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ORIGINAL RESEARCH

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INFLUENCE OF ANAESTHESIA ON THE IMMUNE STATUS OF PATIENTS WITH MALIGNANT NEOPLASMS IN THE OROPHARYNGEAL REGION

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The immune system, as the main factor in protecting the body from the action of infectious, viral agents, as well as performing anticancer surveillance, undergoes a number of negative changes during surgery. With surgical intervention that causes a stress response and the effects of anesthetics, immunosuppression is formed, which in turn reduces the quality of medical care to patients, increases the duration of hospital stay, as well as the development of a number of complications. The purpose of the study was to evaluate the effect of pre-carbohydrate loading and perioperative administration of dalargin on immunity indicators in patients who underwent surgery for malignant neoplasms of the oropharyngeal region. Materials and methods. 58 patients operated on for malignant neoplasms of the oropharyngeal region were examined. Patients are divided into 2 groups. In the main group (n=29), patients received a carbohydrate load of 400 ml for 12 hours and 200 ml for 2 hours before surgery, used multicomponent general anesthesia with the introduction of dalargin at a dosage of 45-55 mcg/kg/min, at the end of the operation, dalargin was administered 1 mg intramuscularly. In the control group (n=29) was multicomponent general anesthesia. The morphological composition of blood, the content of cytokines (IL-1β, -6, -8, -10, INF-γ and TNF-α) and immunoglobulins (IgA, IgM, IgG) were determined. Results. The level of lymphocytes in the postoperative period up to 7 days was significantly higher in the main group than in the control group, where there was a decrease in this indicator relative to the preoperative level. A significant increase in rod-shaped neutrophils in the control group also persisted up to 7 days after surgery. On the 1st day after surgery, the cytokine content significantly increased in both groups. The values of IL-1ß, IL-6, IL-8, INF-γ, TNF-α were significantly higher in the control group, however, on the 7th day after surgery, significant differences between the groups remained only in the indicators of IL-8, INF-γ. When assessing the level of immunoglobulins, statistically significant differences were revealed between the groups – in the main group, the concentration of IgA on day 1 and IgG on day 7 after surgery was higher. The content of CRP in both groups increased significantly on the next day after surgery, and in the main group the indicators were statistically significantly lower compared to the control group. The level of CRP in both groups remained above the initial values up to 7 days after surgery. Conclusion. The use of enkephalin, dalargin, as a component of anesthetic support in the perioperative period in the surgical treatment of malignant neoplasms of the oropharyngeal region is associated with a lower concentration of pro-inflammatory interleukins, an increase in IgG concentration compared with endotracheal multicomponent anesthesia and may contribute to the activation of an antitumor immune response.

Keywords: dalargin, anesthesia, immunity, depression, stress protection.

Introduction. The state of the immune system is of great importance in the life of the human body, having a significant impact on the incidence of postoperative complications, the duration of postoperative rehabilitation, and, most importantly, can affect the final result of treatment of the underlying disease. On the other hand, the surgical stage of treatment can have a negative impact on the immune status of patients.

In modern medical practice, there is substantial and convincing evidence confirming the almost inevitable occurrence of postoperative immunosuppression [11]. Such immunodeficiency can manifest itself in varying degrees and is the result of a complex interaction of many factors.

Surgical methods of treatment, through the activation of various components of humoral and cellular immunity, are accompanied by local or systemic inflammatory reactions and lead to disturbances in carbohydrate metabolism - insulin resistance [14]. In this condition, excess glucose independently causes hyperproduction of proinflammatory cytokines [15]. This, in turn, increases catabolism and mobilization of energy substrates, which also negatively affects the patient's postoperative recovery and the prognosis of his treatment.

It is important to emphasize that a negative effect on the immune system is characteristic not only of surgical intervention, but also of anesthesia compo-

nents [10,6]. One of the leading roles in this is provided by analgesics – opioids. Despite the significant positive role of this group of drugs, without which it is impossible to carry out traumatic surgical interventions, they also have a number of disadvantages such as inhibition of phagocytosis by neutrophils, inhibition of the proliferative ability of macrophages, decreased production of anti-inflammatory cytokines IL-10 and IL-12, immunoglobulins, IL-2 , INF-γ, NK cell activity, and inhibition of lymphocytic proliferation [16,8]. All this, along with stimulation of angiogenesis [**19] is a significant factor in the suppression of the immune system and can contribute to the progression of the tumor process [13].**Consequently, the developed dysregulation of the immune system must be neutralized by choosing anesthetics that minimally inhibit immune reactions.

In the context of immunomodulation, an important link and mechanism that corrects the systemic inflammatory response to stress, prevents immunosuppression and increases the body's stress immunity is the use of a combination of a preliminary carbohydrate load and dalargin. The prerequisites for the use of dalargin in an anesthetic regimen were data on antinociceptive, antistress, immunomodulatory, and organoprotective effects [12,20]. In addition, a number of studies have confirmed the safety of using dalargin in cancer pathology [1].

Purpose of the study. To evaluate the effect of preoperative carbohydrate loading and stress protection with dalargin, as a component of anesthesia, on the immune status of patients with malignant neoplasms of the oropharyngeal region

Materials and methods. The presented work is a single-center prospective study. The formation of groups of patients was carried out using the case-control method. The study was conducted with permission from the local ethics committee of the Oncology Research Institute of the Tomsk National Research Medical Center (protocol No. 2 of 01/18/2023).

Inclusion criteria:

- availability of voluntary informed consent of the patient;
- diagnosis of cancer of the oral cavity and oropharynx T1-4 N0-3 M0 stage;
- patient age from 18 to 75 years;
- Class II–III according to the classification of the physical status of patients of the American Society of Anesthesiologists;
- areas of surgical intervention: oral cavity, oropharynx, +/- lymph node dissection of the neck (according to indications);
- normal white blood cell count.

Non-inclusion criteria:

- refusal of treatment;
- disseminated or inoperable tumor process;
- concomitant decompensated diseases;
- history of diabetes mellitus;
- emergency operations;
- perioperative blood transfusions.

The study included 58 patients (Table 1) with operable cancer of the oropharyngeal region who were treated at the Department of Head and Neck Tumors of the Oncology Research Institute of the Tomsk National Research Medical Center. Patients were comparable in age, anthropometric data and ASA.

The patients underwent the following surgical interventions as planned (Table 2):resection of the lower jaw with a reconstructive plastic component, glossectomy with reconstructive plastic component, wide excision of the cheek tumor with reconstructive plastic component, combined resection of the oropharynx. If indicated, lymph node dissection of the neck was performed on one or both sides. During surgical intervention, as well as in the postoperative period, there was no need for transfusion of blood components.

All patients were divided into 2 clinical groups, 29 people in each.

Characteristics of perioperative management. Preoperative preparation was carried out for patients of the main group. Zand 10-12 hours before surgery, patients received 400 ml of a carbohydrate drink (Provide Extra drink, Fresenius Kabi). 2-3 hours before surgery - another 200 ml. Premedication in both groups included diazepam solution 0.5% - 2 ml intramuscularly 30 minutes before surgery. Further anesthesia, after the administration of propofol 1.5-2 mg/kg, rocuronium bromide 0.6 mg/kg, was carried out with Sevoflurane 2.0-2.5 vol% (MAC 1.0) with a bolus injection of fentanyl 2-4 mcg /kg/ at the moment of the greatest stress response. The difference between the main group in the anesthetic care was that these patients, from the moment of admission to the operating room, received an intravenous infusion of dalargin at a dosage of 45-55 mcg/kg/h,and at the end of the surgical intervention, 1 mg of dalargin was administered intramuscularly once. Intraoperative monitoring was carried out according to the Harvard standard [8].

Determination of the morphological composition of blood was assessed during a general clinical blood test. Venous blood was collected: the day before surgery, immediately after surgery, 1 day after surgery, 7 days after surgery.

Determination of the concentration of cytokines (IL-1β, -6, -8, -10, INF-γ and TNF-α) and immunoglobulins (IgA, IgM, IgG) in blood serum was performed using test systems for enzyme immunoassay (JSC "Vector -Best", Russia). Blood

Table 1

Characteristics of the studied patients

Indicator	Main group (N=29)	Control group (N=29)
Age, years	60±8.5 years	59.6±9.3 years
Male/female, n (%)	15 (51.7) / 14 (48.3)	14 (48.3) / 15 (51.7%)
BMI,kg/m^2	24.5±2.7	25.2±3.1
ASA II/III, n (%)	21 (72.4) / 8 (27.6)	23 (79.3) / 6 (20.7)

Table 2

Scope of surgery

Operation name	Main group (N=29)	Control group (N=29)
Combined resection of the oropharynx	7 (24)	6 (20.7)
Combined resection of the tongue. floor of the mouth. lower jaw	8 (27.6)	9 (31)
Resection of the lower jaw	6 (20.7)	5 (17.2)
Tongue resection	6 (20.7)	5 (17.2)
Skin resection of the buccal area	2 (6.9)	4 (13.8)
Lymph node dissection of the neck	26 (89.7)	25 (86.2)

Table 3

Dynamics of leukocyte formula indicators

Indicator	Group	Before surgery	After surgery	1 day after surgery	7 days after surgery
Lymphocytes, %	Main	25.1±1.5	25±1.5 #. *	27±3.4 #	27.0±1.9 #
	Control	24.7±0.9	22.5±0.9 *	19.7±0.4 *	21±0.1 *
Neutrophils s/i, %	Main	52.0±6.4	52.1±6.4 #	54.7±6.2 #	54.5±3.3 #
	Control	50.4±6.8	49.7±0.9 *	59.3±0.8	57.2±0.5
Neutrophils p/i, %	Main	0.9±0.3	1.0±2.3 #	0.5±1.6 #,*	0.5±0.6 #,*
	Control	0.8±0.2	1.6±0.1 *	2.0±0.1 *	0.95±0.1
Monocytes, %	Main	5.8±2.1	5.8±0.5	6.0±1.1 #	4.6±1.5 #,*
	Control	5.9±2.4	5.9±0.2	4.5±0.5 *	4.5±0.1 *
Eosinophils, %	Main	2.4±0.5	2.5±0.3	2.5±0.4	3.1 ±0.4 *
	Control	2.3±0.2	2.4±0.1	2.5±0.1	3.3±0.2 *

* - p < 0.05 compared with the preoperative stage, # - p < 0.05 between groups

samples were collected in tubes containing ethylenediaminetetraacetic acid (preservative) and centrifuged for 10 min at 4°C immediately after collection. Venous blood samples were taken for immunity indicators: the day before surgery, 1 day after surgery, 7 days after surgery. All studies were performed on the day of blood collection.

For statistical analysis, the Microsoft Excel software package "Statistica 10.0" was used. Normality of distribution was assessed using the Shapiro-Wilk test. Depending on the distribution, the data were presented as arithmetic mean and standard deviation (M ± α). The significance of differences depending on the distribution was assessed using parametric and non-parametric tests: Student's t-test or Mann-Whitney U-test. To analyze qualitative characteristics, the χ2 test, χ2 test with Yates correction, or Fisher's exact test were used. P values <0.05 for all tests were considered statistically significant.

Results. Before anesthesia, the morphological composition of the blood of patients in both groups was homogeneous and did not have statistically significant differences (Table 3). The level of leukocytes in both groups during the entire evaluation period did not go beyond the normal range. However, after surgery, changes affected the percentage of lymphocytes: in the main group its value was significantly higher (25±1.5% versus 22.5±0.9% in the control group). 1 day after the operation, these changes, both in quantitative terms and in percentage, became more pronounced and also affected neutrophils and monocytes. The changes that occurred persisted up to 7 days after surgery.

Before anesthesia and surgery, the concentration of cytokines did not differ significantly between the groups (Table 4). On the 1st day of the postoperative period in both groups, the content of both anti- and proinflammatory cytokines increased significantly in comparison with the initial indicators and between groups. Values of pro-inflammatory cytokines IL-1β, IL-6, IL-8,INF-γ, and alsoTNF-αwere significantly higher in the control group. On the 7th day after surgery, significant differences between the groups remained only in IL-8,INF-γ.

The concentration of the anti-inflammatory cytokine IL-10 in the main and control groups one day after surgery significantly exceeded preoperative values. On the 7th day, the indicator decreased to initial values in both groups.

The levels of all immunoglobulins underwent changes at some stage of the study. However, statistically significant differences between the groups were recorded only in IgA on the 1st day and IgG on the 7th day after surgery.

The content of CRP in both groups on the next day after surgery increased significantly, and in the main group the values were statistically significantly lower compared to the control group. On the 7th day of the postoperative period, the level of CRP in both groups decreased, however, it was significantly higher compared to the initial values.

Discussion of results. Long-term surgical interventions in the oropharyngeal region are a stress factor and are accompanied by significant tension in all protective regulatory systems of the body, which is manifested by the development of a surgical stress response and, as a consequence, immunosuppression [3]. It has been demonstrated in animal models that areas of surgical trauma may be preferential sites for local tumor progres-

Table 4

Dynamics of immunity and CRP indicators

Indicator	Group	Before surgery	1 day after surgery	7 days after surgery
IL-1β, pg/ml	Main	3.5±0.7	6.6±2.5 #,*	3.4±0.9
	Control	3.3±0.6	9.4±1.4 *	3.4±0.7
IL-6, pg/ml	Main	4.0±0.9	20.3±9.3 #,*	4.3±1 *
	Control	4.2±0.9	40.3±6.2 *	4.6±0.9 *
IL-8, pg/ml	Main	3.5±0.6	8.7±2.7 #,*	3.5±0.8 #
	Control	3.4±0.5	15.2±1.6 *	3.9±0.6 *
IL-10, pg/ml	Main	3.0±0.4	19.2±3.8 *	3.0±0.5
	Control	2.8±0.6	18.4±5.5 *	3.1±0.6
INF-γ pg/ml	Main	3.1±0.9	5.4±2.3 #,*	4.4±1.4 #,*
	Control	3.3±0.7	8.7±1.9 *	6.3±1.0 *
TNF-α, pg/ml	Main	5.2±1.2	6.4±0.7 #,*	5.3±0.8
	Control	5.4±08	8.6±0.4 *	5.4±0.7
IgA, g/l	Main	2.7±1.0	2.5±0.8 #,*	2.7±1
	Control	2.3±1.1	1.7±0.9 *	2.2±0.9 *
IgM, g/l	Main	1.1±0.6	1.2±0.7	1.2±0.5
	Control	1.2±0.7	1.0±0.5 *	1.3±0.2
IgG, g/l	Main	10.6±2.2	10.8±2.0 *	11.3±2.1 #
	Control	10.2±2.3	9.4±2.2 *	9.2±2.0 *
SRB, mg/l	Main	15.7±7.9	35.2±41.9 #,*	17.7±16.1 #,*
	Control	20.1±7.2	68.5±22.4 *	29.8±11 *

sion, and it has previously been shown that surgery may indirectly stimulate the development of locoregional metastases [23]. A number of published studies describe that surgical trauma leads to systemic changes that accelerate tumor development [26,25]. Thus, surgery causes both local and systemic changes that may contribute to tumor progression. However, tumor cell migration during surgery alone cannot fully explain the high recurrence rate. The generally accepted opinion at the moment is that surgery inevitably leads to injury, which initiates a stress response covering a wide range of endocrinological, immunological and hematological consequences, and this in turn indirectly affects long-term surgical and oncological treatment results.

The anesthetics used also have a negative effect on the functioning of the immune system [24]. However, it should be noted that such effects are short-lived and of little significance for patients with a normal immune system. However, in patients with existing immune disorders, including cancer patients with previous chemoradiotherapy [17], as well as in high-risk patients, the influence of drugs in the anesthetic regimen may have important clinical implications for the perioperative period and immune imbalance.

During the study, there was a significant increase in the level of band neutrophils and a decrease in the content of one of the most important components of the immune system, lymphocytes, compared to the initial data in the control group immediately after surgery, which may indicate the presence of the most pronounced stress reactions in the perioperative period.

It is known that both surgical intervention and the components of anesthesia indirectly affect the appearance in the blood of certain cytokines that can regulate the processes of proliferation, differentiation, functioning, apoptosis of cells and can have a pro- or anti-oncogenic effect [2]. Although inflammation is a normal protective response to injury and infectious agents, tumor cells can use this process for their own survival and progression [21]. In addition, an acute inflammatory response to surgical trauma promotes the transfer of tumor cells to areas of the body remote from the lesion. For example, proinflammatory cytokines such as IL-1 and TNF-α stimulated the adhesion of circulating cancer cells [27]. However, it should be noted that acute inflammatory reactions after surgical trauma are often transient and do not lead to significant deterioration in oncological results.

In this regard, it is important to assess the content of pro- and anti-inflammatory cytokines in the blood. In the study, the increase in pro-inflammatory cytokines was significant on the next day after surgery, however, when using a preliminary carbohydrate load and dalargin, this phenomenon was less pronounced. This fact indicates that immune function was less suppressed under enkephalin conditions. This is also confirmed by the concentration of IFN-γ, which, with a moderate increase, is capable of exerting antitumor activity [9]. Despite a significant increase in IL-1β, IL-6, IL-8, there is a corresponding compensation by the high activity of anti-inflammatory IL-10.

Another important aspect reflecting the state of the immune system in the perioperative period is antitumor immunity. A marker of weakened antitumor, as well as antimicrobial immunity, is an increase in the level of IL-6 [18], which stimulates tumor growth by inhibiting apoptosis and inducing tumor angiogenesis.TNF-α has a largely similar tumorigenic effect [5,29]. Moreover, in addition to the direct effect on the formation of tumor tissue, TNF-α promotes the growth of blood vessels and the expression of adhesion molecules involved in the metastasis of transformed cells.Therefore, significantly low levels of these pro-inflammatory cytokines in the group using dalargin can be considered as a positive factor in protecting the body from the development of tumors.

It is known that overproduction of cytokines, including IL-1, IL-6 and TNF-α, plays a significant role in the prolongation of the hypermetabolic state [4,7]. An increase in the level of IL-6 also stimulates the production of antibodies, and a decrease in the formation of albumin and transferrin occurs. On this side, the increased concentration of these cytokines is one of the factors that slow down the recovery of patients in the postoperative period and increases the risk of infection.

Proinflammatory cytokines also increase the liver's production of CRP, which in turn is an inflammatory factor [22,28]. Therefore, a more significant decrease in the concentration of CRP in the blood of patients in the main group, according to the patterns of inflammation, should also be associated with a decrease in the activity of pathological processes.

Assessment of humoral immunity by determining the content of immunoglobulins showed that the immunological profile of patients in whom dalargin was present in the perioperative period was characterized by better indicators. Immunglobulins IgA and IgM in the control group tended to decrease on day 1 after surgery, which characterizes the state of immunity as suppression. In the main group, these antibodies remained without significant changes. A positive role of dalargin in increasing IgG by 7 days after surgery is also noted.

The study showed that the developed anesthesia method with the inclusion of enkephalin,was able to reduce immunosuppression and the activity of proinflammatory cytokines, which may create favorable preconditions for improving the oncological results of combined treatment of patients with malignant tumors of the oropharyngeal region.

Conclusion. The key role played by the immune system in the perioperative period highlights the importance of both reducing the morbidity of surgical interventions and finding new anesthetic agents aimed at reducing immunosuppressive effects. Support and moderate enhancement of the immune response in the perioperative period without dysregulation may potentially bring a number of benefits.

The results of this work can provide additional fundamental information on the use of enkephalin (dalargin) as a component of anesthesia. Its use in the perioperative period in patients with malignant neoplasms of the oropharyngeal region is associated with a lower concentration of pro-inflammatory interleukins, an increase in the concentration of IgG compared to endotracheal multicomponent anesthesia and may contribute to the activation of an antitumor immune response.

References

1. Vasiliev AV, Bukharova TB, Volkov AV, [et al.]. Vliyanie dalargina na proliferaciyu mul'tipotentnyh mezenhimal'nyh kletok dermal'nyh fibroblastov i kletok osteosarkomy cheloveka in vitro [Effects of dalarginum on proliferation of multipotent mesenchymal stromal cells, dermal fibroblasts, and human osteosarcoma cells in vitro]. Geny i kletki [Genes and Cells. 2014;9(4):76–80 (In Russ.).] doi: 10.23868/gc120391.

2. Matveeva LV, Mosina LM. Rol' citokinov semejstva interlejkina-1 v zheludochnom kancerogeneze [The role of interleukin-1 and associated cytokines in gastric carcinogenesis]. Vestnik RAMN [Annals of the Russian academy of medical sciences. 2012;67(11):59-65 (In Russ.).] doi:10.15690/vramn.v67i11.473.

3. Ovechkin AM. Hirurgicheskij stress-otvet, ego patofiziologicheskaja znachimost' i sposoby moduljacii [Surgical stress-response, its pathophysiological significance and methods of modulation]. Regionarnaja anestezija i lechenie ostroj boli Regionarnaja anestezija i lechenie ostroj boli [Regional organization and treatment of acute pain. 2008;2:49-62 (In Russ.).]

4. Larina ON, Bekker AM, Repenkova LG, et

al. Plazmaticheskie pokazateli jekspressii mediatorov reakcii ostroj fazy v nachal'nye sroki adaptacii k antiortostaticheskomu polozheniju [Plazmaticheskie pokazateli jekspressii mediatorov reakcii ostroj fazy v nachal'nye sroki adaptacii k antiortostati-cheskomu polozheniju]. Citokiny i vospalenie [Cytokines and inflammation]. 2011;10(1):3-5 (In Russ.).

5. Fujiki H, Suganuma M, Komori A, et al. A new tumor promotion pathway and its inhibitors. Cancer Detect Prev. 1994;18(1):1-7.

6. Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. J Anesth. 2008;22(3):263-277. doi:10.1007/s00540-008-0626-2

7. Barton BE. IL-6-like cytokines and cancer cachexia: consequences of chronic inflammation. Immunol Res. 2001;23(1):41-58. doi:10.1385/IR:23:1:41.

8. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell. 2006;127(4):679-695. https://doi.org/10.1016/j.cell.2006.11.001.

9. Sasada T, Kimura M, Yoshida Y, et al. CD4+CD25+ regulatory T cells in patients with gastrointestinal malignancies: possible involvement of regulatory T cells in disease progression. Cancer. 2003;98(5):1089-1099. doi:10.1002/cncr.11618.

10. Choi WJ, Baek S, Joo EY, et al. Comparison of the effect of spinal anesthesia and general anesthesia on 5-year tumor recurrence rates after transurethral resection of bladder tumors. Oncotarget. 2017;8(50):87667-87674. doi: 10.18632/oncotarget.21034.

11. Liu W, Wu L, Zhang M, et al. Effects of general anesthesia with combined epidural anesthesia on inflammatory response in patients with early-stage gastric cancer undergoing tumor resection. Exp Ther Med. 2019;17(1): 35–40. doi: 10.3892/etm.2018.6898.

12. Garmaeva DV. Effect of Leu-Enkephalin Analogue on the Myeloid Compartment of the Blood System in Hypothyroid White Rats under Stress Conditions. Bull Exp Biol Med. 2022 May;173(1):1-4. doi: 10.1007/s10517-022-05479-2.

13. Haroutounian S. Postoperative opioids, endocrine changes, and immuno- suppression. PAIN Reports. 2018;3(2):640-644. doi;10.1097/PR9.0000000000000640.

14. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999;2(1):69-78. doi:10.1097/00075197-199901000-00012.

15. He J, Usui I, Ishizuka K, et al. Interleukin-1alpha inhibits insulin signaling with phosphorylating insulin receptor substrate-1 on serine residues in 3T3-L1 adipocytes. Mol Endocrinol. 2006;20(1):114-124. doi:10.1210/me.2005-0107.

16. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med. 2018;16(1):8. doi:10.1186/s12967-018-1389-7.

17. Verastegui EL, Morales RB, Barrera-Franco JL, et al. Long-term immune dysfunction after radiotherapy to the head and neck area. Int Immunopharmacol. 2003;3(8):1093–1104. doi:10.1016/S1567-5769(03)00013-4.

18. Naugler WE, Karin M. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. Trends in Molecular Medicine. 2008;14:109-119. doi: 10.1016/j.molmed.2007.12.007.

19. Zylla D, Gourley BL, Vang D, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer. 2013;119(23):4103-4110. doi:10.1002/cncr.28345.

20. Sazonova EN., Lebedko OA, Pinaeva OG, et al. Role of Amino Acid Arginine and Nitric Oxide in Mechanisms of Cytoprotective Effect of Non-Opiate Leu-Enkephalin Analogue In Vitro. Bull Exp Biol Med. 2021. 172(2):270-275. doi:10.1007/s10517-021-05374-2.

21. Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. J Clin Invest. 2015;125(9):3347-3355. doi:10.1172/JCI80007.

22. Singh PP, Voleti B, Agrawal A. A novel RBP-J kappa-dependent switch from C/EBP beta to C/EBP zeta at the C/EBP binding site on the C-reactive protein promoter. J Immunol. 2007;178(11):7302-7309. doi:10.4049/jimmunol.178.11.7302.

23. Abramovitch R, Marikovsky M, Meir G, et al. Stimulation of tumour growth by wound-derived growth factors. Br J Cancer. 1999;79(9-10):1392-1398. doi:10.1038/sj.bjc.6690223.

24. Ackerman RS, Luddy KA, Icard BE, et al. The Effects of Anesthetics and Perioperative Medications on Immune Function: A Narrative Review. Anesth Analg. 2021;133(3):676-689. doi:10.1213/ANE.0000000000005607.

25. Georges C, Lo T, Alkofer B, et al. The effects of surgical trauma on colorectal liver metastasis. Surg Endosc. 2007;21(10):1817-1819. doi:10.1007/s00464-007-9290-0.

26. Murthy SM, Goldschmidt RA, Rao LN, et al. The influence of surgical trauma on experimental metastasis. Cancer. 1989;64(10):2035-2044. doi:10.1002/1097-0142(19891115)64:10<2035::aid-cncr2820641012>3.0.co;2-l.

27. Van der Bij GJ, Oosterling SJ, Beelen RH, et al. The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. Ann Surg. 2009;249(5):727-734. doi:10.1097/SLA.0b013e3181a3ddbd.

28. Tachyla SA, Marochkov AV, Lipnitski AL, et al. The prognostic value of procalcitonin, C-reactive protein and cholesterol in patients with an infection and multiple organ dysfunction. Korean J Anesthesiol. 2017;70(3):305-310. doi:10.4097/kjae.2017.70.3.305.

29. Komori A, Yatsunami J, Suganuma M, et al. Tumor necrosis factor acts as a tumor promoter in BALB/3T3 cell transformation. Cancer Res. 1993;53(9):1982-1985.

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THE 15-YEAR RISK OF COLORECTAL CANCER: PROGNOSTIC SIGNIFICANCE OF RISK FACTORS FOR CHRONIC NON-COMMUNICABLE DISEASES WITH AGING

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Objective: to investigate the prognostic significance of risk factors for chronic non-communicable diseases in the development of colorectal cancer (CRC) in an ageing population cohort (Novosibirsk).

Materials and methods: The study was performed on a representative population sample (Novosibirsk) examined in the HAPIEE project (2003-2005). The analysis included 6061subjects, 152 of whom (73 men, 79 women) had an incident CRC diagnosed during the 15-year follow-up (2003-2015). Cases were identified by linking cancer registry with the cohort database, ICD-10 was used. We used Cox regression models to analyze the association between risk factors and CRC.

Results: The multivariable-adjusted 15-year risk of CRC in men was higher compared to women (HR=1.76; 95% CI:1.12-2.77). The risk of CRC was positively associated with age in both men (HR per year 1.11; 95% CI:1.07-1.15) and women (HR per year 1.09; 95% CI:1.05-1.14). In men with a positive family history of malignant neoplasms (MN) of any location, the risk of CRC was increased (HR=1.90; 95% CI:1.14-3.17). The presence of type 2 diabetes mellitus was associated with the risk of CRC in women (HR=1.97; 95% CI:1.10-3.53).

Conclusions: In studied population cohort aged 45-69, the risk of CRC is positively associated with male gender. Positive associations were also identified between CRC and age in both sexes, the family history of MN of any location in men, and the presence of type 2 diabetes in women.

Keywords: colorectal cancer, smoking, alcohol consumption, blood lipids, type 2 diabetes, body mass index.

Introduction. Today, oncological diseases occupy one of the main places in the overall structure of morbidity and mortality. However, cancer has been known since ancient times. The Ebers Papyrus, dated 1500 BC, contains the first descriptions of possible tumors of soft tissues, skin, uterus, stomach, and also the rectum. More precise evidence of the presence of tumors is provided by mummies. Not long ago, Zimmerman M.R. [18] described the first histologically confirmed case of rectal cancer, detected in an unnamed mummy of a man who lived in Doha in 200-400 AD. Despite centuries of effort to understand the nature of cancer and the undoubted colossal progress in the study of malignant tumors, questions still remain.

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Modern studies have identified a link between the occurrence of CRC and an increased body mass index (BMI) [9, 36], a diet low in dietary fiber [35] and high in red meat [36], cigarette smoking [46, 36], alcohol consumption [5], low physical activity [46, 36], a history of type 2 diabetes [53], a family history of CRC [36], and chronic bowel diseases [46]. Most of the identified risk factors for CRC are modifiable (more than 75%) - associated with the environment and lifestyle. However, the degree of influence of these factors on the risk of CRC varies in different populations, and the results of studies are sometimes ambiguous. For example, in the EPIC study, BMI was positively associated with colon cancer in men (29.4 kg/m^2 vs <23.6 kg/m^2, RR=1.55; 95% CI:1.12-2.15), but no significant association was found with rectal cancer (29.4 kg/m^2 vs <23.6 kg/m^2, RR=1.05; 95% CI:0.72-1.55). In contrast, in women in this study, BMI was not associated with either colon cancer (28.9 kg/m^2 vs <21.7 kg/m^2, RR=1.06; 95% CI:0.79-1.42) or rectal cancer. (28.9 kg/m^2 vs <21.7 kg/m^2, RR=1.06; 95% CI:0.71–1.58) [14]. In another study in women, both low BMI (<18.5 kg/m^2) and obesity (>= 30 kg/m^2) were positively associated with the risk of developing colon cancer. Moreover, low BMI was more associated with the proximal colon, and obesity with the distal colon [13]. There are also conflicting data regarding alcohol consumption. In the EPIC (Norfolk Intervention Study) study, total alcohol consumption did not influence the risk of developing CRC (HR=0.80; 95% CI: 0.51–1.26 for alcohol consumption ≥21 units/week or 24 g ethanol/day compared with non-drinkers), while daily consumption of ≥1 unit of wine (≥8 g ethanol/day) was inversely associated with the risk of developing CRC (HR=0.61; 95% CI:0.40–0.94) [11]. In another study (meta-analysis), an increase in the risk of CRC was found with moderate (>1–4 drinks/day, equivalent to 12.6–49.9 g/day of ethanol) and heavy (≥4 drinks/day, equivalent to ≥50 g/day of ethanol) alcohol consumption by 21% and 52%, respectively [5]. However, in the same study, according to the dose-risk analysis, a significant increase in the risk of CRC by 7% was found with consumption of 10 g of alcohol per day [5].

These data indicate the need for further research in this area, as it is not only of scientific interest, but also makes a practical contribution to the prevention of malignant neoplasms, especially for cancers (including colorectal cancer), where modifiable risk factors make a significant contribution to their occurrence, mainly at an older age, the correction of which will reduce morbidity and mortality from tumors of these localizations.

Objective: to investigate the prognostic significance of risk factors for chronic

non-communicable diseases in the development of colorectal cancer (CRC) in an ageing population (Novosibirsk).

Materials and methods: The work was carried out on a representative population sample (Novosibirsk), examined within the framework of the international project HAPIEE, 2003-2005 (the principal researchers of the Novosibirsk center are Prof. S.K. Malyutina, Academician of the Russian Academy of Sciences Yu.P. Nikitin). The basic study involved 9360 people aged 45-69 years, including 4266 men and 5094 women. The study protocol (dated 14.03.2002) was approved by the local ethics committee of The Research Institute of Internal and Preventive Medicine. Each participant in the study signed an informed consent before inclusion in the project. In the framework of this work, data from 6061 people were analyzed, of which 152 people (73 men and 79 women) were included in the main group, in whom "new cases of CRC were identified" during the follow-up period from 2003-2005, up to December 31, 2019, the comparison group included 5909 people (2287 men, 3622 women), in whom "CRC was not identified" during the same follow-up period. The analysis did not include 3299 people, among them: 2527 persons who died during the past follow-up period from various causes (except of fatal cases from CRC); 587 persons with new cases of cancer other than colorectal cancer, were identified during the follow-up period; as well as 185 persons with prevalent cancer of any localization diagnosed before inclusion in this study.

To identify all cases of cancer, the HAPIEE databases and data from the cancer registry were compared (the registry is maintained in the Research Institute of Internal and Preventive Medicine in cooperation with Novosibirsk Regional Clinical Oncologic Dispensary with the support of the RAS budget topic № FWNR-2024-0002). The diagnosis of CRC was established according to the codes of the International Classification of Diseases, 10th revision (ICD 10): C18 - colon; C19 - rectosigmoid junction; C20 - rectum. This work was carried out according to the design of a prospective cohort study and was supported by the Russian Science Foundation (20-15-00371-П).

The average follow-up period for men was 15.21±1.58 years, for women – 15.53±1.32 years.

At the stage of basic screening, socio-demographic data were collected, including information on alcohol consumption, smoking, level of education, presence of malignant neoplasms in first-degree relatives without specifying the localization of the process, anthropometric data, blood pressure (BP) was measured, and some biochemical parameters of the blood were determined.

Blood was collected from the cubital vein on an empty stomach. Blood serum samples were stored in a low-temperature chamber (-70° C). Determination of the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) was carried out on KoneLab 300i (USA) autoanalyzer using Biocon kits (Germany). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the formula of WT Friedewald et al. (1972) [24]: LDL-C=TC − (TG / 2.2 + HDL-C) (mmol/L). Serum glucose was converted to FPG using the formula of the European Association for the Study of Diabetes, 2007 [28]: FPG (mmol/L) = −0.137 + 1.047 × serum glucose (mmol/L). Blood pressure (BP) was measured three times (the average of three BP readings was analyzed) using an Omron M5-I automatic tonometer (Japan). Body weight was determined using a balance scale. Body mass index (BMI) was calculated using the formula: BMI = body weight (kg)/height2(m2). Height was measured with a vertical stadiometer. Waist circumference (WC) and hip circumference (HC) were measured with a tape measure: WC - in the middle between the lower edge of the costal arch and the sacral part of the ilium, HC - along the greater trochanter. All details of the study protocol have been published previously [19].

Statistical analysis was performed using SPSS v.13.0. The obtained data are presented as absolute and relative values, as well as M±SD, where M is the arithmetic mean, SD is the standard deviation. Statistical hypotheses about the type of distribution were tested using the Kolmogorov-Smirnov criterion. To compare two groups from populations with a normal distribution, Student's t-test for two independent samples was used. The Pearson $\chi 2$ criterion was used to compare categorical variables (tables 1 and 2 for men and women, respectively). The prognostic significance of the main risk factors in the development of CRC was assessed using Cox regression methods (proportional hazards models) in age-standardized and multivariate models for men (table 3) and for women (table 4). Model 0 included each studied factor separately adjusted for age. Model 1 included age, smoking status, and alcohol consumption (average dose per session). Model 2 included age, smoking status, alcohol consumption (average dose per session), education level, and family history of malignant neoplasms. Model 3 additionally included the following covariates: BMI, TG level, presence of hypertension, and presence of type 2 diabetes.

The critical significance level for testing statistical hypotheses in this study was taken to be 0.05.

Results and discussion. Over the 15-year follow-up period, the incidence rate of new CRC cases in the population cohort was 2.5% (3.1% for men and 2.1% for women). At the time of CRC diagnosis, the average age was 69.23±7.89 years in men and 69.85±7.98 years in women. The baseline characteristics of the survey participants are presented in tables 1 and 2. At the time of the baseline examination, both men and women who developed CRC during the follow-up period were more than 4 years older ($p<0.0001$) than men and women in the comparison group. The proportion of male patients with hypertension (HT) and with a family history of cancer of any localization was higher in the CRC group than in the comparison group ($p=0.012$ and $p=0.013$, respectively). The percentage of women with type 2 diabetes was higher in the group with CRC than in the comparison group ($p<0.0001$).

Next, we examined the results obtained in the Cox regression analysis. According to our study, the assessment of proportional hazards for both sexes established a positive significant association between CRC and male sex compared to females: HR=1.57; 95% CI:1.14-2.16 in Model 0 and HR=1.76; 95% CI:1.12-2.77 in Model 3. Our results are indirectly confirmed by published statistical data: in all regions of the world (Global Cancer Observatory, 2022), the incidence of CRC is higher in men than in women (1,069,446 versus 856,979 [21,9 versus 15,2 per 100,000 people]) [27]. In addition, according to McCashland TM, at al. (2001) the risk of developing polyps and colon cancer in men is higher than in women: 1,5 and 1,4 times, respectively [17], and in the study of Hsu SH, at al. (2022) the risk of CRC in men is more than 2 times higher than in women (HR = 2.119; 95% CI:1.386–3.241) [50]. At the same time, men have an 83% higher chance of progressive colorectal neoplasia to be detected than women [26]. These differences can be explained by the putative protective effect of estrogens in relation to the risk of CRC development in women [40], as well as the fact that men tend to smoke more often [2], consume more alcohol [25], and adhere

Table 1

The characteristics of men 45–69 years old at the baseline examination for those who developed (main group)/did not develop (comparison group) the incident colorectal cancer over a 15-year observation period (population cohort, Novosibirsk, 2003-2005)

Parameters/Examined		Comparison group (2287 men)	Main group (73 men)	p
Age at baseline examination, M(SD)		56.15 (6.77)	60.77 (6.97)	0.0001
Systolic blood pressure, mmHg, M(SD)		140.78 (22.07)	144.77 (21.26)	0.128
Diastolic blood pressure, mmHg,M(SD)		89.84 (12.75)	90.27 (10.97)	0.776
Cardiovascular diseases, n(%)		267 (11.7)	11 (15.1)	0.380
AH, n(%)		1355 (59.2)	54 (74.0)	0.012
Type 2 diabetes,n(%)		211 (9.4)	7 (10.0)	0.867
Presence of family heredity for cancer of any location, n(%)		453 (20)	23 (31.9)	0.013
Education:	Primary, n(%)	177 (7.7)	5 (6.8)	0.779
	Secondary, n(%)	771 (33.7)	19 (26)	0.171
	Professional, n(%)	503 (22)	23 (31.5)	0.055
	Higher, n(%)	836 (36.6)	26 (35.6)	0.869
Marital status:	Single/Not married, n(%)	58 (2.5)	0	0.168
	Married, n(%)	2006 (87.7)	64 (87.7)	0.991
	Live with a partner outside of marriage, n(%)	53 (2.3)	1 (1.4)	0.564
	Divorced or separated, n(%)	116 (5.1)	4 (5.5)	0.876
	Widower/Widow, n(%)	54 (2.4)	4 (5.5)	0.090
TC, mmol/l, M(SD)		5.98 (1.16)	6.16 (1.14)	0.199
HDL-C, mmol/l, M(SD)		1.48 (0.37)	1.54 (0.41)	0.166
LDL-C, mmol/l, M(SD)		3.82 (1.04)	3.94 (0.96)	0.365
FPG, mmol/l, M(SD)		5.94 (1.48)	5.89 (0.88)	0.809
TG, mmol/l, M(SD)		1.48 (0.81)	1.49 (0.91)	0.912
BMI, kg/m2, M(SD)		26.74 (4.25)	26.85 (3.76)	0.826
WC (cm), M(SD)		93.75 (11.69)	95.12 (10.12)	0.322
Alcohol consumption, average dose per session (g), M(SD)		52.90 (42.95)	53.36 (37.43)	0.929
Current smoker (at the time of baseline survey), n(%)		1042 (45.7)	25 (34.2)	0.056
Past smoker (quit smoking at some point before baseline), n(%)		558 (24.5)	21 (28.8)	0.393
Never smoked, n(%)		682 (29.9)	27 (37.0)	0.188
Average number of cigarettes per day currently smoked (at baseline), M(SD)		17.78 (8.38)	16.25 (7.65)	0.376
Average number of cigarettes per day, past smoking (quit smoking at some point before baseline survey), M(SD)		19.21 (11.13)	18.05 (7.26)	0.635

Note. In table 1-2: Data are presented in the form M (SD) - mean (standard deviation), as well as in the form of absolute and relative frequency - n (%).

to a diet with less fiber and more red and processed meat [6].

However, some studies show existing sex differences in terms of tumor localization in the colon and its histological type: women have a higher risk of developing right-sided colon cancer (RSCC) with a higher percentage of poorly differentiated and locally advanced tumors than men [16]. Many assumptions have been made about the reasons for such differentiation, but they require further research.

Age is the main risk factor for sporadic CRC. This neoplasia is rare under the age of 40 years, and more than 90% of all cases of detected CRC occur in people over 50 years of age. However, recently there have been reports of a steady increase in the number of new cases of CRC at a younger age (under 50 years) [34, 30]. Nevertheless, the risk of CRC increases with age, and the peak of the disease occurs at approximately the age of 70 years [1]. According to Hsu SH, at al. (2022) in individuals aged 46 to 54 years and over 55 years, the risk of developing CRC is 2.7 and 5.5 times higher than in individuals under 45 years of age [50]. In our study, the risk of CRC is positively associated with age in both men and women (tables 3 and 4).

In addition, we found an increased risk of CRC in men with a positive family history of malignant neoplasms of any localization, including colon and rectal tumors (table 3).

According to the published data, having a positive family history of CRC leads to an increased risk of developing this disease in a proband, while the strength of the association depends on the number of relatives with CRC and their degree of relationship with a proband, as well as the age at which the disease was diagnosed.

Table 2

The characteristics of women 45–69 years old at the baseline examination for those who developed (main group)/did not develop (comparison group) the incident colorectal cancer over a 15-year observation period (population cohort, Novosibirsk, 2003-2005)

Parameters/Examined		Comparison group (3622 women)	Main group (79 women)	p
Age at baseline examination , M(SD)		56.82 (6.92)	60.99 (6.68)	0.0001
Systolic blood pressure, mmHg, M(SD)		141.99 (24.68)	140.50 (20.95)	0.594
Diastolic blood pressure, mmHg, M(SD)		89.57 (13.11)	88.69 (11.66)	0.554
Cardiovascular diseases, n(%)		291 (8)	6 (7.6)	0.885
AH , n(%)		2328 (64.3)	58 (73.4)	0.093
Type 2 diabetes, n(%)		333 (9.4)	16 (21.3)	0.001
Presence of family heredity for cancer of any location, n(%)		935 (25.9)	26 (32.9)	0.159
Education:	Primary, n(%)	279 (7.7)	9 (11.4)	0.226
	Secondary, n(%)	1205 (33.3)	25 (31.6)	0.762
	Professional, n(%)	1135 (31.3)	24 (30.4)	0.856
	Higher, n(%)	1003 (27.7)	21 (26.6)	0.827
Marital status:	Single/Not married, n(%)	179 (4.9)	4 (5.1)	0.961
	Married, n(%)	2176 (60.1)	49 (62.0)	0.726
	Live with a partner outside of marriage, n(%)	62 (1.7)	1 (1.3)	0.762
	Divorced or separated, n(%)	528 (14.6)	11 (13.9)	0.870
	Widower/Widow, n(%)	677 (18.7)	14 (17.7)	0.827
TC, mmol/l, M(SD)		6.47 (1.29)	6.69 (1.29)	0.139
HDL-C, mmol/l, M(SD)		1.56 (0.34)	1.55 (0.39)	0.695
LDL-C, mmol/l, M(SD)		4.20 (1.16)	4.38 (1.13)	0.170
FPG, mmol/l, M(SD)		5.87 (1.42)	6.17 (1.36)	0.070
TG, mmol/l, M(SD)		1.55 (0.86)	1.66 (0.75)	0.247
BMI, kg/m2, M(SD)		29.89 (5.48)	30.13 (5.48)	0.702
WC (cm), M(SD)		90.91 (12.83)	92.74 (12.22)	0.210
Alcohol consumption, average dose per session (g), M(SD)		21.58 (16.65)	21.88 (15.58)	0.870
Current smoker (at the time of baseline survey), n(%)		387 (10.7)	4 (5.1)	0.108
Past smoker (quit smoking at some point before baseline), n(%)		152 (4.2)	2 (2.5)	0.463
Never smoked, n(%)		3079 (85.1)	73 (92.4)	0.067
Average number of cigarettes per day currently smoked (at baseline), M(SD)		8.82 (6.01)	7.33 (2.52)	0.669
Average number of cigarettes per day, past smoking (quit smoking at some point before baseline survey), M(SD)		6.77 (6.02)	3.50 (0.71)	0.445

In one study, the presence of first-degree relatives with CRC increased the risk of developing a tumor of this localization in a proband from 1.91 times in the presence of 1 first-degree relative with a history of CRC to 19.86 times in the presence of 5 or more first-degree relatives with this disease (individuals likely to have hereditary CRC syndromes). In addition, the presence of only second-degree relatives also increased the risk of this disease in a proband, but to a much lesser extent, and the presence of only third-degree relatives did not lead to a significant increase in risk. The totality and combination of the affected relatives in the family history of a proband led to an intermediate increase in the risk of CRC. [44]. In another study (meta-analysis), having a first-degree relative with a family history of CRC increased the risk of developing this malignant tumor by more than 2 times (RR=2.25; 95% CI: 2.00-2.53), having more than one relative with CRC by 4 times (4.25; 95% CI:3.01-6.08), and having a relative with this disease under 45 years of age by 3.8 times (3.87; 95% CI:2.40-6.22) [33]. Both women and men with a first-degree family history of CRC were at increased risk of CRC, and a family history of CRC in both men and women was associated with an increased risk of colon cancer, but not rectal cancer. The same study (a prospective study) showed that the relative risk of CRC associated with a family history of the disease was higher in younger participants and gradually decreased with age in both women and men.[3] Similar data were obtained in the work of Jung YS, at al., where it was noted that the risk of CRC in women with a

Table 3

15-year risk of incident colorectal cancer in men, results of analysis of prognostic predictors in Cox regression models

	Covariates	Model 0	Model 1	Model 2	Model 3
HR (95%CI)	Age, years (for 1 year)		1.1 (1.06-1.14)	1.11 (1.07-1.15)	1.11 (1.07-1.15)
	Smoking: Never smoked (reference)	1.0	1.0	1.0	1.0
	Current smoker	0.82 (0.47-1.43)	0.81 (0.46-1.41)	0.87 (0.49-1.53)	1.00 (0.56-1.79)
	Past smoker	0.97 (0.55-1.71)	0.96 (0.54-1.69)	1.01 (0.57-1.80)	1.01 (0.56-1.84)
	Alcohol, average dose, g/session:	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
	Education: Higher education (reference)	1.0		1.0	1.0
	Secondary education	0.91 (0.50-1.64)		1.02 (0.55-1.86)	1.02 (0.54-1.91)
	Professional education	1.46 (0.83-2.56)		1.62 (0.91-2.86)	1.70 (0.95-3.05)
	Primary education	0.63 (0.24-1.65)		0.71 (0.27-1.89)	0.76 (0.29-2.04)
	Family history of any cancer: No (reference)	1.0		1.0	1.0
	Yes	1.83 (1.11-3.00)		1.82 (1.11-2.99)	1.90 (1.14-3.17)
	BMI < 25 kg/m² (reference)	1.0			1.0
	≥25 kg/m²	1.31 (0.77-2.24)			1.17 (0.65-2.11)
	TG level <1.7 mmol/l(reference)	1.0			1.0
	≥1.7 mmol/l	1.22 (0.73-2.02)			1.03 (0.58-1.83)
	HT BP < 140/90 mmHg without treatment (reference)	1.0			1.0
	BP ≥ 140/90mmrtst or treatment	1.64 (0.97-2.77)			1.48 (0.86-2.55)
	Presence of type 2 diabetes <7.0 mmol/l and no history of diabetes (reference)	1.0			1.0
	≥ 7.0 mmol/l or history of diabetes	0.93 (0.42-2.02)			0.86 (0.38-1.94)

Note. In table 3-4: Model 0 – standardization by age. Models 1-3 are multi-variant.

family history of CRC, compared with all women without a family history of CRC, gradually decreases with age from 1.92 (95% CI:1.55–2.38) at 40-49 years to 1.06 (95% CI:0.67–1.69) at ≥80 years. A similar trend was observed in men in this study from 1.58 (95% CI:1.27–1.96) at 40-49 years to 0.54 (95% CI:0.29–1.06) at ≥80 years [7]. In our study, women with first-degree relatives with cancer of any localization did not have an increased risk of CRC. This may be partly explained by the study design: the family history reflects the presence of not only CRC but also any other cancer in first-degree relatives, which may make our data less specific, since some types of malignancies do not increase the risk of developing CRC. Newschaffer CJ et al. reported that women with previous breast cancer were 5% less likely to develop colon cancer and 13% less likely to develop rectal cancer than women in the general population [47]. Most likely, the result obtained in the work of Newschaffer CJ et al. reflects the known negative effect of estrogens on breast carcinogenesis [48] and a possible protective effect on the occurrence of CRC [40]. On the other hand, there is a study (meta-analysis) confirming a significant association between the presence of a family history of CRC or any type of cancer with CRC, increasing the risk of developing malignant neoplasms of this localization (OR=2.12; 95% CI:1.65-2.73) [8]. However, this meta-analysis presents an assessment of the risk only for individuals of both sexes, but not separately for men and women, which, in our opinion, is important in this situation, given the obvious sex differences in the incidence of CRC.

