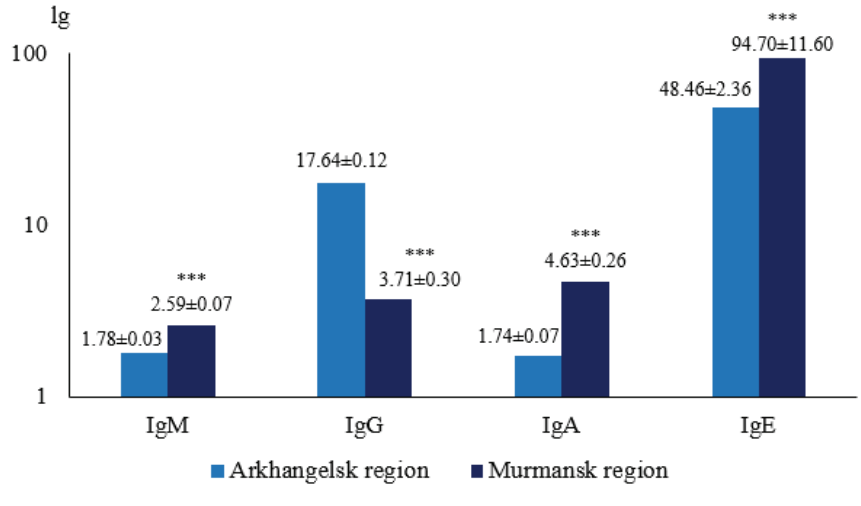

Fig. 1. The average level of immunoglobulins in the inhabitants of the Arkhangelsk and Murmansk regions

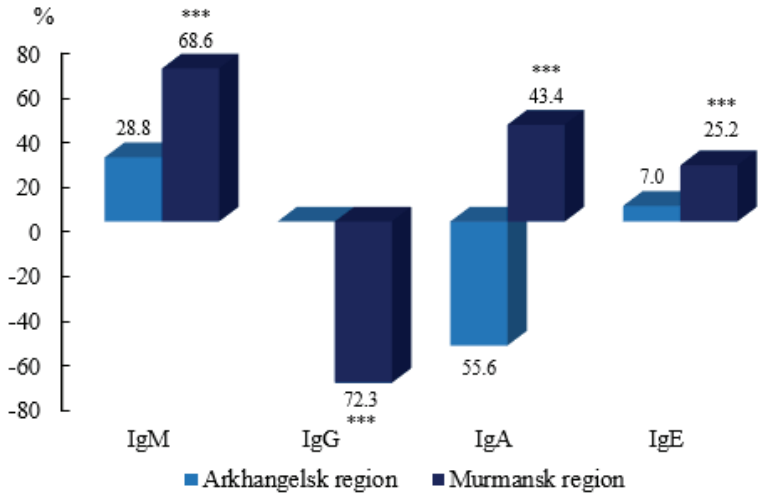

Fig. 2. The frequency of registration of increased and decreased levels of immunoglobulins in residents of the Arkhangelsk and Murmansk regions

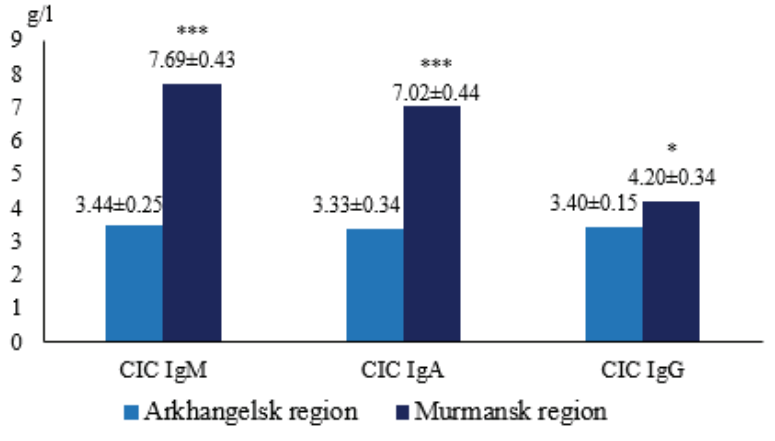

Fig. 3. The average content of immune complexes in residents of the Arkhangelsk and Murmansk regions

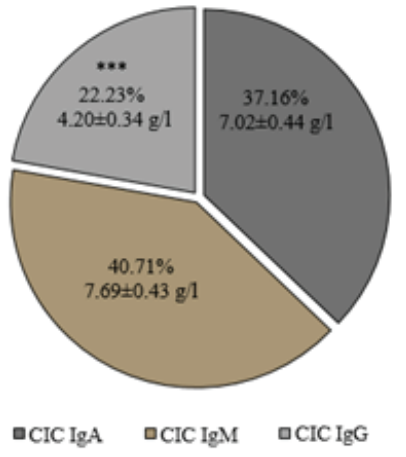

Fig. 4. The frequency of registration of elevated concentrations of CIC IgM, IgA, IgG in residents of the Arctic.

ence limit of the content (>50.0 pg/ml), respectively, from 17.40±4.95 to 73.24±8.21 pg/ml, p<0.001. Under the action of IFN-γ on B-lymphocytes, the synthesis of immunoglobulins (antibodies, autoantibodies) is enhanced.

The high frequency of registration of elevated concentrations of autoantibodies and their diversity in Arctic residents confirms the activation of the process of autosensitization (p <0.01-0.001) (*table 1*). The frequency of elevated levels of autoantibodies depends on the intensity of photoperiodism, the deficit of solar radiation and the increase in the activity of ionomagnetic oscillations. The variety of autoantibodies can mimic their heterospecificity and the possibility of cross-reaction [3].

Simultaneous increase in IgM and IgA concentrations is associated with an increase in the content of neutrophil granulocytes (from 3.23±0.36 to 4.38±0.32×109 cl/l, p <0.001), which is confirmed by a higher frequency of registration of increased concentrations of neutrophils (> 5.5×109 cl/l) in 20.63% of individuals. At the same time, there was no increase in phagocytic activity (48.04±0.76 and 53.52± 0.61%) and an increase in the intensity of phagocytosis by phagocytic number (5.02±0.13 and 5.62± 0.17, conl. units). It can be assumed that an increase in the neutrophil content occurs mainly with an increase in the activity of secretory external exocytosis. Activation and enhancement of external exocytosis of neutrophils is possible with the interaction of immune complexes of a certain valence with FcγRI and with an increase in the expression of genes of receptors to the Fc-fragments of immunoglobulins under the influence of IFN-γ. Serine leukocyte proteases (SLP) released from activated neutrophils modulate expression, activity of cellular receptors and cytokine activity [7]. Under the action of SLP, the proteolytic cleavage of membrane antigens of immunocompetent cells leads to the formation of soluble forms [11].

It was found that an increase in IgM and IgA concentrations was associated with an increase in sCD71 content (from 1464±70 to 2232±90 ng/ml; p<0.05). The level of sCD71 mainly reflects the intensity of erythropoiesis. Hypoxic conditions in the Arctic are widespread. An increase in the intensity of erythropoiesis under hypoxic conditions is aimed at providing tissues with oxygen as a result of HIF-1

Average content and frequency of registration of elevated concentrations of autoantibodies in Arctic residents

	Mean titers and mean levels of antibody	Reference levels	The frequency of registration of elevated concentrations
autoleukoagglutinins. log_2	1.38±0.11	< 1.0	25.26%
autogemagglutinins. log_2	1.46±0.22	< 1.0	14.64%
ds-DNA. MU/ml	81.52±0.71	< 50	57.14%
anti-RNP. MU/ml	2.27±0.65	< 1.0	10.41%
autoantibodies to cardiolipin. U/ml	25.41±0.72	< 10.0	28.26%
autoantibodies to oLDL. mU/ml	242.37±19.60	< 315	16.27%

Note: ds-DNA – autoantibodies to double-stranded DNA, RNP – ribonucleoproteins, oLDL – oxidized-modified low-density lipoproteins.

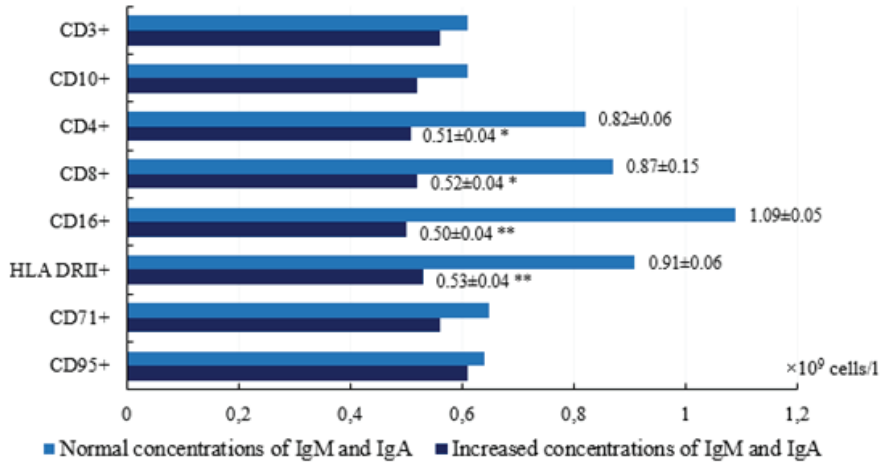

Fig. 5. The content of the main phenotypes of lymphocytes in residents of the Arctic with an increase in the concentrations of IgM and IgA

activation. Activation of HIF-1 is associated with metabolic rearrangements: cells switch to the glycolytic type of metabolism, which is typical for effector lymphocytes and lymphocytes with high cytotoxic activity [16]. In inhabitants of the Arctic, an increase in the content of IgM and IgA is associated with a decrease in the content of T-helpers (CD4+), T-cytotoxic lymphocytes (CD8+), natural killer cells (CD16+), MHC class II molecules (HLA DRII+) ($p < 0.05$-0.01) (*figure 5*), which indicates a decrease in the level of cytotoxic activity of lymphocytes. A decrease in cell-mediated cytotoxicity is quite possible as a result of a compensatory reaction of the priority formation of humoral reactions, including autoimmune ones. Activation of the humoral link of immunity is generally characteristic of northerners [5]. Limitation of the intensity of the immune response can occur when autoantibodies interact with membrane receptors of immunocompetent cells [9]. It is possible that autosensitization is formed against the background of suppression of the differentiation of immunocompetent cells.

Conclusion. Immunoglobulins are transport structures, characterized by high specificity of interaction with the substrate. It was found that the average concentration of IgM, IgA and IgE in the peripheral venous blood of the residents of the Murmansk region was higher by 1.5-2 times and the registration frequency of elevated levels was higher by 2.4-8.6 times than of the people living in more favorable climatic conditions.

Activation of autosensitization processes in Arctic residents is accompanied by a high frequency of recording of increased concentrations of autoantibodies to leukocytes, erythrocytes, ds-DNA, RNP, cardiolipin, oLDL at 10.41-57.14%. The increased content of autoantibodies, immunoglobulins, immune complexes indicates their joint participation in the transport and excretion of antigens. A significant excess of the concentrations of CIC containing IgA and IgM, compared with those including IgG, indirectly confirms the activation of reactions by preventive inflammation and a more significant binding ability of secretory antibodies.

Increased concentrations of IgM and IgA in inhabitants of the Arctic are associated with a decrease in cell-mediated cytotoxicity, which is possible as a result of the priority formation of humoral reactions. Limiting the intensity of cytotoxic activity is possibly aimed at reducing energy-consuming processes at the cellular level to ensure adaptation to hypoxia in the Arctic. Under hypoxic conditions, an increase in the content of sCD71 reflects an increase in the intensity of erythropoiesis by the activation of HIF-1, in the cytokine-mediated regulation of which IFN-γ participates. Under the action of IFN-γ on B-lymphocytes, the synthesis of immunoglobulins is enhanced, on neutrophilic granulocytes - their secretory function, external exocytosis.

Activation of IFN-γ secretion, effector functions of segmented neutrophils, and immunoglobulin synthesis increases the efficiency of clearance of waste products under hypoxic conditions.

The study was performed as a part of the program of fundamental scientific studies of the Laboratory of regulative mechanisms of the immunity on the issue "Mechanisms of interaction of systemic and local immune reactions in persons working in the Arctic (Barentsburg village arch. Svalbard, village Revda and Lovozero of the Murmansk region) " (No. 122011800217-9).

Reference

1. Vinogradova VV. Prirodno-klimaticheskie i bioklimaticheskie usloviya zhizni naseleniya Murmanskoj oblasti [Nature and Bioclimatic Life Conditions of the Population of the Murmansk Oblast]. Izvestiya RAN. Seriya geograficheskaya [Regional Research of Russia. 2015; 6: 90-99 (In Russ.).]

2. Gushchin IS. Fiziologiya immunoglobulina E [Immunoglobulin E (IgE) physiology]. Rossijskij fiziologicheskij zhurnal im. I.M. Sechenova [Russian Journal of Physiology. 2000; 86[3]: 268-279 (In Russ.).]

3. Dobrodeeva LK, Samodova AV, Karyakina OE. Vzaimosvyazi v sisteme immuniteta [Interrelations in the immune system]. Ekaterinburg: publishing house of the Ural branch of the Russian Academy of Sciences, 2014. – 200 p. (In Russ.).]

4. Dobrodeeva LK. Soderzhanie IgE v syvorotke krovi u lyudej, prozhivayushchih na Evropejskoj territorii Rossii [Maintenance immunoglobulin E in whey of blood in norm and pathology at the people living in the European territory of Russia]. Ekologiya cheloveka [Human Ecology. 2010. No. 5. P. 3-10 (In Russ.).]

5. Evseeva IV. Pokazateli immunnogo statusa v dvuh korennyh etnicheskih gruppah Severa [Indicator of two radical ethnic group immune status in the far north]. Ekologiya cheloveka [Human Ecology. 2010. No. 10. P. 37-41 (In Russ.).]

6. Klimovich VB, Samojlovich MP. Immunoglobulin A (IgA) i ego receptory [Immunoglobulin A (IgA) and its receptors. Med. Immunol. 2006; 8[4]: 483-500. (In Russ.).]

7. Kravtsov AL, Shmelkova TP. Sekretornaya degranulyaciya nejtrofilov kak trigger vospaleniya i regulyator immunnogo otveta: rol' serinovyh lejkocitarnyh proteaz i proteoliticheski aktiviruemyh receptorov [Neutrophil secretory degranulation as a trigger of inflammation and regulator of immune response: role of serine leukocyte proteases and protease-activated receptors]. Epidemiologiya i vakcinoprofilaktika [Epidemiology and Vaccinal Prevention. 2011. No. 56. P. 79-87 (In Russ.).]

8. Krasavtseva EA, Sandimirov SS. Sostoyanie vodnyh ob"ektov v zone vliyaniya gorno-pererabatyvayushchih predpriyatij na primere OOO «Lovozerskij GOK» [Voda i ekologiya: problemy resheniya State of water bodies in the area of influence of mining and processing enterprises (case study of Lovozersky mining and processing plant]. Voda i ekologiya: problemy resheniya [Water and Ecology: solution problems. 2021; 2(86): 4-12 (In Russ.).] DOI: 10.23968/2305-3488.2021.26.2.3-13

9. Myagkova MA, Morozova VS. Estestvennye antitela i ih fiziologicheskie funkcii [Nature antibodies and their physiological function]. Immunopatologiya, allergologiya, infektologiya [Immunology, Allergology, Infectology. 2014; 3: 75-81 (In Russ.).] DOI: 10.14427/jipai.2014.3.75.

10. Nikiforova NA, Karapetyan TA, Dorshakova NV. Osobennosti pitaniya zhitelej Severa [Feeding habits of the northerners (literature review)]. Ekologiya cheloveka [Human Ecology]. 2018; 11: 20-22. (In Russ.).]

11. Novikov VV, Baryshnikov AYu, Karaulov AV. Rastvorimye formy membrannyh antigenov kletok immunnoj sistemy [Antigen membrane soluble forms of immune system cells. Immunology. 2007; 4: 249-254 (In Russ.).]

12. Sedykh SE, Buneva VN, Nevinsky GA. Polireaktivnost' prirodnyh antitel. Obmen HL-fragmentami [Polyreactivity of natural antibodies: exchange by HL-fragments]. Biochemistry. 2013; 78 (12): 1651-1669 (In Russ.).]

13. Chuchalin A.G. Bolezni, associirovannye s IgG [Diseases associated with immunoglobulin

G]. Terapevticheskij arhiv [Therapeutic archive. 2018; 3: 4-9 (In Russ.).]

14. Yakovlev E, Druzhinina A, Druzhinin S, et al. Assessment of physical and chemical properties, health risk of trace metals and quality indices of surface waters of the rivers and lakes of the Kola Peninsula (Murmansk Region, North–West Russia). Environmental Geochemistry and Health. 2021. DOI: 10.1007/s10653-021-01027-5

15. Moiseenko TI, Morgunov BA, Gashkina NA, et al. Ecosystem and human health assessment in relation to aquatic environment pollution by heavy metals: Case study of the Murmansk region, northwest of the Kola Peninsula Environmental Research Letters. 2018; 13 (6). DOI: 10.1088/1748-9326/aab5d2

16. Tao JH, Barbi J, Pan F. Hypoxia-inducible factors in T lymphocyte differentiation and function. AJP-Cell Physiol. 2015; 309 (9): 580-589. DOI: 10.1152/ajpcell.00204.2015.

17. Mestecky J, Russell MW, Jackson S, Brown TA. The human IgA system: a reassessment. Clin. Immunol. Immunopathol. 1996; 40 (1): 105–114.

18. Metzger H. Molecular versatility of antibodies. Immunological Reviews. 185: 186-205. DOI: 10.1034/j.1600-065x.2002.18516.x.

19. Tomasi TB, Grey HM. Structure and function of immunoglobulin A. Progress in Allergy. 1972; 16: 81-213.

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ANALYSIS OF Y-CHROMOSOME LINES OF RUSSIAN OLD-RESIDENTS IN THE VILLAGE RUSSKOYE USTYE

DOI 10.25789/YMJ.2022.79.19

УДК 612.017.1(470.21)

Among the indigenous peoples of the Arctic coast of Yakutia (Yukaghirs, Chukchi, Evens, Evenks, Yakuts) there have long been enclaves of Russian old-settlers. The question of their origin remains unclear, but it is assumed that the ancestors of the Russian old settlers moved to the lower reaches of Indigirka in 16th century. To study the population genetic history we have analyzed for the first time Y-chromosome lineages of unrelated men from the village of Russkoe Ustye of Allaikhovsky ulus of the Sakha Republic (Yakutia) (n=12). It was found that more than half (83.4%) of the lineages of the Russkoustinians are characteristic of populations of the Russian North (N3a4, N3a1, R1a, R1b) and only 16.6% are typical for population of Eastern Siberia (C3). The dominance of N3a4-lineages (58.4%) which are absent in the gene pool of indigenous population of North-Eastern Eurasia and found among the northern Russians of the Arkhangelsk and Vologda regions, testifies more in favor of the Pomor hypothesis of the origin of the Russkoustinians.

Keywords: Russian old-settlers, Russkoye Ustye, Y-chromosome, Republic of Sakha, Eastern Siberia.

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Introduction. Russian Arctic old-settlers are the descendants of the first European colonists who settled the northern coast of Eastern Siberia, presumably in the 16th century. Despite the small number, long-term deep isolation from the main Russian population and close interaction with the indigenous peoples of Siberia (Yukaghirs, Chukchis, Evens, Evenks, Yakuts), the Russkoustinians were able to preserve the unique Old Russian culture with their own special dialect with archaisms of the 16th century. [6].

The first mention of the Russian Ustye in the scientific literature is found in the reports of a member of the Great Northern Expedition D.Ya. Laptev in 1739 [1]. According to official data, the first Russian settlements in the delta of the Indigirka River was founded by the Cossacks from the detachment of Ivan Rebrov, who in 1638 built a winter hut, which later became a prison, and then the village of Russkoye Ustye [1]. In 1639, the Cossacks, led by Posnik Ivanov, founded upstream the Indigirka River is the city of Zashiversk, some of whose inhabitants moved to the Russkoye Ustye at the beginning of the 19th century [1], after the abolition of the city in 1805 due to a smallpox epidemic [7]. Despite the fact that 1638 is recognized as the official year of the foundation of the Russkoye Ustye and the Cossacks are considered the founders of the settlement, there are several other hypotheses for the appearance of Russians on the Indigirka River.

According to local legends, the Russkoye Ustye was founded by people from Veliky Novgorod, who arrived in Indigirka in the 1570s along the Northern Sea Route, fleeing the persecution of the guardsmen of Ivan the Terrible [12]. There is also a version according to which the ancestors of the russkoustinians were not Novgorodians, but people from different cities of Russia (Astrakhan, Vyatka, Veliky Ustyug), who fled to Siberia from heavy military service under Ivan the Terrible in the 16th century [4]. According to some legends, the ancestors of the russkoustinians were disgraced boyars exiled to the North, who arrived at the mouth of the Indigirka River by sea on kochi with its own farm [8; 9].

According to one of the modern hypotheses, the inhabitants of Russkoe Ustye are the descendants of Russian navigators (Pomors), who settled the Arctic coast of Eastern Siberia in the 16th century. Archaeologist and ethnographer E.A. Strogova, who studied the formation of the Russian population of Yakutia according to written sources, concluded that the formation of Russian settlements

on the northern coast was based on industrial people, mainly people from the eastern regions of the Russian North and the Urals. According to E.A. Strogova, they were the first to reach the lower reaches of the Indigirka River, showing commercial interest in the traditional crafts of local residents, as well as in the collection of mammoth ivory [11].

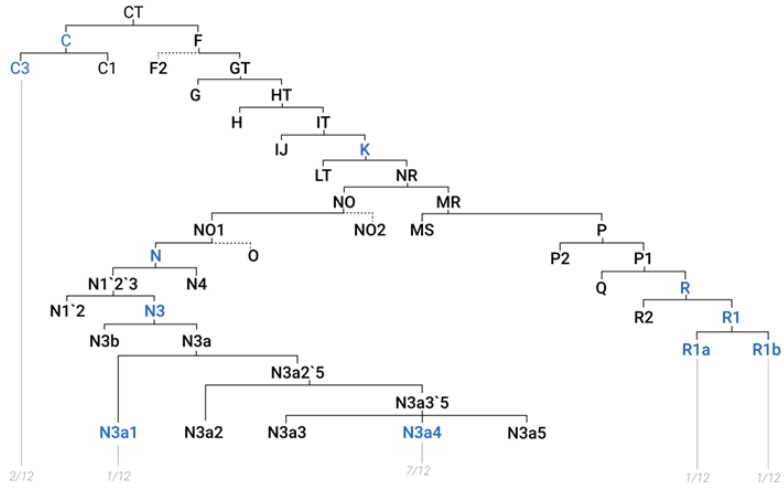
In this work, for the first time, we have analyzed the Y-chromosome lines of men from Russkoye Ustye in order to compare the obtained data with the hypotheses of the origin of the Russkoye Ustye.

Materials and methods. The total population of the village of Russkoye Ustye, Allaikhovsky Ulus of the Republic of Sakha (Yakutia), according to the current archive of the administration was 148 people in 2012-2014 [6]. For research during expeditions in 2018-2019 we collected DNA samples from 12 unrelated men, native russkoustinians, aged 7 to 66 years (average age 42.4±17.4 years).

All DNA samples were tested for Y-chromosome markers C-M130 and K-M9 using real-time PCR. Then, using previously published primer sequences, PCR-RFLP analysis of SNP markers of haplogroups C-M216, R-M207, N-M231, and Q-M242 was performed [26; 23; 17]. Subsequently, in accordance with the defining marker, the following markers were hierarchically typed by PCR-RFLP: R1a-M420 [27], R1b-M343 (original sequence), C1-F3393 [21], C1b-F1370 [21], C2`4 -B477 (original sequence), C3b-P39 (original sequence), N2a1-P43 [19], N3-TAT/M46 (original sequence), N3a1-B211 (original sequence), N3a3-VL29 [20], N3a4-Z1936 [21], N3a5*-F4205 (original sequence), N3a5*-B202 [20]. The C3-M217 marker [25] was identified using Sanger sequencing. The original primer sequences were selected using FastPCR v.6.7.58 (trial) software.

The haplogroup nomenclature used is based on Karmin et al., 2015 [14], which provides the basic YCC 2002 (The Y Chromosome Consortium 2002) nomenclature with updated data from Jobling & Tyler-Smith, 2003 [21], Karafet et al., 2008 [23] and van Oven et al., 2014 [25].

Results and discussions. In the studied sample of Russkoye Ustye residents, five lines of the Y-chromosome



Location of samples from the village of Russkoye Ust'ye on the topology of Y-chromosome haplogroups according to Karmin, 2015 [13]

N3a4-Z1936, N3a1-B211, R1a-M420, R1b-M343 and C3-M217 were identified, which belong to three haplogroups: N3 (8/12; 66.7%), R1 (2/12; 16.6%) and C3 (2/12; 16.6%) (Table 1).

The topological position of the identified Russkoye Ustye lineages on the Y-chromosome phylogenetic tree is shown in Figure 1. Haplogroup designations correspond to the nomenclature proposed by Karmin et al., 2015 [14]

Haplogroup N3 (8/12; 66.7%) dominating in this sample is distributed throughout Northern Eurasia, from Japan to Scandinavia [20]. A more detailed analysis of the N3-lines of the russkoustinians showed that most (~58.4%) of the samples belong to the N3a4 subhaplogroup (Table 1), which was found mainly in North-Eastern Europe among northern Russians, Sami, Veps, Karelians, and Finns [20] and is not found in the gene pool of the neighboring peoples of Yakutia and Chukotka [16]. It should be noted that the N3a4 subhaplogroup and the N3a3 branch phylogenetically close to it are the most informative for the differentiation of the two so-called “poles” of the Russian gene pool, northern and southern Russians [3]. In the populations of northern Russians, the haplogroup N3a4 is associated with the ancient pre-Slavic (Finno-Ugric) component of the gene pool [3; 10].

One sample (8.3%) belongs to the N3a1 subhaplogroup, which is more typical for the Finno-Ugric populations of the Udmurts, Mari Komi-Zyryans and Komi-Permyaks [20], neighboring with the populations of northern Russians.

The Eurasian haplogroup R1 is found in more than half of men in Europe [15]. In the studied sample of Russkoye Ustye residents, haplogroup R1 is represented by two lines: R1a (~8.3%) and R1b (~8.3%), which are widespread in the Slavic populations of Eastern Europe (Russians, Ukrainians, Belarusians, Poles) [2; 3]. In the gene pool of the Yukaghirs, Evens, Evenks and Yakuts, these lines were found in small numbers and their origin is associated with the processes of miscegenation with Russians and, possibly, other Eastern European ethnic groups that have settled the territory of Yakutia since the time of joining the Russian Empire in the 17th century [16].

The frequency of the Asian haplogroup C3 among the russkoustinians was ~16.6%. This haplogroup is one of the most widespread in East Asia [24], including Siberia [16,19]. In Yakutia, haplogroup C3 occurs with high frequencies in the populations of Yukaghirs (46%), Evens (60%), and Evenks (54%) adjacent to the Russkoye Ustye people [16].

Thus, the frequency distribution of the Y-chromosome haplogroups in the studied sample of the Russkoye Ustye residents shows the dominance of lines characteristic of European populations (83.4%), of which more than half is the subhaplogroup N3a4. In the populations of the indigenous peoples of the northeast of Eurasia (Yukaghirs, Evens, Evenks, Yakuts, Dolgans, Chukchi, Eskimos), the N3a4 subhaplogroup was not found [16; 20]. The gene pool of the indigenous peoples of Yakutia and Chukotka is characterized by an insignificant

The frequency of haplogroups (%) of the Y-chromosome in residents of the village Russkoye Ustye

Haplogroup	C3		N3		R1
	C3-M217	N3a1-B211	N3a4-Z1936	R1a-M420	R1b-M343
n	1	7	1	1	2
%	8.3%	58.4%	8.3%	8.3%	16.7%

contribution of haplogroups of Western Eurasian origin (less than 10%) [16].

If we consider the distribution of haplogroups of the Russkoye Ustye people from the point of view of their origin, then we can assume that the dominance of the lines characteristic of the populations of the northeast of Europe most likely reflects the connection with the Russian North. It is known that the northern populations of Russians are characterized by similarities with the Finno-Ugric and Baltic peoples [3], while the central and southern populations of Russians are genetically closer to other Slavic populations [2; 22; 26]. The line N3a4 (58.7%), which dominates among the Russkoye Ustye people, is considered not typical for the Slavic populations in general, however, the highest frequencies of this subhaplogroup were found in the northern Russians of the Arkhangelsk and Vologda regions and much lower frequencies – among the Novgorodians [3].

Conclusions. As a result of the analysis of Y-chromosome lines, 83.4% of haplogroups (N3a4, N3a1, R1a, R1b), more characteristic of Western Eurasian populations, and 16.6% of East Eurasian lines (C3) were found in residents of the village of Russkoye Ustye. The paternal lines of the inhabitants of the village of Russkoye Ustye are represented mainly by Y-chromosome haplogroups, common in the populations of northeastern Europe. The dominant subhaplogroup is N3a4 (58.7%), which is absent in the gene pool of the neighboring peoples of Yakutia and Chukotka and occurs with high frequencies in the populations of the Russian North and among the Finnish-speaking peoples of Finland and Karelia. The results obtained are more in line with the Pomor hypothesis of the origin of the russkoustinians.

Acknowledgements. *The work was carried out within the framework of the State Assignment of the Ministry of Science and Higher Education of the Russian Federation (FSRG-2020-0016), as well as with the support of RFBR grant No. 19-34-60023*

Reference

1. Alekseev, A.N. Pervye russkie poseleniya XVII-XVIII vv. na severo-vostoke YAkutii [The first Russian settlements of the 17th-18th centuries. in the north-east of Yakutia]. RAS Siberian Branch Institute of Archeology and Ethnography; executive editor V.E. Larichev. Novosibirsk, 1996: 151 (In Russ.).] ISBN 5-7803-0011-9.

2. Balanovsky O.P. Genofond Evropy [Gene pool of Europe]. Moscow: Association of Scientific. ed. KMK, 2015: 354 (In Russ.).]

3. Balanovskaya EV, Agdzhoyan AT, Skhalyakho RA, et al. Genofond novgorodcev: mezhdu Severom i Yugom [Gene pool of Novgorodians: between North and South]. Genetics. 2017; 53 (11): 1338-1348 (In Russ.).]. DOI 10.7868/S0016675817110029.

4. Zenzinov V.M. Starinnye lyudi u holodnogo okeana: Russkoe Ust'e YAkutskoj oblasti Verhoyanskogo okruga [Ancient people near the cold ocean: Russian Mouth of the Yakutsk region of the Verkhoyansk district]. Printing house P.P. Ryabushinsky, 1914: 122 (In Russ.).]

5. Itogi Vserossijskoj perepisi naseleniya 2010 goda: v 11 tomah: oficial'noe izdanie / Rossijskaya Federaciya, Federal'naya sluzhba gos. statistiki; (podgot.: E.S. Nabiullina - ruk. rabochej gruppy i dr). [Results of the All-Russian population census of 2010: in 11 volumes: official publication. Russian Federation, Federal State Service. statistics; (prepar.: E.S. Nabiullina – manuscript of the working group, etc.). Moscow: Statistics of Russia, 2012: 30 (In Russ.).] ISBN 978-5-4269-0002-8.

6. Nikitina, SE. Russkie arkticheskie starozhily Respubliki Saha (YAkutiya): problemy sohraneniya unikal'noj kul'tury. Russkie arkticheskie starozhily YAkutii: Sbornik nauchnyh statej [Russian Arctic old-timers of the Republic of Sakha (Yakutia): problems of preserving a unique culture. Russian Arctic old-timers of Yakutia: Collection of scientific articles. Yakutsk: IGIiPMNS, 2019: 16-33 (In Russ.).]

7. Okladnikov AP, Gogolev ZV, Ashchepkov EA. Drevnij Zashiversk. Drevnerusskij zapolyarnyj gorod [Ancient Zashiversk. Old Russian polar city. Moscow: Nauka, 1977: 212 (In Russ.).]

8. Skvortsov EF. V pribrezhnyh tundrah YAkutii: Dnevnik astronoma Lensko Kolymskoj ekspedicii. Trudy komissii po izucheniyu YAkutii. T. 15: Lensko Kolymskaya ekspediciya 1909 goda pod nachal'stvom K.A. Vollosovicha [In the coastal tundra of Yakutia: Diary of an astronomer of the Lensko-Kolyma expedition. Proceedings of the commission for the study of Yakutia]. Lensko-Kolyma expedition of 1909 under the command of K.A. Vollosovich, 1930; 15: 1–244 (In Russ.).]

9. Skvortsov EF. Russkie na Indigirke. Topografo-geodezicheskij zhurnal [Russians on the Indigirka. Topographic and geodetic journal]. 1910: 10 (In Russ.).]

10. Chukhryaeva MI, Pavlova ES, Napolskikh VV, et al. Sohranilis' li sledy finno-ugorskogo vliyaniya v genofonde russkogo naseleniya YAroslavskoj oblasti? Svidetel'stva Y-hromosomy [Are traces of Finno-Ugric influence preserved in the gene pool of the Russian population of the Yaroslavl region? Evidence of the Y-chromosome. Genetics. 2017; 53 (3): 378-389 (In Russ.).] DOI 10.7868/S0016675817030043.

11. Strogova, E. A. Obrazovanie etnicheskoj territorii i formirovanie postoyannogo russkogo naseleniya na Severe YAkutii v XVII-XVIII vv.[[Formation of an ethnic territory and the formation of a permanent Russian population in the North of Yakutia in the 17th-18th centuries]. Russkie arkticheskie starozhily YAkutii: Sbornik nauchnyh statej [Russian Arctic old settlers of Yakutia: Collection of scientific articles. Yakutsk: IGIiPMNS, 2019: 7-15 (In Russ.).]

12. Chikachev AG. Russkoe serdce Arktiki [Russian heart of the Arctic. Yakutsk: Literary Fund, 2010: 478 (In Russ.).]

13. Rootsi S, Zhivotovsky LA, Baldovic M, et al. A counter-clockwise northern route of the Y-chromosome haplogroup N from Southeast Asia towards Europe. Eur. J. Hum. Genet. 2007;15:204–211

14. Karmin M, Saag L, Vicente M, et al. A recent bottleneck of Y chromosome diversity coincides with a global change in culture. Genome Res. 2015; 25: 459–466 (In Russ).].

15. Myres N, Rootsi M, Lin S, et al. A major Y-chromosome haplogroup R1b Holocene era founder effect in Central and Western Europe. European journal of human genetics: EJHG, 2011; 19(1), 95–101. https://doi.org/10.1038/ejhg.2010.146

16. Fedorova SA, Reidla M, Metspalu E, et al. Autosomal and uniparental portraits of the native populations of Sakha (Yakutia): implications for the peopling of Northeast Eurasia. BMC Evol. Biol. 2013;13:127.

17. Cinnioğlu C, King R, Kivisild T, et al. Excavating Y-chromosome haplotype strata in Anatolia. Hum Genet. 2004 Jan;114(2):127-48. doi: 10.1007/s00439-003-1031-4.

18. Zhong H, Shi H, X.B. Qi, et al. Global distribution of Y-chromosome haplogroup C reveals the prehistoric migration routes of African exodus and early settlement in East Asia. J Hum Genet; 2010; 55, 428–435. https://doi.org/10.1038/jhg.2010.40

19. Karafet TM, Osipova LP, Gubina MA, et al. High levels of Y-chromosome differentiation among native Siberian populations and the genetic signature of a boreal hunter-gatherer way of life. Hum. Biol. 2002;74:761–789

20. Ilumäe AM, Reidla M, Chukhryaeva M, et al. Human Y Chromosome Haplogroup N: A Non-trivial Time-Resolved Phylogeography that Cuts across Language Families. Am J Hum Genet. 2016;99(1):163-173. doi:10.1016/j.ajhg.2016.05.025

21. International Society of Genetic Genealogy. Y-DNA Haplogroup Tree 2019, Version: [15.73], Date: [11 July 2020], http://www.isogg.org/tree/ [Date of access: 10.06.2021].

22. Jobling M.A., Tyler-Smith C. The human Y chromosome: an evolutionary marker comes of age. Nat Rev Genet. 2003 Aug;4(8):598-612. doi: 10.1038/nrg1124. PMID: 12897772.

23. Karafet TM, Mendez FL, Meilerman MB, et al. New binary polymorphisms reshape and increase resolution of the human Y chromosomal haplogroup tree. Genome Res. 2008;18(5):830-838. doi:10.1101/gr.7172008

24. Malyarchuk B, Derenko M, Denisova G, et al. Phylogeography of the Y-chromosome haplogroup C in northern Eurasia. Annals of human genetics, 2010; 74(6), 539–546. https://doi.org/10.1111/j.1469-1809.2010.00601.x

25. Van Oven M, Van Geystelen A, Kayser M, et al. Seeing the wood for the trees: a minimal reference phylogeny for the human Y chromosome. Hum Mutat. 2014 Feb;35(2):187-91. doi:10.1002/humu.22468.

26. Underhill PA, Passarino G, Lin AA, et al. The phylogeography of Y chromosome binary haplotypes and the origins of modern human populations. Annals of Human Genetics, 2001. 65(1): 43–62. https://doi.org/10.1046/j.1469-1809.2001.6510043.x

27. Hinds DA, Stuve LL, Nilsen GB, et al. Whole-genome patterns of common DNA variation in three human populations. Science. 2005; 307:1072–1079.

SCIENTIFIC REVIEWS AND LECTURES

DOI 10.25789/YMJ.2022.79.20

УДК 616.517:577.12(048)

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IMMUNE AND METABOLIC RELATIONSHIPS OF PSORIASIS WITH COMORBID CONDITIONS

Psoriasis is a polygenic disease in which chronic inflammation in the skin develops as a result of an interaction between genetic predisposing factors and environmental triggers. The self-sustaining inflammatory response of the skin coexists with autoimmune and autoinflammatory components. From an immunological point of view, psoriasis is characterized by profound changes, including sustained activation of the tumor necrosis factor alpha axis with interleukins 23 and 17 (TNF-α/IL-23/IL-17), as well as high expression of early pro-inflammatory cytokines.

The study of the pathogenesis of psoriasis is still relevant. Numerous studies have established that concomitant ("comorbid") diseases are associated with psoriasis, which may be due to individual links in the pathogenesis of the underlying disease, including through immuno-metabolic disorders.

The purpose of this review was to analyze current data on the relationship between psoriasis and comorbid conditions. The review presents new data on comorbid associations of psoriasis with metabolic syndrome, cardiovascular diseases, intestinal dysbiosis, and other pathologies.

The object of the study was publicly available scientific information, the search for which was carried out in the databases: PubMed, Medline, Scopus, Web of Science, RSCI, without language restrictions. An analysis of the literature data showed that psoriasis should be considered as a systemic inflammatory condition underlying comorbid associations. The pathogenesis of metabolic disorders in psoriasis is associated with constitutionally determined immune hyperreactivity. In turn, the developed metabolic abnormalities increase immune inflammation due to newly formed molecular patterns of dangers (DAMPs). Promising in understanding the causes of the formation of comorbid conditions and diseases in psoriasis is the study of general metabolic parameters, which will expand the understanding of the mechanisms of formation of comorbidity in psoriasis. In addition, this will allow the development of complex pathogenetic therapy, taking into account the correction of violations of metabolic processes in the body of patients. The analysis of scientific information shows that the systemic nature of psoriasis implies a personalized approach to its diagnosis and treatment, taking into account comorbid (comorbid) conditions.

Keywords: psoriasis, metabolic syndrome, cardiovascular disease, psoriatic arthritis, intestinal dysbiosis, metabolic profile.

Introduction. Psoriasis is a chronic inflammatory skin disease that affects 1-2% of the population and has a serious impact on the quality of life of those affected by the disease [15].

Psoriasis results from an interaction between genetic predisposing factors and environmental triggers, leading to a self-sustaining inflammatory skin response in which autoimmune and autoinflammatory components coexist [11, 46]. The condition usually manifests as erythematous, well-defined plaques covered with grayish-white scales, and 30% of affected individuals may develop inflammatory arthritis, psoriatic arthritis (PsA) [39].