We also found a positive association between the risk of CRC and the presence of type 2 diabetes in women (table 4). Our results are partially confirmed by numerous studies; however, there are differences in the information available to date. In some meta-analyses, the risk of CRC was increased in both women and men with type 2 diabetes, but the degree of association in women in some studies was higher than in men, [29] in others, the association of CRC with diabetes was more pronounced in men [20] or the risk was approximately the same in both sexes [56]. A prospective study by Campbell PT, at al. [45] reported an increased risk of developing CRC only in male patients with type 2 diabetes, but not in female patients. Other studies noted an increased risk of developing CRC among women with type 2 diabetes, but not among men

Table 4

15-year risk of colorectal cancer in women, results of analysis of prognostic predictors in Cox regression models

	Covariates	Model 0	Model 1	Model 2	Model 3
HR (95%CI)	Age, years (for 1 year)		1,09(1,05-1,13)	1,09(1,06-1,14)	1,09(1,05-1,14)
	Smoking: Never smoked (reference)	1.0	1.0	1.0	1.0
	Current smoker	0.75 (0.27-2.12)	0.68 (0.24-1.95)	0.68 (0.24-1.94)	0.55 (0.17-1.83)
	Past smoker	0.93 (0.22-3.84)	0.90 (0.22-3.74)	0.90 (0.22-3.75)	0.97 (0.23-4.03)
	Alcohol, average dose, g/session:	1.01 (0.99-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)
	Education: Higher education (reference)	1.0		1.0	1.0
	Secondary education	0.89 (0.50-1.60)		0.89 (0.49-1.59)	0.89 (0.48-1.65)
	Professional education	1.03 (0.57-1.84)		1.03 (0.57-1.86)	1.10 (0.60-2.02)
	Primary education	0.89 (0.40-1.99)		0.89 (0.40-2.00)	0.94 (0.42-2.13)
	Family history of any cancer: No (reference)	1.0		1.0	1.0
	Yes	1.41 (0.88-2.26)		1.42 (0.89-2.27)	1.42 (0.88-2.30)
	BMI < 25 kg/m2 (reference)	1.0			1.0
	≥25 kg/m²	1.13 (0.73-1.76)			1.04 (0.64-1.67)
	TG level <1.7 mmol/l(reference)	1.0			1.0
	≥1.7 mmol/l	1.54 (0.98-2.40)			1.39 (0.86-2.25)
	HT BP < 140/90 mmHg without treatment (reference)	1.0			1.0
	BP ≥ 140/90mmrtst or treatment	1.13 (0.68-1.88)			1.03 (0.59-1.79)
	Presence of type 2 diabetes <7.0 mmol/l and no history of diabetes (reference)	1.0			
	≥ 7.0 mmol/l or history of diabetes	2.25 (1.29-3.91)			1.97 (1.10-3.53)

[42]. The degree of association between CRC and diabetes depends on the duration of the latter: according to some data, the risk of CRC decreases after 8 years of type 2 diabetes compared to individuals without type 2 diabetes, the maximum increase in the risk of CRC is observed in individuals with a duration of type 2 diabetes of less than 3 years [56]. According to other data, the risk of CRC decreases in individuals with a diabetes duration of 10 years or more, and individuals with a type 2 diabetes duration of 2 to 5 years, compared with diabetes duration of 5 to 10 years, in this study are most susceptible to an increased risk of CRC (HR=2.55; 95%, CI: 1.77-3.67) [55]. In addition, methods of diabetes therapy are important: taking metformin reduces the risk of CRC in diabetes [41], while insulin treatment, on the contrary, increases the risk of CRC [31].

In our study, we did not identify an association between colorectal cancer and such factors as smoking, alcohol intake, BMI, hypertension, education level, and TG levels. There are reported evidences that either confirm or refutes the connection of the above mentioned factors with CRC.

In one meta-analysis, colorectal cancer was significantly associated with smoking in both former and current smokers, but the association with smoking was greater in colorectal cancer. Also in this study, smoking increased the risk of CRC in men in both former and current smokers; in women, the risk of CRC was increased only for former smokers [15]. Another meta-analysis (based on EMRO Eastern Mediterranean studies) found a significant association between smoking and CRC (OR=1.40; 95% CI:1.11–1.78). However, subgroup analysis revealed a negative correlation between CRC and current smoking, although the association was not significant (OR=0.94; 95% CI:0.59–1.51). Former smoking increased the risk of developing CRC, but was also not statistically significant (OR=1.53; 95% CI:0.96–2.45) [10]. One study shows a significant increase in the risk of developing colon cancer in women who smoke regularly, but not in men [51]. In addition, an increased risk of CRC has been reported to be associated with the number of cigarettes smoked per day, longer smoking period, or higher number of packs per year [15, 54].

One meta-analysis provided strong evidence of an association between moderate (2–3 drinks/day or 12.6–49.9 g/day ethanol) and high (≥ 4 drinks/day or ≥ 50 g/day ethanol) alcohol consumption and risk development of colorectal cancer in both men and women. In addition,

light (1 drink/day or less than 12.5 g/day of ethanol) alcohol consumption in women was a protective factor, while in men it increased the risk of CRC, but in both cases the results were not significant. [5]. In another meta-analysis, the risk of CRC was increased only in men and only with high alcohol consumption (>42 g/day ethanol); light/moderate alcohol consumption (1.1–28 g/day ethanol) reduced the risk of CRC in women (OR=0.88; 95% CI:0.82-0.95), as well as in men (OR=0.96; 95% CI:0.88-1.05) [37].

In other data (case-control), moderate alcohol consumption (12-35 g/day ethanol) compared with light (less than 12 g/day ethanol) was associated with a significantly reduced likelihood of developing colorectal cancer in men and women; conversely, high alcohol consumption (>48 g/day ethanol) was associated with an increased risk of CRC in men (OR=3.45; 95% CI:1.35–8.83) but not in women (OR=3.40; 95% CI:0.50-22.92) [4]. In Korea, any alcohol consumption, including even one alcoholic drink per day, is associated with an increased risk of developing cancer of the esophagus, stomach and colorectal cancer, however, subgroup analysis showed a significant increase in the risk of colorectal cancer in men with light/moderate and heavy alcohol consumption; in women the risk was reduced insignificantly [52].

There are not many studies related to hypertension and an increased risk of CRC. One meta-analysis reported an increased risk of CRC in men with hypertension, but not in women, and there were no significant associations between systolic blood pressure or diastolic blood pressure and the risk of CRC [8]. An association between blood pressure and the risk of colorectal cancer in men was also found in the Me-Can study (RR=1.10; 95% CI:1.02–1.18) [38] In contrast, in the EPIC study (European Prospective Investigation into Cancer and Nutrition), Christakoudi S, at al. reported that diastolic blood pressure was positively associated with the risk of colon cancer in both men and women, and systolic blood pressure was positively associated with the risk of CRC in men only. [12]. At the moment, the connection between hypertension and colorectal cancer is difficult to explain and requires additional research.

Educational data are inconsistent: in some reports, people with a college degree or higher had a lower risk of developing CRC than those with elementary school completion or less [21], these data are consistent with another study showing that the overall incidence of CRC was significantly higher among people with low levels of education or living in areas of low socioeconomic status [49]. According to other data (EPIC study - European Prospective Study of Cancer and Nutrition), the risk of CRC, especially in the proximal colon, is lower in subjects with a lower level of education compared with those with a higher level of education. [22].

Most reviews, articles, and meta-analyses report a positive association of BMI with CRC [43, 32], but Nilsen TI, at al. did not find an association between BMI and the risk of developing CRC, which is consistent with our study [42].

Elevated TG levels in the Me-Can study (cohort study) were associated with an increased risk of CRC, but only in men: RR=1.17; 95% CI:1.06–1.28 [38]; in another cohort study, high TG levels increased the risk of CRC [50], but this study did not analyze separately for each sex. According to Aleksandrova K, at al. (2011) an increased level of serum TG does not lead to an increased risk of developing CRC [39].

Limitations of the study. The study has several limitations, it concerns the modest number of men and women with CRC identified over the 15-year follow-up period, however, the study included all new cases of CRC that occurred in the cohort (9360) over the study period (average 15 years of follow-up); this increases the likelihood that we have obtained a representative sample of typical CRC for the population.

Conclusions

1. In the cohort 45-69 years old, the 15-year risk of developing colorectal cancer was higher in men compared to women.

2. CRC risk was positively associated with age in men and women.

3. In men with a positive family history of malignant neoplasms of any location in first-degree relatives, the risk of colorectal cancer was increased.

4. The presence of type 2 diabetes mellitus was associated with an increased risk of CRC in women.

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References

1. Zlokachestvenny`e novoobrazovaniya v Rossii v 2020 godu (zabolevaemost` i smertnost`) [Malignant neoplasms in Russia in 2020 (morbidity and mortality). Edited by Kaprina A.D., Starinsky V.V., Shakhzadova. A.O. Moscow: Herzen Moscow Research Oncology Institute - Federal State Budgetary Institution National Medical Research Center of Radiology of the Ministry of Health of Russia, 2021. P. 252.

2. Higgins ST, et al. A literature review on prevalence of gender differences and intersections with other vulnerabilities to tobacco use in the United States, 2004-2014. *Prev Med.* 2015; 80: 89-100. doi: 10.1016/j.ypmed.2015.06.009.

3. Fuchs CS, et al. A prospective study of family history and the risk of colorectal cancer // *N Engl J Med.* 1994. №331(25). 1669-74. doi: 10.1056/NEJM199412223312501.

4. Kontou N, et al. Alcohol consumption and colorectal cancer in a Mediterranean population: a case-control study. *Dis Colon Rectum.* 2012; 55(6): 703-10. doi: 10.1097/DCR.0b013e31824e612a.

5. Fedirko V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol.* 2011; 22(9): 1958-1972. doi: 10.1093/annonc/mdq65

6. Feraco A, et al. Assessing gender differences in food preferences and physical activity: a population-based survey. *Front Nutr.* 2024; 11: 1348456. doi: 10.3389/fnut.2024.1348456

7. Jung YS, et al. Association between A Family History of Colorectal Cancer and the Risk of Colorectal Cancer: A Nationwide Population-Based Study. *J Pers Med*. 2022; 12(10): 1566. doi: 10.3390/jpm12101566.

8. Seretis A, et al. Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Sci Rep.* 2019; 9(1): 8565. doi: 10.1038/s41598-019-45014-4.

9. Zhang C, et al. Association between cardiovascular risk factors and colorectal cancer: A systematic review and meta-analysis of prospective cohort studies. *EClinicalMedicine.* 2021; 34: 100794. doi: 10.1016/j.eclinm.2021.100794.

10. Keivanlou MH, et al. Association between smoking and colorectal cancer in Eastern Mediterranean Regional Office (EMRO): A systematic review and meta-analysis. *Saudi J Gastroenterol.* 2023; 29(4): 204-211. doi: 10.4103/sjg.sjg_163_23.

11. Park JY, et al. Baseline alcohol consumption, type of alcoholic beverage and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition-Norfolk study. *Cancer Epidemiol.* 2009; 33(5): 347-54. doi: 10.1016/j.canep.2009.10.015.

12. Christakoudi S, et al. Blood pressure and risk of cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2020; 146(10): 2680-2693. doi: 10.1002/ijc.32576.

13. Oxentenko AS, et al. Body size and incident colorectal cancer: a prospective study of older women. *Cancer Prev Res (Phila)*. 2010; 3(12): 1608-20. doi: 10.1158/1940-6207

14. Pischon T, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* 2006; 98(13): 920-31. doi: 10.1093/jnci/djj246.

15. Tsoi KK, et al. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*. 2009; 7(6): 682-688.e1-5. doi: 10.1016/j.cgh.2009.02.016.

16. Benedix F, et al. Colon/Rectum Carcinomas (Primary Tumor) Study Group. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum.* 2010. №53(1). 57-64. doi: 10.1007/DCR.0b013e3181c703a4

17. CORI Research Project. Gender differences in colorectal polyps and tumors / McCashland T.M. [et al] // *Am J Gastroenterol*. 2001; 96(3): 882-6. doi: 10.1111/j.1572-0241.2001.3638_a.x.

18. David A.R., Zimmerman M.R. Cancer: an old disease, a new disease or something in between? *Nat Rev Cancer.* 2010; 10(10): 728-33. doi: 10.1038/nrc2914.

19. Peasey A, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: rationale and design of the HAPIEE study. *BMC Public Health.* 2006; 6: 255-264. doi: 10.1186/1471-2458-6-255.

20. Luo W, et al. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. *Colorectal Dis.* 2012; 14(11): 1307-12. doi: 10.1111/j.1463-1318.2012.02875.x.

21. Li L, et al. Educational level and colorectal cancer risk: the mediating roles of lifestyle and dietary factors. *Eur J Cancer Prev*. 2022; 31(2): 137-144. doi: 10.1097/CEJ.0000000000000697.

22. Leufkens AM, et al. Educational level and risk of colorectal cancer in EPIC with specific reference to tumor location. *Int J Cancer*. 2012; 130(3): 622-30. doi: 10.1002/ijc.26030.

23. Keivanlou MH, et al. Family history of cancer as a potential risk factor for colorectal cancer in EMRO countries: a systematic review and meta-analysis. *Sci Rep.* 2023; 13(1): 17457. doi: 10.1038/s41598-023-44487-8.

24. Friedewald W.T., Levy R.I., Fredrickson D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18(6): 499-502.

25. Wilsnack RW, et al. Gender and alcohol consumption: patterns from the multinational GENACIS project. *Addiction.* 2009; 104(9): 1487-500. doi: 10.1111/j.1360-0443.2009.02696.x.

26. Nguyen SP, et al. Gender as a risk factor for advanced neoplasia and colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2009; 7(6): 676-81.e1-3. doi: 10.1016/j.cgh.2009.01.008.

27. Global Cancer Observatory 2022. https://gco.iarc.fr/en

28. Rydén L, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur. Heart J. 2007; 28: 88–136. doi: 10.1093/eurheartj/ehl260.

29. Guraya S.Y. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J Gastroenterol.* 2015; 21(19): 6026-31. doi: 10.3748/wjg.v21.i19.6026.

30. Vuik FE, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut. 2019; 68(10): 1820-1826. doi: 10.1136/gutjnl-2018-317592.

31. Bu WJ, et al. Insulin therapy and the risk of colorectal cancer in patients with type 2 diabetes: a meta-analysis of observational studies. *Br J Clin Pharmacol*. 2014; 78(2):301-9. doi: 10.1111/bcp.12350.

32. Mandic M, et al. Is the association of overweight and obesity with colorectal cancer underestimated? An umbrella review of systematic reviews and meta-analyses. *Eur J Epidemiol.* 2023; 38(2): 135-144. doi: 10.1007/s10654-022-00954-6.

33. Johns L.E., Houlston R.S. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol*. 2001; 96(10): 2992-3003. doi: 10.1111/j.1572-0241.2001.04677.x.

34. Loomans-Kropp H.A., Umar A. Increasing Incidence of Colorectal Cancer in Young Adults. *J Cancer Epidemiol*. 2019; 11: 9841295. doi: 10.1155/2019/9841295.

35. Chen K, et al. Meta analysis of risk factors for colorectal cancer. *World J Gastroenterol*. 2003; 9(7): 1598-600. doi: 10.3748/wjg.v9.i7.1598.

36. Johnson CM, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control.* 2013; 24(6): 1207-22. doi: 10.1007/s10552-013-0201-5.

37. McNabb S, et al. Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. *Int J Cancer.* 2020; 146(3): 861-873. doi: 10.1002/ijc.32377.

38. Stocks T, et al. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can). *Cancer.* 2011; 117(11): 2398-2407. doi: 10.1002/cncr.25772.

39. Aleksandrova K, et al. Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancerand Nutrition Study. *Cancer Prevention Research.* 2011; 4(11):1873-1883. doi: 10.1158/1940-6207.capr-11-0218.

40. Barzi A, et al. Molecular pathways: Estrogen pathway in colorectal cancer // *Clin Cancer Res.* 2013; 19(21): 5842-8. doi: 10.1158/1078-0432.CCR-13-0325.

41. Nie Z., Zhu H., Gu M. Reduced colorectal cancer incidence in type 2 diabetic patients treated with metformin: a meta-analysis. *Pharm Biol.* 2016; 54(11): 2636-2642. doi: 10.1080/13880209.2016.1176057.

42. Nilsen T.I., Vatten L.J. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br J Cancer.* 2001; 84(3): 417-22. doi: 10.1054/bjoc.2000.1582.

43. Ma Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. *PLoS One.* 2013; 8(1): e53916. doi: 10.1371/journal.pone.0053916.

44. Taylor DP, et al. Population-based family history-specific risks for colorectal cancer: a constellation approach. *Gastroenterology.* 2010; 138(3): 877-85. doi: 10.1053/j.gastro.2009.11.044.

45. Campbell PT, et al. Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. *Gastroenterology*. 2010; 139(4): 1138-46. doi: 10.1053/j.gastro.2010.06.072.

46. Lewandowska A, et al. Risk Factors for the Diagnosis of Colorectal Cancer. *Cancer Control.* 2022; 29: 10732748211056692. doi: 10.1177/10732748211056692

47. Newschaffer CJ, et al. Risk of colorectal cancer after breast cancer. *Lancet.* 2001; 357(9259): 837-40. doi: 10.1016/S0140-6736(00)04197-0

48. Key TJ, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol.* 2013; 14(10): 1009-19. doi: 10.1016/S1470-2045(13)70301-2.

49. Doubeni CA, et al. Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study. *Cancer.* 2012; 118(14): 3636-44. doi: 10.1002/cncr.26677.

50. Hsu SH, et al. The Association between Hypertriglyceridemia and Colorectal Cancer: A Long-Term Community Cohort Study in Taiwan. *Int J Environ Res Public Health.* 2022; 19(13): 7804. doi: 10.3390/ijerph19137804.

51. Parajuli R, et al. The increased risk of colon cancer due to cigarette smoking may be greater in women than men. *Cancer Epidemiol Biomarkers Prev*. 2013; 22(5): 862-71. doi: 10.1158/1055-9965.EPI-12-1351.

52. Choi YJ, et al. The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: A nationwide population-based cohort study of South Korea. *PLoS One.* 2017; 12(10): e0185778. doi: 10.1371/journal.pone.0185778.

53. Peeters PJ, et al. The risk of colorectal cancer in patients with type 2 diabetes: associations with treatment stage and obesity. *Diabetes Care.* 2015; 38(3): 495-502. doi: 10.2337/dc14-1175.

54. Zhao J, et al. Tobacco smoking and colorectal cancer: a population-based case-control study in Newfoundland and Labrador. *Can J Public Health*. 2010; 101(4):281-9. doi: 10.1007/BF03405287.

55. Lawler T, et al. Type 2 Diabetes and Colorectal Cancer Risk. *JAMA Netw Open*. 2023; 6(11): e2343333. doi: 10.1001/jamanetworkopen.2023.43333.

56. Yang Y.X., Hennessy S., Lewis J.D. Type 2 diabetes mellitus and the risk of colorectal cancer. *Clin Gastroenterol Hepatol.* 2005; 3(6): 587-94. doi: 10.1016/s1542-3565(05)00152-7.

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THE RATIO OF CAPILLARY AND VENOUS PERIPHERAL BLOOD, ASSESSMENT OF THEIR CHANGES AFTER SHORT-TERM COOLING

A comparative analysis of capillary and venous blood parameters in practically healthy people before and after general cooling was carried out. It has been established that in capillary blood a higher level of leukocytes is provided mainly by mature forms of monocytes, neutrophils, eosinophils and basophils. There were no significant differences in the level of lymphocytes. The response to cooling, depending on the hematological test, is an increase in the circulating pool of leukocytes in capillary blood due to increased cell migration and activation of lymphocyte recycling, and in venous blood - an increase in the output of neutrophils from the depot. Red blood cells in capillary blood have a large degree of variation in size. After cooling, erythrocyte indices of capillary and venous blood have the same tendency to increase, with a higher rate of increase in the capillary sample, which may reflect their importance in the regulation of the homeostasis of small vessels during cooling. In capillary blood the level of platelets is lower, but their population is more heterogeneous and the content of large cells is higher. With general cooling, platelet parameters, regardless of the hematological test, did not change significantly. Thus, changes in the composition of venous blood reflect the classic response to stress with an increase in the level of segmented neutrophils. Changes in capillary blood parameters are aimed at maintaining the homeostasis of small vessels, increasing the pool of functionally active and recirculating cells that provide an effective response to antigenic influence.

Keywords: capillary blood, venous blood, leukogram, hemogram, general cooling, adaptation.

Introduction. A complete blood count is the most commonly performed test needed to evaluate a patient's condition. Capillary blood is usually used as an alternative to venous blood when conducting general clinical analysis on hematology analyzers. However, there are a number of differences in the determined indicators of these types of blood. Capillary blood has a higher average hemolysis index, which must be taken into account if the analysis is not performed within 24 hours after blood collection (8,26). In addition, it has been shown that the thin aperture of the hematology analyzer (75 micron capillary) can become clogged with epithelial destruction products and other tissue fragments when taking capillary blood, which are automatically counted as blood cells, distorting the actual picture (2). Venous and capillary blood serum cannot be interchangeable when assessing the concentration of lipids and lipoproteins, the levels of which are significantly lower in capillary blood (12). Comparative studies of the content of potassium, chloride, sodium, calcium, phosphorus, creatinine, total protein, urea, bilirubin, AST, ALAT, LD, insulin, thyroxine, thyroid-stimulating hormone (TSH), glucose in the serum of venous and capillary blood (8, 13, 18, 21, 29). In addition, these indicators change significantly under the influence of physical activity, stress, etc. [27, 28]. Assessment of the levels of erythrocyte, platelet and leukocyte indicators of venous and capillary blood is also very controversial, although it is generally accepted that differences in indicators are not clinically significant (6, 11, 14, 15). According to most sources, the number of platelets in venous blood exceeds their content in capillary blood (1, 2, 3, 5, 24). This may be due to the activation of tissue platelet aggregation factors released when finger tissue is pierced. In addition, in the tissue fluid there is a high titer of antibodies mediating binding to the surface glycoproteins of the platelet in the presence of an anticoagulant such as EDTA (1, 2, 11). A feature of capillary endothelial cells is the high expression of HLA-DRII molecules and adhesion molecules, which allows them to actively capture, adhere and infiltrate immune cells [25]. The number of red blood cells in capillary blood is higher according to data (1, 5, 24). Other studies have shown that the content of red blood cells, hemoglobin, lymphocytes, neutrophils and hematocrit of venous blood is slightly lower than or equal to their number in capillary blood (2, 10). The level of hemoglobin and hematocrit of capillary blood is higher than that of venous blood according to data (1, 2, 5, 24). Assessment of hemoglobin in capillary blood is not recommended when diagnosing anemia, because indicators are often underestimated compared to venous blood, which leads to a false diagnosis [23]. There is evidence that blood parameters related to red blood cells are more stable than those related to leukocytes or platelets (10). According to some data, the level of leukocytes in capillary blood is higher (1, 2, 5, 24). Detected differences in the content of leukocyte and erythrocyte parameters in capillary and venous blood may be the result of immediate local accumulation of leukocytes upon stimulation of skin puncture, as well as due to the absence of an additional amount of tissue fluid in capillary blood samples, which affects the ratio of liquid and cellular components of hematological samples (2). The level of leukocytes in the blood changes dynamically under the influence of various factors, such as physical activity, stress, changes in diet, influence of climatic conditions, etc. We have previously shown that after general short-term cooling, 3 response options are formed on the part of lymphocytes, which is manifested in maintaining their level, reducing, or increasing their number in circulation in the venous blood (4). Small peripheral vessels are primarily ex-

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posed to low temperatures, their spasm occurs, cell aggregation, their migration and functional activity changes, which determines dynamic changes in blood parameters aimed at maintaining the homeostasis of the body. Assessment of the background level and changes in leukocyte, erythrocyte and platelet parameters in different hematological samples during short-term general cooling will allow us to determine the features and correlation of the formation of adaptive reactions, which is necessary when studying the influence of stress factors and interpreting the results when using different hematological samples. Knowledge of the ratio of reactions in capillary and venous blood under normal conditions, with pathology or the influence of some external factors is necessary, because Capillary sampling has recently been increasingly considered as an alternative to venous sampling due to greater accessibility, less discomfort for the patient, and the possibility of more frequent and faster sample collection and analysis.

Aim. To conduct a comparative analysis of adaptive changes in leukocyte, erythrocyte and platelet parameters of capillary and venous blood after general short-term cooling in practically healthy people.

Abbreviations: WBC - leukocytes, RBC - erythrocytes, HGB - hemoglobin, HCT - hematocrit, MCV - average erythrocyte volume, MCH - average hemoglobin content in an erythrocyte, MCHC - erythrocyte hemoglobin saturation, RDW-SD - erythrocyte distribution index, RDV-CV - degree of deviation of red blood cell size from normal, PLT - platelets, PDW - platelet distribution width, MPV - mean platelet volume, P-LCR - percentage of large platelets, PCT - thrombocrit.

Materials methods. A study of hematological and immunological parameters was carried out in 212 practically healthy people of working age before and immediately after general cooling for 5 minutes in a cold chamber (USHZ-25N, Russia) at -25°C. The volunteers wore cotton clothes under constant video surveillance, did not have any acute or exacerbation of chronic diseases during the study period, and had not previously or currently engaged in hardening. Blood was collected by qualified medical personnel before and immediately after being in the cold chamber from the cubital vein into Vaccuette vacuum tubes with EDTA to obtain plasma and conduct hematological studies; with a blood clotting activator to produce serum. Serum and plasma were separated by centrifugation. The samples were frozen once at a temperature of minus 20°C. The leukogram and hemogram were determined using a hematology analyzer XS-1000i (Sysmex, Japan). In blood smears stained according to Romanovsky-Giemsa on a Nikon HemaVision microscope at immersion magnification ×40, a lymphocytogram was studied according to the method of Kassirsky I.A., with determination of the content of large (more than 12 μm), medium (from 8 to 12 μm) and small (up to 8 μm) lymphocytes; monocytogram according to O.P. Grigorova's method, with differentiation of mononuclear cells into promonocytes, monocytes and polymorphonuclear cells; a neutrogram with a count of up to 100 neutrophilic leukocytes, among which cells with 1, 2, 3, 4, 5 or more nuclear segments were isolated. The research results were processed using the Statistica 6.0 application package (StatSoft, USA). To check the data for normality of distribution, the Shapiro–Wilk normality test was used. The median (Me) and 25–75 percentiles were used to describe the data. The statistical significance of differences was determined using the nonparametric Wilcoxon T-test. The critical significance level (p) when testing statistical hypotheses was taken equal to 0.05. To assess the rate of change in indicator levels, growth and loss rates were calculated.

Research results and discussion. A comparative analysis of venous and capillary blood parameters before general cooling is presented in Table 1. No significant differences were established in the levels of erythrocytes, HGB, MCH, MCHC and lymphocytes. When studying the lymphocytogram, it was shown that in venous blood the content of large forms of lymphocytes is higher, the levels of small and medium lymphocytes do not differ significantly. In capillary blood, such indicators as HCT, MCV, RDW-SD, RDW-CV, PDW, MPV, P-LCR are higher. The average level of leukocytes, eosinophils, basophils, monocytes and neutrophils is also higher in capillary blood. A higher level of neutrophils in capillary blood is provided by mature segmented cells with two, three and four nuclear segments. The monocytogram of capillary blood is characterized by a higher content of mature monocytes and polymorphonuclear cells.

A comparative analysis of changes in venous and capillary blood parameters after general short-term cooling was carried out. It was found that the number of leukocytes in venous blood increases from 5.13 (4.13 – 6.14) to 5.46 (4.06 – 6.52) × 10^9 cells/l (p = 0.006), in capillary blood – from 5 .55 (4.74 – 6.57) to 6.07 (5.00 – 7.36) ×10^9 cells/l (p=0.001). To assess the dynamics of changes in capillary and venous blood parameters, the rates of growth and loss of leukocytes were calculated. It was determined that the rate of increase in the number of leukocytes in capillary blood was actually 3 times higher and amounted to 9.4%, versus 3.61% in venous blood.

Changes in neutrophil levels. In capillary blood, the total number of neutrophils increases from 2.86 (2.15 – 3.59) to 3.15 (2.34 – 4.09) × 10^9 cells/l (p = 0.001), without a significant change in the level of band cells concentration which before and after general cooling were 0.20 (0.09 – 0.28) and 0.18 (0.10 – 0.26) × 10^9 cells/l, respectively. An increase in the content of segmented neutrophils was recorded from 2.82 (2.14 – 3.45) to 3.06 (2.31 – 3.38) × 10^9 cells/l (p = 0.027). When studying the structure of the segmentogram, an increase in the number of cells with 2, 3 and 4 nuclear segments was established (Table 2). In venous blood, the level of neutrophils also significantly increases from 2.46 (2.00 – 3.19) to 2.89 (2.09 – 3.72) × 10^9 cells/l (p = 0.001), without changing the level of band cells (0.18 (0.09 – 0.29) and 0.18 (0.10 – 0.32) ×10^9 cells/l) and with an increase in the number of segmented neutrophils from 2.27 (1.78 – 2.98) to 2.62 (1.90 – 3.44) ×10^9 cells/l (p=0.001). In the structure of the segmentogram, the number of cells with 2, 3 and 4 nuclear segments increases.

Despite the same dynamics of changes in the circulation of neutrophils, the growth rates vary significantly. In capillary blood, the growth rate of the total number of neutrophils was 10.1%, segmented cells – 9.65%; in venous blood, the growth rate for neutrophils was 17.8%, for segmented forms – 15.4%. A more active increase in the number of neutrophils and their segmented forms in the venous blood is a classic reaction to an irritating factor and may be associated with the release of cells from the depot in response to stress, because such a short period of influence of a negative factor eliminates the possibility of cell accumulation due to activation of proliferation. However, chronic exposure to a stress factor affects the functional activity of neutrophils, with the activation of their formation of neutrophil traps, which significantly changes the microenvironment and the likelihood of damage to surrounding tissues, which is more clearly manifested in pathological conditions [9, 20].

Changes in monocyte levels. There was no change in the level of monocytes in venous blood (0.43 (0.30 – 0.56) ×10^9

Table 1

Indicators of venous and capillary blood before general cooling, Me (25-75)

Indicator name	Capillary blood, n=212	Venous blood, n=212	The level of significance of the differences, p
WBC (leucocyte), 10^9 cells/liter	5.55 (4.74 – 6.57)	5.13 (4.13 – 6.14)	0.002
RBC (erythrocyte), 10^{12} cells/liter	4.61 (4.28 – 4.96)	4.58 (4.22– 4.90)	-
HGB (hemoglobin), grams/liter	137 (126 – 150)	136 (124 – 143)	-
HCT (hematocrit), %	40.3 (38.0 – 44.5)	39.1 (36.8 – 42.3)	0.029
MCV (average volume erythrocyte), femtoliter	88.1 (85.2 – 92.1)	86.3 (82.6 – 90.0)	-
MCH (the average hemoglobin content in the erythrocyte), picograms	29.8 (28.7– 31.2)	29.3 (28.4 – 30.5)	-
MCHC (saturation of erythrocytes with hemoglobin) , grams/liter	338 (329 – 344)	340 (332 – 349)	-
RDW-SD (distribution index of erythrocytes), femtoliter	41.8 (39.5 – 44.4)	39.8 (37.5 – 42.3)	0.018
RDW-CV (the degree of deviation of the size of erythrocytes from the normal), %	13.3 (12.6 – 14.1)	12.9 (12.4 – 13.6)	0.001
PLT (thrombocyte), 10^9cells/liter	192 (161 – 239)	228 (181 – 266)	0.001
PDW (thrombocytes distribution width), %	15.1 (13.5 – 16.6)	13.9 (12.7 – 15.7)	0.001
MPV (average thrombocytes volume), femtoliter	11.5 (10.7 – 12.2)	10.9 (10.3 – 11.6)	0.001
P-LCR (percentage of the content of large thrombocytes), %	37.5 (31.3 – 42.9)	33.3 (29.0 – 39.0)	0.001
PCT (thrombocrit), %	0.22 (0.18 – 0.27)	0.25 (0.22 – 0.29)	0.001
Eosinophils 10^9 cells/liter	0.14 (0.09 –0.20)	0.11 (0.06 – 0.17)	0.001
Basophils, 10^9 cells/liter	0.04 (0.02 – 0.11)	0.02 (0.01 – 0.03)	0.001
Neutrophils and segmentogram			
Neutrophils, 10^9 cells/liter	2.86 (2.15 – 3.59)	2.63 (2.04 – 3.34)	0.013
Rod-shaped neutrophils 10^9 cells/liter	0.20 (0.09 – 0.28)	0.18 (0.09 – 0.29)	-
Segmented neutrophils, 10^9 cells/liter	2.82 (2.14 – 3.45)	2.27 (1.78 – 2.98)	0.005
Neutrophils with 2 core segments, 10^9 cells/liter	0.94 (0.59 – 1.23)	0.74 (0.55 – 1.03)	0.001
Neutrophils with 3 core segments, 10^9 cells/liter	1.27 (1.00 – 1.60)	0.95 (0.73 – 1.31)	0.031
Neutrophils with 4 core segments, 10^9 cells/liter	0.57 (0.37 – 0.81)	0.39 (0.25 – 0.56)	0.001
Neutrophils with 5 core segments, 10^9 cells/liter	0.07 (0.04 – 0.11)	0.06 (0.03 – 0.11)	-
Lymphocytes and lymphocytogram			
Lymphocytes, 10^9 cells/liter	1.79 (1.21– 2.15)	1.80 (1.36 – 2.26)	-
Small lymphocytes, 10^9 cells/liter	1.10 (0.79 – 1.43)	1.10 (0.79 – 1.59)	-
Average lymphocytes, 10^9 cells/liter	0.54 (0.40 – 0.74)	0.56 (0.39 – 0.73)	-
Large lymphocytes, 10^9 cells/liter	0.14 (0.11 – 0.20)	0.18 (0.12 – 0.25)	0.005
Monocytes and monocytogram			
Monocytes, 10^9 cells/liter	0.53 (0.43 – 0.64)	0.43 (0.30 – 0.56)	<0.001
Promonocytes, 10^9 cells/liter	0.14 (0.01 – 0.24)	00.14 (0.09 – 0.22)	-
Monocytes, 10^9 cells/liter	0.230 (0.162 – 0.337)	0.135 (0.078 – 0.224)	<0.001
Polymorphonuclear monocytes, 10^9 cells/liter	0.07 (0.05 – 0.10)	0.04 (0.03 – 0.06)	<0.001

cells/l – before general cooling and 0.44 (0.28 – 0.58) ×10^9 cells/l – after). There were also no significant differences in the structure of the monocytogram. The number of promonocytes was 0.14 (0.09 – 0.22) and 0.14 (0.08 – 0.25) ×10^9 cells/l, respectively, before and after cold exposure; mature monocytes – 0.14 (0.08 – 0.22) and 0.12 (0.07 – 0.23) ×10^9 cells/l; polymorphonuclear – 0.05 (0.03 – 0.06) and 0.04 (0.02 – 0.06) ×10^9 cells/l. In capillary blood, the content of monocytes significantly increases from 0.57 (0.46 – 0.82) to 0.65 (0.49 – 0.88) × 10^9 cells/l (p = 0.001). Assessing the structure of the monocytogram, we can say that the increase in the total level of monocytes occurs primarily due to promonocytes (0.14 (0.01 – 0.24) – before cooling and 0.16 (0.01 – 0.26) × 10^9 cells/l – after cooling, p=0.021). The content of mature monocytes and polymorphonuclear forms does not actually change and amounts to 0.23 (0.16 – 0.34) and 0.25 (0.16 – 0.35) ×10^9

cells/l, respectively; 0.07 (0.05 – 0.10) and 0.07 (0.05 – 0.10) ×10^9 cells/l. An increase in the number of monocytes in capillary blood indicates the need for these cells to enter tissues to participate in adaptive processes. Considering the absence of venous blood monocyte levels in the dynamics, it can be assumed that the increase in the number of cells occurs due to the active migration of cells into smaller vessels from the parietal pool of larger vessels, and not due to the circulating part of the population. Prolonged and chronic exposure to a stress factor through increased levels of glucocorticoids activates the trafficking of monocytes from the spleen, and their level in the circulation exceeds the rate of release into the tissue [7].

Changes in the level of lymphocytes. In both capillary and venous blood, the absolute number of lymphocytes does not change significantly. In capillary blood, the content of lymphocytes was 1.80 (1.21 – 2.15) – before cooling and 1.74 (1.32 – 2.19) × 10^9 cells/l – after; in the venous – 2.02 (1.42 – 2.58) and 1.90 (1.46 – 2.47) ×10^9 cells/l, respectively. A decrease in the relative levels of lymphocytes was established: in venous blood from 39 (32.5 – 46.0) to 36.0 (30.0 – 43.1) % (p = 0.001); in the capillary – 30.3 (24.2 – 35.3) to 28.2 (23.1 – 34.8) × 10^9 cells/l (p = 0.001). Assessing the structure of the lymphocytogram, it was shown that in capillary blood the number of small forms of lymphocytes increases, with a decrease in medium and large forms (Table 3). The same trend is recorded in venous blood.

The rate of decrease in the level of lymphocytes in capillary blood was lower and amounted to -6.9%, in venous blood this figure was -7.7%. Despite the similar dynamics in the structure of lymphocytograms, the rates of increase and decrease indicate a more rapid increase in the number of small forms of lymphocytes in capillary blood (growth rate of 11.9% versus 5% in venous blood) and a slower decrease in medium and large forms of lymphocytes (rate of decrease -15.1% and -10.3% – in capillary blood; -24.9% and -28.0% – in venous blood). Small lymphocytes represent the main population of recirculating long-lived cells, i.e. an increase in their level in capillary blood indicates the participation of this part of lymphocytes in maintaining homeostasis when exposed to low temperatures with their subsequent migration to lymph nodes and organs for antigen-stimulated differentiation and proliferation [16]. A decrease in the number of large and medium-sized lymphocytes probably occurs due to an increase in their adhesion and transition to the parietal pool. It is known that large and medium-sized lymphocytes for the most part do not recirculate, but migrate to the lamina propria of the small intestine, where they are transformed into plasma cells.

Table 2

Structure of the neutrogram before and immediately after short-term general cooling, Me(25-75)

Indicator of name	Before short-term general cooling	After short-term general cooling	The level of significance of the differences, p
Capillary blood			
Neutrophils with 2 core segments, 10^9 cells/liter	0.94 (0.59 – 1.23)	1.03 (0.75 – 1.58)	0.025
Neutrophils with 3 core segments, 10^9 cells/liter	1.27 (0.99 – 1.61)	1.50 (1.18 – 2.03)	0.001
Neutrophils with 4 core segments, 10^9 cells/liter	0.57 (0.37 – 0.81)	0.65 (0.41 – 0.920)	0.001
Neutrophils with 5 core segments, 10^9 cells/liter	0.07 (0.04-0.11)	0.09 (0.06-0.13)	0.060
Capillary blood			
Neutrophils with 2 core segments, 109 cells/liter	0.74 (0.55 – 1.03)	0.80 (0.54 – 1.18	0.046
Neutrophils with 3 core segments, 109 cells/liter	0.95 (0.73 – 1.32)	1.06 (0.72 – 1.44)	0.002
Neutrophils with 4 core segments, 109 cells/liter	0.39 (0.25 – 0.56)	0.42 (0.27 – 0.67)	0.001
Neutrophils with 5 core segments, 109 cells/liter	0.06 (0.03-0.11)	0.06 (0.04-0.14)	0.146

Table 3

Structure of the lymphocytogram before and immediately after short-term general cooling, Me(25-75)

Indicator of name	Before short-term general cooling	After short-term general cooling	The level of significance of the differences, p
Capillary blood			
Small lymphocytes, 10^9 cells/liter	1.01 (0.79 – 1.43)	1.23 (0.86 – 1.54)	0.001
Average lymphocytes, 10^9 cells/liter	0.54 (0.41 – 0.73)	0.46 (0.34 – 0.64)	0.006
Large lymphocytes, 10^9 cells/liter	0.14 (0.11 – 0.20)	0.12 (0.07 – 0.20)	0.025
Venous blood			
Small lymphocytes, 10^9 cells/liter	1.10 (0.79 – 1.60)	1.15 (0.87 – 1.62)	0.036
Average lymphocytes, 10^9 cells/liter	0.56 (0.39 – 0.73)	0.42 (0.28 – 0.64)	0.001
Large lymphocytes, 10^9 cells/liter	0.18 (0.12 – 0.25)	0.13 (0.09 – 0.18)	0.001

Changes in the level of eosinophils and basophils. In capillary blood, the content of eosinophils increases from 0.16 (0.10 – 0.25) to 0.32 (0.16 – 1.00) × 10^9 cells/l (p = 0.019), without a significant change in the level of basophils (0. 04 (0.02 – 0.11) and 0.04 (0.02 – 0.09) ×10^9 cells/l). In venous blood, the content of eosinophils decreases from 0.11 (0.06 - 0.17) to 0.10 (0.06 - 0.17) × 10^9 cells/l (p = 0.002) also without a change in the level of basophils (0. 02 (0.01 – 0.03) and 0.02 (0.01 – 0.04) ×10^9 cells/l). Thus, it has been shown that changes in the size of the basophil population are little susceptible to short-term cold influences. An increase in the level of eosinophils is associated with the need for the participation of these effector cells in the formation of innate immune responses in response to adrenergic stimuli [17, 19]. However, an excessive increase in eosinophils can lead to their aggregation, blockage of small vessels and tissue ischemia.

Changes in platelet levels and platelet parameters. After general short-term cooling, no significant changes in the

level of platelets and platelet parameters were found, either in venous or capillary blood (Table 4). Thus, it can be assumed that platelet parameters in practically healthy people are more stable and less susceptible to the influence of short-term exposure to low temperatures.

Changes in the level of red blood cells and erythrocyte parameters. In capillary and venous blood, similar reactions from erythrocytes and erythrocyte parameters are recorded (Table 5). Increased levels of red blood cells (RBC), hemoglobin (HGB) and hematocrit (HCT) were found. The rate of increase in indicators in capillary blood was higher than in venous blood and amounted to 2.80 and 1.74% for RBC, 2.20 and 1.41% for HGB, and 1.70 and 1.29% for NCT, respectively. Red blood cells are involved in the regulation of endothelial dysfunction by altering the balance between levels of nitric oxide (NO) and reactive oxygen species to prevent the induction of vascular oxidative stress [22]. Thus, an increase in the number of erythrocytes in practically healthy individuals during short-term general cooling can be considered as a positive adaptive reaction that ensures the maintenance of vascular homeostasis.

Conclusion. The background levels of venous and capillary blood parameters in practically healthy people living in the North differ somewhat, but are within the physiological norm. Red blood cells of capillary blood have a large degree of variation in size and the degree of deviation of their sizes from normal. After general cooling, erythrocyte indicators such as RBC, HGB and HCT have the same tendency to increase, but in capillary blood a higher rate of increase is recorded, which may indicate their importance in regulating the maintenance of homeostasis of small vessels during cooling. The total number of platelets is higher in venous blood, while in capillary blood the platelet population is more heterogeneous and the content of large cells is higher. During cooling, the levels of platelets and platelet parameters are more stable and do not change significantly in both capillary and venous blood. It has been shown that in capillary blood there is a higher level of leukocytes mainly due to mature forms of monocytes, neutrophils, eosinophils and basophils. This distribution is probably due to the fact that these cells exhibit the main functional activity in tissues and it is in the capillary pool that there are cells ready to respond to antigens. In response to general short-term cooling, regardless of the hematological test, adaptive reactions are recorded with an increase in the total level of leukocytes. At the same time, in capillary blood a more rapid replenishment of this pool occurs mainly due to small forms of lymphocytes, promonocytes and eosinophils, while in venous blood the increase in the number of leukocytes is supported by an increase in the content of segmented neutrophils. Thus, it has been shown that even short-term stress leads to changes in the cellular composition of capillary and venous blood, reflecting increased reactions of cell release from the depot, maintenance of vascular homeostasis, migration of leukocytes from larger vessels to small ones and activation of lymphocyte recycling.