The clinical and histological features of psoriatic skin lesions reflect some key mechanisms of the disease, such as hyperproliferation and angioneogenesis. Immunologically, psoriasis is characterized by profound changes involving sustained activation of the tumor necrosis factor alpha axis with interleukins 23 and 17 (TNF-α/IL-23/IL-17) as well as high expression of early proinflammatory cytokines [7, 53]. Numerous studies have shown the prevalence of autoinflammation at the systemic level [14, 31].

Of particular importance are metabolic disorders, which can be independent or induced by primary immune hyperreactivity [38].

Numerous studies have established that associated ("comorbid") diseases are associated with psoriasis, which may be caused by individual links in the pathogenesis of the underlying disease, including through immune and metabolic disorders [3].

According to S.G. Lykova et al. (2020) the concept of "comorbidity" (lat. co - together, morbus - disease) was introduced by A. Feinstein in 1970, putting into this term the idea of the presence of "any distinct additional clinical picture that existed or could arise in the patient during the clinical course of the index (main) disease" [3].

The presence of comorbidity in psoriasis is considered within the framework of the "psoriatic march" concept, which consists in the presence of causal links between dermatosis and pathology of other organs [19].

On this basis, the aim of this review was to analyze the current data on the immune-metabolic relationship of psoriasis with comorbid conditions.

Materials and methods of the study. The object of the study was publicly available scientific information, which was searched in the databases: PubMed, Medline, Scopus, Web of Science, RSCI, without language restrictions. In the process of writing the article the method of analysis and synthesis of information was used.

Results and discussion.

Molecular mechanisms of comorbidity formation in psoriasis. Our analysis of the literature showed that inflammation mediated by type 1 (Th1) T-helper lymphocytes, which is one of the main links in the pathogenesis of psoriasis, is a fundamental factor in the development of obesity, metabolic syndrome, diabetes, atherosclerosis and myocardial infarction [56].

In addition to the abnormal immune cell responses observed in the pathogenesis of psoriasis, recent pathophysiological studies have focused on the activation of the interleukin (IL)-23/IL-17 system, which increases abnormal keratinocyte proliferation and causes psoriasis [56]. Although the exact role of IL-17A in cardiovascular disease is still controversial, accumulation of IL-17-producing cells and elevated IL-17A levels have also been observed in atherosclerotic lesions [10, 17]. According to the literature, the "two plaques, one syndrome" hypothesis

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has been proposed, due to the fact that the molecular mechanisms of these two diseases have striking similarities with T-cell-mediated inflammation [6]. The hypothesis states that psoriasis is a chronic systemic inflammatory disease leading to insulin resistance through suppression of insulin receptors. In addition, decreased expression of insulin receptors in endothelial cells leads to decreased nitric oxide (NO), a vasodilatory agent. This leads to the development of vasoconstriction and increased arterial stiffness. As a result, the cited study reported an increased incidence of myocardial infarctions (MI) and strokes. It has been shown that the use of an insulin stimulator (glucagon-like peptide 1 - GLP-1) can improve the course of psoriasis, emphasizing the effect of insulin resistance in inflammation [38, 45].

According to the literature, elevated levels of the amino acid homocysteine are detected in the blood of psoriasis patients. On the one hand, hyperhomocysteinemia is a sign of unhealthy lifestyle, and together with such risk factors as smoking, dyslipidemia and markers of metabolic syndrome significantly increases the risk of coronary heart disease (CHD) in psoriasis [4]. On the other hand, due to the presence of a large number of dividing cells in the skin in psoriasis, huge amounts of methyl groups are consumed, which may lead to impaired homocysteine metabolism. Also, high levels of homocysteine may indicate vitamin deficiencies (folic acid - B_9, B_6, B_{12}), impaired renal function [1, 22]. At the same time, some medications used in the treatment of psoriasis (methotrexate, methylprednisolone), among others, contribute to an increase in blood homocysteine levels, apparently due to their antimetabolic effect on folic acid.

Numerous studies have confirmed the pathophysiological link between psoriasis and obesity. Adipocytes are known to be the predominant cell type in adipose tissue, secreting important hormones and signaling molecules such as adipokines. At the same time, adipokines can mediate cutaneous inflammation, suggesting a role in the pathogenesis of psoriasis and the development of obesity. In obesity, adipocytes produce increased amounts of proinflammatory adipokines, while the production of this class of anti-inflammatory molecules is reduced. Cytokines characteristic of psoriasis, such as TNF-b, IL-1c, and IL-6, affect adipose tissue by participating in key mechanisms of triglyceride (TG) metabolism and preadipocyte differentiation, including an increased risk of obesity. Secreted adipokines such as leptin, chemerin, retinol-binding protein 4 (RBP4), visfatin, fetuin-A, apelin-36, and lipocalin-2 may enhance the immune response and contribute to immune-mediated disease through their proinflammatory effects; however, adiponectin and omentin show anti-inflammatory effects, but their levels are significantly reduced in obese patients.

In obesity, the hormone leptin plays a key role in the pathogenesis. Numerous studies have demonstrated that plasma leptin levels are elevated in both obese and psoriasis patients, and elevated concentrations correlate positively with body mass index (BMI) and psoriasis area and severity index (PASI) scores, indicating a common important role for leptin in psoriasis and obesity. Indeed, several meta-analyses evaluated circulating concentrations of important adipokines and found that leptin concentrations were significantly higher in patients with psoriasis and without obesity [33, 51], indicating that increased leptin levels in patients with psoriasis may come not only from adipocytes but also from keratinocytes and endothelial cells [26].

It is recognized that obesity is a risk factor for psoriasis, exacerbates existing psoriasis, and that weight reduction can reduce the severity of psoriasis in overweight people [25, 35].

Impaired lipid metabolism is considered an important hallmark in the etiology and pathogenesis of psoriasis. S. Srinivas et al (2019) studied plasma lipid profiles and cardiovascular risk markers in 200 people, among whom 100 patients had psoriasis. The results of the studies revealed a significant increase in lipid profile parameters, cardiovascular risk and atherogenicity index in psoriasis patients compared to the control group [8].

Al Harthi F et al (2014) found that Saudi Arabian psoriasis patients had significantly higher serum cholesterol, triglyceride, and LDL levels compared with controls. The lipid profile results confirm that psoriasis is one of the independent risk factors for hyperlipidemia and emphasize the need for cardiovascular disease screening in patients with psoriasis [9].

In the studies of G. B. Huraib et al (2019) found that106 patients with Saudi Arabian psoriasis vulgaris had significantly elevated body mass index, fasting glucose, total cholesterol, low-density lipoproteins, triglycerides, and C-reactive protein, known markers of cardiovascular disease, compared with controls [30].

In recent years, several studies have shown that nonalcoholic fatty liver disease (NAFLD) is common in patients with psoriasis [37]. The term NAFLD encompasses a wide range of liver lesions, from simple fatty hepatosis to nonalcoholic steatohepatitis (NASH), including various degrees of liver fibrosis, cirrhosis, and even hepatocellular carcinoma [28, 59]. The global prevalence of NAFLD in the general population is estimated at 25% [18], and it is currently one of the leading causes of liver cirrhosis and liver transplantation [32]. NAFLD is now a growing epidemic, partly because of obesity, insulin resistance, and metabolic syndrome [5], but also because of psoriasis [58]. Strikingly, the same comorbidities, especially those associated with metabolic abnormalities that may contribute to hepatic steatosis, have been associated with systemic inflammation in psoriasis. Moreover, specific proinflammatory mediators have been shown to cause a chronic inflammatory state in NAFLD, psoriasis, and the metabolic syndrome [36, 50]. This similarity may indicate a related pathogenesis between psoriasis and NAFLD with potentially increased risk of progressive liver disease [5]. The prevalence of NAFLD in patients with psoriasis is high and is associated with a higher prevalence of metabolic syndrome signs, bacterial translocation, and a higher proinflammatory state.

Clinical manifestations of comorbidity in psoriasis.

Based on the data presented above on the molecular mechanisms of comorbidity formation in psoriasis, the clinical associations are understandable.

There is now accumulating evidence proving comorbid associations of psoriasis with type 2 diabetes mellitus (DM2) [41, 44], the metabolic syndrome and its components: arterial hypertension [23], obesity [34, 35]; cardiovascular disease [40, 43] and other pathologies.

Similar to plaque psoriasis [52, 57], pustular psoriasis is associated with a metabolic syndrome, including hypertension, hyperlipidemia, diabetes, and obesity [13, 49]. A systemic body response has been revealed in psoriasis and psoriatic arthritis patients, which is manifested by unidirectional metabolic disorders and changes in the cellular composition of the blood [2].

Given these observations, there has been a paradigm shift from viewing psoriasis simply as a "skin disease" to a systemic inflammatory condition [27]. Chronic inflammation and genetic determinants appear to underlie comorbid associations.

In recent years, cardiovascular disease has been recognized as an important comorbid condition. Various epidemiological studies have reported a significantly increased risk of serious cardiovascular events such as MI, stroke [40] and venous thromboembolism (VTE) [42] in individuals with psoriasis. Studies by M.J.E. Visser et al (2021) add to the accumulating evidence about the systemic nature of psoriasis and the subsequent risk of associated cardiovascular disease, possibly due to acquired hypercoagulation. Because the processes of inflammation and coagulation are interrelated, persistent systemic inflammation may contribute to the development of a prothrombotic state in psoriasis patients. In this study, the prothrombotic state in patients with psoriasis was characterized by endothelial (elevated sICAM-1 levels) and platelet activation (elevated sP-selectin levels), hypercoagulation (TEG results) and abnormal fibrin deposition (SEM analysis) [47].

Wolska A et al. (2014) found histological similarity between psoriatic and atherosclerotic plaques. Both plaques have increased levels of activated Th1 and T helper lymphocytes type 17 (Th17), which cause inflammation in various tissues [29].

An imbalance of gut microorganisms (dysbiosis) has important functional consequences and is associated with many digestive diseases, as well as with diabetes, obesity, metabolic syndrome, psoriatic arthritis, celiac disease, psychiatric disorders and other diseases [12, 24, 54, 55].

There is ample evidence that intestinal dysbiosis is a possible cause of chronic skin inflammation, particularly psoriasis [16, 20, 21, 48].

Thus, in recent years, the study of the metabolic profile has become increasingly important in the diagnosis of psoriasis as a systemic disease, since certain metabolites can influence the mechanisms of psoriasis formation. Systematic study of metabolic parameters can lead to better understanding of the pathogenesis of psoriasis and eventually to the development of new methods of treatment and diagnostics.

Prospects for therapy of psoriasis with comorbid diseases.

On the basis of the above, new perspectives open up for the treatment of psoriasis in relation to comorbid conditions.

Given the commonality of the pathophysiological processes of psoriasis with comorbid conditions, it becomes possible, on the one hand, to avoid polypragmasy and reduce the toxic load on the body and, on the other hand, to develop maximum targeted therapy in several directions at once. In particular, it has been shown that the use of an insulin stimulator (glucagon-like peptide 1 - GLP-1) can improve the course of psoriasis by emphasizing the effect of insulin resistance in inflammation [38, 45].

There is evidence in the literature that treatment with IL-17A monoclonal antibodies can not only improve psoriatic lesions but also restore impaired lipid metabolism to normal levels in psoriasis patients. Given that impaired regulation of lipid metabolism is considered a critical factor in cardiovascular disease, restoration of lipid metabolites in psoriasis patients indicates that IL-17A monoclonal antibodies may have a potential protective effect against associated cardiovascular disease.

An important direction in the treatment of psoriasis in association with comorbid conditions is lifestyle modification, avoidance of bad habits, and normalization of body weight as significant factors influencing the intensification of systemic inflammation.

It is important to evaluate patients with psoriasis from both a dermatological and a metabolic perspective. The complex interaction of psoriasis with various comorbidities suggests the need for a multidisciplinary approach in the management of psoriasis patients.

Conclusion. Thus, the review of the literature shows that the study of the pathogenesis of psoriasis is still relevant. Currently, there is accumulated data proving comorbid associations of psoriasis with metabolic syndrome, cardiovascular diseases, intestinal dysbiosis and other pathologies. Given these observations, there has been a paradigm shift from viewing psoriasis simply as a "skin disease" to a systemic inflammatory condition. Chronic inflammation and genetic determinants, underlie comorbid associations.

Promising in understanding the causes and diagnosis of psoriasis is a comprehensive study of general metabolic indices and immunoregulatory messengers, which will not only expand our understanding of the mechanisms of psoriasis formation, but also develop a comprehensive pathogenetic therapy with the correction of immune and metabolic disturbances in patients. Analysis of scientific information shows that the systemic nature of psoriasis suggests a personalized approach to its diagnosis and treatment, taking into account comorbid (concomitant) conditions.

Reference

1. Sinkeev MS,. Skvortsov YuI, Bogdanova TM, Skvortsov KYu. Aminokisloty krovi v patogeneze i klinike ishemicheskoj bolezni [Blood amino acids in the pathogenesis and clinic of ischemic disease]. Mezhdunarodnyj zhurnal prikladnyh i fundamental'nyh issledovanij [International Journal of Applied and Fundamental Research. 2014; 11(3): 480-484 (In Russ.).]
2. Orlov EV, Arnautova MS, Gergel NI. Ocenka metabolicheskogo statusa i kletochnogo sostava krovi pri psoriaze i psoriaticheskom artrite [Assessment of the metabolic status and cellular composition of blood in psoriasis and psoriatic arthritis]. Medicinskij al'manah [Medical almanac. 2013; 5 (29): 197-200 (In Russ).].
3. Lykova SG, Morzhanaeva MA, Nemchaninova OB, Svechnikova EV. Psoriaz u pacientov s metabolicheskim sindromom: klinicheskie aspekty problem [Psoriasis in patients with metabolic syndrome: clinical aspects of the problem]. Klinicheskaya dermatologiya i venerologiya [Clinical dermatology and venereology. 2020; 19 (2): 214-222 (In Russ.).] DOI: 10.17116/klinderma202019021214.
4. Skvorcov YuI, Korolkova AS. Gomocistein kak faktor riska razvitiya IBS (obzor) [Homocysteine as a risk factor for the development of coronary artery disease (review)]. Saratovskij nauch.-medicin. Zhurnal [Saratov Journal of Medical Scientific Research]. 2011; 7 (3): 619-624.
5. Awosika O, Eleryan MG, Rengifo-Pardo M, et al. A Case-control Study to Evaluate the Prevalence of Nonalcoholic Fatty Liver Disease Among Patients with Moderate-to-severe Psoriasis. Journal of Clinical and Aesthetic Dermatology. 2018; 11(6): 33-37.
6. Armstrong AW, Voyles SV, Armstrong EJ, et al. A tale of two plaques: convergent mechanisms of T-cell-mediated inflammation in psoriasis and atherosclerosis. Exp Dermatol. 2011; Jul. 20(7): 544-9. Doi: 10.1111/j.1600-0625.2011.01308.x.
7. Georgescu SR, Tampa M, Caruntu C, et al. Advances in understanding the immunological pathways in psoriasis. International Journal of Molecular Sciences. 2019; 20: 739. Doi: 10.3390/ijms20030739.
8. Srinivas S, Nagendra S, Goudappala P, Kashinath RT. Alterations in plasma lipid profile and cardiovascular risk indicators in clinically subgrouped psoriasis. International Journal of Research in Dermatology. 2019; 5 (2): 2455-4529.
9. Al Harthi F, Huraib GB, Zouman A, et al. Apolipoprotein E gene polymorphism and serum lipid profile in Saudi patients with psoriasis. Disease Markers. 2014; 239645. Doi: 10.1155/2014/239645.
10. Smith E, Prasad KM, Butcher M, et al. Blockade of interleukin-17A results in reduced atherosclerosis in apolipoprotein E-deficient mice. Circulation. Free PMC article. 2010; 20, 121(15): 1746-55. Doi: 10.1161/CIRCULATIONAHA.109.924886.
11. Boehncke, WH, Schön Psoriasis MP. Lancet. 2015; 386: 983-994. DOI: 10.1016/S0140-6736(14)61909-7.
12. Gulas E, Wysiadecki G, Strzelecki D, et al. Can microbiology afect psychiatry? A link between gut microbiota and psychiatric disorders. Psychiatria Polska. 2018; 52: 1023-1039.
13. Choon SE, Lai NM, Mohammad NA, et al. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. International Journal of Dermatology. 2014; 53: 676–684. Doi: 10.1111/ijd.12070.
14. Grän F, Kerstan A, Serfling E, et al. Cur-

rent developments in the immunology of psoriasis. Yale Journal of Biology and Medicine. 2020; 93: 97–110.

15. Domagała, A, Szepietowski J, Reich A. Antihistamines in the treatment of pruritus in psoriasis. Advances in Dermatology and Allergology. 2017; 5: 457-463. DOI: 10.5114/ada.2017.71112.

16. Huang L, Gao R, Yu N, et al. Dysbiosis of gut microbiota was closely associated with psoriasis. Sci China Life Sci. 2018; 62(6): 807-815 https://doi.org/10.1007/s1142 7-018-9376-6.

17. Erbel C, Dengler TJ, Wangler S, et al. Expression of IL-17A in human atherosclerotic lesions is associated with increased inflammation and plaque vulnerability. Basic Res Cardiol. 2011; 106 (1): 125-134. Doi: 10.1007/s00395-010-0135-y.

18. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology & Hepatology. 2018;15(1):11-20. Doi: 10.1038/nrgastro.2017.109.

19. Nast A, Boehncke WH, Mrowietz U, et al. Guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges. 2012; 10(2): 1-95. – Doi: 10.1111/j.1610-0387.2012.07919.x.

20. Codoñer FM, Ramírez-Bosca A, Climent E, et al. Gut microbial composition in patients with psoriasis. Scientific Reports. 2018: 3812. Doi: 10.1038/s41598-018-22125-y.

21. Hidalgo-Cantabrana C, Gómez J, Delgado S, et al. Gut microbiota dysbiosis in a cohort of patients with psoriasis. British Journal of Dermatology. 2019; 181(6): 1287-1295. Doi: 10.1111/bjd.17931. https://doi. org/10.1111/bjd.17931.

22. Tobin AM, Hughes R, Leong T, et al. Homocysteine status and cardiovascular risk factors in patients with psoriasis: a case-control study. Clin. Exp. Dermatol. 2011; 36 (1): 19-23.

23. Hypertension and risk of psoriasis incidence: an 11-year nationwide population-based cohort study / H. N. Kim, K. Han, S. W. Song, J. H. Lee // PLoS ONE. – 2018. – e0202854. – Doi: 10.1371/journal.pone.0202854.

24. Y.-J. Chen, Hsiu Ho, Ching-Hung Tseng, et al. Intestinal microbiota profling and predicted metabolic dysregulation in psoriasis patients. Experimental Dermatology. 2018; 27(12): 1336-1343. DOI:10.1111/exd.13786.

25. Jensen, P, Skov L. Psoriasis and obesity. Dermatology. 2016; 232: 633-639. Doi: 10.1159/000455840.

26. Poeggeler B, Schulz C, Pappolla MA, et al. Leptin and the Skin: A New Frontier. Experimental Dermatology. 2010; 19 (1): 12-18. Doi:10.1111/j.1600-0625.2009.00930.x.

27. Dowlatshahi EA, van der Voort EA, Arends LR, Nijsten T. Markers of systemic infammation in psoriasis: a systematic review and meta-analysis. British Journal of Dermatology. 2013; 169: 266–282. Doi: 10.1111/bjd.12355.

28. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Annals of Medicine. 2011; 43(8): 617-49. Doi: 10.3109/07853890.2010.518623.

29. Wolska A, Michalsk-Jakabus M, Pietrzak A, et al. Metabolic syndrome in patients with psoriasis. Polski Merkuriusz Lekarski. 2014; 36 (213): 215-219.

30. Huraib GB, Harthi FA, Arfin M, et al. Methylenetetrahydrofolate Reductase C677T Gene Polymorphism as Risk Factor for Psoriasis in Saudis Biomark Insights. 2019; 14:1-5. Doi: 10.1177/1177271919830973.

31. Mylonas, A, Conrad C. Psoriasis: Classical vs. paradoxical. Te Yin-Yang of TNF and type I interferon. Front. Immunol. 2019; 9: 2746.

32. Pais R, 4th Barritt AS, Calmus Y, et al. NAFLD and liver transplantation: Current burden and expected challenges Journal of Hepatology. 2016; 65(6): 1245-1257. Doi: 10.1016/j.jhep.2016.07.033.

33. Johnston A, Arnadottir S, Gudjonsson JE, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. British Journal of Dermatology. 2008; 159(2): 342-50. Doi: 10.1111/j.1365-2133.2008.08655.x.

34. Snekvik I, Smith CH, TIL. Nilsen, et al. Obesity, waist circumference, weight change, and risk of incident psoriasis: prospective data from the HUNT study. Journal of Investigative Dermatology. 2017; 137: 2484-2490. Doi: 10.1016/j.jid.2017.07.822.

35. Danielsen K, Wilsgaard T, Olsen AO, Furberg AS. Overweight and weight gain predict psoriasis development in a population-based cohort. Acta Dermato-Venereologica. – 2017; 97(3): 332-339. DOI: 10.2340/00015555-2530.

36. Gisondi P, Bellinato F, Girolomoni G, Albanesi C. Pathogenesis of chronic plaque psoriasis and its intersection with cardiometabolic comorbidities. Front. Pharmacol. 2020; 11-117. Doi: 10.3389/fphar.2020.00117.

37. Abedini R, Salehi M, Lajevardi V, Beygi S. Patients with psoriasis are at a higher risk of developing nonalcoholic fatty liver disease. Clinical and Experimental Dermatology. 2015; 40: 722-727. Doi: 10.1111/ced.12672.

38. Zindancı I, Albayrak O, Kavala M, et al. Prevalence of metabolic syndrome in patients with psoriasis. Scientific World Journal. 2012:312463. Doi: 10.1100/2012/312463.

39. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. Journal of the American Academy of Dermatology. 2013; 69: 729-735.

40. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: Implications for management. Journal of the American Academy of Dermatology. 2017; 76: 393-403. Doi: 10.1016/j.jaad.2016.07.065.

41. Wan MT, Shin DB, Hubbard RA, et al. Psoriasis and the risk of diabetes: a prospective populationbased cohort study Journal of the American Academy of Dermatology. 2018; 78: 315–322. Doi: 10.1016/j.jaad.2017.10.050.

42. Ahlehoff O, Gislason GH, Lindhardsen J, et al. Psoriasis carries an increased risk of venous thromboembolism: a Danish nationwide cohort study PLoS ONE. 2011; 6: e18125. Doi: 10.1371/journal.pone.0018125.

43. HY Chiu, WL Chang, MN Shiu, et al. Psoriasis is associated with a greater risk for cardiovascular procedure and surgery in patients with hypertension: A nationwide cohort J Dermatol. 2018; 45(12): 1381-1388. Doi: 10.1111/1346-8138.14654.

44. H. Yeung, J. Takeshita, N. N. Mehta, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatology. 2013; 149(10): 1173-9. Doi: 10.1001/jamadermatol.2013.5015.

45. Ganzetti G, Campanati A, Molinelli E, Offidani A. Psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease: Three different diseases on a unique background World J Cardiol. 2016; 8(2): 120-31. Doi: 10.4330/wjc.v8.i2.120.

46. Y. Liang, M. K. Sarkar, L. C. Tsoi, J. E Gudjonsson. Psoriasis: A mixed autoimmune and autoinfammatory disease. Curr. Opin. Immunol. 2017; 49 (1-8).

47. Visser MJE, Venter C, Roberts T, et al. Psoriatic disease is associated with systemic inflammation, endothelial activation, and altered haemostatic function Scientific Reports. 2021; 11: 13043. Doi: 10.1038/s41598-021-90684-8.

48. Quan C, Chen XY, X. Li, et al. Psoriatic lesions are characterized by higher bacterial load and imbalance between Cutibacterium and Corynebacterium. Journal of the American Academy of Dermatology. 2020; 82(4): 955-961. Doi: 10.1016/j.jaad.2019.06.024.

49. Trattner H, Blüml S, Steiner I, et al. Quality of life and comorbidities in palmoplantar pustulosis-a cross-sectional study on 102 patientsJournal of the European Academy of Dermatology and Venereology. 2017; 31: 1681-1685. – Doi: 10.1111/jdv.14187.

50. Phan K, Onggo L, Charlton O, Smith SD. Relationship between psoriasis and non-alcoholic fatty liver disease: Updated systematic review and adjusted meta-analysis Australasian Journal of Dermatolog. 2019; 60: e352–e355.

51. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG. Serum Leptin, Resistin, and Adiponectin Concentrations in Psoriasis: A Meta-Analysis of Observational Studies. Dermatology. 2017; 233(5): 378-389. – Doi: 10.1159/000481882.

52. Serum sphingolipid level in psoriatic patients with obesity / D. Kozłowska, E. Harasim-Symbor, H. Myśliwiec [et al] // Postępy Dermatologii i Alergologii. – 2019. – 36. – 714–721. Doi: 10.5114/ada.2019.91422.

53. Casciano F, Pigatto PD, Secchiero P, et al. T cell hierarchy in the pathogenesis of psoriasis and associated cardiovascular comorbidities. Front Immunol. 2018; 9: 1390. – DOI: 10.3389/fimmu.2018.01390.

54. Carrera-Quintanar L, Ortuño-Sahagún D, Franco-Arroyo NN, et al. The human microbiota and obesity: a literature systematic review of in vivo models and technical approaches. International Journal of Molecular Sciences. 2018; 19: 3827.

55. Gilis E, Mortier C, Venken K, et al. The role of the microbiome in gut and joint infammation in psoriatic arthritis and spondyloarthritis. Journal of Rheumatology Supplement. 2018; 94: 36-39.

56. Lowes MA, Russell CB, Martin DA, et al. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol. 2013; 34(4): 174-81. Doi: 10.1016/j.it.2012.11.005.

57. Namiki K, Kamata M, Shimizu T, et al. Thyroid dysfunction in patients with psoriasis: higher prevalence of thyroid dysfunction in patients with generalized pustular psoriasis. J. Dermatol. 2020; 47: 133–139. Doi: 10.1111/1346-8138.15178.

58. Icen M, Crowson CS, McEvoy Mt, et al. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol. 2009; 60(3): 394-401. Doi: 10.1016/j.jaad.2008.10.062.

59. Wenk, KS, Arrington KC, Ehrlich A // Psoriasis and non-alcoholic fatty liver disease. Journal of the European Academy of Dermatology and Venereology. 2011; 25: 383-391. DOI:10.1111/j.1468-3083.2010.03841.x.

DOI 10.25789/YMJ.2022.79.21

УДК 616.89-008

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SUBJECTIVE COGNITIVE AND SUBTLE COGNITIVE IMPAIRMENTS

Cognitive impairments are one of the leading problems of neurology and psychiatry due to their wide prevalence, especially in the elderly and senile age, the difficulty in diagnosis and treatment. In addition, the increase in life expectancy of the population in Russia and in the world will undoubtedly cause a rapid increase in patients with dementia and other cognitive impairments. However, dementia in most cases does not develop overnight; its development is preceded by a long period of time when the existing cognitive impairments do not yet disrupt the patient's household and professional activity. Cognitive impairment of this degree is called "pre-dementia" and is divided into subjective cognitive decline, subtle and mild cognitive impairments. This article discusses the key problems of subjective cognitive decline and subtle cognitive impairment, the interpretation and diagnosis of which raises the most frequent questions among clinicians. So, based on a review of Russian and foreign literature, the authors substantiate how it is possible to distinguish between subjective cognitive decline and subtle cognitive impairment, and discuss where the line with moderate cognitive impairment is. Separately, diagnostic algorithms and treatment tactics for subjective cognitive decline and subtle cognitive impairment are presented.

Keywords: subjective cognitive impairment, mild cognitive impairment, moderate cognitive impairment, dementia, neuropsychological testing.

Introduction. Cognitive impairment is one of the topical issues of modern neurology and psychiatry. This is evidenced by the geometric increase in the number of articles in foreign and domestic journals. So, if in 2000 only 1,301 articles with the keywords “cognitive impairment” were published in PubMed, then their number reached 4,536 in 2010, and 15,665 in 2021. In the Russian scientific database "Elibrary.ru" in 2000 there was not a single article with the keywords "cognitive impairment", in 2010 94 articles were published, in 2015 - 191 articles, and in 2021 their number increased to 252 articles.

The increased interest in cognitive impairment is justified, since a dementia pandemic is expected in the world, primarily due to the increase in life expectancy of the population. According to one major meta-analysis, there were 35.6 million people with dementia worldwide in 2010, and this number will double every 20 years, reaching 65.7 million by 2030 and 115.4 million by 2050 [22].

For comparison, according to Russian Federal State Statistics Service, the population of Moscow in 2022 amounted to 12.6 million people. Thus, already in 2010, all patients with dementia would “inhabit” the three Moscows of 2022. However, dementia in the vast majority of cases does not develop overnight; its development is preceded by a long period of time when the existing cognitive impairments do not yet disrupt the patient's household and professional activity. Cognitive impairments of this degree are called "pre-dementia" and are divided into subjective, subtle, and mild [2, 3]. In this article, we will consider the issues of diagnosis and treatment of the most diagnostically and prognostically complex pre-dementia disorders - subjective cognitive decline (SCD) and subtle cognitive impairment (SCI)

Prevalence of subjective cognitive decline and subtle cognitive impairment. Data on the prevalence of pre-dementia cognitive impairments vary widely, which is explained by their wide etiological heterogeneity and various clinical approaches to their detection [3]. Unfortunately, most studies on the prevalence of pre-dementia cognitive impairment are limited to mild cognitive impairment (MCI) and the inclusion of elderly people. As for SCD and SCI, there is practically no data on their prevalence.

Etiology of pre-dementia cognitive impairment. In elderly and senile patients, a decrease in cognitive abilities will be alarming in terms of the development, first of all, of neurodegenerative and cerebrovascular diseases, such as Alzheimer's disease (AD), frontotemporal degeneration, and small vessel disease of the brain [1, 4, 7, 14]. As for young and middle-aged people, diabetes mellitus, alcoholism, diffuse connective tissue diseases, neurosyphilis, neuroAIDS, hypothyroidism, normotensive hydrocephalus, vitamin B12 deficiency, etc. can be the cause of cognitive decline [8]. The search for the cause of cognitive impairment is much easier if the patient has other signs of a somatic or neurological disease. However, in the vast majority of patients with SCI and SCD, especially in young patients, apart from complaints of memory loss and absent-mindedness, there are no focal symptoms and external signs of somatic diseases. Professor E.Z. Yakupov notes that affective disorders, sleep disturbance, gadget addiction, multitasking, pain, COVID-19 are the hidden causes that lead to the development of SCI [11].

Subjective cognitive decline. Although this concept has been known for a long time [21], the official definition was formed only in 2014 due to the expansion of the stages of AD [13, 20]. Thus, SCD is understood as the appearance of complaints about a decrease in cognitive functions (it is emphasized that not only memory) during normal performance of neuropsychological testing (that is, without objectification of cognitive impairments). The authors state that SCD can be caused not only by AD, however, they cite signs in which the relationship of VCI with the subsequent development of AD increases:

1) subjective decrease in memory, and not in other cognitive function;

2) presence of complaints during the last 5 years or more;

3) age of onset at 60 or later;

4) the presence of anxiety associated with SCD;

5) a feeling of worse academic performance compared to people of the same age group;

6) confirmation of the patient's complaints by another person;

7) the presence of the APOE ε4ε4 genotype;

8) presence of AD biomarkers.

Items 6–8 are performed if they are available [13].

SCD is a risk factor for the develop-

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ment of MCI in the future in at least 14% of patients [19].

Subtle cognitive impairment. SCI is understood as a decrease in cognitive functions compared to a higher initial level, but not beyond the age norm or slightly deviating from the norm [12]. Under the leadership of academician Yakhno N.N. in Russia, a comparative analysis of cognitive functions was carried out in SCD, SCI, and in healthy controls. The results of the study confirmed that there are no statistically significant differences between SCD and healthy controls. At the same time, between patients with SCD and SCI, the greatest differences were observed in terms of literal (12.08 vs. 14.78 words) and categorical (14.75 vs. 17.56 words) associations, the total score on the Mini-Mental State Examination (28.67 vs. 29.3 points) and Frontal Assessment Battery (16.42 vs. 17.38) [9].

Professor O.S. Levin rightly emphasizes that the term "SCI" can mean a deterioration in the performance of neuropsychological tests by a patient in dynamics with going beyond the limits of the individual norm, but within the limits of acceptable age values [6]. Thus, in order to expose SCI, dynamic monitoring of the patient is necessary.

The long-term functional preservation of cognitive functions in some patients with pre-dementia disorders, even in the presence of neurodegeneration on neuroimaging and positive AD biomarkers, is explained by the concept of cognitive reserve. This concept suggests that socio-behavioral indicators such as high education, intellectual pursuits, and other activities contribute to the creation of more stable neural connections that protect cognitive functions. In other words, people with a high cognitive reserve are more resistant to dementias, in particular, to AD [5, 15].

Diagnosis of subjective and mild cognitive impairments. Table 1 shows a comparative description of pre-dementia cognitive impairment and marks the most common diseases associated with them. In contrast to MCI in SCD and SCI, the performance of screening neuropsychological tests (MMSE, FAB, MoCA) does not go beyond the age norm.Vakhnina N.V. Vascular cognitive impairments / N.V. Vakhnina // Neurology, neuropsychiatry, psychosomatics. – 2014. – Vol. 1. – P. 74-79. DOI:10.14412/2074-2711-2014-1-74-79

Most patients with SCD and SCI complain of memory loss. However, this complaint may hide not only a true amnestic deficit, but also bradyphrenia, depression, and anxiety. Therefore, in our practice, we ask patients leading questions that allow us to more specificize complaints. For example, can the patient forget what he ate in the morning or what he did the day before? Is it hard to find words? can forget the name of the objects? Is it difficult to understand the in-

Table 1

Characteristics of pre-dementia cognitive impairments

Degree of cognitive decline	Main features	Associated diseases
Subjective cognitive decline	The presence of complaints of cognitive decline (not just memory) Normal performance of neuropsychological tests	In elderly patients, especially if there are complaints of memory loss, to have alertness in terms of the development of Alzheimer's disease In the absence of obvious somatic and neurological causes, one should think about the patient's anxiety, depression, sleep disorders, multitasking, gadget addiction, and past COVID-19
Subtle cognitive impairment	Decreased cognitive ability compared to higher baseline. Does not go beyond the age norm or slightly deviates from the norm Difficulties performing complex neuropsychological tests	
Mild Cognitive Impairment	Decrease in cognitive abilities compared with the individual and with the average norm Out of the age range Detected when performing neuropsychological tests The patient's independence is not affected, slight problems are tolerated when performing complex tasks	In the presence of the amnestic type and in the detection of biomarkers for beta-amyloid and neuronal damage, there is a very high risk of developing Alzheimer's disease. The non-amnestic type can occur within cerebrovascular disease, Parkinson's disease, post-traumatic encephalopathy, etc.

Table 2

Neuropsychological tests

Test	Instruction	Reference
Phonetic speech association	Name within 1 minute words that begin with a certain letter (for example, "L")	> 10 words
Semantic speech association	Name within 1 minute words belonging to the same category (for example, animals)	> 17 words
Visual memory test	The patient is asked to memorize 12 pictures, after an interfering task they are asked to remember them (delayed reproduction), then learn from the presented 48 pictures (delayed recognition)	Delayed reproduction + delayed recognition = 12 pictures, no false recognitions
Auditory memory test	The patient is asked to memorize 12 words, after an interfering task they are asked to remember them (delayed reproduction), then to recognize them by belonging to a category (delayed recognition)	Delayed reproduction + delayed recognition = 12 words, no false recognitions
Trail making test, part A	Connect the given numbers in ascending order, starting from 1 and ending with 25	Execution without fixes or with immediate fixes
Trail making test, part B	Connect in ascending order and alternating the numbers and letters presented (1-A-2-B, etc.)	

terlocutor? Is it difficult to navigate in an unfamiliar place? etc.

To assess SCD and SCI, screening scales used in clinical practice, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), will not be sensitive enough and their results will be within the age norm [10, 16–18]. At the same time, in our opinion, this is the erased and very conditional boundary between MCI and SCI. In patients with MCI, the results of screening neuropsychological tests are outside the normative values, but the patient's daily activities are not impaired (unlike dementia).

In the diagnosis of SCI, more complex scales may be more informative, such as the Semantic or Phonetic Association Test, the Visual memory test, the Auditory memory test, the Trail making test (part A and part B), and the Stroop test. Table 2 presents the normative values of the listed scales.

As noted above, anxiety and depressive disorders can be the cause of cognitive impairments, especially SCD and SCI, so it is necessary to clarify the emotional sphere in patients, to conduct a screening assessment of anxiety and depression (for example, the Hospital Anxiety and Depression Assessment Scale - HADS, the Depression Scale Beck, questionnaire GTR-7).

In some cases, a blood test for thyroid hormones, vitamin B12, folic acid, vitamin D, and iron is required. Currently, there are no unified recommendations in which cases to prescribe one or another blood test, however, there is no doubt that a deficiency of hormones, vitamins, and substances may be accompanied by the development of cognitive complaints. Some classes of drugs can also lead to cognitive decline, such as antidepressants with anticholinergic effects (amitriptyline).

MRI of the brain is the most informative method. Here, it is important to assess mainly hippocampal atrophy, which, along with the amnestic type of cognitive impairment, may alert in terms of the development of AD. The presence of hyperintensity of the white matter, criblura, foci of cerebral infarction, on the contrary, indicate a cerebrovascular disease.

Treatment of subjective cognitive decline and subtle cognitive impairment. If the cause of cognitive impairment (eg, depression, anxiety, iron deficiency) is identified, treatment should be aimed at correcting it. The evidence base for the pharmacotherapy of pre-dementia, especially pre-mild cognitive impairment, is much weaker; studies were mainly conducted with MCI. The emphasis in the treatment of pre-moderate cognitive impairment is on the modification of risk factors, as well as on the maintenance of cognitive reserve.

Conclusion. Pre-dementia cognitive impairment is a heterogeneous syndrome with multiple benign and serious causes. This is the main limiting factor preventing large-scale studies and obtaining reliable results. The key link in the diagnosis of cognitive impairment remains the conduct of a neuropsychological test.

The authors declare no conflict of interest.

Reference

1. Vakhnina NV. Sosudistye kognitivnye narusheniya [Vascular cognitive impairments]. Nevrologiya, nejropsihiatriya, psihosomatika [Neurology, neuropsychiatry, psychosomatics]. 2014;1:74-79 (in Russ).]. DOI:10.14412/2074-2711-2014-1-74-79

2. Zakharov VV, Kabaeva A.R. Nedementnye kognitivnye narusheniya: sub"ektivnye, legkie i umerennye [Non-demented cognitive impairment: subjective, subtle and mild]. Nervnye bolezni [Nervous diseases. 2017;4:3-9 (in Russ).].

3. Zakharov VV, Novikova MS, Kabaeva AR. Profilaktika demencii u pacientov s umerennymi kognitivnymi narusheniyami [Prevention of dementia in patients with mild cognitive impairment]. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova [S.S. Korsakov Journal of Neurology and Psychiatry. 2020;120(8):167-174 (in Russ).]. DOI:10.17116/jnevro2020120081167

4. Bogolepova AN, Vasenina EE, Gomzyakova AA, et al. Klinicheskie rekomendacii "Kognitivnye rasstrojstva u pacientov pozhilogo i starcheskogo vozrasta" [Clinical guidelines "Cognitive disorders in elderly and senile patients"]. ZHurnal nevrologii i psihiatrii im. S.S. Korsakova [S.S. Korsakov Journal of Neurology and Psychiatry. 2021;121(10):141. (in Russ).]. DOI:10.17116/jnevro20211211036

5. Koberskaya NN, Tabeeva GR. Sovremennaya koncepciya kognitivnogo rezerva [Modern concept of cognitive reserve]. Nevrologiya, nejropsihiatriya, psihosomatika [Neurology, neuropsychiatry, psychosomatics. 2019;11(1):96-102 (in Russ).]. DOI:10.14412/2074-2711-2019-1-96-102

6. Levin O.S. Preddementnye nejrokognitivnye narusheniya u pozhilyh [Pre-dementia neurocognitive disorders in the elderly]. ZHurnal nevrologii i psihiatrii im. S.S. Korsakova [S.S. Korsakov Journal of Neurology and Psychiatry. 2019;119(9):10-17 (in Russ).]. DOI:10.17116/jnevro201911909210

7. Lobzin VYu, Kolmakova KA, Emelin AYu. Novyj vzglyad na patogenez bolezni Al'cgejmera: sovremennye predstavleniya o klirense amiloida [New view on the pathogenesis of Alzheimer's disease: modern ideas about amyloid clearance]. Obozrenie psihiatrii i medicinskoj psihologii [Review of psychiatry and medical psychology]. 2018;2:22-28 (In Russ.).] doi:10.31363/2313-7053-2018-2-22-28

8. Smirnov AA, Gustov AV, Kopishinskaya SV, et al. Preddementnye sostoyaniya i demenciya u lic molodogo vozrasta [Pre-dementia conditions and dementia in young people]. Nevrologiya, nejropsihiatriya, psihosomatika [Neurology, neuropsychiatry, psychosomatics. 2014;2:41-43 (in Russ).]. DOI:10.14412/2074-2711-2014-2-41-43

9. Yakhno NN, Zakharov VV, Koberskaya NN, et al.. Predumerennye (sub"ektivnye i legkie) kognitivnye rasstrojstva [Premild (subjective and subtle) cognitive impairments. Nevrologicheskij zhurnal [Neurological journal. 2017;4:198-204 (in Russ).]. DOI:10.18821/1560-9545-2017-22-4-198-204

10. Starchina YuA. Nedementnye kognitivnye narusheniya: sovremennyj vzglyad na problem [Non-demented cognitive impairment: a modern view of the problem]. Nevrologiya, nejropsihiatriya, psihosomatika [Neurology, neuropsychiatry, psychosomatics. 2017;9 (2):71-76 (in Russ).]. DOI:10.14412/2074-2711-2017-2-71-76

11. Yakupov EZ, Zhamieva RA. Sub"ektivnye kognitivnye narusheniya – voprosov bol'she, chem otvetov [Subtle cognitive impairment – more questions than answers]. Nevrologicheskij vestnik [Neurological Bulletin. 2021;LIII(2):71-80 (in Russ).]. DOI:10.17186/nb71485

12. Yahno N.N. Kognitivnye rasstrojstva v nevrologicheskoj klinike [Cognitive disorders in the neurological clinic]. Nevrologicheskij zhurnal [Neurological journal. 2006;1 1(Appendix1):4-12 (in Russ).].

13. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. F. Jessen, R. Amariglio, M. Van Boxtel [et al.]. Alzheimer's Dement. 2014;10(6):844-852. doi:10.1016/j.jalz.2014.01.001

14. Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. D. Eratne, S.M. Loi, S. Farrand [et al.]. Australas Psychiatry. 2018;26(4):347-357. doi:10.1177/1039856218762308

15. Cognitive reserve, Alzheimer's neuropathology, and risk of dementia: a systematic review and meta-analysis. M.E. Nelson, D.J. Jester, A.J. Petkus [et al.]. Neuropsychol Rev. 2021;31(2):233-250. doi:10.1007/s11065-021-09478-4

16. Comparison of the short test of mental status and the Mini-mental state examination in mild cognitive impairment. D.F. Tang-Wai, D.S. Knopman, Y.E. Geda [et al.]. Arch Neurol. 2003;60(12):1777. doi:10.1001/archneur.60.12.1777

17. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. N. Ciesielska, R. Sokołowski, E. Mazur [et al.]. Psychiatr Pol. 2016;50(5):1039-1052. doi:10.12740/pp/45368

18. Lancu I. The minimental state examination--an up-to-date review. I. Lancu, A. Olmer. Harefuah. 2006;145(9):687-690.

19. Subjective cognitive decline and risk of MCI: The Mayo Clinic Study of Aging. A.C. van Harten, M.M. Mielke, D.M. Swenson-Dravis [et al.]. Neurology. 2018;91(4):e300-e312. doi:10.1212/WNL.0000000000005863

20. Subjective cognitive decline: preclinical manifestation of Alzheimer's disease. L. Yan, S. Pei, J. Wen [et al.]. Neurol Sci. 2019;40(1):41-49.

21. The Global Deterioration Scale for assessment of primary degenerative dementia. B. Reisberg, S.H. Ferris, M.J. De Leon [et al.]. Am J Psychiatry. 1982;139(9):1136-1139. doi:10.1176/ajp.139.9.1136

22. The global prevalence of dementia: A systematic review and metaanalysis. M. Prince, R. Bryce, E. Albanese [et al.]. Alzheimer's Dement. 2013;9(1):63-75. doi:10.1016/j.jalz.2012.11.007

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THE ROLE OF BROWN ADIPOSE TISSUE IN ANIMAL AND HUMAN METABOLISM. NEW APPROACHES TO THE STUDY

DOI 10.25789/YMJ.2022.79.22

УДК 611.018.26:616-056.52

This review presents the main and latest stages of the study of brown adipose tissue in humans and animals, as well as the potential role of this tissue in their energy metabolism.

Keywords: brown adipose tissue, obesity, thermogenesis, UCP-1, energy metabolism.

Introduction. The first description of brown adipose tissue (BAT) dates back to 1551, when the German scientist Gessner in his atlas of anatomy described this tissue as "nec pinguitudo nec caro", which means "neither fat nor flesh" [1]. However, as an organ producing heat for mammalian thermoregulation, it was recognized only less than half a century ago [2]. Since the second half of the XX century, it was believed that BAT is present only in newborns and over the course of one year this tissue is reduced [2,3].

However, few studies have suggested the presence of BAT in the body of adults [1,4-9], and only with the widespread use of positron emission tomography with 18-fluorodeoxyglucose (18FDG-PET), a method of functional imaging evaluating areas of increased metabolic activity, have become more often used in the observation of certain types of cancer. Due to this diagnosis, BAT was detected in at least one subgroup of the adult human population [2,10-14]. This surprising discovery aroused great interest among researchers in this field and supported the hypothesis that the presence or absence of brown adipose tissue may be the cause of such common non-communicable diseases as obesity and type II diabetes, and can also be used as a potential therapeutic strategy, since non-contractile thermogenesis contributes to the expenditure of excess energy in the human body.

Function and structure of brown adipose tissue. The main function of brown adipose tissue is thermoregulation through non-contractile thermogenesis [1]. This thermogenesis occurs due to a unique and specific enzyme called UCP-1 (uncoupling protein-1), which disables the production of ATP energy in mitochondria, generating heat instead [1,15]. UCP1 is a unique protein that promotes proton leakage through the inner membrane of mitochondria, reducing the transmembrane electrochemical gradient of protons, and thus thus provides non-contractile thermogenesis by generating heat [1,15]. UCP-1 is a marker of thermogenic adipocytes (not only classic brown, but also recently discovered beige adipocytes), and it is believed that this is the only protein physiologically capable of causing non-contractile thermogenesis, since mice with UCP-1 knockout can produce heat only with chills [2,16].

BAT is activated by sympathetic noradrenergic receptors, mainly through beta-3 adrenoreceptors [2]. Cold is the main physiological stimulator for this noradrenergic activation, since mammals need to maintain thermoneutrality, but it has long been assumed that it can also be activated by food [2,16,17].

Microscopic examination of BAT shows cells with many fat droplets and numerous mitochondria positively expressing UCP-1 [2,18,19]. Classical white adipocytes have one large fat vacuole and a smaller number of mitochondria, which indicates their energy storage function [19].

Recent studies have shown that with a relatively small mass of BAT in the mammalian body, its activation can increase the energy consumption of the animal fourfold, since tissue perfusion increases [15,19-21]. To generate heat, not only fat stored in lipid droplets is used, but also free fatty acids and glucose from the systemic circulation, which exponentially increases the thermogenic potential [15]. This is of particular importance for winter-sleeping animals because there is an urgent need to increase body temperature after micro-arousals that occur during hibernation [2,19,20]. During hibernation, metabolism proceeds under hypothermic conditions, and the animal's body should achieve thermoregulation as soon as possible during microarousal or after the end of the hibernation period [2, 19]. Only thermogenic tissue with high capacity is able to provide adequate short-term thermoregulation [22]

In addition to winter-sleeping animals, the important role of brown adipose tissue is well known for small mammals (rodents), in which the body surface area is larger in proportion to the internal volume [2,22,23]. This large area increases heat loss to the environment and requires more energy used by the BAT to maintain thermoregulation. For example, infants have a high area/volume ratio, and it has long been proven that BAT is present in the human body at an early age [2,21]. However, with a gradual decrease in the surface area relative to the internal volume, the energy costs of thermoregulation decrease, and therefore it was believed that BAT undergoes gradual involution until it completely disappears in early childhood [21]. However, the invention, and then the introduction into practice of 18FDG-PET, changed this point of view, since it was hypothesized that at least a small part of people still have BAT in adulthood, since the detection of metabolic activity in some of the surveyed sites increases the likelihood of the existence of unnoticed thermogenic fat [15,21].

New stages in the study of brown adipose tissue in adults. 18 FDG-PET is a functional study characterized by the ability to detect metabolically active sites absorbing 18-fluorodeoxyglucose (18FDG), a glucose radioisotope [19,24,25]. It began to be used in the 90s, mainly in the diagnosis of oncology, to detect tumors and metastases, which usually have a high metabolic rate and, consequently, high glucose uptake. With 18 FDG-PET scans, organs such as the heart and brain are also constantly detected, as these organs are known to have a pronounced glucose intake, even during fasting [24,25].

PET studies revealed bilateral symmetrical absorption regions of 18 FDG

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in the supraclavicular, cervical and parasternal regions, which could not be interpreted as tumors due to the described characteristics [7,24,26]. Highly active areas were anatomically located in areas of fat weakening on computed tomography, which indicates the presence of metabolically active fat. A high proportion of images with such characteristics on 18FDG-PET in individuals diagnosed with pheochromocytoma, in whom catecholamine-producing tumors are known as intense noradrenergic activation, aroused suspicion that these areas were actually unrecognized brown adipose tissue that proliferated under the influence of chronic noradrenergic stimuli [7,27,28].

The interest of endocrinologists and specialists in metabolism increased in 2007 after the publication of an article in which convincing evidence was presented that, from a functional point of view, these areas detected by 18FDG-PET scanning are brown adipose tissue [15]. However, just two years later, after the publication of three articles, the scientific community recognized that at least some adults have brown adipose tissue [12,13,14]. Brief research results are presented in the table (Table 1).

Cypess and his colleagues analyzed 3,640 18FDG-PET scans performed to detect neoplasms and found absorption sites indicating the presence of BAT in 7.5% of women and 3.1% of men [12]. Indicators such as age, body mass index (in the elderly), outdoor temperature and fasting glucose levels were inversely proportional to positive PET results, and the use of beta blockers was associated with a lower probability of detecting absorption sites. However, after multivariate analysis, glucose concentration and BMI lost their statistical significance, but BMI continued to have a significant negative association with absorption in older people.

A scientific group led by Van Marken Lichtenbelt conducted 18FDG-PET in 24 people after exposure at low temperatures (16 C° for two hours), in light clothing and without body chills [13]. According to the study, 96% of positive results were revealed, and an inverse proportional relationship was obtained between the level of absorption (kilobecquerels) and BMI (conditional amount of body fat). Only one obese subject had negative absorption after exposure to cold. Also, adipose tissue samples obtained from areas with positive uptake of 18FDH had high immunoreactivity to the UCP-1 protein, which indicated the presence of metabolically active BAT.

In a recent paper published in the aforementioned publication, Virtanen and co-authors analyzed tissue biopsies from PET-positive areas visualized in three young people and found positive expression of UCP-1, confirming the presence of brown adipose tissue [14]. Considering that only 10% of the energy used by BWT is glucose and 90% is fatty acids, the Finnish group calculated by mathematical analysis based on the absorption of FDG in these people an increase in energy consumption by 7%, which corresponds to a weight loss of 4.1 kg per year.

None of the studies were aimed at assessing the causal relationship between BMI and the presence or absence of BAT, which leads to countless hypotheses. One hypothesis is that because obese people have more fat protection, they may feel less cold, which in turn means that they need less activation of BAT. Another version that requires further study is that the absence of brown adipose tissue may be, at least in part, due to weight gain and a decrease in blood glucose levels in a certain subgroup of people.

The role of brown adipose tissue in human metabolism. After the appearance of the first 18FDG-PET images, it was hypothesized that the BAT is a residual organ, like other organs that often do not involute during embryo development. Data from Van Marken Lichtenbelt studies demonstrated almost 100% absorption during cold stimulation and made this hypothesis less likely [13].

The total mass of brown adipose tissue in humans does not exceed 60-100 grams, which is only a small part of the mass of white adipose tissue, even in people with low body weight [21]. However, as already noted, BAT perfusion increases significantly with noradrenergic stimulation, which leads to high peripheral absorption of glucose and fatty acids, which makes BAT an energy-intensive tissue, as well as an important regulator of glucose homeostasis [2,20,21,29,30]. This tissue has an insulin-dependent ability to absorb glucose and promotes the clearance of free fatty acids, which is closely related to insulin resistance [24].

Some studies have tried to estimate the increase in energy consumption after the activation of BAT, and data were obtained on fluctuations from 5 to 77% compared to the basal level [21]. As described earlier, Virtanen and co-authors suggested an increase in basal metabolism by 7% [14]. Orava and co-authors found a similar increase of 8% after exposure to cold, but when the analysis was carried out only in 18FDG-PET-positive people, the increase increased to 22% [29]. Quellett and colleagues decided to measure energy consumption by indirect calorimetry, before and after exposure to cold in a shirt soaked with water at a temperature of 18 °C [31]. The percentage increase in this study reached 77% after exposure to cold. A scientific group led by Yoneshiro divided the positive and nega-

Table 1

Summary of the results of three articles of the New England Journal of Medicine in 2009, which confirmed to the scientific community the presence of brown adipose tissue in adults

Van Marken Lichtenbelt and cols.	Virtanen and cols.	Cypess and cols.
Active BAT was detected with FDG-PET in 96% of people after acute exposure to cold	Cold-induced absorption of PET-FDG was 15 times higher in paracervical and supraclavicular adipose tissue in five subjects	Positive scan results were noted in 7.5% of women and 3.1% of men
Significantly lower activity in overweight and obese individuals (the only subject with a negative PET result was obese)	Mathematical analysis showed a decrease in body weight by 4.1 kg during 1 year in patients with active brown adipose tissue	The probability of detecting active BAT is inversely proportional to the outdoor temperature, years, and BMI in the elderly
Higher activity has a significant direct positive correlation with resting metabolic rate and negatively correlates with BMI and body fat mass of the studied	Biopsy samples of three subjects were collected, which demonstrated levels of messenger RNA and UCP-1 protein, as well as other markers of brown fat (such as PGC1a, DIO2, PRDM16 and ADRB3), and morphological assessment showed an abundance of multilocal adipocytes	The probability of detection is inversely proportional to fasting glycemia in univariate analysis, but is not significant in multivariate analysis

tive results of PET-FDG in relation to the activation of BWT and found a stimulated 25% increase in energy consumption in the positive group, which corresponds to 358 kcal [31]. However, the hypothesis about adipostats asserts that an increase in energy consumption must necessarily lead to a parallel increase in energy consumption in order to avoid weight fluctuations [33,34]. In order to better understand what happens to the energy balance in a situation of increased energy consumption due to thermogenesis, it is necessary to evaluate animal studies, since there are not so many studies in this area in the human body.

Cannon and Nedergaard found an increase in oxygen and energy consumption in animals exposed to lower temperatures, while the increase in nutrition was proportional to oxygen consumption, but animals living in the cold did not gain weight [32]. However, several authors, based on different results in different experiments, still believe that any increase in energy consumption will be easily compensated by an increase in food intake, and that isolated activation of BAT will not lead to weight loss [16,23,35,36]. Ravussin and co-authors put forward an original assumption that the activation of BAT in combination with an anorexigenic drug can cause weight loss synergy due to the dissociation of increased energy consumption with food consumption, however, the results of his studies combining acute intermittent exposure to cold with AM251, an antagonist of endocannabinoid receptors, showed neither synergy nor weight loss in the group exposed to cold and not receiving this substance [36].

Yoneshiro and co-authors, who analyzed the differences between BAT-positive and BAT-negative people based on their uptake of 18FDG-PET, reported that BAT-positive people did not gain weight with age [37]. On the other hand, the BAT-negative subjects had a high body mass index, a high percentage of body fat and abdominal fat mass, which confirms the assumption that the activation of BAT contributes to weight control and prevents the development of obesity.

Gadea and colleagues described a case of a rare BAT tumor called a hibernoma in a 68-year-old woman who lost 10 kg of weight in 6 months during this disease [37]. Within a year after the operation, the woman gained 15 kg, but after resection there was no decrease in energy consumption and an increase in food intake was observed. The description of this case suggests, although obviously with all the limitations of the evaluation of a single case, that BAT is capable of causing weight loss, at least when it is present in large quantities and stimulated. Another situation that deserves mention is hyperthyroidism. Thus, Lahesmaa and co-authors have found that hyperthyroidism, which often leads to significant weight loss, is associated with a threefold increase in the absorption of glucose by BAT, increased energy consumption and high consumption of lipids as an energy substrate [38]. The relationship between BAT and thyroid hormones has been known for several decades and has been described by many authors [2,39].

Diet-induced thermogenesis and metabolic inefficiency. The components of daily energy consumption are the basal metabolic rate, energy costs for physical activity and the thermal effect of food [40]. Food thermogenesis is classically regarded as the energy costs of digesting and storing calories. However, several decades ago, a hypothesis was put forward about another concept of thermogenesis caused by diet and associated with energy expenditure, which is closely related to BWT, although it was insufficiently recognized, and only a few researchers tried to follow this path until recently [16,17].

In 1979, Rothwell and Stock demonstrated in a fundamental study published in the journal Nature that rats chronically fed a "cafeteria diet" consisting of a diet with high energy value, rich in fats and carbohydrates and poor in proteins, had a disproportionate increase in energy consumption, which could not be explained only by the energy value of food [17]. The rats gained less weight than predicted, and it was suggested that they spent part of the incoming energy in the form of heat. In accordance with these findings, higher rectal and interscapular temperatures were observed in rats in the postprandial period. Tissue analysis of these rats confirmed an increase in the mass of brown adipose tissue by 260% compared to control rats fed a standard diet, which suggests that the energy consumed came from replenishment and activation of brown adipose tissue.

Despite the impact of the study, diet-induced thermogenesis has been almost forgotten, at least by human physiologists. However, in 1999 Stock put together a series of studies on overeating, the purpose of which was to evaluate interindividual reactions to weight gain based on possible differences between percentages of fat mass and fat-free mass [39]. Using the law of thermodynamics, Stock calculated that it takes from 30 to 45 kJ/kg to increase body weight by one kilogram. However, some people needed values up to 100 kJ/kg to gain one kilogram. The only possibility, according to the author, is that such a large spread is due to the inefficiency of metabolism and thermogenesis. Recently, Wijers and colleagues found a linear correlation between energy costs for weight gain of 1 kg and energy costs caused by cold, suggesting that the same mechanism is involved in thermogenesis caused by cold, which leads to metabolic inefficiency, possibly caused by the influence of BAT activity [40].

A recent study in which postprandial 18FDG-PET was evaluated, with all the resulting reservations regarding interpretation due to postprandial glucose uptake

Table 2

Prevalence of positive uptake of PET-FDG in different population groups from different countries

Ambient temperature	Acute exposure to cold
USA (Cohade, and others) – 13,7% (winter), 4,% (the rest of the year)	Netherlands (von Marken Lichtenbelt, and others) – 97%
USA (Yeung, and others) – 3,7% (neck fat)	Finland (Virtanen, and others) – 100%
USA (Cypess, and others) – 7,5% (women), 3,1% (men)	Japan (Saito, and others) – 53%
England (Au-Yong, and others) – 7,2% (winter), 2,5% (summer)	Japan (Yoneshiro, and others) – 46%
Canada (Ouellet, and others) – 6,8%	
Australia (Lee, and others) - 8,5%	
Germany (Stefan, and others) – 3,05%	

by muscles, showed that, compared with thermoneutrality, after a hypercaloric and hyperprotein diet, glucose uptake of BAT is observed, similar to that which occurs after cold activation [41]. However, another similar study questioned the significance of thermogenesis caused by diet, demonstrating that chronically overfed people (200% overfed) did not increase the absorption of glucose by BAT when comparing the results of 18FDG-PET scans before and after the period of overfeeding [42]. Scanning for 18 FDG-PET in overeating patients was performed four hours after meals using a low-carb diet. The timing and composition of the diet could distort the results.

It was also noted that in persons with constitutional thinness, even under thermoneutral conditions, glucose uptake in the BAT was 16.7 times higher compared to persons with normal weight [43]. On the contrary, in women with anorexia nervosa who have a weight similar to that of people with constitutional thinness, the glucose uptake of BAT was practically zero, which suggests that the role of BAT is metabolically ineffective in this rare but interesting subgroup of people.

Although it is difficult to imagine the evolutionary advantage of metabolic inefficiency, since it is generally believed that obesity is the result of an economical phenotype adapted to energy storage in food shortage conditions, a possible explanation may be that it is active with a low-protein diet, and thermogenesis is important for the animal to constantly look for protein sources [2,16]. In fact, it has been demonstrated in humans that low-protein diets are associated with greater metabolic inefficiency, and high-protein diets lead to high thermogenesis, and the latter is mainly due to the high rate of digestion, metabolism and storage of this macronutrient [44].

Despite the fact that this concept is highly controversial and refuted by some researchers, the idea that brown adipose tissue contributes to the expenditure of excess calories in the form of heat and makes it difficult for some people to gain weight deserves further study and may lead to the development of drugs that activate these mechanisms.

The prevalence of brown adipose tissue. Concepts of recruitment and activation. As noted earlier, in 2009 Cypress and colleagues found that 7.5% of women and 3.1% of men were BAT-positive at ambient temperature [12]. Similar results were obtained in previous studies conducted under similar conditions, with slight variations [23]. Van Marken Lichtenbelt and co-authors identified 96% of BAT-positive individuals (only one obese man was BAT-negative) after acute cold exposure [13], however, in the Japanese population this number decreased to 40% [31]. There are no published studies on this topic in Brazil, but unpublished data indicate an even lower level. Table 2 shows the differences in the absorption of BAT in different populations, at ambient temperature and after exposure too cold [12,13,14,21,24,31]. What could be the reason for such differences in similar experiments?

To better understand this difference, we need to go back to physiology and research on mice. If an animal lives in conditions of complete thermoneutrality and is exposed to the harsh effects of cold, its first reaction is chills to protect the internal temperature of the body [2]. At this moment, the animal does not have brown adipose tissue ready to activate and maintain the basic body temperature. As the duration of exposure to cold, the animal begins to gain weight of BAT and activate it, reducing shivering. When the recruitment of this tissue reaches its maximum, the animal ceases to tremble, and all heat production occurs due to the activation of BAT, hence the mitochondrial cleavage of UCP-1. After returning to thermoneutrality, the animal retains the recruited BAT, inactive, but ready to activate in case of a new exposure to cold. This is demonstrated by the administration of norepinephrine before and after recruitment. The increase in energy consumption after recruitment is significant, which proves that the BAT has been recruited and is ready for activity, unlike what happens earlier, when the BAT is not recruited for rapid activation after acute stimulation with norepinephrine.

This is a fundamental concept, since it helps explain why there is such a population spread in the uptake of 18FDG-PET - daily chronic exposure to cold is likely to recruit BAT, which may become more active after an acute decrease in ambient temperature. This hypothesis was confirmed by the studies of two scientific groups, which found a significant activation of BAT after chronic and daily exposure to cold, as well as an increase in energy consumption during acute exposure to cold after chronic stimulation compared with acute exposure to cold at the beginning of the experiment [45,46].

Based on this hypothesis, a higher percentage of BAT-positive individuals was identified in the winter season. Another interesting theory that helps explain this difference is that photoperiodism can also interfere with the set of BAT. With the reduction of daylight hours, on the eve of winter, BAT can be slowly recruited in order to have a sufficient level ready for the onset of cold weather, and to prevent the dependence of the body's thermoneutrality on shivering. Melatonin plays a significant role in this process, so in an animal study during hibernation, a higher content of BWT mass was shown in animals that received melatonin [47], and in a recent study, a high body temperature was observed in mice receiving a melatonin supplement in the amount of 10 mg/kg, which was detected using infrared thermography [48].

New imaging techniques for detecting brown adipose tissue. In the study of BAT, there may be difficulties partly related to detection methods. Thus, 18FDG-PET was fundamental for the identification of BAT in adults, but it is an expensive method that uses ionizing radiation and the method depends on the activation of this tissue for detection [16]. Since only 10% of BAT absorption occurs due to glucose, the sensitivity of the method using mainly glucose absorption may be low [15].

Therefore, new imaging methods are proposed to replace 18FDG-PET in scientific research and in clinical practice [47]. Validation studies of magnetic resonance have already been conducted on animals, with promising results and good opportunities for detecting depots of brown adipocytes in white adipose tissue [48]. Experimental studies have also been conducted on humans and have shown good sensitivity with the additional advantage of detecting even inactive tissue [49,50].

Another available research option is infrared thermography (IT), a non-invasive and simple method that evaluates body temperature in various tissues by image (this method has long been used in civil engineering and in medical conditions such as anastomosis and cancer) [51,52]. The possibility of obtaining results using IT makes this method promising and useful, as evidenced by a study by Lee and colleagues, which describes an increase in temperature in the corresponding areas of BWT after exposure to cold and eating in humans [53]. Studies in children using infrared thermography have also shown promising results [54]. Borga and co-authors presented a new version of the study using dual-energy computed tomography (DCT) [47].

In conclusion, it should be noted that the study of brown adipose tissue has been greatly developed after the discovery of 18FDG-PET in adults, becoming an intensive area of research not only in general biology, but also in medicine.

Most of them are recent discoveries and therefore need further study and justification.

Activation of BAT mediated thermogenesis may have therapeutic potential in the treatment of patients with obesity, diabetes and metabolic syndrome, providing new therapy options.

Reference

1. Gessner K. Historiae Animalium: Lib I De Quadrupedibus viviparis. 1551.
2. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84(1):277-359.
3. Tam CS, Lecoultre V, Ravussin E. Brown adipose tissue: mechanisms and potential therapeutic targets. Circulation. 2012;125(22):2782-91.
4. Himms-Hagen J. Obesity may be due to a malfunctioning of brown fat. Can Med Assco J. 1979;121:1361-4.
5. Joy RTJ. Responses of cold-acclimated men to infused norepinephrine. J Appl Physiol. 1963;18:1209-12.
6. Jung RT, Leslie P, Nicholls DG, Cunningham S, IslesTE. Energy expenditure in normal and diabetic man: the role of brown adipose tissue. Health Bull (Edinb). 1988;46(1):55-62.
7. Kang BS, Han DS, Paik KS, Park YS, Kim JK, Kim CS, et al. Calorigenic action of norepinephrine in the Korean women divers. J Appl Physiol. 1970;29:6-9.
8. Lesna I, Vybıral S, Jansky L, Zeman V. Human nonshivering thermogenesis. JTherm Biol. 1999;24:63-9.
9. Bouillaud F, Villarroya F, Hentz E, Raimbault S, Cassard AM, Ricquier D. Detection of brown adipose tissue uncoupling protein mRNA in adult patients by a human genomic probe. Clin Sci. 1988;75:21-7.
10. Hany TF, Gharehpapagh E, Kamel FM, Buck A, Himms-Hagen J, von Schulthess GK. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. Eur J Nucl Med Mol Imaging. 2002;29(10):1393-8.
11. Nedergaard J, Bengtsson T,Cannon B.Unexpected evidencefor active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab. 2007;293:E444-52.
12. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509-17.
13. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360 (15):1500-8.
14. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360(15):1500-8.
15. Nedergaard J, BengtssonT, Cannon B. Three years with adult human brown adipose tissue. Ann NY Acad Sci. 2010;1212:E20-36.
16. Chechi K, Nedergaard J, Richard D. Brown adipose tissue as an antiobesity tissue in humans. Obes Rev. 2014;15:92-106.
17. Rothwell NJ, Stock MJ. A role for brown adipose tissue in diet- induced thermogenesis. Nature. 1979;281(5726):31-5.
18. Cinti S. The adipose organ at a glance. Dis Model Mech. 2012;5(5):588-94.
19. Smith RE, Hock RJ. Brown fat: thermogenic effector of arousal in hibernators. Science. 1963;140:199-200.
20. Smith RE.Thermoregulatory and adaptive behavior of brown adipose tissue. Science. 1964;146:1686-9.
21. Lee P, Swarbrick MM, Ho KK. Brown adipose tissue in adult humans: a metabolic renaissance. Endocr Rev. 2013;34(3):413-38. Silva JE. Thermogenic mechanisms and their hormonal regula- tion. Physiol Rev. 2006;86(2):435-64.
22. Ravussin E, Galgani JE. The implication of brown adipose tissue for humans. Ann Rev Nutr. 2011;31:33-47.
23. Hatai S. On the presence in human embryos of an interscapular gland corresponding to the so-called hibernating gland of lower mammals. Anat Anz. 1902;21:369-73.
24. Hironaka FH, Sapienza MT, Ono CR, Lima MS, Buchpiguel CA. Base do estudo PET com FDG. In: Medicina Nuclear: Princípios e Aplicações. Ed Atheneu. 2012;15;332-5.
25. Barrington SF, Maisey MN. Skeletal muscle uptake of fluorine18-FDG: effect of oral diazepam. J Nucl Med. 1996;37:1127-9.
26. Lean ME, James WP, Jennings G,Trayhurn P. Brown adipose tissue
in patients with phaeochromocytoma. Int J Obes. 1986;10:219-27.
27. Hadi M, Chen CC, Whatley M, Pacak K, Carrasquillo J. Brown fat imaging with 18F-6-Fluorodopamine PET/CT, 18F-FDG PET/CT, and 123I-MIBG SPECT: a study of patients being evaluated for pheochromocytoma. J Nucl Med. 2007;48:1077-83.
28. Orava J, Nuutila P, Lidell ME, Oikonen V, Noponen T, Viljanen T, et al. Different metabolic responses of human brown adipose tissue
to activation by cold and insulin. Cell Metab. 2011;14:272-9.
29. Peirce V, Vidal-Puig A. Regulation of glucose homeostasis by brown adipose tissue. Lancet. 2013;1(4):353-60.
30. Ouellet V, Labbe SM, Blondin DP, Phoenix S, Guérin B, Haman F, et al. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J Clin Invest. 2012;122:545-52.
31. Yoneshiro T, Aita S, Matsushita M, Kameya T, Nakada K, Kwai Y, et al. Brown adipose tissue, whole body energy expenditure and thermogenesis in healthy adult men. Obesity (Silver Spring). 2011;19:1755-60.
32. Cannon B, Nedergaard J. Thermogenesis challenges the adipostat hypothesis for body weight control. Proc Nutr Soc. 2009;68(4):401-7.
33. Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc Royal Soc Lond B Biol. Sci. 1953;140:578-92.
34. Barnett SA. Adaptation of mice to cold. Biol Rev Camb Philos Soc. 1965;40:5-51.
35. Ravussin Y, Xiao C, Gavrilova O, Reitman ML. Effect of intermittent cold exposure on brown fat activation, obesity and energy homeostasis in mice. PLoS ONE. 2014;9(1):e85876.

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THE ROLE OF VITAMINS AND VITAMIN-CONTAINING PRODUCTS IN REDUCING ACUTE INFECTIOUS DISEASES OF THE POPULATION OF THE NORTH

DOI 10.25789/YMJ.2022.79.23

УДК 613.292

The literature review presents current data from the study of domestic and foreign literature of recent years on the effect of vitamins, vitamin-containing products and other nutrients on the reduction of acute infectious diseases in the population of the Far North.

The purpose of the study: to identify the possibilities of preventing acute respiratory viral diseases by increasing the effectiveness of preventive measures using modern methods of optimizing the nutrition of the population of the North.

Methodical approaches. The study of the literature was carried out in sections: “Seasonal fluctuations in acute infectious respiratory diseases”, “Peculiarities of human immunity in different seasons of the year”, “Nutrition and the immune system”, “Possibilities of using local raw materials in the diets of the population of the North for preventive purposes”

Results. The patterns of formation of seasonal transient immunodeficiencies and immune dysfunctions against the background of alimentary-dependent deficiency of macro- and microelements, unbalanced with the nutritional needs of the population living in the North, were determined. The existing and priority fundamental approaches to the formation of diets using products of the local raw material base are analyzed. It is necessary to diversify the diet of the population of the North by including vitamin-mineral complexes and products with immunomodifying properties. Industrially produced functional foods should be used, which can increase immune defenses and reduce the prevalence of viral respiratory diseases and their consequences.

Conclusion. The analyzed publications indicate that an increased incidence in a certain season can be considered as a problem of the formation of transient induced immunodeficiency in the Far North. One of the reasons for this is the peculiarity of the functioning of the immune system in conditions of seasonal rhythms. Modern possibilities of nutrition science allow to actively form a balanced daily human diet. The increase in immunity is achieved through the use of vitamins and vitamin-containing complexes and other nutrients that can increase the level of immune protection and, accordingly, reduce the prevalence of viral respiratory diseases and their consequences, which is extremely important for the population living in the extreme conditions of the Arctic zone.

Keywords: population of the North, seasonality, immunity, respiratory diseases, preventive nutrition.

Introduction. Despite the abundance of publications, the issues of full-fledged human life and the protection of his health are far from being solved in the extreme natural and climatic conditions of the North [1, 24].

Significant efforts in the field of public health do not lead to a significant decrease in the prevalence of viral respiratory diseases among the population living in vast territories that make up more than 64% of the territory of Russia [22],

In this regard, the Decree of the Chief State Sanitary Doctor of the Russian Federation "On measures to prevent influenza and acute respiratory viral infections, including a new coronavirus infection (COVID-19) in the 2020-2021 epidemic season" was adopted (it was registered with the Ministry of Justice of Russia July 29, 2020 N 59091) [7].

This document defines purely anti-epidemic measures. But scientific publications describe the experience of solving problems with the help of nutrition correction through the use of vitamins and microelements, probiotics, specialized food products. The possibility of positive dynamics of increasing immunity, reducing the frequency of diseases, improving their prognosis in different seasons of the year has been proven.

Extreme and sub-extreme climatic and geographical conditions of the North are characterized by a pronounced cold effect (prevailing negative air temperature), low absolute air humidity, periodic strong winds, changes in light photoperiodicity (polar night, polar day), lack of oxygen, sudden changes in atmospheric pressure, instability of the magnetosphere, adaptation to which is achieved at the cost of a significant morphological and functional stress of the human body [5, 22].

Scientific publications describe the experience of solving problems with the help of nutrition correction through the use of vitamins and trace elements, probiotics, prebiotics, specialized foods. The possibility of positive dynamics of immunity indicators, reduction of the frequency of diseases, improvement of their prognosis has been proved. The use of this experience is especially expedient for the population of the North.

One of the significant components of the morbidity of the population of the North are acute respiratory viral infections (ARVI), which includes a number of diseases of predominantly upper respiratory tract of viral etiology.

The diseases caused by these different etiological agents share common mechanisms of transmission, many stages and features of pathogenesis, as well as clinical manifestations. The situation with the spread of SARS in the North is characterized by an excess of morbidity rates in all age groups of the population of

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the North compared to the corresponding indicators in the Russian Federation. An analysis of the incidence of children and adolescents in the northern territories indicates that the Nenets, Yamalo-Nenets Autonomous Okrug (YaNAO) fall into the risk zone, in which, according to the class of respiratory diseases, the incidence is 1.3–1.7 higher than in the Russian Federation [5] (Table).

According to various authors, a severe course and deaths were observed in various acute respiratory viral infections (adenoviral disease, parainfluenza, respiratory syncytial infection), which occurred both in the form of mono and mixed infection [9].

Typical for the North are conditions associated with a lack of intake of vitamins and minerals in the body, with increased needs for them, especially in unfavorable seasons of the year. To meet the physiological needs of the body, a whole complex of nutrients is needed, the composition and quantity of which change throughout life. Essential amino acids, polyunsaturated fatty acids, vitamins, minerals, pro- and prebiotics are vital. Unfortunately, the actual nutrition of the population of the North among almost all age, ethnic and professional groups of those surveyed has a large number of deviations towards deficiency and imbalance in micronutrients [22].

For example, studies have shown that the winter diet of the inhabitants of Yakutia is represented by low-calorie food, not only low in the main macronutrients (proteins, fats, carbohydrates), but also with a lack of vital micronutrients such as Ca, Fe, Mg, Se, as well as vitamins. : A, D, C, group B, both in the city and in the villages [23]. These intertwining circumstances necessitate the search for new ways to prevent acute respiratory diseases. The present article is devoted to the solution of the question: "How to solve these problems?".

The purpose of the study: to identify the possibilities of preventing acute respiratory viral diseases by increasing the effectiveness of preventive measures, using modern possibilities for optimizing the nutrition of the population of the North.

Seasonal fluctuations in acute infectious respiratory diseases. Respiratory viral diseases are seasonal. The reference, in fact, to the winter epidemic of respiratory infectious diseases is contained in the ancient Greek records of Hippocrates - the "Book of Epidemics", written around 400 BC. e. and translated from Greek in 1941 and 1944 [6].

Seasonality of respiratory infections is a phenomenon of fluctuations in the incidence of various respiratory tract infections during the year, while maintaining a similar pattern of fluctuations from year to year in the same periods. There is some relationship between the incidence and severity of disease on the one hand, and low temperature and humidity on the other.

It is believed that cold air reduces the natural resistance to infection in the nasal passages. It is not excluded and the launch of the processes of violation of the immune system. There are other hypotheses on the effect of temperature on morbidity. Each of them can, to one degree or another, contribute to the incidence [39].

According to most researchers, the main factors contributing to seasonality are changes in environmental parameters in the form of temperature and humidity, which increase the resistance of the virus and its rate of transmission. This is due to the fact that the annual epidemics of SARS, including influenza, spread faster and more intensively in the winter and pre-winter seasons of the year [9, 14].p

In the same seasons of the year, peculiar processes of modeling congenital and acquired in the course of life human immune responses to viral infections of the respiratory tract are observed. A relationship has been established between the prevalence of respiratory viral infections and an increase in the incidence of pneumonia [18].

Nevertheless, the decrease in the negative consequences of seasonal fluctuations in acute respiratory diseases can be minimized by knowing the characteristics of immunity in different seasons of the year.

First detected morbidity in the population of the northern territories of the Russian Federation in 2014

Territories	Incidence by class B per 1000 population			All population per 100 thousand	
	whole population	children DOR	teenagers	ARD. URT	Flu
Russian Federation	333.4	1170.5	674.7	19474.7	9
Republic of Karelia	481.5	1757.6	1099.5	36195.2	28.1
Komi Republic	484.6	1809.3	882.3	36777.3	10.1
Arkhangelsk region	440.8	1679.7	991.3	33113.8	38.1
including:					
Nenets Autonomous Okrug	665.4	2058.4	1148.1	38639.8	27.8
Arkhangelsk Region (excluding the Nenets Autonomous Okrug)	432.3	1660.6	983.4	32905.2	38.5
Tyumen region	362.2	1181.9	690.8	30712	12.1
including:					
Khanty-Mansi Autonomous Okrug-Yugra	385.3	1253.2	649.9	28052.9	9.5
Yamalo-Nenets Autonomous District	497.5	1570.1	855.9	36772.5	26.5
Tyumen region without autonomous regions	284.8	923.3	659.8	31413.2	9.6
Republic of Sakha (Yakutia)	493.9	1532.1	718	22604.2	18.4
Magadan Region	319.6	1285.5	516.1	20812.8	84.5
Chukotka Autonomous District	504.8	1527.4	944.8	15357.7	4

Notes: Efimova N.V., Gornov A.Yu., Tikhonova I.V., Zarodnyuk T.S. INFLUENCE OF ENVIRONMENTAL FACTORS ON THE INCIDENCE OF RESPIRATORY BODIES IN THE POPULATION OF THE NORTHERN REGIONS // Modern problems of science and education. - 2016. - No. 6; URL: http://science-education.ru/ru/article/view?id=25581 (date of access: 20.07.2021), where (DOR) - diseases of the organs respiratory; ARD - acute respiratory diseases; URT - upper respiratory trac

Features of human immunity in different seasons of the year. According to our assumption, seasonality of infectious diseases and their pathologies is based on changes in the activity of the immune system. Among the factors that directly affect immunity are seasonal changes in temperature, absolute humidity, weather severity, duration and intensity of insolation. These listed factors can be classified as seasonal environmental changes. They are supplemented by environmental features, the nature of work or study, living conditions. In any case, in order to take measures that increase the effectiveness of reducing diseases and preventing their undesirable consequences, it is important to know the seasonally determined patterns of immunity formation. The analysis of publications makes it possible to shade some of these regularities [36, 41].