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Table 4

Changes in platelet levels and platelet parameters before and immediately after short-term general cooling, Me (25-75)

Name of indicator	Before general cooling	After general cooling	Level of significance of differences, p
Capillary blood			
PLT, 10^9 cells/liter	192 (161.0 - 239.0)	208.5 (162.0 - 247.0)	0.133
PDW, %	15.10 (13.50 - 16.60)	15.3 (13.2 - 16.8)	0.340
PCT, %	0.22 (0.18 - 0.27)	0.230 (0.200 - 0.280)	0.368
MPV, femtoliter	11.5 (10.7 – 12.2)	11.4 (10.7 – 12.1)	0.239
P-LCR, %	37.5 (31.3 – 42.9)	37.1 (30.8 – 42.5)	0.081
Venous blood			
PLT, 10^9 cells/liter	228 (181 – 266)	230 (181 – 275)	0.488
PDW, %	13.9 (12.7 – 15.7)	14.1 (12.6 – 15.4)	0.324
PCT, %	0.25 (0.22 - 0.29)	0.260 (0.210 - 0.290)	0.132
MPV, femtoliter	10.9 (10.3 – 11.6)	10.9 (10.3 – 11.5)	0.114
P-LCR, %	33.3 (29.0 – 39.0)	33.6 (28.7 –38.5)	0.115

Table 5

Changes in the level of erythrocytes and erythrocyte parameters before and immediately after short-term general cooling, Me(25-75)

Name of indicator	Before general cooling	After general cooling	Level of significance of differences, p
Capillary blood			
RBC, 10^{12} cells/liter	4.61(4.28-4.96)	4.74(4.28-5.10)	0.022
HGB, grams/liter	137(126-150)	140(126-153)	0.020
HCT, %	40.3(38-44.5)	41(38.6-45.4)	0.022
MCV, femtoliter	88.1(85.2-92.1)	88.3(85.8-92.2)	0.042
MCH, picograms	29.8(28.7-31.2)	29.7(28.7-31.1)	0.450
MCHC, grams/liter	338(329-344)	325(335-344)	0.065
RDW-SD, femtoliter	41.8(39.5-44.4)	41.7(39.6-44.5)	0.937
RDV-CV, %	13.3(12.6-14.1)	13.2(12.6-14.1)	0.775
Venous blood			
RBC, 10^{12} cells/liter	4.58 (4.22 – 4.90)	4.64 (4.35 – 5.02)	0.001
HGB, grams/liter	136 (124 – 143)	138 (127 – 146)	0.005
HCT, %	39.1 (36.8 – 42.3)	39.7 (37.6 – 42.2)	0.014
MCV, femtoliter	86.3(82.6-90.0)	86.1(82.4-89.9)	0.007
MCH, picograms	29.3(28.4-30.5)	29.3(28.3-30.5)	0.828
MCHC, grams/liter	340 (332 – 349)	341 (335 – 349)	0.153
RDW-SD, femtoliter	39.8(37.5-42.3)	39.8(37.7-42.2)	0.367
RDV-CV, %	12.9(12.4-13.6)	12.9(12.4-13.7)	0.075

References

1. Mingacheva A.A., Gergel N.I., Kosov A.I., Kudinova E.V., Karslyan L.S., Kosyakova Yu.A. Gematologicheskie pokazateli klinicheski zdorovyh lic [Hematological indicators of health of healthy people]. Medicinskij al'manah. [Medical almanac. 2011. No. 3(16). P. 175-176 (In Russ.).]

2. Mingacheva A.A., Maksimov A.B., Zimanova O.G., Babichev A.V., Baisheva G.M., Pervova Yu. IN. K voprosu ob optimizacii raboty KDL: sravnitel'naya ocenka pokazatelej venoznoj i kapillyarnoj krovi [On the issue of optimizing the work of CDL: comparative assessment of venous and capillary blood parameters]. Remedium Privolzh'e [Remedium Volga region. 2014. P. 33-35 (In Russ.).]

3. Mingacheva A.A. Sravnitel'naya ocenka formennyh elementov venoznoj i kapillyarnoj krovi [Comparative assessment of the formed elements of venous and capillary blood]. Aspirantskij vestnik Povolzh'ya [Postgraduate Bulletin of the Volga region. 2011; 1-2: 193-194 (In Russ.).]

4. Patrakeeva V.P., Samodova A.V. Vliyanie kratkovremennogo obshchego ohlazhdeniya na migraciyu, recirkulyaciyu i energeticheskij resurs immunokompetentnyh kletok periphericheskoj krovi cheloveka [The influence of short-term general cooling on the migration, recycling and energy resource of immunocompetent cells of human peripheral blood]. Vestnik Ural'skoj medicinskoj akademicheskoj nauki [Bulletin of the Ural Medical Academic Science. 2017; 14 (4): 362-368 (In Russ.).] DOI: 10.22138/2500-0918-2017-14-4-362-368)

5. Daae LN, Halvorsen S, Mathisen PM, Mironska KA. Comparison between haematological parameters in 'capillary' and venous blood from healthy adults. Scand J Clin Lab Invest. 1988; 48(7): 723-6. doi:10.1080/00365518809085796.

6. Bates-Fraser LC, Moertl KM, Stopforth CK, Bartlett DB, Ondrak KS, Jensen BC, Hanson ED. A practical approach for complete blood count analysis following acute exercise: Capillary vs. venous blood sampling. Advanced Exercise and Health Science. 2024; 1(1): 43-50. https://doi.org/10.1016/j.aehs.2024.01.002

7. M. van de Wouw, et al. Acute stress increases monocyte levels and modulates receptor expression in healthy females. Brain, Behavior, and Immunity. 2021; 94: 463-468. https://doi.org/10.1016/j.bbi.2021.03.005

8. Maroto-García J, Deza S, Fuentes-Bullejos P, Fernández-Tomás P, Martínez-Espartosa D, Marcos-Jubilar M, Varo N, González Á. Analysis of common biomarkers in capillary blood in routine clinical laboratory. Preanalytical and analytical comparison with venous blood. Diagnosis (Berl). 2023; 10(3): 281-297. doi: 10.1515/dx-2022-0126.

9. He XY, et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment. Cancer Cell. 2024; 42(3): 474-486.e12.https://doi.org/10.1016/j.ccell.2024.01.013

10. Yang ZW, Yang SH, Chen L, Qu J, Zhu J, Tang Z. Comparison of blood counts in venous, fingertip and arterial blood and their measurement variation. Clin Lab Haematol. 2001; 23(3): 155-9. doi: 10.1046/j.1365-2257.2001.00388.x.

11. Chavan P, Bhat V, Tiwari M, Gavhane U, Pal S.K. Comparison of complete blood count parameters between venous and capillary blood in oncology patients. J Lab Physicians. 2016; 8: 65-66. doi:10.4103/0974-2727.176238.

12. Kupke IR, Zeugner S, Gottschalk A, Kather B. Differences in lipid and lipoprotein concentrations of capillary and venous blood samples. Clin Chim Acta. 1979; 97(2-3): 279-83. doi: 10.1016/0009-8981(79)90426-1.

13. Falch DK. Clinical chemical analyses of serum obtained from capillary versus venous blood, using Microtainers and Vacutainers. Scand J Clin Lab Invest. 1981; 41(1): 59-62. doi: 10.3109/00365518109092015.

14. Baggio S, Togni G, Eckerle I, Vuillemier N, Kaiser L, Gétaz L. Feasibility of home-based ELISA capillary blood self-testing for anti-SARS-CoV-2 antibodies. Practical Laboratory Medicine. 2022; 31(1): e00290. DOI:10.1016/j.plabm.2022.e00290.

15. Goodrum JM, Lewis LA, Fedoruk MN, Eichner D, Miller GD. Feasibility of microvolumetric capillary whole blood collections for usage in Athlete Biological Passport analysis. Drug Test Anal. 2022; 14(7): 1291-1299. doi: 10.1002/dta.3254.

16. Gowans J. L. The lymphocyte – a disgraceful gap in medical knowledge // Immunology Today. 1996; 17(6): 288-291. doi.org/10.1016/0167-5699(96)80547-0.

17. Howell A, Arsic N, Griebel P. Resting and activated bovine neutrophils and eosinophils differ in their responses to adrenergic agonists. Veterinary Immunology and Immunopathology. 2024; 272: e110758. https://doi.org/10.1016/j.vetimm.2024.110758.

18. Kupke IR, Kather B, Zeugner S. On the composition of capillary and venous blood serum. Clin Chim Acta. 1981; 112(2): 177-85. doi: 10.1016/0009-8981(81)90376-4.

19. Li R, Zeng J, Ren T. Expression of DEL-1 in alveolar epithelial cells prevents lipopolysaccharide-induced inflammation, oxidative stress, and eosinophil recruitment in acute lung injury. International Immunopharmacology. 2022; 110: e108961. https://doi.org/10.1016/j.intimp.2022.108961

20. Zhu Y, et al. Low shear stress exacerbates atherosclerosis by inducing the generation of neutrophil extracellular traps via Piezo1-mediated mechanosensation. Atherosclerosis. 2024; 391: e117473. https://doi.org/10.1016/j.atherosclerosis.2024.117473

21. Macleod K, Katz LB, Cameron H. Capillary and Venous Blood Glucose Accuracy in Blood Glucose Meters Versus Reference Standards: The Impact of Study Design on Accuracy Evaluations. J Diabetes Sci Technol. 2019; 13(3): 546-552. doi: 10.1177/1932296818790228.

22. Zhuge Z, et al. Red blood cells from endothelial nitric oxide synthase-deficient mice induce vascular dysfunction involving oxidative stress and endothelial arginase I / // Redox Biology. 2023; 60: e102612. doi.org/10.1016/j.redox.2023.102612

23. Shapiro KE, Buhimschi IA, Fleisher J. Accuracy of anemia screening by point-of-care hemoglobin testing in patients seeking abortion. Contraception. 2022; 105: 51-54. https://doi.org/10.1016/j.contraception.2021.09.003

24. Kayiran SM, Ozbek N, Turan M, Gürakan B. Significant differences between capillary and venous complete blood counts in the neonatal period. Clin Lab Haematol. 2003; 25(1): 9-16. doi: 10.1046/j.1365-2257.2003.00484.x.

25. Li Q, Zhu Z, Wang L, Lin Y, Fang H, Lei J, Cao T, Wang G, Dang E. Single-cell transcriptome profiling reveals vascular endothelial cell heterogeneity in human skin. Theranostics. 2021;11(13): 6461-6476. doi: 10.7150/thno.54917. eCollection 2021

26. Doeleman MJH, Esseveld A, Huisman A, de Roock S, Groenestege WMT. Stability and comparison of complete blood count parameters between capillary and venous blood samples. Int J Lab Hematol. 2023; 45(5): 659-667. doi: 10.1111/ijlh.14080.

27. Cullen T, Thomas AW, Webb R, Hughes MG. The relationship between interleukin-6 in saliva, venous and capillary plasma, at rest and in response to exercise. Cytokine. 2015; 71(2): 397-400. doi: 10.1016/j.cyto.2014.10.011.

28. de Oliveira DCX, Frisselli A, de Souza EG, Stanganelli LCR, Deminice R. Venous versus capillary sampling for total creatine kinase assay: Effects of a simulated football match. PLoS One. 2018; 13(9): e0204238. doi: 10.1371/journal.pone.0204238.

29. Woolley T, Rutter E, Staudenmaier M. Comparability and stability of serum creatinine concentration in capillary and venous blood. Br J Biomed Sci. 202380. P. 11402. doi: 10.3389/bjbs.2023.11402.

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SORPTION ACTIVITY OF THE EPITHELIUM OF THE ORAL CAVITY IN RESIDENTS OF ARKHANGELSK DEPENDING ON BODY MASS INDEX

The purpose of the study: to study the features of the sorption activity of the epithelium of the oral mucosa, depending on the body mass index. A survey of 61 practically healthy women living in Arkhangelsk aged 19 to 45 years was conducted. According to the results of the distribution, two groups were formed depending on BMI: BMI > 25 (30 people) and BMI < 25 (31 people). To exclude the metabolic syndrome, a study of the main parameters of the lipid profile was conducted. The sorption activity of the epithelium in the separated oral mucosa in the group with a BMI >25 was lower compared with the group of subjects with normal weight. The average number of peripheral blood leukocytes in the examined group with a BMI>25 was statistically significantly higher (6.67±0.88 ×10^9 cells/l compared with 4.94±0.06 ×10^9 cells/l) due to neutrophil granulocytes (3.75±0.27 ×10^9 cells/l versus 2.50±0.18 ×10^9 cells/l). Their content levels did not go beyond the reference values. The average level of the proinflammatory cytokine IL-1β in the supernatant of oral fluid in individuals with a BMI >2.5 was twice as high (20.19±2.95 pg/ml compared with 10.95±1.80 pg/ml). The average levels of IL-1β in peripheral blood in individuals of both groups studied do not exceed the physiological norm, and the average levels of this proinflammatory cytokine in the supernatant of oral fluid are 2-4 times higher than in the cut, it can be assumed that the local synthesis of this cytokine. low levels of sorption activity of the oral epithelium in individuals with a BMI >25 may indicate a risk of developing metabolic syndrome.

Thus, in individuals with a BMI > 25, a decrease in the levels of sorption activity of the oral epithelium was revealed, as well as a twofold increase in the average levels of IL-1β in the supernatant of the oral fluid, which suggests a more intense inflammatory reaction of the oral mucosa, the chronization of which can lead to metabolic changes, and, as a result, can contribute to the development of metabolic syndrome. At the same time, the average levels of IL-1β in peripheral blood do not change, which emphasizes the relative autonomy of the local immune response. Concentrations of the proinflammatory cytokine IL-1β in the oral fluid, which are many times higher than the average levels of IL-1β in peripheral blood, indicate a predominantly local synthesis of this inflammatory mediator.

Keywords: Sorption, epithelium, obesity.

Introduction. The innate immune system of the oral cavity functions as the first line of defense against infection, provides immune tolerance to commensal bacteria and food antigens. Epithelial cells of the mucous membranes of the oral cavity are the main components of the innate immune system, providing relative impermeability of the epithelial barrier to microorganisms. The microbiota of the oral cavity plays an important role in maintaining the health of the human body. Deviation from the symbiotic balance between the host and the microbiota can lead to oral and systemic diseases. Epidemiological studies confirm the connection between oral dysbiosis and metabolic dysregulation. Dysbiosis of the oral microbiome can contribute to inflammatory changes and impaired metabolic regulation in obesity. Significant differences in the composition of the oral microbiome between people with normal weight and obesity have been revealed [3, 7, 8].

Increased permeability of the intestinal wall in obesity is associated with changes in the composition of proteins of dense compounds and thinning of the mucous layer of the epithelial barrier, which leads to translocation of food and bacterial antigens into the bloodstream. The microflora of the oral cavity initiates immune reactions and contributes to increased metabolic inflammation of adipose tissue. Two approaches linking oral bacteria with inflammatory and metabolic effects in distant organs are discussed in the literature. Translocation of oral bacteria into the intestine and effects on the composition of the intestinal microbiome are one of the approaches. Translocation of oral bacteria and inflammatory molecules into the bloodstream leads to bacteremia, systemic damage and various immune reactions. This causes systemic inflammation and local inflammation in remote areas [6]. Local increase in proinflammatory cytokine levels and remodeling of dense compound proteins play a key role in the manifestation of epithelial barrier dysfunction in obesity [2].

There are fundamental restrictions on the capture of bacteria by epithelial cells in the gastrointestinal tract and other cavities. Endocytosis, as a consequence of the fundamental principles of biology, is based on molecular and cellular recognition, which plays an important role in bacterial adhesion to host cell receptors. Adsorption and receptor-mediated protein endocytosis is a universal property of cells, and especially in the epithelium of mucous membranes. Some absorbed proteins are transported intact through the cells and thus provide specialized functions, such as the transfer of immunity from mother to child. However, mostly absorbed proteins are transported to lysosomes, where they undergo complete hydrolysis to amino acids. This process is important for the homeostasis of circulating proteins [9].

The sorption activity of the epithelium depends on the size of the sorbed particles. Studies of the sorption capacity of epithelial cells of the mucous membranes of the esophagus show that latex microspheres larger than 1 μm adhered to epithelial cells, but were not subjected to phagocytosis [4]. Microspheres with a diameter of 0.01 and 0.1 microns. microspheres, but not 1.0 microns, were internalized rather than simply attached to the outer surface of the cell [5].

Studies simulating the consequence

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of diabetes mellitus in the oral cavity have demonstrated a decrease in the sorption capacity of oral epithelial cells against the background of an increase in the number of heterogeneous microflora and low leukocyte activity. There were also trends towards a significant decrease in the index of cellular differentiation and an increase in the nuclear-cytoplasmic ratio against the background of intensive processes of desquamation of the mucosal epithelium, exacerbating local inflammatory reactions [10].

At the local level, cytokines ensure the development of all stages of the immune response to the influence of a pathogenic factor: they limit its spread, removal and restoration of damaged tissue. Low concentrations of cytokines form adequate local inflammation, higher ones cause a systemic inflammatory reaction of a protective nature, extremely high ones lead to the development of pathological conditions. The source of cytokines in the oral fluid is serum transudate and salivary glands, and they are also produced by epithelial cells of the oral mucosa upon contact with microorganisms. In addition, cytokines are actively produced by lymphocytes and macrophages embedded in the epithelial layer of the mucous membrane. Separately, it should be noted that the content of cytokines in the oral fluid does not correlate with their level in the blood, which indicates the relative autonomy of local immunity. The diagnostic value of determining cytokines increases when they are examined directly in the focus of inflammation.

The initial mucosal response is triggered by the activation of toll-like receptors, which act as the most important inflammatory mediators within the innate immune system. Activation of immune cells such as macrophages and T cells contributes to the creation of a pro-inflammatory environment, which leads to an increase in the level of inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-13 and IL-1β. Moreover, inflammatory cytokines can affect the main regulator of the function of dense compound proteins.

Studies prove that metabolic inflammation of adipose tissue in individuals with a high body mass index has a negative effect on the epithelial layer of the mucous membranes, weakening the secretion of proteins of dense compounds, increasing the permeability of the epithelial layer due to paracellular transport. The degree of permeability of the epithelial barrier is regulated by proteins of intercellular tight contacts both under physiological conditions and under conditions of a pathological process [1].

Table 1

Average levels of body mass index and peripheral blood lipid metabolism, depending on BMI

Parameters	BMI >25, M±m	BMI <25, M±m
Body Mass Index	31.59±3.65*	21.84±2.25
Total cholesterol, mmol/l	3.54±0.47	3.98±0.74
Triglycerides, mmol/l	0.83±0.33	0.96±0.20
Phospholipids, mmol/l	2.08±0.60	2.48±0.70
Glucose, mmol/l	5.02±0.43	5.26±0.41
aspartate transaminase, E/L	21.42±6.14	20.77±3.07
Alanine aminotransferase, E/L	12.71±4.78	15.16±3.70
Gamma-glutamyltranspeptidase, E/L	20.37±21.22	20.72±14.22
Amylase, E/l	49.25±18.07	49.23±19.84

* - p<0.05

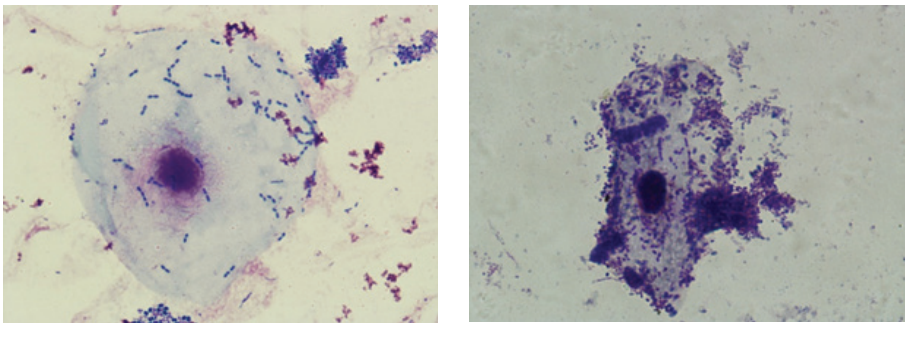
Table 2

The sorption activity of the epithelium in the oral fluid of the subjects, depending on BMI

Parameters	BMI > 25	BMI < 25
Average sorption activity of the epithelium, bacterium / cell	69.66±3.92*	86.29±2.25
% of individuals with epithelial sorption activity <100 bacterium / cell	55.17	32.29
% of individuals with epithelial sorption activity <50 bacterium / cell	27.59	0

* - p<0,05

a b



Epithelial cell of the oral cavity with a low number (a) and a large number (b) of sorbed microorganisms. Staining according to Romanovsky-Giemsa. Magnification ×1000

The purpose of the work: to study the features of the sorption activity of the epithelium of the oral mucosa depending on the body mass index.

Materials and methods. On the basis of the Laboratory of Environmental Immunology of the Institute of Physiology of Natural Adaptations of the the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences, a survey of 61 practically healthy women living in Arkhangelsk aged 19 to 45 years was conducted. The average age of the subjects was 33.52±8.17 years. The examination was conducted during the absence of exacerbation of chronic diseases. All studies were conducted with the consent of volunteers and in accordance with the requirements of the Helsinki Declaration of the World Medical Association on Ethical Principles of Medical Research. Permission was received from the Ethical commission of the Institute of Physiology of Natural Adaptations of the the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sci-

Table 3

Erythrocyte and leukocyte indices of peripheral blood depending on BMI

Parameters	ИМТ >25, M±m	ИМТ <25, M±m
Erythrocytes, 10^6 cells/μl	4.81±0.49	4.79±0.39
Hemoglobin, g/l	132.40±18.64	131.06±14.93
Hematocrit, %	37.11±4.34	37.11±3.33
Red blood cell volume, fL	77.25±5.91	77.59±4.32
The volume of hemoglobin in erythrocytes, pg	27.53±2.74	27.38±2.15
The average concentration of hemoglobin in erythrocytes, g/l	355.83±13.74	352.42±11.86
Platelets, 10^3 cells/μl	281.67±64.97	256.00±53.53
The estimated width of the distribution of red blood cells by volume, standard deviation, fL	38.63±3.06	36.80±2.18
The calculated width of the distribution of erythrocytes by volume, coefficient of variation, %	14.21±2.00	13.36±1.26
Estimated platelet distribution width, fL	14.40±2.48	13.90±2.19
Platelet volume, fL	11.03±1.04	10.79±0.89
The coefficient of large platelets, %	34.17±8.30	32.31±7.15
Thrombocrit, %	0.31±0.06	0.27±0.05
White blood cells, 10^9 cells/l	6.67±0.88*	4.94±0.06
Neutrophils, 10^9 cells/l	3.75±0.27*	2.50±0.18
Neutrophils, %	55.86±0.90	50.39±0.51
Lymphocytes, ×10^9 cells/l	2.12±0.79	1.82±0.62
Lymphocytes, %	32.10±0.50	36.82±1.18
Monocytes, ×10^9 cells/l	0.56±0.15	0.45±0.11
Monocytes, %	1.87±0.07*	1.55±0.07
The ratio of neutrophils to lymphocytes (NLR)	8.60±0.60	9.26±0.87
Eosinophils, ×10^9 cl/l	0.19±0.14	0.16±0.11
Eosinophils, %	2.98±0.01	3.15±0.05
Basophils, ×10^9 cells/l	0.03±0.02	0.02±0.01
Basophils, %	0.44±0.06	0.41±0.02

* - p<0.05

ences (Protocol No. 8 dated March 30, 2022) to conduct the study.

All the subjects had their height and body weight measured, and the body mass index was calculated using the formula: BMI = weight (kg) / height $(m)^2$.

Oral fluid was taken in the morning, on an empty stomach, into plastic tubes, which were immediately frozen for 72 hours, then unscrewed on a centrifuge. A smear was made from the sediment and stained according to Romanovsky-Gimse. The average number of microbial bodies per 100 epithelial cells was calculated in the smear. The infusion fluid was used to determine IL-1β by enzyme immunoassay.

The complex of immunological research included the study of a hemogram of venous blood taken on an empty stomach in the morning (the number of platelets, erythrocytes, leukocytes, total hemoglobin in the blood, leukograms) on an automatic hematology analyzer XS–500i (Sysmex, Japan). Cytokines IL-1β, IL-6, TNF-α, IL-10 (Vector Best, Russia) of peripheral blood and the supernatant of oral fluid were determined by the enzyme immunoassay using the Multiskan FC enzyme immunoassay analyzer (Thermo Scientific, USA).

The study of the lipid profile included the determination of total cholesterol, glucose, triglycerides, phospholipids, and insulin using a Shimadzu UV-1800 spectrophotometer (Japan) and Vector–Best reagents (Russia).

Statistical processing with the determination of the arithmetic mean and standard error (M ± m) was carried out using the Microsoft Excel software package. The significance of the differences was assessed using the Student's t–test when conducting statistical analysis using the Statistica software package. The significance of the differences was taken into account at $p < 0.05$.

Table 4

Average levels of peripheral blood cytokines and oral fluid supernatant

Cytokines	BMI >25, M±m	BMI <25, M±m
IL-17F, pg/ml	26.54±23.93	28.47±13.62
IL-1β, pg/ml	4.75±1.92	4.63±3.65
IL-1β (saliva), pg/ml	20.19±2.95*	10.95±1.80
IL-4, pg/ml	11.88±1.85	10.17±2.71
IL-6, pg/ml	2.72±2.06	3.2±2.47
TNF-α, pg/ml	6.21±6.9	7.04±6.2
IL-10, pg/ml	4.53±4.1	5.03±6.44

* - p<0.05

Results and discussion. According to the results of the distribution, two groups were formed depending on BMI: BMI > 25 (30 people) and BMI < 25 (31 people). To exclude the metabolic syndrome, a study of the main parameters of the lipid profile was conducted. The results of the lipid metabolism parameters studied by us are shown in Table 1.

The main parameters of the lipid profile in all subjects did not exceed the limits of the physiological norm.

We found that a high body mass index is associated with a decrease in the sorption activity of epithelial cells of the mucous membranes of the oral cavity. The average levels of sorption activity of epithelial cells of the oral fluid, as well as the percentage of persons with reduced sorption levels are shown in Table 2.

The sorption activity of the epithelium in the separated oral mucosa in the group with a BMI >25 was lower compared with the group of subjects with normal weight (Figures 1, 2). At the same time, the average level of epithelial cell sorption capacity did not reach 100 bacterium / cell. in half of the subjects in the BMI group >25, and 50 bacterium / cell in a third of the volunteers in this group. A decrease in the levels of the sorption capacity of epithelial cells may indicate a weakening of the protective properties of epithelial cells of the mucous membranes of the oral cavity in persons with high BMI due to the negative influence of factors of metabolic inflammation of adipose tissue.

Figure 1. Epithelial cell of the oral cavity with a low number of sorbed microorganisms. Romanovsky-Giemse coloring. Increase ×1000.

To clarify the nature of metabolic inflammatory processes, it was of interest to study peripheral blood parameters, the results of which are presented in Table 3.

The indicators of erythrocyte and platelet components of peripheral blood in both groups of subjects had no significant differences and were within the physiological norm.

The average number of peripheral blood leukocytes in the examined group with a BMI>25 was statistically significantly higher (6.67±0.88 ×10^9 cells/l compared with 4.94±0.06 ×10^9 cells/l) due to neutrophil granulocytes (3.75±0.27 ×10^9 cells/l versus 2.50±0.18 ×10^9 cells/l). Their content levels did not go beyond the reference values. To assess the likely systemic inflammation, the average values of the neutrophil-lymphocytic index in the subjects were calculated, it was determined that those with a high BMI were higher than those of volunteers with normal body weight (1.87±0.07 compared with 1.55±0.07).

The average concentrations of the mediators of inflammatory reactions of peripheral blood and the supernatant of oral fluid studied in individuals with different BMI levels are shown in Table 4.

The studied levels of peripheral blood cytokines in the subjects in both groups had no statistically significant differences. However, the average level of the proinflammatory cytokine IL-1β in the oral fluid supernatant in individuals with a BMI >2.5 was twice as high (20.19±2.95 pg/ml compared with 10.95±1.80 pg/ml). Elevated levels of the inflammatory mediator IL-1β in the oral fluid indicate a local immune response, play an important role in the development of inflammation and a decrease in the effectiveness of the protective function of the epithelial barrier in obesity. Since the average levels of IL-1β in peripheral blood in individuals of both groups studied do not exceed the physiological norm, and the average levels of this proinflammatory cytokine in the supernatant of oral fluid are 2-4 times higher than in the cut, it can be assumed that local synthesis of this cytokine. It is important to keep in mind that the average values may vary depending on the individual characteristics of the body.

The relatively elevated level of c-reactive protein (2.46±0.17 micrograms/ml compared with 1.97±0.19 micrograms/ml), even with normal cholesterol levels in practically healthy individuals, makes it possible to predict the risk of metabolic disorders that can lead to the development of metabolic syndrome, since individuals with a BMI > 30 have average concentrations of c-reactive protein. proteins tend to increase (4.20±1.86 micrograms/ml).

Conclusion. Thus, in individuals with a BMI > 25, a decrease in the levels of sorption activity of the oral epithelium was revealed, as well as a twofold increase in the average levels of IL-1β in the supernatant of the oral fluid, which suggests a more intense inflammatory reaction of the oral mucosa, the chronization of which can lead to metabolic changes, and, as a result, can contribute to the development of metabolic syndrome. At the same time, the average levels of IL-1β in the peripheral blood do not change, which highlights the relative autonomy of the local immune response. Concentrations of the proinflammatory cytokine IL-1β in the oral fluid, which are many times higher than the average levels of IL-1β in peripheral blood, indicate a predominantly local synthesis of this inflammatory mediator.

The work was carried out within the framework of the program of fundamental scientific research on the Laboratory of Environmental Immunology of the Institute of Physiology of Natural Adaptations of the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences No. 122011300377-5.

References

1. Fedorin MM, Livzan MA, Gauss OV. Sindrom povyshennoj epitelial'noj pronicaemosti u bol'nyh sindromom razdrazhennogo kishechnika, associirovannym s izbytochnoj massoj tela i ozhireniem [Syndrome of increased epithelial permeability in patients with irritable bowel syndrome associated with overweight and obesity]. RMZh. Medicinskoe obozrenie [Medical Review. 2023; 7(7): 424-431 (In Russ.).] doi:10.32364/2587-6821-2023-7-7-4

2. AlMarzooqi SK, et al. Deciphering the complex interplay of obesity, epithelial barrier dysfunction, and tight junction remodeling: Unraveling potential therapeutic avenues. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2024. e13766. doi:10.1111/obr.13766

3. Endo Y, et al. Experimental Periodontitis Induces Gene Expression of Proinflammatory Cytokines in Liver and White Adipose Tissues in Obesity. J Periodontol. 2010; 81(4): 520–6. doi:10.1902/jop.2009.090574

4. Hopwood D, et al. Endocytosis of fluorescent microspheres by human oesophageal epithelial cells: comparison between normal and inflamed tissue. Gut. 1995; 37(5): 598–602. doi:10.1136/gut.37.5.598

5. Innes NP, Ogden GR. A technique for the study of endocytosis in human oral epithelial cells. Archives of oral biology. 1999; 44(6): 519–523. doi:10.1016/s0003-9969(99)00027-8

6. Lee YH, et al. Progress in oral microbiome related to oral and systemic diseases: An update. Diagnostics. 2021; 11(7): 1283. doi:10.3390/diagnostics11071283

7. Prince Y, et al. The Relationship between the Oral Microbiota and Metabolic Syndrome. Biomedicines. 2023; 11(1): 3. doi:10.3390/biomedicines11010003

8. Stefura T, et al. Differences in compositions of oral and fecal microbiota between patients with obesity and controls. Medicina (Lithuania). 2021; 57(7): 678. doi:10.3390/medicina57070678

9. Wall DA, Maack, T. Endocytic uptake, transport, and catabolism of proteins by epithelial cells. The American journal of physiology. 1985; 248(1 Pt 1). C12-C20. doi:10.1152/ajpcell.1985.248.1.C12

10. Zhurakivska OY, Atamanchuk OV. Morphological characteristics of diabetic glossitis. Wiadomosci lekarskie (Warsaw, Poland: 1960). 2022; 75(3): 619-623.

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ESCALATION OF VITAMIN D DEFICIENCY FROM BIRTH TO EARLY AGE

The vitamin D supply of healthy newborns and young children living in the Khabarovsk Territory was analyzed. Using a random sampling method, the study included children of two age groups: at birth and the mothers of these children (n=67) and at the age of 1-3 years (n=58), undergoing examination in medical organizations of the Ministry of Health of the Khabarovsk Territory, Khabarovsk. Low vitamin D status was detected in every third child aged 0 to 3 years (29.4%): vitamin D deficiency and insufficiency were diagnosed in 14.4% and 15.0% of children respectively, severe deficiency was defined in 4.0 % of cases. A decrease in the concentration of 25(OH)D in the blood serum was found with increasing age of the child. It was determined that the median concentration of 25(OH)D in the blood serum of children in the first three years of life was 2.5 times higher compared to the control group. The data obtained as a result of the study demonstrate the high prevalence of low vitamin D status among the child population of Khabarovsk, while there is an increase in the deficiency state as they grow older and, as a consequence, the most vulnerable group is adolescents.

Keywords: vitamin D, newborns, young children, teenagers.

Introduction. Recently, there has been an accumulation and rethinking of scientific research on the level of vitamin D in different age categories around the world, since the supply of vitamin D has become a key factor determining the health of both adults and children. Vitamin D deficiency is an internationally recognized health problem of particular importance in certain geographic regions and in certain social and demographic segments of the population. Currently, there is evidence that vitamin D deficiency affects from 24 to 49% of people, insufficiency ranges from 5 to 18%, depending on the region of the world [8]. Numerous studies indicate the diversity of the biological significance of vitamin D and have long been not limited to the “classical” and go far beyond simply “prevention of rickets” and “bone metabolism”, its modern undeniable role in the development and functioning of the central nervous system in children, its influence on development chronic somatic pathology and implementation of reproductive function.

The modern scientific idea of research in this area is to summarize the available data and formulate a unified concept for the prevention and treatment of vitamin D deficiency in the pediatric population, taking into account age periodization. On the territory of the Khabarovsk Territory, since 2019, systematic work has been carried out to form a base of vitamin D supply depending on the age of the child from 0 to 18 years [5, 6], since studies of the vitamin D supply of children of different age groups in the Khabarovsk Territory, in accordance with modern diagnostic criteria, have not previously been carried out, which served as the basis for conducting this study. Maintaining adequate vitamin D levels is important throughout childhood because vitamin D deficiency negatively affects children's health.

The largest study of vitamin D levels in children included 1230 studies in 7 regions of the Russian Federation [2]. According to the results of the study, low levels of vitamin D were detected in children from 0 to 3 years of age in the cities of the Far Eastern Federal District - Khabarovsk, Vladivostok and Blagoveshchensk (73.3%, 87.9% and 62.8%, respectively) [2]. Also, low levels of vitamin D in preschool and adolescent children were detected in the Amur region (80.0% and 88.3%, respectively) [1].

The analysis of vitamin D supply in the children's population of various countries revealed some age-related features. European adolescents aged 15-18 years demonstrate a higher prevalence of vitamin D deficiency (12-40%) compared to children aged 1-14 years (4-7%) [9]. The prevalence of vitamin D deficiency and insufficiency among children in mainland China was 7% and 16%, respectively, while the lowest levels of provision were found in newborns (deficiency – 55%, insufficiency – 33%), adolescents had low vitamin D status in 18% and 35% of cases, respectively [11].

The disparity of the results of previous studies regarding the prevalence of vitamin D deficiency depending on the age of the child requires further study with an emphasis on children of the younger age group, since it is in this period of life that the child's health and development program is laid in subsequent years.

The aim of the study: to determine the features of vitamin D supply in healthy newborns and young children living in the Khabarovsk Territory.

Materials and methods of research. An observational, analytical, cross–sectional study was conducted, in which children aged 0 to 3 years (n=125) were included by random sampling, undergoing examination in medical organizations of the Ministry of Health of the Khabarovsk Territory, Khabarovsk - the consultative and diagnostic department of the Children's City Clinical Hospital named after V.M. Istomin and the KGBUZ Perinatal Center named after Professor G.S. Postol. According to the age periodization, the children were divided into study groups: newborns (n=67) and young children (1-3 years old, n=58). The control group consisted of adolescent children

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(10-18 years old, n=30). In addition, the analysis of vitamin D supply in 67 mothers of newborns included in the study was carried out.

Inclusion criteria: conditionally healthy children aged 0-3 years, born with average physical development from a singleton physiological pregnancy and the mothers of these children, from whom had a sampling done umbilical cord blood (newborns) and venous blood (mothers of the early postpartum period and children 1-15 years old), living in the Khabarovsk and undergoing examination in selected medical organizations at the time of the study, from whose legal representatives a written voluntary informed consent to participate in the study was obtained.

Quantification of the level of 25-hydroxyvitamin D (25(OH)D) in blood serum was performed by solid-phase enzyme immunoassay based on the principle of competitive binding using a set of reagents 25-OH-Vitamin D ELISA (DRG Instruments GmbH, Germany). The range of detectable concentrations is 25(OH)D was (according to the instructions of the test manufacturer) 2.89–130 ng/ml. No results beyond the specified values were found in this study. The study was performed on a Model 680 Microplate Reader photometer (Bio-Rad, USA). The biomaterial set was carried out in the autumn-winter period of 2021-2022. The level of vitamin D supply was determined according to the recommendations set out in the national program [7].

The study was approved by the local Ethics Committee at the Far Eastern State Medical University of the Ministry of Health of the Russian Federation (Protocol No. 10 of 06/10/2020), conducted in accordance with the ethical principles of conducting medical research involving people as subjects (Helsinki, 1964; revised - Scotland, October 2000).

Statistical analysis of the results of the study was carried out using statistical programs Statistica 12.0 (StatSoft Inc., USA) and IBM SPSS Statistics 20. The description of quantitative indicators was performed indicating the average value (M), the error of the arithmetic mean (m), the median (Me), the 25th and 75th percentiles. The normality of the data distribution was checked using the Shapiro-Wilk criterion. The statistical significance of the differences in the study groups was assessed by the Student's t-test for independent samples with a normal distribution of data. The comparison of quantitative indicators in the comparison groups with the distribution of data that do not have a normal distribution was carried out using the Mann-Whitney criterion. The statistical significance of the differences in relative indicators was assessed using Pearson's $\chi 2$ criterion and Fisher's exact criterion. Spearman's rank correlation coefficient was used to determine the degree of correlation between the indicators. To quantify the relationship between a certain outcome and a risk factor, when comparing two groups, the statistical indicator odds ratio (OR) was used with the calculation of a 95% confidence interval (CI). The differences between the groups were considered statistically significant at $p<0.05$.

Results and discussion. According to the study, a low vitamin D status was detected in every third child aged 0 to 3 years (29.6±4.1%). At the same time, vitamin D deficiency and insufficiency were diagnosed equally in 14.4±3.1% and 15.0±3.2% of children, respectively, severe deficiency was determined in 4.0±1.8% of cases, the optimal vitamin D level was in 70.4±4.1% of the examined children.

Concentration analysis of 25(OH)D in the blood serum of children in the comparison groups showed significant differences in vitamin D supply depending on age ($p<0.001$) (Table 1). The highest

Table 1

Concentrations of 25(OH)D in the blood serum of the examined children of the comparison groups

Vitamin D supply. abs. (%)	Age groups		*p*
	Newborns	1-3 years	
Concentration of 25(OH)D. ng/ml (Me (25%; 75%))	49.1 (39.3; 60.0)	34.5 (22.0; 53.0)	0.001
Supply of vitamin D. abs. (%): Deficiency	4 (6.0)	14 (24.1)	0.005
Severe deficiency	3 (4.5)	2 (3.4)	1.000
Insufficiency	6 (8.9)	13 (22.4)	0.066
Optimal level	57 (85.1)	31 (53.4)	< 0.001

Table 2

Comparative analysis of vitamin D supply in the examined young children with the control group (adolescents)

Vitamin D supply, abs. (%)	Age groups		*p*
	1-3 years	Adolescents	
Concentration of 25(OH)D, ng/ml (Me (25%; 75%))	46.0 (27.0; 59.0)	18.2 (12.0; 28.0)	< 0.001
Supply of vitamin D, abs. (%): Deficiency	18 (14.4)	17 (56.7)	< 0.001
Severe deficiency	5 (4.0)	7 (23.3)	0.002
Insufficiency	19 (15.0)	7 (23.3)	0.425
Optimal level	88 (70.4)	6 (20.0)	< 0.001

Table 3

Comparative analysis of vitamin D supply in children of the studied age groups living in Khabarovsk and Moscow

Vitamin D supply, abs. (%)	Age groups					
	0-3 years	**0-3 years**	p	Adolescents	**Adolescents**	p
Deficiency	18 (14.4)	**45 (17.5)**	0.014	17 (56.7)	**496 (65.0)**	0.041
Severe deficiency	5 (4.0)	**4 (1.6)**		7 (23.3)	**75 (9.8)**	
Insufficiency	19 (15.0)	**69 (27.0)**		7 (23.3)	**211 (27.7)**	
Optimal level	88 (70.4)	**142 (55.5)**		6 (20.0)	**56 (7.3)**	

Note: the data published by Kondratieva E.I. et al. are highlighted in bold [4]

levels of vitamin D in the child's body, corresponding to a sufficient level of supply, were found in the group of newborns. The median concentration is 25(OH)D was 49.1 ng/ml and was higher than calcidiol concentrations in young children (34.5 ng/ml, p = 0.001).

As a result of the study, it was found that vitamin D deficiency and insufficiency occurred in young children in 46.4±6.6% of cases, much less often in newborns – 14.9±4.4% (p<0.001). There were no statistically significant differences in the prevalence of vitamin D insufficiency in children of the comparison groups (p = 0.066) (Table 1).

When determining the relationship between the level of vitamin D supply and the age group of children, a statistically significant negative relationship was established as a result of correlation relations (r = -0.349, p < 0.001). Thus, a decrease in the concentration of 25(OH) was determined in the blood serum with an increase in the age of the child.

It is interesting to note that a multicenter, prospective, cohort pharmacoepidemiological study conducted about 10 years ago to assess the supply of vitamin D in the younger age group of children in the Russian Federation "Rodnichok" revealed a high prevalence of vitamin D deficiency (42.9±6.6%) and vitamin D insufficiency in children in Khabarovsk (30,4±6,1%) [2]. Vitamin D deficiency in young children according to the results of this study amounted to 24.1±5.6%, which is almost 2 times less than in the Rodnichok study (p = 0.035). The number of children with a sufficient level of security was increced from 26.8±5.9% to 53.4±6.6% (p = 0.004). The improvement in the level of vitamin D supply is probably due to the implementation by pediatricians of the recommendations on cholecalciferol subsidies set out in the National Program for the Elimination of Vitamin D Deficiency, greater awareness and commitment of parents to alimentary correction of deficiency using vitamin and mineral complexes containing cholecalciferol.

In a pairwise comparison of concentrations of 25(OH)D in blood serum, as well as relative indicators of varying degrees of vitamin D supply in children aged 0-3 years (main group) and adolescents (control group), statistically significant differences were revealed (p < 0.001). The median concentration is 25(OH)D in the blood serum of children of the first three years of life was 2.5 times higher compared with the control group (46.0 and 18.2 ng/ml, respectively, p<0.001), the prevalence of low vitamin D status was 3 times less (29.6±4.1% and 80.0±7.3%, respectively, p = 0.049) (table 2).

When calculating the odds ratio, it was found that the prevalence of vitamin D deficiency in adolescent children was almost 8 times higher (OR = 7,774; 95% CI 3,231-18,703) compared with children from 0 to 3 years old. It was found that adolescents were 4 and 20.5 times more likely to be deficient in vitamin D than young children and newborns (respectively, OR = 4.110; 95% CI 1,606-10.519 and OR = 20.596; 95% CI 5,948-71.323). The obtained comparative analysis data indicate, probably, a greater commitment to cholecalciferol subsidies in children of the first three years of life and its absence in older age groups.

The data obtained in the course of our study are consistent with the results of Kondratieva E.I. et al. in a continuous study of groups (from children less than 3 years old to adults 76 years old and older). A study by Kondratieva E.I. et al., conducted in 2021 in Moscow, showed that the content of 25(OH)D is at a sufficient level only at a younger age, immediately after the child reaches the age of 3 years, there is a biochemical manifestation of a deficiency of 25(OH)D, and then insufficiency and deficiency of 25(OH)D persist throughout the rest of life. The lowest concentration of 25(OH)D was noted precisely during the period of active growth of the body (from 11 to 21-22 years old) and in old age [4] (Table 3).

References

1. Borisenko E.P., Romantsova E.B., Babtseva A.F. Obespechennost' vitaminom D detskogo i vzroslogo naseleniya Amurskoj oblasti [Vitamin D provision of children and adults in the Amur region]// Byulleten' fiziologii i patologii dyhaniya.[Bulletin of Physiology and Pathology of Respiration. 2016; 60:57–61 (In Russ.).]

2. Zakharova IN, et al. Rezul'taty mnogocentrovogo issledovaniya «RODNICHOK» po izucheniyu nedostatochnosti vitamina D u detej rannego vozrasta v Rossii [Results of the multicenter study “RODNICHOK” to study vitamin D deficiency in young children in Russia]. Pediatriya. Zhurnal im. G.N. Speranskogo. [Pediatrics. Journal named after G.N. Speransky. 2015; 94(1): 62–67 (In Russ.).]

3. Kodentsova V.M., Risnik D.V. Vitamin D – alimentarnyj faktor profilaktiki zabolevanij, obuslovlennyh ego deficitom [Vitamin D is a nutritional factor in the prevention of diseases caused by its deficiency]. Medicinskij sovet. [Medical Council. 2022; 16 (6): 181–191 (In Russ.).] DOI: 10.21518/2079-701X-2022-16-6-181-191.

4. Kondratieva EI, et al. Ocenka obespechennosti vitaminom D v razlichnye vozrastnye periody [Assessment of vitamin D supply in different age periods]. Medicinskij sovet. [Medical Council. 2021; 12: 294–303 (In Russ.).] DOI: 10.21518/2079-701X-2021-12-294-303.

5. Senkevich OA, et al. Usugublenie deficita vitamina D ot rozhdeniya do starshego shkol'nogo vozrasta v g. Habarovska v osenne-zimnij sezon [Worsening of vitamin D deficiency from birth to high school age in Khabarovsk in the autumn-winter season]. Voprosy prakticheskoj pediatrii. [Issues of Practical Pediatrics. 2023; 18(6): 84–88 (In Russ.).]

6. Senkevich O.A., Chernobrovkina M.A., Kovalskiy Yu.G. Obespechennost' vitaminom D detej v vozraste 7–8 let, prozhivayushchih v raznyh geograficheskih zonah (48–52° severnoj shiroty): odnomomentnoe issledovanie [Vitamin D provision of children aged 7–8 years living in different geographical zones (48–52° northern latitude): a cross-sectional study]. Voprosy sovremennoj pediatrii. [Issues of Modern Pediatrics. 2022; 21 (6): 487-49. (In Russ.).] DOI: 10.15690/vsp.v21i6.2461.

7. Unity of pediatricians of Russia, et al. 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.”. M. Pediatr". 2021: 116 (In Russ.).]

8. Cashman K.D. Global differences in vitamin D status and dietary intake: a review of the data. Endocr Connect. 2022; 11(1): e210282. DOI: 10.1530/EC-21-0282.

9. Cashman KD, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016; 103:1033–44. DOI: 10.3945/ajcn.115.120873.

10. Chen Z., Lv X., Hu W., Qian X., Wu T., Zhu Y. Vitamin D Status and Its Influence on the Health of Preschool Children in Hangzhou. Front Public Health. 2021; 9: 675403. DOI: 10.3389/fpubh.2021.675403.

11. Yang C., Mao M., Ping L., Yu D. Prevalence of vitamin D deficiency and insufficiency among 460,537 children in 825 hospitals from 18 provinces in mainland China. Medicine (Baltimore). 2020; 99(44): e22463. DOI: 10.1097/MD.0000000000022463.

DIAGNOSTIC AND TREATMENT METHODS

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INTERVENTIONAL METHODS FOR TREATING CHRONIC PAIN SYNDROME IN ONCOLOGICAL PRACTICE: A SYSTEMATIC REVIEW

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Currently, chronic pain syndrome (CPS) is considered an independent pathology holding significant importance in cancer patients. It has been established that at the early stage of malignant neoplasms (MN), patients experience chronic pain in 35-47% of cases, during full manifestations the number goes up to 78%, and in 98% of patients with generalized forms of malignant neoplasms, chronic pain is the dominant symptom. Despite numerous studies devoted to CPS in oncology, this problem remains relevant.

Purpose of the Study: conducting a systematic review of the literature based on the results of using interventional methods for treating CPS in oncological practice.

Materials and Methods: the authors carried out a systematic search on the subject for articles in English and Russian published between January 1970 and December 2023 using the following databases: Medline, Cochrane Library, and eLibrary.

Results: the systematic review included 15 studies that used interventional treatments for cancer-related CPS. We have established that the use of the analyzed methods in most cases has provided a sufficient level of pain relief in patients with CPS.

Conclusion. Based on the results of the systematic review, we see that there is a need to develop specialized criteria for choosing an interventional method and creating an algorithm for treating drug-resistant CPS in oncology patients.

Keywords: chronic pain syndrome, cancer pain, neurolysis of the celiac plexus, neurodestruction , neuromodulation , palliative care, malignant neoplasm

Introduction. In the last decade, there has been a trend toward increased morbidity and mortality from malignant neoplasms (MN) [7, 8]. According to the Global Cancer database Observatory (GLOBOCAN), newly diagnosed cases of MN are expected to increase by 47% (28.4 million) by 2040 with a steady increase in patients with chronic pain syndrome (CPS) caused by the tumor process.

CPS in oncological practice is one of the main symptoms causing emotional and physical suffering in patients with cancer. It has been established that in 78-90% of patients with generalized forms of MN, pain is the leading symptom of the underlying disease, which significantly reduces their quality of life, representing a serious medical and social problem [7, 23].

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The International Association for the Study of Pain (IASP) has developed a new classification, which provides for the etiology and pathogenesis of CPS in MN [9].

In the treatment of pain, narcotic and non-narcotic analgesics are used according to the three-step WHO Analgesic Ladder [1, 2]. Data from studies of pain therapy indicate that its effectiveness reaches 35-80%. If the analgesic ladder is insufficiently effective, WHO recommends using interventional methods in treating CPS [1, 3, 5, 21]. Such methods of treating CPS can be divided into two categories: neuromodulation and neurodestruction [1-3, 8]. We have analyzed and systemized the information on using neuromodulation and neurodestruction methods in CPS in cancer patients for the basis of this study.

Purpose of the Study: conducting a systematic review of the literature based on the results of using interventional methods for treating CPS in oncological practice.

Materials and Methods. ***Search and Selection Strategy for Literary Data.*** The authors have carried out a systematic search of specialized literature in Russian and English using Medline, Cochrane Library, and eLibrary databases published between January 1970 and December 2023 on interventional methods of treating CPS in cancer patients. The search was carried out using the following keywords for English-language databases: "neurolysis of the celiac plexus", "intrathecal opioid administration in the treatment of pain in cancer patients", "peripheral nerve blocks for oncology", and for eLibrary: "celiac plexus neurolysis", "morphine pumps in oncology", "peripheral blockades in oncology". The data obtained were assessed by two independent experts, and any disagreements between the experts were resolved through group discussion. At the second and third stages, we have analyzed abstracts and articles that did not meet the inclusion criteria were excluded. We have also examined full-text publications (Figure).

This study was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [28].

Criteria for Selecting Literary Sources:

(1) The study includes retrospective and prospective cohort studies, case-control studies, systematic reviews, and clinical cases studying minimally invasive surgical interventions for the treatment of CPS in oncology practice.

(2) Types of interventions: percutaneous and transgastric celiac plexus neurolysis, implantable programmable morphine pumps, peripheral nerve plexus blocks.

(3) Study design: includes all types of studies describing the use of interventional methods for treating CPS in cancer patients.

Assessing the Risk of Bias and Systematic Error in Studies. The risk of systematic errors was determined us-

ing the Newcastle-Ottawa Scale (NOS) [30].

Results. ***Literary Data Search.*** This systematic review included 15 publications that used interventional methods for treating CPS in oncological practice [1, 4, 5, 6, 10, 11, 14, 15, 17, 18, 20, 22, 24, 26]. The characteristics of the studies included in the systematic review are presented in Table 1.

The systematic review presents the most commonly used methods for treating CPS in oncological practice.

Neuromodulatory Treatment for CPS. Intrathecal and Intraspinal Opioids Administration. Neuromodulatory treatment methods include intrathecal and epidural administration of opioids [23, 27, 29]. For the first time in 1979, Wang et al. applied and proved the effectiveness of intrathecal morphine injections in treating CPS in cancer patients. The main advantage of such methods of administration is adequate pain relief with low doses of opioids and a long effective period, which significantly reduces the likelihood of developing adverse drug effects [25]. This therapy positively affects the gelatinous substance of the dorsal horns of the spinal cord [5, 20, 23].

When choosing a method of interventional treatment of CPS, there has to be a detailed selection of patients, which includes determining the general somatic and mental status, the etiology and pathogenesis of CPS, as well as the predicted life expectancy [11, 14].

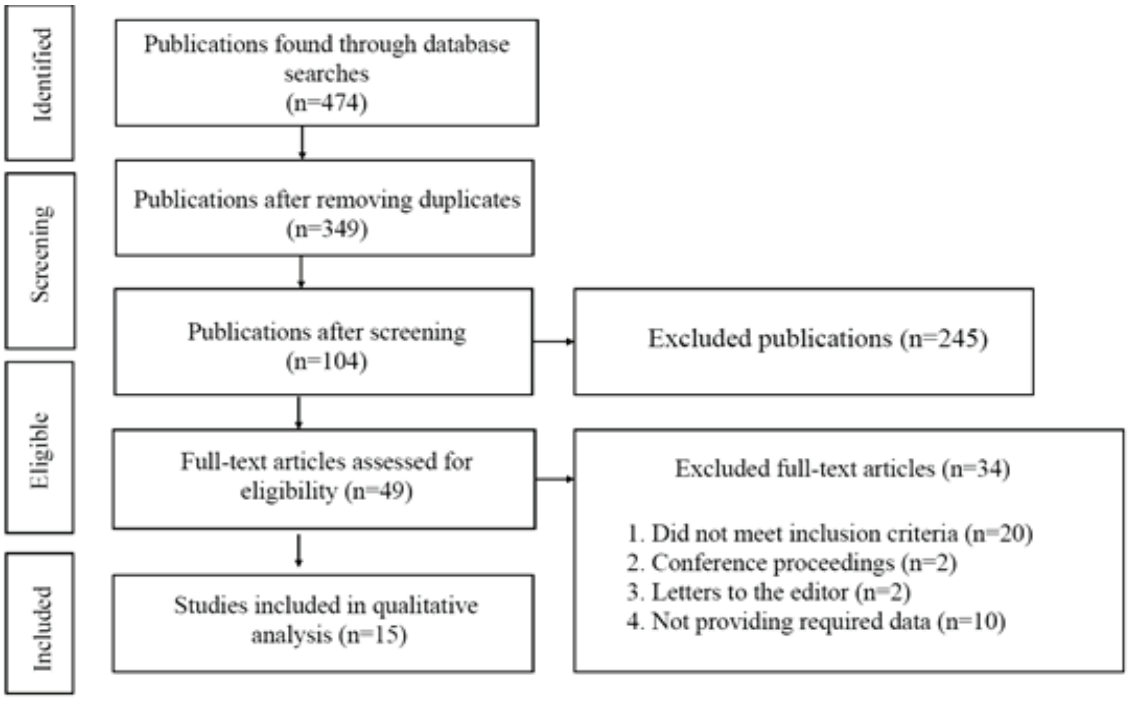
Percutaneous implantable epidural catheters today are in most cases used in the early postoperative period to relieve acute pain, and they are also used for a test study before installing long-term intrathecal therapy with a morphine pump, especially with a relatively unfavorable prognosis (less than 3 months) [20, 23]. The disadvantages of these devices include local and generalized infection, migration, kinking, and obstruction of catheters [5, 14]. In the work published by Hsieh et al., the authors have assessed the effectiveness and safety of epidural opioid administration in cancer patients with end-stage cancer. The systematic review included 9 randomized trials (n=340) and 15 observational studies (n=926). The authors found that epidural administration of opioids in combination with local anesthetics or adjuvants had the best analgesic effect. There was also no significant difference in the dynamics of pain between bolus administration and continuous epidural infusion of morphine [13].

Today, there is also the method of dosed intrathecal administration of opioid analgesics using programmable pumps being successfully applied. One of the advantages of these systems is maintaining lower morphine concentrations in the cerebrospinal fluid [13, 16, 20, 25].

The work of narcotic analgesics administered intrathecally is inhibiting the release of neurotransmitters by opioid receptors located in lamina II of the dorsal horn of the spinal cord. Programmable pumps are suitable for patients with a life expectancy of more than 6 months [21, 23]. Complications of such analgesia include urinary retention, sweating, nausea, vomiting, euphoria, central depression, orthostatic hypotension, and tachyphylaxis [4, 13, 14].

In the study Carvajal et al. The results of surgical treatment of 93 patients with pancreatic MN were studied: in 70 cases, a programmable morphine pump was implanted and in 23, ports and external pumps were implanted. All patients received a mixture of morphine and analgesics – ropivacaine (n=89), ziconotide (n=75), clonidine (n=25). Median survival was 91 days. The authors found that a halving of pain was noted by 78.8% of patients with an implanted system and 44.4% of patients with external pumps and ports [5].

In a multicenter prospective study on 1403 oncology respondents with CPS, the effectiveness and safety of intrathecal therapy with opioid analgesics was assessed . The most common locations of MN were lungs, breast, colon/rectum, pancreas, and prostate. The authors assessed life expectancy after pump implantation: six-year life expectancy was 39%, one-year – 24%, two-year – 16%, three-year – 11%, ten-year – 5%. The authors managed to collect information about the dynamics of pain severity from 283 patients. It was found that intrathecal administration of opioids reduced pain



Search and selection strategy for the systematic review

General Characteristics of Studies included in the Systematic Review

Authors	Number of patients	Average age of patients	Study design	Level of evidence	Newcastle -Ottawa Scale score	Interventional treatment method	Observation timeframe (months)
Carvajal et al., 2018 [5]	93	61.1	Retrospective	3	2	Implantable programmable morphine pumps	3
Stearns et al, 2020 [20]	1403	59	Prospective, cohort	3	6	Implantable programmable morphine pumps	12
Pacheco-Feijoó et al., 2023 [17]	-	-	Meta-analysis	1	6	Transgastric neurolysis of the celiac plexus	-
Gevorkyan T. G. et al., 2023 [1]	12	-	Retrospective, cohort	3	2	Transgastric neurolysis of the celiac plexus	2
Koulouris et al., 2021 [15]	727	-	Systematic review and meta-analysis	1	6	Transgastric neurolysis of the celiac plexus	-
Wong et al., 2007 [22]	25	55	Retrospective, cohort	3	3	Intercostal blocks	1
Darabad et al., 2020 [10]	3	65	Clinical case	3	-	Selective blockade of the stellate ganglion	3
Luo et al., 2022 [26]	-	-	Literature review	5	-	Puncture interventions on the stellate ganglion	-
Motoyama et al., 2023 [24]	1	55	Clinical case	3	-	Transgastric neurolysis of the celiac plexus	-
Sakamoto et al., 2010 [18]	67	-	Retrospective, cohort	3	2	Transgastric neurolysis of the celiac plexus	1
Capozza et al, 2021 [23]	-	-	Literature review	5	-	Implantable programmable morphine pumps	-
Bentley et al., 2014 [4]	5	64	Retrospective, cohort	3	2	Implantable programmable morphine pumps	3
Candido et al., 2017 [6]	-	-	Literature review	1	-	Neurolysis of the celiac plexus, selective blocks	-
Zheng et al., [11]	54	66.40±18.52	Prospective, cohort	3	3	Implantable programmable morphine pumps	3
Duarte et al., [14]	3043	-	Meta-analysis	1	6	Implantable programmable morphine pumps	16

levels and maintained the effect after 6 (n = 103) and 12 (n = 55) months. There was also an improvement in the quality of life according to the EuroQol -5 D questionnaire (n = 41) 6 months after the procedure. In 3.2% of patients, complications associated with the operation of the pump were registered that required its replacement [20].

A meta-analysis including 22 studies showed that intrathecal use of opioid analgesics and spinal cord stimulation are effective and safe methods in the treatment of CPS of oncological origin [14].

Neurodestructive methods of treating chronic pain syndrome. Percutaneous and transgastric neurolysis of the celiac plexus. Neurodestructive methods of treating CPS in cancer patients are used when the "analgesic ladder" is ineffective, in patients with uncontrolled pain syndrome [2,20]. The most commonly used neurodestructive methods include neurolysis of the celiac plexus, peripheral and plexus blockades, laser and radiofrequency destruction of the spinal nerve roots [3,12,17,24].

Neurolysis (neurolysis, neuroablation) is a process of persistent destruction of afferent fibers of the peripheral nervous system (surgical, chemical, thermal), which is based on the introduction of a 96% ethyl alcohol solution into the celiac plexus [12]. The most typical complications of the manipulation are: orthostatic hypotension, diarrhea, post-injection hematoma, pneumothorax, abscess and peritonitis [3,17]. Neurolysis of the celiac plexus is indicated for patients with MN of the upper gastrointestinal tract, mainly with inoperable lesions of the pancreas [18,24].

In a meta-analysis by Pacheco-Feijoó et al . compared the effect of percutaneous endoscopic neurolysis and traditional pharmacological treatment of patients with chronic heart disease and MN localized in the upper abdominal cavity. A total of 744 publications were examined between 2000 and 2021 in the PubMed, Cochrane, Scopus, Web of Science and Google Scholar databases . Of these, 13 manuscripts were selected for qualitative analysis, 3 of which met the criteria for quantitative synthesis and procedural efficiency. It was found that pain was significantly reduced in the neurolysis group compared to the group that used only pharmacological treatment. Among the side effects of manipulation, orthostatic hypotension, diarrhea and pain at the puncture site were recorded in 21-37% of cases [17].

In a study by Gevorkyan et al., the results of neurolysis in 12 patients with inoperable pancreatic MN associated with CPS were studied retrospectively. The authors reported that in 9 (75%) cases there was a persistent decrease in pain, while in 3 (25%) repeated neurolysis was required due to persistent pain [1].

Transgastric neurolysis of the celiac

plexus under endoscopic ultrasonography control (EUS) is currently one of the most popular methods of treating CPS of the upper gastrointestinal tract, which was introduced in 1966 by Wiersema MJ and Wiersema LM [1].

In a meta-analysis by Koulouris et al., the effectiveness and safety of endoscopic neurolysis for pancreatic MN was studied depending on the needle access point: central, bilateral, or celiac ganglion neurolysis. Of the 136 publications on this topic, 26 were used for full-text qualitative analysis. The authors reported that there was no significant difference in the dynamics of pain reduction between the three access points; the overall reduction in pain after EUS was 68% (61-74%) in the second week after manipulation and 53% (45-62%) in the fourth week [15].

Peripheral Nerve Plexus Blocks. Peripheral and plexus blocks in oncological practice are used as an additional method of pain relief in combination with the analgesic ladder and are combined with a multimodal approach [3]. Such methods are used for CPS that occurs in innervation of one or more nerves [3, 22, 26].

Intercostal nerve blockade is a common method for relieving CPS that occurs in rib destruction by a metastatic lesion in MN of the breast, lungs, and sternum and is associated with a high probability of pneumothorax. There is practically no information in the specialized literature about the results of using this method. In 2007, a clinical series of 25 patients who underwent neurolytic intercostal blockade was published. It was found that 80% of patients experienced a reduction in pain by more than 50% [22].

Patients with MN in the head and neck area represent the most vulnerable group with a frequent risk of developing opioid dependence due to the high need for use of narcotic medications. Today, ultrasound-guided blockade of the stellate ganglion is effectively used to relieve pain in this group of patients [3, 26]. This neural structure is located along the lateral border of the C6 and Th1 vertebral bodies, and in some cases on the lower edge of the C6 vertebral body. A contraindication to the blockade is contralateral pneumonectomy, which is accompanied by the risk of pneumothorax [26]. The study by Darabad et al. presents data from 3 patients with head and neck MN who underwent stellate ganglion blockade using 0.25% Bupivacaine. As a result, the authors report a reduction in pain by an average of 5.33 ± 4.16 cm, the effectiveness of which was maintained for up to three months. The authors stated that there were no complications after the procedure [10].

References

1. Gevorkyan T.G., Fainstein. I.A, Stilidi I.S. Nejrolizis chrevnogo spleteniya v lechenii hronicheskogo bolevogo sindroma u pacientov s nerezektabel'nym rakom podzheludochnoj zhelezy [Neurolysis of the celiac plexus in the treatment of chronic pain syndrome in patients with unresectable pancreatic cancer]. Tazovaya hirurgiya i onkologiya [Pelvic surgery and oncology. 2023; 13(2): 11–16 (In Russ.).]

2. Byvaltsev V.A., Kalinin A.A., Okoneshnikova A.K., Satardinova E.I. Punkcionnye metody lecheniya v nejrohirurgicheskoj praktike: uchebnoe posobie [Puncture Methods of Treatment in Neurosurgical Practice: Textbook]. Irkutsk, ISMU. 2023. 97 p.

3. Byvaltsev VA, Goloborodko VY, Kalinin AA, Shepelev VV, Pestryakov YY, Riew KD. A Standardized Anesthetic/Analgetic Regimen Compared to Standard Anesthetic/Analgetic Regimen for Patients With High-Risk Factors Undergoing Open Lumbar Spine Surgery: A Prospective Comparative Single-Center Study. Neurosurgical Review. 2023; 46: 95. DOI: 10.1007/s10143-023-02005-4

4. Bentley JN, Viswanathan A, Rosenberg WS, Patil PG. Treatment of Medically Refractory Cancer Pain With a Combination of Intrathecal Neuromodulation and Neurosurgical Ablation: Case Series and Literature Review. Pain Med. 2014;15(9): 1488–1495. DOI: 10.1111/pme.12481.

5. Carvajal G, Dupoiron D, Seegers V. Intrathecal Drug Delivery Systems for Refractory Pancreatic Cancer Pain: Observational Follow-up Study Over an 11-Year Period in a Comprehensive Cancer Center. Anesth Analg. 2018; 126(6): 2038–2046. DOI: 10.1213/ANE.0000000000002903

6. Candido K, Kusper TM, Knezevic NN. New Cancer Pain Treatment Options. Curr Pain Headache Rep. 2017; 21(2): 12. DOI: 10.1007/s11916-017-0613-0.

7. Rodriguez C, Ji M, Wang HL, Padhya T, McMillan SC. Cancer Pain and Quality of Life. J Hosp Palliat Nurs. 2019; 21(2): 16–123. DOI: 10.1097/NJH.0000000000000507.

8. Sica A, Casale B, Dato MTD, Calogero A, Spada A, Sagnelli C, Santagata M, Buonavolontà P, Fiorelli A, Salzano A, Dodaro CA, Martinelli E, Saracco E, Troiani T, Tammaro D, Ciardiello F, Papa A. Cancer and Non-cancer Related Chronic Pain: From the Physiopathological Basics to Management. Open Med (Wars). 2019; 7(14): 761–766. DOI: 10.1515/med-2019-0088.

9. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWC, Wang SJ. Chronic Pain as a Symptom or a Disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019; 160(1): 19–27. DOI: 10.1097/j.pain.0000000000001384.

10. Darabad R.R., Kalangara J.P., Woodbury A. Case Series: Cancer-Related Facial Pain Treated with Stellate Ganglion Block. Palliat Med Rep. 2020; 2(1): 290 – 295. DOI: 10.1089/pmr.2020.0042.

11. Zheng S, He L, Yang X, Li X, Yang Z. Evaluation of Intrathecal Drug Delivery System for Intractable Pain in Advanced Malignancies: A Prospective Cohort Study. Medicine (Baltimore). 2017; 96(11): 6354. DOI: 10.1097/MD.0000000000006354.

12. Pérez-Aguado G, de la Mata DM, Valenciano CM, Sainz IF. Endoscopic Ultrasonography-Guided Celiac Plexus Neurolysis in Patients With Unresectable Pancreatic Cancer: An Update. World J Gastrointest Endosc . 2021; 16 (10): 460–472. DOI: 10.4253/ wjge . v13. i10.460.

13. Hsieh YL, Chen HY, Lin CR, Wang CF. Efficacy of Epidural Analgesia for Intractable Cancer Pain: A Systematic Review. Pain Pract. 2023; 23(8): 956–969. DOI: 10.1111/papr.13273.

14. Duarte R, Copley S, Nevitt S, Maden M, Al-Ali AM, Dupoiron D, Eldabe S. Effectiveness and Safety of Intrathecal Drug Delivery Systems for the Management of Cancer Pain: A Systematic Review and Meta-Analysis. Neuromodulation. 2023; 26 (6): 126-1141. DOI: 10.1016/j.neurom.2022.03.003. Epub 2022 Apr 11. PMID: 35422368.

15. Koulouris AI, Alexandre L, Hart AR, Clark A. Endoscopic Ultrasound-Guided Celiac Plexus Neurolysis (EUS-CPN) Technique and Analgesic Efficacy in Patients with Pancreatic Cancer: A Systematic Review and Meta-Analysis. Pancreatology. 2021; 21(2). P. 434 – 442. DOI: 10.1016/j.pan.2020.12.016.

16. Oh DC, Rispoli L, Ghosh P, Gulati A. Epidural Steroid Injections for the Management of Spinal Malignancy-Related Pain: A Pragmatic Review and Retrospective Study. Pain Pract. 2021; 21(3): 85–298. DOI: 10.1111/papr.12957.

17. Pacheco- Feijoó GM, Amado- Tineo JP, Plancarte-Sánchez R, Valdivia CC, López-Millán JM. Efficacy and Safety of Celiac Plexus Neurolysis in the Treatment of Chronic Pain Secondary to Oncological Pathology of the Upper Hemiabdomen: A Systematic Review and Meta-Analysis. Indian J Palliat Care. 2023; 29(4): 394–406. DOI 10.25259/IJPC_203_2022.

18. Sakamoto H, M. Kitano M, Kamata K, Komaki T, Imai H, Chikugo T, Takeyama Y, Kudo M. EUS-Guided Broad Plexus Neurolysis Over the Superior Mesenteric Artery Using a 25-Gauge Needle. Am J Gastroenterol. 2010; 105(12): 2599–2606. DOI: 10.1038/ajg.2010.339.

19. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209-249. DOI: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338

20. Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, Weaver T. Intrathecal Drug Delivery Systems for Cancer Pain: An Analysis of a Prospective, Multicenter Product Surveillance Registry. Anesth Analg . 2021; 30(2): 289–297. DOI: 10.1213/ANE.0000000000004425. PMID: 31567325

21. Habib MH, Schlögl M, Raza S, Chwistek M, Gulati A. Interventional Pain Management in Cancer Patients-a Scoping Review. Ann Palliat Med. 2023; 12(6): 1198–1214. DOI 10.21037/apm-23-433.

22. Wong FC, Lee TW, Yuen KK, Lo SH, Sze WK, Tung SY. Intercostal Nerve Blockade for Cancer Pain: Effectiveness and Selection of Patients. Hong Kong Med J. 2007; 13: 266 –2 70.

23. Capozza MA, Triarico S, Mastrangelo S, Attinà G, Maurizi P, Ruggiero A. Narrative Review of Intrathecal Drug Delivery (IDD): Indications, Devices and Potential Complications. Ann Transl Med. 2021; 9(2): 186. DOI: 10.21037/atm-20-3814.

24. Motoyama Y, Sato H, Nomura Y, N. Obata, S. Mizobuchi Percutaneous Retrocrural Versus Ultrasound-Guided Coeliac Plexus Neurolysis for Refractory Pancreatic Cancer Pain. BMJ Support

Palliat Care. 2023; 3: 81–83. DOI: 10.1136/bmjspcare-2020-002246.
25. Wang JK, Nauss LA, Thomas JE. Pain Relief by Intrathecally Applied Morphine in Man. Anesthesiology. 1979; 50(2): 149–151. DOI: 10.1097/00000542-197902000-00013. PMID: 373503.
26. Luo Q, Wen S, Tan X, Yi X, Cao S. Stellate Ganglion Intervention for Chronic Pain: A review. Ibrain. 2022; 28:8(2): 210–218. DOI: 10.1002/ibra.12047.
27. Caylor J, Reddy R, Yin S, Cui C, Huang M, Huang C, Ramesh R, Baker DG, Simmons A, Souza D, Narouze S, Vallejo R, Lerman I. Spinal Cord Stimulation in Chronic Pain: Evidence and Theory for Mechanisms of Action. Bioelectron Med. 2019; 28: 5 – 25 DOI: 10.1186/s42234-019-0023-1.
28. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. J. Clin. Epidemiol. 2009; 62(10): 34. DOI: 10.1016/j.jclinepi.2009.06.006.
29. Sindt JE, Larsen SD, Dalley AP, Collier WH, Brogan SE. The Rate of Infectious Complications After Intrathecal Drug Delivery System Implant for Cancer-Related Pain Is Low Despite Frequent Concurrent Anticancer Treatment or Leukopenia. Anesth Analg. 2020; 131(1): 280–287. DOI: 10.1213/ANE.0000000000004639
30. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (Nos) for Assessing the Quality of Non-Randomized Studies in Meta-Analyses. URL: http:// www.ohri.ca/programs/clinical_epidemiology/oxford.asp

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CLINICAL EXPERIENCE OF CORRECTION OF THE MOTOR-EVACUATION FUNCTION OF DUODENUM IN ACUTE DESTRUCTIVE PANCREATITIS IN THE FIRST PHASE OF THE DISEASE

The purpose of the study was to clinically evaluate the effectiveness of the treatment tactics we developed using the Dextran-40 colloidal solution in patients with duodenal MEF disorders with ADP in the first phase of the disease. The use of a technique using a colloidal solution of Dextran-40 showed greater effectiveness in terms of the rate of reduction in intraduodenal pressure compared to the standard method of prolonged nasogastrojejunal decompression of the upper gastrointestinal tract used for this purpose. Among other things, this made it possible to improve the immediate results of treatment.

Keywords. Acute pancreatitis, motor-evacuation function, duodenostasis.

Introduction. Currently, the problem of acute destructive pancreatitis (ADP) and its complications is one of the most difficult in modern emergency surgery of the abdominal organs. Despite the successes achieved in improving various diagnostic methods, intensive care tactics, surgical treatment using minimally invasive technologies, mortality in destructive pancreatitis over the last decade remains at a fairly high level and amounts to 15-40% [9], with infected forms and the development of pancreatogenic sepsis can reach 65% [3].

In the pathogenesis of many diseases of the pancreatobiliary system, including acute pancreatitis, a special place is occupied by the problem of impaired motor-evacuation function (MEF) of the duodenum [8]. In the medical literature, this pathology can be described under different names: duodenal stasis, megaduodenum, chronic duodenal obstruction, duodenal dyskinesia, etc. However, with ADP, unlike many other situations, duodenal stasis (DS) is acute [4]. In addition, DS is an integral part of a more significant process that develops against the background of ADP, which includes intestinal failure syndrome (IFS). In turn, IFS, as some researchers believe [1,2,4,10], is the cause of the development of a wide range of infectious complications in ADP. A non-trivial task is that correction of duodenal MEF in ADP can be carried out over a fairly long period of time, taking into account the phase nature of the disease, the presence or absence of certain forms of complications of the disease, the need for surgical interventions, which can also affect the effectiveness of the corrective measures. All this creates the prerequisites for a more in-depth study of this problem by modern emergency pancreatology, and the search for ways to quickly resolve this issue.

Despite the fact that in our time, significant progress has been made in understanding the general principles of treatment of ADP and some of its complications, the issues of correcting disorders of the MEF of the duodenum remain unresolved, as we indicated above. At different periods of time, different authors proposed certain methods for correcting disturbances in the MEF of the duodenum in ADP [4,6,8,11,12]. In particular, it was pointed out that the most severe MEF disorders are diagnosed in the initial stages of the disease (I A-B phase). However, to this day, despite regular revisions of clinical recommendations for the treatment of acute pancreatitis and its complications, there are no protocols devoted to the correction of duodenal MEF disorders in ADP. It is for this reason that we tried to evaluate the clinical effectiveness of the treatment tactics used in the clinic in relation to patients who were diagnosed with symptoms of duodenal MEF disorders in the first phase of the disease. It is during this period that a pronounced pathomorphological transformation of pancreatic necrosis occurs, ranging from enzymatic peritonitis and parapancreatitis to peripancreatic infiltrate and the formation of delimited fluid accumulations.

The **aim** of the study – to evaluate the clinical effectiveness of the developed treatment tactics in patients with disorders of the duodenal MEF during ADP in the first phase of the disease.

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Material and methods. The study was conducted in a multidisciplinary surgical clinic in the Yakutsk – Republican Hospital № 2 – Center for Emergency Medical Care (RH №2-CEMP) in the period from 2022 to 2024. A non-randomized, single-center, retrospective-prospective study included 61 patients with ADP and who had disorders of the duodenal MEF. The average age of the patients was 38,1±5,4 years, there were 35 (57,4%) men, 26 (42,6%) women. The diagnosis of ADP was established on the basis of a standard examination. During the presented period, we were guided by the classification of acute pancreatitis adopted on october 30, 2014 in St. Petersburg at a meeting of the Russian Society of Surgeons and the Association of Hepatopancreatobiliary Surgeons of the CIS countries [5]. Inclusion criteria for the study were: moderate to severe acute pancreatitis; the age of the studied patients was from 18 to 74 years; patients who have not undergone surgical treatment in other health care facilities, in case of their evacuation to a multidisciplinary surgical hospital; absence of surgical or pancreatogenic violations of the integrity of the duodenum at the time of admission to the clinic, absence of death in the first 72 hours from the start of surgical care. Taking into account the fact that today there is no standardized scheme for correcting disturbances in duodenal MEF in ADP, all patients were divided into two groups depending on the treatment tactics used. The first group, the control group, included 34 (55,7%) patients who, in order to relieve gastrostasis and intestinal paresis, underwent prolonged nasogastric and, if possible, nasogastrointestinal decompression with the installation of a probe 30 cm distal to the Treitz ligament, as recommended in current clinical practice recommendations for the treatment of acute pancreatitis [7]. The second, the main one, included 27 (44,3%) patients who used a scheme developed by us in the clinic and proposed for correcting disturbances in the MEF of the duodenum in ADP. The MEF correction scheme was carried out as follows. During infusion-detoxification therapy, regardless of the need for surgical intervention, 200 ml of a 10% colloidal solution of Dextran-40 with a molecular weight of 35-45 kDa is injected into the duodenum via a two-channel probe 4 times a day for 3-5 days. The procedure for administering the solution is continued until normal values of intraduodenal pressure are achieved (100-130 mm water column). If necessary, the procedure is repeated during the treatment process. An indispensable condition before introducing the solution was to flush the intestinal lumen to «clean waters» through a previously installed two-channel duodenal tube, preheated in a water bath to 37 °C with physiological solution. To determine the form (severity) of duodenostasis and the level of intraduodenal pressure using the open catheter method, we used the method proposed by Kurish R.V. [6]. So, at a level of intraduodenal pressure of 180-190 mm water column, and a fluid flow rate of 20-25 ml, DS was considered compensated, with a level of intraduodenal pressure of 220-230 mm water column, and fluid flow is 30-35 ml, subcompensated and the level of intraduodenal pressure is 260-270 mm water column, and a fluid flow rate of more than 40 ml, decompensated, which is consistent with other authors who studied DS using this method [4,8]. The choice of solution for the purpose of correcting disturbances in duodenal MEF was due to the fact that the colloidal solution Dextran-40, in comparison with other solutions known and used for this purpose, is a drug that has passed state registration and accreditation with known characteristics, is widely used in practical medicine, does not requires the creation of laboratories, personnel training, and has a minimum of recorded side effects.

Statistical processing of the received material was carried out using the modern computer program «Stat Plus 2021» for Microsoft office. To determine the hypothesis and determine the type of distribution of the values of the studied characteristics, the Shapiro-Wilk quantitative test was used. In the groups to be compared, the arithmetic mean – (M) and standard deviation – (σ) were determined. Parametric data are presented as M±σ. The reliability coefficient of differences – ρ groups with a normal distribution was determined by the t-test. The critical value was taken to be $p \leq 0,05$.

Results and discussion. It is well known that difficulties in diagnosing disturbances in the MEF of the duodenum in ADP and a number of other pathological conditions arise due to the prevalence of symptoms of destructive pancreatitis itself. In addition, there are serious limitations on the possibility of using informative research methods (x-ray, multichannel floor-by-floor manometry, determination of the bioelectrical activity of various parts of the intestine, angiography of the superior mesenteric artery, etc.), which have proven themselves in determining the severity of disorders in chronic processes. This is primarily due to the severity of the condition of patients with ADP, as well as the presence of pain, the presence of encephalopathy, which does not allow the patient to maintain contact with the researcher and follow his recommendations, restrictions on the use of contrast agents in the presence of organ dysfunction, etc. In connection with the existing diagnostic features, we supported the symptoms associated with disruption of the MEF of the duodenum

Table 1

Comparative dynamics of duodenomanometry and duodenodebitometry indices during correction of duodenal MEF in ADP in groups 1 and 2

Indicators	Group	Time period from the start of therapy			
		1 day (M±σ)	3 day (M±σ)	5 day (M±σ)	7 day (M±σ)
IA-phase of the disease					
Basal intraduodenal pressure	1-st 2-nd	228.1±3.2* 200.3±3.3	200.7±3.0* 160.4±4.1	180.1±3.0* 151.1±2.4	164.1±3.3* 129.7±1.8
Residual intraduodenal pressure	1-st 2-nd	231.1±4.4* 225.1±3.1	215.1±3.3* 183.1±5.6	192.3±3.5* 158.4±3.3	174.1±1.5* 141.1±2.0
Duodenal content flow	1-st 2-nd	40.3±1.1 38.6±2.2	31.3±1.2* 24.1±1.7	26.3±2.1* 20.1±2.2	20.3±1.3* 15.0±4.1
IB phase of the disease					
	Group	8-е сут (M±σ)	10-и сут (M±σ)	12-е сут (M±σ)	14-е сут (M±σ)
Basal intraduodenal pressure	1-st 2-nd	312.2±2.3* 291.3±1.1	286.4±3.1* 272.1±2.3	262.1±3.0* 232.0±1.3	178.1±1.2* 146.3±2.1
Residual intraduodenal pressure	1-st 2-nd	325.2±1.3* 310.2±1.2	287.4±2.3* 247.1±1.6	257.0±1.2* 239.0±2.2	236.4±1.6* 219.0±1.1
Duodenal content flow	1-st 2-nd	49.1±2.2 43.5±1.1	43.0±1.3* 34.1±2.5	37.1±2.1* 24.0±1.3	26.0±1.3 20.2±3.3

Note. In table 1-2: *Statistically significant differences between groups ($\rho \leq 0.05$).

in acute destructive pancreatitis with data obtained during duodenomanometry and duodenodebitometry. The above research methods are simple, informative and accessible for disorders of the MEF of the gastrointestinal tract and are ideal for patients with ADP.

According to our observations, upon admission to the clinic, all 61 (100%) patients with ADP were found to have disturbances of the duodenal MEF of varying severity. The most pronounced changes were observed in the first 3 days in patients in phase IA of the disease and throughout the entire period in phase IB of the pathological process (table 1).

It should be noted that within 1 day from the start of treatment for ADP, there were no significant differences in the groups in terms of the results of correction of DS using either the regimen recommended by the Russian Society of Surgeons or the one proposed by us. At the same time, starting from the 2-nd day of therapy in patients in phase IA of the disease and starting from 2-3 days in patients in phase IB, a clear trend towards a more rapid decrease in intraduodenal pressure in patients of the second group could be observed , and in whom the treatment regimen we developed was used for this purpose.

In our opinion, in many respects, the positive clinical effect of the administration of 10% Dextran-40, in contrast to prolonged nasogastrointestinal decompression, or the administration of saline hypertonic solutions, is ensured by the very nature of high-molecular compounds. In particular, a small volume injection of a solution containing dextran is required – 100-200 ml. Dextran solutions provide the viscosity of solutions, increase the prolonging effect of other substances (if they are used together) included in the solution, are able to reduce the toxic level of the active substance by eliminating sharp fluctuations in concentration, have a pronounced decongestant effect, provide a detoxification effect due to the ability to adsorb on their surfaces various endo- and exotoxins. In addition, during the hydrolysis of dextran, α-oligosaccharides are formed, which are well absorbed into the blood and improve tissue microcirculation by reducing the aggregation of formed elements, thereby preventing thrombus formation. In our case, the positive effect of introducing a colloidal solution of Dextran-40 into the lumen of the duodenum was due to the ability of high-molecular compounds to increase oncotic pressure – colloid-osmotic pressure. In this regard, excess water molecules were removed from the interstitial space of the intestinal wall and lumen, thereby ensuring a fairly rapid and effective reduction in intraduodenal pressure and restoration of motor-evacuation function.

In parallel with the decrease in intraduodenal pressure and restoration of duodenal function, the symptoms of the disease also changed. At the same time, more pronounced changes that appeared in the early stages occurred in patients of the 2-nd observation group. Thus, a weakening of the main symptoms of duodenal MEF disorders (nausea and vomiting) in the 2-nd group of the study was observed already by 2-3 days from the start of therapy – in 78,5% of patients, while in the 1st group, these symptoms persisted for a longer period of time, and a feeling of bitterness in the mouth and

Table 2

Comparative dynamics of relief of dyspeptic disorders in the correction of duodenal MEF with ADP in the 1-st and 2-nd groups

Clinical sign	Group	Time period from the start of therapy			
		1 day (M±σ)	3 day (M±σ)	5 day (M±σ)	7 day (M±σ)
IA-phase of the disease					
Feeling of bitterness in the mouth, %	1-st 2-nd	70.1±4.4 65.1±2.2	63.4±1.1* 55.3±3.3	44.1±3.2* 35.1±2.2	25.5±3.3* 15.2±2.4
Heartburn, %	1-st 2-nd	81.4±3.1* 71.3±3.5	69.3±4.2 65.4±3.3	56.1±3.0* 35.0±3.3	30.1±2.2* 17.0±4.2
Nausea, %	1-st 2-nd	91.2±4.8* 78.5±3.1	82.3±4.2* 35.2±2.4	60.0±1.5* 28.7±3.1	40.2±4.1* 12.1±1.1
Vomit, %	1-st 2-nd	79.3±1.5* 70.2±2.2	60.1±1.3* 50.3±4.2	30.1±2.3* 18.7±3.2	16.2±3.2 12.0±1.3
IB phase of the disease					
	Group	8-е сут (M±σ)	10-и сут (M±σ)	12-е сут (M±σ)	14-е сут (M±σ)
Feeling of bitterness in the mouth, %	1-st 2-nd	85.3±1.5* 77.2±1.2	72.2±1.3 66.1±3.3	63.2±1.4* 52.4±1.2	49.3±1.5* 39.2±1.3
Heartburn, %	1-st 2-nd	89.2±2.2* 83.3±1.2	78.3±1.2* 68.6±2.2	72.1±1.0 69.3±1.4	70.0±1.0* 46.2±1.2
Nausea, %	1-st 2-nd	99.3±3.1 95.2±2.2	92.0±1.5* 77.1±3.3	74.2±1.2* 55.0±1.4	56.5±3.3* 23.2±2.2
Vomit, %	1-st 2-nd	95.0±2.2* 83.0±3.2	72.3±3.3* 56.0±5.2	56.0±2.2* 42.3±1.5	36.4±3.3* 26.0±1.3

Table 3

Comparative characteristics of surgical interventions for ADP in the first phase of the disease in patients of the 1-st and 2-nd observation groups

Type of surgery	Number of patients			
	1-st group (n=34)		2-nd group (n=27)	
	abs.	%±σ	abs.	%±σ
IA-phase of the disease				
Therapeutic and diagnostic laparoscopy	3	8.8±4.9	1	3.7±3.6
Percutaneous drainage of the abdominal cavity under ultrasound guidance	3	8.8±4.9	2	7.4±5.0
Projection interventions using a mini-assistant (minilaparotomy)	1	2.9±2.9	1	3.7±3.6
IB phase of the disease				
Therapeutic and diagnostic laparoscopy	2	5.9±4.0	1	3.7±3.6
Percutaneous drainage of the abdominal cavity under ultrasound guidance	5	14.7±6.1	2	7.4±5.0
Projection interventions using a mini-assistant (minilaparotomy)	5	14.7±6.1	1	3.7±3.6

heartburn could be observed at later periods of control (table 2).

An integral part of the treatment process for ADP is surgical correction for emerging complications of the disease. In turn, timely surgical correction according to indications (they must be strictly verified) will be the key to successful relief, including violations of the motor-evacuation function of the gastrointestinal tract. As a rule, in the first phase of ADP (periods 1-2), there are no indications for traditional «open» interventions. This is caused by the severity of the patients condition, the presence of pancreatogenic shock, transient or persistent organ failure, and the low likelihood of developing an infectious process during this period of time. During this period, as a rule, surgical correction is carried out using minimally invasive technologies (laparoscopy, percutaneous drainage of the abdominal cavity under ultrasound guidance, projection interventions using mini-assistants (minilaparotomy), etc.). To confirm our words, we provide a comparative table of the types of surgical interventions (all of them are minimally invasive) that were used in patients in the 1st and 2-nd observation groups in the first phase of the disease (table 3).

It is necessary to comment that, as a rule, in phase IA of the disease, when it comes to the presence of enzymatic fluid in the abdominal cavity (enzymatic peritonitis), preference was given to percutaneous drainage of the abdominal cavity in sloping areas under ultrasound guidance: in group 1 – 8,8% of patients, in group 2 – 7,4% of patients. Therapeutic and diagnostic laparoscopy was performed somewhat less frequently. In most cases, it was of a diagnostic nature (suspicion of a combined nature of the disease or the development of an intra-abdominal complication). In group 1 – 8,8% of patients, in group 2 – 3,7% of patients. In phase IB, the proportion of percutaneous drainage interventions and projection minilaparotomy increased significantly. Thus, in the 1-st group it amounted to 29,4% of patients, in the 2-nd group – 11,1% of patients. This circumstance can be explained by the lack of clinical, laboratory and instrumentally confirmed dynamics of relief of the inflammatory process, expressed in the preservation and/or increase of free fluid (mainly in the projection of the omental bursa) and the onset of sequestration. In severe forms of ADP, during this period infection of acute necrotic and peripancreatic fluid accumulations and areas of necrotic destruction may begin, which prompts the surgeon to act. At the same time, at the end of phase I of the disease (end of the 2-nd beginning of the 3-rd week from the onset of the disease) during puncture-drainage and minilaparotomy interventions in 5 (14,7%) cases in the 1-st group and in 1 (3,7%) case in the 2-nd observation group, when conducting a microbiological study of the exudate in the postoperative period, microflora was detected. This fact once again confirms that, if possible, earlier relief of MEF disorders in the proximal gastrointestinal tract prevents the development of pancreatogenic infectious complications. At the same time, which, apparently, is also due to earlier leveling of the source of endotoxemia, a decrease in the mortality rate was noted in the group of patients who underwent correction of duodenal MEF disorders using the method we proposed. Mortality in the 1-st group of observations was 15,5%, in the 2-nd group – 9,8%.

References

1. Baymakov SR, Ashirmetov AKh, Rasulov KhK. Sindrom enteralnoy nedostatochnosti pri ostrom pankreatite, mekhanizmy razvitiya i puti vyyavleniya [Enteral insufficiency syndrome in acute pancreatitis, mechanisms of development and ways of detection].Vestnik ekstrennoy meditsiny [Bulletin of emergency medicine. 2021; 1: 65-76 (In Russ.).]

2. Kiselev VV, Petrikov SS, Zhigalova MS, et al. Vosstanovleniye propulsivnoy funktsii kishechnika u patsiyentov s tyazhelym ostrym pankreatitom v usloviyakh otdeleniya reanimatsii i intensivnoy terapii [Restoration of intestinal propulsive function in patients with severe acute pancreatitis in the intensive care unit]. Zhurnal im. N.V. Sklifosovskogo «Neotlozhnaya meditsinskaya pomoshch» [N.V. Sklifosovsky Journal Emergency Medical Care. 2023; 2: 210-216 (In Russ.).]

3. Gulikyan G.N. Ostryy pankreatit v khirurgicheskoy patologii [Acute pancreatitis in surgical pathology]. Moskovskiy khirurgicheskiy zhurnal [Moscow surgical journal. 2022; 2: 20-27 (In Russ.).] doi: 10.17238/2072-3180-2022-2-20-27.

4. Evdokimenko V.V. Osobennosti motorno-evakuatornoy funktsii dvenadtsatiperstnoy kishki pri pankreatite: Diss. …kand. med. nauk [Features of the motor-evacuation function of the duodenum in pancreatitis: Diss. ...cand. med. Sciences. Krasnoyarsk, 2006. 112 p. (In Russ.).]

5. Bagnenko SF, Goltsov VR, Savello VE, et al. Klassifikatsiya ostrogo pankreatita: sovremennoye sostoyaniye problemy [Classification of acute pancreatitis: current state of the problem]. Vestnik khirurgii [Bulletin of surgery. 2015; 5: 86-92 (In Russ.).]

6. Kurish R.V. Khirurgicheskaya taktika i prognozirovaniye rezultatov lecheniya khronicheskogo kholetsistita s uchetom sostoyaniya prokhodimosti zhelchnykh putey i dvenadtsatiperstnoy kishki: Diss. …kand. med. nauk [Surgical tactics and prediction of treatment results for chronic cholecystitis, taking into account the state of patency of the bile ducts and duodenum: Diss. ...cand. med. Sciences]. Ivano-Frankovsk, 1990. 169 p. (In Russ.).]

7. Kulikov DV, Korolkov AYu, Morozov VP, et al. Nereshennyye voprosy lecheniya ostrogo destruktivnogo pankreatita [Unresolved issues in the treatment of acute destructive pancreatitis]. Vestnik eksperimental'noy i klinicheskoy khirurgii [Bulletin of experimental and clinical surgery. 2019; 2: 134-140 (In Russ.).]

8. Vinnik YuS, Petrushko SI, Yakimov SV, et al. Primeneniye ozonoterapii v lechenii duodenostaza pri otechnykh i destruktivnykh formakh ostrogo pankreatita [The use of ozone therapy in the treatment of duodenostasis in edematous and destructive forms of acute pancreatitis]. Baykalskiy meditsinskiy zhurnal [Baikal Medical Journal. 2003; 4: 41-44 (In Russ.).]

9. Protsenko DN, Tsvetkov DS, Shifman EM. Taktika infuzionnoy terapii u bolnykh s ostrym destruktivnym pankreatitom: obzor literatury [Tactics of infusion therapy in patients with acute destructive pancreatitis: a review of the literature]. Vestnik intensivnoy terapii imeni A.I. Saltanova [A.I. Saltanov Bulletin of Intensive Care. 2024; 2: 94-106 (In Russ.).] doi: 10.21320/1818-474X-2024-2-94-106.

10. Skutova VA, Danilov AI, Feoktistova ZhA. Acute pancreatitis: current issues of diagnosis and complex treatment [Ostryy pankreatit: aktualnyye voprosy diagnostiki i kompleksnogo lecheniya]. Vestnik Smolenskoy gosudarstvennoy meditsinskoy akademii [Bulletin of the Smolensk State Medical Academy. 2016; 2: 78-84 (In Russ.).]

11. Tsuchiya T, Sofuni A, Itoi T. Successful EUS-guided gastrojejunostomy with very long-term patency for duodenal obstruction after severe acute pancreatitis. J. Hepatobiliary Pancreat Sci. 2022; 29 (6): 59-60. doi: 10.1002/jhbp.936.