The problem of maintaining immunity is especially important for survival in the harsh winter conditions of the North, which exposes people to severe physiological stress, which is defined as an adaptive process [22].

Many diseases and physiological processes have an annual frequency. More than 4,000 protein-coding mRNAs have been found in leukocytes and adipose tissue that have seasonal expression profiles, with inverted patterns observed between Northern regions. It was found that the cellular composition of the blood varies depending on the season [10, 41].

Suggested to explain the periodicity of the expression of genes responsible for the immune response, not only in ARVI, but also in autoimmune diseases, which constitutes a deep pro-inflammatory transcriptomic profile during the European winter, accompanied by an increased level of soluble IL-6 receptors and C-reactive protein, risk biomarkers these diseases. The peak of these diseases occurs in winter [36].

It has been suggested that it is possible to use the evolutionarily determined mechanisms of human immunity to predict periods of immunologically complex states. The primary ecological signal by which the season can be anticipated is changes in daily photoperiodicity.

Other environmental factors, interacting with the photoperiod, affect immune function and pathological processes. Data on seasonal fluctuations that occur against this background and change the structure and immune functions of lymphatic organs and pathological processes, as well as their possible interaction with environmental stressors, are considered. Seasonal peaks in the size and structure of the lymphatic organs usually occur in late autumn or early winter. It has also been suggested that impaired immune function may occur during particularly severe winters when stressors override the increase in immune function caused by short daylight hours [36, 41].

Thus, the priorities of the determinants of the emergence and spread of infectious diseases in the winter season are diverse, and especially in the conditions of the North. The integrating mechanism that determines the likelihood of occurrence, course and outcome of ARVI is the readiness of the immune system to respond and its reaction in the event of adverse epidemiological situations.

These regularities are confirmed by the fundamental work, which presents in detail the information that the immune system, in connection with its functional tasks, is the key to protecting the body from pathogenic external and internal factors. The variant of the immune response chosen by the body is determined by the general structure of metabolism in its various manifestations: energy, plastic, utilization [28].

Thus, an increased level of morbidity in a certain season can be considered as a problem of the formation of a transient induced immune disorder. In the Far North, the cause of such disorders is the non-optimal adaptation of the body to environmental conditions. All this makes it possible to form the principles of non-specific activities using evidence-based recommendations on nutrition.

Nutrition and the immune system. The problem is reflected in the guide to healthy nutrition, prepared by a team of authors edited by academician V. A. Tutelyan [15], in articles reflecting various aspects of the relationship between nutrition and immunity [34],

The following postulates are relevant to the problem under discussion. The immune system is a powerful multi-component homeostatic system that needs a large number of energy and plastic components. A balanced, wholesome diet allows the maintenance of immune cell function, the initiation of effective responses against pathogens, and a rapid response to prevent chronic inflammation [34, 38].

The exact composition of a varied, balanced and healthy diet depends on individual characteristics (such as age, gender, lifestyle and degree of physical activity), locally available foods and dietary customs. The need for the main ingredients of food depends on the traditions of the peoples of the North and the nature of labor activity [22, 23].

To maintain the optimal regulation of the immune system, it is also necessary to provide the body with microelements. Some trace elements play a key role in the function of the immune system, vitamins (C, D, A, E, B6, B12, folic acid), minerals (zinc, iron, copper, selenium, magnesium). They help maintain the structural and functional integrity of mucosal cells, provide the synthesis of antimicrobial factors and antibodies, are involved in the differentiation, proliferation, functioning and migration of innate and adaptive immunity cells, antigen recognition, play an important role in inflammation, antioxidant effects. Micronutrient deficiencies and imbalances lower immune defenses, making a person more susceptible to infections. [10,28,38,40,42].

Almost all forms of immunity suffer from protein-energy deficiency. The reason is the role of amino acids with immunoactive properties. These amino acids include: aspartic and glutamic acids, serine, alanine, arginine, lysine. They accelerate the transformation in the bone marrow of the precursors of immune cells - T-lymphocytes into mature cells. Along with tryptophan, they stimulate thymus-dependent immunity.

Immune active amino acids enhance the production of specific antibodies. They also accelerate the production of leukocytes necessary to combat viruses and bacteria [4,10,15,28].

Glutamine is found in lymphocytes and macrophages and determines the level of cellular immunity. Lymphocytes are involved in the production of antibodies. Macrophages are inhibited and inactivated by viral and bacterial agents. Methionine, arginine, and valin provide cell immunity energy. Serotonin, like its predecessor, tryptophan provides overall body resistance [38].

The deficiency of polyunsaturated fatty acids that make up the spectrum of lipids reduces immunity. The activity of T-cells, as well as macrophages, depends on their presence in the body. They stimulate the production of prostaglandins, substances that have a pronounced anti-inflammatory effect. They provide protection of the respiratory tract from infections, preventing the occurrence of acute respiratory viral infections [10, 28].

The influence of vitamins on the regulatory mechanisms of the immune system is widely presented in the specialized literature. But they are presented most profoundly at a high evidence level in relation to vitamin D [8,40]. The immune regulatory properties are described, the effectiveness and prospects of its use in the prevention of acute respiratory viral

infections are proved. The results of numerous studies indicate that vitamin D is a bioregulator with a wide range of properties. This made it possible to use the wide possibilities of using this nutrient in prevention (ARVI), including during the current pandemic of coronovirus infection [21, 29].

In 2017, a meta-analysis was conducted of 25 randomized controlled trials involving a total of 11,321 people aged 0 to 95 years. Relationships between vitamin D intake and the incidence of acute respiratory infections have been identified. It turned out that with the addition of vitamin D, the risk of developing at least one case of SARS decreased by 12%. With regular use of vitamin D, the preventive effect was even more evident. The results were more striking among people who had low vitamin D sufficiency [40].

The role of vitamin D in the prevention of acute respiratory diseases is shown in the works of V.B. Spirichev and his students that the importance of vitamin D use is especially clear when combined with 12 vitamins [12].

Relatively recently conducted randomized trials have shown the effectiveness of the use of probiotics and probiotic-containing products in the prevention of widespread winter acute respiratory infections. The effect was traced among children of the first year of life, among preschoolers and schoolchildren. The high reproducibility of the results has been proven when comparing experimental groups and groups receiving placebo [25, 27].

Among the molecular mechanisms by which probiotic bacterial strains influence the antiviral response, the role of stimulation of Toll-like receptors (TLR) and NOD-like membrane receptors has been proven in recent years. TLR-2 recognizes lipoteichoic acids and bacterial cell wall lipoproteins. TLR-4/MD-2 are lipopolysaccharide sensors of gram-negative bacteria, TLR-9 recognize unmethylated CpG-sequences of bacterial DNA [25].

Currently, there are publications on the prevention of coronovirus infection and its likely complications using nutrient correction options. It has been suggested that vitamin C, having antioxidant and anti-inflammatory properties, contributes to the neutralization of free radicals and protects lung cells from the aggressive effects of the virus [35].

Vitamin C, being an immunostimulant, enhances the production of interferon proteins, which are among the first to fight viruses [20].

A number of studies have shown that sufficient intake of vitamin D affects antiviral protection and shows the role of this vitamin in reducing the risk of respiratory tract infection. It has been suggested that vitamin D may be useful in the prevention of coronovirus infection [17, 37].

Currently, the ability of zinc to block the activity of the coronavirus RNA polymerase enzyme and prevent its reproduction is being studied, which is also important in preventive work to prevent an increase in the number of diseases [42].

Possibilities of using raw materials in the diets of the population of the North for preventive purposes. The ecological features of the regions of the Far North contributed to the adaptation of the human body to extreme environmental conditions and the development of certain specific features in nutrition, which made it possible to use many products of the local raw material base as food, which ensure the normal growth and development of the body [19].

Of particular importance is the use of products that grow in local conditions. These products include wild berries. Due to the harsh growing conditions, the northern berries contain a smaller amount of vegetable sugars, but in terms of the content of vitamin C and other useful substances, they are in no way inferior to the berries of the southern regions.

Among the northern berries, the most common are cloudberries, blueberries, lingonberries, cranberries, blueberries. These berries contain macro and microelements necessary for the human body (phosphorus, iron, magnesium, cobalt, silicon, calcium), vitamins of groups B, A and E, fatty acids (omega-3 and omega-6), sugars, pectin and tannins. , fiber, which play an important role in maintaining health.

In addition to products of plant origin, the diet of northerners contains products of animal origin. The combination in the diet of products of plant and animal origin is necessary to strengthen the immune system and can be regarded as biologically more complete due to the mutual enrichment of some proteins with amino acids of others. At the same time, the daily requirement for protein should fill both the total protein consumption and the need for essential amino acids.

The North is especially rich in sea and river fish: whitefish, muksun, nelma, omul, broad whitefish, vendace. Northern fish has an excellent taste, contains a number of amino acids, polyunsaturated fatty acids (omega-3), which have an anti-sclerotic effect on blood vessels, improve their elasticity, and lower blood cholesterol levels. In addition, northern fish is a natural source of substances such as iodine, vitamin D, phosphorus and high-quality protein with a full spectrum of amino acids. [13,17,19,22].

The indigenous inhabitants of the Far North traditionally harvest marine animals: walruses, beluga whales, seals, as well as game: partridge, goose, duck. But the reindeer is of particular importance. Its meat contains up to 12 mg% of vitamin C, which is 13 times more than in cattle meat (0.9 mg%), 6% more protein than beef, less fat. Not only deer meat and milk are used in food - blood and internal organs are also valuable. [13,30].

At the same time, in order to increase the effectiveness of ARVI prevention in epidemiologically unfavorable seasons of the year, it is necessary to diversify the diet of the population of the North by including vitamin-mineral complexes, food products enriched with them, fermented milk products containing probiotics ("BIOYBALANS", "BIOKEFIR", etc.). .).

It is also advisable to use food products with immunomodifying properties: rose hips, lemon, honey, ginger, propolis, turmeric, garlic and seafood.

It is necessary to use functional foods of industrial production, or products prepared on the basis of the use of cryotechnologies.

Examples of natural and specialized food products, vitamins, multivitamin-microelement complexes, probiotic products that have an evidence-based basis for the safety and effectiveness of preventing acute respiratory viral infections can be given: Yakut national dairy products [19,31]; Deer meat [13,30]; Ultra-pasteurized milk drink enriched with a multivitamin premix "SCHOOL MILK" [2,26]; Vitamin and vitamin-mineral complexes [4,11,16]; Vitamin D [17,33]; Probiotic products [32].

Conclusion. Features of the functioning of the immune system in the Far North increase the risk of the emergence and spread of SARS, including COVID-19. The modern possibilities of nutritional science make it possible to actively shape the daily diet of a person and, accordingly, reduce the prevalence of acute respiratory viral infections and their consequences, which is extremely important for the population living in these regions.

The analyzed publications indicate that an increased level of morbidity in a certain season of the year can be considered as a problem of the formation of a transient induced immune disorder in the Far North. One of the reasons for this is the peculiarity of the functioning of the immune system in conditions of seasonal rhythms.

These works describe the experience of solving the problem by correcting diets through the use of vitamins and vitamin-containing complexes, micro- and macroelements, probiotics, prebiotics, specialized products with immunomodifying properties and functional foods of industrial production, as well as products of local raw materials that can increase the level of immune protection and reduce the prevalence of viral respiratory diseases and their consequences.

Reference

1. Aftanas LI, Voevoda MI, Puzyrev VP. Arkticheskaya medicina: vyzovy XXI veka. V kn.: Nauchno-tekhnicheskie problemy osvoeniya Arktiki: Nauchnaya sessiya Obshchego sobraniya chlenov RAN. V kn.: Nauchno-tekhnicheskie problemy` osvoeniya Arktiki: Nauchnaya sessiya Obshhego sobraniya chlenov RAN. [Arctic medicine: challenges of the XXI century. In the book: Scientific and technical problems of the development of the Arctic: Scientific session of the General meeting of members of the Russian Academy of Sciences. M.: Nauka, 2014: 104-110 (In Russ.).]

2. Belousova TV, Loskutova SA. Dinamika otdel'nyh pokazatelej zdorov'ya uchashchihsya gimnazii na fone priema «SHKOL'NOGO MOLOKA». (data obrashcheniya: 27.01.2022)

[Dynamics of individual indicators of the health of pupils of the gymnasium against the background of the reception of "SCHOOL MILK". date of the application: 27.01.2022). Voprosy` detskoj dietologii. [Problems of pediatric nutritiology. 2014; (3): 8-12 (In Russ.).] URL: https://rucont.ru/efd/611568

3. Vitaminnaya obespechennost' vzroslogo naseleniya Rossijskoj Federacii (1987–2017 gg.). Kodentsova VM, Vrzhesinskaya OA, Nikityuk DB, Tutelyan VA. [Vitamin supply of the adult population of the Russian Federation (1987–2017)]. Voprosy` pitaniya. [Nutrition issues .2018; 87(4):62-68 (In Russ.).] DOI: 10.24411/0042-8833-2018-1004

4. Vliyanie dopolnitel'noj vitaminizacii na metabolizm limfocitov krovi Prakhin EI, Akimova NS, Savchenko AA, Gerasimchuk AN. [The effect of additional vitaminization on the metabolism of blood lymphocytes].Sibirskoe mediczinskoe obozrenie. [Siberian Medical Review]. 2008; (5): 50-54 (In Russ.).]

5. Vliyanie faktorov sredy obitaniya na zabolevaemost' organov dyhaniya naseleniya severnyh regionov.. [The influence of environmental factors on the incidence of respiratory organs in the population of the northern regions. Efimova NV, Gornov AYu, Tikhonova IV, Zarodnyuk TS. Sovremennye problemy nauki i obrazovaniya. [Modern problems of science and education. 2016; (6): 74 (In Russ.).]

6. Gippokrat-sochineniya-t-2-gosudarstvennoe-izdatelstvo-medicinskoj-literatury [Gippokrat. Sochineniya. 2. Gosudarstvennoe izdatel`stvo mediczinskoj literatury`. [Modern publishing house of medical literature. M.-L.: Medgiz, 1944: 510 (In Russ.).]

7. Gosudarstvennyj-doklad-federalnoj-sluzhby-po-nadzoru-v-sfere-zashchity-prav-potrebitelej-i-blagopoluchiya-cheloveka-o-sostoyanii-sanitarno-ehpidemiologicheskogo-blagopoluchiya-naseleniya-v-rossijskoj-federacii-v-2020-godu-m-tfederalnaya-sluzhba-po-nadzoru-v-sfere-zashchity-prav-potrebitelej-i-blagopoluchiya-cheloveka. Gosudarstvennyj-doklad-federalnoj-sluzhby-po-nadzoru-v-sfere-zashchity-prav-potrebitelej-i-blagopoluchiya-cheloveka-o-sostoyanii-sanitarno-ehpidemiologicheskogo-blagopoluchiya-naseleniya-v-rossijskoj-federacii-v-2020-godu-m-tfederalnaya-sluzhba-po-nadzoru-v-sfere-zashchity-prav-potrebitelej-i-blagopoluchiya-cheloveka. [State report of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare "On the state of sanitary and epidemiological welfare of the population in the Russian Federation in 2020]. M. Federal'naya sluzhba po nadzoru v sfere zashchity prav potrebitelej i blagopoluchiya cheloveka. [Federal Service for Supervision of Consumer Rights Protection and Human Welfare. 2021: 256 (In Russ.).]

8. Gromova OA, Toroshchin IYu. Vitamin-d-smena-paradigmy [Vitamin D – a paradigm shift]. M: MCNMO. 2016: 464 (In Russ).

9. Karetkina GN. Gripp i ORVI: lechenie i profilaktika v nastupivshem epidsezone 2015-2016 gg. [Influenza and ARVI: treatment and prevention in the coming epidemiological season 2015-2016] «Lechashchij vrach». [Attending doctor. 2015; (11):46-54 (In Russ.).]

10. Klinicheskaya-immunologiya. Kozlov VA, Savchenko AA, Kudryavtsev IV, Kozlov IG, Kudlai DA, Prodeus AP. et al. [Clinical Immunology. Krasnoyarsk: Polikor, 2020: 386 (In Russ.).]

11. Kodentsova VM, Vrzhesinskaya OA. Vitaminno-mineralnye-kompleksy-sootnoshenie-doza-ehffekt [Vitamin-mineral complexes: dose-effect ratio]. Voprosy`. Pitaniya. [Journal of Nutrition. 2006; 75(5): 30–39 (In Russ.).]

12. Kodentsova VM, Risnik DV, Moiseenok AG. Koncepciya-spiricheva-v-b-d3-12-vitaminov-razvitie-i-vnedrenie [The concept of VB. Spirichev. D3 + 12 vitamins. Development and implementation]. M.: Biblio-Globus. [Moscow: Biblio-Globus. 2020: 236 (In Russ.).] DOI: 10.18334/9785907063655

13. Lebedeva UM, Stepanov KM. Monitoringovye-issledovaniya-ocenki-fakticheskogo-pitaniya-i-prodovolstvennoj-bezopasnosti-v-respublike-saha-yakutiya [Monitoring studies to assess actual nutrition and food security in the Republic of Sakha (Yakutia)]. Voprosy` pitaniya [Journal of Nutrition. 2016; 85 (S2): 105 (In Russ.).]

14. Maly VP, Andreichin MA, Lyadova TI. Gripp-sezonnyj-ptichij-pandemicheskij-i-drugie-ORVI. [Influenza (seasonal, avian, pandemic) and other acute respiratory viral infections] M.: GE`OTAR-Media. [Moscow: GEOTAR-Media. 2012: 320 (In Russ.).]

15. Nauchnye-osnovy-zdorovogo-pitaniya. Tutelyan VA, Vyalkov AI, Razumov AN, Mikhailov VI, Moskalenko KA. M.: [Scientific foundations of healthy eating] Izdatel`skij dom «PANORAMA» [Publishing house "PANORAMA". 2010: 816 (In Russ.).]

16. Novitskaya VP, Prakhin EI. Vozrastnye-osobennosti-aktivnosti-fermentov-limfocitov-i-ih-vzaimosvyaz-u-detej-Krajnego-Severa [Age features of the activity of lymphocyte enzymes and their relationship in children of the Far North] Yakutskij mediczinskij zhurnal. [Yakut medical journal. 2020; 4(72): 94-97 (In Russ.).]

17. O-protivovirusnyh-ehffektah-vitamina-D Meditsinskiy sovet. Gromova OA, Torshin IYu, Frolova DE, Lapochkina NP, Limanova OA. [About antiviral effects of vitamin D] Medicinskij sovet [Medical advice. 2020; (3): 152-158 (In Russ.).] https://doi.org/10.21518/2079-701X-2020-3-152-158

18. Opyt-sravnitelnogo-analiza-zabolevaemosti-pnevmoniyami-i-ostrymi-respiratornymi-infekciyami-verhnih-dyhatelnyh-putej-posle-vnedreniya-sistemy-ehpidemiologicheskogo-monitoringa-pnevmonij. Kravchenko NA, Gavrilova TA, Khakimova.MI, Kazanova VB, Vasilyeva EI, Botvinkin AD. [The experience of comparative analysis of the incidence of pneumonia and acute respiratory infections of the upper respiratory tract after the introduction of the pneumonia epidemiological monitoring system] E`pidemiologiya i vakczinoprofilaktika. [Epidemiology and vaccination. 2019; 18(1): 96-104 (In Russ.).] https://doi.org/10.31631/2073-3046-2019-18-1-96-104

19. Ocenka-fakticheskogo-pitaniya-kachestva-i-bezopasnosti-prodovolstvennogo-syrya-i-pishchevyh-produktov-v-respublike-Saha-(Yakutiya) Lebedeva UM, Rumyantseva AN, Stepanov KM, Ignatieva ME, Grigoriev VP. [Assessment of actual nutrition, quality and safety of food raw materials and food products in the Republic of Sakha (Yakutia)] . Yakutskij mediczinskij zhurnal. [Yakut medical journal. 2015; 3(51): 64-9 (In Russ.).]

20. Parakhonsky A.P, Induktory-interferona-v-profilaktike-i-lechenii-infekcionnyh-zabolevanij [Interferon inducers in the prevention and treatment of infectious diseases]. Fundamental'nye issledovaniya [Basic Research]. 2007; (11):124-125 (In Russ.).

21. Pigarova EA, Plescheva AV, Dzeranova LK. Vliyanie-vitamina-D-na-immunnuyu-sistemu [Effects of vitamin D on the immune system]. Immunologiya. [Immunology] 2015; 36 (1):62-66 (In Russ.).]

22. Pitanie-i-Sever-gigienicheskie-problemy-Arkticheskoj-zony-Rossii-(obzor-literatury) [Nutrition and the North: hygienic problems of the Arctic zone of Russia (literature review).]. Istomin AV, Fedina IN, Shkurikhina SV, Kutakova NS. Gigiena i Sanitariya. [Hygiene and Sanitation. .2018; 96(6): 557-563 (In Russ.).]

23. Politika-v-oblasti-zdorovogo-pitaniya-naseleniya-respubliki-Saha-Yakutiya Tutelyan VA, Gorokhov AV, Mikhailova EI, Vladimirov LN, Lebedev MP, Ignatieva ME. et al. [Policy in the field of healthy nutrition of the population of the Republic of Sakha (Yakutia)]. Yakutskij mediczinskij zhurnal. [Yakut medical journal. 2015; 3(51): 6-9 (In Russ.).]

24. Principialnye-podhody-k-razrabotke-prioritetnyh-i-perspektivnyh-programm-prodleniya-dlitelnosti-i-uluchsheniya-kachestva-trudosposobnogo-perioda-zhizni-cheloveka-v-ehkstremalnyh-usloviyah-na-osnove-optimizacii-pitaniya-i-privedenie-ego-v-sootvetstvie-s-ehtnogeneticheskimi-i-populyacionnymi-osobennostyami-naseleniya-Severa. Kasparov EV, Vasiliev VA, Prakhin EI, Manchuk VT. Problemy-sohraneniya-i-obespecheniya-sanitarno-ehpidemiologicheskogo-blagopoluchiya-naseleniya-v-arktike-materialy-nauchno-prakticheskoj-konferencii-s-mezhdunarodnym-uchastiem-5-6-oktyabrya-2017-g-SanktPeterburg [Fundamental approaches to the development of priority and promising programs for extending the duration and improving the quality of the working period of a person's life in extreme conditions based on the optimization of nutrition and bringing it into line with the ethnogenetic and population characteristics of the population of the North. Problems of preserving and ensuring sanitary and epidemiological well-being of the population in the Arctic]. Materialy` nauchno-prakticheskoj konferenczii s mezhdunarodny`m uchastiem 5-6 oktyabrya 2017 on October 5-6 2017 [Materials of the scientific and practical conference with international participation October 5-6, 2017. Saint-Petersburg: OOOIPK Costa, 2017: 114-117 (In Russ.).]

25. Probiotiki v kompleksnoj profilaktike respiratornyh-infekcij Gorelov AV, Ploskireva AA, Bondareva AV, Kanner EV. [Probiotics in the

complex prevention of respiratory infections]. Voprosy` prakticheskoj pediatrii [Questions of practical pediatrics]. 2014; 9(5): 77-83 (In Russ.).

26.Rezultaty-vnedreniya-programmy-«Shkolnoe-Moloko-v-Rossii-i-na-Ukraine. Kondratyeva EI, Gorelova JYu, Ladodo KS, Prakhin EI, Shadrin OG, Davtyan KA, Dyogteva GN, Labinov VV, Khapacheva DE, Guznischeva OA. [Results of implementation of the SCHOOL MILK program in RUSSIA and UKRAINE.] Voprosy detskoj dietologii. [Problems of pediatric nutritiology. 2013; 11(1): 69-78. (In Russ.).]

27. Rol' probioticheskih sredstv v profilaktike sezonnoj zabolevaemosti ORVI. Kunelskaya NL, Izotova GN, Bessarab MV, Nagibina MV, Laryushkin YuV. [The role of probiotic agents in the prevention of seasonal incidence of ARVI]. Meditsinskiy sovet. [Medical advice. 2013; (2): 46-50 (In Russ.).] DOI: 10.21518/2079-701X-2013-2-46-50

28. Savchenko AA, Borisov AG. Osnovy klinicheskoj immunometabolomiki RAMN SO NII Medicinskih problem Severa. [Fundamentals of Clinical Immunometabolomics RAMN SO Research Institute of Medical Problems of the North. Novosibirsk: «NAUKA», 2012: 263 (In Russ.).]

29. Snopov SA. Mekhanizmy dejstviya vitamina D na immunnuyu sistemu.2014; 16(6): 499–530. [Mechanisms of Vitamin D's Action on the Immune System]. Mediczinskaya immunologiya. [Medical immunology. 2014; 16(6): 499-530 (In Russ.).]

30. Stepanov KM. Olen'e moloko biologicheski cennyj produkt. [Deer milk biologically valuable product] Molochnaya promy`shlennost` [Dairy industry. 2010; (2): 32-34 (In Russ.).]

31. Stepanov KM, Lebedeva UM, Eliseeva LI. Biohimicheskie i mikrobiologicheskie osnovy proizvodstva YAkutskih nacional'nyh kislomolochnyh produktov novogo pokoleniya. (data obrashcheniya: 18.03.2021). [Biochemical and microbiological foundations of the production of the Yakut national fermented milk products of a new generation (date of access: 03/18/2021).]. Fundamental`ny`e issledovaniya. [Basic research]. 2014; (9-8): 1756-1759 (In Russ.).] URL: http://www.fundamental-research.ru/ru/article/view?id=35135

32. Usenko DV. Probioticheskie produkty v profilaktike respiratornyh infekcij. [Probiotic products for the prevention of respiratory infections]. Consilium Medicum [Consilium Medicum. 2007; 9(3): 82-6 (In Russ.).]

33. Schwartz GYa. Renessans vitamina D: molekulyarno-biologicheskie, fiziologicheskie i farmakologicheskie aspekty. Medicinskij Sovet. Renessans vitamina D: molekulyarno-biologicheskie, fiziologicheskie i farmakologicheskie aspekty. [Renaissance of Vitamin D. molecular biological, physiological and pharmacological aspects]. Medicinskij Sovett [Medical advice. 2015; (18):102-103 (In Russ.).]

34. Calder PC. Feeding the immune system. Proc. Nutr. Soc. 2013; 72(3): 299-309. DOI: 10.1017/S0029665113001286

35. Carr AC, Maggini S. Vitamin C and Immune Function. Nutrients. 2017; 9(11): 1211. DOI: 10.3390/nu9111211.

36. Demas GE, Nelson RJ. Seasonal changes in immune function. Q Rev Biol. 1996; 71(4):511-48. DOI: 10.1086/419555.

37. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020; 32(7): 1195-1198. DOI: 10.1007/s40520-020-01570-8.

38. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Nutrients. 2020; 23; 12(4):1181. DOI: 10.3390/nu12041181.

39. Price RHM, Graham C, Ramalingam S. Association between viral seasonality and meteorological factors :Sci Rep. 2019; 30;9(1):929. DOI: 10.1038/s41598-018-37481-y.

40. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P. et al. BMJ (Online), 2017: 356. DOI: https://doi.org/10.1136/bmj.i6583

41. Widespread seasonal gene expression reveals annual differences in human immunity and physiology. Dopico X, Evangelou M, Ferreira R. et al. Nature Communications, 2015; 6, 7000 ISSN 2041-1723 (online)

42. Zinc and respiratory tract infections: Perspectives for COVID 19 (Review). Skalny A, Rink L, Ajsuvakova O. et al. Int J Mol Med.2020; 46, 1: 17-26. DOI: 10.3892/ijmm.2020.4575

POINT OF VIEW

DOI 10.25789/YMJ.2022.79.24

УДК 572.79

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TOPICAL ISSUES OF ETHNICITY TYPING IN THE ANATOMICAL AND ANTHROPOLOGICAL RESEARCH

Numerous scientific studies in various fields of medicine have reliably shown the presence of features in the predisposition, occurrence, course, treatment, rehabilitation and prevention of various nosological forms in representatives of certain ethnic groups. This article presents a review of the scientific literature on the study of the history of the emergence of ethnic groups. Various theories and concepts of the ethnos based on different methodological approaches are described. Despite the centuries-old numerous studies of scientists around the world, there is still no unity in the scientific community in the approach to the definition of ethnicity and ethnicity. The analysis of scientific literature has shown that domestic researchers in their works, when dividing into groups, use different principles for determining ethnicity. Currently, the active migration processes observed all over the world, the expansion of socio-cultural borders have led to the formation of ethnically mixed groups of the population for several generations. A new anthropological type of population (mestizos) is being formed, which has distinctive morphofunctional indicators and, possibly, a specific level of climatogeographic, social adaptation. Thus, the study of morphofunctional characteristics, patterns of physical development, individual typological features of a large stratum of the population (mestizos) at different segments of the ontogenetic cycle seems relevant and timely, and will make it possible to compile a morphofunctional portrait of the modern population of the Republic of Sakha (Yakutia).

Keywords: ethnos, mestizos, morphofunctional indicators, Yakutia.

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Since ancient times, the study of the historical development of the peoples of the world, their origin, speech, culture, economy, territory of residence, appearance and much more have aroused the scientific interest of ethnographers [1, 2]. An important place in ethnography is occupied by the study of the history of the emergence of ethnic groups and the study of interethnic relations. The purpose of our research is to summarize extensive scientific information concerning the issues of theories, concepts of ethnos and analysis of classifications of races in anatomical and anthropological studies. To achieve this goal, we have set the following tasks: to conduct a theoretical analysis of scientific and educational literature on the problem of research; to systematize the information studied; to consider the main racial classifications of modern anthropologists; to describe the basic principles of ethnic differentiation in modern biomedical

research; to make a conclusion on the issues of this work.

In Soviet and Russian ethnography, the term "ethnos" has been widely used in scientific research since 1923, the author of which in its modern meaning, as well as the founder of an independent theory of ethnos, was the Russian orientalist, anthropologist, ethnographer and ethnologist Sergei Mikhailovich Shirokogorov [38]. Despite the centuries-old, numerous studies of scientists around the world, there is still no unity in the scientific environment in the approach to the definition of ethnicity and ethnicity [23, 36]. There are many theories and concepts of ethnos based on different approaches, for example: ethnoses as social communities that arose as a result of a historical process; as the socio-economic integrity of society; as the biological side of human nature; as the interaction of developing ethnoses with the surrounding landscape and other ethnoses (Leo Gumilev's passionate theory of ethnogenesis). Despite the diversity of theories and concepts, according to most scientists, the main conditions for the emergence of an ethnic group and its subsequent main features are the commonality of the territory and language. Additional factors in the formation of an ethnos can be the community of religion, the proximity of the components of the ethnos in racial terms, the presence of mestizo (transitional) groups. In the course of ethnogenesis, specific features of material, spiritual culture, everyday life, and psychological characteristics are formed for a certain ethnic group. The formed ethnic community is a social organism that reproduces itself through predominantly ethnically homogeneous marriages and the transfer of language, culture, and traditions to a new generation [5].

It is known that along with the listed ethnic differences between people, there are also morphofunctional differences [5, 26]. Physical or anatomical and anthropological differences between territorial groups that are remote from each other and live in different climatic and geographical conditions are especially noticeable. In science, such differences are called "racial". Racial differences are always hereditary, have a group character, which allows researchers to define the concept of "race" as territorial groups of people based on genetic kinship, manifested in a certain physical similarity in many ways. A large number of classifications of human races are presented in the scientific anthropological literature [5, 23]. According to historical sources, people have long paid attention to the presence of territorial differences in the appearance of a person. The main distinguishing morphological feature was primarily considered skin color (pigmentation). Even in the Bible, three races are distinguished, descended from the sons of Noah, Shem (yellow-skinned), Ham (black), Japhet (white-skinned). In ancient Egypt in the middle of the 3rd millennium BC, four colors were used when depicting people of different origins. Egyptians were depicted in red, yellow was used to depict the peoples of the East, northern and southern peoples were depicted in white and black.

The problem of classification of races is still actively debated [18, 38]. It's necessary in this work to consider the main racial classifications of modern anthropologists. The famous Soviet ethnographer and anthropologist Nikolai Cheboksarov (1951) gave a classification of racial types, in which he identified three large races: equatorial (Australo-Negroid), Eurasian (Caucasoid) and Asian-American [36]. Large races are divided into 22 small races, or races of the second order. The scheme of racial relations proposed by the Soviet anthropologist Georgy Debets (1958) is interesting. In his scheme, the author identified three large races: Negro-Australoid, Caucasoid and Mongoloid. Each large race is divided into several branches, small races are allocated in each branch, and types are allocated in small races. The intertwining and merging of racial branches reflect the processes of mixing at different stages of human evolution. In the classification of Yakov Roginsky and Maxim Levin (1963), three large races are also distinguished: Eurasian, equatorial, Asian-American. Large races are divided into 5-6 small races, six intermediate races are distinguished between the large races. In the names of races, the authors applied the geographical principle, for example, Ural, Arctic, Ethiopian. Soviet anthropologist and anatomist Viktor Bunak presented the racial classification in the form of a tree (1980). The author called the main divisions of the tree racial trunks: tropical, southern, western and eastern. V.V. Bunak divided the hierarchy of tree trunks and branches on the basis of the diacriticism of individual anthropological types.

Modern biomedical science has a wide range of knowledge about the ethnic features of morphofunctional characteristics of the human body. Numerous studies in various fields of medicine have reliably shown the presence of features in the predisposition, occurrence, course, treatment, rehabilitation and prevention of various nosological forms in representatives of certain ethnic groups [12, 30, 40]. The analysis of scientific literature has shown that quite often domestic researchers use the principle of race in their work when dividing into groups. Within the framework of this work, it is not possible to fully describe all scientific works based on the principle of racial differentiation. So, V.S. Gladkaya et al. (2008) in the study of the peculiarities of the course of pregnancy and childbirth in women of Khakassia, she divided the subjects into khakasian women and caucasian women [12]. In the work, studying the molecular genetic analysis of the polymorphism of the interleukin-4 gene of the population of the Kemerovo region, A.V. Ostaptseva et al. (2006) identified groups - a small indigenous population (Teleutes and Shorians) and caucasians [22]. The terms "mongoloids" and "caucasoids" are used in their genetic studies of the population of Eastern Siberia by L.I. Kolesnikova (2014) [19], in the anatomical and anthropological study of the male population of Yakutia by T.G. Degtyareva (2015) [16] and others [10, 17, 39]. The concept of "aborigines" is often found in scientific works. For example, T.P. Bartosh et al. (2013) [24], A.L. Maksimov et al. (2011) [20] in their scientific works the population of the Magadan region was divided into aboriginal and caucasian populations.

A large number of researchers are adherents of dividing the surveyed population into "indigenous and non-indigenous (newcomers)". Thus, investigating the physiology of the micronutrient status of children of Ugra, V.M. Chiglintsev et al. (2017) divided the subjects into groups of persons of indigenous and non-indigenous nationalities [37]. A similar typification was used in the study of the somatic health of students of Kazakhstan J.T.Suyundikova et al. (2012) [34], I.V. Kononova et al. (2021) [4] when analyzing the incidence of cervical cancer in the Arctic zone of the Russian Federation, N.V. Borisova et al. (2020) [6] in the study of anthropofunctional indicators of residents of the Republic of Sakha (Yakutia) and other researchers [8, 14, 33, 35]. In addition, there are other terminological typifications of ethnicity. For example, persons of Slavic nationality, Turkic peoples, Caucasian peoples, Altai peoples, etc. [9, 29, 41].

V.G.Nikolaev et al. (2015) in numerous studies of the morphofunctional status of the population of Eastern Siberia adheres to a more specific division of the

population by nationality, for example, Khakas, Tuvans, Russians, Buryats, Dolgans, Evens, etc. [26]. A similar approach was used in the works of L.V. Sindeeva [31], A.B. Guryeva [15], V.A. Alekseeva [3], R.D. Yusupov [40], O.A. Berseneva [7], E.N. Sivtseva [21], S.I. Sofronova [32] and many others. The overwhelming majority of scientists, when determining ethnicity, use the survey method and take into account the nationality of ancestors in three generations to exclude mestization.

Having considered some of the extensive scientific ethnic differentiations, it should be noted that there is no unified approach to this issue. The authors do not undertake to judge which typification is more acceptable, since in each specific work scientists set certain goals and objectives, there are certain conditions for conducting scientific work, commitment to a scientific school and many other facets of research activity. After studying the literature, we came to the conclusion that it is becoming increasingly difficult for modern science to identify ethnicity phenotypically and by survey, because currently, the active migration processes observed all over the world, the expansion of socio-cultural borders have led to the formation of ethnically mixed groups of the population for several generations. Thus, new anthropological types of the population (mestizos) are being formed, which have distinctive morphofunctional indicators and, possibly, a specific level of climatogeographic, social adaptation. In the scientific literature there are medical and biological studies of the mixed population [11, 25, 27, 28]. T.V. Godovyh (2011), studying the physical development of the child population of Chukotka, takes into account the processes of mestization of aborigines [13]. In the group of mestizos, the author included children whose one of the parents did not belong to the small peoples of the North. T.V. Godovyh points to the morphofunctional features of the components of the growth and development of children and suggests that the mestization of aborigines leads to the formation of an "adaptive type".

Thus, morphofunctional characteristics at different segments of the ontogenetic cycle, patterns of physical development, individual typological features of a large stratum of the population (mestizos) remain insufficiently studied. It seems to us the most interesting at this stage of scientific research to study the morphofunctional and individual typological characteristics of the mixed youth population of the Republic of Sakha (Yakutia).

Reference

1. Alekseev A.N., Bravina R.I. Formirovanie yakutskogo naroda [Formation of the Yakut people]. V knige: Istoriya YAkutii. Alekseev A.N., Alekseeva E.K., Argunov V.G. i dr. v 3-h tomah. Novosibirsk: Novosibirskij filial Federal'nogo gosudarstvennogo unitarnogo predpriyatiya "Akademicheskij nauchno-izdatel'skij i knigorasprostranitel'skij centr "Nauka" [In the book 'History of Yakutia'. Alekseev A.N., Alekseeva E.K., Argunov V.G. et al. In 3 vol. Novosibirsk Branch of the Federal State Unitary Enterprise "Academic Scientific Publishing and Book Distribution Center "Nauka", 2020: 223-230]. (In Russ.).]

2. Alekseev A.N., Bravina R.I., Romanova E.N. Zaklyuchenie [Conclusion]. V knige: Istoriya YAkutii. Alekseev A.N., Alekseeva E.K., Argunov V.G. i dr. v 3-h tomah. Novosibirsk: Novosibirskij filial Federal'nogo gosudarstvennogo unitarnogo predpriyatiya "Akademicheskij nauchno-izdatel'skij i knigorasprostranitel'skij centr "Nauka" [In the book 'History of Yakutia'. Alekseev A.N., Alekseeva E.K., Argunov V.G.et al. In 3 vol. Novosibirsk Branch of the Federal State Unitary Enterprise 'Academic Scientific Publishing and Book Distribution Center 'Nauka', 2020: 475-478 (In Russ.).]

3. Alekseeva V.A. Osobennosti gabaritnyh i komponentnyh pokazatelej u zhenshchin 75-90 let russkoj nacional'nosti YAkutska / V.A. Alekseeva, A.B. Gur'eva // Uspekhi gerontologii. - 2017. - T. 30, № 4. - S. 538-541. [Alekseeva V.A. Features of overall and component indicators in women aged 75-90 years of russian nationality of Yakutsk / V.A. Alekseeva, A.B. Gur'eva // Advances in Gerontology. 2017; 30 (4): 538-541.] (In Russ.)