12. Zerem E. Treatment of severe acute pancreatitis and its complications. World J. Gastroenterol. 2014; 20 (38): 13879-13892. doi: 10.3748/wjg.v20.i38.13879.

HEALTHY LIFESTYLE. PREVENTION

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FEATURES OF INDICATORS OF 24-HOUR BLOOD PRESSURE MONITORING IN INTERNET-DEPENDENT ADOLESCENTS

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The ever-increasing problem of Internet addiction (IA) in adolescents dictates the need to study its impact on the body, which is intensively developing in this age period, as the most susceptible to various adverse factors. At the same time, the relationship of Internet addiction with the pathology of the cardiovascular system has not yet been sufficiently investigated.

Purpose: In this regard, the purpose of our work was: to identify the main changes in the indicators of SMAD and their relationship with psycho-emotional state in children with Internet addiction.

Materials and methods: 69 children aged 11-18 years were examined with the help of 24-hour ambulatory blood pressure monitoring (ABPM) (TIR-NS-02s "Voskhod") on the basis of the Pediatric Department of the hospital in Krasnoyarsk. Internet addiction was identified by questionnaire using the Chen questionnaire (CIAS). The presence of psychological problems was determined by R. Goodman's questionnaire "Strengths and difficulties".

Results: As a result, children with unadapted Internet use have a tendency to increased variability in blood pressure indicators with an increase in hypotension indicators during the day and hypertension at night, which is a risk factor for the development of arterial hypertension (AH). At the same time, children with deviations in ABPM indicators were more likely than in the control group to have problems with behavior, hyperactivity and problems communicating with peers, as well as higher rates of personal anxiety with low levels of situational anxiety.

Conclusion: Thus, children with ID should be recommended to undergo ABPM in order to early identify established risk factors for the development of hypertension and its prevention with the mandatory use of psychotherapeutic techniques.

Keywords: daily blood pressure monitoring; adolescents; Internet addiction; blood pressure variability; R. Goodman questionnaire "Strengths and difficulties"

Introduction: Currently, the Internet is intensively introduced into all spheres of life. At the same time, the problem of Internet addiction (IA) among adolescents, as the least stable category of the population in the motivational-emotional sphere, is constantly growing [1, 6]. In this regard, studies on the impact of IA on health status are gaining momentum of particular relevance. The most attention is paid to the study of the risk of cardiovascular pathology development as the most frequent and serious problem in modern society [2-5, 7, 9, 14]. All kinds of ways and mechanisms contributing to the development of this pathology in Internet addiction are considered. Excessive time spent in front of a screen has been found to be associated with poor sleep [11] and cardiovascular risk factors such as high blood pressure, obesity, low High-density lipoproteins (HDL) cholesterol, poor stress regulation (high sympathetic arousal and cortisol dysregulation) and insulin resistance [12]. Anxiety-depressive symptoms and suicidal moods associated with poor sleep also contribute to the development of arterial hypertension (AH) [9]. In addition, early and prolonged exposure to violent and dynamic content that activates dopamine and reward pathways is associated with Attention deficit hyperactivity disorder, risk of antisocial behavior, and decreased prosocial behavior [12]. All these psycho-emotional abnormalities reduce the ability to cope with social problems, which increases the level of stress and, consequently, the degree of risk for the development of cardiovascular pathology [9]. Taking this into account, the majority of works are devoted to the study of autonomic regulation of heart rhythm in Internet addiction [2, 13].

However, despite the special significance of the problem of early detection of cardiovascular pathology in childhood, when it is still possible to prevent it, research on this topic is extremely insufficient. There are still no clear criteria for risk factors of AH development in children. Many authors pay attention to the important role of 24-hour ambulatory blood pressure monitoring (ABPM) in the preclinical detection of early signs of hypertension in children. Nevertheless, there are no studies devoted to the study of the parameters of ABPM in children with Internet addiction in the available literature [4, 7]. Taking this into account, the aim of our study was to identify the main changes in ABPM parameters and their relationship with psycho-emotional state in children with Internet addiction.

Materials and Methods: 69 children (37 boys and 32 girls) from 11 to 18 years of age (44 aged 11-14 years and 25 aged 15-18 years) were examined using a device of daily blood pressure monitoring - ABPM (MDP-NS-02s "Voskhod") on the basis of the Pediatric Department of the hospital in Krasnoyarsk. IA was determined using a self-completed questionnaire Chen (CIAS), according to the results of which all children were categorized into 3 groups:

1 - adaptive Internet users (AIU) with the sum of questionnaire scores up to 42 points (30 people / 17 boys, 13 girls),

2 - non-adaptive Internet users (NIU) with the sum of scores from 43 to 64 points (31 people / 18 boys, 13 girls),

3 - pathological Internet users (PIU) with a sum of 65 points or more (8 people / 3 boys, 5 girls).

However, given the small volume of group 3, it was decided to combine it with group 2:

1 - AIU (30 people / 17 boys, 13 girls),

2 - NIU (39 people / 21 boys, 18 girls).

In addition, all children were divided

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into 3 groups according to the sum of scores on Chen's questionnaire according to the value distribution:

1 - up to 25% inclusive (from 26 to 38 points on the CIAS scale) - 19 people / 10 boys, 9 girls;

2 - up to 75% inclusive (from 39 to 55 points on the CIAS scale) - 34 people / 19 boys, 15 girls;

3 - more than 75% (more than 55 points on the CIAS scale) - 16 people / 8 boys, 8 girls.

To identify psychological problems we used R. Goodman's questionnaire "Strengths and difficulties", as well as previously tested questionnaires with questions about the presence of sleep disorders, daytime sleepiness, asthenic syndrome (author Tereshchenko S.Yu, Professor, Head of the Clinical Department of Somatic and Mental Health of Children, "Federal Research Center" Krasnoyarsk Scientific Center of the Siberian Branch of the Russian Academy of Sciences " Scientific Research Institute of Medical Problems of the North, Krasnoyarsk, Russia), the Toronto Alexithymia Scale, Spielberger-Hanin questionnaire (to identify levels of personality and situational anxiety).

Statistical processing of the results was performed in the computer program "STATISTICA, 10" using the Mann-Whitney (M-W) criterion for comparison of two independent groups, Kraskell-Wallis (K-W) and median test (MT) for comparison of several independent groups, and Pearson Chi-square (PCS) for comparison of qualitative features. The 95% confidence interval was calculated using the «Exact Confidence Intervalor a Proportion calculator». Quantitative results are presented as Mean values with standard deviation and as medians with 25-75% interval; qualitative traits are presented as percentages with 95% confidence interval (CI). The results were considered reliable at a significance level of $p<0.05$; a trend toward reliable differences was defined at $p<0.1$.

Results and Discussion: The parameters of ABPM in children with Internet addiction are summarized in Table 1.

According to the obtained data (Table 1): average and maximum values of SBP and DBP in children with NIU do not differ from those in the control group, and minimum values tend to be lower. DNR of SBP does not differ from the control group, and DNR of DBP tends to increase. In addition, there is an increased variability of MeBP values, especially at night, and a tendency to increase the variability of DBP. Corresponding changes (decrease in minimum values, increased variability and lower decrease at night) are also observed with MeBP and PBP indices. Compensatory to this, there is an increase in PS values during the daytime.

The morning dynamics of BP indices in children with NIU had no significant differences from the control group. Hypertension indices for SBP also in our sample did not differ from the results of measurements in the control group, while hypotension indices for SBP were significantly elevated, especially in the morning and afternoon. For DBP, on the contrary, the hypertension indices tended to be higher in the afternoon, while the hypotension indices did not differ from the corresponding ones in the control group. This is also reflected in the decrease in the mean integral indices of PBP.

When analyzing the results obtained when dividing the children into 3 groups according to the centile distribution according to the sum of CIAS scores, similar results were obtained (Table 2).

In addition, now for group 3 there is a tendency to increase the variability of SBP. Also markedly increased DNR of SBP and MeBP, but only in group 2, in group 3 it does not differ from the control group. At the same time, lower hypertension indices (HMI_SBP, HTI_SBP, HAI_SBP) are registered for group 2, especially at night. However, in the morning, they show a faster recovery (rise) of SBP, as reflected by an increase in SI_

Table 1

Parameters of ABPM in children with Internet addiction / Median (25%-27%)

ABPM parameters	AIU, n=30	NIU, n=39	p (M-W)
Min SBP	81 (75-88)	78 (74-85)	0.074
Variability DBP_	12.7 (10.8-14.5)	14 (12-15.4)	0.056
DNR DBP	12.8 (7.8-18.9)	16.5 (11.7-22.1)	0.078
Min_MeBP	64 (61-69)	61 (57-66)	0.061
Min_MeBP night	70 (64-74)	66 (60-70)	**0.041**
Variability MeBP	10.4 (9.1-11.8)	11.9 (10.1-13.3)	0.074
Variability MeBP night	8.5 (7.3-9.5)	10.1 (7.2-12.3)	**0.022**
Variability MeBP morning	9.5 (8.2-12.4)	12.2 (10.5-14.0)	0.071
Me PBP	46.9 (41.5-48.8)	43.4 (39.9-46.4)	0.072
Min_PBP morning	28 (23-32)	25 (20-28)	0.089
Me PS	76.4 (70.6-84.7)	83.1 (75.7-88)	0.055
Me PS day	82.1 (76.2-89.5)	88.5 (79.8-93.3)	**0.042**
HMI SBP morning	8.6 (0-24)	0 (0-10)	0.084
HypoMI SBP	5.3 (2.7-14.5)	10.5 (5.9-20)	**0.022**
HypoMI SBP day	7.1 (3.6-16.3)	12.3 (6.3-22.9)	**0.031**
HypoMI SBP_morning	0 (0-6.0)	7.7 (5.6-16.7)	**0.009**
HypoTI SBP	3.9 (1.5-10.4)	7.6 (4.1-20.1)	**0.029**
HypoTI SBP day	5.7 (2.8-13.8)	10.8 (6.1-23.4)	0.058
HypoTI SBP morning	0 (0-4.9)	4.6 (1.1-21.3)	**0.023**
HypoAI SBP	4.3 (1.2-15.8)	10.4 (4.7-34.3)	**0.030**
HypoAI SBP day	4.3 (1.2-14.2)	9.6 (4.6-33.7)	0.058
HypoAI SBP morning	0 (0-1.7)	1.1 (0-5.7)	**0.033**
NHypoAI SBP	0.2 (0.1-0.7)	0.4 (0.2-1.5)	**0.038**
NHypoAI SBP day	0.3 (0.1-1.0)	0.6 (0.3-2.1)	0.072
NHypoAI SBP morning	0 (0-0.3)	0.2 (0-0.9)	**0.031**
HAI DBP _day	2.4 (0.8-9.5)	6.1 (1.4-24.1)	0.082

Note: The table shows only data with a significance level of differences between the groups under study $p<0.1$. SBP - systolic blood pressure, mmHg, DBP - diastolic blood pressure, mmHg, MeBP - mean BP, mmHg, PBP - pulse BP, mmHg, PS - pulse rate, ppm, Me - mean-integral, Max - highest, Min - lowest, DNR - degree of nocturnal reduction, %, HMI - hypertension measurement index, %, HypoMI - hypotension measurement index, %, HypoTI - hypotension time index, %, HypoAI - hypotension area index mm Hg*hour, NHypoAI - normalized hypotension area index, mm Hg,

Table 2

ABPM parameters in children depending on centile distribution of the sum of CIAS scores / Mean - M (+/- standard deviation); Median - Me (25%-27%)

ABPM parameters *	AIU, n=18	NIU, n=34	PIU, n=16	p (K-W, MT)**
Me SBP_day , Me	116.2 (112-120.7)	114.1 (109.3-120.8)	113.2 (110-118.6)	0.088
Min_SBP , Me	82 (78-88)	78 (74-87)	77.5 (72.5-82.5)	0.088
Min_SBP_day, M	86.4 (76.9-95.9)	83.1 (73.3-92.8)	78 (71.8-84.2)	**0.038**
Variability SBP, M	12.1 (9.0-15.2)	13.2 (9.9-16.4)	14.1 (11.3-17.0)	0.089
Variability_SBP day, M	11.9 (8.5-15.3)	12.6 (9.7-15.5)	14.2 (11.5-17.0)	0.057
Variability SBP night, Me	9.8 (8.1-11.6)	9.6 (7.2-11.3)	11.1 (7.5-15.1)	0.083
DNR SBP, M	5.0 (-0.9-10.9)	9.0 (3.5-14.5)	4.6 (-2.0-11.3)	**0.017**
Min DBP night, Me	47.5 (44-50)	43 (40-47)	43.5 (38.5-49.5)	**0.030**
Variability DBP, M	12.8 (9.7-15.8)	13.6 (10.9-16.3)	14.6 (11.6-17.6)	0.081
Variability_DBP day, M	11.2 (8.9-12.9)	12.3 (10.2-14.7)	14.3 (11.6-16.0)	0.062
Min_MeBP, Me	64 (62-69)	61 (57-65)	62 (58-66.5)	**0.040**
Min_MeBP morning, Me	73 (69-76)	68 (63-75)	68 (63-74.5)	0.060
Variability MeBP, Me	10.1 (8.4-11.5)	11.3 (9.9-13.2)	12.3 (10.6-13.5)	0.052
Variability MeBP morning, M	9.5 (5.8-13.1)	12.1 (7.4-16.8)	13.1 (8.8-17.5)	0.090
DNR MeBP, M	6.9 (1.4-12.3)	10.4 (4.9-15.8)	7.4 (1.4-13.5)	0.072
Me PBP, Me	47.5 (43.0-48.8)	43.8 (40.2-48.1)	43.3 (40.2-44.4)	**0.023**
Min_PBP, M	20.8 (17.1-24.6)	21.0 (17.7-24.3)	18.3 (15.3-21.3)	**0.029**
Min_PBP day, M	21.6 (17.2-26.1)	22.4 (17.9-26.8)	18.6 (15.6-21.6)	**0.008**
DNR PBP, M	-6.1 (-16.1-4.0)	-2.5 (-9.4-4.5)	-11.8 (-23.1-0.5)	**0.015**
Me_PS, Me	74.5 (68.2-87.3)	80.3 (74.3-65.3)	83.3 (79-88.5)	**0.047**
Me_PS_morning, Me	68.9 (64.6-87.4)	76.7 (67.8-84.0)	82.3 (78.3-90.8)	**0.032**
Min PS, Me	53 (50-61)	57 (50-63)	60 (55.5-64.5)	**0.022**
Min PS night, Me	53 (50-61)	57 (50-63)	60 (55.5-65.5)	**0.022**
Min PS morning, Me	54 (52-61)	58 (51-66)	63.5 (59-68.5)	**0.047**
MMR PS, Me	48 (34-69)	53.5 (40-73)	42 (34.5-51.5)	0.083
HTI_SBP_night, Me	11 (1.5-22.9)	3.3 (0-10.4)	13.5 (0.5-35.9)	0.059
HAI SBP night, Me	4.8 (0.1-16.0)	1.2 (0-3.8)	4.3 (0-17.7)	**0.020**
NHAI SBP night, Me	0.4 (0.0-1.7)	0.1 (0.0-0.4)	0.7 (0.0-3.7)	**0.020**
HypoMI SBP, M	9.8 (-2.2-21.7)	15.2 (-1.7-32.1)	16.3 (4.6-27.9)	**0.029**
HypoMI SBP day, M	12.1 (-3.1-27.3)	18.0 (-2.5-38.5)	19.7 (5.6-33.9)	**0.037**
HypoMI SBP morning, Me	0 (0-5.3)	5.6 (0-16.7)	9.7 (5.9-16.7)	**0.009**
HypoTI SBP, M	7.9 (-3.5-19.3)	13.2 (-2.5-28.8)	12.9 (1.4-24.3)	0.061
HypoTI SBP day, M	11.6 (-5.6-28.8)	17.0 (-3.3-37.2)	17.7 (3.2-32.2)	0.064
HypoTI SBP morning, M	4.2 (-6.8-15.1)	12.3 (-5.2-29.8)	8.4 (-1.3-18.1)	0.060
HypoAI SBP, M	10.7 (-6.8-28.2)	19.9 (-6.6-46.4)	21.1 (-0.3-42.5)	**0.029**
HypoAI SBP day, M	10.3 (-7.1-27.7)	18.2 (-6.8-43.3)	20.6 (-0.3-41.6)	**0.035**
HypoAI SBP morning, M	1.8 (-3.2-6.8)	3.7 (-1.3-8.6)	2.8 (-1.4-6.9)	0.060
NHypoAI SBP, M	0.5 (-0.3-1.2)	0.8 (-0.3-1.9)	0.9 (-0.0-1.8)	**0.038**
NHypoAI SBP day, M	0.7 (-0.4-1.9)	1.2 (-0.4-2.7)	1.3 (0.0-2.6)	**0.044**
NHypoAI SBP morning, M	0.3 (-0.6-1.1)	0.6 (-0.2-1.4)	0.5 (-0.2-1.2)	0.061
HTI DBP, Me	8.0 (5.7-13.2)	10.4 (4.1-22)	13.4 (6.4-21.8)	0.057
HypoMI DBP morning, Me	5.3 (0-8.3)	22.2 (0-30.8)	12.2 (0-17.6)	0.088

Note: * - for each parameter the mean (M) or median (Me) is presented; ** - for the mean value the p for the Kraskell-Wallis criterion (K-W) is presented, for the median - p for the median test (MT). SBP - systolic blood pressure, mm Hg, DBP - diastolic BP, mm Hg, MeBP - mean BP, mmHg, PBP - pulse BP, mmHg, PS - pulse rate, ppm, Me - mean-integral, Max - highest, Min - lowest, DNR - degree of nocturnal reduction, %,, MMR - the magnitude of the morning rise, mm Hg, HTI - hypertension time index, %, HAI - hypertension area index, mm Hg*h, NHAI - normalized hypertension area index, mm Hg, HypoMI - hypotension measurement index, %, HypoTI - hypotension time index, %, HypoAI - hypotension area index mm Hg*hour, NHypoAI - normalized hypotension area index, mm Hg,

SBP, compared to the other groups. In this respect, group 2 appears to be more adaptive. This may be due to the fact that they do not have IA yet, and they use the Internet as a way to relieve stress and solve psychological problems, which may be deprived of children from the control group, who use the Internet to a lesser extent and experience or suppress stress in themselves more, which is manifested in sleep disturbance and various vegetative symptoms.

As for hypotension indices, they were significantly higher (mainly in the afternoon and morning) in both group 2 and group 3, compared to the control group.

When analyzing the frequency of occurrence of deviations from normal values of ABPM in children with NIU (Table 3), compared to the control group, instability of BP is noted. They have more frequent deviations of SBP, a tendency to increased variability of DBP during the daytime with an increase in HTI of DBP, and an increased reduction of DBP at night (Over-Dipper).

When analyzing the frequency of deviations from normal values of ABPM parameters in children in the groups distributed by centile intervals (Table 4), children in Groups 2 and 3 also showed a marked tendency for a more frequent increase in daytime DBP variability. In addition, they also showed an increase in nighttime SBP variability. And as noted above, group 2 has a significantly less frequent increase in nighttime HTI SBP and DBP.

Thus, children with NIU and PIU are prone to increased variability of BP parameters with an increase in hypotension during the day and hypertension at night. Increased BP variability is considered as a risk factor for the development of arterial hypertension (AH) [3, 10]. The findings are in line with the expected results, since literature sources and our previous studies suggest that sleep disturbance in children with Internet addiction (due to decreased melatonin production under the influence of blue radiation from gadget screens) is accompanied by insufficient BP reduction at night and thus contributes to an increased risk of hypertension [11, 12]. However, although in our study in children in group 3 (with high CIAS scores) there is a predominance of elevated HTI of SBP and DBP at night, but the same trend is noted in the control group. This is probably due to the fact, that nowadays almost all children spend time before bedtime at gadget screens, which is confirmed by the same frequency (60-70%) of insufficient nocturnal reduction of SBP values in all children (Table 3). This may also be due to the fact, that they tend to be hypotensive during the day. In our study, this can also be explained by the fact that the children were hospitalized and spent most of the day in a state of hypodynamia. In addition, the control group itself consisted of children suffering from somatic pathology (bronchial asthma, obstructive bronchitis, allergic rhinitis, headaches). Nevertheless, the prevalence of children with lowered DNR SBP revealed by us has an unfavorable value, as according to the results of many researchers it is a serious risk factor for the development of cardiovascular pathology. Thus, children in the group of "non-dippers", compared to "dippers", were found to have a higher concentration of total cholesterol in blood, significantly lower mean values of left ventricular end-diastolic dimension, and more frequent detection of protein in urine [4].

Also unfavorable prognostic significance in terms of AH development is the increase in HTI BP at night, even with normal values of other BP parameters [3]. According to O.V. Kozhevnikova et al. in 21% of cases in such children hypotension was even noted during the daytime [7], which is also observed in our study (Tables 1-2). This situation was observed by the authors in children with chronic otolaryngological pathology [7], which is also characteristic of our sample of children.

On the other hand, there are studies that confirm a disorder of autonomic

Table 3

Frequency of occurrence of deviations from the normal values of ABPM in children with Internet addiction, % (95%-CI)

ABPM parameters	AIU, n=30	NIU, n=39	P
Me SBP			
normal	100 (88.8-100)	87.2 (73.2-94.3)	0.042
low	0	5.1 (1.6-16.9)	0.209
elevated	0	7.7 (2.8-20.4)	0.120
Variability SBP			
normal	83.3 (66.3-92.5)	71.8 (56.1-83.4)	0.262
elevated	16.7 (7.5-33.7)	28.2 (16.6-43.9)	0.262
DNR SBP			
Dipper	13.3 (5.5-29.8)	25.6 (14.6-41.2)	0.208
Non-dipper	73.3 (55.4-85.8)	64.1 (48.3-77.3)	0.416
Over-Dipper	0	2.6 (0.6-13.2)	0.374
Night-Peaker	13.3 (5.5-29.8)	7.7 (2.8-20.4)	0.445
Variability DBP			
normal	43.3 (27.3-60.9)	30.8 (18.6-46.5)	0.284
elevated	56.7 (39.1-72.7)	69.2 (53.5-81.4)	0.284
Variability DBP day			
normal	70.0 (52.0-83.3)	48.7 (33.8-63.8)	0.076
elevated	30.0 (16.7-48.0)	51.3 (36.1-66.2)	0.076
Variability DBP night			
normal	56.7 (39.1-72.7)	41.0 (27.0-56.7)	0.196
elevated	43.3 (27.3-60.9)	59.0 (43.3-73)	0.196
DNR DBP			
Dipper	60.0 (42.2-75.5)	53.8 (38.5-68.5)	0.607
Non-dipper	23.3 (11.9-41.1)	17.9 (9.1-32.8)	0.580
Over-Dipper	6.7 (2.0-21.4)	25.6 (14.6-41.2)	0.040
Night-Peaker	10.0 (3.6-25.8)	2.6 (0.6-13.2)	0.193
HTI_DBP_day			
normal	93.3 (78.6-98)	76.9 (61.5-87.3)	0.065
elevated	6.7 (2.0-21.4)	23.1 (12.7-38.5)	0.065

regulation of the cardiovascular system in children with Internet addiction [2, 13, 14], which may also be associated with increased BP variability and a tendency to hypotension in our study. In children with lability of the autonomic nervous system, as a rule, there is also lability of the emotional sphere, which is also characteristic of children with Internet addiction [6, 8] and through dysregulation of the autonomic nervous system (ANS) can contribute to the development of increased BP variability.

Also of interest is the fact that children at risk of Internet addiction (group 2), compared to other children, are more likely to have normal BP values, in particular, they do not tend to be hypertensive at night. Perhaps, as mentioned above, they adapt more easily to stress and experience problems using the Internet as a way of psychotherapy, unlike the control group (with low CIAS scores), who may be more reserved and suppress emotions in themselves, or the group with obvious Internet addiction, who may have more psychological problems.

Some explanation for this situation can be found in the study of heart rate variability (HRV) in adolescents with different degrees of Internet addiction [2], according to which in children with severe withdrawal symptoms during withdrawal from the Internet, sympathicotonia and a decrease in vagus regulation of heart

Table 4

Frequency of occurrence of deviations from the normal values of ABPM in children with Internet addiction, %

ABPM parameters	AIU, n=18	NIU, n=34	PIU, n=16	p (PCS)
Variability SBP				
normal	83.3	79.4	62.5	0.306
elevated	16.7	20.6	37.5	
Variability SBP day				
normal	88.9	85.3	75	0.519
elevated	11.1	14.7	25	
Variability SBP night				
normal	88.9	97.1	68.8	0.015
elevated	11.1	2.9	31.3	
Variability DBP day				
normal	77.8	55.9	37.5	0.058
elevated	22.2	44.1	62.5	
Variability DBP night				
normal	55.6	47.1	37.5	0.575
elevated	44.4	52.9	62.5	
DNR DBP				
Dipper	61.1	55.9	50	0.224
Non-dipper	16.7	23.5	18.8	
Over-Dipper	5.6	20.6	25	
Night-Peaker	16.7	0	6.3	
HTI_SBP_night				
normal	47.4	73.5	37.5	0.030
elevated	52.6	26.5	62.5	
HTI_DBP_night				
normal	26.3	47.1	25	0.182
elevated	73.7	52.9	75	

Table 5

Frequency of psychological problems in children with ABPM abnormalities characteristic of Internet addiction, % (95%-CI)

Problems	Variability DBP		HTI SBP night		HTI DBP night	
	normal	elevated	normal	elevated	normal	elevated
Goodman Scale:	N=22	N=32	N=31	N=23	N=20	N=34
Total score, deviance	9.1 (2.8-28)	21.9 (11.1-38.9)	16.1 (7.2-32.8)	17.4 (7.1-37.4)	20 (8.2-41.9)	14.7 (6.6-30.3)
Prosocial scale, deviance	9.1 (2.8-28)	0 (0-10.6)*	6.5 (2.0-20.8)	0 (0.1-14.2)	5 (1.2-23.8)	2.9 (0.7-14.9)
Behavior problems	0 (0.1-14.8)	12.5 (5.1-28.2)*	6.5 (2.0-20.8)	6.7 (2.7-27)	10 (3-30.4)	5.9 (1.8-19.2)
Emotional scale, deviation	9.1 (2.8-28)	12.5 (5.1-28.2)	12.9 (5.3-29.0)	6.7 (2.7-27)	15 (5.4-36.3)	8.8 (3.2-23.1)
Hyperactivity	4.5 (1.1-21.9)	25.0 (13.3-42.3)**	19.4 (9.3-36.4)	13.0 (4.7-32.4)	25.0 (11.3-47.2)	11.8 (4.8-26.7)
Problems communicating with peers	4.5 (1.1-21.9)	12.5 (5.1-28.2)	3.2 (0.8-16.2)	17.4 (7.1-37.4)*	5 (1.2-23.8)	11.8 (4.8-26.7)
Alexithymia	54.5 (34.5-73.2)	46.3 (32.0-61.3)	48.6 (32.9-64.5)	50.0 (32.5-67.5)	52.4 (32.2-71.8)	47.6 (33.3-62.3)
Situational anxiety	40.9 (23.2-61.5)	31.4 (18.6-48.1)	55.2 (37.4-71.7)	14.3 (5.8-31.7)**	45.0 (25.7-66)	29.7 (17.5-45.9)
Personality anxiety	77.3 (56.3-89.8)	88.6 (73.9-95.3)	82.8 (65.3-92.3)	85.7 (68.3-94.2)	75 (52.8-88.7)	89.2 (75.2-95.6)
Asthenic syndrome	13.6 (5.0-33.6)	16.7 (8-32)	15.6 (7-31.9)	15.4 (6.3-33.7)	19.0 (7.8-40.3)	13.2 (5.9-27.4)
Daytime sleepiness	9.0 (2.8-28)	20.0 (10.1-36)	18.8 (9-35.5)	12.0 (4.4-30.2)	14.3 (5.2-34.9)	16.7 (8-32)
Insomnia	5.0 (1.2-23.8)	24.2 (12.9-41.2)*	17.2 (7.7-34.7)	16.7 (6.8-36.1)	31.6 (15.4-54.3)	8.8 (3.2-23.1)

* $p<0.1$; ** $p<0.05$.

Table 6

Frequency of psychological problems in children with inadequate nocturnal lowering of SBP, % (95%-CI)

Goodman Scale	Dipper N=12	Non-dipper N=37	p
Total score, deviation	25.0 (9.1-53.8)	13.5 (6.0-28.1)	0.349
Prosocial scale, deviance	0 (0.2-24.7)	5.4 (1.7-17.7)	0.411
Behavior problems	8.3 (1.9-36)	8.1 (2.9-21.4)	0.983
Emotional scale, deviance	16.7 (5.0-45.4)	10.8 (4.4-24.8)	0.588
Hyperactivity	16.7 (5.0-45.4)	16.2 (7.7-31.3)	0.968
Problems communicating with peers	0 (0.2-24.7)	10.8 (4.4-24.8)	0.235
Alexithymia	41.7 (19.2-68.4)	54.5 (40.0-68.3)	0.441
Situational anxiety	50.0 (25.1-74.9)	33.3 (20.6-49.1)	0.299
Personality anxiety	83.3 (54.6-95)	86.8 (72.6-94.1)	0.762

rhythm were established, while in individuals with minimal withdrawal symptoms, total HRV and vagus nerve activity remained higher and their temporal assessment effective. Other researchers also testify to the predominance of sympathicotonia in Internet addiction [13].

Thus, the propensity to develop AH in children with Internet addiction can be explained by the presence of common psychological risk factors, such as stress exposure and anxiety-depressive disorders [5, 8, 9].

Thus, when analyzing psychological deviations in children with insufficient nocturnal BP reduction, no reliable differences (possibly due to small group sizes) were revealed. However, some tendency to more frequent problems in communication with peers and less pronounced situational anxiety against the background of high personality anxiety and frequent alexithymia was also noted.

Conclusions:

1) Children with Internet addiction have increased variability of SBP and DBP with predominance of hypotension (HypoMI and HypoTI) during the day and hypertension at night (HTI), which is a risk factor for AH development

2) More than half of children in both the group with Internet addiction and the control group have insufficient degree of nocturnal reduction of SBP "non-dippers", which is also a risk factor for the development of AH.

3) Children at risk of developing Internet addiction, but without obvious Internet addiction, do not show an increase in nighttime HTI, which is characteristic of the control group and the group with Internet addiction, possibly due to fewer psychological problems, as well as the ability to relieve tension on the Internet, while children without Internet addiction may be more restrained, responsible and disciplined, which affects their psychological state

4) In children with deviations of ABPM indicators there are more frequent behavioral problems, hyperactivity and problems of communication with peers, as well as lower indicators of situational anxiety with high indicators of personality anxiety, which, according to our previous studies, as well as studies by other authors, is also characteristic of individuals with Internet addiction [6].

5) Thus, we can conclude that the psychological features and deviations present in children with Internet addiction through the ANS regulation disorder affect systemic hemodynamics and lead to the development of AH. In addition, sleep disorders in children with Internet addiction due to insufficient melatonin production under the influence of blue radiation from gadget monitors contribute to this. This is confirmed by the decrease in the degree of nocturnal decrease in SBP.

6) Thus, it is necessary to recommend children not to use gadgets before bedtime with obligatory control by parents; all children with obvious Internet addiction should be recommended to perform ABPM for early detection of established risk factors for the development of AH and its prevention with an obligatory psychotherapeutic component.

References

1. Kibitov AO, Trusova AV, Egorov AYu. Internet-zavisimost': klinicheskie, biologicheskie, geneticheskie i psihologicheskie aspekty [Internet addiction: medical, biological, genetic and psychological aspects]. Voprosy narkologii [Questions of Narcology. 2019; 3(174): 22-47 (In Russ.).] DOI 10.47877/0234-0623_2019_3_22.

2. Krivonogova O, Krivonogova E, Poskotinova L. Variabel'nost' serdechnogo ritma, ocenka vremeni i internet-zavisimoe povedenie podrostkov 16-17 let: issledovanie v rossijskoj Arktike [Heart rate variability, time estimation and Internet-dependent behavior of adolescents 16-17 years old: a study in the Russian Arctic]. Zhizn' (Bazel') [Life (Basel). 2021;11 (6): 497 (In Russ.).] doi: 10.3390/life11060497

3. Plotnikova IV, Bezlyak VV, Trushkina IV, Churilova VO, Kovalev IA. Osobennosti pokazatelej sutochnogo monitorirovaniya arterial'nogo davleniya u podrostkov pri essencial'noj arterial'noj gipertenzii [Features of 24-hour blood pressure monitoring indicators in adolescents with essential arterial hypertension]. Pediatriya. Zhurnal im. G.N. Speranskogo [Pediatrics. Journal named after G.N. Speransky]. 2010; 89 (3): 45-51 (In Russ.).]

4. Korolev AV, Delyagin VM, Urazbagambetov A, Kilikovskiy VV, Olimpieva SP. Ocenka informativnosti stepeni nochnogo snizheniya arterial'nogo davleniya u detej dlya vyyavleniya faktorov riska po rezul'tatam provedeniya sutochnogo monitorirovaniya arterial'nogo davleniya [Assessing the information content of the degree of nocturnal decrease in blood pressure in children to identify risk factors based on the results of 24-hour blood pressure monitoring]. Meditsinskiy Sovet [Medical advice. 2013; 8: 99-101. https://doi.org/10.21518/2079-701X-2013-8-99-101

5. Kosovtseva AS, Kolesnikova LI, Rychkova LV, Polyakov VM, Bairova TA. Psihologicheskie osobennosti podrostkov s essencial'noj arterial'noj gipertenziej [Psychological characteristics of adolescents with essential arterial hypertension]. Acta Biomedica Scientifica (Vostochno-Sibirskij biomedicinskij zhurnal) [Acta Biomedica Scientifica (East Siberian Biomedical Journal). 2018; 3 (2): 56-62 (In Russ.).] DOI 10.29413/ABS.2018-3.2.10.

6. Semenova NB, Tereshhenko SU, Jevert LS, Shubina MV. Harakteristika psihicheskogo statusa internet-zavisimyh podrostkov: gendernye i vozrastnye osobennosti [Characteristics of the mental status of Internet-addicted adolescents: gender and age characteristics] / Profilaktich-eskaja medicina [Preventive medicine. 2022; 25(8): 83–89 (In Russ.).] https://doi.org/10.17116/profmed20222508183

7. Kozhevnikova OV, Namazova-Baranova LS, Margieva TV, Abashidze JeA, Balabanov AS. Faktory riska i markery nochnoj gemodinamiki dlya personificirovannoj profilaktiki serdechno-sosudistyh boleznej u detej [Risk factors and markers of nocturnal hemodynamics for personalized prevention of cardiovascular diseases in children]. Pediatricheskaja farmakologija [Pediatric pharmacology. 2017; 14 (3): 156-164. DOI: 10.15690/pf.v14i3.1739

8. Tereshchenko S, Kasparov E, Semenova N, Shubina M, Gorbacheva N, Novitckiy I, Moskalenko O, Lapteva L. Generalized and Specific Problematic Internet Use in Central Siberia Adolescents: A School-Based Study of Prevalence, Age-Sex Depending Content Structure, and Comorbidity with Psychosocial Problems. Int J Environ Res Public Health. 2022; 19(13): 7593. doi: 10.3390/ijerph19137593.

9. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens. 2015; 28(11): 1295-302. doi: 10.1093/ajh/hpv047.

10. Sogunuru GP, Kario K, Shin J, Chen CH, Buranakitjaroen P, Chia YC, Divinagracia R, Nailes J, Park S, Siddique S, Sison J, Soenarta AA, Tay JC, Turana Y, Zhang Y, Hoshide S, Wang JG.

J HOPE Asia Network. Morning surge in blood pressure and blood pressure variability in Asia: Evidence and statement from the HOPE Asia Network. Clin Hypertens (Greenwich). 2019; 21(2): 324-334 (In Russ.).] doi: 10.1111/jch.13451.

11. Tereshchenko S, Kasparov E, Smolnikova M, Shubina M, Gorbacheva N, Moskalenko O. Internet Addiction and Sleep Problems among Russian Adolescents: A Field School-Based Study. Int J Environ Res Public Health. 2021; 18(19): 10397 (In Russ.).] doi: 10.3390/ijerph181910397.

12. Lissak G. Adverse physiological and psychological effects of screen time on children and adolescents: Literature review and case study. Environ Res. 2018; 164: 149-157. doi: 10.1016/j.envres.2018.01.015.

13. Lu DW, Wang JW, Huang AC. Differentiation of Internet addiction risk level based on autonomic nervous responses: the Internet-addiction hypothesis of autonomic activity. Cyberpsychol Behav Soc Netw. 2010; 13(4): 371-8. doi: 10.1089/cyber.2009.0254.

14. Poskotinova LV, Krivonogova OV, Zaborsky OS. Cardiovascular response to physical exercise and the risk of Internet addiction in 15-16-year-old adolescents. J Behav Addict. 2021; 10(2): 347-351. doi: 10.1556/2006.2021.00021

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ASSESSMENT OF THE BODY RESISTANCE OF ATHLETES FROM YAKUTIA TO HYPOXIA

The article reflects the assessment of the body resistance of students of the «North-Eastern Federal University named after M.K. Ammosov», living in the Far North, to hypoxic conditions. 146 people took part in the study – 119 boys and 27 girls. Of these, the study group consisted of 74 student – athletes (59 boys, 15 girls), the control group consisted of 72 students engaged in physical education according to the general program of the University (60 boys, 12 girls). The average age of the surveyed was 21± 2,5 years. To identify the assessment of the body's resistance to hypoxia in Yakutia athletes, the following functional tests were conducted: the Stange test (breath holding on inhalation) and the Genchi test (breath holding on exhalation). The obtained results of the study allowed us to see the prevailing excellent criterion (assessment "excellent") in athletes and the average criterion (assessment "good") in the control group, the results with an unsatisfactory criterion (assessment "unsatisfactory") were less. The conducted assessment shows a positive level of non-specific adaptive capabilities of the respiratory system in the studied students. The functional resistance of the respiratory system to hypoxia in young men was significantly higher than in girls.

Keywords: athletes of Yakutia, students, hypoxia, Stange's test, Genchi test

Introduction: The physiological state of the human body is determined by oxygen consumption. Oxygen is necessary for breathing, saturation of cells and tissues of the body with oxygen, oxidation of proteins, fats, carbohydrates, amino acids, as well as for many other biochemical processes. Oxygen enters the tissues and cells of the body through the respiratory and cardiovascular systems. If these body systems fail to function, hypoxia may develop. During diagnostics of the human respiratory system, the volume of the lungs, the rhythm of breathing, its depth are determined, and standard methods of functional tests are used to determine resistance and adaptation to hypoxia. Functional breath-holding tests, such as the Stange test (breath-holding on inhalation) and the Genchi test (breath-holding on exhalation), can reveal hidden disorders in the body's functioning that cannot always be determined by standard methods. These tests help assess the body's resistance to hypoxia and endurance. Such tests are easy to perform, so you can test yourself and assess whether there are any problems with the respiratory system.

In the works of a number of authors it has been noted that the longer the breath-holding time, the higher the adaptive capacity of the respiratory and cardiovascular systems to hypoxia and high functional capabilities of the body [1, 3, 7]. In case of dysfunction of the oxygen-transport system of the body, for example, in case of iron deficiency anemia, the duration of breath-holding is reduced [8, 9].

The aim of the study. To assess the resistance of the body of students of Yakutia to hypoxia depending on physical activity on the possibility of holding the breath on inhalation and exhalation.

Materials and methods of the study: 146 students of NEFU named after M.K. Ammosov were examined. Of these, the study group consisted of 74 athletes (59 boys, 15 girls), the control group consisted of 72 students involved in physical education according to the general program of the university (60 boys, 12 girls). The average age of the examined was 21±2.5 years.

The athletes were involved in the following sports: track and field - 20 people, mas-wrestling - 34 people, national jumping - 8 people, shooting - 5 people, freestyle wrestling - 7 people.

The following functional tests were used in the study to determine the body's sensitivity to oxygen deficiency:

Stange test. Method of performance: the subject inhales, then exhales, and again takes a deep breath and holds his breath for the maximum possible time. The time of breath holding is recorded. The norm for men = 50–60 sec; the norm for athletes = 65–75 sec and more; the norm for women = 35–45 sec; the norm for female athletes = 45–55 sec. Evaluation of results: “excellent” – for men from 60 sec, for women from 50 sec; “good” – for men from 50 to 59 sec, for women from 40 to 49 sec; “satisfactory” – for men from 35 to 49 sec, for women from 30 to 39 sec; “unsatisfactory” – for men less than 35 sec, for women less than 30 sec.

Genchi test. Method of execution: it is carried out similarly to the Stange test,

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the only difference being that the breath is held after a deep exhalation. The average result is a breath-holding time of 30 seconds or longer. The norm for healthy people = 20–40 sec; the norm for athletes = 40–60 sec. Evaluation of results: “excellent” – for men from 50 sec, for women from 40 sec; “good” – for men from 40 to 49 sec, for women from 32 to 39 sec; “satisfactory” – for men from 30 to 39 sec, for women from 25 to 31 sec; “unsatisfactory” – for men less than 29 sec, for women less than 24 sec.

The obtained data were processed using the IBM SPSS Statistics 23 application package. Standard methods of variation statistics were used: calculation of the median and the 25th and 75th quartiles (Me [Q25; Q75]). To compare two independent groups, statistical analysis was performed using the nonparametric Mann-Whitney U-test. The relationship between variables was assessed using the Spearman method (for variables measured on a rank scale), where p is the significance of the result.

Results and discussion: The data we obtained on the Stange test (Table 1) showed that the functional capabilities of the athletes' body in terms of the ability to hold their breath on inhalation in young men and women corresponded to the grade "excellent". In the control group, when holding their breath on inhalation in young men and women, the indicators were significantly lower than in trained athletes, which corresponded to the grade "good".

The breath holding time according to the Genchi test (Table 2) in male and female athletes was equal to that of untrained individuals and corresponded to the assessment of "satisfactory". In the control group, the indicators of male and female athletes differed significantly from those of athletes and corresponded to the assessment of "unsatisfactory".

The functional state according to the Stange test (Fig. 1) in 77.7% of young athletes confirms “excellent” and “good” results in the ability to hold breath on inhalation for trained people, only 3,4% had hypoxia. In 80% of female athletes, an “excellent” assessment is confirmed in the ability to hold breath on inhalation for trained people, hypoxia was not noted. In the studied comparison groups, no statistically significant differences were found.

In the control group, the functional state of the body according to the Stange test is insignificantly lower than that of student athletes. In 63,3% of young men, the "excellent" and "good" assessment of the results is confirmed in the ability to hold the breath on inhalation, hypoxia

Table 1

Indicators of the functional state of the body according to the Stange test, sec

	Groups	N	Me (Q1; Q3)	P
1	Athletes young men	59	62.72 (51.33; 76.00)*	P_{1-3}=0.029
2	Athletes girls	15	57.89 (40.94; 62.27)**	P_{2-4}=0.013
3	Young men control	60	56.64 (43.43; 62.89)*	
4	Girl control	12	39.94 (28.81; 47.65)**	

Table 2

Indicators of the functional state of the body according to the Genchi test, sec

Groups		N	Me (Q1; Q3)	P
1	Athletes young men	59	30.72 (25.55; 40.59)*	P_{1-3}=0.0
2	Athletes girls	15	29.60 (22.59; 35.47)**	P_{2-4}=0.046
3	Young men control	60	28.43 (23.10; 38.29)*	
4	Girl control	12	23.37 (18.40; 29.72)**	

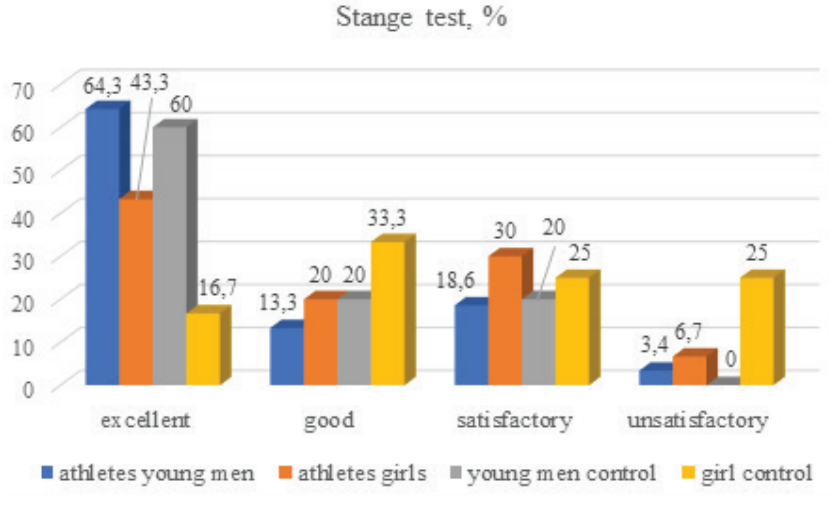

Рис. 1. Evaluation of functional state indicators according to the Stange test, %

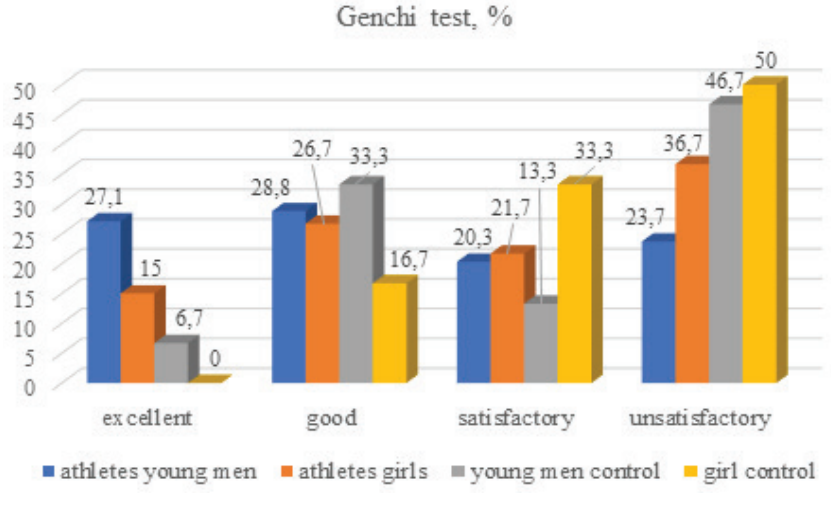

Рис. 2. Evaluation of functional state indicators according to the Genchi test, %

Table 3

Indicators of the functional state of the body according to the Stange test depending on the type of sport, sec

Sport	N	Me (Q1; Q3)
Athletics	20	68.47 (54.24; 84.34)
Mas wrestling	34	58.98 (48.87; 68.04)
National jumps	8	61.74 (44.67; 78.06)
Bullet shooting	5	55.06 (44.95; 69.09)
Freestyle wrestling	7	62.03 (42.76; 76.49)
Young men control	60	56.64 (43.43; 62.89)
Girl control	12	39.94 (28.81; 47.65)

Table 4

Indicators of the functional state of the body according to the Genchi test depending on the type of sport, sec

Sport	N	Me (Q1; Q3)
Athletics	20	28.32 (22.99; 37.64)
Mas wrestling	34	30.41 (25.34; 37.64)
National jumps	8	31.41 (21.02; 36.52)
Bullet shooting	5	37.12 (26.64; 44.91)
Freestyle wrestling	7	31.81 (29.00; 51.06)
Young men control	60	28.43 (23.10; 38.29)
Girl control	12	23.37 (18.40; 29.72)

was recorded in 6,7% of the subjects. In 16,7% of girls from the control group, the result is assessed as "excellent", and in 33.3%, the indicators are determined to be "good". Hypoxia was detected among 25% of girls in the control group.

The functional state according to the Genchi test (Fig. 2) in 55,9% of young male athletes confirms the assessment of "excellent" and "good" in terms of the ability to hold one's breath on exhalation for trained people, hypoxia was detected in 23,7% of the athletes studied. In 6,7% of female athletes, the results of the study according to the Genchi test confirm the assessment of "excellent", and in 33,3% the assessment of "good" in terms of the ability to hold one's breath on exhalation for trained people, hypoxia was recorded in 46,7%.

In the control group, the functional state indicators according to the Genchi test are insignificantly lower than those of student athletes. 15% of young men showed excellent indicators and 26,7% showed good results in the ability to hold their breath on exhalation, hypoxia was observed in 36,7%. Among the girls in the control group, an excellent indicator was not recorded, an indicator with a "good" rating was noted in 16,7%. Hypoxia was noted among 50% of the girls in the control group.

Table 3 presents the functional state data according to the Stange test by sports. All athletes have average values within the range of "excellent" and "good". The best value is noted among track and field athletes. This is probably due to the fact that this is the most popular sport, which includes various disciplines: race walking, running, running and cross-country, all-around, jumping, throwing, shot put. All these sports activities are characterized by high aerobic load. It is believed that physical activity consisting of aerobic exercises is the most beneficial for health [2, 4].

Table 4 presents the functional state data for the Genchi test by sports. All athletes have average breath-holding rates on exhalation that are below the norm, within the "satisfactory" rating. Of these, the best rate was observed in athletes involved in target shooting. The worst result was observed in track and field athletes, which reflects weak adaptation to hypoxia. This may be specific to these athletes, who are characterized by high aerobic loads, since overcoming a distance is accompanied by an increased frequency and depth of breathing [5].

During the work, significant differences in the main functional indicators of external respiration were identified in athletes and students who do not regularly engage in sports. In the work of a number of authors, it was noted that the external respiration system of freestyle wrestlers and boxers is 50,14% weaker than that of mas-wrestlers [6].

Conclusion. Comparative assessment of the functional state of breathing using the Stange and Genchi test in young men and women involved in sports revealed gender differences: young men had higher rates of breath holding on inhalation and exhalation than young women. The rates indicate oxygen supply and the general level of fitness of athletes.

A comparative assessment of the functional state of respiration using the Stange and Genchi test in athletes and the control group revealed that in athletes, breath holding on inhalation and exhalation is significantly higher than in the control group, which confirms that physical activity improves health, increases the body's resistance to hypoxia and demonstrates a high rate of non-specific adaptive capabilities of the respiratory system in athletes from Yakutia.

Although the results obtained clearly show differences in physiological parameters, it is necessary to analyze a larger sample to obtain more reliable data and confirm the results of the study.

References

1. Ali Muhammad A., Prokop'ev N.YA., Semizorov E.A. Proby SHtange i Genchi v ocenke funkcii vneshnego dyhaniya u yunoshej sbornoj komandy Sirii po shossejnym gonkam na predsorevnovatel'nom etape provedeniya trenirovochnogo processa [Stange and Gench tests in assessing the function of external respiration in young men of the Syrian national road racing team at the pre-competition stage of the training process. Sciences of Europe. 2022; 88 (2): 48-53 (In Russ.).]

2. Bekembetov R. A., Konakbaev B.M. Znachenie trenirovochnoj nagruzki maloj aerobnoj moshchnosti v edinoborstvah [The importance of low aerobic power training load in martial arts] Teoriya i metodika fizicheskoj kul'tury. 2022; 1(67): 166-173. DOI 10.48114/2306-5540_2022_1_166. – EDN XIVJHO.

3. Bakhtina TN, Osechkina TA, Lesheva NS, Plotnikova SS. Dinamika pokazatelej prob SHtange i Genchi studentov SPBGLTU imeni S.M. Kirova, zanimayushchihsya ozdorovitel'noj hod'boj [Dynamics of indicators of Stange and Genchi samples of students of St. Petersburg State Forestry University named after S.M. Kirov, engaged in recreational walking]. Kul'tura fizicheskaya i zdorov'e. 2023; 3(87); 12-16 (In Russ.).] DOI 10.47438/1999-3455_2023_3_12. – EDN UJPEEC.

4. Zaharina AN, Golubina OA. Vliyanie zanyatij legkoj atletikoj na organizm studenta [The influence of athletics on the student's body]. Mezhdunarodnyj studencheskij nauchnyj vestnik. 2022. № 6. URL: https://eduherald.ru/ru/article/view?id=21071 (data obrashcheniya: 09.07.2024).

5. Kolomejchuk OV. Osobennosti ustojchivosti k gipoksii u predstavitelej razlichnyh vidov sporta [Features of resistance to hypoxia in representa-

tives of various sports]. Fizicheskaya kul'tura v obshchekul'turnoj i professional'noj podgotovke studenta: sbornik materialov vtoroj Vserossijskoj s mezhdunarodnym uchastiem nauchnoj konferencii, Rostov-na-Donu, 04–08 aprelya 2016 goda. Rostov-na-Donu: YUzhnyj federal'nyj universitet, 2016; 64-68.

6. Gavrilieva KS, Handy MV, Solovyova MI, Kuzmina SS. Osobennosti funkcional'nogo sostoyaniya i antioksidantnoj sistemy u yunyh sportsmenov, zanimayushchihsya mas-restlingom [Features of functional state and antioxidant system in young athletes engaged in mass wrestling]. Vestnik sportivnoj nauki. 2016; 1: 29-33. EDN WLBCPX.

7. SHvetskij FM, Potievskaya VI, Polonskaya AS, CHerenkova VA. Proba SHtange i Genchi – zabytye rutinnye pokazateli ustojchivosti nejronnyh setej k giperkapnii pri adaptacii k sportivnym trenirovkam [Stange and Genchi test - forgotten routine indicators of the resistance of neural networks to hypercapnia during adaptation to sports training]. Ekologo-fiziologicheskie problemy adaptacii: materialy XVII Vserossijskogo simpoziuma. Ryazan', 23-26 Maya [Ecological-physiological issues of adaptation: materials of the XVII All-Russian symposium. Ryazan. May 23-26. 2017; 246-247 (In Russ.).]

8. D'Alessandro A, et al. AltitudeOmics: Red Blood Cell Metabolic Adaptation to High Altitude Hypoxia. J Proteome Res. 2016. Oct 7; 15(10): 3883-3895. doi: 10.1021/acs.jproteome.6b00733. Epub 2016 Sep 27. PMID: 27646145; PMCID: PMC5512539.

9. Rogers RS, et al. Hypoxia extends lifespan and neurological function in a mouse model of aging. PLoS Biol. 2023 May 23; 21(5): e3002117. doi: 10.1371/journal.pbio.3002117. PMID: 37220109; PMCID: PMC10204955.

ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

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PROVISION OF SPECIALIZED MEDICAL CARE IN THE REPUBLIC OF SAKHA (YAKUTIA) TO PATIENTS WITH COGNITIVE DISORDERS

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The article presents an analysis of statistical data on dementia from official sources of state statistics, medical and scientific organizations, as well as the provision of specialized medical care in the Republic of Sakha (Yakutia) to patients with cognitive disorders.

Keywords: neurodegenerative diseases, healthcare organization, specialized medical care, Alzheimer's disease, dementia, cognitive disorder.

Relevance of the problem. In the Republic of Sakha (Yakutia) (further RS (Y)) one of the main medical and social problems is cognitive disorder (CI), including Alzheimer's disease (AD). Despite the obvious deficit in AD diagnostics, the situation, as in the world, is becoming extremely important [2]. AD is a disease of old age and increasing age is becoming one of the main reasons for the increase in the incidence and prevalence of AD in the world. In Russia, according to 2019 data, the mortality rate from AD was 0.13%, while out of 188,132 patient visits to a doctor with a diagnosis of dementia, 6,381 cases were due to AD [11].

In the United States, according to the AD Association, in 2021, 6.2 million Americans aged 65 and older suffer from dementia associated with Alzheimer's disease. This number may grow to 13.8 million by 2060. In the United States in 2019, mortality from AD was in 6th place, and among the elderly aged 65 and older in 5th place. Official death certificates recorded 121,499 deaths from AD, or an increase in deaths from AD by more than 145%. In 2020, mortality from AD increased against the backdrop of the COVID-19 pandemic. At the same time, mortality from acute cerebrovascular accidents, heart diseases and HIV decreased between 2000 and 2019 [5,9]

A study of mortality from AD and other dementias in China showed that the overall mortality rate from AD and other dementias increased from 3.7 per 100,000 to 6.2 per 100,000 population in 2011-2020. Studies have shown that there is an increasing trend in the overall mortality rate from AD and other dementias with a decreasing age-standardized mortality rate, indicating the further development of population aging and dementia mortality in the past and future decades [7].

In Brazil, from 2000-2019, 211,658 deaths from Alzheimer's disease were recorded among the elderly, with an increasing trend in mortality at the age of 60 to 80 years and older, which is also consistent with the global trend [8].

According to a retrospective multicenter study in Spain, BA is the cause of an increase in the proportion of hospitalizations and an increase in in-hospital mortality from BA, which leads to an increase in the cost of medical care and emphasizes the importance of early detection and optimization of care for patients with BA [3].

Given the increase in mortality rates and the number of patients with dementia in Russia, taking into account the global situation, there is currently a need to conduct epidemiological studies and develop methods for the early diagnosis and prevention of CI in the Russian Federation. The goal of these activities should be to improve diagnostics, extend the period of a person's full working life and active longevity among the elderly population.

According to Rosstat for the Republic of Sakha (Yakutia), from 2021 to 2023, the number of elderly people aged 60 years and above increased from 148.4 thousand people. up to 154.6 thousand people, respectively, and the average life expectancy was 72.7 in 2022, in 2023 al-

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ready 73.02 years, in the Russian Federation this figure is 73.4 years.

The creation of methods for early diagnosis and prevention of cognitive disorder requires an integrated approach from the federal and regional governments in consolidation with scientific and educational organizations. The solution to this important medical and social problem will also lead to a reduction in the economic and financial burden on public health.

Materials and methods. The following materials were used in the study:

1. reporting data of the YARMIAC (federal form No. 12 of statistical observation);

2. hospital registry for cognitive disorder No. 2021622297 registered in Rosreestr on October 27, 2021. Copyright holder FGBNU YNC KMP;

3. regulatory documents of the Ministry of Health of the Republic of Sakha (Yakutia) and the Republic of

4. reporting data of the Main Bureau of the Medical and Social Expertise in the Republic of Sakha (Yakutia) on disability;

5. data of the Territorial Statistical Fund for the Republic of Sakha (Yakutia).

The descriptive statistics method was used based on the research materials.

The article presents the results of data collection of information and analytical materials using health indicators for the period from 2019-2023. These data come from 34 uluses (districts) of the Republic of Sakha (Yakutia) and the city of Yakutsk.

Results and discussion. The area of the territory of the Republic of Sakha (Yakutia) is 3083.5 thousand km2. There are 34 uluses (districts) on the territory of the Republic of Sakha (Yakutia), the capital Yakutsk is a city of republican significance and the remaining cities in the republic are cities of republican subordination. Population as of 01.01.2024: 1,001,664 people, of which 677,004 people are urban and 324,660 people are rural. [12]

In order to provide specialized medical care (SMC) for dementia and non-dementia CI in the Republic of Sakha (Yakutia), since 2018, joint activities have been implemented with the Federal State Budgetary Scientific Institution "Yakutsk Scientific Center for Complex Medical Problems" (YSC CMP) and the Ministry of Health (RS (Yakutia) to organize SMC for patients with neurodegenerative diseases (NDZ). Thus, in 2018, a memory room was opened in the YSC CMP outpatient clinic on a reimbursable basis, since the specialty of a neuropsychologist is not included in the compulsory medical insurance program. The collective work of the YSC CMP with the Ministry of Health of the RS (Yakutia) made it possible to approve the order of 14.02.2019 No. 01-07/184 "On the procedure for routing patients with a neurological profile suffering from neurodegenerative diseases at the outpatient and hospital stages." In 2019, a neurological department for patients with neurodegenerative diseases was opened at the YSC KMP By the Order of the Ministry of Health of the Republic of Sakha (Yakutia) dated 17.12.2020 No. 01-07/1945, the republican action plan ("road map") was approved for the implementation of a set of measures to identify and early diagnose cognitive disorder in elderly and senile citizens within the framework of the regional project "Development and implementation of a program of systemic support and improving the quality of life of elderly citizens "Older Generation" (hereinafter referred to as the Set of Measures) in the Republic of Sakha (Yakutia) for 2021. In 2021, the Scientific and Technical Council of the Ministry of Health of the Republic of Sakha (Yakutia) developed and approved methodological recommendations "Early diagnosis of cognitive disorder in older citizens in social and medical organizations." By the order of the Ministry of Health of the Republic of Sakha (Yakutia) dated September 22, 2020 No. 01-07/1326 "On the opening of a memory disorder cabinet at the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Clinical Hospital No. 3" a memory cabinet was opened. In 2021, a hospital registry of dementias "Clinical and demographic study of dementias in the Republic of Sakha (Yakutia)" was created. Copyright holder: FGBNU YSC CMP. Certificate of state registration of the database No. 20211622297. Four diseases are included in the hospital registry: Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and progressive supranuclear palsy (Fig. 1). As of 01.01.2023, there are 61 patients in the registry

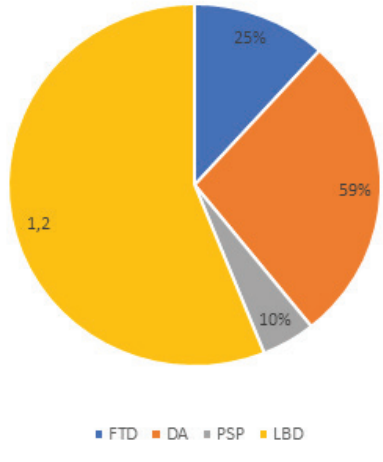

Fig. 1. The number of patients with dementia in the hospital registry of the NDD Center of the YNC KMP

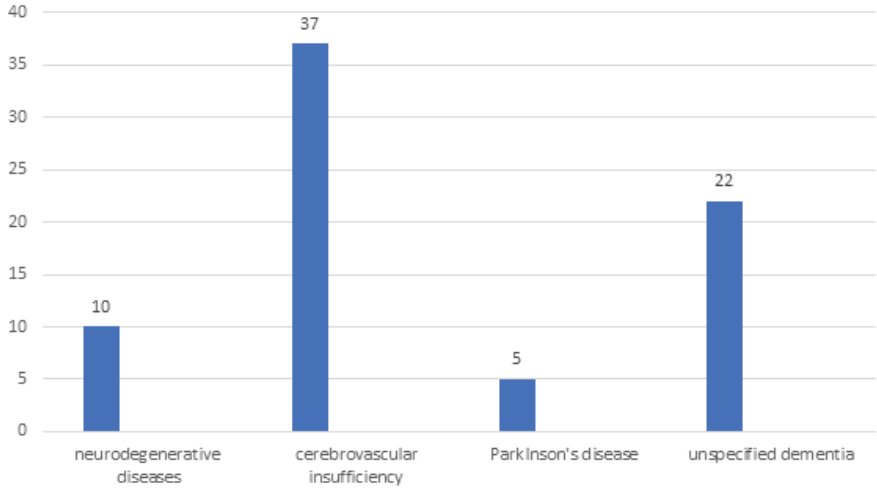

Fig. 2. The number of patients with cognitive impairment referred for clarification of NDD, cerebrovascular encephalopathy (CE), Parkinson's disease (PD) and other unspecified dementia

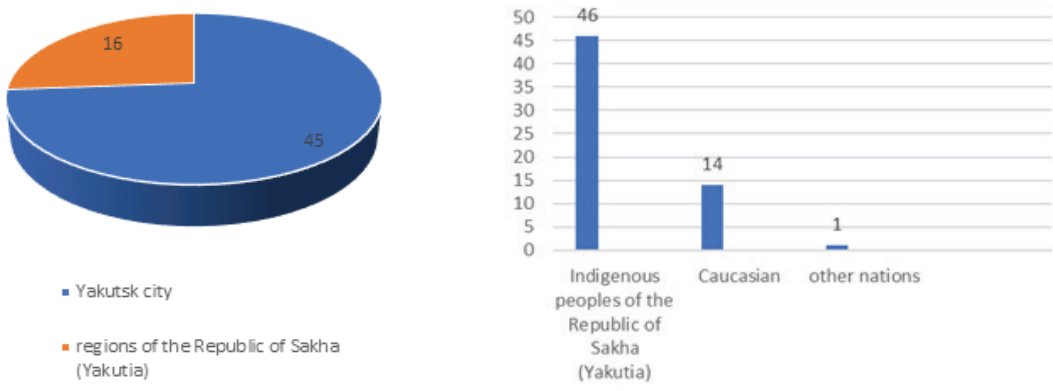

Fig. 3. The number of patients referred from the regions of the RS (Yakutia) and the city of Yakutsk with dementia and their division by ethnicity to the neurological department of the Clinic of YNC KMP

Fig. 1. Number of patients with dementia in the hospital registry of the NDS Center of the Yaroslavl Scientific Center of Cardiology and Medicine.

Fig. 2. Number of patients with cognitive disorder referred for clarification of neurodegenerative disease (NDD), cerebrovascular insufficiency (CVI), Parkinson's disease (PD) and other unspecified dementia and Fig. 2 shows that the largest number of referred patients are those with CVI (n=37) and unspecified dementia (n=22).

Fig. 3. The number of patients referred from the districts of the Republic of Sakha (Yakutia) and the city of Yakutsk with dementia and their division by ethnicity.

At the same time, patients were referred more often from the city of Yakutsk than from the uluses of the republic, which can be explained by the opening of memory rooms and specialized neurological departments of the Yakut Scientific Center for Clinical Medicine and the M.E. Nikolaev Republican Clinical Hospital No. 1 in Yakutsk. By ethnicity, representatives of the indigenous population are mainly registered with dementia in the hospital registry, rather than representatives of the Caucasian race. This is due to the fact that the indigenous population (Yakuts and others) predominates in the territory of the Republic of Sakha (Yakutia) [12].

Routing of patients with cognitive disorders for the provision of psychiatric and medical-psychological care.

Elderly and senile patients with cognitive disorders who have applied to a medical organization providing primary health care, if there are indications, are examined by a psychiatrist at the central district hospital, and residents of the city of Yakutsk and suburban villages at the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Psychoneurological Dispensary" (hereinafter YARPND). In the absence of a psychiatrist in the MO, patients are sent to the outpatient department of the YARPND located in the city of Yakutsk. At the same time, if an elderly and senile patient with cognitive disorders who has applied to the MO poses a danger to himself or others due to his mental state, then any doctor of the medical organization makes an emergency call to the ambulance team for hospitalization in the 24-hour hospital of the YARPND. Thus, specialized medical care for patients with cognitive disorder in the Republic of Sakha (Yakutia) is currently provided at the outpatient stage in the memory room of the Active Longevity Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Regional Clinical Hospital No. 3" and in the cognitive disorders room of the YNC KMP Clinic. The inpatient stage of specialized medical care for patients with cognitive disorder includes treatment in the neurological department for patients with neurodegenerative diseases in the YNC KMP Clinic and in the geriatric neurology department of the Geriatric Center of RCH No. 3. Patients with cognitive disorder and dementia who pose a danger to themselves and others are referred to the YRCND. According to a study by employees of the Department of Neurology and Psychiatry of the Medical Institute of NEFU and the YNC KMP, the minimum predicted number of patients with AD in the Republic of Sakha (Yakutia) is 4166 people, and the maximum is 8429 people. At the same time, in the industrial uluses of the republic, which are located in the southern part of the Republic of Sakha (Yakutia) and are engaged in the extraction of minerals (Neryungri, Mirninsky, Aldansky), the largest number of patients with bronchial asthma is predicted - with a minimum of 671 people and a maximum of 1467 people. In the central (Khangalassky, Namsky, Gorny), eastern (Ust-Aldansky, Churapchinsky, Tattinsky, Amginsky, Ust-Maisky) and western (Vilyuysky, Verkhnevilyuysky, Nyurbinsky, Suntarsky) uluses, the predicted number of patients suffering from bronchial asthma is significantly lower and is a minimum of 121 people, a maximum of 418 people. The Arctic and northern uluses are expected to have the smallest number of patients with bronchial asthma, especially in Eveno-Bytantaysky (6.9-11.1 people) and Anabarsky (4.8-10.5 people). According to official data from the YARMIAC for 2022, 45 patients with a diagnosis of bronchial asthma have been registered in the Republic of Sakha (Yakutia), of which 36 (80%) people live in the city of Yakutsk, the rest in the central regions and in the Vilyuy group of districts. Of the Arctic uluses, 1 patient has been registered in the Abyysky District. When comparing the predicted number of patients with bronchial asthma with official statistics, an excessively low level of bronchial asthma diagnosis was found in the Sakha Republic (Yakutia). Currently, bronchial asthma diagnosis in the RS (Y) is only 1% of the predicted number [2].

It should be noted that in the International Classification of the 10th Revision (ICD-10), the diagnosis of dementia is coded only by psychiatrists in the class "Mental and behavioral disorders":

Neurologists code cerebrovascular diseases in ICD-10 as "I67-I69" without specifying dementia, since this classification does not allow this. In the "Comprehensive interdisciplinary and interdepartmental program for the prevention, early detection, diagnosis and treatment of cognitive disorders in the elderly and senile individuals until 2025" Appendix 2 specifies the codes to encode vascular dementia, dementia with Lewy bodies, dementia in Parkinson's disease and frontotemporal degeneration (Table 1). Although these dementia diseases are not

Dementia codes in ICD-10

Dementia in ICD-10	Diseases Class "Diseases of the nervous system" (G) section "Cerebrovascular diseases" (I)	Class "Mental and behavioral disorders" (F)
Alzheimer's disease	G30 Alzheimer's disease G30.0 Early-onset Alzheimer's disease G30.8 Other forms of Alzheimer's disease G30.9 Unspecified Alzheimer's disease F00 Dementia in Alzheimer's disease	F00.0 Early-onset dementia in Alzheimer's G30.1 Late-onset Alzheimer's disease disease F00.1 Late-onset dementia in Alzheimer's disease F00.8 Atypical or mixed dementia in Alzheimer's disease F00.9 Unspecified dementia in Alzheimer's disease
Dementia in cerebrovascular diseases Post-stroke dementia Dementia in cerebrovascular encephalopathy	I69 Sequelae of cerebrovascular diseases I67.3 Progressive vascular leukoencephalopathy I67.8 Other specified cerebrovascular diseases F01 Vascular dementia	F01.0 Vascular dementia with acute onset F01.1 Multi-infarct dementia F01.2 Subcortical vascular dementia. F01.3 Mixed cortical and subcortical vascular dementia. F01.8 Other vascular dementia F01.9 Vascular dementia, unspecified
Dementia with Lewy bodies	G31.8 Other specified degenerative diseases of the nervous system	F02.8 Dementia in other specified diseases classified elsewhere
Dementia in Parkinson's disease	G20 Parkinson's disease	F02.3 Dementia in Parkinson's disease
Frontotemporal dementia	G31.0 Localized cerebral atrophy	F02.0 Dementia in Pick's disease
Infectious diseases	G05.0 Encephalitis, myelitis and encephalomyelitis in bacterial diseases classified elsewhere Encephalitis, myelitis or encephalomyelitis (in): syphilis: congenital (A50.4+)late (A52.1+) G05.1 Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere B22.0 HIV disease with manifestations of encephalopathy	F02.4 Dementia in diseases caused by human immunodeficiency virus (HIV) F07.1 Postencephalitic syndrome Posttraumatic encephalopathy
Posttraumatic encephalopathy	T90.5 Sequelae of intracranial injury	F04 Organic amnestic syndrome not caused by alcohol or other psychoactive substances

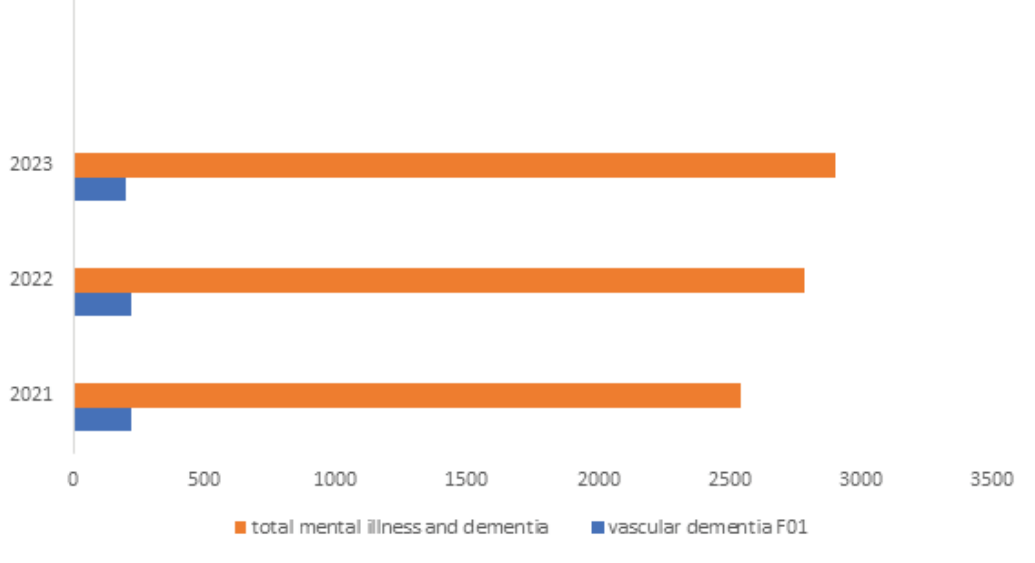

Fig. 4. Number of patients with mental illnesses and dementia in the group over 60 years old according to the Yakutsk Psychoneurological Dispensary

specified in the ICD-10 coding. Thus, the diagnosis of dementia cannot be taken into account in statistics by neurologists.

The number of patients with CI, vascular and mixed dementias in cerebrovascular diseases is unknown, since their number in these groups remains outside the state statistics. According to the YARMIAC, in 2023, 23,745 patients with the code "I67" were registered, of which 1,897 were newly diagnosed. Therefore, in the current situation, we can judge the number of patients with vascular dementia only by the YARPI data (Fig. 4).

Fig. 4. The number of patients diagnosed with DE (I67) and vascular dementia (F 01-F01.3) in the group of people aged 60 years and older.

According to the data provided by the Main Bureau of Medical and Social Expertise (MBMSE) for the Republic of Sakha (Yakutia) of the Ministry of Labor of Russia, the number of newly established disabilities due to dementia (G30.0-G31.0) from 2019-2023 averages 4 people per year, which is also associated with underdiagnosis of dementia.

In the Russian Federation, in general medical practice, the diagnosis of AD is also established in only 1% of cases [1]. Worldwide, 1.6 million people died from dementia in 2019, which makes it the seventh leading cause of death [6]. According to researchers in the USA, North and South America, Japan and China, the study of cognitive health problems and the impact on public health are currently of paramount importance. Particular attention is paid to areas related to early diagnosis and methods of preventing the development of dementia, as well as symptomatic and pathogenetic therapy of Alzheimer's disease and other diseases accompanied by cognitive disorder [3,4,6,7,8,10]. Since 2021, interdepartmental cooperation has been carried out in the Republic of Sakha (Yakutia) to train social workers. Republican Clinical Hospital No. 3, together with ANO "Long Life", implemented the social project "School of Home Care for Elderly Citizens and Disabled People Who Have Lost the Ability to Self-Care." The project team, consisting of doctors and nurses of palliative care, trains social workers in addition to relatives. For several years, a joint project "Medical and social patronage" has been implemented with the aim of developing a model of interaction between social services and primary health care in the interests of elderly and senile people, as well as people with limited mobility, for the implementation of technologies for organizing a long-term care system.

In the Republic of Sakha (Yakutia), research is being conducted aimed at studying the characteristics of the course of dementia and non-dementia cognitive disorders, and hospital morbidity and mortality are being analyzed. For example, the Yakutia Scientific Center for Clinical and Medical Care is conducting research work "Epidemiological, medical and genetic aspects and development of methods of translational and personalized medicine for neurodegenerative diseases in the Republic of Sakha (Yakutia)".

It is important to note that in the organization of anti-dementia measures, the key factors are the prevention and detection of dementia and non-dementia cognitive disorder at an early stage of the development of these conditions. Given the global trend towards an increase in AD, mixed dementias, which is a pressing medical and social problem both in the world and in individual countries and their regions, in 2018 the Russian Federation adopted the "Comprehensive interdisciplinary and interdepartmental program for the prevention, early detection, diagnosis and treatment of cognitive disorders in the elderly and senile until 2025". The development of this program was led by the Ministry of Health of the Russian Federation, the First Moscow State Medical University named after I.M. Sechenov of the Ministry of Health of Russia, the "Russian National Research Medical University named after N.I. Pirogov", as well as the Russian Association of Gerontologists and Geriatricians, the Russian Society of Psychiatrists, the All-Russian Society of Neurologists, the Russian Scientific Medical Society of Therapists, and the Union for the Protection of Mental Health. In July 2024, the regional project "Development and implementation of a program of systemic support and improvement of the quality of life of senior citizens" was developed in the Republic of Sakha (Yakutia) within the framework of the national project "Demography", in which the departments involved in this problem took part: the Ministry of Health of the Republic of Sakha (Yakutia), the Ministry of Labor of the Republic of Sakha (Yakutia), the Federal State Budgetary Scientific Institution Yakut Scientific Center for Comprehensive Medical Research, the Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University named after M.K. Ammosov", the North-Eastern Federal University, the Academy of Sciences of the Republic of Sakha (Yakutia). Since 2006, the Department of Neurology and Psychiatry of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov has included the discipline "Neurodegenerative Diseases" in the optional part of the curriculum for 6th-year students majoring in "General Medicine". The plan includes lectures and practical classes on dementia, Alzheimer's disease and other neurodegenerative diseases in which cognitive disorder and dementia develop are studied.

Conclusion. The conducted analysis of the obtained statistical data from official sources of state statistics, YARPINC reports, the hospital registry of the YRC CMP and regulatory documents of the Ministry of Health of the Republic of Sakha (Yakutia) showed that there is:

- discrepancy between the detected cases of dementia in the YARPINC, YARPINC and in the hospital registry of the YRC CMP, which indicates insufficient medical examination of patients with CI and the absence of a single registry of dementias;
- underdiagnosis of dementias in NDD and AD;
- overdiagnosis of CVD with CI as the main cause of dementia;
- lack of routing of patients with CI;
- lack of a palliative care department for patients with dementias;
- lack of epidemiological studies, which does not allow a reliable assessment of the situation with dementias in the Republic of Sakha (Yakutia);
- the existing classification of dementias in the international classification of diseases ICD-10 does not allow neurologists to code cognitive disorder and dementia in cerebrovascular diseases, which leads to an inadequate assessment of the current situation with dementias.

Organization of consolidated efforts of health authorities, scientific institutions of the medical profile and state bodies of social protection to eliminate the above-mentioned shortcomings will help to identify early and moderate cognitive disorders for the timely initiation of pathogenetic therapy, including AD, which will lead to an extension of active longevity and an improvement in the quality of life.

References

1. Koberskaya NN. Bolezn` Al`czgejmera: novy`e kriterii diagnostiki i terapevticheskie aspekty` v zavisimosti ot stadii bolezni.[Alzheimer's disease: new diagnostic criteria and therapeutic aspects depending on the stage of the disease]. Meditsinskiy sovet [Medical Council. 2017;(10):18-24 (In Russ.).] doi. org/10.21518/2079-701X-2017-10-18-24

2. Tappakhov A.A., Nikolaeva T.Ya., Struchkov A.M., Popova T.E. Bolezn` Al`czgejmera v Respublike Saxa (Yakutiya): realii i ozhidaniya

[Alzheimer's disease in the Republic of Sakha (Yakutia): realities and expectations] Yakutskij medicinskij zhurnal [Yakut Medical Journal. 2023;4:88-92. (In Russ.).] DOI: 10.25789/YMJ.2023.83.10

3. Darbà J, Marsà A. Hospital incidence, mortality and costs of Alzheimer's disease in Spain: a retrospective multicenter study. 2021 Oct;21(5):1101-1106. doi: 10.1080/14737167.2020.1820328.

4. Giaume C, Sáez JC, Song W. et al./ Connexins and pannexins in Alzheimer's disease. Neurosci Lett 2019 Mar 16:695:100-105.

5. Global status report on the public health response to dementia: executive summary; 2021, P-3

6. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Akinori Nakamura et al. Nature 2018 Feb 8;554(7691):249-254.

7. Bin Lv, et al. Mortality of Alzheimer's Disease and Other Dementias in China: Past and Future Decades. Int J Public Health 2023 Feb 3:68:1605129.

8. Paschalidis M, et al. Trends in mortality from Alzheimer's disease in Brazil. Epidemiol. Serv Saude., 2023 Mar-Jun;32(2):e2022886. doi: 10.1590/S2237-96222023000200002.

9. The Alzheimer's Association. Alzheimers Dement. 2023 Apr;19(4):1598-1695. doi: 10.1002/alz.13016.

10. Wong SL, Gilmour H, Ramage-Morin PL./Alzheimer's disease and other dementias in Canada. Health Rep. 2016 May 18;27(5):11-6.

11. www.lvrach.ru/partners/alzepil/15438646

12. https: // 14.rosstat.gov.ru/

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METHODOLOGY FOR DETERMINING THE MEDICAL DETERMINANT OF PUBLIC HEALTH WITH THE IDENTIFICATION OF MEDICAL RISK FACTORS FOR HEALTH DISORDERS IN OTORHINOLARYNGOLOGY (ON THE EXAMPLE OF ANALYZING THE TREATMENT OF POLYPOSIS RHINOSINUSITIS)

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An algorithm for assessing the professional potential of an otorhinolaryngologic based on the identification of medical risk factors in the provision of medical care to patients with rhinosinusitis has been developed. A total of 627 otorhinolaryngologic from 32 subjects of the Russian Federation were screened and the treatment of patients with polyposis rhinosinusitis was analyzed. The proposed methodological approach was successfully used to assess the knowledge and skills of physicians of other specialties and formed the basis for the methodology of studying the professional potential of physicians, for which the author's invention certificates were also obtained.

Keywords: public health, medical determinant of public health, medical personnel, human potential, professional potential, staff potential, medical risks, quality, interaction efficiency, medical effectiveness, polyposis rhinosinusitis, antibiotics, topical glucocorticosteroids, antiseptics, otorhinolaryngologic, sociological research.

Introduction. In accordance with the Decree of the President of the Russian Federation the national interest of Russia is: saving the people of Russia, development of human potential, improvement of the quality of life and well-being of citizens. The possibility of saving the people directly depends on the development of human resources potential of health care system employees as a key component affecting the quality of medical determinant of public health. Comprehensive analysis of the attitude of doctors to their activities is significant from the position of preserving and increasing public health. Medical determinant of public health takes into account the state, resource provision and management processes of public health care, which as a result of synergy ultimately affect the quality of public health. Its components are the state of resource endowment of the industry, including staffing, level of professional potential, quality of professional development institutions, processes of medical care and the results associated with their use in the field of prevention, diagnosis, treatment, rehabilitation, which ultimately improve the quality of public health [5]. Low quality of rendered medical services and, as a consequence, low medical efficiency, negatively affect the state of public health, which is why it is necessary to take into account the state

of medical determinants in order to develop a productive system of public health management. [5].

The state of staffing and the level of professional potential, as components of the medical determinant of public health, are one of the main components of the health care system in addressing the degree of achievement of medical outcomes. The methodological peculiarity of the work was the use of the following definitions as working concepts, which were proposed by researchers at different stages of human resources study: human potential, professional potential and human resources potential of health care workers [4,6,9]. One Nobel laureate Armantia Sen defined the key goal of society development as the increase of human potential, and as the main characteristic of human potential he indicated the possibility of free choice of value-oriented activities by an individual, and another Nobel laureate James Heckman further developed the concept of human potential, linking it to the development of internal abilities of an individual, to the activation of his creativity. However, there is still no unified interpretation of this concept. Human potential can be considered as a certain "resource" that is used both in the employment market and outside it. Its main components will be education and level of expertise, but the content of this term is expanding by adding such personal characteristics as, for example, the structure of interests and values.

Health status as one of the forms of human capital is included in the "core" of human potential and makes it possible to analyze the level of economic return in the form of added value at the macro level, and in the form of income from labor activity or increased consumer demand at the micro level [14]. Comprehensive studies of the current state of human potential of health care are insufficient, and the existing methodological approaches to its assessment are characterized by fragmentation, lack of an integral approach and determine the need for further improvement of expert assessment methodology not only at the individual but also at the societal level [4].

The characteristic of a medical worker is included in the criteria for assessing his/her human potential when proving the reliably more effective preservation of life, health, success of professional and labor activity of a medical worker and higher quality of medical care provided by him/her [9]. Human potential is defined as a set of properties and qualities that determine the ability of an individual to achieve the highest success in individual professional activity through self-expression and self-development. The risk-oriented approach can be used as a methodological basis for methodological approaches to measuring human potential.

In accordance with the Rules for the development and approval of professional standards approved by the Government of the Russian Federation of 22.01.2013 № 23, the introduction of professional standards in medical organizations in Russia was accompanied by research in the field of professional competencies of medical workers, which can be considered as a methodological basis for the introduction of the term "professional potential of health care workers". This term can be used not only in terms of assessing the professional competencies of medical workers, but also as a characteristic of the readiness of medical personnel to form and maintain their professional identity, increase their professional expertise, and improve their knowledge, skills and abilities within the medical specialty. Based on the expert assessment, the authors propose a unified concept of human resource potential of the health care sector, which corresponds to the purpose and objectives of our study.

Human resource potential of the health care sector is the ability of a professionally trained and organized workforce - health workers - to achieve the goals of improving the quality of public health to the fullest extent possible. It includes such components as the structure of labor resources and their even distribution; expected duration of labor activity in the sphere of health care; continuous improvement by medical personnel of professional knowledge, skills and abilities in the field of medical prevention, treatment and rehabilitation, medical deontology and ethics; high external assessment of professional competencies of labor resources; inclusion of work in the priority of life values; satisfaction with both the chosen specialty and the present work. Physicians' job satisfaction, motivation to work and medical workers' confidence in their work are also important integral indicators of the professional potential of medical personnel, taking into account the state's personnel policy in the field of health care and public health. The relevance of the development of a new tool for studying and assessing the professional potential of medical personnel is associated with the increased need to provide the health care system with qualified medical personnel as a component of the medical determinant of public health.

Diseases of the ENT organs occupy a significant place in the general structure of morbidity and do not show a downward trend Knowledge of the state and causes of the decline in physicians' competence, human potential and factors determining them would be the basis for making adequate management decisions to improve the quality of medical otorhinolaryngologic care [10]. The estimated incidence of acute rhinosinusitis (ARS) ranges from 1.39% to 9% per year, and chronic rhinosinusitis (CRS), affects about 14 in every 100 people, and about 2-4 out of 100 have polyposis rhinosinusitis (PRS) [10]. Previously, defects in the provision of medical care to patients with rhinosinusitis have been identified in our country [8]. In ORS there is a risk of inflammation transition to a chronic form and development of CRS, Improper treatment of CRS leads to frequent relapses, repeated courses of antibiotic therapy, risk of antibiotic resistance development, increased need for surgical treatment, which increases the material costs of the state on the one hand, and further reduces the quality of life of these patients on the other hand. In ORS, improper treatment of patients, in addition to the recurrence of polyp growth, may worsen the drug control of comorbid pathology in the form of bronchial asthma (BA) and allergic rhinitis due to the common mechanism of development of these pathological conditions.

The aim of this study was to assess the professional competence of otorhinolaryngologic in the subjects of the Russian Federation, as a component of the medical determinant of public health, by means of a quantitative social survey using a questionnaire developed by the authors to assess the knowledge and skills of a doctor [11], using automated systems for collecting and processing information [8].

Materials and methods of research. On the basis of the obtained data of the quantitative sociological survey we analyzed the provision of medical care to patients with rhinosinusitis with the identification of medical risk factors associated with the professional training of otorhinolaryngologic as a component of medical determinants affecting public health.

The assessment of the correctness of the answers of the interviewed doctors was based on comparison with the reference value (standards of medical care). The proposed algorithm (Fig. 1) allows us to assess the level of professional competence of otorhinolaryngologic, the level of their knowledge and skills as a component of the medical determinant of public health with the possibility of identifying medical risk factors in otorhinolaryngology and to identify the main problems,

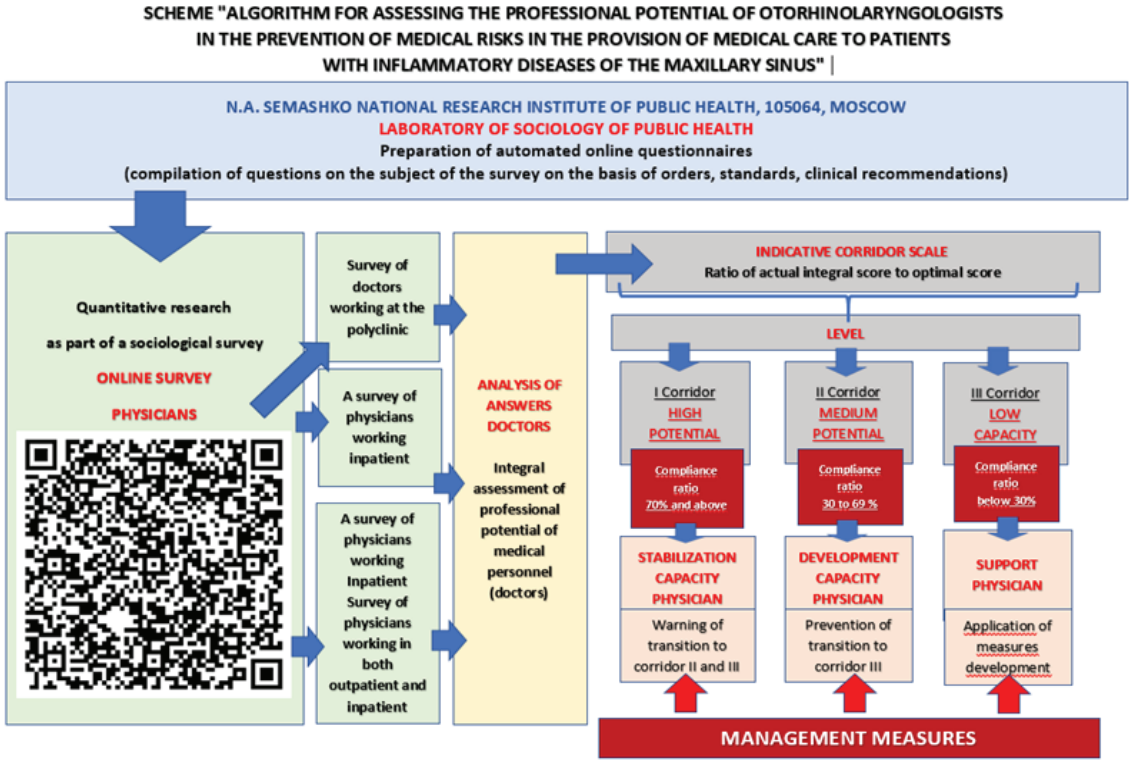
the solution of which through the development of a set of measures can improve the training of medical personnel and ensure the quality of medical care [11].

A pilot approbation of the methodology was carried out by questioning 627 otorhinolaryngologic working in state hospitals or polyclinics from 39 subjects of the Russian Federation. Among the respondents there were 46.25% men and 53.75% women, age up to 44 years was in 49.44% of cases, 45-59 years - in 46.09% of cases and over 60 years - in 4.47% of cases. Work experience up to 10 years was 197 (31.42%), 10-15 years was 119 (18.98%), 16-20 years was 108 (17.22%), 21-25 years was 94 (14.99%), 26-30 years was 68 (10.85%) and more than 30 years was 41 (6.54%). The link to the online form was sent to respondents by e-mail or using the messengers "WhatsApp" and "Telegram". The data of the sociological survey were automatically accumulated on Google Drive in the form of an Excel table for automatic summary, processing and analysis of the data of respondents' answers to the scale of predicting the quality of otorhinolaryngological care, taking into account the characteristics of an otorhinolaryngologic and his competencies, which are a set of interrelated basic qualities of personality and include the application of knowledge, skills and abilities. The survey data were fed into the automated system of information collection and processing "System of automatic data processing and questionnaire administration (SODA version 1)". Computer program registration certificate № 2024613395 [8].

Results. The electronic form of the questionnaire included 229 questions divided into two sections (outpatient, inpatient) with answer choices and open-ended question options with the possibility to give and reflect suggestions from the interviewed otorhinolaryngologic. QR Code to the electronic form of the online questionnaire. (Figure).

The questions for the sociological survey are formulated taking into account clinical recommendations, standards and orders of medical care in the profile of "Otorhinolaryngology", as well as the results of the analysis of theoretical and empirical concepts. The online questionnaire is designed to survey primary care otorhinolaryngologic, as well as otorhinolaryngologic working in a specialized hospital, and consists of three parts:

The proposed algorithm allows us to analyze the average and individual characteristics of the sample, to investigate the consistency of the questionnaire items. The questionnaire includes three blocks of questions:



Scheme "Algorithm for assessing the professional potential of otorhinolaryngologic in preventing medical risks in providing medical care to patients with inflammatory diseases of the maxillary sinus". Industrial design patent No. 139327. [11]

Algorithm of evaluation of answers to the questionnaire questions

Indicator	Scales	Question numbers (number)	Mini-maximum score	Maxi-maximum score
Survey of doctors working in the polyclinic	indicative corridor scale	10-135 (125)	125	375
Survey of physicians working in the hospital	indicative corridor scale	167-229 (62)	62	186
Manipulations/operations performed	indicative corridor scale	136-162 (26)	26	78
Criteria for assessing the quality of medical care. Quality of work of a doctor	importance rating scale in points	163-166 (3)	3	9

-1st block of questions is a survey of doctors working in the polyclinic;

-The -2nd block of questions is a survey of physicians working in the hospital;

-3rd block of questions - a survey of doctors working in both polyclinic and hospital.

The questionnaire also includes two scales: the indicative corridors scale (the ratio of the actual integral assessment to the optimal one), when analyzing and automated processing of respondents' answers using integral assessment of indicators, they are divided into three assessment levels or three indicative corridors:

Corridor I - high physician potential (number of points: 161-240);

Corridor II - average physician capacity (number of points: 81-160);

Corridor III - low physician potential (number of points: up to 80).

The indicators of the scales were developed on the basis of analyzing the existing body of research on this issue. The scales provide an opportunity to diagnose the causes and define indicative corridors of the level of professional potential of a doctor (high, average, low) and makes it possible to take timely management measures, both general and individual. in cases of marking questionnaires or filling them out in the personal cabinet of the automated workplace of a doctor.

Thus, if the physician's potential is high (Figure), take measures to prevent the transition to II and III (medium and low) indicative corridor (level) by stabilizing the process.

At medium potential, developmental measures should be taken to prevent the transition to low potential - Level III.

At low potential (Level III), measures for physician support and professional development should be applied.

The methodology questionnaire includes 229 questions, of which direct 220 questions and 9 -socio-demographic indicators

For each question of the methodology, only one answer can be selected and assigned a score. Each indicator is a value calculated for a specific respondent, expressed in points. Scoring is carried out in manual or automatic mode with determination of the correspondence coefficient: from 70 to 100% and above - high; from 30 to 69% - average; below 30% - low (Table).