4. Kononova IV, Kirillina MP, Sofronova SI, Zaharova FA. Analiz zabolevaemosti rakom shejki matki v Arkticheskoj zone Rossijskoj Federacii dlya vyyavleniya regionov ostro nuzhdayushchihsya v ego profilaktike [Analysis of the incidence of cervical cancer in the Arctic zone of the Russian Federation to identify regions in dire need of its prevention. Yakut medical journal. 2021; 4 (76): 103-106. (In Russ.).]

5. Hrisanfova EN, Perevozchikov IV. Antropologiya: uchebnik [Antropology: Student's book. 4 edition. Moscow publishing house. University: Science. 2005; 400. (In Russ.).]

6. Afanasieva EB. Borisova NV. Sostoyanie antropofunkcional'nyh pokazatelej u korennyh i prishlyh zhitelej Respubliki Sakha (YAkutiya) [State of anthropofunctional indicators in indigenous and alien residents of the Republic of Sakha (Yakutia)]. Zhurnal mediko-biologicheskih issledovanij [Journal of Biomedical Research. 2020; 8 (3):309-313.] (In Russ.).]

7. Bersenyova OA, Ageeva ES. Etno-populyacionnye osobennosti pitaniya pacientov s metabolicheskim sindromom [Ethno-population features of nutrition in patients with metabolic syndrome]. Sibirskoe medicinskoe obozrenie [Siberian Medical Review. 2019; 5 (119): 38-46. (In Russ.).]

8. Bikbulatova LN, Korchin VI, Korchina TYa. Elementnye markery vozdejstviya na organizm svinca i kadmiya u nekorennogo i korennogo naseleniya YAmalo-Neneckogo avtonomnogo okruga [Elemental markers of exposure to lead and cadmium in the non-indigenous and indigenous population of the Yamalo-Nenets Autonomous]. Mikroelementy v medicine [Microelements in medicine. 2021; 22 (4): 43-49 (In Russ.).]

9. Bohan NA, Matveeva NP, Afonskaya MI. Etnokul'turalynye osobennosti techeniya alkogol'nyh psihozov v Respublike Saha (YAkutiya) [Ethnocultural features of the course of alcoholic psychoses in the Republic of Sakha (Yakutia)]. Sibirskij vestnik psihiatrii i narkologii [Siberian Bulletin of Psychiatry and Narcology. 2010; 2 (59): 125-128 (In Russ.).]

10. Darenskaya MA, Rychkova LV, Semyonova NV, Kolesnikov SI. Vyyavlenie naibolee informativnyh metabolicheskih pokazatelej u devushek-podrostkov dvuh etnicheskih grupp s ekzogenno-konstitucional'nym ozhireniem [[Identification of the most informative metabolic parameters in adolescent girls of two ethnic groups with exogenous constitutional obesity]. Tekhnologii zhivyh system [Technologies of living systems. 2021; 18 (3): 58-66 (In Russ.).]

11. Gladkaya VS, Verigo LI. Assessment of the physical development of women in Khakassia using the index of sexual dimorphism [Ocenka fizicheskogo razvitiya zhenshchin Hakasii s primeneniem indeksa polovogo dimorfizma]. Morfologicheskie vedomosti [Morphological Newsletter. 2008; 3-4: 108-111 (In Russ.).]

12. Gladkaya VS, Egorova AT. Etnicheskie i konstitucional'nye osobennosti techeniya beremennosti i rodov u zhenshchin Hakasii [Ethnic and constitutional features of the course of pregnancy and childbirth in women of Khakassia]. Voprosy ginekologii, akusherstva i perinatologii [Issues of gynecology, obstetrics and perinatology. 2008; 7 (3): 23-26 (In Russ.).]

13. Godovyh T.V. Ontogeneticheskie transformacii fizicheskogo razvitiya detskoj populyacii CHukotki [Ontogenetic transformations of the physical development of the child population of Chukotka]. Vestnik antropologii [Herald of Anthropology. 2011; 20: 79-84 (In Russ.).]

14. Gricinskaya V.L. Pokazateli rosta i razvitiya detej v Respublike Tyva v zavisimosti ot vida vskarmlivaniya / V.L. Gricinskaya, N.O. Sanchat // Children's Medicine of the North-West. - 2021. - T. 9, № 2. - S. 38-44. [Gricinskaya V.L. Indicators of growth and development of children in the Republic of Tyva depending on the type of feeding / V.L. Gricinskaya, N.O. Sanchat // Children's Medicine of the North-West. 2021; 9 (2): 38-44.] (In Russ.)

15. Gurieva AB, Nikolaev VG, Alekseeva VA. Etnovozrastnye osobennosti fizicheskogo statusa zhenskogo naseleniya Respubliki Saha (YAkutiya) [Ethnic and age features of the physical status of the female population of the Republic of Sakha (Yakutia)]. Sovremennye problemy nauki i obrazovaniya [Modern problems of science and education. 2018; 4: 181. (In Russ.).]

16. Degtyareva TG, Gurieva AB. Nekotorye aspekty anatomo-antropologicheskih issledovanij muzhskogo naseleniya Respubliki Saha (Yakutiya) [Some aspects of anatomical and anthropological studies of the male population of the Republic of Sakha (Yakutia)]. Sovremennye problemy nauki i obrazovaniya [Modern problems of science and education. 2015; 3: 118 (In Russ.).]

17. YUshchuk ND, Malov IV, Baatarkhuu O, Savilov ED, et al. Kliniko-epidemiologicheskie proyavleniya gepatocellyulyarnoj karcinomy v etnicheskih gruppah evropeoidov i mongoloidov, prozhivayushchih na territorii Severovostochnoj Azii [Clinical and epidemiological manifestations of hepatocellular carcinoma in ethnic groups of Caucasians and Mongoloids living in Northeast Asia]. ZHurnal mikrobiologii, epidemiologii i immunobiologii [Journal of Microbiology, Epidemiology and Immunobiology. 2018; 6: 25-31 (In Russ.).]

18. Kozincev AG. Evropeoidy, mongoloidy, avstraloidy: stadial'nost' ili metisaciya? [Caucasoids, Mongoloids, Australoids: stadiality or miscegenation?] Radlovskij sbornik. Nauchnye issledovaniya i muzejnye proekty MAE RAN v 2013 g. [Radlovsky collection. Scientific research and

museum projects of the MAE RAS in 2013, St. Petersburg, 2014: 27-35 (In Russ.).]

19. Kolesnikova LI, Bairova TA, Pervushina OA. Rasprostranennost' polimorfizma ALA-16VAL gena SOD2 v vyborkah mongoloidov i evropeoidov, prozhivayushchih na territorii Vostochnoj Sibiri [The prevalence of the ALA16VAL polymorphism of the SOD2 gene in samples of Mongoloids and Caucasians living in Eastern Siberia]. Byulleten' Vostochno-Sibirskogo nauchnogo centra Sibirskogo otdeleniya Rossijskoj akademii medicinskih nauk [Bulletin of the East Siberian Scientific Center of the Siberian Branch of the Russian Academy of Medical Sciences. 2014; 2 (96): 29-31 (In Russ.).]

20. Maksimov AL, Loskutova AN. Osobennosti struktury kardioritma u normotonikov aborigenov i evropeoidov, postoyannyh zhitelej pribrezhnoj zony Magadanskoj oblasti [Features of the structure of the heart rhythm in normotonic natives and Caucasians, permanent residents of the coastal zone of the Magadan region]. Ekologiya cheloveka [Human ecology. 2011; 6: 11-16 (In Russ.).]

21. Sivceva EN, SHadrina SS, Sivceva AI, Mel'nikov VN, et al. Mikroelementnyj sostav syvorotki u dolgan YAkutii v usloviyah promyshlennogo osvoeniya territorij prozhivaniya [Microelement composition of serum in dolgans of Yakutia in the conditions of industrial development of territories of residence]. Mikroelementy v medicine [Microelements in medicine. 2021; 22 (4): 50-61 (In Russ.).]

22. Ostapceva AV, SHabaldin AV, Ahmat'yanova VR, Minina VI, et al. Molekulyarno-geneticheskij analiz polimorfizma gena interlejkina-4 u teleutov, shorcev i evropeoidov Kemerovskoj oblasti [Molecular genetic analysis of polymorphism of the interleukin-4 gene in Teleuts, Shors and Caucasoids of the Kemerovo region]. Medicinskaya immunologiya [Medical immunology. 2006; 8 (5-6): 737-740 (In Russ.).]

23. Narody. Rasy. Kul'tury. / CHeboksarov N.N., CHeboksarova I.A. - M.: Nauka, 1985. - 272 s. [People. Races. Culture / CHeboksarov N.N., CHeboksarova I.A. - M.: Nauka, 1985: 272.] (In Russ.)

24. Bartosh TP, Maksimov AL, Bartosh OP, Mychko MV. Nejrodinamicheskie pokazateli starsheklassnikov razlichnyh etnicheskih grupp magadanskoj oblasti [Neurodynamic parameters of high school students of various ethnic groups of the Magadan region. Reproduktivnoe zdorov'e detej i podrostkov [Reproductive health of children and adolescents. 2013; 2: 51-58.] (In Russ.).]

25. Distel VA, Skripkina GI, Karnickij AV, Mateshuk EA. Osobennosti formirovaniya i razvitiya zubochelyustnoj sistemy u metisov na primere klinicheskogo nablyudeniya [Features of the formation and development of the dentoalveolar system in metisis on the example of clinical observation]. Aktual'nye voprosy detskoj stomatologii: sbornik vserossijskoj nauchno-prakticheskoj konferencii s mezhdunarodnym uchastiem [Actual issues of pediatric dentistry: collection of the All-Russian scientific and practical conference with international participation, Kirov, November 25–26, 2020. Kirov: Federal'noe gosudarstvennoe byudzhetnoe obrazovatel'noe uchrezhdenie vysshego obrazovaniya "Kirovskij gosudarstvennyj medicinskij universitet" Ministerstva zdravoohraneniya Rossijskoj Federacii [Federal State Budget Higher Education Institution "Kirov State Medical University" of the Ministry of Health of the Russian Federation]. 2021: 80-83. (In Russ.).]

26. Nikolaev VG, Medvedeva NN, Nikolenko VN, Petrova MM et al. Ocherki integrativnoj antropologii [Essays on Integrative Anthropology]. Professor V.F. Voyno-Yasenetsky Krasnoyarsk State Medical University named after, 2015: 326 (In Russ.).]

27. Tabihanova LE, Osipova LP, CHurkina TV, Voronina EN, Filipenko ML. Polimorfizm gena citohroma R450 CYP1A1 (ILE462VAL) u potomkov smeshannyh brakov tundrovyh nencev s russkimi [Polymorphism of the cytochrome P450 gene CYP1A1 (ILE462VAL) in descendants of mixed marriages of tundra nenets with russians]. V knige: Biomedicina-2016. sbornik materialov foruma [In the book: Biomedicine-2016. collection of forum materials. 2016: 135 (In Russ.).]

28. Starostin VG, Nikiforov NV, Alekseeva LS, Filippov NS, et al. Polovoj dimorfizm po morfologicheskim pokazatelyam u yunoshej i devushek smeshannoj nacional'nosti (metisov), prozhivayushchih v Respublike Saha (YAkutiya) [Sexual dimorphism in morphological parameters in boys and girls of mixed nationality (metisis) living in the Republic of Sakha (Yakutia)]. Kul'tura fizicheskaya i zdorov'e [Physical culture and health. 2019; 1 (69): 84-86 (In Russ.).]

29. Pocheshkhova E.A. Ocenka mezhetnicheskih razlichij narodov Zapadnogo Kavkaza (po mul'tiallel'nym autosomnym dnk-markeram) [Evaluation of interethnic differences among the peoples of the Western Caucasus (by multiallelic autosomal DNA markers]. Medicinskaya genetika [Medical genetics. 2008; 7, № 2 (68): 3-9 (In Russ.).]

30. Alekseeva TI, Balanovskaya EV, Baholdina VYu, et al. Problema rasy v rossijskoj fizicheskoj antropologii Institut etnologii i antropologii RAN [The problem of race in Russian physical anthropology] Institut etnologii i antropologii im. N.N. Mikluho-Maklaya RAN [Institute of Ethnology and Anthropology RAS]. 2002: 96 (In Russ.).]

31. Sindeeva LV, Zamkova EV, Kazakova GN. Harakteristika komponentnogo sostava tela studentov razlichnyh etnicheskih grupp v kontekste doktriny zdorov'ya [Sindeeva L.V. Characteristics of the component composition of the body of students of various ethnic groups in the context of the doctrine of health]. The Newman in Foreign Policy. 2019; 48 (92): 13-15 (In Russ.).]

32. Sofronova SI, Romanova AN, Nikolaev VM. Osobennosti lipidnogo i uglevodnogo obmenov u korennogo naseleniya YAkutii v zavisimosti ot etnicheskoj prinadlezhnosti [Features of lipid and carbohydrate metabolism in the indigenous population of Yakutia depending on ethnicity]. Atherosclerosis. 2018; 14 (3): 34-38 (In Russ.).]

33. Olesova LD, Mironova GE, Krivoshapkina ZN, Semenova EI, et al .Sravnitel'naya ocenka chastoty dislipidemii sredi korennogo naseleniya arkticheskoj zony YAkutii [Comparative assessment of the frequency of dyslipidemia among the indigenous population of the Arctic zone of Yakutia]. Yakut medical journal. 2018; 2 (62): 30-34 (In Russ.).]

34. Suyundikova ZhT, Shibkova DZ. Ocenka somaticheskogo zdorov'ya studentok korennogo i prishlogo naseleniya Respubliki Kazahstan [Assessment of somatic health of female students of the indigenous and alien population of the Republic of Kazakhstan]. Vestnik YUzhno-Ural'skogo gosudarstvennogo universiteta. Seriya: Obrazovanie, zdravoohranenie, fizicheskaya kul'tura [Bulletin of the South Ural State University. Series: Education, healthcare, physical culture. 2012; 21(280): 16-19 (In Russ.).]

35. Uchakina RV, Suprun SV, Kozlov VK. Funkcionirovanie shchitovidnoj zhelezy u beremennyh zhenshchin korennogo i prishlogo naseleniya Priamur'ya [The functioning of the thyroid gland in pregnant women of the indigenous and alien population of the Amur region]. Dal'nevostochnyj medicinskij zhurnal [Far Eastern Medical Journal. 2012; 4: 93-95 (In Russ.).]

36. Nesturh MF. CHelovecheskie rasy [[Human races]. Publ. by N.N. CHeboksarov. Edition. 3-e, red. M.: Prosveshchenie, 1965: 104 (In Russ.).]

37. CHiglincev VM, Privalova AG. Fiziologicheskij status mikroelementov u detej shkol'nogo vozrasta, prozhivayushchih v klimaticheskih usloviyah HMAO-YUgry mire nauchnyh otkrytij [Physiological status of trace elements in schoolchildren living in the climatic conditions of Khanty-Mansi Autonomous Okrug-Yugra]. V mire nauchnyh otkrytij [In the world of scientific discoveries. 2016; 11 (83): 170-181. (In Russ.).]

38. Shirokogorov S.M. Etnos. Issledovanie osnovnyh principov izmeneniya etnicheskih i etnograficheskih yavlenij [Ethnos. Study of the basic principles of change in ethnic and ethnographic phenomena]. SHanhaj: Otdel'nyj ottisk iz LXVII Izvestij Vostochnogo fakul'teta Gosudarstvennogo Dal'nevostochnogo universiteta [Shanghai: Separate imprint from LXVII Izvestia of the Eastern Faculty of the State Far Eastern University (Selected works and materials, Book 1, Vladivostok, Publishing House of Far Eastern University, 2001; 1923: 134]. (In Russ.)

39. Malov SI, Malov IV, Savilov ED, Gantulga D, et al. Epidemiologicheskie razlichiya gepatita S u predstavitelej evropeoidnoj i mongoloidnoj ras s uchetom populyacionnogo polimorfizma genov interferona [Epidemiological differences of hepatitis C in representatives of Caucasian and Mongoloid races, taking into account population polymorphism of interferon genes]. Epidemiologiya i vakcinoprofilaktika [Epidemiology and vaccination]. 2015; 14, № 3 (82): 31-36 (In Russ.).]

40. YUsupov R.D., Dmitrienko S.V., CHizhikova T.S., CHizhikova T.V., Magomadov I. Etnicheskie osobennosti zubochelyustnyh dug u naseleniya Vostochnoj Sibiri [Ethnic features of dentoalveolar arches in the population of Eastern Siberia]. Mezhdunarodnyj zhurnal prikladnyh i fundamental'nyh issledovanij [International Journal of Applied and Basic Research. 2015; 3-4: 715-720. (In Russ.).]

41. Dolinina DO, Solopekin NV, Tolstikova AV, Shchetinina AYu. Etnoterritorial'nye variacii haraktera raspredeleniya genov biotransformacii etanola v populyaciyah tyurkoyazychnyh narodov Zapadnoj Sibiri [Ethnoterritorial variations in the nature of the distribution of ethanol biotransformation genes in the populations of the Turkic-speaking peoples of Western Siberia]. Medicinskaya genetika [Medical genetics. 2016; 15, № 4 (166): 32-35. (In Russ.).]

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FEATURES OF THYROID GLAND ULTRASONIC ANATOMY IN YOUTHS LIVING IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.25

УДК 611.411.

In this study regional reference ranges for normal ultrasound anatomy of the thyroid gland in boys and girls aged 16-21 living in the Republic of Sakha (Yakutia) were established. A total of 166 adolescents were examined, of which there were 84 boys (50.6%) and 82 girls (49.4%). The subjects underwent an ultrasound examination with the measurement of linear dimensions and the determination of thyroid volume. According to the results of the study in both groups, the linear dimensions and volume of the right lobe of the thyroid gland prevailed over the indicators of the left lateral lobe. The average thyroid volume in boys was higher and amounted to 11.4±2.6 cm3 and 9.7 ± 3.6 cm3, respectively. The quantitative characteristics of the thyroid gland, obtained as a result of the study, made it possible to identify patterns of variability in the intravital anatomy of this variable organ in adolescents living in the Republic of Sakha (Yakutia) depending on gender. When compared with the data of foreign authors, the values obtained in this study were somewhat higher, which indicates the need for an in-depth study of the regional characteristics of anatomical norm indicators for the thyroid gland.

Keywords: thyroid gland; ultrasound; the volume of the thyroid gland; linear dimensions.

Introduction. Currently, early diagnosis of pathological changes in the thyroid gland is the key to successful treatment, with the main role being played by intravital research methods. High-resolution ultrasound is considered the best imaging modality for thyroid evaluation because it is affordable, non-invasive, and highly sensitive in terms of detection and characterization of thyroid nodules [4, 10, 15, 22]. It is known that linear dimensions and thyroid volume are subject to individual fluctuations [3, 7, 13, 17, 23]. In this regard, anatomical standards are often necessary in practice, taking into account the age and gender of the person. At the moment, the question of the variability of thyroid gland forms in residents of different regions remains relevant [11, 14, 16]. Due to the fact that the diagnosis of thyroid pathology is associated with ultrasound examination, more detailed information about the regional features of the thyroid gland anatomical norm indicators is an urgent scientific and practical task.

Materials and Methods: We have examined 193 students aged 16 to 21 living in the Republic of Sakha (Yakutia). All subjects underwent an ultrasound examination of the thyroid gland according to the method of Mitkov V.V. [4] on a Mindray M7 Portable Ultrasound Sonograph, using a 7.5 MHz linear encoder. According to the results of ultrasound examination, we found echopathology of the thyroid gland in 27 subjects, which served as an exclusion criterion. We performed a descriptive and quantitative analysis of 166 thyroid scans without echopathology. The subjects were divided into 2 groups according to gender: female — 82, male — 84. In each group, we assessed the linear dimensions and volume of the thyroid gland. The shape of the thyroid gland was determined using the method described by Kosyanchuk [2]. Quantitative data were subjected to variational statistical processing. The work performed does not infringe on the rights and does not endanger the well-being of research subjects in accordance with the requirements of biomedical ethics, approved by the Declaration of Helsinki of the World Medical Association (2000). The study was conducted on voluntary informed consent.

Results and Discussions: According to the results of ultrasound examination, in 166 examined persons, the thyroid gland had a normal location, with even, clear contours, a homogeneous structure, and average echogenicity.

Individual differences in the linear dimensions of the lateral lobes of the thyroid gland are presented in Table 1. In both groups of subjects, there is a significant range of linear parameters of the right lateral lobe of the thyroid gland. When analyzing the thickness (anteroposterior size) of the right lobe in a group of young men, the indicators range from 12.3 mm to 21.5 mm, with an average value of 16.1±1.9 mm. The width varies within 11.3-26.7 mm, with an average value of 17.2±1.8 mm. Individual differences in the length of the right lateral lobe range from 33.3 mm to 56.7 mm, with an average value of 45.1±4.8 mm. In the female group, when assessing the linear parameters of the right lateral lobe of the thyroid gland, we obtain the following data: the thickness of the right lobe ranges from 11.2 mm. up to 19.5 with an average value of 14.8±1.8 mm. The width ranged from 10.3 mm to 25.4 mm, with an average value of 16.7±3.3 mm. The quantitative indicator of length is within 28.7 mm up to 53.3 mm, the average value is 41.0 ± 4.2 mm.

When analyzing the ultrasonic parameters of the left lateral lobe, we have the following results. In the male group, the average length is 43.6±3.8 mm, the minimum is 30.9 mm and the maximum is 55.9 mm. In the female group, the average length of the left lateral lobe is less than in the male group and amounts to 40.3 ± 3.4 mm, the minimum and maximum values are 28.9 mm and 50.4 mm, respectively. The width of the left lobe in the female group ranges from 11.3 to 23.4 mm (mean value 16.1 ± 2.8 mm), thickness — from 10.5 mm to 19.1 mm. (average value 14.3± 2.1 mm). For the male group, these figures range from 12.3 to 20.7 mm (average value 16.4±1.5

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Table 1

Quantitative Parameters of the Volume of the Thyroid Gland

Indicator	Male			Female		
	Average Volume (cm^3)	Min.	Max.	Average Volume (cm^3)	Min.	Max.
Right Lobe	6.1±1.7	3.1	14.4	5.0±1.9	2.2	12
Left Lobe	5.2 ±1.1	2.8	8.0	4.6±1.9	1.9	11.7
Overall Volume	11.4 ±2.6	5.7	20.4	9.7±3.6	4.1	17.6

Table 2

Distribution of Shapes of the Thyroid Gland

Shape	Male		Female	
	Abs.	Rel. (%)	Abs.	Rel.
Thyroid Gland in the Shape of a "Butterfly"	51	60.7	43	52.4
Thyroid Gland in the Shape of the Letter "H"	18	21.4	24	29.3
Navicular Shape	4	4.8	3	3.7
Semilunar Shape	9	10.7	11	13.4
Thyroid Gland Without Isthmus	2	2.4	1	1.2

mm), thickness — from 12.3 mm to 19.1 mm. (average value 15.1 ±1.3 mm) .

When calculating the size of the thyroid gland, we pay particular attention to the thyroid volume. The volume is calculated according to the formula by Brown (1981), , where: V is the volume of a fraction of cm^3, A is the length of the fraction in cm, B is the thickness of the fraction in cm, C is the width of the fraction in cm, 0.479 is the adjusted coefficient of π/6. Data on thyroid volume are presented in Table 1.

Morphometric analysis of the right and left lateral lobes in both groups shows that the linear parameters and thyroid volume of the right lobe exceed those of the left lobe with a significant difference between the maximum and minimum values.

To determine the shape of the thyroid gland by ultrasound, we have chosen a method for assessing the isthmus and the distance of the upper and lower poles of the lateral lobes of the thyroid gland. The distribution of forms of the thyroid gland is presented in Table 2. In both groups, the butterfly-shaped thyroid gland is most common (thin and narrow isthmus, large lateral lobes, the distance between the upper poles of the lateral lobes is greater than between the lower poles) in young men 60.7%, girls have 52.4%. The shape of the thyroid gland in the form of the letter "H" (narrow and thin isthmus, high lateral lobes and an insignificant difference between the distance between the upper and lower poles of the lateral lobes) prevails in the group of girls and was found in 29.3% of cases. Significantly less often in both groups there were forms with a pronounced isthmus: navicular and crescentic forms.

When comparing our results with the data of other studies conducted in the world [8, 12, 18, 19, 20, 21, 24], the thyroid volume is in a slightly high range of values, but comparable with the data of other regions of Russia [1, 5, 6], most likely this is due to the climatic and geographical iodine deficiency state of the region, micronutrient deficiencies, etc. In this connection, there is a need for additional studies: hormonal status, consultation of an endocrinologist to exclude endocrine pathology, including subclinical hypothyroidism.

Conclusion. In the course of the work performed, a significant variability in the linear dimensions and shapes of the thyroid gland depending on gender was revealed. Formed regional ranges of individual differences in the thyroid gland depending on gender in adolescents. As a result of the research, it was found that the linear parameters and the total volume of the thyroid gland in young men are on average 8% larger than in girls. The largest difference (17%) was found in the volume of the right lobe, the smallest (1.5%) in the width of the left lobe. The volume of the thyroid gland is larger in boys ($p<0.05$) than in girls (11.4±2.6 cm3 and 9.7±3.6 cm3, respectively). Since thyroid volume depends on anthropometric and clinical determinants, we believe that further research is needed to establish regional standards for thyroid volume in the Republic of Sakha (Yakutia).

Reference

1. Ageenko KI, Gorbachev AL, Shubert EE. Makroanatomiya shchitovidnoj zhelezy u zhitelej g. Magadana [Macroanatomy of the thyroid gland among residents of the city of Magadan]. Fundamental'nye issledovaniya [Fundamental research. 2011; 6: 18–22 (In Russ.).]

2. Kosyachuk NA, Chernykh AV. Rezul'taty ul'trazvukovogo obsledovaniya shchitovidnoj zhelezy zhitelej Voronezhskoj oblasti [The results of ultrasound examination of the thyroid gland of residents of the Voronezh region]. Nauka i obrazovanie: sovremennye trendy [Science and education: modern trends]. 2015; 1 (7) :29-38 (In Russ.).]

3. Lyutaya ED, Zmeev SA. Raspredelenie somatotipov i konstitucional'nye osobennosti razmerov shchitovidnoj zhelezy u lic 8 - 15 let Volgogradskogo regiona [Distribution of somatotypes and constitutional features of the size of the thyroid gland in persons 8 - 15 years of the Volgograd region]. Vestnik Volgogradskogo gos. un-ta [Bulletin of Volgograd State University. 2011; 2 (38): 79 – 82 (In Russ.).]

4. Mit'kov V.V. Obshchaya ul'trazvukovaya diagnostika: praktich. rukovod. po ul'trazvukovoj diagnostike [Practical guide to ultrasound diagnostics: General ultrasound diagnostics. Moscow: Vidar-M, 2019: 756 (In Russ.).]

5. Mukhina TS, Kharchenko VV, Dolzhikov AA. Organometricheskoe issledovanie shchitovidnoj zhelezy v svyazi s polom, vozrastom i somaticheskoj patologiej [Organometric study of the thyroid gland in relation to gender, age and somatic pathology]. CHelovek i ego zdorov'e: Kurskij nauchno-praktich. Vestnik [Man and his health: Kursk scientific and practical bulletin. 2007; 4: 62–67 (In Russ.).]

6. CHaplygina EV, Kuchieva MB. Zakonomernosti ul'trazvukovoj anatomii shchitovidnoj zhelezy i ih klinicheskoe znachenie [Patterns of ultrasonic anatomy of the thyroid gland and their clinical significance]. Nauch.-medicin. vestnik Central'nogo CHernozem'ya [Scientific and Medical Bulletin of the Central Chernozem Region. 2013; 52: 128-134 (In Russ.).]

7. Ahidjo A., Tahir A., Tukur M. Ultrasound determination of thyroid gland volume among adult Nigerians. The Internet Journal of Radiology. 2005; 2 (4): 2-5.

8. Aydiner O, Karakoc AE, İhsan A, Serap T, Abdullah B. Normative data of thyroid volume ultrasonographic evaluation of 422 subjects aged 0-55 years. Journal of clinical research in pediatric endocrinology. 2015; 7(2): 98–101. DOI:10.4274/JCRPE.1818

9. Brunn J., Block V., Ruf G. et al. Volumetric analysis of thyroid lobes by realtime ultrasound. Dtsch.Med.Wschr. 1981; 106: 1338-1340.

10. Germano A, Schmitt W., Rio M., Rui M. Normal ultrasound anatomy and common anatomical variants of the thyroid gland plus adjacent structures – A pictorial review. Clinical Imaging. 2019; 58: 114-128. DOI: 10.1016/j.clinimag.2019.07.002

11. Ivanac G., Rozman B., Skreb F. Brkljacic, B., Pavic, L. Ultrasonographic measurement of the thyroid volume. Collegium Antropologicum. 2004; 28: 287-291.

12. Kaloumenou I., Alevizaki M., Ladopoulos C., Antoniou A., Duntas L.H., Mastorakos G., Chiotis D., Mengreli C., Livadas S., Xekouki P., Dacou-Voutetakis K. Thyroid volume

and echostructure in schoolchildren living in an iodine-replete area: relation to age, pubertal stage, and body mass index. Thyroid: official journal of the American Thyroid Association. 2007; 17: 875-881. DOI:10.1089/thy.2006.0327

13. Kamran M., Hussan N., Ali M. Correlation of thyroid gland volume with age and gender in a subset of Karachi population. Pakistan Journal of Medical Dent. 2014; 3(2): 26-32.

14. Kayastha P., Paudel S., Shrestha D., Ghimire R., Pradhan S. Study of thyroid volume by ultrasonography in clinically euthyroid patients. Journal of Institute of Medicine Nepal. 2010; 32: 36-43 (In Russ.).]

15. Langer J.E. Sonography of the thyroid. Radiologic Clinics of North America. 2019; 57: 469-483.

16. Lee D., Cho K., Sun D., Hwang S., Kim D., Kim M., Cho S. Thyroid dimensions of Korean adults on routine neck computed tomography and its relationship to age, sex, and body size. Surgical and Radiologic Anatomy. 2006; 28(1): 25–32. DOI: 10.1007/s00276-005-0042-3

17. Maevskij A., Sikora V., Gnennaya V., Shayuk A. Relations sonographic parameters of thyroid gland wit hindicators of structure and size of the body in healthy men and women up to 25 years. Biomedical and biosocial anthropology. 2016; 1(26): 57-61.

18. Morna M., Tuoyire D., Jimah B., Rahman G., Eliason S, Appiah A. A community – based ultrasound determination of normal thyroid volumes in the adult population, Assin North District, Ghana. The Pan African medical journal. 2020; 37: 251. DOI: 10.11604/pamj.2020.37.251.20778.

19. Sahin E., Elboga U., Kalender E. Regional Values of Thyroid Gland Volume in Turkish Adults. Serbian Archives of Medicine. 2015; 143 (3-4): 141-145.

20. Suzuki S., Midorikawa S., Fukushima T., Shimura H., Ohira T., Ohtsuru A. Systematic determination of thyroid volume by ultrasound examination from infancy to adolescence in Japan: The Fukushima Health Management Survey. Endocrine journal. 2015; 62 (3): 261-268.

21. Turcios S., Lence-Anta J., Santana J. Thyroid volume and its relation to anthropometric measures in a healthy Cuban population. European thyroid journal. 2015; 4 (1): 651-655. DOI:10.1159/000371346

22. Viduetsky A., Herrejon C. Sonographic evaluation of thyroid size: a review of important measurement parameters. Journal of Diagnostic Medical Sonography. 2019; 35 (3): 206-210. DOI:10.1177/8756479318824290

23. Yousef M., Sulieman A., Ahmed B., Abdella A., Eltom K. Local reference ranges of thyroid in Sudanese normal subjects using ultrasound. Journal of Thyroid Research. 2011; 935141. DOI: 10.4061/2011/935141

24. Zou Y., Ding G., Lou X. Factors influencing thyroid volume in Chinese children. European Journal of Clinical Nutrition. 2013; 67: 1138-1141.

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INTRODUCTION OF GENETIC TECHNOLOGIES INTO THE PRACTICAL HEALTHCARE OF YAKUTIA ON THE EXAMPLE OF SPINOCEREBELLAR ATAXIA TYPE 1 IN THE CONTEXT OF TRANSLATIONAL MEDICINE

DOI 10.25789/YMJ.2022.79.26

УДК 616-009.26(571.56)(091)

The article summarizes the history of scientific research translation into the practical healthcare in the Republic of Sakha (Yakutia) on the example of spinocerebellar ataxia type 1, the most common hereditary disease in the Yakut population.

In the duration of twenty years, translational medicine has developed in Yakutia, approaches to personalized medicine are being developed and the use of genomic technologies has become a reality of our time.

Keywords: spinocerebellar ataxia type 1, DNA diagnostics, genomic technologies, translational medicine.

Introduction. Undoubtedly, the most important of the many discoveries in the field of genetics at the end of the 20th century, anticipating the entry of mankind into the genomic era, are the following: DNA – the main universal molecule of the genome of living systems - was artificially altered using vector viruses and plasmids, as a result, recombinant DNA was obtained for the first time; in the 80s, a revolutionary method was discovered - polymerase chain reaction (PCR), which accelerated the development of technologies that made it possible to decipher the genome of living organisms and humans, to understand many molecular genetic mechanisms of transmission of genetic information [3.25]. Since 1999, sequencing (decoding) of the human genome has been accelerated by the use of a large number of simultaneously operating robotic installations of a company called "Celera", and in 2001 the nucleotide sequence of the human genome was fully read, systematized and made available to researchers in the field of genetics [24].

Thus, general and medical genetics received powerful research tools in the field of human molecular genetics, especially in finding out the causes (gene mutations) of hereditary diseases. Researchers began to use the genotypes of individuals as a kind of mechanism on the principle of "divide" and "study" [32]. To date, a huge number of genes responsible for many monogenic and multifactorial human diseases have been identified in the world, the structures of these genes have been fully deciphered, and they themselves have been cloned [20,27].

Genomic research has challenged society and has become the object of increased public interest in genetics in countries with different state systems, religion and culture, and, in this regard, there is a danger of misconceptions or inflated expectations from the use of genetic technologies. International public organizations (UN, UNESCO, WHO, WMA) have paid close attention to the use of genetic technologies in medical practice with the requirements to respect human rights and prevent abuse in this area of science. Bioethical research began to be conducted within one of the three general directions of the Human Genome program ELSI (Ethical, Legal and Social Implications) [18,21].

Currently, new terms related to the integration of molecular genetics and medicine have entered medical practice: molecular medicine, genomic medicine, pharmacogenetics, oncogenetics, etc., in addition, modern directions "translational

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medicine", "personalized medicine" have emerged [28,30]. In parallel, the transformation of traditional medical ethics into bioethics took place. This was due to the use of the latest medical technologies and the search for solutions to moral dilemmas that affected the basic principles of biomedical ethics: the principle of "do no harm", "do good", the principle of respect for individual autonomy, the principle of justice [19].

Translational medicine (TM) is a direction in medical science that studies the mechanisms and principles of the introduction of modern achievements (methods) of fundamental science, such as molecular genetics, cellular technologies, reproductive technologies, etc. into medical practice. Predictive and personalized medicine are closely related to translational medicine – current areas of modern medicine. For example, predictive medicine significantly reduces health care costs, and personalized medicine implies such technologies of diagnosis and treatment of the patient, in which the quality of life of the patient improves, the period of working capacity lengthens and life expectancy, as well as satisfaction with the quality of medical care provided, increases. TM is multidisciplinary in nature, closely related to biology, biomedicine and social sciences. Translational medicine has several stages of research: fundamental research; the introduction of the results of fundamental research into clinical practice, the search for more effective ways (methods) and ensuring the safety of a particular technology and/or drug treatment; evaluation of the effectiveness of a new technology introduced into medical practice and its economic output [12,16,22].

In the early 2000s, methods of molecular genetic diagnostics (DNA diagnostics) of monogenic diseases were introduced for the first time in the Republic of Sakha (Yakutia). The purpose of this article is to summarize the history of translation of molecular genetic technologies into the medical practice of Yakutia over a 20-year period by the example of the most common hereditary disease in the Yakut population - spinocerebellar ataxia type 1.

Translation of genomic technologies into clinical practice in Yakutia on the example of spinocerebellar ataxia type 1 (SCAI)

1. Fundamental epidemiological, population and molecular genetic studies of SCA1 have been carried out, geno-phenotypic characteristics of the disease have been established.

Hereditary cerebellar ataxia (HCA), classified as one of the clinical forms of Vilyuisk encephalomyelitis, was isolated into an independent nosology as a neurodegenerative hereditary disease in the 70s of the last century [4,7]. In 1992, an in-depth study of HCA began within the framework of the state research program "Biology of Vilyui encephalomyelitis". Joint project of the Neurogenetics Department of the National Institute of Nervous Diseases (NINDS/NIH) of The United States and the research and practical center for Vilyuisk encephalomyelitis of the Republic of Sakha was named: "Identification of genes and genetic mechanisms that cause hereditary neurological diseases". In 1993 , the work of Dr. H. Orr et al on identification of the Spinocerebellar ataxia type 1 (*SCA1*) gene was published [33], and in 1994 - the results of the molecular-genetic study of HCA in the Yakut population was published as well, which revealed an allelic association of highly informative markers D6S274 and D6S89 flanking the locus of the *SCA1* gene on the 6th chromosome, with HCA. A strong association was observed in the case of the microsatellite D6S274, whereas coupling with the marker D6S89 was observed only in 2 families, suggesting a possible historical recombination and the far-off time of mutation in the population [29]. Population studies and the propagation frequency of the disease have established HCA as the largest Siberian focus of accumulation of the disease known in the world and identified it as Spinocerebellar ataxia type 1 (SCA1) [23]. According to F.A. Platonova (2003) the prevalence of SCA1 in the Yakut population is 38.6 per 100,000. The detection of homozygotes by the mutant allele of the SCA1 gene confirms the extremely wide propagation of the disease for hereditary dominant pathologies of the central nervous system [14,15].

2. Approaches to the use of DNA diagnostics of SCA1 have been studied

For the first time in 1999, preparations were made for the introduction of DNA diagnostics of SCA1 in the molecular genetic department of the clinical laboratory of Medical Genetic Consultation (MGC) of the Republican Hospital No. 1 (National Center of Medicine). Regulatory documents, orders and instructions of the Ministry of Health of the Russian Federation on the molecular genetic diagnosis of hereditary diseases were not developed at that time, respectively, we adopted our own algorithm for DNA diagnostics of SCA1 as a routine clinical analysis: referral of the patient for DNA analysis, the stages of the method of DNA isolation from peripheral blood lymphocytes, PCR and electrophoresis of amplification products, documentation of the results and its issuing to the clinical department of MGC. The duties of a medical laboratory doctor/biologist, laboratory assistant and orderlies of the molecular genetic department of the MGC were differentiated [2,8].

3. The method of direct DNA diagnostics of SCA1 has been introduced into the practice of medical and genetic consultation of the Republican Hospital No. 1.

Spinocerebellar ataxia type 1 belongs to the group of hereditary neurodegenerative diseases with dynamic mutations and late manifestation. The mutation is an uncontrolled increase in CAG repeats in the coding part of the SCA1 *gene*. Normally, the number of repeats is 25-33, pathological alleles contain 39-72 repeats.

Currently, according to the Republican Genetic Register of Hereditary and Congenital Pathology of the Republic of Sakha (Yakutia), 401 patients with SCA1 have been registered[5,13].

The detection of a mutation in the *SCA1* gene was carried out by direct DNA diagnostics by PCR with subsequent visualization of DNA fragments in agarose gel. Fig. 1

According to published data, from 2000 to 2013, at the MGC of the Republican Hospital No.1 - DNA testing was performed in 1,841 patients, a dynamic mutation in the SCA1 gene *was* detected in 606 patients (33%)[6].

4. Prenatal DNA diagnostics (PD) of SCA1 has been introduced into the clinical practice of the MGC.

We analyzed the demand for PD technology for burdened families (n =36 people) from 2002 to 2008 [10,11]. There were 46 referrals in total, of which 7 women underwent prenatal DNA testing several times (4 women – twice and 3 women – 3 times). There were more refusals from PD than consents, so 25 PD procedures were carried out over 6 years, of which in 12 cases a mutation of SCA1 was detected in fetuses: 10 pregnancies with a positive result (the presence of a mutation) were terminated with the consent of the families, 2 pregnancies were preserved. Table 1.