The information obtained from the results of the survey of the applied methodology allows to assess the level of professional competence of medical personnel (doctors), to identify the main problems, the solution of which through the development of a set of measures can improve the training of medical personnel and ensure the quality of medical care.

The use of the proposed methodology of the algorithm for assessing the professional potential of a doctor allows to identify medical risk factors in otorhinolaryngology. The questionnaire revealed inconsistencies in the treatment of polyposis rhinosinusitis in the form of irrational prescription of systemic antibiotic therapy in 89.31% of cases, local application of solutions with antibiotics in 52.8% of cases and antiseptics in 36.7% of cases, prescription of vasoconstrictors in 64.8% of cases [2]. Also, 17.5% of otorhinolaryngologic do not recommend intranasal glucocorticosteroids as a basic therapy for MRS, which is the main means of preventing the recurrence of polyp growth, and 48.5% of physicians recommend drugs that have no indications for use in MRS in their instructions.

Discussion. Thus, the initial analysis of the data obtained during the questionnaire revealed inconsistency in the provision of medical care by otorhinolaryngologic in the treatment of ORS in the form of unjustified prescription of systemic and local antibacterial drugs, recommendation of topical GCS "off label" or absence of GCS in the recommendations, which are the basic therapy of ORS, as well as frequent use of decongestants. Inappropriate treatment of ORS leads to uncontrolled growth of polyposis tissue and formation of more severe forms of ORS, and concomitant pathologic conditions in the form of AD and respiratory allergy [2,7]. Given the multifactorial nature of the mechanisms involved in the development of polyposis rhinosinusitis, the identification of inconsistencies in the management of these patients will allow the development of interventions to address them.

Conclusion. The level of professional competence as part of the professional potential of medical personnel in otorhinolaryngology is extremely important as one of the components of the medical determinant of public health, to improve medical efficiency in the prevention, diagnosis, treatment and rehabilitation of ENT diseases of the Russian population.

The proposed algorithm for assessing the professional potential of otorhinolaryngologic in the prevention of medical risks in the provision of medical care to patients with rhinosinusitis [11] was successfully transported to other profiles of medical care is the basis of the methodology for studying the professional potential for physicians of specialists of different profiles of care, influencing medical efficiency in the field of prevention, diagnosis, treatment and rehabilitation, which ultimately improves the quality of public health [12, 13]. The Ministry of Health of the Russian Federation can use the proposed methodology and the obtained results of scientific research in the development of approaches to assess and improve the professional potential of physicians in order to increase the public health of the country.

References

1. Savlevich EL, et al. Analiz klinicheskogo techenija polipoznogo rinosinusita i patomorfologicheskogo sostava tkani nosovyh polipov u pacientov, prozhivajushhih v razlichnyh regionah Rossijskoj Federacii. [Analysis of clinical course of chronic rhinosinusitis with nasal polyp (CRSWNP) and pathomorphological composition of nasal polyp tissue in patients living in different regions of the Russian Federation. Golova i sheja. Rossijskij zhurnal. [Head and neck. Russian Journal. 2021;9(3):15–24 (In Russ.).] DOI: https://doi.org/10.25792/HN.2021.9.3.15–24

2. Analiz shem lechenija polipoznogo rinosinusita v Rossijskoj Federacii / Savlevich E.L. [et al.] [The analysis of polypous rhinosinusitis treatment regimens in the Russian Federation. Rossijskaja otorinolaringologija [Russian otorhinolaryngology. 2019;18(1):124–134 (In Russ.).] DOI: https://doi.org/10.18692/1810-4800-2019-1-124-134

3. Varvjanskaya AV, Lopatin AS. Topicheskie nazal'nye dekongestanty: sravnitel'naja harakteristika i obzor pobochnyh jeffektov. [Topical nasal decongestants: Comparative characteristics and a review of side effects. Rossijskaja rinologija [Russian Rhinology. 2015;23(4):50-56 (In Russ.).] DOI: https://doi.org/10.17116/rosrino201523450-56

4. Klyukina EO. Osobennosti razvitija chelovecheskogo potenciala v sisteme zdravoohranenija. Al'manah sovremennoj nauki i obrazovanija. [Features of human potential development in the health care system. 2015. Al'manah sovremennoj nauki i obrazovanija. Tambov: Gramota, № 4 [Almanac of modern science and education. Tambov: Gramota, No. 4] 2015;(94):85-88 (In Russ.).] Available at: https://www.gramota.net/materials/1/2015/4/19.html

5. Metodicheskij podhod k ocenke kachestva obshhestvennogo zdorov'ja / Vasil'eva T.P. [et al.] [Methodological Approach to Assessing the Quality of Public Health.Public. Zdorov'e naselenija i sreda obitanija [Health and Life Environment] 2023;31(11):15-22 (In Russ.).] DOI: https://doi.org/10.35627/2219-5238/2023-31-11-15-22

6. Pliskevich N.M. Instituty, cennosti i chelovecheskij potencial v uslovijah sovremennoj modernizacii. [Institutions, values and human potential in the context of modern modernization. Mir Rossii [World of Russia] 2022;31(3):33–53 (In Russ.).] DOI: https://doi.org/10.17323/1811-038X-2022-31-3-33-53

7. Svistushkin V.M., Sin'kov Je.V. Jeffektivnyj kontrol' simptomov u pacientov s allergicheskim rinitom. [Effective control of symptoms at patients with allergic rhinitis. Medicinskij Sovet [Medical council] 2019;(12):54-56 (In Russ.).] DOI: https://doi.org/10.21518/2079-701X-2019-12-54-56

8. Zudin AB, et al. Sistema avtomaticheskoj obrabotki dannyh- i provedenie anketirovanija (SODA versija 1) [System of Automatic Data Processing and Questionnaire Administration (SODA

version 1) Certificate of registration of computer program №2024613395 (In Russ.).] Available at: https://www.fips.ru/registers-doc-view/fips_servlet

9. Soboleva IV. Chelovecheskij potencial rossijskoj jekonomiki. [The human potential of the Russian economy. Moskva, Izdatel': Nauka [Moscow, Publisher: Science]. 2007; 207 (In Russ.).]

10. Dajhes N A, et al. Sostojanie otorinolaringologicheskoj sluzhby Rossijskoj Federacii / [The state of otorhinolaryngological service of the Russian Federation. Rossijskaja otorinolaringologija [Russian otorhinolaryngology] 2019;18(3):9–16 (In Russ.).] DOI: https://doi.org/10.18692/1810-4800-2019-3-9-16

11. Russkih SV, et al. Shema «Algoritm ocenki professional'nogo potenciala medicinskih kadrov vrachej-otorinolaringologov, v preduprezhdenii medicinskih riskov pri okazanii medicinskoj pomoshhi pacientam s vospalitel'nymi zabolevanijami verhnecheljustnoj pazuhi na osnove integral'noj ocenki kolichestvennyh i kachestvennyh pokazatelej sociologicheskih issledovanij». Patent na promyshlennyj obrazec № 139327, 21.11.2023. Zajavka №2023503029 ot 20.06.2023. Dostupno po adresu: https://fips.ru/EGD/5d4a7dab-13a2-4a2d-b577-532a0ab6fed2 [Scheme «Algorithm for assessing the professional potential of medical personnel of doctors-otorhinolaryngologists, in the prevention of medical risks in the provision of medical care to patients with inflammatory diseases of the maxillary sinus on the basis of an integral assessment of quantitative and qualitative indicators of sociological research» Design patent №139327, 21.11.2023. Application №2023503029 from 20.06.2023 (In Russ.).] Available at: https://fips.ru/EGD/5d4a7d-ab-13a2-4a2d-b577-532a0ab6fed2

12. Russkih SV, et al. Shema «Algoritm ocenki professional'nogo potenciala medicinskih kadrov vrachej – detskih jendokrinologov, v preduprezhdenii medicinskih riskov pri okazanii medicinskoj pomoshhi detjam i podrostkam s saharnym diabetom I tipa na osnove integral'noj ocenki kolichestvennyh i kachestvennyh pokazatelej sociologicheskih issledovanij». Patent na promyshlennyj obrazec 140653, 19.02.2024. Zajavka № 2023503639 ot 21.07.2023. Dostupno po adresu: https://fips.ru/EGD/52527565-6cc5-42de-a55c-8d1e799c3942 [The scheme "Algorithm for assessing the professional potential of medical personnel of pediatric endocrinologists in preventing medical risks in providing medical care to children and adolescents with type I diabetes mellitus based on an integrated assessment of quantitative and qualitative indicators of sociological research." Design patent № 2023503639, 21.07.2023 (In Russ.).] Available at https://fips.ru/EGD/52527565-6cc5-42de-a55c-8d1e799c3942

13. Russkih SV, et al. Shema «Algoritm ocenki professional'nogo potenciala medicinskih kadrov vrachej-pediatrov v preduprezhdenii medicinskih riskov pri okazanii medicinskoj pomoshhi pacientam s miodistrofiej Djushenna na osnove integral'noj ocenki kolichestvennyh i kachestvennyh pokazatelej sociologicheskih issledovanij (informirovannost' vrachej-pediatrov o redkom geneticheskom zabolevanii)». Patent na promyshlennyj obrazec №139328, 21.11.2023. Zajavka № 2023503030 ot 20.06.2023. Dostupno po adresu: https://fips.ru/EGD/283b5040-482d-4062-a0c3-d7e656d9b3bd [Scheme "Algorithm for assessing the professional potential of medical personnel of pediatricians in preventing medical risks in providing medical care to patients with Duchenne myodystrophy on the basis of integral assessment of quantitative and qualitative indicators of sociological research (awareness of pediatricians about a rare genetic disease)" Design patent No. 139328, 21.11.2023. Application No. 2023503030 from 20.06.2023 (In Russ.).] Available at https://fips.ru/EGD/283b5040-482d-4062-a0c3-d7e656d9b3bd

14. Fedotov A.A. Chelovecheskij potencial i chelovecheskij kapital: sushhnost' i otlichie ponjatij. [Human potential and human capital: essence and difference of concepts. Jekonomika i biznes: teorija i praktika [Journal of Economy and Business] 2021;77(7):148-155 (In Russ.).] DOI: https://doi.org/10.24412/2411-0450-2021-7-148-155

Khe Mi Ran

MEDICAL AND STATISTICAL ANALYSIS OF THE PREVALENCE OF ABORTIONS IN THE SAKHALIN REGION

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UDC 614.2:311.313(571.64)

The article analyzes the structure and dynamics of abortions in the Sakhalin region for the period 2013-2022 based on statistical data from the Sakhalin region and the State Federal Statistical Observation No. 13 'Information on pregnancy with an abortive outcome'. Despite a significant decrease in the absolute number of abortions in the Sakhalin Region, which is partly due to a decrease in the number of women of fertile age, a high level of abortions per 1,000 women aged 15-49 years remains, almost twice as high as the same indicator in the Russian Federation. There is an increase in the proportion of spontaneous abortions, as well as abortive outcomes associated with other abnormal products of conception, which may indicate problems of women's reproductive health and a decrease in reproductive potential. These changes are also related to the adoption of new statistical forms of registration of abortions in Russia in 2015-2016. In the structure of the terms of termination of pregnancy, the main part during the study period is abortions up to 12 weeks, but there is a tendency to increase the proportion of abortions at a later date of 12-21 weeks - by 44.8%. In turn, not a single case of abortion for social reasons was noted during the study period, but the share of criminal abortion increased, so in 2021 there were seven cases of illegal termination of pregnancy up to 12 weeks and five cases in 2022. There has also been an increase in medical (legal) abortions in non-governmental medical organizations, which indicates the need to develop measures aimed at interaction between state and non-state medical institutions providing abortion services. In addition, there is no data on abortions among first-time pregnancies in non-governmental medical organizations, which leads to an underestimation of this indicator in the overall structure of abortions. According to the data of the State Federal Statistical Observation No. 13, there has been a steady increase in the share of abortions among first-time pregnancies in the structure of all abortions, including in the share of medical (legal) abortions by 31.9% over the period from 2016-2022. This indicates the need to develop preventive measures aimed at increasing the availability of contraception and medical literacy in the field of reproductive health and the formation of responsible reproductive behavior among the population of the Sakhalin region.

Keywords: abortion, fertility, reproductive choice, Sakhalin region

Introduction. More than 30 years ago, the World Health Organization recognized abortion as a serious problem in the field of women's reproductive health. Despite a significant decrease in abortions in Russia over the past decades, abortion remains one of the main methods of birth control. At the same time, the list of social indications for termination of pregnancy has been significantly reduced, since 2012, the only reason is pregnancy resulting from rape, a special time time has been introduced between the woman's treatment and the abortion procedure itself – "week of silence". In addition, since 2016, mandatory demonstration of the fetus and its heartbeat during ultrasound examination has been introduced for women planning to resort to abortion [4]. Thus, abortion preven-

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tion in modern Russia is mainly aimed at preserving unplanned pregnancy, rather than measures for the prevention and planning of pregnancy, which include increasing contraceptive literacy of the population and the formation of responsible reproductive behavior [2, 3].

Results and discussion. The analysis revealed a significant decrease in the absolute number of abortions over the past 10 years, more than twofold [1]. (Figure. 1).

However, the fact of a decrease in the number of women of fertile age over the same period should also be taken into account, thereby the indicator calculated for 1000 women of fertile age will be more reliable (Figure. 2).

Despite the fact that this indicator has significantly decreased over 10 years, it remains consistently higher than the average for the Russian Federation. In addition, the rate of decline has slowed down since 2018 and a stable value has been observed over the past 2 years, as well as in Russia as a whole. In the structure of the terms of termination of pregnancy, the main part during the study period is abortions up to 12 weeks, but there is a tendency to increase the proportion of abortions at later periods of 12-21 weeks by 44.8%. (Table 1).

The reduction in the total number of abortions was mainly due to a decrease in medical (legal) abortions, the share of which in the structure of abortions decreased by 24.9%, but they still make up the bulk of the structure of abortions, the share of medical (legal) abortion in 2022 was 58.3%. However, there is an increase in the share of spontaneous abortions, which can to testify about problems in the field of women's reproductive health and a decrease in reproductive potential. In 2022, the share of spontaneous abortions amounted to 20.9% among abortions of pregnancy up to 12 weeks, compared to 2013, this figure was 10.2% in the structure of all abortions up to 12 weeks. There is also a significant decrease in the proportion of abortions for medical reasons up to 12 weeks, in 2022 this figure was 0.5% in the structure of abortions up to 12 weeks, however, this decrease is due to changes in filling out the statistical form since 2016. Also in 2016, abortions associated with other abnormal products of conception were allocated to a separate group. Unfortunately, this indicator has a negative trend both in the structure of abortions before 12 weeks and from 12-21 weeks. In turn, not a single case of abortion for social reasons was noted during the study period, but the share of criminal abortion

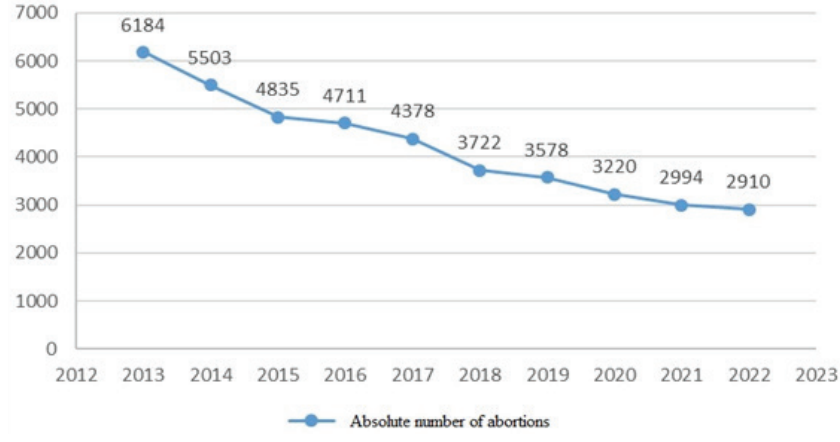

Fig. 1. The absolute number of abortions

Fig. 2. Dynamics of the number of abortions per 1,000 women aged 15-49 years. 2013-2022

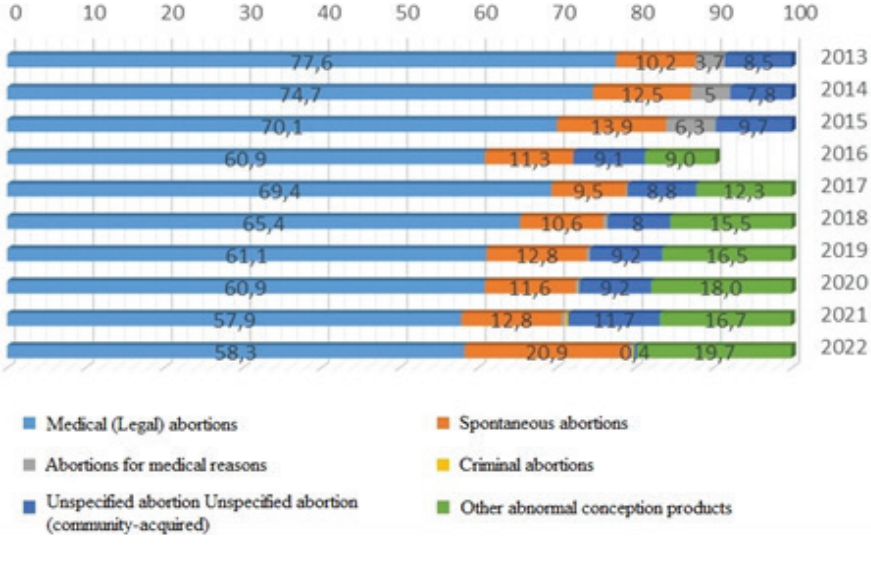

Fig. 3. The structure of terminations of pregnancy up to 12 weeks for the period 2013-2022,%

increased, so in 2021 there were 7 cases of illegal termination of pregnancy up to 12 weeks and 5 cases in 2022. (Figure 3, Figure 4). This once again confirms the inadmissibility of banning abortions at the legislative level, as well as restrictions related to the availability of medical (legal) abortions.

The share of abortions in non-governmental medical organizations out of the total number of abortions in the Sakhalin Region increased by 116.5% over 10 years [1]. The years 2021 and 2022 became record-breaking in the number of abortions in non-governmental medical organizations and accounted for 22.1% and 18.4%, respectively, of the total number of abortions (Figure.5). The sharp decrease in abortions in 2018 may be due to the Decree of the Ministry of Health of the Russian Federation, which defined new requirements for non-governmental medical organizations providing abortion services.

Also in 2021, according to the data "Information on pregnancy with an abortive outcome (absolute data by subjects and groups of organizations)", there was a paradoxical increase in abortions in non–governmental medical organizations among girls aged 15-17 years - 238 cases, which is 36% of the total number of abortions performed in non-governmental institutions. It should be noted that in 2022 there was not a single case of abortion among girls aged 15-17 years, and in 2020 this figure was 3 cases (Figure. 6). Based on this, it can be assumed that the information about abortions in non-governmental medical organizations for 2021 is incorrect. For 10 years, there has been a decrease in the number of abortions among girls aged 15-17 in the Sakhalin Region, 37 cases were registered in 2022 (Figure. 6). In general, the structure of age groups among women who terminated pregnancy is dominated by women aged 18-44 years, until 2016, statistical forms included more age ranges in increments of 5 years, which made it possible to study in more detail the features of abortions by age group. So for the period from 2013-2015, it can be concluded that the majority of girls who terminated pregnancy were between the ages of 25-29 years [1].

Another negative trend is a steady increase in the share of abortions among first-time pregnancies in the structure of all abortions, including in the share of medical (legal) abortions by 31.9% over the period from 2016-2022. It is incorrect to compare the data up to 2016 due to the change in the accounting of statistical data on abortions in pre-pregnant women

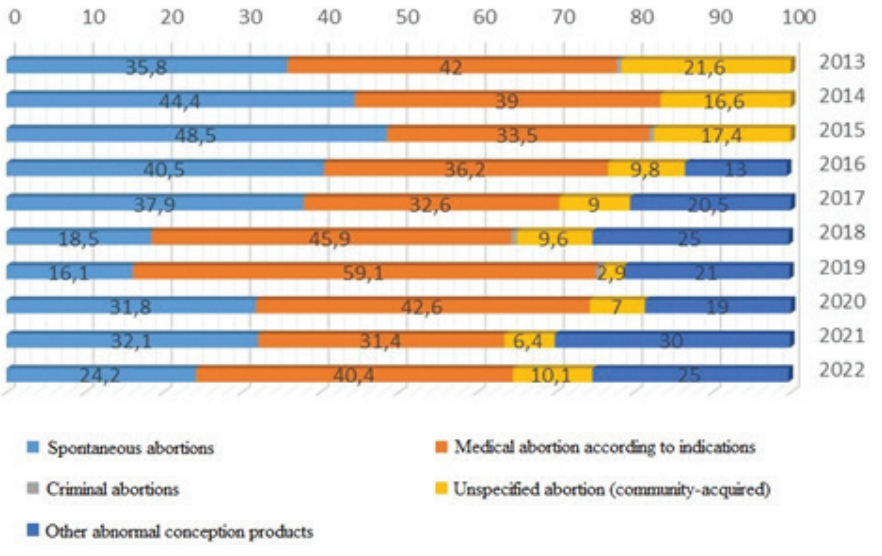

Fig. 4. The structure of terminations of pregnancy up to 12-21 weeks (2013-2022), %

The structure of the terms of termination of pregnancy, %

The timing of termination of pregnancy	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Up to 12 weeks	97.1	96.2	96.3	96.3	96.5	96.3	95.8	95.5	93.9	95.8
12-21 weeks	2.9	3.8	3.7	3.7	3.5	3.7	4.2	4.5	6.1	4.2

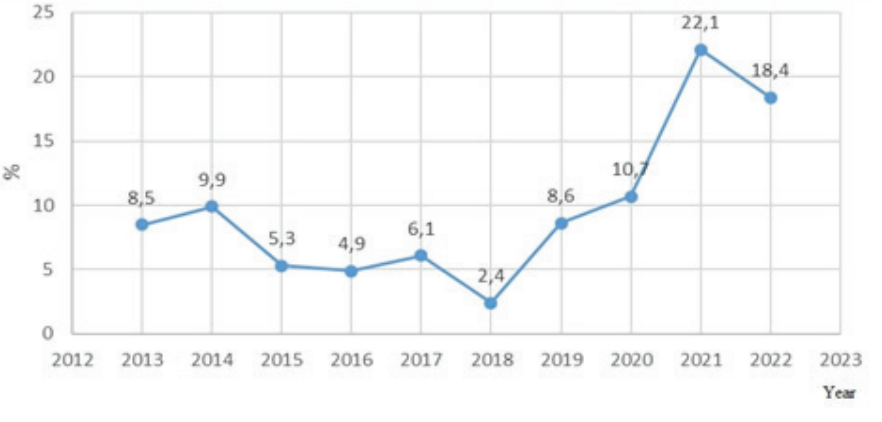

Fig. 5. The share of abortions in non-governmental medical organizations of the total number of abortions in the Sakhalin region 2013-2022, %

in the structure of abortions. In addition, there is no data on abortions among first-time pregnancies in non-governmental medical organizations, which leads to an underestimation of this indicator in the overall structure of abortions (Figure. 7, Figure. 8).

Conclusion. Thus, despite the decrease in the absolute number of abortions over the past 10 years, a fairly high level of abortions per 1,000 women of fertile age remains, almost 2 times higher than the average in the Russian Federation. In addition, over the past 2 years, the indicator has stabilized, with a slight downward trend. In the structure of abortions, a large part is occupied by medical (legal) abortions, despite a decrease in their share in state-owned medical organizations, their number is increasing in non-governmental institutions. Unfortunately, there is no interaction between medical organizations of different forms of ownership, which leads to a lack of understanding about the real dynamics of medical (legal) abortions among representatives of government organizations that deal with preventive measures. Also, the casuistic statistical data of non-state-owned medical organizations for 2021

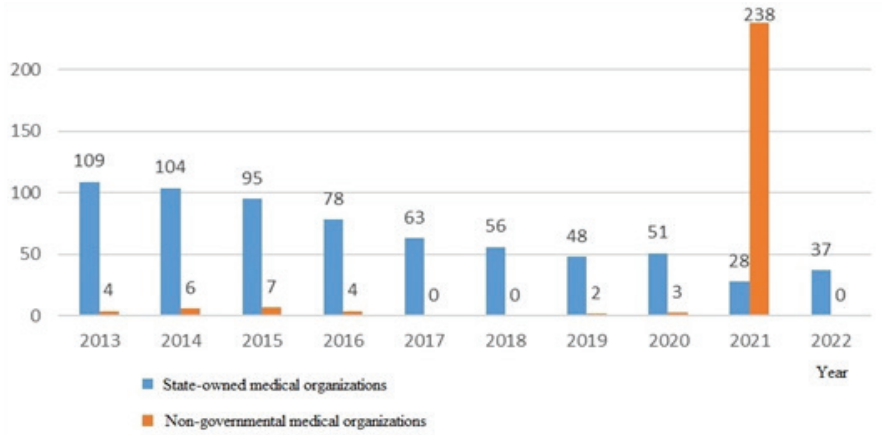

Fig. 6. The number of abortions at the age of 15-17 years in medical organizations of the Sakhalin region, depending on the form of ownership

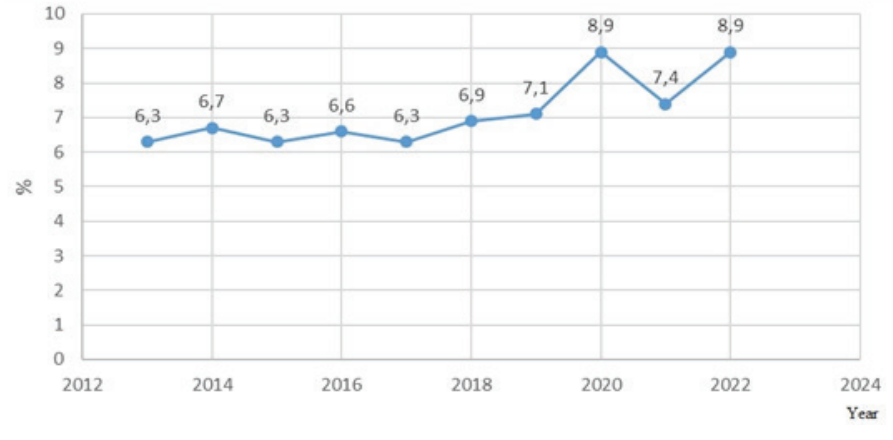

Fig. 7. The proportion of abortions in first-time pregnancies from the total number of abortions (state institutions), %

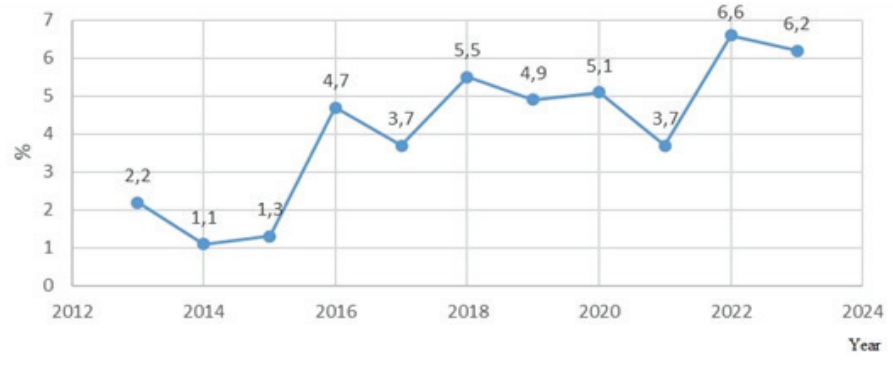

Fig. 8. The proportion of abortions of pregnancy in first-time pregnancies from the total number of medical (legal) abortions (state institutions), %

confirm the need for control by higher health authorities. Unfortunately, the proportion of spontaneous abortions has increased, as well as abortions associated with other abnormal products of conception, which may indicate a decrease in women's reproductive potential and deterioration of their health. The increase in the share of abortions among pre-pregnant women in the structure of medical (legal) abortions indicates a change in psychological values, low contraceptive culture and irresponsible reproductive behavior among young people. However, it is unacceptable to ban abortion or restrict its availability, due to the reported caskes of criminal abortion, the proportion of which has been increasing in recent years. All of the above indicates the need to develop preventive measures aimed at increasing the availability of contraception and medical literacy in the field of reproductive health and the formation of responsible reproductive behavior among the population of the Sakhalin region.

References

1. Oficial`nyj sajt Federalnoj sluzhby gosudarstvennoj statistiki [The official website of the Federal State Statistics Service]. Access mode: https://rosstat.gov.ru / (accessed 05/20/2024)

2. Vishnevsky A.G.Denisov B.P.Sakevich V.I. Kontraceptivnaya revolyuciya v Rossii [The contraceptive revolution in Russia] Demograficheskoe obozrenie [Demographic Review]. 2017. P. 6-34.

3. Kalachikova O.N. Gramotnost` naseleniya v voprosax reprodukcii [Literacy of the population in matters of reproduction] Vestnik KrasGAU. [Bulletin of KrasGAU]. 2012; 1:196-202

4. Sakevich V.I., Denisov B.P., Rivkin-Fish. M. Neposledovatel`naya politika v oblasti kontrolya rozhdaemosti i dinamika urovnya abortov v Rossii [Inconsistent policy in the field of birth control and dynamics of the abortion rate in Russia] Zhurnal issledovanij social`noj politiki [Journal of Social Policy Research] 2016; 14 (4): 461-475.

HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

Z.V. Maraktaev, V.V. Sidorova, T.A. Bayanova

MENINGOCOCCAL INFECTION IN THE REPUBLIC OF BURYATIA: FEATURES OF EPIDEMIOLOGY AND SPECIFIC PROPHYLAXIS

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The article presents manifestations of the epidemic process of MI in the Republic of Buryatia: the dynamics of morbidity in different age groups of the population, mortality, serogroup characteristics of meningococcal strains. An assessment of the state of the level of collective immunity is given based on serological monitoring data and an analysis of immunoprophylaxis against infectious diseases. Period 2021-2023 characterized by a worsening of the epidemiological situation (increasing morbidity and mortality; involvement of different age groups of the population; increase in the number of seronegative individuals). Conducting serological and bacteriological monitoring, increasing the volume of immunization against MI and strengthening awareness-raising work among the population about the possibilities of vaccine prevention of MI will help improve epidemiological surveillance of this infection.

Keywords: epidemiology, meningococcal infection, morbidity, serological monitoring, vaccine prevention.

Introduction. In modern conditions, the problem of meningococcal infection (MI) remains relevant due to its high medical and social significance, due to the high level of mortality and disability [2, 6, 14]. Approximately half a million cases of invasive forms of myocardial infarction are registered annually worldwide, and the incidence varies significantly depending on geographic regions [14]. The relevance of the problem of the spread of MI throughout the world is due to the diversity of sources of infection, serological heterogeneity and variability of the pathogen, and the difficulties of epidemiological surveillance [12]. For a number of years, the Russian Federation (RF) has been characterized by epidemiological well-being in terms of MI. At the same time, in recent years there have been clear signs of a worsening epidemiological situation, including: an increase in the incidence rate, registration of outbreaks with multiple cases of disease, and an increase in the mortality rate [1, 10]. In this regard, the existing systems of epidemiological surveillance and prevention require improvement, primarily at the level of constituent entities of the Russian Federation [1, 3]. In the Republic of Buryatia (RB), the incidence of MI remains a pressing problem [11]. There remain risks of complicating the epidemiological situation, since throughout the country there are signs of the beginning of another rise in morbidity [1,6,8,10]. At the same time, the Republic of Belarus is characterized by a heterogeneous demographic composition, vast territories, and cross-border migration creates the preconditions for the spread of infectious diseases, including such dangerous ones as MI.

Purpose of the study: to study the regional epidemiological features of MI in the context of a selective population vaccination strategy.

Materials and methods of research. A descriptive epidemiological study was conducted for the period 2014-2023. according to reporting form No. 2 "Information on infectious and parasitic diseases" in the Republic of Belarus; state reports "On the state of sanitary and epidemiological well-being of the population in the Russian Federation", "On the state of sanitary and epidemiological well-being of the population in the Republic of Buryatia". The dynamics of the incidence of MI, including HFMI, by age groups was studied. The structure of morbidity was assessed by the proportion of each age group: the total population, adults, children 0-14 years old. An assessment of the state of the level of collective immunity is given based on serological monitoring data. An analysis of the state of immunoprophylaxis against MI is presented according to the data of reporting form No. 5 "Information on preventive vaccinations." Statistical processing of data was carried out using standard methods for calculating intensive and extensive indicators and 95% confidence intervals. Graphic data processing was performed using Microsoft Excel 2016.

Results and discussion. The observation period was characterized by a trend towards a decrease in the incidence of MI and HFMI among the total population of the Republic of Belarus, as well as in the Russian Federation as a whole [10]. For 2014-2019 The average long-term indicator (AMI) of MI of the total population was 0.9 per 100 thousand. The average incidence rate of HFMI of the total population was at the level of 0.6 per 100 thousand. In 2020, no cases of MI were registered. In 2023, the rate increased 2.5 times compared to last year, reaching 0.53 per 100 thousand (Table 1).

Among children, the SMP was 1.7 per 100 thousand of the population, among adults - 0.35 per 100 thousand. The incidence of the child population of the Republic of Bashkortostan during the analyzed period steadily decreased (Fig. 1, Table 1). The average incidence rate of HFMI in children exceeded that among the general population by 3 times, and in adults by 4.6 times. In 2023, the incidence rate in children exceeded the incidence rate in adults by 4 times. Among the child population, the age group at risk for the incidence of HFMI was children under one year old (13.5 per 100 thousand). The incidence of children in other age groups was significantly lower. Thus, the incidence of children 3-6 years old, 1-2 years old, 15-17 years old was 1.4; 2.6; 0.6 per 100 thousand, respectively.

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The lowest incidence rate was recorded in children 7-14 years old - 0.4 per 100 thousand population.

The share of children under 14 years of age in the structure of MI cases prevailed and amounted to 67.0%, the share of adolescents and adults was 4.0% and 29.0%, respectively. Children of all age groups were involved in the epidemic process of MI [8, 13]. At the same time, the largest proportion of cases of MI and HFMI fell on children under one year of age (45.0 and 46.0%, respectively). Among adults, the largest share was among persons 30-49 years old – 38.0% and 18-29 years old – 31.0%.

Registration of HFMI for the analyzed long-term period occurred throughout the year with the largest number of cases in the autumn-spring period, the maximum number of cases was registered in March and October (8 cases each). Perhaps this distribution of morbidity is associated with closer contacts of the population in enclosed spaces, a decrease in the body's resistance, as well as an increase in the circulation of meningococcus during the formation of organized groups.

From 2020, only SFMI are subject to statistical accounting and registration in reporting form No. 2. For 2014-2019 the share of HFMI was 89.0% of the total number of MI diseases. In all foci, one case of HFMI was recorded. Considering the airborne transmission route, which occurs during close contact (within a radius of up to 1 meter from an infected person), it can be assumed that the source of infection was bacteria carriers and patients with meningococcal nasopharyngitis in the patient's environment. Thus, the source of infection in foci of generalized forms was established in 12.3%.

The instability of meningococcus to various environmental factors, the influence of the quality of selection, sample delivery, and sensitivity to chemotherapy do not allow the source of infection to be established in all cases. In addition, according to the provisions of SanPiN 3.3686-21 (section XXXIX Prevention of meningococcal infection), identification of patients with acute nasopharyngitis of meningococcal etiology is carried out in the outbreak for the purpose of treatment. Patients with acute nasopharyngitis in the focus of SFMI are not subject to registration and recording.

It is known that MI has various clinical forms [7]. In the structure of clinical forms of patients with HFMI during the analyzed period, meningitis (53.0%) and meningococcemia (28.0%) predominated; the proportion of mixed forms did not exceed 19.0%.

Table 1

Dynamics of the incidence of MI and HFMI in the total population of the Republic of Buryatia in comparison with the Russian Federation (per 100 thousand population)

	Years									
	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Morbidity of the total population										
MI RB	0.92	1.53	0.71	1.02	1.02	0.31	-	-	-	-
MI RF	0.68	0.67	0.5	0.58	0.7	0.75	-	-	-	-
HFMI RB	0.82	1.23	0.61	0.92	1.02	0.31	0	0.21	0.21	0.53
HFMI RF	0.6	0.59	0.43	0.48	0.52	0.59	0.26	0.22	0.43	0.41
Morbidity in children under 14 years of age										
MI RB	2.84	4.14	1.79	3.16	3.57	0.89	-	-	-	-
HFMI RB	2.84	2.76	1.34	3.16	3.57	0.89	0	0.91	0.9	1.38

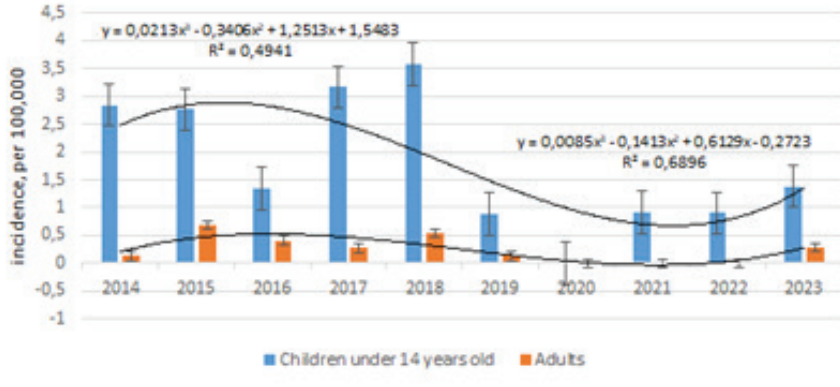

Fig. 1. Dynamics of incidence of HFMI among adults and children in the Republic of Buryatia, 2014-2023.

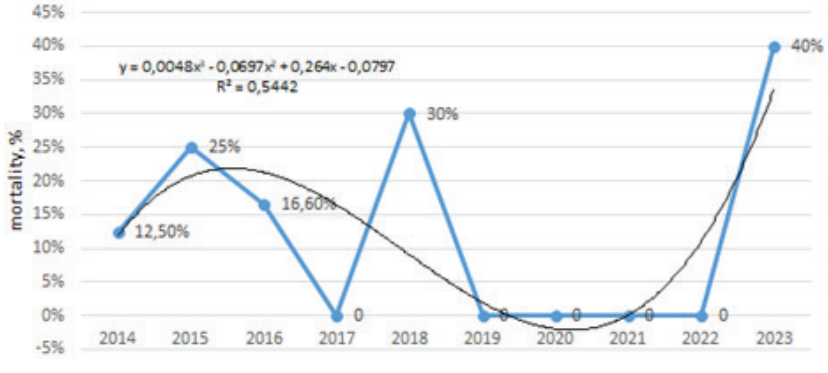

Fig. 2. Dynamics of mortality due to HFMI in the Republic of Buryatia, 2024-2023.

Table 2

Dynamics of immunization volumes against infectious diseases in the Republic of Buryatia and the Russian Federation (absolute values)

Years	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
RF total	35371	55899	62967	119479	175715	299856	374786	435343	476681	841459
RB total:	206	22	8	19	16	53	2168	10468	5020	6690
of which children under 14 years of age	198	21	8	18	16	48	2091	10337	4213	4825

The course of MI is characterized by various forms of the infectious process, which determines the importance of timely diagnosis of the disease [1, 3]. "Meningococcal infection. Meningitis" as the primary diagnosis was made in 68.4% of cases, "ARVI", "Rash of unknown etiology" and other diagnoses - in 17.5; 7.0 and 7.0% of cases, respectively. More than 90.0% of patients were hospitalized on the first day of presentation.

Mortality during this period varied from 12.5 to 40.0% (Fig. 2). Fatal cases were recorded mainly among children: 5 cases – among children under one year old (50.0%), 1 case – in a child 3-6 years old (10.0%), 4 cases – in adults (40.0%) . Please note that 50.0% of all deaths occurred among residents of the republic's districts, which amounted to 22.0% of all registered cases, i.e. every 5th case in the district resulted in death. Half of the deaths occurred among residents of Ulan-Ude.

Studying the serogroup landscape of meningococcal strains is a priority for monitoring MI [8, 12, 13]. During the analyzed period, in 49 cases (86.0%) the pathogen N. meningitidis was detected in the cerebrospinal fluid of patients; in 8 cases (14.0%) the diagnosis was not confirmed by laboratory tests. In the serogroup characteristics of invasive strains, N. meningitidis serogroups A (13 cases; 23.0%), B (12 cases; 21.0%), C (7 cases; 12.0%), Y/W (4 cases; 12.0%) were identified. 7.0%), W (2 cases; 4.0%). In 33.0% of cases, the serogroup characteristics were not determined (19 strains).

Long-term monitoring of the landscape of meningococci isolated from sick people indicates its heterogeneity. Thus, in 2015, meningococcus B dominated predominantly (50.0% of the isolated strains), in 2016 - serogroup W135/Y (80.0% of the isolated strains); in 2017 and 2018, serogroup A was in the lead (71.4 and 50.0% of isolated strains, respectively).

Registration of HFMI for the analyzed long-term period occurred throughout the year with the largest number of cases in the autumn-spring period, the maximum number of cases was registered in March and October (8 cases each). Perhaps this distribution of morbidity is associated with closer contacts of the population in enclosed spaces, a decrease in the body's resistance, as well as an increase in the circulation of meningococcus during the formation of organized groups.

To characterize the immunological structure of the population, annually in the Republic of Belarus, within the framework of the decree "On the organization and implementation of serological monitoring of the state of collective immunity," monitoring of risk groups is carried out, which makes it possible to track the prevalence of carriage and the landscape of circulating strains on the territory of the republic. Since bacteria carriers are important in the spread of the disease [3, 6], it is important to maintain monitoring among "indicator groups". These studies are carried out on the basis of the bacteriological laboratory of the Federal Budgetary Institution of Health "Center for Hygiene and Epidemiology in the Republic of Belarus" twice a year (September, December) among "indicator" risk groups (students of grades 9-11 of secondary schools, lyceums; persons who have been in contact with a patient with MI ; persons living in dormitories, as well as patients with nasopharyngitis). The criterion for selecting a survey area is, first of all, the registration of cases of HFMI in the previous year. To characterize the immunological structure of the population, at least 150 sera are examined annually in the autumn-winter period using the RPGA method with meningococcal erythrocyte diagnostics. Transmission of the MI pathogen, Neisseria meningitides, is carried out by airborne droplets, and the development of healthy carriage is possible, the prevalence of which varies widely [8]. Over a ten-year period from 2014-2023. 2802 biosamples of nasopharyngeal mucus were examined, 13 positive results were identified, which amounted to 0.5%. The years with a high number of positive results are 2014-2016, the share was 76.9%. The highest proportion of positive seedings was observed in the city of Ulan-Ude - 92.3%.

The results of the study demonstrate an extremely low number of seropositive individuals in the population. Thus, the proportion of seronegative/seropositive to N. meningitidis serogroups A and C was 90.2/99.3 and 9.8 and 0.7%, respectively. Over the past 2 years (2022-2023), 100.0% of those examined were seronegative. The predominance of seronegative sera indicates a large number of susceptible ones.

The priority method of combating MI is proactive vaccine prevention [4, 9]. At the same time, the relevance of vaccine prevention of meningococcal infection with multicomponent vaccines is increasing [5].

Before 2020, vaccination coverage against MI was low. Over the past 5 years, there has been a significant increase in vaccination volumes: among the total population by more than 120 times, among children by 100 times. In 2023, the share of children accounted for more than 70.0% of the total number of vaccinated people (Table 2).

Immunization was carried out with the Mencevax and Menactra vaccines, primarily among children, contacts in outbreaks of infectious diseases, and persons subject to conscription for military service.

In order to implement the powers of the Republic of Belarus for immunization of the population within the framework of the Calendar of Preventive Vaccinations for Epidemic Indications and in accordance with the Federal Law of 04/05/2013 No. 44-FZ "On the contract system in the field of procurement of goods, works, services to meet state and municipal needs", in accordance with the Decree of the Government of the Republic of Belarus dated November 19, 2018 No. 644 "On approval of the Procedure for financial provision of immunoprophylaxis according to epidemic indications of the population of the Republic of Buryatia," the Order of the Ministry of Health of the Republic of Buryatia No. 108-r dated February 25, 2021 was initiated on the purchase of immunobiological drugs against MI for immunization of children population from 2 years of age living in an area with a high incidence of MI and persons subject to conscription for military service, as well as vaccination against chickenpox, viral tick-borne encephalitis, rotavirus infection, viral hepatitis A, etc., which led to an increase in vaccination volumes in 2021

The selection of persons for vaccination was carried out in medical and educational organizations. Vaccination was carried out with the quadrivalent conjugate vaccine "Menactra". Despite the increase in vaccination volumes, a statistically insignificant strong inverse relationship ($\rho = -0.670$, $p>0.05$) between the number of vaccinated individuals and the incidence of MI was noted over the years. This may be due to insufficient vaccination volumes and does not have a significant impact on the epidemic process.

Conclusion. Despite the downward trend in the incidence of MI, including HFMI, in long-term dynamics, the period 2021-2023. characterized by rising morbidity and mortality rates; involving different age groups of the population; an increase in the number of seronegative individuals. Taking into account the epidemiological features of MI in the Republic of Belarus, in order to improve epidemiological surveillance, it is advisable to continue carrying out serological and bacteriological monitoring to be able to take prompt preventive and anti-epi-

demic measures against MI; increase the volume of immunization against MI [4, 8]; Strengthen awareness-raising work among the population about vaccine prevention of MI.

References

1. Gritsay M.I. E`pidemiologicheskie osobennosti meningokokkovoj infekcii na sovremennom e`tape: Avtoref. dis. … kand. med. nauk [Epidemiological features of meningococcal infection at the present stage: thesis .... PhD in Medicine. M., 2022; 23 (In Russ.).]

2. Dostizhenie celej v oblasti bor`by` s meningitom na period do 2030 g.: global`naya dorozhnaya karta. Vsemirnaya organizaciya zdravooxraneniya, 2021 r. [Achieving the meningitis control goals for the period up to 2030: a global roadmap. World Health Organization, 2021. URL :https://www.who.int/docs/default-source/immunization/meningitis/defeatingmeningitisroad ap-ru.pdf (11.05.2024) (In Russ.).]

3. Koroleva I.S., Koroleva M.A. Meningokokkovaya infekciya: sovremenny`e tendencii [Meningococcal infection: modern trends]. Infekcionny`e bolezni v sovremennom mire: e`volyuciya, tekushhie i budushhie ugrozy`: Sbornik trudov XV Ezhegodnogo Vserossijskogo Kongressa po infekcionny`m boleznyam imeni akademika V.I. Pokrovskogo. [Infectious diseases in the modern world: evolution, current and future threats: Proceedings of the XV Annual All-Russian Congress on Infectious Diseases named after Academician V.I. Pokrovsky, Moscow, March 27-29, 2023. Moscow: Limited Liability Company 'Medical Marketing Agency'. 2023; 107-108 (In Russ.).]

4. Koroleva MA, Gritsay MI, Koroleva IS, Akimkin VG, Mel'nikova AA. Gnoynyye bakterial'nyye meningity v Rossiyskoy Federatsii: epidemiologiya i vaktsinoprofilaktika [Purulent bacterial meningitis in the Russian Federation: epidemiology and vaccine prevention]. Zdorov'ye naseleniya i sreda obitaniya. [Population health and habitat. 2022; 30 (12): 73–80. doi: https://doi.org/10.35627/2219-5238/2022-30-12-73-80. (In Russ.)]