5. Ethical rules of DNA testing have been introduced into the practice of the MGC

The final third phase of the translation of genomic technologies into the healthcare system, according to researchers, is the revision and development of legal and bioethical norms, taking into account the use of molecular genetic diagnostics, as well as the establishment of recommendations for the effective and safe use

of new medical technologies in order to satisfy the patient with the process of providing medical care [12].

Introduced for the first time in the Republic in the year 2000. DNA diagnostics of SCA1 immediately acquired the status of routine clinical analysis, at the same time there was a need to develop bioethical rules for the use of genetic technologies in the medical practice of the MGC. This was the beginning of scientific research on applied bioethics in the Republic of Sakha (Yakutia).

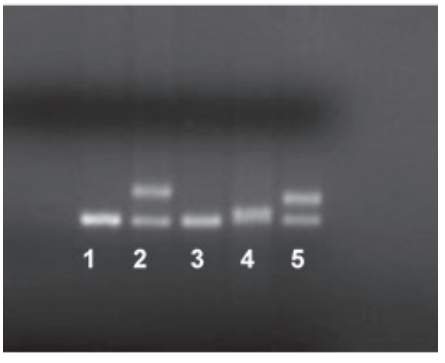
Thus, for the first time, we have developed and implemented bioethical rules for genetic counseling, DNA testing and prenatal diagnosis of SCA1[1,17,26] in the practice of medical and genetic counseling of the Republican Hospital No. 1.

6. The Center for Neurodegenerative Diseases was organized in the clinic of the Yakut Scientific Center for Complex Medical Problems (YSC CMP).

SCA1 is a disease with a progressive neurodegenerative process that leads the patient to disability and social maladaptation. Patients with SCA1 need medical examination, psychological, social assistance and hospital treatment at least twice a year. A study conducted in 2019 showed an insufficient number of inpatient beds that would meet the needs of patients with neurodegenerative diseases (NDD) in the Republic[9]. In this regard, in pursuance of the order of the Ministry of Health of the Russian Federation "On approval of the procedure for providing medical care to adults with diseases of the nervous system" (No. 926n dated 11/15/2011), the Ministry of Health of the Republic issued an order "On the procedure for routing neurological patients suffering from neurodegenerative diseases at the outpatient and inpatient stages" (No. 01-07/184 dated 02/14/2019). Thus, the specialized Center for Neurodegenerative Diseases opened in 2019 at the YSC CMP with a personalized approach to patients is an improved model of providing medical care to patients with NDDs and an example of successful consolidation of medical science and practical healthcare in the Republic[9].

7. The Association of patients with SCA1 and other neurodegenerative diseases has been established

The Association was established to provide medical, social and psychological assistance to patients with NDDs and their relatives. The objectives of the organization are to consolidate the support of social partners to overcome the problems of NDDs in the Republic, informing patients, relatives and society, legal protection of patients with NDDs. On January 17, 2020, a Certificate of state registration of a non-profit organization of the regional public organization "Association of Patients with spinocerebellar ataxia type 1 and other neurodegenerative diseases in the Republic of Sakha (Yakutia)", registration number 1201400000757 was received. With the support of the Presidential Grants Foundation of the Russian Federation and the grant of the Head of the Republic of Sakha (Yakutia), the necessary medical equipment and consumables were purchased, scientific and practical medical expeditions are conducted to assess the health of patients in the areas of the greatest accumulation of NDDs, as well as lectures, seminars, radio and television appearances, publications in the press.



Direct DNA diagnostics of SCA1 in 2% agarose gel: 1, 3, 4 – healthy patients, 2 – a patient with a known number of CAG repeats of 30/50; 5 – a patient with an elongated allele of the SCA1 gene

8. The NDD Center develops methods of physical rehabilitation of patients with SCA1

Patients suffering from NDZ have low motivation to engage in physical education, because firstly, there are many external obstacles, primarily the lack of an accessible environment for recreational activities; secondly, patients have psychological problems (fear, embarrassment, disappointment); thirdly, patients are demotivated by physical ailments (muscle weakness, stiffness, unsteadiness of gait, etc.). At the same time, studies have proved that the targeted use of physical exercises improves the impaired functions of the body, and has a general healing effect[31]. Currently, scientifically based approaches to the physical rehabilitation of patients with SCA1 are being developed using modern methods such as stabilometry.

Conclusion. An example of successful translation of scientific studies of spinocerebellar ataxia type 1, the most common hereditary disease in the Yakut population, into practical healthcare of the Republic of Sakha (Yakutia) is presented. Population-genotypic studies of SCA1 were carried out, the DNA diagnostic method was introduced into the practice of medical genetic counseling at the Republican Hospital No. 1 of the National Center of Medicine, prenatal DNA testing of SCA1 is used, bioethical rules of medical genetic counseling are applied, the Center for Neurodegenerative Diseases and the Association of Patients with SCA1 and Other NDDs were creat-

Prenatal diagnosis of spinocerebellar ataxia type 1

Medical and social characteristics	Results of PD SCA1 (n=36)
Age	19 -40 лет
Education: higher(%)/secondary (%)	22 (61) / 8 (22)
Accommodation: city (%)/village (%)	11 (30) / 25 (69)
Burdened inheritance by line: mother(%)/father(%)/ husband(%)	10 (28) / 10 (28) / 11 (30)
Presence of clinical manifestations of the disease: yes (%)/no (%)	1 (3) / 24 (96)
The family's decision on the proposed PD: consent(%)/ rejection(%)	16 (44) / 20 (56)
Number of PD requests: total (%) / repeated(%)	46 (100) / 7 (15)
The term of pregnancy when applying: 1st trimester(%)/2nd trimester(%)	26 (57) / 20 (43)
The number of PD performed invasively	25
Prenatal DNA testing results: negative(%)/positive(%)	13 (52) / 12 (48)
Pregnancy outcome in the presence of fetal mutation: preservation (%)/termination(%)	2 (17) / 10 (83)
Terms of termination of pregnancy in the presence of a mutation in the fetus: 1st trimester (%) / 2nd trimester (%)	5 (50) / 5 (50)

ed. Approaches to the development of predictive and personalized medicine are being studied. As we can see, transition of research from the laboratory to the clinic does not happen quickly, translational medicine has been developing in Yakutia for twenty years, molecular genetic diagnostic methods are becoming routine, but at the same time it is necessary to continue research on the problems of using genomic technologies in practical medicine.

Reference

1. Kononova SK, Sidorova OG, Sukhomyasova AL, Khusnutdinova EK. Bioeticheskie problemy presimptomaticheskoj DNK-diagnostiki spinocerebellyarnoj ataksii 1-go tipa v praktike mediko-geneticheskoj konsul'tacii YAkutii [Bioethical problems of the presymptomatic DNA diagnosis of spinocerebellar ataxia type1 in the practice of medical-genetic consultation in Yakutia]. Medicinskaya genetika [Medical genetics.2005; 12: 583-588 (In Russ.).]

2. Kononova SK, Fedorova SA, Izhevsk VL, et al. Vnedrenie rutinnoj DNK-diagnostiki nasledstvennyh monogennyh zabolevanij v Respublike Saha (YAkutiya) [Introduction of routine DNA diagnostics of hereditary monogenic diseases in the Republic of Sakha (Yakutia)]. Vestnik SVFU [Bulletin of NEFU. 2012; 9 (4): 21-26 (In Russ.).]

3. Glik B, Pasternak J. Molekulyarnaya biotekhnologiya. Principy i primenenie [Molecular biotechnology. Principles and application]. M.: Mir, 2002: 589 (In Russ.).]

4. Zubri GL, Goldfarb LG, Petrov PA, et al. Differencial'naya diagnostika vilyujskogo encefalomielita: Izuchenie nasledstvennoj mozzhechkovoj ataksii v YAkutii [Differential diagnosis of Vilyuisk encephalomyelitis: The study of hereditary cerebellar ataxia in Yakutia]. Aktual'nye problemy virusologii i profilaktiki virusnyh zabolevanij [Actual Problems of Virology and Prevention of Viral Diseases. Moscow: USSR Academy OF Medical Sciences.1972: 201-210 (In Russ.).]

5. Nogovitsyna AN, Maksimova NR, Sukhomyasova AL, et al. Mediko-geneticheskaya sluzhba naseleniyu Respubliki Saha (YAkutiya). Yakut Medical Journal. 2014; 2 (46): 6-11 (In Russ.).]

6. Stepanova SK, Zakharova VA, Tapyev EV. Molekulyarno-geneticheskie metody diagnostiki monogennyh boleznej v Respublike Saha (YAkutiya) [Molecular genetic methods of diagnosis of monogenic diseases in the Republic of Sakha (Yakutia)]. Geneticheskie issledovaniya naseleniya YAkutii [Genetic studies of the population of Yakutia]. Edited by V.P.Puzyrev, M.I. Tomsky. Yakutsk: CIP NBR Sakha, 2014: 233-245 (In Russ.).]

7. Zubri GL, Goldfarb LG, Savinov AP, et al. Nasledstvennaya mozzhechkovaya ataksiya v YAkutii [Hereditary cerebellar ataxia in Yakutia]. Materialy Pervoj Vsesoyuznoj konferencii po medicinskoj genetike [Proceedings of the First All-Union Conference on Medical Genetics. Moscow: USSR Academy OF Medical Sciences.1975: 60-62 (In Russ.).]

8. Kononova SK, Fedorova SA, Stepanova SK, et al. Organizacionnye, metodicheskie i eticheskie problemy DNK-diagnostiki monogennyh zabolevanij v praktike mediko-geneticheskoj konsul'tacii YAkutii [Organizational, methodological and ethical problems of DNA diagnostics of monogenic diseases in the practice of medical-genetic consultation in Yakutia]. Mat. Vseross. nauch.-prakt.konf. «Molekulyarno-geneticheskaya diagnostika monogennyh zabolevanij: vozmozhnosti i perspektivy». Medicinskaya genetika [Mat. All-Russian Scientific and Practical conference "Molecular genetic diagnostics of monogenic diseases: opportunities and prospects". Medical genetics. 2006; 5: 14-17 (In Russ.).]

9. Davydova TK, Kononova SK, Sidorova OG, et al. Opyt sozdaniya specializirovannogo centra medicinskoj pomoshchi dlya bol'nyh s nejrodegenerativnymi zabolevaniyami na baze kliniki nauchnogo uchrezhdeniya [The experience of creating a specialized medical care center for patients with neurodegenerative diseases on the basis of a clinic of a scientific institution]. Yakut Medical Journal. 2020; 4(72): 53-57 (In Russ.).] [DOI 10.25789/YMJ.2020.72.14.]

10. Gotovtseva LV, Sukhomyasova AL, Pavlova, TY, et al. Prenatalnaya diagnostika v Respublike Saha (YAkutiya) [Prenatal diagnostics in the Republic of Sakha (Yakutia). Yakut Medical Journal. 2014; 2(46): 53-56 (In Russ.).]

11. Sidorova OG, Kononova SK, Sukhomyasova AL, Khusnutdinova EK. Problemy prenatal'nogo mediko-geneticheskogo konsul'tirovaniya monogennyh boleznejs dinamicheskimi mutaciyami v YAkutii [Problems of prenatal medical-genetic counseling of monogenic diseases with dynamic mutations in Yakutia]. Yakut Medical Journal. 2007; 1(17): 33-35 (In Russ.).]

12. Paltsev MA, Belushkina NN. Translyacionnaya medicina – novyj etap razvitiya molekulyarnoj mediciny [Translational medicine – a new stage in the development of molecular medicine]. Molekulyarnaya medicina [Molecular Medicine]. 2012; 4: 3-6 (In Russ.).]

13. Sukhomiysova AL, Maksimova NR, Nogovitsina AN, et al. Raznoobrazie nasledstvennoj patologii v Respublike Saha (YAkutiya) po dannym Respublikanskogo geneticheskogo registra nasledstvennoj i vrozhdennoj patologii [Diversity of hereditary pathology in the Republic of Sakha (Yakutia) according to the Republican Genetic Register of Hereditary and Congenital Pathology]. Geneticheskie issledovaniya naseleniya YAkutii [Genetic studies of the population of Yakutia. 2014: 78-85 (In Russ.).]

14. Fedorov AI, Sukhomyasova AL, Golikova PI, et al. Rasprostranyonnost' spinocerebellyarnoj ataksii 1 tipa v YAkutii: sovremennoe sostoyanie [Prevalence of spinocerebellar ataxia type 1 in Yakutia: current state]. Medicinskaya genetika [Medical genetics. 2020; 19: 7(216): 29-30 (In Russ.).] DOI 10.25557/2073-7998.2020.07.29-30.

15. Platonov FA, Illarioshkin SN, Kononova SK, et al. Spinocerebellyarnaya ataksiya pervogo tipa v YAkutii: rasprostranennost' i kliniko-geneticheskie sopostavleniya [Spinocerebellar ataxia of the first type in Yakutia: prevalence and clinical and genetic comparisons]. Medicinskaya genetika [Medical genetics. 2004; 3 (5): 242-248 (In Russ.).]

16. Shcherbo SN. Translyacionnaya medicina [Translational medicine]. Medicinskij alfavit [Medical Alphabet. 2012; 2 (10): 5-6 (In Russ.).]

17. Kononova SK, Sidorova OG, Stepanova SK, et al. Eticheskie aspekty prenatal'noj diagnostiki pozdnomanifestiruyushchih nasledstvennyh zabolevanij c dinamicheskimi mutaciyami [Ethical aspects of prenatal diagnosis of late-manifesting hereditary diseases with dynamic mutations]. Medicinskaya genetika [Medical Genetics. 2010; 9. No. 9 (99): 10-15 (In Russ.).]

18. Finley Austin MJ , Kreiner T Integrating genomics tecnologies in health care: practice and policy challenges and opportunities. Phisiol Genomics. 2002;8:33-40.

19. Fletcher JC, Berg K, Tranoy KE. Ethical aspects of medical Genetics. A proposal for guidelines in genetic counseling, prenatal diagnosis and screening. Clinical Genetics.1985; 27:199-205.

20. Frank AL. Ethical and practical aspects of human studies. Mutation Research.2001;480:333-336.

21. Gyngell C, Bowman-Smart H, Savulescu J. Moral reasons to edit the human genome: picking up from the Nuffield report. J Med. 2019 ; 45 (8):514-523. doi: 10.1136 / medethics-2018-105084.

22. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. Trans. Res., 2009, 54(6): 277–87.

23. Goldfarb LG, Vasconcelos O, Platonov F.A. et al. Unstable Triplet Repeat and Phenotypic Variability of Spinocerebellar Ataxia Type 1 . Ann. Neurol. 1996;39(4):500-506.

24. International HapMap Consortium. The International HapMap Project. Nature. 2003; 426(6968):789-96. doi: 10.1038/nature02168.

25. Jackson DA, Symons RH, Berg P. “Biochemical method for inserting new genetic information into DNA of Simian Virus 40: circular SV40 DNA containing lambda phage genes and the galactose operon of Escherichia coli,” Proc. Nat. 1972; 2904-2909.

26. Kononova SK, Fedorova SA, Khusnutdinova EK. Bioethical aspects of genetics and genomics in Yakut (Siberia). Genomics and Health in the Developing World.2012; 1426-1430. DOI: 10.1093/med/9780195374759.001.0001

27. Leonard Debra GB The future of molecular genetic testing. Clinical Chemistry.1999;45:726-731.

28. Lindahl R., Jonson VP. Molecular medicine: a primer for clinicians. PartVI: Introduction to genetic testing. SDJ Med.1994;47(11):392-5.

29. Lunkes A., Goldfarb LG, Platonov FA et al. Autosomal dominant spinocerebellar ataxia (SCA) in a Siberian Founder Population: assignment to the SCA1 locus. Experimental neurology.1994;126:310-312.

30. Moldrup C. Ethical, Social and Legal Implications of Pharmacogenomics: A Critical Revie.Community Genetics.2001;4(4): 204-214.

31. Newitt R, Barnett F , Crowe M. Understanding factors that influence participation in physical activity among people with a neuromusculoskeletal condition: a review of qualitative studies. Disabil Rehabil. 2016;38(1):1-10. doi: 10.3109/09638288.2014.996676.

32. Renzong Q. Human genome and philosophy: what ethical challenge will human genome studies bring to the medical practices in the 21st century? CRAcad.Sci.III, 2001;324(12):1097-102.

33. Orr HT, Chang MY, Banfi S. et al. Expansion of an unstable trinukleotide CAG repeat in spinoserebellar ataxia type 1. Nature Genet.1993;4:221-226.

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CHARACTERISTICS OF EXTERNAL BREATHING IN YOUNG MEN OF THE INDIGENOUS ETHNIC GROUP OF YAKUTIA WITH DIFFERENT BODY TYPES

DOI 10.25789/YMJ.2022.79.27

УДК 574.24: 612.24

The features of the functional organization of the external respiration system in students, young Yakuts, with different body types were studied. If in normosthenics the relationship of 13 studied parameters of the respiratory system was traced at the level of weak correlations, then in hypersthenics, on the contrary, rather strong correlations between the components of the respiratory act were revealed. The possibility of using the identified features of the organization of intrasystemic connections to predict the adaptive capabilities of students with different types of somatic constitution is considered. The lower, relative to normosthenics and hypersthenics, values of capacitance indicators and throughput of large bronchi in asthenics are compensated by a significant increase in the patency of respiratory bronchioles.

Keywords: indicators of external respiration; north; Yakut youths; body type; correlation relationships.

Introduction. The study of the adaptive capabilities of the body of student youth in Yakutia is of particular importance, since this population will form the main labor resource of one of the most remote, but strategically important regions of Russia. The functional reserves of the body are largely determined by the external respiration apparatus, which is the most important link in the oxygen transport system. In the North, dry cold air, acting directly on the mucous membrane of the airways, causes reflex bronchospasm, which leads to significant tension in the respiratory system [10]. A negative correlation has been established between the air temperature and the resistance of the bronchial tree: the lower the temperature of the air that cools the airways, the higher the degree of bronchospasm [13].

In assessing the state of human health and its adaptation to the environment, it is important to use the constitutional approach, which provides for the establishment of links and interdependence of the somatic and functional characteristics of the whole organism. The need to study the constitutional features of the individual is currently due to the increasing influence of anthropogenic and social environmental factors, which is reflected in the biological organization of modern man in the North [7, 9, 12, 16].

Purpose: To reveal the features of the functional organization of the external respiration system in young Yakuts with different body types.

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Materials and methods: The study involved young Yakuts, students of the North-Eastern Federal University (n=93), aged 18 to 21 years with different body types (asthenics, normosthenics, hypersthenics). Body length (BW, cm), body weight (BW, kg), chest circumference (WGC, cm) were measured, body mass index (BMI, kg/m2) was determined. Body type was assessed using the Pinier index [11]. Registration of 13 volumetric, velocity and volume-velocity indicators of external respiration [15] was carried out on the spirograph of the Valenta computer diagnostic system. All the main characteristics were automatically compared with the proper values, originally included in the software of the device and representing the data obtained for the inhabitants of the Central European part of Russia. The study was carried out taking into account the ethical standards of the Declaration of Helsinki. All subjects gave voluntary informed consent to participate in the research. Since the results of the study of respiratory system parameters did not obey the normal distribution law, the nonparametric Mann-Whitney method was used for statistical processing of the obtained data and the values were presented as a median (Me), first (Q1) and third (Q3) quartiles. Differences between groups were considered significant at $p < 0.05$. The assessment of the strength and nature of the relationship between the indicators of external respiration was carried out with the calculation of the Spearman pair rank correlation coefficients (r) taking into account statistically significant correlation coefficients at $p < 0.05$.

Results and discussion. The results of the study of the indicators of physical development of all the examined students (Table 1) are consistent with the previously obtained data [7], which established significantly lower values of anthropometric indicators in Yakut boys compared to Caucasian boys living in Yakutia. With almost the same body length, the values of MT, OGK and BMI in groups with different physiques differed significantly. The value of BMI in asthenics was at the lower level, and in hypersthenics - at the upper level of the norm (preobesity). The study of capacitive indicators of external respiration of VC, FVC and FEV1 revealed a decrease in their values relative to the due ones, and, to a greater extent, this affected FVC (Table 2). Data on low values of capacitive characteristics in young Yakuts are consistent with the results of a number of authors who examined young men who are representatives of indigenous ethnic groups living in regions with a sharply continental climate [5, 8, 14]. Significantly higher values of VC and FVC were observed by us in normosthenics and hypersthenics, who have a large chest circumference relative to asthenics. High VC values are indicated in male students, ethnic groups of territories with extreme natural and climatic conditions, with a hypersthenic body type [2, 4].]. Of the lung volumes that make up the VC, significant differences between the examined groups were found only in one indicator of the reserve breathing capacity (ROout), the value of which is higher in normosthenics compared to asthenics. Significant differences between the values of capacitive characteristics and lung volumes between the groups of normosthenics and hypersthenics were not found.

The study of the state of the air system revealed significantly higher patency of large bronchi in normosthenics and hypersthenics than in asthenics (Table 2). However, in bronchi of medium caliber (MOS50%), the throughput becomes the same in all groups. Further, in the small

Table 1

Indicators of physical development (M±m) of the examined students according to anthropometry data, depending on the body type (M ± m)

Indicator	Asthenic (1) n =27	Normosthenic (2) n = 47	Hypersthenic (3) n = 19	All n = 93
Body Length (cm)	174.3±1.13	173.3±0.88	172.0±1.58	173.2±0.56
Body weight (kg)	56.3±1.25*	63.8±0.92*	73.8±1.67*	64.2±0.95
Chest circumference (cm)	80.7±0.63*	87.6±0.62*	95.5±0.70*	87.3±0.84
Body mass index (kg/m^2)	18.48±0.27*	21.2±0.18*	24.9±0.30*	21.2±0.32

Note: * - significance of differences at - p < 0.001, 1-2; 2-3; 1-3.

respiratory bronchi (MOS75%), the patency increases relative to the proper values in all groups, but to the greatest extent in asthenics. The literature indicates an excess of the proper level of patency of small bronchi in the natives of the North-East of Russia [8], which may be due to increased production of surfactant in bronchioles and alveoli under the influence of low temperatures [6]. Surfactant, stabilizing the lumen of the bronchioles and alveoli at maximum exhalation, prevents the narrowing of the lumen of the small bronchi, which ensures a high airflow rate in them. The low airiness of the proximal bronchi in asthenics is compensated by a statistically more significant increase in the patency of small (MOS75%) bronchi than in normosthenics and hypersthenics. Additional opening of the respiratory bronchioles allows to increase the volume of functional dead space, the amount of residual warm air in the pulmonary tree necessary to warm the cold air coming from outside. A significant increase in the airiness of the respiratory bronchi allows increasing the intensity of gas exchange, which is important for maintaining oxygen homeostasis [10].

To study the features of the functional organization of the external respiration system in residents of regions with extreme climatic conditions, a correlation analysis of the relationships between the individual components of the respiratory act was used [3, 8]. In our studies, the results of the analysis of the values of the pairwise rank correlation coefficients between all 13 studied characteristics of the external respiration system: capacitive (VCvd, FVC, FEV1), lung volumes (TO, ROVd, ROVd), volume-velocity (POS, MOS25%, MOS50, MOS75) revealed differences in the number and strength of correlations in young men with different physiques (Table 3).

In normosthenic young men, oxygen homeostasis is ensured due to the plastic interrelation of the parameters of the external respiration system. In this group, intrasystem interaction was traced at the level of weak correlations; only one strong correlation was found at the level of 0.74-0.79 in the POS-MOS25 pair. It is possible that the relative autonomy of the functioning of the constituent components in the external respiration system in normosthenics allows it to have large reserve capabilities in satisfying the oxygen demand. In hypersthenics, the density of interaction of external respiration indicators was high due to a greater number of close relationships - the number of connections at the level of 0.71-0.9 was 9. In asthenics, the number of equally close connections was 4. Excessively high tension of intrasystemic connections in hypersthenics can lead to decrease in the adaptive capabilities of the respiratory system in the environmental and social

Table 2

The main parameters of the external respiration system in students with different body types (Me, Q1–Q3)

Parameters	Body Types			Reliability of differences, p
	Asthenic (1)	Normosthenic (2)	Hypersthenic (3)	
VLCins (L)	3.58 (3.23-4.1)	3.87 (3.41-4.31)	3.87 (2.96-4.4)	1-2 < 0.05
VLCins (% reference)	74 (66.2-81.5)	81.5 (75.5-90.5)	84 (59.5-93)	-
IRV (L)	2.22 (1.53-2.24)	1.67 (1.27-2.28)	1.72 (0.85-2.28)	-
ERV (L)	0.84 (0.6-1.21)	1.14 (0.85-1.34)	1.01 (0.88-1.26)	1-2 < 0.01
RV (L)	0.82 (0.67-0.96)	0.85 (0.71-0.97)	0.92 (0.79-1.03)	-
FVC (L)	3.18 (2.87-3.5)	3.47 (2.89-3.78)	3.44 (3.12-3.66)	1-2 < 0.05
FVC (% referens)	67 (62-72.7)	75.5 (69-84)	75 (71-81.5)	1-2 < 0.01 1-3 < 0.05
FEV1 (L)	3.03 (2.84-3.4)	3.06 (2.7-3.37)	3.17 (2.66-3.44)	-
FEV1 (% referens)	72 (67.5-82.2)	75 (69-84)	80.0 (70-85)	-
FEV1/FVC (%)	99.7 (95.2-100)	92.5 (84.9-99.2)	90.8 (86.8-94.1)	1-2 < 0.01 1-3 < 0.01
PEF (L/s)	6.76 (6.09-7.16)	7.07 (6.26-7.86)	7.33 (6.26-8.04)	1-2=0.072
PEF (% referens)	75 (68.2-81.7)	81 (75-89)	81 (69-92.5)	1-2 < 0.05
FEF25% (L/s)	6.14 (5.5-6.73)	6.24 (5.74-7.25)	6.21 (5.68-7.61)	1-2=0.057
FEF25% (% referens)	76 (70.2-84.5)	83 (76.5-91.5)	76 (71.5-99.5)	1-2< 0.01
FEF50% (L/s)	5.29 (4.72-5.93)	5.11 (4.14-5.55)	4.75 (4.09-5.46)	-
FEF50% (% referens)	98 (87.2-107.7)	93 (76.5-102.5)	90 (68.5-97.5)	1-3 < 0.05
FEF75% (L/s)	3.37 (3.11-3.74)	2.91 (2.37-3.81)	3.01 (2.44-3.44)	1-3 < 0.05
FEF75% (% referens)	129 (110-132.7)	114.5 (90.2-144.7)	106 (90.5-130)	1-3=0.057
TFVC (s)	1.05 (0.92-1.38)	1.33 (1.05-1.9)	1.53 (1.33-1.87)	1-2< 0.01 1-3< 0.01
TPEF (s)	0.31 (0.22-0.39)	0.26 (0.18-0.38)	0.22 (0.16-0.44)	-

Note. A dash indicates the absence of statistically significant differences between the compared groups.

conditions of the North. Our earlier studies of the morphological and functional characteristics of young Yakuts revealed a tendency to hypersthenization of the physique, against which the adaptive capabilities of the circulatory system decrease [9]. These results are consistent with the data of a study of young students in the city of Magadan, according to which a pronounced tension in the work of the cardiorespiratory system and a decrease in its functional reserves were found in hypersthenics relative to other somatotypes. [8]. By definition, P.K. Anokhin, the maintenance of vital constants of the internal environment of the body can be achieved both by reducing the strength of connections between the parameters of functional systems, and by strengthening the relationship [1]. The data obtained in this work indicate that the same reserve capabilities of the external respiration system in young men with normosthenic and hypersthenic types of somatic constitution are achieved by different ways of organizing the interaction of individual components of this system.

Conclusion. Despite the lower values of the main indicators of lung ventilation relative to the proper values developed for residents of the Central European part of Russia, we believe that our data are adequate to the level of physical development of the surveyed young men - representatives of the urbanized ethnic group of Yakutia, who have significantly lower anthropometric parameters relative to their peers - Caucasoids of the same region. In young men of normotonic and hypersthenic body types, the same, higher compared to asthenics, reserve possibilities of external respiration were established. However, the strategy for providing oxygen demand to the body of young Yakuts has specific features depending on their belonging to one or another type of somatic constitution. In young men with a normotonic physique, flexible connections between the components of external respiration were revealed, which, in our opinion, allows us to have large reserve capabilities in satisfying the oxygen demand. In young men with a hypersthenic type of constitution, a large number of strong correlations were found between the components of the respiratory act, which limits the plasticity of intrasystemic connections and can make the body less adaptive in the environmental and social conditions of the North. The low values of capacitance and throughput of large bronchi in asthenics, in comparison with normosthenics and hypersthenics, should not affect the homeostasis of blood gas composition, since young men of this somatotype showed a significant opening of respiratory bronchioles, which allows increasing the intensity of gas exchange in the lungs.

Table 3

Correlations between indicators of external respiration system

Correlation relationship	Asthenic	Normosthenic	Hypersthenic
VLCins - FVC	0.65***	0.49***	0.78**
VLCins – FEV1	0.5**	0.47***	0.86***
FVC - FEV1	0.85***	0.56***	0.74***
VLCins - RV	0.61***	0.38**	0.3
VLCins - IRV	0.49**	0.67***	0.84***
VLCins - ERV	0.45*	0.3*	0.35
FVC - RV	0.63***	0.28*	0.28
FVC - IRV	0.04	0.13	0.51*
FVC - ERV	0.4*	0.18	0.38
FEV1 - RV	0.55**	0.22	0.32
FEV1 - IRV	0.03	0.32*	0.85***
FEV1 - RV	0.33	0.1	0.02
VLCins - PEF	0.1	0.18	0.66**
VLCins – FEF25%	0.05	0.17	0.45*
VLCins – PEF50%	0.35	0.03	0.36
VLCins – PEF75%	0.31	0.12	-0.01
FVC - PEF	0.24	0.17	0.58**
FVC - FEF25%	0.26	0.12	0.29
FVC - FEF50%	0.58**	-0.08	0.10
FVC – FEF75%	0.49**	-0.33*	-0.24
FEV1 – PEF	0.48**	0.30*	0.86***
FEV1 – FEF25%	0.49**	0.29*	0.65**
FEV1 – FEF50%	0.43*	0.1	0.41
FEV1 – FEF75%	0.41*	0.11	0.1
PEF – FEF25%	0.86***	0.94***	0.9***
PEF – FEF50%	0.43*	0.5**	0.6**
PEF – FEF75%	0.4*	0.38**	0.27
FEF25% - FEF50%	0.58**	0.59***	0.76***
FEF25% - FEF75%	0.49**	0.46**	0.47*
FEF50% - FEF75%	0.78***	0.66***	0.66**

Note: The correlation between the indicators is statistically significant:
* - $p < 0.05$ - ** $p < 0.01$ - *** $p < 0.001$.

Reference

1. Anokhin P.K. Ocherki po fiziologii funkcional'nyh system [Essays on the physiology of functional systems. Moscow: Medicine, 1975; 448. (In Russ.)].

2. Bazarbaeva SM, Dinmukhamedova AS, Aizman RI. Regional'nye morfofunkcional'nye osobennosti razvitiya studentov kazahskoj nacional'nosti [Regional features of the morphofunctional development of students of kazakh nationality]. Gigiena i sanitariya [Hygiene and sanitary. 2019; 4(98): 449-454. (In Russ.)] Doi: 10.18821/0016-9900-2019-98-4-449-454.

3. Gudkov A.B., Shcherbina F.A., Chupakova L.V. et al. Sezonnaya funkcional'naya organizaciya sistemy vneshnego dyhaniya u detej starshego shkol'nogo vozrasta, zhitelej Arkticheskogo regiona [Seasonal functional organizati on of the external respiration system in children of senior school age, residents of the Arctic region]. Yakut medical journal. 2019; 2(66): 79-82 (In Russ.).] Doi: 10.25789/YMJ.2019.66.24.

4. Krasilnikova V.A., Burhinova I.V. Ocenka sostoyaniya sistemy vneshnego dyhaniya studentov tuvinskogo gosudarstvennogo universiteta v zavisimosti ot tipov konstitucii [Status evaluation of external respiration system of students of Tuva state university depending on constitution types]. Vestnik Tuvinskogo gosudarstvennogo universiteta. Estestvennye i sel'skohozyajstvennye nauki [Bulletin of Tuvan State University. Natural and agricultural sciences. 2018; 2: 23-29. (In Russ.)].

5. Nifontova O.L., Konkova K.S. Osobennosti parametrov vneshnego dyhaniya korennyh zhitelej Hanty-Mansijskogo avtonomnogo okruga YUgry v vozraste 11–14 let [Specific character of the external respiration of the indigenous residents of Khanty-Mansiysk autonomous aistrict Ugra aged 11-14 years]. Ekologiya cheloveka [Ecologya cheloveka. 2019; 8:18–24 (In Russ.).] Doi: 10.33396/1728-0862-8-18-24.

6. Smolina V.S., Zavyalova A.A. Dinamika staticheskih legochnyh ob"emov i emkostej v godich-

nom cikle u detej mladshego shkol'nogo vozrasta, zhitelej Evropejskogo Severa [Dynamics of static pulmonary volumes and capacities in annual cycle in children of primary school age, residents of the european north]. Ekologiya cheloveka [Ecologya cheloveka. 2013; 10: 55-59. (In Russ.).]

7. Stepanova G.K. Fizicheskaya rabotosposobnost' i ee svyaz' s morfofunkcional'nymi harakteristikami u razlichnyh etnosov YAkutii [Exercise Performance: Its Relationship with Morphological and Functional Characteristics in Two Ethnic Groups of Yakutia]. Fiziologiya cheloveka [Human Physiology. 2005; 31(3): 352-357 (In Russ.).] Doi: 10.1007/s10747-005-0056-6.

8. Suhanova I.V., Maksimov A.L., Vdovenko S.I. Osobennosti adaptacii u yunoshej Magadanskoj oblasti: morfofunkcional'nye perestrojki (soobshchenie 1 [Features of adaptation in young men of the Magadan region: morphofunctional rearrangements (message 1)]. Ekologiya cheloveka [Human ecology]. 2013; 8: 3-1. (In Russ.)].

9. Ustinova M.V., Stepanova, G.K., Nikolaeva I.V. i dr. Dinamika morfofunkcional'nyh harakteristik yunoshej-yakutov za 20 let [Dynamics of morphological and functional characteristics of young Yakuts for 20 years]. Gigiena i sanitariya [Hygiene and sanitary]. 2021; 3(100): 274-278. (In Russ.)]. Doi: 10.47470/0016-9900-2021-100-3-274-278.

10. Shishkin G.S., Ustyuzhaninova N.V. Funkcional'nye mekhanizmy izmenenij vneshnego dyhaniya pri osenne-zimnem ponizhenii temperatury vozduha [Mechanisms of respiratory function changes as result of autumn and winter air temperature fall]. Ekologiya cheloveka [Human Ecology. 2012; 7: 3-6. (In Russ.)].

11. Yuriev V.V., Simahodskiy A.S., Voronovich N.N. et al. Rost i razvitie rebenka [The growth and development of the child]. SPb.: Piter, 2003; 272 (In Russ.).]

12. Harrison G A. Urbanization and stress. L, 1980; 55-72.

13. Islam MS. Jahresrhythmus des Atemwegswiderstandes und des intrathorakalen Gasvolumens bei gesunden Frauen und Mannera. Respiration.1981; 42(3): 193-199. Doi: 10.1159/000194428.

14. Kozlov A, Vershubsky G, Kozlova M. Indigenous peoples of Northern Russia: Anthropology and health. International journal of circumpolar health. 2007; 66(1): 1-184. Doi: 10.1080/22423982.2007.11864604B.

15. Langan RC, Goodbred AJ. Office spirometry: indications and interpretation. American Family Physician. 2020; 101(6): 362-368.

16. Van Oostdam J, Donaldson SG, Feeley M. Human health implications of environmental contaminants in Arctic Canada: a review. Science of the total environment. 2005; 352: 165-246. Doi:10.1016/j.scitotenv.2005.03.034.

DOI 10.25789/YMJ.2022.79.28

УДК 611.019

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COMPARATIVE ANALYSISOF SOMATOMETRIC AND ORCHIDOMETRIC INDICATORS OF YOUNG MEN LIVING IN THE REPUBLIC OF SAKHA (YAKUTIA), ENGAGED AND NOT ENGAGED IN SPORTS

In sports practice, high motor activity is heavily demanding on the physique of a person and body composition – a factor which largely affects body's functional capabilities. Many authors emphasize the urgent need for constant monitoring of the physiological development of the reproductive functions of the male body. This determined the purpose of the study: to conduct a comparative morphological analysis of somatometric and orchidometric parameters in young men living in the Republic of Sakha (Yakutia) and their sports activity.

We have established statistically significant intergroup differences between young men not engaged in sports and engaged in sports: there were higher indicators of body weight, body mass index, higher phase angle indicators, rates of lean body mass (LBM), active cell mass (ACM), %ACM, and ejection fraction (EF) yet the latitudinal dimensions of the body are inferior to those of young men not engaged in sports. In addition, in this group, there were marked differences between the minimum and maximum values of weight, height and body mass index. This indicates a more intense metabolism and the level of metabolic processes of basal metabolic rate (BMR) and mass-specific basal metabolic rate (mass-specific BMR) in young men involved in sports.

A comparative analysis showed that the volume of the left testicle in non-athletes is greater than that of athletes, while the right testicle is the opposite.

All orchidometric parameters of the studied groups had statistically significant bilateral differences with their right-sided predominance. The results of the study can become an information basis for the consultative and diagnostic practice of sports medicine doctors, exercise therapy. These results can also help trainers dealing with practical issues of clinical, instrumjental, and laboratory monitoring of the current state of athletes and working on methods of maintaining and improving sports performance.

Keywords: somatometry, orchidometry, body composition, athletes, young men.

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Introduction. In sports practice, motor activity imposes special requirements on the physique of a person, largely affecting their functional capabilities — that being the manifestations of physical qualities (speed, strength, endurance, etc.). One of the most adequate approaches in assessing the physical condition of a person is the method of complex research, which allows to control the health status and dynamics of the development of athletes objectively, effectively, and based on standardized approaches [5, 7, 13].

The most widely recommended somatometric measurements include body length and weight, body mass index (BMI), and circumference of body parts. Other useful measurements include the shoulder, thigh, and lower leg, the thickness of the subcutaneous fat fold on the back and inner surface of the shoulder and forearm, thigh and lower leg, as well as the abdominal region [3, 5, 7]. Also, many authors emphasize the urgent need for constant monitoring of the physiological development of the reproductive functions of the male body [8]. It should be noted that some domestic and foreign

researchers analyzed the relationship of genitometric parameters with general anthropometry data and somatotype as conjugate parameters of physical status and reproductive functions [2, 8, 12, 14, 17].

When analyzing scientific sources, we did not find previous data containing information on complex studies of the effect of directed physical activity on somatometric or orchidometric indicators of the male population living in the Republic of Sakha (Yakutia). Due to the technical and ethical features of such studies, there are limitations to their comprehensive assessment, but despite this, the problem requires special analysis. In connection with the foregoing, a comparative analysis of somatometric and orchidometric indicators of young men in the Republic of Sakha (Yakutia) engaged and not engaged in sports is relevant.

Aim: conducting a comparative morphological analysis of somatometric and orchidometric parameters in young men living in the Republic of Sakha (Yakutia) engaged and not engaged in sports.

Materials and Methods: The work was carried out on the basis of the Medical Institute of the M.K. Ammosov North-Eastern Federal University (NEFU) and the Churapcha Institute of Physical Culture and Sports (CIPCS) in 2019–2022. The subjects were divided into 2 groups: Group 1 — 79 students of NEFU of different specialties not engaged in sports, Group 2 — 74 students of CIPCS engaged in different sports for at least 6 years. In both groups we examined young men of indigenous nationality aged 18-20, permanently residing in the Republic of Sakha (Yakutia). We used the standard accepted methods for the study [9, 10]. Anthropometric measurements included measurements of total dimensions and body weight: length (cm), body mass (BM, kg), chest circumference (CC, cm), waist circumference (WC, cm) and hip circumference (HC, cm). We assessed body composition using the method of bioimpedancemetry with Medass-ABC-01.

We performed ultrasound examination of the scrotum in the supine position on a high-end portable Mindray M7 Ultrasonic Sonograph using a linear transducer with a frequency of 7.5 MHz. According to the generally accepted standard, ultrasound scanning of the testicles was done in three projections: the width and thickness were determined in the transverse projection, and the length in the longitudinal projection. Testicular volume in ml was calculated according to the formula described by Brown (1981): V=0.52*ABC where A is the length, B is the width and C is the thickness of the testis in mm, while 0.52 is the corrected coefficient of π/6. We carried out statistical processing of the obtained results using the SOMAX analytical database system. For data with a normal distribution, the mean (M) and the step of the confidence interval (m) were calculated. We assessed the significance of differences in the mean values of the samples using Student's t-test; for features with non-parametric distribution, we used the Mann-Whitney method U-test. The results were considered statistically significant at $p < 0.05$. This approach provided a comprehensive and reliable study of the material obtained.

The measurements were carried out in compliance with the principles of voluntariness, the rights and freedoms of the individual, guaranteed by Articles 21 and 22 of the Constitution of the Russian Federation. The work performed does not infringe on the rights and does not endanger the well-being of research subjects in accordance with the requirements of biomedical ethics, approved by the Declaration of Helsinki of the World Medical Association (2000). All participants gave individual informed consent to participate in the study.

Results and Discussion. Results obtained by us in terms of height and BMI correspond to the average indicators for assessing the physical development of children at puberty, according to WHO clinical recommendations [9]. The average BMI of young men was 22.08±3.58 in Group 1 and 22.78±0.97 in Group 2, $p \leq 0.05$. Normal body weight was determined in 74.7% of young men, while 13.3% of young men not engaged in sports were overweight; in the second Group, everyone had normal body weight. We did not find cases of obesity in the surveyed groups of young men.

As can be seen from Table 1, the data obtained confirm the main patterns of differences in anthropometric indicators between young men not engaged in sports and engaged in sports: in Group 1, there are higher indicators of body mass, body mass index, but the latitude dimensions of the body are inferior to those of young men in Group 2. In addition, in Group 1, there are pronounced differences between the minimum and maximum indicators of weight, height and body mass index.

In earlier studies, we saw that chest circumference in Group 2 is 87.72±10.63 cm; in Group 1 — 84.30±10.53 cm, which we associated with indicators of lung vital capacity (VC): 3734.32±162.49 ml and 3454.93±157.82 ml ($p < 0.01$), respectively. Higher VC values in Group 2 indicate high functional reserve capabilities, which is an important mechanism for adaptation to physical loads [4].

Assessing body composition is an essential part of the constitutional diagnosis of athletes and is important in indirectly assessing their physical performance and their bodies' adaptation to the physical load, as well as in correcting their training structure [6]. Comparative analysis of the results of bioimpedance analysis (BIA) of the two groups is presented in Table 2.

As can be seen from Table 2, in the group of young men engaged in sports, there are higher phase angle indicators than among young men not engaged in sports. The values of the phase angle (PA) are commonly interpreted as follows: PA < 4.4° — high probability of catabolic shifts; 4.4° < PA < 5.4° — hypodynamia; 5.4° < FU < 7.8° — normal; 7.8° < FU — increased values typical for athletes [6]. The maximum indicator for young athletes in our study is 7.96°. The pre-start performance of an athlete in high-achievement sports is predicted by the magnitude of their phase angle.

Table 2 of the bioimpedance body composition study also reflects the differences between groups in the following parameters: body fat mass (BFM), percentage of body fat (%BFM), lean body mass (LBM), active cell mass (ACM), percentage of ACM content in lean body mass (%ACM), skeletal muscle mass (SMM), percentage of skeletal muscle mass in lean mass (%SMM), basal metabolic rate (BMR), mass-specific (normalized to body surface area) basal metabolic rate (MSBMR), total body water (TOW), and extracellular fluid volume (ECF).

As the study showed, in Group 2 the numbers for BFM and %BFM are lower, while LBM, ACM, and %ACM are higher than in Group 1. This indicates the absence of problems with the consumption and assimilation of the protein part of the diet. %ACM in lean mass serves as a correlate of motor activity and physical performance of the athletes. The value of %ACM in the group of young athletes is lower than the accepted norms of current masters of sports in cyclic and game sports types, where the values of %ACM should exceed 62–63% [11].

In addition, the study showed low SMM and %SMM values in athletes. The value of SMM relative to the interval of normal values is used for a general characteristic of physical development. The value of %SMM in lean mass is one of the three key characteristics of the physical performance of an athlete, along with

%BFM and phase angle. Any decrease in the muscle component indicates a lack of energy resources in the athlete's body and accumulated or current under-recovery and inhibition of protein synthesis processes, which can lead to a decrease in performance and recovery.

We established an increase in the content of extracellular fluid in the group of non-athletes, which indicates fluid retention, due, for example, to the consumption of foods with a high content of table salt. Sports weight loss procedures can lead to a short-term decrease in the content of extracellular fluid.

In addition, higher rates of LBM, ACM, %ACM, and PA indicate a more intense metabolism and the level of metabolic processes of BMR and MSBMR in young athletes than in non-athletes. The reason for changes in the MSBMR in the latter may be endocrinological disorders, the effects of drugs, etc.

Studies available in the literature show that the size of the penis and other genitometric parameters, even within the same age groups, are subject to significant individual, group, racial, and ethnic variability [8]. The data on the correlation of phallometric data and the principles of their typology from the point of view of the constitutional approach are contradictory. There are few studies in which the dimensional characteristics of the external genitalia would be compared with the corresponding data on the hormonal background and orchidometry. Despite the colossal volume of various data, including data from foreign scientific literature, the results of studies of genitometric parameters in Russian groups published in scientific literature sources for the last ten years are not available. Undoubtedly, the best and most objective clinical marker of puberty in men is the assessment of testicular volume [15].

Comparative analysis of orchidometric indicators of young men of the two groups found that the volume of the left testicle in Group 1 is greater than in Group 2: 15.36±0.57 and 15.29±0.98 mm^3; the results for the right testicle are vice versa: Group 1 — 15.46±0.51 and Group 2 — 16.31±1.19 mm^3, $p \leq 0.05$. The total volume of testicles was higher in Group 2. All orchidometric parameters of the studied groups have statistically significant bilateral differences with their right-sided predominance.

These data correlate with the data of a large study by Tambov State University, which shows significant differences between different ethnic groups: Russians, Africans, Indians, Greeks, etc. In general, the average volume of the right testicle in the whole sample was 12.10 mm^3, the left — 12.13 mm, both — 24.22 mm^3 [8].

To further clarify the nature of the relationship between the absolute values of the measured traits and indicators of body composition, we carried out a factor analysis. However, we found no statistically significant correlation coefficients between orchidometric and somatometric parameters. In our previous studies, we found a weak correlation between the average testicular volume and indicators of active cell mass, skeletal muscle mass, and a moderate correlation with the phase angle. The results obtained are of interest and require further study.

Table 1

Statistical characteristics of general anthropometric parameters. p ≤0.05

Data	Group 1		Group 2	
	min	max	min	max
Body weight, kg	65.61	74.39	65.18	71.45
Height, m	168.19	176.53	170.58	175.45
Waist circumference, cm	75.52	79.30	76.50	82.07
Hip circumference, cm	90.37	95.04	91.44	95.56
Waist/hip ratio	0.81	0.88	0.83	0.87
Body mass index	16.51	27.66	21.80	23.75

Table 2

Indicators of bioimpedansiometry of young men, p ≤ 0,05

Data	Group 1		Group 2	
	min	max	min	max
Phase angle 50 kHz(deg.)	6.89	7.37	7.47	7.96
Fat mass (kg)	9.68	17.85	8.76	11.49
Proportion of fat mass (%)	14.59	19.31	13.19	15.91
Lean mass (kg)	54.97	57.48	55.92	60.46
Active cell mass (kg)	32.83	35.52	33.98	37.26
Proportion of active cell mass (%)	58.97	62.39	60.25	62.09
Skeletal muscle mass (kg)	31.92	39.84	30.90	33.46
Proportion of skeletal muscle mass (%)	57.01	69.42	54.96	55.66
Basic metabolism (kcal)	1652.89	1738.06	1689.83	1793.13
Specific basal metabolism (kcal/sq.m)	910.88	950.15	942.97	977.58
Water (kg)	40.24	42.07	40.94	44.27
Extracellular water (kg)	18.33	25.57	15.94	17.28
Intracellular water (kg)	22.71	26.84	23.47	27.14

Conclusions

We show the main patterns of differences in anthropometric indicators between young men not engaged and engaged in sports: in Group 1, there are higher indicators of body mass, body mass index, but the latitudinal dimensions of the body are inferior to those of young men in Group 2. In addition, in Group 1, there are pronounced differences between the minimum and maximum indicators of weight, height, and body mass index. We have established that in the group of young men engaged in sports, there are higher phase angle indicators than among young men not engaged in sports. The maximum indicator of young athletes in our study is 7.96°. We show that in young athletes the rates of BFM and %BFM are lower, while LBM, ACM, %ACM are higher than that of non-athletes. In addition, the study showed low SMM and %SMM values in athletes. We establish an increase in the content of extracellular fluid in the group of non-athletes, which indicates fluid retention. Higher rates of LBM, ACM, %ACM, and PA indicate a more intense metabolism and the level of metabolic processes of BMR and MSBMR in young athletes than in non-athletes. A comparative analysis showed that the volume of the left testicle in non-athletes is greater than that of athletes, the right testicle is the opposite. All orchidometric parameters of the studied groups have statistically significant bilateral differences with their right-sided predominance.

The scientific and practical significance of the results of the study is in the analysis of the main somatometric and orchidometric indicators of pubertal youths engaged and not engaged in sports, which can be used to assess their reproductive health and somatic pathology resulting from poor reproductive health (occurring due to individual anthropometric indicators and changes in body composition). The results of the study can become an information basis for the consultative and diagnostic practice of sports medicine doctors, exercise therapists, trainers dealing with practical issues of clinical, instrumental and laboratory monitoring of athletes, as well as for creating methods of maintaining and improving sports performance.

Reference

1. Blinova EG, Akimova IS, Chesnokova MG, Demakova LV. Rezul'taty analiza antropometricheskih i bioimpedansometricheskih issledovanij u studentov goroda Omska [The results of the analysis of anthropometric and bioimpedance studies among students of the city of Omsk]. Nauchnoe obozrenie. Medicinskie nauki [Scientific Review. Medical Sciences. 2015; 1: 79 (In Russ.).]

2. Burgart Vyu, Medvedeva NN. Konstitucionnye osobennosti ob'ema yaichek i osnovnyh pokazatelej eyakulyata u unoshej goroda Krasnoyarsk [Constitutional features of the volume of the testicles and the main indicators of ejaculate in the young women of the city of Krasnoyarsk]. Estestvoznanie i gumanizm: sb. nauch. rabot [Natural science and humanism. Collection of scientific works]. Tomsk. 2006; 3 (1): 66-67 (In Russ.).]

3. Vinokurova SP, Sentizova MI, Nemseva TV. Vliyanie zanyatij sportom na morfofunkcional'nye pokazateli organizma yunoshej-studentov [Influence of sports activities on the morphological and functional indicators of the body of young students]. Teoriya i praktika fizicheskoj kul'tury [TiPFC. 2020; 9:14 (In Russ.).]

4. Vybornaya KV, Semenov MM, Lavrinenko SV, Radzhabkadiev RM. Sravnitel'nyj analiz pokazatelej fizicheskogo razvitiya mal'chikov i yunoshej, prozhivayushchih v raznyh regionah Rossijskoj Federacii [Comparative analysis of indicators of physical development of of boys and youths living in different regions of the Russian Federation]. Ibid. 2020; 9: 65-67 (In Russ.).]

5. Vybornov VD, Nikityuk DB, Batdieva VA, Sorokin AA. Sravnitel'nyj analiz pokazatelej fizicheskogo razvitiya yunoshej-sambistov i normativnyh pokazatelej podrostkov, ne zanimayushchihsya sportom [Comparative analysis of indicators of physical development of young sambists and normative indicators of adolescents not involved in sports]. ZHurnal anatomii i gistopatologii [Journal of Anatomy and Histopathology. 2018;7(4): 33–39 (In Russ.).]

6. Komar EB, Suvorova IM, Banetskaya NV. Possibilities of using bioimpedancemetry in sports [II European Games-2019: psychological, pedagogical and medical-biological aspects of training athletes: materials of the international scientific and practical. conf.]. II Evropejskie igry-2019: psihologo-pedagogicheskie i mediko-biologicheskie aspekty podgotovki sportsmenov: mat-ly mezhdunarod. nauch.-prakt. konf. [II European Games-2019: psychological, pedagogical and medical-biological aspects of training athletes: materials of international. science-practical. conf.]. Minsk, 2019; 2: 155-158 (In Russ.).]

7. Lopsan AD, Budukool LK. Sravnitel'nyj analiz morfofunkcional'nogo i psihofiziologicheskogo sostoyaniya tuvinskih yunoshej s razlichnoj dvigatel'noj aktivnost'yu [Comparative analysis of the morphofunctional and psychophysiological state of Tuvan youths with different motor activity]. Chelovek. Sport. Medicina [Man. Sport. Medicine. 2017; 2: 20-29 (In Russ.).]

8. Maksinev D.V. Genitometricheskaya harakteristika studentov-yunoshej [Genitometric characteristics of young students]. Sciences of Europe. 2021; 63(2): 31-35 (In Russ.).]

9. Peterkova VA, Nagaeva EV, Shiryaeva TYu. Ocenka fizicheskogo razvitiya detej i podrostkov: metodich. [Assessment of the physical development of children and adolescents]. Rekomendacii [Guidelines]. M., 2017: 98 (In Russ.).]

10. Peshkov MV, Sharaikina EP. Gendernye osobennosti pokazatelej bioimpedansometrii v zavisimosti ot indeksa massy tela studentov [Gender features of bioimpedancemetry indicators depending on the body mass index of students]. Sibirskoe medicinskoe obozrenie [Siberian Medical Review. 2014; 6: 52-57 (In Russ.).]

11. Sukach ES, Budko LA. Kompozicionnyj sostav tela yunyh sportsmenov, zanimayushchihsya ciklicheskimi vidami sporta [Body composition of young athletes involved in cyclic sports]. Problemy zdorov'ya i ekologii [Problems of health and ecology. 2018; 1: 55 (In Russ.).]

12. Tihonov DA, Khairullin RM. Anatomo-antropologicheskie aspekty issledovaniya izmenchivosti fallometricheskih pokazatelej zdorovyh muzhchin [Anatomical and anthropological aspects of the study of the variability of phallometric indicators of healthy men]. Morfologicheskie vedomosti [Morphological sheets. 2016; 2:52–59 (In Russ.).]

13. Tutelyan VA, Nikityuk DB, Klochkova SV. Ispol'zovanie metoda kompleksnoj antropometrii v sportivnoj i klinicheskoj praktike: metodich. Rekomendacii [The use of the method of complex anthropometry in sports and clinical practice: method. Recommendations. M: Sport, 2018: 64.

14. Aslan Y, Atan A, Omur A. Aydın Penile length and somatometric parameters: a study in healthy young Turkish men. Asian J Androl. 2013;13(2): 339-341

15. Biro, FM, Lucky AW, Huster GA, Morrison JA. The period of puberty in boys. J Pediatr. 1995; 127 (1): 100 - 102

16. Blinov, DS, Smirnova OA, Chernova NN, Balykova OP, Lyapina SA. The results of the analysis of the students' body composition by bioimpedance method]. Vestnik Mordovskogo universiteta [Mordovia University Bulletin. 2016; 2(26): 192-202 (In Russ.).] DOI: 10.15507/0236-2910.026.201602.192-202

17. Foresta, C, Garolla A, Frigo A. Anthropometric, penile and testis measures in post-pubertal Italian males. J Endocrinol Invest. 2013; 36(5): 287-292. DOI: 10.3275/8514

CLINICAL CASE

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CASES OF ADRENOCORTICAL CANCER IN CHILDREN IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.79.29

УДК: 616-006.88

The article describes cases of primary tumor of the adrenal cortex and adrenocortical cancer in two children. In one case, the tumor turned out to be hormone-active, with increased cortisol secretion with the development of Icengo-Cushing syndrome. In the first case, stage II of the tumor process was established, in the second – stage IV. The children received combined treatment, surgery and chemotherapy. In the first patient, the treatment was successful, the child is in remission for 4 years, in the second case, the outcome is fatal, due to the progression of the malignant process.

Keywords: adrenocortical cancer, children.

Introduction. Adrenocortical cancer (ACR) is a rare high–grade tumor originating from the cortical layer of the adrenal gland. The incidence of ACR is 0.2 cases per 1 million children per year, and its share of all malignant neoplasms in children and adolescents is about 0.2%. [1]. There are 2 peaks in the incidence of ACR: this is the 1st and 4th decade of life, in children it is the age of up to 5 years. Girls get sick more often than boys [5].

Most ACS are sporadic, but in children it is often associated with hereditary syndromes (Lee–Fraumeni, Gardner, multiple endocrine neoplasia type 1). In childhood, secretory active ACR is diagnosed in 70-80% of cases, and the most common symptom occurring in 50-80% of cases is virilization [4]. According to Dark A.S. et al. (2021) in children with ACR, in 71.1% of cases, pathological secretion of one hormone or more occurred. Clinical Cushing's syndrome was observed in 26.3% of patients [1, 2]. The prognosis (outcome) of the disease depends on the stage of the tumor. Thus, in patients with stage I and II of cancer, the five–year survival rate is 80 and 50%, respectively, and in patients with stage III and IV - 20 and 10% [3].

The purpose of the study: to present cases of ACR, a rare pathology in children.

Material and methods of research. The article presents a description of two children with ACR who passed through the oncology department of the Pediatric Center of the Republican Hospital No. 1 – National Center of Medicine (PDC RB No. 1-NCM).

Results and discussion. The first patient. The girl, 11 months old, was admitted to the department with complaints of overweight, emotional lability, a rash on her face, stopped walking and resting on her legs.

The child's mother is 43 years old, the father is 41 years old. A girl from 6 pregnancies, 2 births. The first and second half of pregnancy proceeded with the threat of termination. Delivery on time at 37 weeks, operative. Body weight at birth is 3030 g, body length is 50 cm. The Apgar score is 8/9 points, she screamed immediately, the scream is loud. Attached to the breast immediately, sucked actively. The umbilical cord residue disappeared on the 5th day in the hospital. They were discharged home on the 7th day. Breastfeeding for up to 6 months, then artificial. Psychomotor, mental development by age.

3 months before hospitalization, increased appetite appeared, including at night, and began to gain weight. Over time, the girl began to limp on her right leg, then stopped walking, resulting in turning to the reception and diagnostic department of the PSC AI RS (Y) "RH No. 1-NCM". During ultrasound of the abdominal cavity, the formation of the adrenal gland, liver was detected.

The condition of the child at admission is severe, due to the tumor process. Well-being is moderately disturbed. The child's height is 75 cm, weight is 10 kg, BMI is 17.78. Matronism, moon-shaped face, bulemia, can't follow through the night without feeding. The skin is of normal color, clean, hypertrichosis. Acne on the cheek, chin (fig. 1). Peripheral lymph nodes are not enlarged. Does not walk, rests on the legs with difficulty. Breathing is puerile, there are no wheezes. The heart tones are rhythmic, clear. Heart rate – 120 beats per minute. Arterial pressure (BP) 201/124 mmHg. The abdomen is enlarged in size, there is a dense formation in the right hypochondrium, protruding 7 cm from under the costal arch. Stool is formed. Urination is not disturbed.

In the hemogram at admission – moderate polycythemia (leukocytes 15.6 thousand / ml, erythrocytes 5.16 million / ml, hemoglobin 160 g / l, hematocrit 44.8%, ESR – 2 mm / h). The daily rhythm of cortisol and ACTH was 655.6 nmol/l and 46.67 pg/ml at 08:00 and 606.6 nmol/l and 53.06 pg/ml at 22:00, respectively (cortisol norm 28-966, ACTH up to 46). The level of cortisol in the daily urine is 724.8 mcg / day at a rate of up to 190 mcg / day. The levels of metanephrine and normetanephrine in the daily urine were within the normal range. Electrolyte disturbances in the form of hypokalemia – 2.3 mmol / l.

During computed tomography (CT), MRI of the abdominal organs with contrast enhancement (CU) in the projection of the right adrenal gland, a formation

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with clear, somewhat uneven contours, heterogeneous structure due to small linear and ring-shaped calcinates, dimensions on axial sections of 6.0 * 6.6 cm and vertical size of 7.2 cm was revealed. After CU, hypodensic decay sites were detected in the formation. The formation squeezed the right lobe of the liver, displaced and squeezed down the right kidney, displaced the inferior vena cava inside (Fig. 2). The left adrenal gland was unchanged. In addition, cysts and concretions of both kidneys, doubling of the left kidney with incomplete doubling of the ureters were found. Osteoscintigraphy with technetium showed no signs of focal bone damage.

To verify the diagnosis, a fine needle biopsy of the formation was performed. The material was sent to the Federal State Budgetary Institution "NMRC PHOI named after Dmitry Rogachev". Histological conclusion: the pathological change and immunophenotype correspond to an adrenocortical tumor, reliable determination of its malignant potential is not possible due to the small volume of material. Taking into account high arterial hypertension, therapy with Amlodipine at a dose of 2.5 mg / day and Bisoprolol 1 mg / day was prescribed. In the future, the girl was sent for specialized treatment at the FSBI "National Medical Research Center of Endocrinology" (NMRCE) of the Ministry of Health of the Russian Federation in Moscow.

Correction of antihypertensive therapy was carried out in the children's department of the NMRCE and the diagnosis was verified: cortisol-producing adrenal tumor. Then the girl was transferred to the surgery department, where an operation was performed – an open removal of the right adrenal gland with a tumor. The result of histological examination of the formation is Adenocortical cancer of the right adrenal gland (5 points on the Weineke scale), Ki67 15-20%. According to the instrumental methods of investigation, metastatic lesions of regional lymph nodes and distant metastases were not detected.

After the operation, replacement therapy with Cortef and Cortineff was started. The child's condition improved, she began to get up, walk with support, anxiety disappeared, external manifestations of Cushing's syndrome decreased, blood pressure normalized (100-110 / 65-75 mmHg). Given the high degree of malignancy, as well as iatrogenic damage to the tumor capsule, as a result of an earlier puncture biopsy, the girl was prescribed chemotherapy, Mitotan (Lysodren). Against the background of mitotane therapy (the dose of the drug was corrected according to its concentration in blood serum) at the age of 1 year 7 months, an estrogen–like side effect developed - an increase in mammary glands, the size of the uterus by ultrasound up to 8-9 years, a slight increase in estrogens. There was no acceleration of bone age. Hypothyroidism was detected, probably associated with taking a chemotherapy drug, and therefore L-thyroxine was connected to therapy. In the future, against the background of taking mitotan, there was a progressive increase in the mammary glands, the appearance of mucous secretions from the genital tract. At the control examination in NMRCE at the age of 2 years, there were no signs of relapse and metastases, chemotherapy was canceled. Permanent replacement therapy with gluco- and mineralocorticoids and L-thyroxine is recommended.

Currently, the girl is 5 years old, physical development corresponds to age, speech development delay. A year ago, Cortef and Cortineff were canceled, 9 months ago – L-thyroxine.

The second patient. A boy, 3 years old, was admitted to the department with complaints of an increase in the size of the abdomen. According to the ultrasound examination of the abdominal organs, a huge abdominal formation was visualized, the exact localization of which could not be determined.

In the oncology department, examinations were conducted to clarify the anatomical localization and nature of the formation, and an assessment of the prevalence of the process was also performed. Computed tomography revealed in the left half of the abdominal cavity a huge solid formation emanating from the left adrenal gland of a heterogeneous structure due to areas of softening and calcification, the size of 12,3*9,2*15.4 see, after contrast enhancement, the formation moderately unevenly accumulates a contrast substance. The formation squeezes, shifts down, does not separate from the left kidney, shifts up the spleen, stomach, intestinal loops are pushed to the right (fig. 3). The left adrenal gland is not traced against the background of the tumor. In S5 of the left lung, a lesion up to 0.9 cm in size was detected, with an intensive accumulation of contrast agent, regarded as metastasis. There is also a small lesion up to 0.2-0.3 mm in the S9 of the right lung Intra-thoracic lymph nodes up to 0.7-0.8 cm in size.

Taking into account the age of the child, the localization of the tumor, a differential diagnosis was made between tumors of the adrenal cortex and neuroblastoma. The study of hormonal status (thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH), renin, cortisol) revealed no pathology. Neuron-specific enolase within normal values. Scintigraphy of the skeleton with technetium of the lesion of the bones of the skeleton did not reveal.

To verify the diagnosis, a fine needle biopsy of the formation was performed. Histological examination showed that the tumor is alveolar-nested structure, with extensive foci of necrosis. Neoplastic tissue is constructed from medium-sized and large cells with abundant eosinophilic or optically empty cytoplasm. Nuclei with pronounced pleomorphism, there

Fig. 1. A girl of 11 months with Itsengo-Cushing syndrome, with a hormone-active ACR

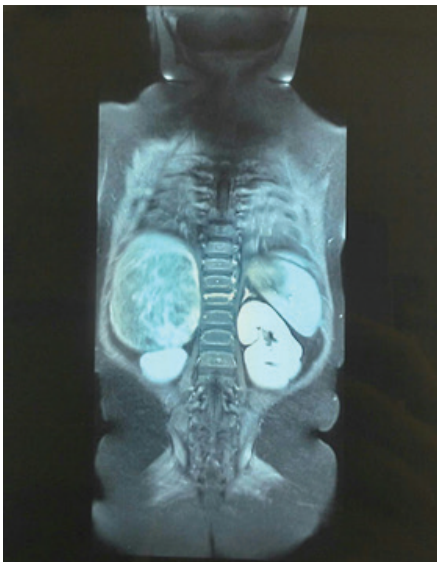

Fig. 2. MRI of the abdominal organs of the girl 11 months. Formation of the right adrenal gland

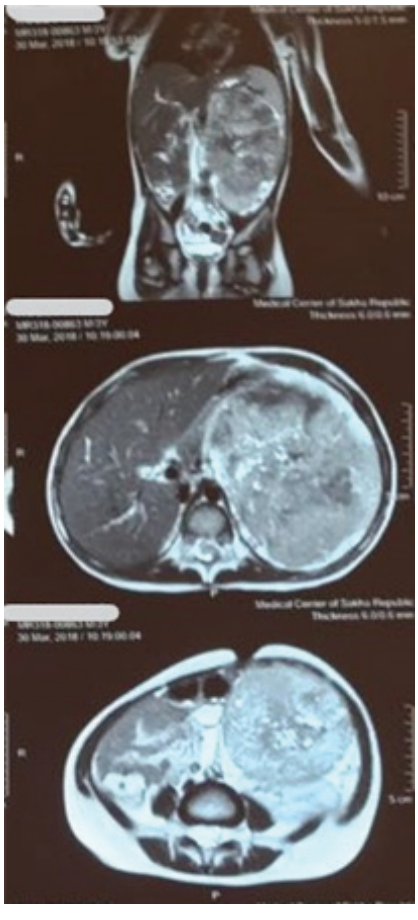

Fig. 3. Abdominal CT with contrastenhance 3 years old boy, demonstrating a large heterogeneous mass in the left adrenal gland. The overall size of this mass was1742 cm3

are large hyperchromic nuclei with the presence of pseudo-inclusions. Mitotic activity of 7 mitosis figures in 5 fields of view at magnification of the microscope x 400. An immunohistochemical study was performed with antibodies to Chromogranin A, HMB45, Inhibincc1, Ki67 up to 40-45%. The reaction with the rest of the antibodies is negative. Histological conclusion: correspond to adrenocortical carcinoma, ICD-0 code 8370/3.

The tactics of the child's treatment were discussed with leading pediatric oncologistsNational Medical Center of Pediatric Hematology and Oncology (NMC PHO) named after D. Rogachev. 2 courses of chemotherapy according to the EDP/M scheme (etoposide, doxorubicin, cisplatin, mitotan) were carried out in the oncological department of the PC NMC.

For the surgical stage of treatment, the child was sent to the Federal Center (NMC PHO) named after D. Rogachev, where the operation was performed: laparotomy, arteriolysis and venolysis of the left renal pedicle, adrenalectomy on the left, ipsilateral retroperitoneal lymph

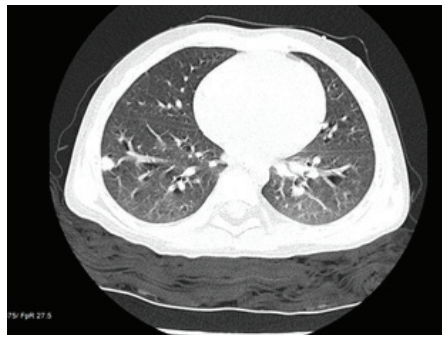

Fig. 4. Axial sections of contrastenhanced breast CT, demonstrating metastases of S9 right lung

dissection. Histological conclusion: Adrenocortical carcinoma (8 criteria on the Weiss scale; 28.4 points on the VanSlooten scale, 5 criteria on the AFIP scale for tumors of the adrenal cortex in children). Taking into account the histological type of the tumor and the prevalence of the tumor process, chemotherapy according to the EDP/M scheme was continued at the place of residence. During the control examination after 4 courses of chemotherapy, according to lung RCT, there was an increase in the formation of the right lung in S9 to 8mm (fig. 4), a decrease in the focus in S5 of the left lung. For histological verification and removal of the formation, resection of the formation in S9 of the right lung was performed. Histological examination showed that the tumor tissue with nodular growth of a solid structure, constructed from fields of cells with abundant eosinophilic cytoplasm and large nuclei with pronounced polymorphism (the histological structure of the tumor is identical to that in previous biopsies). Therapeutically induced changes are not pronounced. Perifocal hemorrhages, focal lymphocytic infiltration. Thus, histologically, metastasis to the lung was confirmed.

In total, 8 courses of chemotherapy were carried out according to the EDP/M scheme. Taking into account the stabilization of the process and the intensity of polychemotherapy, the child was left under dynamic observation while taking mitotan. After 6 months, the progression of the disease was established: during the control examination, an increase in the previously detected solid formation in the basal zone of the right lung, with clear contours, dimensions, was noted 3,4*3,3*3,0 cm, with moderate accumulation of contrast agent.Education is distributed in segments S2, S4. Management and treatment tactics were discussed jointly with leading pediatric oncologists of the D.Rogachev National Research Medical Center. Based on the data of the international literature and practical recommendations for the treatment of cancer of the adrenal cortex RUSSCO, an attempt was made to treat with second-line therapy according to the gemcitabine/capecitabine scheme. However, after 2 blocks according to this scheme, there was a continued growth of metastases in the lungs. Due to the lack of standards for the treatment of children with relapses / progression of ACR, tumor progression in the treatment of 2 lines, curative methods are considered exhausted. The child was referred for palliative care at the place of residence.

Conclusion. Thus, the clinical picture of adrenal cortex cancer depends on the hormonal activity of the tumor, the hyperproduction of certain steroid hormones, which contributes to an earlier diagnosis. Hormone-inactive tumors go on for a long time without clinical manifestations, they are often detected during examination for another disease. In the first case, in an 11-month-old girl, the tumor proceeded with hyperproduction of cortisol with the development of Icengo-Cushing syndrome, in the second patient the tumor was hormonally inactive. The prognosis of the disease depends on the stage of the tumor. In the first case, stage II of the tumor process was established, in the second – stage IV with distant metastases. The children received combined treatment, surgery and chemotherapy. In the first patient, the treatment was successful, the child is in remission for 4 years, in the second case, the outcome is fatal, due to the progression of the malignant process.

Reference

1. Temniy A.S., Kazantsev A.P., Kerimov P.A., Kalinchenko N.Yu., Rubanskaya M.V., Sardalova S.A., Varfolomeeva S.R. Results of surgical treatment of localized and locally advanced adrenocortical cancer in children. Russian Journal of Pediatric Hematology and Oncology 2021; 8(2):42–9.

2. Temnyy A.S., Kazantsev A.P., Kerimov P.A., Rubanskaya M.V., Varfolomeeva S.R. The role of surgical treatment in stage IV adrenocortical cancer. Russian Journal of Pediatric Hematology and Oncology. 2021; 8(4):31-38.

3. Sharoev T.A., Ivanova N.M., Bondarenko S.B. Adrenocortical cancer in children./ Oncopediatria 2015; 2 (1): 16-25.

4. Behrman R.E., Kliegman R., Jenson H.B. Adrenocortical Tumors. Nelson Textbook of Pediatrics, 20th Edition. Philadelphia WB Saunders; 2015; 2726-2727.

5. Charles G. D. Brook, Peter E. Clayton, Rosalind S. Brown. Endocrine neoplasia in childhood. Brook's Clinical Pediatric Endocrinology, 6th Edition, UK, WileyBlackwell; 2009; 428-432.

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CLINICAL CASE OF PULMONARY THROMBOEMBOLISM DIAGNOSED IN THE SUB-ACUTE PERIOD

DOI 10.25789/YMJ.2022.79.30

УДК 616.13.1-005.7-06:617.58-005.6

The article presents a clinical case of pulmonary embolism associated with thrombosis of the veins of the lower extremities. The disease remained unrecognized at the onset due to the absence of hemodynamic instability and was diagnosed only in the subacute period. Within two weeks of the suspected episode of thromboembolism, the patient developed symptoms of peripheral venous thrombosis, right ventricular heart failure, post-embolic pulmonary hypertension, and severe respiratory failure.

Keywords: pulmonary embolism, deep vein thrombosis of the lower extremities, post-embolic pulmonary hypertension, respiratory failure.

Pulmonary embolism (PE) is an acute occlusion of the arterial bed of the lungs by embolism (thromboembolism) of various sizes. The source of thromboembolic masses is most often located in the basin of the inferior vena cava, rarely in the right heart and veins of the upper extremities, so deep vein thrombosis (DVT) and PE are most often considered as part of a single venous thromboembolism syndrome [4]. The leading source of PE is thrombosis of the veins of the lower extremities.

The absence of clear clinical signs and diagnostic criteria, the often erased course of the disease explains the fuzziness of epidemiological data on the prevalence of PE. The annual incidence of pulmonary embolism in Europe ranges from 39 to 115 people per 100 thousand population, DVT - from 53 to 162 per 100 thousand population. It is known that venous thromboembolism takes the 3rd place in prevalence, second only to myocardial infarction and stroke. Moreover, the prevalence of PE increases with age, in people older than 80 years it is five times higher than in 50-year-olds [3, 5]. There are no accurate statistics on DVT and PE in Russia. Mortality in PE ranges from 16-40%, and in massive thromboembolism reaches 70% and is significantly reduced with timely diagnosis of the disease. [2, 3].

PE is usually accompanied by a reflex spasm of arterioles, which leads to a sharp restriction of blood flow in the lungs. Acute occlusion is a formidable cardiovascular complication of venous thrombosis of the systemic circulation and often manifests itself in the form of acute right ventricular cardiovascular failure and life-threatening arrhythmias. However, the disease clearly manifests in the case of massive (more than 50% of the vascular bed is affected) or submassive (embolism of several lobar or many segmental pulmonary arteries) thrombosis. The typical clinical picture of PE is nonspecific, which explains the difficulty of its diagnosis. In the case of damage to only small branches of the pulmonary artery (less than 30% of the vascular bed), the diagnosis of PE can be difficult [1, 5].

Venous thromboembolism is more common in patients with cardiovascular disease [1, 4, 5]. Other significant predisposing factors are trauma and surgery, prolonged immobilization, peripheral venous catheterization, autoimmune diseases, cancer, obesity, hormonal and chemotherapy.

Timely diagnosis and adequate treatment significantly reduce mortality from this disease. More than 90% of deaths from PE occur in untreated patients. However, PE is diagnosed in vivo only in 7-14% of patients, and most of these patients were hospitalized [1, 4, 5]. The incidence of small branch PE at the outpatient stage is extremely low. At the same time, early diagnosis and timely treatment of venous thromboembolism is important for prolonging and improving the patient's quality of life [4, 6].

Considering the urgency of the problem and the importance of early diagnosis of venous thromboembolism, we present a clinical example of a patient with PE diagnosed on an outpatient basis.

Patient S., 81 years old, complained of a sudden loss of consciousness about two weeks ago. No more active complaints. With active questioning, it was found out that shortness of breath during slight physical exertion, which gradually increases in dynamics over two weeks, dry cough, and swelling of the legs are also disturbing.

From the anamnesis of the disease, it is known that being at home about 2 weeks ago, the patient felt weakness, nausea. When measuring blood pressure, she lost consciousness. She does not remember the duration of the loss of consciousness; blood pressure (BP) during the measurement was 130/80 mm Hg. An emergency team was called. After examining the patient, given the stable condition: target blood pressure values, no chest pain, the patient was not hospitalized, further examination on an outpatient basis was recommended.

Within two weeks, shortness of breath appeared and began to increase to the level of FC 3, a dry cough developed, hyperemia and swelling of the left leg appeared, and then swelling of both legs.

The anamnesis of life without features, the patient has hypertension with selected therapy (perindopril 5 mg) and target BP numbers. Previously, during a dynamic examination, there was an increase in the level of blood cholesterol; she does not receive statin therapy. It can be noted that no risk factors for the development of thromboembolism were found in the anamnesis: surgery with prolonged immobilization, fractures, oncology, taking diuretic drugs and oral contraceptives, etc. Also, the patient denies the transferred coronavirus infection.

Objectively: a state of moderate severity. BMI - 21.2 kg / m2. Skin and visible mucous membranes of normal color, moisture. Breathing in the lungs is hard, carried out in all areas, dry rales in the lower sections on both sides. The respiratory rate is 20 per minute. SpO2 - 84% (there is a decrease within 1.5 weeks from 95%). Heart sounds are muffled, the rhythm is correct, regular, heart rate is 90 beats/min, blood pressure is 105/60 mm Hg. on both hands. The abdomen is moderately swollen on palpation, painless. The liver and spleen are not enlarged. Defecation without features. Diuresis corresponds to the drunk liquid (according to the patient). Peripheral edema of both

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legs, the difference in the volume of the legs is 2 cm (the edema is more on the right), hyperemia of the right lower leg, pain on palpation.

An outpatient examination diagnosed a high probability of PE according to the Geneva scale: age over 65 years - 1 point, unilateral pain in the leg - 3 points, heart rate 75-95/min - 3 points, pain in one leg or unilateral edema - 4 points, total 11 points (high risk, PE likely).

Additional examination data:

Complete blood count: Er - 4.7 * 10^{12} l (3.93-5.22), hemoglobin - 140 g / l, leukocytes - 8.4 * 10^{9} / l (3.98-10.04), hematocrit - 41.6 (34.1-44.9), platelets - 182*10^{9}/l (182-369). Leukocyte formula: neutrophils 54.6%, eosinophils 0.9%, monocytes 10.7%, lymphocytes 33.6%, basophils 0.2%; erythrocyte sedimentation rate - 26 (<20.2) mm/h.

Biochemical blood test: CRP - 78.72 mg / l (0-6.0), glucose - 11.2 mmol / l (4.2-6.4), total cholesterol 4.8 mmol / l (3.1 -5.2), creatinine - 76.4 μmol/l (44-80), uric acid - 364 μmol/l (155-357), glomerular filtration rate - 63 ml/min (CKD-EPI).

Electrocardiogram: sinus rhythm, heart rate 83 per minute. PQ 0.16 s; QRS-0.07s; QT - 0.41 (corrected - 0.45 s). T-wave inversion from V1-V4, in the inferior leads - II, III, aVF - associated with right ventricular overload, pulmonary hypertension. An increase in the P wave more than 2.5 mm in the second lead. SIQIII-TIII, deep S wave in lead 1, T negative in lead 3, deep Q in lead 3. Turning clockwise - shifting the transition point R / S to V6 (Fig.).

Echocardiography: systolic pressure in the pulmonary artery - 62.2 mm Hg. Art., a sharp increase in the right heart, expansion of the pulmonary artery trunk, paradoxical movement of the interventricular septum, contractile function of the left ventricle - 64% (according to Simpson), regurgitation on the tricuspid valve of the 1st degree.

Multispiral computed tomography of the chest organs: a picture of bilateral polysegmental interstitial pneumonia, probably of viral origin, minimal volume (CT-1), the volume of the right lung lesion is 8%, the left lung is 10%.

Ultrasound of the veins of the lower extremities: on the right: the veins (anterior and posterior tibial, peroneal, popliteal, superficial and common femoral, deep femoral, external iliac) on the right are completely passable and compressible by the sensor, the blood flow has a phase character and is associated with the act of breathing. Intraluminal formations are not located. Valves of deep veins (compression test) are well-founded. On the left, in the lumen of the femoral-popliteal segment, heterogeneous thrombotic masses are determined without signs of flotation, the blood flow is not recorded.

The trunk of the great saphenous vein (GSV) on the right is not located, tributaries up to 2.5 mm in diameter are determined. The trunk diameter of the left GSV is up to 3 mm; reflux is not located during compression.

The GSV on the right - the diameter of the orifice is 5.7 mm; during compression, the veno-venous shunt is not located. The GSV on the left has a diameter of the orifice of 5.3 mm; during compression, the veno-venous shunt is not located.

Small saphenous vein (SSV) diameter along the trunk on the right is up to 4.6 mm, the blood flow is distinct, reflux is determined during compression.

The trunk diameter of the left SSV is up to 3.9 mm; reflux is not located during compression.

SSV on the right, the diameter of the mouth is 5.1 mm, with compression, a veno-venous discharge is determined.

SSV on the left is 3.8 mm in diameter; veno-venous discharge is not detected during compression.

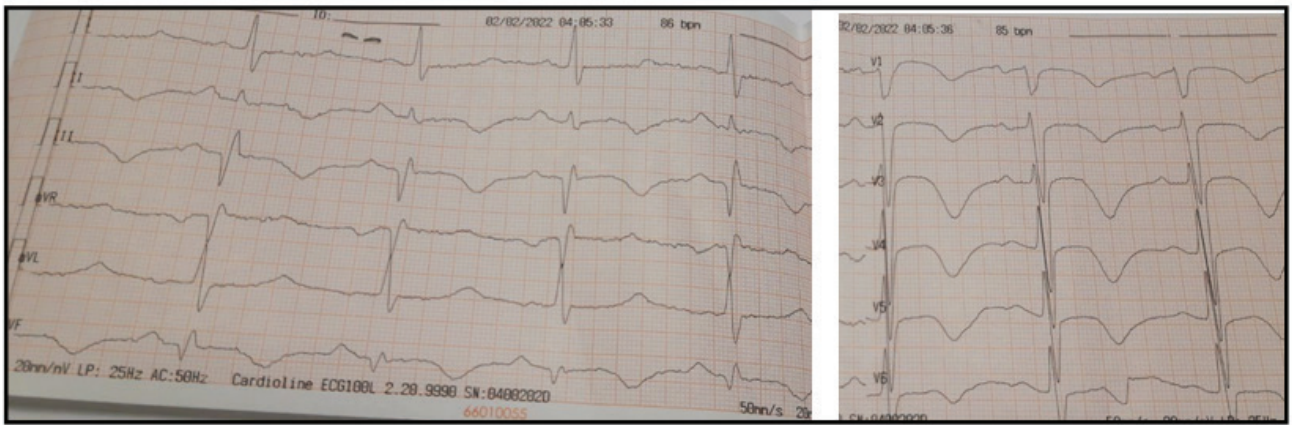
Communicating veins along the inner surface of both legs in the middle and lower thirds with a diameter of up to 2.5 mm, with compression, the veno-venous discharge is not located.

Consulted by a vascular surgeon: subacute phlebothrombosis of the femoral-popliteal segment on the left (no signs of flotation). Chronic venous insufficiency of the lower extremities of 1-2 degrees. Treatment prescribed: tab. Rivaroxaban 20mg, compression hosiery class 2, topically - Detralex ointment. In the future, against the background of treatment, the appearance of edema and hyperemia of the right leg is noted.

On the basis of clinical data, anamnesis, objective examination, laboratory and instrumental data, a preliminary diagnosis was made: Subacute phlebothrombosis of the femoral-popliteal segment on the left (without signs of flotation). Chronic venous insufficiency of the lower extremities of 1-2 degrees. Thromboembolism of small branches of the pulmonary artery. Respiratory failure 3. Pulmonary hypertension. Enlargement of the right heart, expansion of the pulmonary artery. 1st degree tricuspid valve insufficiency. Hypertension controlled, stage 1, risk 3 (age, hyperuricemia, heredity, dyslipidemia).

For further observation, additional examination and correction of treatment, the patient was sent for hospitalization.

Conclusion. PE belongs to the group of life-threatening conditions, so the patient's prognosis directly depends on how timely the diagnosis is established and full-fledged therapeutic measures will be started. The absence of hemodynamic instability at the onset of the disease does not exclude the development and progression of pathological changes, such as respiratory and right ventricular heart failure, as well as an increased risk associated with PE. Only adequate restoration of the patency of the pulmonary arterial bed in the acute period of the disease



ECG of patient C, 81 years old

is a reliable way to avoid severe chronic post-embolic pulmonary hypertension or minimize the long-term hemodynamic consequences of pulmonary embolism [6]. In this clinical situation, based on a number of characteristic clinical data, taking into account the high probability of PE, the disease was diagnosed in the subacute period. Within two weeks after the alleged episode of thromboembolism, despite the absence of hemodynamic instability, the patient developed symptoms of not only right ventricular heart failure, postembolic pulmonary hypertension, respiratory failure, but also DVT of the lower extremities. In this regard, it is necessary not only to be vigilant about venous thromboembolism in primary care physicians, especially in patients of older age groups, but also a thorough analysis of clinical and instrumental data, an additional assessment of the risk level of pulmonary embolism, followed by correction of patient management tactics.

Reference

1. Vertkin A.L., Gritsanchuk A.M. Tromboemboliya legochnoy arterii: epidemiya, o kotoroy vse molchat [Pulmonary embolism: an epidemic that everyone is silent about]. Arkhiv" vnutrenney meditsiny [The Russian Archives of Internal Medicine. 2014;(1):33-39. (In Russ.)] DOI: 10.20514/2226-6704-2014-0-1-33-39

2. Kapsultanova D.A., Polzik G.B., Sadykova Sh.S. [et al.]. Klinicheskiy sluchay retsidiviruyushchey tromboembolii lëgochnoy arterii [Clinical case of a recidivous tromboemboliya of a pulmonary artery]. Vestnik Kazakhskogo natsional'nogo meditsinskogo universiteta [Bulletin of the Kazakh National Medical University. 2017;(2):41-43. (In Russ.)]

3. Nikulina N.N., Terekhovskaya Yu.V. Epidemiologiya tromboembolii legochnoy arterii v sovremennom mire: analiz zabolevayemosti, smertnosti i problem ikh izucheniya [Epidemiology of pulmonary embolism in today's context: analysis of incidence, mortality and problems of their study]. Rossiyskiy kardiologicheskiy zhurnal [Russian Journal of Cardiology. 2019;(6):103-108. (In Russ.)] DOI: 10.15829/1560-4071-2019-6-103-108

4. Essien EO, Rali P, Mathai SC. Pulmonary Embolism. Med Clin North Am. 2019;103(3):549-564. DOI:10.1016/j.mcna.2018.12.013

5. Konstantinides SV, Meyer G, Becattini C [et al.]. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. DOI:10.1093/eurheartj/ehz405

6. Martinez Licha CR, McCurdy CM, Maldonado SM, Lee LS. Current Management of Acute Pulmonary Embolism. Ann Thorac Cardiovasc Surg. 2020;26(2):65-71. DOI:10.5761/atcs.ra.19-0015

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CLINICAL CASE: POSTCOVID MULTISYSTEM SYNDROME IN A 7 MONTH OLD CHILD

DOI 10.25789/YMJ.2022.79.31

УДК 616.9-053.36

The article presents a clinical case of multisystem inflammatory syndrome as a relsult of a new coronavirus infection in a 7 months old child. The clinical picture is similar to Kawasaki syndrome.

Keywords: postcovid multisystem syndrome, COVID-19, SARS-Cov-2, kawasaki-like syndrome.

On March 11, 2020, WHO declared the COVID-19 pandemic. At the end of December 2019, an outbreak of a new coronavirus infection (COVID-19) caused by the SARS-Cov-2 coronavirus, leading to severe acute respiratory syndrome, was recorded in Wuhan (Hubei Province, China). [1, 3, 5, 6]. Clinical picture in children, as a rule, is less severe than in adults. More than 90% of COVID-19 cases occur in children asymptomatically, in mild and moderate form [2]. The frequency of hospitalizations among children is also low. Thus, according to the CDC report, in the USA this figure was almost 2 times lower (5.7% versus 10% in adults), including fewer admissions to the intensive care unit. [4]. In March 2020, reports of outbreaks of a disease that meets the criteria of Kawasaki disease began to appear, accompanied by the development of a pronounced hyperinflammatory response associated with SARS-Cov-2 infection in previously healthy children. This disease has not been described before, in publications there were such names as "Kawashok", "Koronasaki", "hyperinflammatory shock in children with COVID-19", kawasaki-like disease", "pediatric multisystem inflammatory syndrome (PMIS)", "multisystem inflammatory syndrome in children (MIS-C)" [1].

Multisystem inflammatory syndrome in children (MIS-C)", also known as pediatric inflammatory multisystem syndrome, is a dangerous new children disease that is temporarily associated with a new coronavirus disease (COVID-19). This publication presents a clinical case in a child of 7 months.

Clinical case: a 7 months old child of Sakha ethnicity was admitted with complaints of merging rashes on the body, a runny nose, an increase in body temperature above 39 °C, and vomiting.

From the anamnesis of the disease, it is known that, according to his mother, he became acutely ill on November 8, 2020. The body temperature increased to 38.7 °C, which was treated with nurofen. Also, due to teething, dantinorm was admitted. A rash made an appearance on a back. Consultation with relative with medical expertise was conducted. Acyclovir 1/2 tab x 4rvd inside was admitted. There was no improvement the next day. The rash has spread all over the body, on the head, the scalp, merging with each other. Body temperature increased from 39.1 °C to 39.7 °C, treated with nurofen. Vomiting 1 time after eating. A doctor was called, child was sent to the Children's Infectious Diseases Clinical Hospital.

Epidemiological history: There was no contact with COVID-19 patients for 14 days. The father and mother were ill with COVID-19 in October (control PCR analysis of October 20 was negative).

From the anamnesis of life it is known thatchild was from first pregnancy, which proceeded smoothly. From 1 natural birth. Birth weight 3570 g, length 54 cm.

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Child screamed right away, scream was loud and clear. Attached to the breast on 1st day, sucked actively. Breastfeeding so far, additional feeding with Nutrilon milk formula 180 ml every 4 hours. Discharged from the hospital for 5 days. No pathologies during the newborn period were noted. BCG was injected in the hospital. Psychomotordevelopment of the child was normal. Preventive vaccinations according to an individual plan. Allergic anamnesis: food allergy, cause unknown, drug related allergies – absent. There are no diseases endured. Mother is 27 years old, healthy. Father is 26 years old, healthy, smokes. Living conditions: well-maintained one-bedroom apartment.

Objective status: Body temperature 37.0°C, HR 34 in min., HR 132 in min.

General condition of moderate severity. Well-being is reduced. A boy of the normal physique, satisfactory nutrition. The bone system is without pathologies, the skull is of the correct shape. A large fontanel 2.0x2.0 cm. The skin is pale pink in color, rashes of a spotty-papular nature all over the body, sometimes merging with each other, bright pink in color. Rash all over the body, on the face, on the scalp, abdomen, back, palms, feet. It is more pronounced on the face and back. Subcutaneous fat is moderately developed. Peripheral lymph nodes are palpated, elastic and not enlarged. Soft tissue turgor is preserved. Musculoskeletal system without visible pathology. The visible mucous membranes of the oral cavity are clean, moist. Lips are dryish. The conjunctiva is clean. Pharynx: the soft palate is moderately hyperemic. The tongue is moist, clean. Gums without features. Breathing through the nose is free. There is no discharge from the nose. There is no shortness of breath. Percussion over the lungs - clear pulmonary sound. Breathing in the lungs is puerile,- no wheezing. The heart tones are clear, rhythmic. The abdomen is soft during palpation, not swollen. The liver is not enlarged, the edge is smooth, elastic. The spleen is not palpable. Urination is free. Urine is light yellow. The stool is regular, light green, 1 time mushy.

A preliminary diagnosis was made in the emergency department: J06.9 - Acute upper respiratory tract infection, unspecified. Urticaria. Acute allergic infectious exanthema?

For the purpose of desensitization, intravenous drip prednisolone 20 mg in 100 ml saline solution, "Grippferon" in the nose 1 drop x 4 times a day, "Zodak" 5 drops 1 time a day, oral rehydration in the amount of 400 ml.

By the evening, the rash turned pale, The temperature was subfebrile - 37.2 °C. The next day, the temperature rose to 39 °C, the rash persists, weakness, lethargy, hoarseness of voice, coughing. Anthropometric data: height - 73 cm, weight - 9 kg,

Taking into account fever for three days above 38.5 °C and leukocytosis, antibacterial therapy was prescribed: "Cefotaxime" at the rate of 100mg / kg / day 300mg x 3 rv day intramuscularly. Infusion therapy for desensitization and detoxification. "Enterosgel" 2.5 ml x 3 r per day, inside before feeding.

The next day - an increase in body temperature - 39.2 °C, weakness, anxiety, dry cough, decreased appetite. The general condition is regarded as of moderate severity. Consciousness is clear. The child is sluggish, capricious. Sleep is restless, appetite is reduced. The skin is pale pink in color, there are no new rashes, crusts on the hands and feet. Visible mucous membranes are clean, moist. The pharynx is slightly hyperemic, there are no plaque, the tonsils are edematous and loose. The tongue is clean and moist. The voice is hoarse. In the lungs, breathing is hard, carried out across all fields, single wheezing from the front to the right. The heart tones are rhythmic, clear. The abdomen is soft, of the usual shape, painless. The liver and spleen are not enlarged. According to the mother, the physiological functions are normal.

On the 7th day of being in the hospital, the child's condition is of moderate severity. Body temperature is 36.8 °C.

Table 1

General blood test

	09.11.2020	13.11.2020	16.11.2020	19.11.2020
Erythrocytes, x10 ^{12}/l	4.20	3.42	3.31	3.41
Hemoglobin, g/l	106	88	83	88
Hematocrit	32.1	26.2	25.3	25.9
Leukocytes, x10 ^{9}/l	11.0	13.9	14.2	19.2
Segmentonuclear, %	69.0	51.0	45.0	74.0
Stick - core,%	5.0	9.0	4.0	4.5
Eosinophils,%	2	8.0	5.0	0.5
Basophils,%	-	-	-	1.0
Lymphocytes,%	19.0	21.0	36.0	10.5
Monocytes,%	5	10.0	9.0	9.5
Plasma cells,%		1.0	-	-
Myelocytes	-	-	1	-
Platelets, x10 ^{9}/l	474	407	587	825
Erythrocyte sedimentation rate, mm/h	57	47	59	70

Table 2

Biochemical blood tests

	09.11.2020	13.11.2020	16.11.2020	19.11.2020
Total protein, g/l	59.95	47.22	54.21	58.79
Albumin, g/l	40.57	30.95	33.26	33.78
Total bilirubin, mmol/l	39.17	9.61	7.59	9.06
Straight bilirubin, mmol/l	17.4	2.95	2.88	3.65
Alat, unit/l	227.1	30.2	17.8	16.1
Asat, units/l	197.2	15.8	15.7	16.9
Urea, mmol/l	3	1.8	1.5	1.6
Creatinine, mmol/l	33.7	25.07	28.61	26.69
ASLO, ME/l	29	13	11	22
C-reactive protein, mg/l	3.16	2.81	2.21	5.7
Glucose, mmol/l	4.7	3.9;	5	5.4

Consciousness is clear. Child feels good. Appetite is restoring. The skin and mucous membranes are clean, of the usual color. There is moderate hyperemia in the throat. Peripheral lymph nodes are not enlarged. Breathing through the nose is free. There is no shortness of breath. Percussion over the lungs is determined by the pulmonary sound. During auscultation, hard breathing is heard, single wet wheezing on the right. Respiratory rate is 36 per minute. The heart tones are clear, rhythmic. Heart rate is 135 per minute. SpO_2 97%. The abdomen is of the usual shape, soft, painless with palpation. Liver, spleen are not enlarged. Urination is free, there was no stool.

On the 9th day in the hospital, the temperature rose again to 37.5 °C, small-point rash, weakness, decreased appetite appeared. Zodak is prescribed 5 drops x 1 time a day inside. In the following days, the temperature was 38.0° - 38.6 °C, dry unproductive cough, weakness, anxiety bothered.

On day 10, lamellar peeling of the skin of the fingertips of both hands was observed, the visible mucous membranes were clean. Hyperemia of the sclera of both eyes. In the general blood test, leukocytosis of 19.2 $x10^9$ / l, thrombocytosis up to 825 $x10^9$ / l, acceleration of ESR up to 70 mm/h is noted (Table 1).

In the biochemical analysis of blood, an increase in ALT was observed to 227 units/l (at a rate of 40ed/l), AST 197ed/l (at a rate of 40 units/l), bilirubin 39.17 mmol/l (at a rate of 20.0 mmol/l), CRP 3.16 (norm to 1.0) (Table 2)

In the general analysis of urine, proteinuria was noted (1.0 g/l).

MFA for respiratory viruses from 10.11.2020 - Parainfluenza 3 – positive.

IFA rubella from 12.11.2020 IgG - positive.

ELISA measles from 12.11.2020 is negative.

ELISA hepatitis from 12.11.2020 HAV – negative, hepatitis HAV Ig M / IgM – negative, HBsAg HCV – negative.

PCR on COVID-19 from 10.11.2020 is negative.

ELISA on SARS-CoV-2 12.11. IgM – negative, IgG - positive (23.7).

Stool for enterovirus infection from 13.11.2020 is negative.

The chest X–ray from 11.11.2020 shows signs of acute bronchitis. ECG from 9.11.2020 Conclusion: Sinus rhythm, heart rate-200 beats per minute. Acute tachycardia. The EOS is deflected to the right.

In treatment: replacement of the antibiotic with "Amoxiclav" at the rate of 30mg / kg / day in / in 250 ml x 3 times a day, added "Ambrobene" from 18.11.2020 -19.11.2020

Infusion therapy was performed for the purpose of detoxification.

The child was transferred to the cardiorheumatology department of the Pediatric Center of the Republican Hospital No. 1 – National Center of Medicine with the diagnosis: Underlying disease: U07.2 - Coronavirus infection caused by the COVID-19 virus, the virus has not been identified (COVID-19 is diagnosed clinically or epidemiologically, but laboratory tests are inconclusive or unavailable)

Complication: M30.3 - Mucocutaneous lymphonodular syndrome (Kawasaki): Multi-inflammatory syndrome: Kawasaki-like syndrome?

Concomitant diseases: J20.9 - Acute bronchitis, unspecified: Acute bronchitis, DN0. Parainfluenza 3. An allergic reaction by the type of urticaria?

Upon admission to the cardiorheumatology department, the condition was assessed as severe. Consciousness is clear. Body temperature is 38.0 ° C. Child feels bad. The lymph nodes are not enlarged. Skin: small spotty-papular rash on the body, large-plate peeling of the fingers on the hands. The feet are clean. Lips are dry, cracked with an accentuated red border. The tongue is moist and clean. The conjunctiva is hyperemic. The voice is hoarse. In the lungs, hard breathing is carried out in all fields, there are no wheezing. Heart tones are muted rhythmic. The abdomen is soft, painless, accessible to deep palpation, the liver and spleen are not enlarged. Stool after enema, decorated.

In the blood test, hyperthrombocytosis is 911.9 x $^{10.9}$/l, with an increase in dynamics up to 1200x10 ^{9}/l, leukocytosis is 18x10 ^{9}/l, fibrinogen is 7.78 g/l.

On echocardiography – dilation and compaction of the coronary arteries. The diagnosis was made: Kawasaki-like COVID-associated syndrome. Infusion of IVIG ("Privigen") 2 g / kg was performed.

RCT of OGC was performed – areas of compaction of lung tissue in the dorsal parts of the lower lobes of both lungs. CT-1. The volume of the lesion is 3%.

The body temperature rose every other day to 38.8 °C. He was consulted in absentia at St. Petersburg State Medical University, the condition was regarded as a COVID-associated systemic multi-inflammatory syndrome for children, the appointment of Dexamethasone 10 mg/ ^{m2}, heparin was recommended. Dexamethasone, heparin, and the change of antibacterial therapy to "Cefepim" are connected.

There was no fever, the child was restless, there was sharp anxiety (screaming at night, for 3-4 hours). Piracetam and Cinnarizine were prescribed.

On the 20th day in the hospital there was a cough, shortness of breath up to 60 per minute, crepitating wheezing from 2 sides, a decrease in Sp from $_2$ to 93 was noted%

On RCT OGK 09.12. areas of sealing by the type of frosted glass on 2 sides of CT-1 - 8% volume of lung lesion. Antibiotic therapy was prescribed again. In dynamics from 11/21/2020, positive dynamics - areas of compaction of lung tissue in the dorsal parts of the lower lobe of both lungs, the average risk of viral pneumonia, including COVID-19, CT-1, the volume of lung damage is 3%. ELISA from 10.12.2020 COVID-19 IgM 0.3 IgG 17.88, which indicates a new coronavirus infection.

Echocardiography shows that the diameter of the left coronary artery is 0.40-0.41 cm; the diameter of the right coronary artery is 0.38 cm; The seal of the MK valves with min regurgitation. Ectopic fastening of PSMC chords. Dilation of the coronary arteries. On TC, regurgitation of the 1st- 2nd degree. Slight expansion of the PP (2.48 cm). FV 73.5%. In dynamics from 11/25/2020: Additional features: left coronary artery 0.38 cm. right coronary artery 0.41 cm.; Seal of MK valves with min regurgitation. Ectopic fastening of PSMC chords. The diameter of the left coronary artery is 0.38 cm. The right coronary artery is 0.41 cm. Regurgitation on TC 1 - 2 degrees. Slight expansion of the PP (2.4 cm). FW 74.3%;

For the purpose of anti–aggregation, "Curantil" 12.5 mg x 3 times was prescribed; for anti-inflammatory purposes, "Dexamethasone" 2 mg x 2 times intravenously on 11/29/2020, 0.5 mg x 3 times, "Methylprednisolone" DM 8 mg; Aspirin 0.1 x 3 times (100 mg x 3) for the fever period of 25 mg x 2 times a day; antibacterial therapy was carried out with drugs "Cefotaxime" 500mg x 2 times intravenously; Cefepim 500mg x 2 times intravenously (two courses); Amikacin 75 mg x 2 times intravenously.

Positive dynamics was noted against the background of treatment. Discharged on the 21st day with improvement, recommendations and diagnosis: Mucocutaneous lymphonodular syndrome (Kawasaki-like COVID-associated syndrome). Complication: Syndrome of systemic inflammatory response of infectious origin with organic disorder; encephalosthenic syndrome on the background of a viral infection. Sleep disorder; Iron deficiency

anemia of 1-2 degrees against the background of an infectious process. Concomitant diseases: U07.1 - COVID-19, virus identified. This code is used when COVID-19 has been confirmed by laboratory testing, regardless of the severity of clinical signs or symptoms: a condition after a coronavirus infection; Bilateral polysegmental pneumonia, moderate severity, resolution period.

Thus, with a new coronavirus infection in young children, it is possible to develop a Kawasaki-like COVID-associated syndrome. Pediatricians need to be careful, carefully diagnose after a COVID-19 infection.

Reference

1. Kantimirova M.G., Novikova Yu.Yu., Ovsyannikov D.Yu., et al. Detskij mul'tisistemnyj vospalitel'nyj sindrom, associirovannyj s novoj koronavirusnoj infekciej (COVID-19): aktual'naya informaciya i klinicheskoe nablyudenie [Pediatric multisystem inflammatory syndrome associated with a new coronavirus infection (COVID-19): current information and clinical observation]. Pediatricheskaya farmakologiya [Pediatric Pharmacology]. 2020. 17 (3): 219-229. DOI: 10.15690/pf.v17i3.2126

2. Namazova-Baranova L.S. Koronavirusnaya infekciya (COVID-19) u detej (sostoyanie na aprel' 2020) [Coronavirus infection (COVID-19) in children (status as of April 2020)]. Pediatric pharmacology [Pediatricheskaya farmakologiya]. 2020; 17 (2): 85-94. DOI: 10.15690/ pf.v17i2.2094.

3. Popova T.E., Tikhonova O.G., Romanova A.N. et al. Analiz epidemiologicheskoj situacii po COVID-19 [Analysis of the epidemiological situation on COVID-19]. Yakut Medical Journal. 2020; 3 (71): 63-37. DOI 10.25789/YMJ.2020.71.17

4. CDC COVID-19 Response Team. Coronavirus disease 2019 in children. United States, February 12 – April 2, 2020. MMWR Morb. Mortal Wkly Rep. 2020 Apr 6. DOI:10.15585/mmwr.mm6914e4.

5. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China /Dong Y, Mo X, Hu Y, [et al.]. Pediatrics. 2020. DOI: 10.1542/peds.2020-0702.

6. Zhu N, Zhang D, Wang W, et al. Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727–733. DOI: 10.1056/NEJMoa2001017.

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CLINICAL CASE OF DIFFUSE TOXIC GOITER IN A 12-YEAR-OLD CHILD

DOI 10.25789/YMJ.2022.79.32

УДК 616.401-006.5

This article describes a clinical case of severe thyrotoxicosis on the background of diffuse toxic goiter in a 12-year-old child. Non-systematic intake of thyrostatic drugs led to the development of severe thyrotoxicosis.

Keywords: thyrotoxicosis, thyroid gland, hyperthyroidism, triiodothyronine, thyroid-stimulating hormone, incompetence.

Introduction. The Republic of Sakha (Yakutia) is an endemic region for the content of iodine in the environment [2]. In endemic regions the frequency of endemic goiter and thyroid disease in general has a high prevalence [4].

Diffuse toxic goiter is a systemic autoimmune disease that develops due to the production of antibodies to the thyroid hormone receptor, it is clinically manifested by thyroid involvement with the development of thyrotoxicosis syndrome. It is a rather rare disease [1,3,5]. According to the Scientific Research Center of Endocrinology, the incidence in the Russian Federation during the period of 2018-2020 is 1.94:100,000 children, about 800 new cases are diagnosed annually [5]. Timely diagnosis, adequate therapy, and rigorous implementation of medical recommendations improve the quality of life and health of patients, as well as determine the prognosis of the disease and the tactics of patient management [1,3,4].

Purpose of the study is to describe a clinical case of severe diffuse toxic goiter with thyrotoxicosis of the 4th degree in a 12-year-old child.

I., a 12-year-old Sakha girl, was admitted to the Pediatric Center of the Republican Hospital No. 1 - National Center of Medicine of the Republic of Sakha (Yakutia) with complaints of tachycardia, nervousness, excitability, headaches, nausea, pain in joints of hands and feet.

Past medical history: a child from the first pregnancy, which proceeded smoothly. One, on time, natural childbirth. Weight at birth was 3300g, height was 51 cm. The baby was applied to the breast for 1 day. BCG and vaccinations against hepatitis B in the maternity hospital. Artificial feeding from 1 month old. Preventive vaccinations according to age.

Past illnesses are acute respiratory infections, acute respiratory viral infections. No injuries or surgeries. Heredity on the mother's side was not aggravated. Heredity on the father's side is unknown. No allergic diseases.

From the medical history: Headaches and dizziness have been bothering her since the fall of 2021. The girl dramatically lost weight, periodically noted nausea and vomiting. She was examined by local pediatrician and sent to the admission and diagnostic department of PC RH-1-NCM. She was examined by the physician on duty at the admission and diagnostic department.

On admission: height was 151 cm, weight was 36 kg. Condition was severe, due to signs of thyrotoxicosis, emotional tone is labile. Proportional physique, decreased nutrition. The skin was clean, dark, perioral hyperpigmentation, no strictures. Visible mucous membranes were clean. Nasal breathing was not obstructed. Thyroid gland is enlarged to degree 2, clinically signs of hyperthyroidism. Tremors of the hands. Breathing in the lungs is vesicular, conducted in all fields, no rales. Heart tones were rhythmic, pronounced tachycardia, HR-125 beats per minute, clear. BP 130/80 mmHg. The abdomen was soft and painless. The liver and spleen were not palpable. Physiological excretory functions were normal. NGO of female type, Tanner gender formula -1 (prepubertal).

General blood test of January 13, 2022: hemoglobin (HGB) -94 g/l (RI: 120-160 g/l); red blood cells (RBC) - $4.1x10^{12}$/l (RI: 4.1-5.2x10^{12}/l); platelets (PLT) - 428 10^9/l (RI: 150 - 450x10^9/l); white blood cells (WBC) -7. 0x10^9/l (RI: 4.5 - 13x10^9/l); lymphocytes (LYMF) - 41% (RI 8-10%); monocytes - 6.0x109/l

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(RI: 0.05 - 0.4x10^9/l); stab neutrophils - 1% (RI: 1-5%); segmented neutrophils - 62% (RI: 43 - 60%); eosinophils - 0% (RI: 0-5%); Panchenkow's COE determination -25 mm/h (RI: 1-15 mm/h). General blood analysis revealed hypochromic anemia, increased erythrocyte sedimentation rate, lymphocytosis.

As shown in Table 1, the child has high levels of T3 and T4, antibodies to toxoplasma and antibodies to TSH receptors in the tests dated January 13, 2022. After one week on the background of therapy - decrease of T4 and T3.

Parathormone dated January 13, 2022 44.8 pg/ml (12-95). Corresponds to the norm.

ECG from January 13, 2022: sinus rhythm, tachycardia, heart rate 120 per minute. Impaired repolarization processes.

Echocardiography on January 21, 2022: Ectopic chord attachment with minimal regurgitation. AC prolapse with regurgitation of the 1st degree. Additional LV trabeculae. Cavities were not enlarged. RV 66%.

Electroencephalogram of January 19, 2022: Age-related bioelectrical activity of the brain. Moderate interest of the trunk. No focal and epieactivity.

Consultations of specialists: Neurologist, dated January 24, 2022: Consciousness is clear. Pupils of the rounded shape are equal. No nystagmus. Diploopia. No paresis. Muscle tone of the extremities was moderately reduced. Arm and leg tendon reflexes were equal. Conclusion: Residual encephalopathy.

Medical psychologist, dated January 25, 2022: Neurosis-like disorder on the background of the underlying disease.

Psychiatrist, dated January 24, 2022: Consciousness is not impaired, contact. The patient gives information about herself, her behavior is orderly. Attention is not disturbed. Memory is normal. Thinking of the usual type. The intellect was secure. Conclusion: No psychiatric abnormalities detected.

Clinical diagnosis: Diffuse toxic goiter. Thyrotoxicosis of 3-4 degree (E05.0).

The patient was administered treatment: hospital ward regime, table #15, thyrotoxic therapy - thyamosol (thyrozol) in a daily dose of 15 mg, 1 tablet 3 times a day, anapriline 40 mg 2 times a day, prednisolone 60 mg in glucose 250 ml intravenously drip #5, glycine 0.1 mg under the tongue 3 times a day.

On discharge, clinical signs of thyrotoxicosis had subsided, lability of emotional background was less. The patient was discharged home with improvement in satisfactory condition. In the department, noncompliance of the patient - periodic refusal of procedures and examinations was noted. It is recommended to continue thyreostatic therapy in a maintenance dose under the supervision of endocrinologist, pediatrician at the place of residence.

Table 1

Thyroid hormone levels in the patient at hospitalization in January 2022

Thyroid hormones	13.01.2022	22.01.2022
Thyrotropic hormone	0 mlU/L (0.4-4,0),	0 mlU/L (0.4-4,0),
Free thyroxine (T4)	59.15 pmol/l (9-21)	14.8 pmol/l (9-21)
Triiodothyronine (T3)	12.4 pmol/l(2.6-5.7)	6.08 pmol/l(2.6-5.7)
Thyroperoxidase antibodies (TPA)	493, 87 U/ml (0-30)	
Thyrotropic hormone receptor antibodies (TrTTH)	27,4 U/l (0-1)	

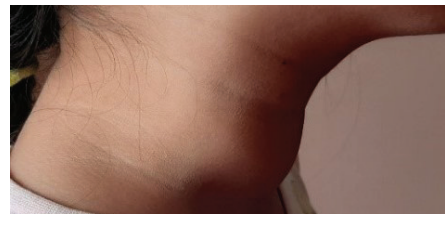
Recommendations: Dispensary observation with a pediatrician, endocrinologist, neurologist. Protective regimen. Sleep at least 9 hours. Thyroid therapy: thiamozole (thyrozole)10 mg 1 tablet 2 times a day in the morning and in the evening, a further dose reduction to 5 mg 2 times a day under the control of an endocrinologist. Monitor the level of TSH, free T4 after 2 months, then quarterly. Thyroid ultrasound monitoring after 6 months. Echocyte control in 6 months.

The patient was re-admitted on April 20, 2022, with complaints of tachycardia, hypervigilance, pastous eyelids, hypertension, dizziness, headaches. Collecting the anamnesis revealed - she took thiamozole (thymazole) in a dose of 5 mg once a day non-systematically.

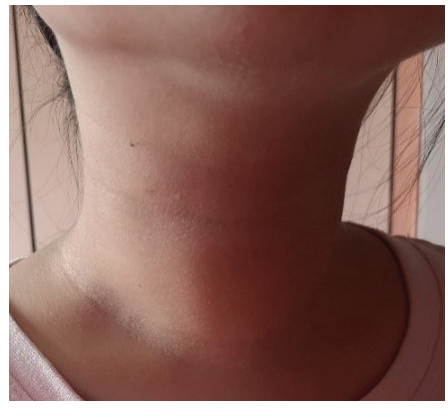
On admission: Height 150 cm. Weight 35 kg. Moderate condition, well-being is not impaired. Proportional build, moderate nutrition, average physical development. The skin was clean, dark, with slight perioral hyperpigmentation. Visible mucous membranes were clean. Nasal breathing was not obstructed. Thyroid gland was diffusely enlarged, visible to the naked eye (Figures a, b), painless. Tremor of hands. Mild exophthalmus. Breathing in the lungs is vesicular, conducted in all fields, no rales. Heart tones rhythmic, pronounced tachycardia, heart rate 120 beats per minute, clear. BP 120/75 mmHg. The abdomen was soft and painless. The liver and spleen were not palpable. Physiological excretory functions were normal. The NGO is of female type, Tanner gender formula -1-2 (prepubertal). Stool and diuresis are not disturbed.

General blood analysis of 22.04.2022: hemoglobin (HGB) -92 g/l (RI: 120-160 g/l); red blood cells (RBC) - 4.11x10^{12}/l

a



b



Diffuse toxic goiter in a 12–year–old girl: a - side view, b - front view

(RI: 4.1-5.2x10^{12}/l); platelets (PLT) - 482 10^9/l (RI: 150 - 450x10^9/l); white blood cells (WBC) -5. 4x10^9/l (RI: 4.5 - 13x10^9/l); lymphocytes (LYMF) - 56% (RI 8-10%); monocytes - 6.0x10^9/l (RI: 0.05 - 0.4x10^9/l); stab neutrophils - 0% (RI: 1-5%); segmented neutrophils - 34% (RI: 43 - 60%); eosinophils - 1.0% (RI: 0-5%); Panchenkow's COE determination -16 mm/h (RI: 1-15 mm/h). Hypochromic anemia and lymphocytosis were noted in general blood analysis.

Biochemical blood test dated 22.04.2022: ALT 8.1 u/L (RI:00-39.00), AST 22.9 u/L (RI: 00-47.0), albumin 39.1 g/L (RI: 38.0-54.0); total bilirubin 5.5 µmol/L (RI:3. 4-17.1), total protein 63.6 g/l (RI: 60.00-80.00), glucose 4.9 mmol/l (RI: 3.3-5.60), creatinine 38.2 µmol/l (RI: 27.00-62.00). Conclusion: the analysis corresponds to the norm.

Thyroid ultrasound dated 4.05.2022:

Table 2

Thyroid hormone levels in the patient in April-May 2022

Thyroid hormones	20.04.2022	26.04.2022	11.05.2022
Thyrotropic hormone	0 mlU/l (0.4-4,0),	0 mlu/l (0.4-4,0),	3.56 mlu/l (0.4-4,0),
Free thyroxine (T4)	23.82 pmol/l (9-21)	13.95 pmol/l (9-21)	13.06 pmol/l (9-21)
Triiodothyronine (T3)	11.6 pmol/l (2.6-5.7)	7.64 pmol/l (2.6-5.7)	7.64 pmol/l (2.6-5.7)
Thyroperoxidase antibodies (TPA)	644. 93 u/ml (0-30)		2.02 u/ml (0-30)
Thyrotropic hormone receptor antibodies (TrTTH)	27.4 u/l (0-1).		

Thyroid gland V=21.6ml. Right lobe V=21.6 cm3, length is 5.0 cm, thickness is 2.4 cm, width is 1.8 cm. The contour is flat. Echostructure is heterogeneous. Echoo density is average, in the CDC blood flow is not changed. The left lobe V=21.6 cm3, 5.0 cm long, 2.4 cm thick, 1.8 cm wide. The contour is flat. Echostructure is heterogeneous. Echoo density is average. In the CDC blood flow was not changed. The isthmus 1.0 cm. Regional lymph nodes: not enlarged. Conclusions: the 3rd degree diffuse goiter. Heterogeneity of the glandular tissue. Chronic thyroiditis.

ECG dated April 21, 2022: sinus rhythm with heart rate of 100 beats per minute, moderate tachycardia, repolarization disorder.

Thyreostatic therapy was prescribed - thiamazole at a dose of 0.42 u/kg/day (according to clinical guidelines, 2021), B-adrenoblocker at a dose of 40 mg/day.

Against the background of therapy, the signs of thyrotoxicosis were achieved. She felt well, was quiet, her sleep normalized, tachycardia disappeared (heart rate up to 112 beats per minute). The dynamics of the thyroid profile are shown in Table 2.

Conclusions: The article clearly shows the dependence of the severity of the disease and the frequency of its exacerbations on adequate therapy. Prescribing an adequate dose of thyrostatic drugs and strict adherence to the doctor's recommendations is a prerequisite for successful treatment. Conversations with the patient and his parents by specialists and control of the local pediatrician are necessary to create patient compliance.

Reference

1. Ivannikova TE, Nagaeva EV, Vasyukova OV. Klinicheskie proyavleniya diffuznogo toksicheskogo zoba u detej [Clinical manifestations of diffuse toxic goiter in children]. Rossijskij vestnik perinatologii i pediatrii [Russian Bulletin of Perinatology and Pediatrics. 2020; 65(4): 324 (In Russ.).]

2. Burtseva TE, Uvarova TE, Dranaeva GG, et al. Joddeficitnye sostoyaniya u detej arkticheskih rajonov Respubliki Saha (YAkutiya) [Iodine deficiency conditions in children of the Arctic regions of the Republic of Sakha (Yakutia)] Yakut Medical Journal. 2008; 4 (24): 55-56 (In Russ.).] https://elibrary.ru/item.asp?id=13009165

3. Chernyshova VS, Stolnikova TG, Evtuhova OV. Osobennosti klinicheskoj kartiny diffuznogo toksicheskogo zoba u detej Voronezhskoj oblasti [Features of the clinical picture of diffuse toxic goiter in children of the Voronezh region]. Medicina: teoriya i praktika [Medicine: theory and practice. 2019; 4 (5): 601 (In Russ.).]

4. Tsurkan L, Gerasimov GA, Parvanta I, et al. Progress v profilaktike i ustranenii jododeficitnyh zabolevanij (JDZ) v regione Evropy i Central'noj Azii (ECAR) v 2010–2020 godah [Progress in the prevention and elimination of iodine deficiency diseases (IDD) in the region of Europe and Central Asia (ECAR) in 2010-2020]. Klinicheskaya i eksperimental'naya tireoidologiya [Clinical and experimental thyroidology. 2021; 17(4): 4-16 (In Russ.).]

5. Ivannikova TE, Shiryaeva TY, Nagaeva EV, et al. Radikal'noe lechenie diffuznogo toksicheskogo zoba u detej [Radical treatment of diffuse toxic goiter in children]. Problemy Endokrinologii [Problems of Endocrinology. 2022; 68(2): 104-111 (In Russ.).]