5. Koroleva IS, Koroleva MA, Gritsay MI. Meningokokkovaya infektsiya i aktual'nost' mer profilaktiki. [Meningococcal infection and the relevance of preventive measures]. Poliklinika. [Policlinic. 2020; 1-2: 47-50 (In Russ.).]

6. Mazankova LN, Tebenkov AV, Rossina AL. Meningokokkovaya infekciya u detej – novy`e vy`zovy` [Meningococcal disease in children - new challenges]. Praktika pediatra [Pediatrician's Practice. 2021; 3: 25-29 (In Russ.).]

7. Markova KV, Skripchenko NV, Lobzin YV, et al. Meningokokkovaya infektsiya v sovremennykh usloviyakh: klinicheskiye, mikrobiologicheskiye i profilakticheskiye aspekty [Meningococcal infection in modern conditions: clinical, microbiological and preventive aspects]. Pediatrician. [Pediatr. 2020; 11 (3): 81–92. https://doi. org/10.17816/PED11381-92 (In Russ.).]

8. Izvekova I.Ya. [et al.] Meningokokkovaya infekciya v Novosibirske: izmenenie e`pidemiologii i problemy` profilaktiki [Meningococcal infection in Novosibirsk: changes in epidemiology and problems of prevention]. E`pidemiologiya i Vakcinoprofilaktika [Epidemiology and Vaccinal Prevention. 2021; 20(3): 60-75. doi:10.31631/2073-3046-2021-20-3-60-75 (In Russ.).]

9. Lobzin YuV, Skripchenko NV, Gorelik YeYU, et al. Meningokokkovaya infektsiya u detey kak mediko-sotsial'naya problema. [Meningococcal infection in children as a medical and social problem].Polyclinic. [Poliklinika. 2020; 3:43-46 (In Russ.).]

10. O sostoyanii sanitarno-e`pidemiologicheskogo blagopoluchiya naseleniya v Rossijskoj Federacii v 2022 godu [On the state of sanitary and epidemiological well-being of the population in the Russian Federation in 2022]. Gosudarstvenny`j doklad. Moskva: Federal`naya sluzhba po nadzoru v sfere zashhity` prav potrebitelej i blagopoluchiya cheloveka. [State report. Moscow: Federal Service for Supervision of Consumer Rights Protection and Human Welfare. 2023. P. 212-214. (In Russ.).]

11. Postanovlenie Glavnogo gosudarstvennogo sanitarnogo vracha po Respublike Buryatiya ot 13.02.2023 №2 "Ob immunizacii v ramkax Kalendarya profilakticheskix privivok po e`pidemicheskim pokazaniyam". [Resolution of the Chief State Sanitary Doctor for the Republic of Buryatia dated 02.13.2023 №. 2 'On immunization within the framework of the Calendar of preventive vaccinations for epidemic indications' (In Russ.).]

12. Svetlichnaya SV, Elagina LA, Popovich LD. Ocenka potencial`nogo e`konomicheskogo e`ffekta pri rasshirenii profilaktiki meningokokkovoj infekcii u detej na osnove real`ny`x e`pidemiologicheskix danny`x [Assessment of the potential economic effect in expanding the prevention of meningococcal infection in children based on real epidemiological data]. Real`naya klinicheskaya praktika: danny`e i dokazatel`stva [Real clinical practice: data and evidence. 2023. 3(2): 31-41. doi.org/10.37489/2782-3784-myrwd-34 (In Russ.).]

13. Rychkova OA, et al. E`pidemiologiya i regional`ny`e programmy` profilaktiki meningokokkovoj infekcii v Tyumenskoj oblasti i Yamalo-Neneczkom avtonomnom okruge [Epidemiology and regional programs for the prevention of meningococcal infection in the Tyumen region and the Yamalo-Nenets Autonomous Okrug]. Voprosy` sovremennoj pediatrii [Issues of modern pediatrics. 2020; 19.(2): 162-167. doi: 10.15690/vsp.v19i2.2110 (In Russ.).]

14. Tzanakaki G, et al. Invasive meningococcal disease in South-Eastern European countries: Do we need to revise vaccination strategies? Hum Vaccin Immunother. 2024; 20(1): 2301186. doi: 10.1080/21645515.2023.2301186.

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ASSESSMENT OF EPIDEMIOLOGIC SAFETY OF DRINKING WATER BY MICROBIOLOGIC INDICATORS IN THE RUSSIAN FEDERATION AND THE REPUBLIC OF BASHKORTOSTAN

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The aim of the study was to assess the epidemiologic safety of drinking water for the population based on the correlation-regression relationship between the incidence of intestinal infections and drinking water samples that do not meet sanitary and microbiologic indicators. Official data on the quality of water from drinking water supply sources and morbidity rates of the population were used for the analysis.

Correlation and regression analysis calculations were performed using the data analysis package in Microsoft Excel. The dependent variable y is the share of water samples non-compliant by microbiological indicators, and the independent variable x is the morbidity rate per 100,000 population by individual nosologies. The sample is equal to n=10 for 2013 and 2022. Variables x are dependent on each other, to exclude multicollinearity between variables, regression analysis was performed stepwise (y1-x1, y1-x2, etc.). Calculations were performed between variables with medium and high correlation coefficients.

The obtained mathematical model can be improved and used to find the relationship between poor-quality drinking water and morbidity of the population also in other diseases.

Keywords: water supply, acute intestinal infections, distribution network, water supply.

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Introduction. Epidemiological safety of drinking water depends on compliance with all requirements at the stage of water treatment and the absence of re-contamination during transportation to the consumer [3]. Acute intestinal infections are a serious public health problem with unfavorable risk factors for the population, such as - unfavorable sanitary living conditions, poor personal hygiene and low public awareness [20, 36].

The World Health Organization (WHO) estimates that unsafe water supply conditions are the cause of non-compliance of drinking water with sanitary and hygienic standards [24, 37, 41]. Contamination of water supplies with pathogenic microorganisms leads to outbreaks of acute intestinal infections of bacterial and viral etiology [4, 12, 13]. State reports indicate that in 9 regions of the Russian Federation (RF) water supplies do not meet sanitary and epidemiological requirements, 17 subjects do not have the necessary complex of treatment facilities, 6 subjects do not have a sufficient number of disinfection plants, also in 14 territories of the RF bacteria of the genus Legionella were detected in tap water, in 10 subjects an increase in the degree of influence of microbiological contamination of drinking water on public health was registered [17].

To control epidemiological safety of drinking water by sanitary-microbiological indicators are used indicators: total microbial count (TMC), thermotolerant coliform bacteria (TCB), total coliform bacteria (TCB), enterococci, coliphages, spores of sulfide-reducing clostridia. TSS characterizes the total content of microorganisms in water without qualitative characterization. TSS are detected in surface, stormwater, or domestic wastewater contamination. When TCB are detected in drinking water samples, coliphages (bacterial viruses) are identified, followed by an emergency reanalysis of the sample and testing for enteroviruses. The Legionella pneumophila indicator was introduced to control the quality of drinking water of hot centralized water supply. Esherechia coli indicator was introduced instead of TCB indicator as an indicator of recent fecal contamination of water [4, 9, 11, 15, 23, 32].

Bacteria of the genus Salmonella and Shigella can be transmitted through drinking water [13, 22-30, 33, 40, 35]. Among the causative agents of acute intestinal infections of viral etiology, rotaviruses and noroviruses can be transmitted via the waterborne route of infection. The causative agent of rotavirus infection belongs to the family Reoviridae, very resistant to low temperatures, stable in the environment [18, 13, 19-26, 31-40]. According to the study of Kosova A.A. [18] it is known that norovirus infection can be contracted not only through drinking water, but also through the water of recreational water sources. The aquatic route of transmission of acute intestinal patho-

gens is not sufficiently studied. Drinking water is not the main source of acute intestinal infections [1, 5].

The aim of the study was to assess the epidemiologic safety of drinking water for the population based on the correlation-regression relationship between the incidence of intestinal infections and drinking water samples non-compliant with sanitary and microbiological indicators.

Material and methods of the study. Data of socio-hygienic monitoring from the state reports on the Russian Federation and the Republic of Bashkortostan for the period 2013-2022 were used as materials. For statistical processing in the correlation-regression analysis were used annual data on morbidity per 100 thousand population and the proportion of drinking water samples that do not correspond to microbiological indicators. The calculations were performed using a statistical package of data analysis in Microsoft Excel, which is manually configurable (Data analysis tools - correlation, regression). As a variable y is the proportion of water samples (water supply, centralized and non-centralized water supply), and as variables x is the incidence of diseases by individual nosologies (hepatitis A, norovirus, rotavirus, salmonella, shigella) [16, 17]. Since x variables are correlated with each other (multicollinearity), regression analysis was performed separately for each variable (y1-x1, y1-x2, etc.). The results of regression analysis are statistically significant ($p<0.05$), reject the null hypothesis and confirm the alternative hypothesis. When the correlation coefficient < 0.30 - the relationship was evaluated as weak, r = 0.30-0.69 - medium, r ≥ 0.70 - strong.

Results. Research results (Table) showed statistically significant correlation between water samples that do not comply with microbiological indicators and morbidity rates per 100 thousand population (salmonellosis, shigellosis, hepatitis A, norovirus, rotavirus).

For RF, the results of correlation and regression analysis (Table) show the relationship:

- between drinking water samples from water pipelines non-compliant by microbiological indicators and incidence of (a) hepatitis A (r=0.50, R2=0.86), (b) salmonellosis (r=0.89, R2=0.96), and (c) shigellosis (r=0.93, R2=0.98);

- between drinking water samples from the distribution network, non-compliant by microbiological indicators and incidence of (d) hepatitis A (r=0.73, R2=0.91), (e) salmonellosis (r=0.95, R2=0.99), (f) shigellosis (r=0.96, R2=0.94);

- between drinking water samples from non-centralized water supply that do not correspond to microbiological indicators and norovirus (g) infection morbidity (r=0.60, R2=0.82);

For RB, the correlation and regression analysis (Table) shows an average relationship:

- between water samples from the distribution network, non-compliant by microbiological indicators and (h) AKI (r=0.38, R2=0.89);

- between samples of water from non-centralized water supply that do not correspond to microbiological parameters and (i) OKI (r=0.35, R2=0.89);

Discussion. The analysis shows that the situation is better in Belarus than in the Russian Federation as a whole. In

Results of correlation-regression analysis of the relationship between the proportion of non-compliant samples and morbidity per 100,000 population in the Russian Federation and RB

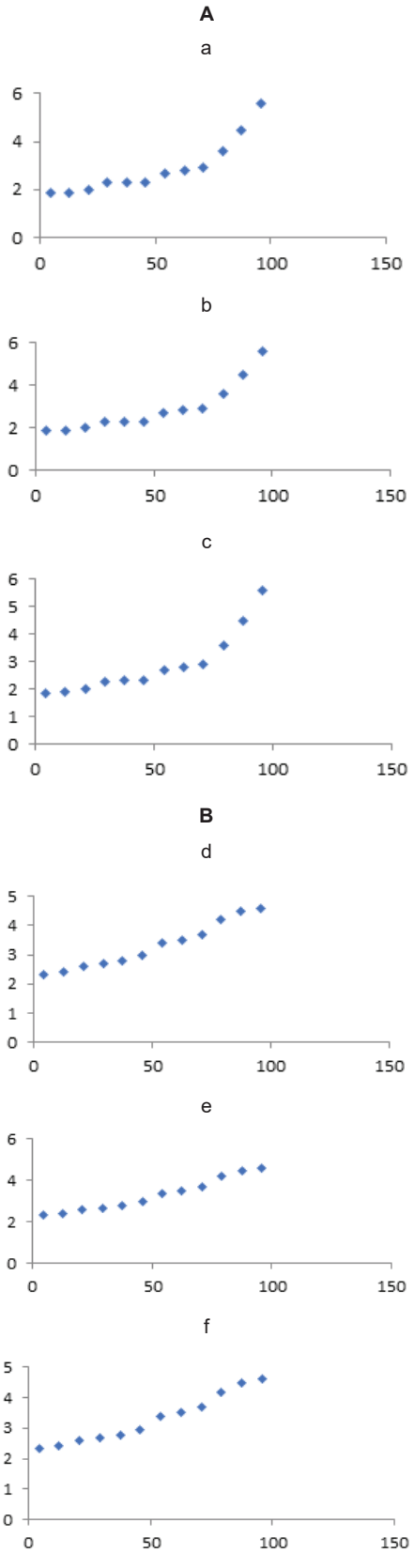
n=10 (number of observations 2013-2022)				correlation r	Regression			
Y		X						
Share (%) of samples non-compliant by microbiological indicators		Incidence per 100,000 population			R^2	F	F significance	P-designation
For the Russian Federation								
Y1	From the water pipes	***X1***	***Hepatitis A***	***0,50***	***0,86***	***67***	***0,00001***	***0,0000054***
		X2	Norovirus	-0,75	-	-	-	-
		X3	Rotavirus	0,23	-	-	-	-
		X4	***Shigellosis***	***0,89***	***0,96***	***249***	***0,00000002***	***0,000000007***
		X5	***Salmonellosis***	***0,93***	***0,98***	***563***	***0,0000000004***	***0,00000000009***
Y2	From the distribution network of centralized water supply systems	X1	***Hepatitis A***	***0,73***	***0,91***	**118**	***0,0000007***	***0,0000003***
		X2	Norovirus	-0,87	-	-	-	-
		X3	Rotavirus	0,37	-	-	-	-
		X4	***Shigellosis***	***0,96***	***0,94***	***178***	***0,0000001***	***0,00000004***
		X5	***Salmonellosis***	***0,95***	***0,99***	***964***	***0,00000000003***	***0,000000000005***
Y3	From non-centralized water supply	X1	Hepatitis A	-0,29	-	-	-	-
		X2	***Norovirus***	***0,60***	***0,82***	***52***	***0,00003***	***0,00002***
		X3	Rotavirus	0,05	-	-	-	-
		X4	Shigellosis	-0,66	-	-	-	-
		X5	Salmonellosis	-0,73	-	-	-	-
Republic of Bashkortostan								
Y1	From the distribution network of centralized water supply systems	X1	Hepatitis A	0,44	0,75	27	0,0008	0,0006
		X2	***Acute intestinal infections (AIE)***	***0,38***	***0,89***	***75***	***0,00002***	***0,00001***
		X3	Enterovirus infections	-0,28	-	-	-	-
Y2	From non-centralized water supply	X1	Hepatitis A	0,41	-	-	-	-
		X2	***Acute intestinal infections (AIE)***	***0,35***	***0,89***	***76***	***0,00002***	***0,00001***
		X3	Enterovirus infections	0,32	0,32	0,69	20	0,002

Belarus, acute intestinal infections of bacterial etiology are more often registered in the pediatric population, and the connection between the water route of transmission is doubtful. Literature data show that food poisoning, causative agents of which are bacteria of the genus Salmonella, is registered in RB. The total incidence of acute intestinal infections (AII) for each year includes the incidence of salmonellosis, dysentery, AII of established and unestablished etiology. Norovirus and rotavirus infections also affect children more frequently. Disease incidence among children is registered in kindergartens and has a group character. Such infections as typhoid fever and polyemelitis have not been registered for many years [2, 14, 17, 18].

For the Russian Federation, general summary data are given for all regions, including those with unfavorable sanitary conditions. For example, the state reports of the Russian Federation state that the Republic of Dagestan recorded cases of outbreaks of acute intestinal infections of waterborne character. This tells us that for correct calculations it is necessary to take several regions and conduct separate correlation and regression calculations with a large sample (for 20 years n=20). According to the latest literature data, the regions that twice exceed the average Russian level of AKI morbidity are the Sakhalin and Tomsk Oblast, Yamalo-Nenets Autonomous Okrug and Khanty-Mansiysk Okrug [16, 17]. Also in RB it is not possible to establish a correlation between drinking water samples and the incidence of rotavirus and enterovirus, as the annual sample contains zero values, and outbreaks of these diseases are rarely registered.

Pathogenic microorganisms are difficult to detect in drinking water because their content is lower than saprophytic microorganisms and they are less stable in the environment. According to the studies of some authors, the compliance of drinking water by microbiological indicators does not give us a guarantee of safety for public health [3, 4, 29, 33, 34]. The disadvantages of virological methods of research are: costliness, low sensitivity, duration, which makes it difficult to detect viral infections of aquatic nature [1, 37].

In our study we used annual data, but it is also worth considering the factor that outbreaks of some infectious diseases have their seasonality. For example, according to Rospotrebnadzor, annual monitoring is conducted during the flood period, as there is a possibility of acute intestinal infections through drinking water [16].



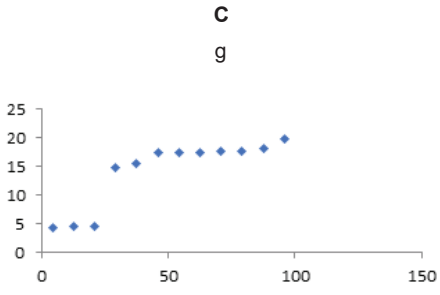


Fig.1. Graphs of the normality of the distribution of variables in the Russian Federation. The relationship between water samples: A – from water supplies and the incidence of: a – hepatitis A, b – salmonellosis, c – shigellosis; B – from the distribution network and incidence of: d – hepatitis A, e – salmonellosis, f – shigellosis; B – from non-centralized water supply and incidence of: g – norovirus infection

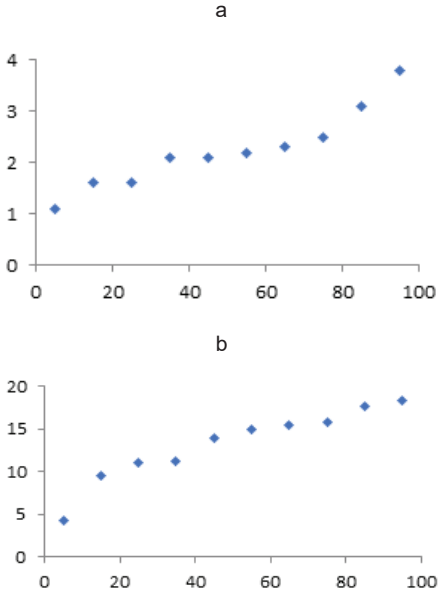


Fig. 2. Graphs of the normality of the distribution of variables in the Republic of Belarus. Dependence between water samples: a – from the distribution network and the incidence of acute intestinal infections, b – from non-centralized water supply and the incidence of acute intestinal infections

Conclusion. Conclusion. When plotting the normality of distribution of variables, a positive curvilinear dependence was found. The results of correlation and regression analysis do not prove a direct cause-and-effect relationship between the variables, for proof we need an experimental approach, for example, under unfavorable conditions - flood period, floods, as well as a large sample, the study of a separate area and the use of other statistical methods.

Literature analysis has shown that in some territories of the Russian Federation drinking water does not comply with microbiological indicators, and the reasons are the lack of sanitary protection zones, treatment facilities and disinfection plants. The majority of water pipelines and water supply sources do not meet the requirements [16]. To improve

the quality of drinking water and its compliance with microbiological indicators, it is recommended to: bring centralized water supply sources to compliance with the requirements of sanitary legislation, provide the water treatment system with the necessary number of disinfection plants and complexes of treatment facilities, provide non-centralized water supply sources with sanitary protection zones.

References

1. Baidakova EV, Ungureanu TN, Mikhailova RI. O kolichestvennoj ocenke mikrobnogo riska, svyazannogo s ekspluataciej kishechnyh virusov v pit'evoj vode [On quantitative assessment of microbial risk associated with the exploitation of intestinal viruses in drinking water]. Analiz riska zdorov'yu [Health Risk Analysis. 2019; 108-114 (In Russ.).]

2. Bakumenko LP, Korotkov PA. Statisticheskij analiz vliyaniya kachestva pit'evoj vody na zdorov'e naseleniya regiona [Statistical analysis of the impact of drinking water quality on the health of the population of the region]. Prikladnaya ekonometrika [Applied Econometrics. 2011; 2 (22): 32-47 (In Russ.).]

3. Kaveshnikov VS, et al. Gigiena vodosnabzheniya naselennyh mest [Hygiene of water supply of populated areas]. Tutorial. Tomsk. 2022: 11-12.

4. Sinitsyna OO, et al. Gigienicheskoe normirovanie razlichnyh vidov vod na sovremennom etape [Hygienic normalization of different types of water at the present stage]. Gigiena i sanitariya. Nauchno-prakticheskij zhurnal [Hygiene and sanitation. Scientific and practical journal. Moscow. 2022; 10: 1151-1157 (In Russ.).]

5. Direktiva Soveta Evropejskogo Soyuza 98/83/ES ot 3.11.98 po kachestvu vody, prednaznachennoj dlya potrebleniya chelovekom [European Union Council Directive 98/83/EC of 3.11.98 on the quality of water intended for human consumption. M., 1999 (In Russ.).]

6. Zagainova AV, Rakhmanin YuA, Talaeva YuG. Ocenka mikrobnogo riska dlya ustanovleniya zavisimosti mezhdu kachestvom vody i zabolevaemost'yu naseleniya kishechnymi infekciyami [Evaluation of microbial risk to establish the relationship between water quality and morbidity of intestinal infections]. Gigiena i sanitariya [Hygiene and Sanitation. 2010; 3:28-31 (In Russ.).]

7. Kupriyanova NY. Epidemiologiya i profilaktika kishechnyh infekcij: ucheb. posobie. Epidemiology and prevention of intestinal infections: textbook. M.: Irkutsk State University. 2014: 35 (In Russ.).]

8. Pozdeeva MA, et al. Kliniko-epidemiologicheskie osobennosti ostryh kishechnyh infekcij u detskogo kontingenta g. Arhangel'ska za 2015-2018 gg. [Clinical and epidemiologic features of acute intestinal infections in the pediatric population of Arkhangelsk in 2015-2018]. Ural'skij medicinskij zhurnal [Ural Medical Journal. P. 115-118 (In Russ.).]

9. Terentyeva NT, et al. Osobennosti klinicheskogo techeniya rotavirusa u detej [Features of the clinical course of rotavirus in children]. Zdravoohranenie Kyrgystana: Kyrgyzskaya gosudarstvennaya medicinskaya akademiya, kafedra detskih infekcionnyh boleznej. Bishkek [Health Care of Kyrgyzstan: Kyrgyz State Medical Academy, Department of pediatric infectious diseases. Bishkek. 2009. P. 169-170 (In Russ.).]

10. Yushchuk ND, et al. Ostrye kishechnye infekcii [Acute intestinal infections]. Rukovodstvo dlya vrachej [Manual for doctors. Moscow: GEOTAR-Media. 2012: 48-84 (In Russ.).]

11. Pivovarova EA. Analiz vzaimosvyazej somaticheskoj zabolevaemosti naseleniya i pokazatelej himicheskoj bezopasnosti pit'evoj vody [Analysis of interrelations of somatic morbidity of the population and indicators of chemical safety of drinking water]. Mezhdunarodnyj nauchno-issledovatel'skij zhurnal [International Research Journal. 2016; 4 (46): 120-121 (In Russ.).]

12. Solomay TV, Kaira AN. Epidemiologicheskie osobennosti vodnyh vspyshek infekcij s fekal'no-oral'nym mekhanizmom peredachi [Epidemiological features of waterborne outbreaks of infections with fecal-oral mechanism of transmission]. Aktual'nye voprosy epidemiologii infekcionnyh boleznej [Actual issues of epidemiology of infectious diseases. 2014; 31-37 (In Russ.).]

13. Soldatkin PK, Gavrilov AV, Dolgikh TA. Enterovirusnye infekcii [Enterovirus infections]. Uchebn. Posobie [Study guide. M. Amur State Medical Academy of the Ministry of Health of Russia. Blagoveshchensk. 2020: 75 (In Russ.).]

14. Sergevnin VI. Ostrye kishechnye infekcii. Vodnyj put' peredachi vozbuditelej [Acute intestinal infections. Water route of pathogen transmission]. Physician. 2013; 7:74-76 (In Russ.).]

15. Trukhina G.M., Yaroslavtseva M.A., Dmitrieva N.A. Sovremennye tendencii sanitarnoj mikrobiologii v realizacii sanitarno-epidemiologicheskogo nadzora za bezopasnost'yu vodnyh ob"ektov [Modern trends of sanitary microbiology in the implementation of sanitary and epidemiological supervision over the safety of water bodies]. Zdorov'e naseleniya i sreda obitaniya [Public health and habitat. 2022; 30(10): 16-24 (In Russ.).]

16. Upravlenie Federal'noj Sluzhby po nadzoru v sfere zashchity prav potrebitelej i blagopoluchiya cheloveka po Respublike Bashkortostan // URL: https://02.rospotrebnadzor.ru/documen/. (Data obrashcheniya: 20.05.2024) [Department of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare in the Republic of Bashkortostan // URL: https://02.rospotrebnadzor.ru/documen/. (Date of reference: 20.05.2024 (In Russ.).]

17. Federal'naya Sluzhba po nadzoru v sfere zashchity prav potrebitelej i blagopoluchiya cheloveka. // URL: https://www.rospotrebnadzor.ru/documents/documents.php. (Data obrashcheniya: 20.05.2024.) [Federal Service for Supervision in the Sphere of Consumer Rights Protection and Human Welfare. // URL: https://www.rospotrebnadzor.ru/documents/documents.php. (Date of reference: 20.05.2024 (In Russ.).]

18. Kosova A.A., et l Epidemiologicheskaya harakteristika norovirusnoj infekcii [Epidemiological characteristics of norovirus infection]. Ural'skij medicinskij zhurnal [Ural Medical Journal. 2022; 21 (3): 114-128 (In Russ.).]

19. Abad F X, Pintó R M, Diez J M, Bosch A. Disinfection of human enteric viruses in water by copper and silver in combination with low levels of chlorine. Appl Environ Microbiol. 1994. P. 2377–2383.

20. Alelign T., Degarege A., and Erko B. Soil-transmitted helminth infections and associated risk factors among schoolchildren in Durbete town, northwestern Ethiopia. Journal of Parasitology Research. 2015. P. 5.

21. Ansari S A, Springhorpe V S, Sattar S A. Survival and vehicular spread of human rotaviruses: possible relation to seasonality of outbreaks. Rev Infect Dis. 1991. P. 448–461.

22. Esmaeili Dooki MR, et al. Bacterial enteropathogens and antimicrobial susceptibility in children with acute diarrhoea in Babol. Caspian J Intern Med. Iran. 2014; 5(1): 30-34.

23. Domínguez À., Prats G., Teixidó À. Guia per a la Prevenció i el Control de les Toxiinfeccions Alimentàries. 2nd ed. Direcció General de Salut Pública; Barcelona, Spain: 2006. 159 p.

24. Stegmaier T, et al. Differences in epidemic spread patterns of norovirus and influenza seasons of Germany: An application of optical flow analysis in epidemiology. Sci. Rep. 2020: 1-14.

25. Dworkin M, Falkow S, Rosenberg E. Le Minor. The genus Salmonella. The Prokaryotes: An Evolving Electronic Resource for the Microbiological Community. 3th ed. Springer-Verlag; New York, NY, USA: 2003. electronic release 314 p.

26. Ogorzaly L, et al. Development of a quantitative immunocapture real-time PCR assay for detecting structurally intact adenoviral particles in water. J Virol Methods. 194:235-241.

27. European Centre for Disease Prevention and Control Prevention of Norovirus Infection in Schools and Childcare Facilities. ECDC: Stockholm. 2013.

28. Emch M., Ali M., Yunus M. Health Place. 2008. P. 96–105.

29. Germani Y, Sansonetti PJ. The Genus Shigella. The Prokaryotes: An Evolving Electronic Resource for the Microbiological Community (Springer-Verlag, New York, US,2003). 314 p.

30. Gray N.F. Drinking water Quality. Problems and solutions. 1994. 344 p.

31. Intestinal parasites prevalence and related factors in school children, a western city sample-Turkey // Okyay P. [et al.] / BMC Public Health, vol. 4, 2004. 64 p.

32. Kühn, et al. I Comparison of Enterococcal Populations in Animals, Humans, and the Environment– An European Study. Int. J. Food Microbiol. 2003. P. 133–145.

33. Klein G. Taxonomy, Ecology and Antibiotic Resistance of Enterococci from Food and the Gastro-Intestinal Tract. Int. J. Food Microbiol. 2003. P. 123–131.

34. Dubois E, et al. Molecular epidemiological survey of rotaviruses in sewage by reverse transcriptase seminested PCR and restriction fragment length polymorphism assay. Appl Environ Microbiol. 1997. P. 1794–1800.

35. Nygard K., Gondrosen B., Lund V. Waterborne disease outbreaks in Norway. Tidsskr. Nor. Laegeforen. 2003; 123 (23): 3410-3413.

36. Popoff MY Le Minor. Genus Salmonella. Bergey's Manual of Systematic Bacteriology. 2nd ed. Part B. Vol. 2. Springer; New York, NY, USA: 2005. P. 764-799.

37. Payment P. Tap water and public health - the risk factor. Water21. 2000; 8: 9.

38. Hein J, et al. Quantitative microbalrisk assessment of distributed drinking water using faecal indicator incidence and concentrations. J. Water Health. 2007; 5 (1): 131-149.

39. Greene S, et al. Recurrent multistate outbreak of Salmonella Newport associated with tomatoes from contaminated fields. Epidemiology and Infection. 2008. P. 157-165.

40. Mehraj, et al. Prevalence and factors associated with intestinal parasitic infection among children in an urban slum of Karachi. PLoS One. 2008; 3 (11): 1-6.

41. WHO, Emerging Issues in Water and Infectious Disease, World Health Organization (WHO), Geneva, Switzerland, 2003. 24 p.

TOPICAL ISSUE

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MEDICAL AND SOCIAL PORTRAIT OF PREGNANT WOMEN WITH COVID-19 IN VARYING SEVERITY

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As a result of a comparative analysis, a number of statistically significant features of the medical and social portrait of pregnant women with COVID-19 of varying severity were identified. An increase in the median age, an increase in the frequency of somatic pathology (chronic arterial hypertension, varicose veins of the lower extremities, overweight, obesity, systemic lupus erythematosus) and polypathies are characteristic as the severity of COVID-19 in pregnant women increases. Mild infection is more common in primigravid women, moderate and severe in pregnant women with a history of childbirth and medical abortion, and extremely severe in multiparous women.

Keywords: new coronavirus infection, COVID-19, pregnancy, social portrait, somatic pathology, gynecological and obstetric history.

Introduction. The COVID-19 pandemic turned out to be a serious challenge with respect to the pregnant women management against the background of SARS-CoV-2 infection manifestation. The available experience of the previous occurrences of the seasonal respiratory infections was insufficient due to the specificity of COVID-19 course and its effect on the body of pregnant women. Research data indicate that during gestation period the severity of COVID-19 course could vary from mild to extremely severe one [3]. Moreover, COVID-19 of any degree of severity could lead to adverse pregnancy outcomes.

Besides, during the gestation period risks of sudden deterioration of a pregnant woman's health condition against the background of primarily stable disease course were noted [1, 8, 9, 11]. During the 1st-4th waves of the pandemic intensive treatment with respiratory support in the intensive care units was required for every 4th pregnant woman with pneumonia [12, 13]. The risk of the adverse maternal and fetal outcome is increasing with the increase in the COVID-19 severity [4, 5, 11]. At the same time the amount of available information about the extremely severe COVID-19 course in the gestation period is limited.

In the meta-analysis by E. R. Smith et al. (2023) that included 12 studies from 12 countries with the participation of 13,136 pregnant women (1,942 women with the confirmed/suspected COVID-19 and 11,194 women without COVID-19 during gestation and at labor) high risk of serious diseases for mothers and newborns, mother lethality against the manifestation of the COVID-19 at any time of the gestation, but more often in the 3rd trimester was determined [10].

On 5th May, 2023 World Health Organization officially announced that Novel Coronavirus Infection (NCI) COVID-19 pandemic no longer constitutes a public health emergency of international concern. However, the mutation and wide circulation of various variants of SARS-CoV-2 virus which retains its high contagiousness persist [2]. The effect of COVID-19 on the gestation course and perinatal outcomes are being actively studied at present time. The data of some studies are contradictory, and the amount of available data is still insufficient for complete understanding of the risks of COVID-19 manifestation during gestation. The data on the specific features of the health and social profile of pregnant women who had SARS-CoV-2-infection of various degree of severity during gestation are limited.

The objective of the study is to analyze the specific features of the health and social profile of pregnant women with COVID-19 of various degrees of severity.

Materials and research methods. A prospective cohort study of 1,476 pregnant women has been performed on the basis of the maternity hospitals of the GBUZ Regional clinical hospital #2, Chelyabinsk, and GAUZ Regional clinical hospital #3, Chelyabinsk, which are the obstetric hospitals of the 2nd level and in general are comparable in terms of the level of equipment and medical care provision to the pregnant, parturient, and puerperant women based on the order of the Ministry of Health of the Russian Federation No. 1130n dated October 20, 2020 "On the procedure for providing assistance in obstetrics and gynecology" and current clinical guidelines in obstetrics and gynecology, approved by the Ministry of Health of the Russian Federation (https://cr.minzdrav.gov.ru/).

The study has been approved by the Ethics Committee of the South Ural State Medical University of the Ministry of Health of the Russian Federation.

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The evaluation of the medical and social characteristics of the studied individuals has been performed based on the labor and delivery records, medical histories of pregnant and puerperant women.

The main group consisted of 1,386 patients with COVID-19 hospitalized over the period from April 2020 to September 2021 (1st-4th wave of COVID-19 pandemic) to the maternity hospital of the GBUZ Regional Clinical Hospital № 2, Chelyabinsk which has been repurposed to a COVID hospital for providing medical assistance to pregnant, parturient, and puerperant women with COVID-19, as well as to the newborns in the territory of the Chelyabinsk City and Chelyabinsk Region. The 1st study group (n=482) included pregnant women with mild COVID-19, the 2nd group (n=718) – those with COVID-19 of moderate severity, the 3rd group – pregnant women with severe COVID-19, and the 4th group (n=21) – patients with extremely severe course of the infection. The comparison group (the 5th group) consisted of 90 pregnant women.

COVID-19 severity was determined in accordance with the existing guidelines (Version 5 (28.12.2021) https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/052/original/BMP_preg_5.pdf). The following main group inclusion/exclusion criteria were developed. Inclusion criteria: confirmed COVID-19 case (U07.1), availability and accessibility of medical records to collect the data for the research, written informed consent of the patients to participation in the study and publication of its findings in the open media, follow-up in women's health clinic, reproductive age.

Exclusion criteria: probable/suspected COVID-19, non-accessibility/lack of medical records, lack of written informed consent to participation in the study and/or publication of its findings in open media, multiple pregnancy, decompensation of somatic diseases, malignant neoplasms, psychiatric illnesses, HIV.

The comparison group (study group 5) comprised 90 pregnant women admitted to the maternity hospital of the GAUZ Regional clinical hospital #3, Chelyabinsk over the period from July 2020 to February 2021 in the 3rd trimester for the pre-delivery preparation and delivery. The comparison group was formed using the nested randomization method. A month was selected randomly. Those pregnant women who were admitted to the maternity hospital during this month were included in the study. The inclusion criteria for this group were: negative SARS-CoV-2 test from the oral cavity and nasopharyngeal cavity at hospital admission, no clinical signs of COVID-19/ acute respiratory viral infection over the course of the current gestation, 3rd trimester of gestation.

Statistical processing of the obtained results was carried out using standard methods using the IBM SPSS Statistics 19 program. As indicators of descriptive statistics, the median (Me) and quartiles (Q1; Q3) were calculated for quantitative characteristics, and the absolute and relative frequencies (in %) were calculated for qualitative characteristics. Differences in quantitative and ordinal parameters between three or more groups were assessed using the Kruskal-Wallis test, and subsequent comparisons between two groups were performed using the Mann-Whitney test. To identify differences between groups in terms of qualitative characteristics, the x2 test or Fisher's exact test was used (if the conditions for applying the x2 criterion were violated). Statistical hypotheses were tested at a critical significance level of 0.05.

Results and Discussion. Median age of the pregnant women was 29 (24;33), 31 (27;35), 32 (28;35), 33 (29;36,5), 29 (25;33) years in groups 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.003; $p_{1,5}$=0.352; $p_{2,3}$=0.310; $p_{2,4}$=0.204; $p_{2,5}$=0.011; $p_{3,4}$=0.392; $p_{3,5}$=0.003; $p_{4,5}$=0.008; $p_{main/comparison(mc)}$=0.132), which is illustrative of the statistically significant increase in the median age of the patients from the 2nd, 3rd, 4th group relative to groups 1 and 5 without statistically significant differences between pregnant women from groups 1 and 5. The data we have acquired are in agreement with the findings of other studies [4, 11, 12]. Patients belonged mainly to East Slavic ethnicity with no statistically significant difference between the studied groups (p_{1-5}=0.325; p_{mc}=0.769).

Patients from the 1st and 2nd group statistically significantly more often were not legally married as compared to pregnant women from the 5th group – 351 (72.8%), 545 (75.9%), 116 (78.9%), 19 (90.5%), 79 (87.8%) cases in the 1st-5th group, respectively (p_{1-5}=0.013; p_{1-5}=0.013; $p_{1,2}$=0.250; $p_{1,3}$=0.161; $p_{1,4}$=0.080; $p_{1,5}$=0.003; $p_{2,3}$=0.458; $p_{2,4}$=0.190; $p_{2,5}$=0.016; $p_{3,4}$=0.376; $p_{3,5}$=0.114; $p_{4,5}$=0.999; p_{mc}=0.007).

There were no statistically significant differences between the groups in terms of the employment pattern (p_{1-5}=0.206; p_{oc}=0.408). As for the substance abuse, then smoking was noted among women with COVID-19 with statistically significant predominance in the 1st and 2nd group – 48 (10.0%), 53 (7.4%), 4 (2.7%), 1 (4.8%), 3 (3.3%) cases in groups 1-5, respectively (p_{1-5}=0.023; $p_{1,2}$=0.137; $p_{1,3}$=0.005; $p_{1,4}$=0.710; $p_{1,5}$=0.044; $p_{2,3}$=0.043; $p_{2,4}$=0.999; $p_{2,5}$=0.189; $p_{3,4}$=0.492; $p_{3,5}$=0.999; $p_{4,5}$=0.573; p_{mc}=0.123). Thus, we did not obtain the risk of COVID-19 severity increase due to smoking in women, although a number of studies point at the increased risk of SARS-CoV-2-infection progressions for smokers relative to those who have never smoked [14, 15].

In general, the prevalence of various kinds of somatic diseases differed statistically significantly only in pregnant women of the 1st, 2nd, and 5th studied group – 311 (64.5%), 504 (70.2%), 119 (81.0%), 19 (90.5%), 78 (86,7%) in 1st -5th group respectively (p_{1-5}<0.001; $p_{1,2}$=0.039; $p_{1,3}$<0.001; $p_{1,4}$=0.014 $p_{1,5}$<0.001; $p_{2,3}$=0.008; $p_{2,4}$=0.044 $p_{2,5}$=0.001; $p_{3,4}$=0.374 $p_{3,5}$=0.254 $p_{4,5}$=0.999; p_{mc}=0.001). This could imply that the very fact of having a somatic disease could have no contribution to the risk of severe COVID-19 development. What is more important is what kind of the somatic disease a pregnant woman has.

In our study the combined somatic pathology (polypathia) was statistically significantly more frequent in group 4 –138 (28.6%), 246 (34.3%), 74 (50.3%), 17 (81.0%), 40 (44.4%) in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$=0.039; $p_{1,3}$<0.001; $p_{1,4}$<0.001; $p_{1,5}$=0.004; $p_{2,3}$<0.001; $p_{2,4}$<0.001 $p_{2,5}$=0.058; $p_{3,4}$=0.010 $p_{3,5}$=0.378 $p_{4,5}$=0.003; p_{mc}=0.062). Therefore, polypathia in pregnant women is associated with the risk of extremely severe COVID-19 which has also been demonstrated in other studies [3, 7]. In case of polypathia chronic arterial hypertension (CAH), varicose veins of the lower extremities (VVLE), hypothyroidism were most often registered.

Circulatory system diseases (CAH, VVLE, congenital heart disease, cusp prolapse, thrombophlebitis in past medical history) were observed in 79.0 (16.4%), 166 (23.1%), 45 (30.6%), 10 (47.6%) and 17 (18.9%) cases in the 1st-5th group, respectively. They were registered statistically significantly more often in groups 3 and 4 (p_{1-5}<0.001; $p_{1,2}$=0.005; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.560; $p_{2,3}$=0.054; $p_{2,4}$=0.009 $p_{2,5}$=0.366; $p_{3,4}$=0.120 $p_{3,5}$=0.046 $p_{4,5}$=0.006; p_{mc}=0.498). Similar results were obtained by the authors in other studies [3, 4, 12]. Chronic anemia was observed statistically significantly more often in patients with COVID-19 from group 3 and 4 – 11 (2.3%), 8 (1.1%), 14 (19.5%), 3 (14.3%), 5 (5.6%) cases in the 1st -5th groups, respectively (p_{1-5}<0.001; $p_{1,2}$=0.112; $p_{1,3}$<0.001; $p_{1,4}$=0.017; $p_{1,5}$=0.152; $p_{2,3}$<0.001;

$p_{2,4}$=0.003; $p_{2,5}$=0.010; $p_{3,4}$=0.450; $p_{3,5}$=0.275; $p_{4,5}$=0.173; p_{mc}=0.104).

The obtained data are in agreement with the findings of other studies demonstrating a higher risk of incidence and development of severe COVID-19 in pregnant women with anemia [3, 4, 6]. Endocrine system diseases, nutrition and metabolic disorders were registered statistically significantly more often in group 3 and 4 relative to group 1 and 2, and the comparison group (p_{1-5}<0.001; $p_{1,2}$=0.604; $p_{1,3}$=0.001; $p_{1,4}$=0.003 $p_{1,5}$=0.051; $p_{2,3}$=0.002; $p_{2,4}$=0.005; $p_{2,5}$=0.025; $p_{3,4}$=0.196; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}=0.011). As for the thyroid diseases (hypothyroidism, hyperthyroidism, autoimmune thyroiditis, nontoxic diffuse-nodular goiter) there were no statistically significant differences between the groups (p_{1-5}=0.174; p_{mc}=0.891). Diabetes mellitus (DM) was registered in 1 (0.2%), 2 (0.3%), 4 (2.7%), 1 (4.8%), 0 (0.0%) cases in the 1st -5th groups, respectively, with higher frequency of occurrence in the 3rd group (p_{1-5}=0.004; $p_{1,2}$=0.999; $p_{1,3}$=0.012; $p_{1,4}$=0.082; $p_{1,5}$=0.999; $p_{2,3}$=0.009; $p_{2,4}$=0.083; $p_{2,5}$=0.999; $p_{3,4}$=0.492; $p_{3,5}$=0.300; $p_{4,5}$=0.189; p_{mc}=0.999).

Most of the studies show high frequency of occurrence of DM in pregnant women with COVID-19, high risk of severe course of the NCI if a patient has this disease [3, 4, 11, 12]. The median of the body mass index differed statistically significantly between the 1st -5th group – 23 (20;27), 24 (21;28), 27 (24;31), 26 (22;32), 21 (19;23.3), respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.003 $p_{1,5}$<0.001; $p_{2,3}$<0.001; $p_{2,4}$=0.055; $p_{2,5}$<0.001; $p_{3,4}$=0.966; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}<0.001). Obesity of various degrees was noted in 80 (16.6%), 140 (19.5%), 49 (33.3%), 9 (42.9%), 6 (6.7%) patients from 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$=0.203; $p_{1,3}$<0.001; $p_{1,4}$=0.005; $p_{1,5}$=0.016; $p_{2,3}$<0.001; $p_{2,4}$=0.022; $p_{2,5}$=0.003; $p_{3,4}$=0.391; $p_{3,5}$<0.001 $p_{4,5}$<0.001; p_{mc}=0.002).

Thus, patients with COVID-19 had metabolic disorders (excess body weight (BMI=25.0-29.9) and obesity) statistically significantly more often. Women from the 3rd and 4th study group had the highest frequency of these disorders relative to the members of the other groups – 186 (38.6%), 356 (49.6%), 97 (66.0%), 14 (66.7%), 18 (20.0%) cases in 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.010; $p_{1,5}$=0.001; $p_{2,3}$<0.001; $p_{2,4}$=0.123; $p_{2,5}$<0.001; $p_{3,4}$=0.951; $p_{3,5}$<0.001 $p_{4,5}$<0.001; p_{mc}<0.001). Association between obesity and risk of COVID-19 development, as well as with the risk of severe course of the disease and adverse obstetric outcomes has also been shown in large-scale studies by J. Allotey et al. (2020), M. Jafari et al. (2021), M. La Verde and al. (2021), E. R. Smith and all. (2023) [10, 11, 12, 13].

Compensated systemic lupus erythematosus (SLE) was registered statistically significantly more frequently in the 4th group of patients with COVID-19 – 1 (0.2%), 1 (0.1%), 1 (0.7%), 2 (9.5%), 0 (0.0%) cases in 1-5th group, respectively (p_{1-5}=0.002; $p_{1,2}$=0.999; $p_{1,3}$=0.413; $p_{1,4}$=0.005 $p_{1,5}$=0.999; $p_{2,3}$=0.311; $p_{2,4}$=0.002; $p_{2,5}$=0.999; $p_{3,4}$=0.041 $p_{3,5}$=0.999; $p_{4,5}$=0.034; p_{mc}=0.999). There were no statistically significant differences between the 1st -5th studied groups in terms of the frequency of occurrence of the diseases of the respiratory system (p_{1-5}=0.949; p_{mc}=0.463), digestive (p_{1-5}=0.090; p_{mc}=0.019) and urogenital (p_{1-5}=0.393; p_{mc}=0.527) systems, diseases of the ear and mastoid process (p_{1-5}=0.360; p_{mc}=0.999), infectious and parasitic diseases (p_{1-5}=0.250; p_{mc}=0.412).

A number of specific features of the obstetric-gynecologic anamnesis has been revealed in the studied patients. Among pregnant women with COVID-19 of the 1st group current pregnancy was the first one statistically significantly more often – 162 (33.6%), 163 (22.7%), 24 (16.3%), 0 (0.0%), 31 (34.4%) patients in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.904; $p_{2,3}$=0.099; $p_{2,4}$=0.007; $p_{2,5}$=0.018; $p_{3,4}$=0.046; $p_{3,5}$=0.002; $p_{4,5}$=0.002; p_{mc}=0.064). The number of multiparous women increased statistically significantly with increasing severity of COVID-19 – 267 (55.4%), 504 (70.2%), 112 (76.2%), 19 (90.5%), 51 (56.7%) cases in the 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.864; $p_{2,3}$=0.144; $p_{2,4}$=0.044; $p_{2,5}$=0.009; $p_{3,4}$=0.169; $p_{3,5}$=0.002; $p_{4,5}$=0.004; p_{mc}=0.073).

In the groups of patients with moderate and severe COVID-19 the number of women with 3 and more deliveries in the past history increased statistically significantly – 23 (4.8%), 71 (9.9%), 18 (12.2%), 3 (14.3%), 5 (5.6%) patients in group 1-5, respectively (p_{1-5}=0.004; $p_{1,2}$=0.001; $p_{1,3}$=0.001; $p_{1,4}$=0.088; $p_{1,5}$=0.789; $p_{2,3}$=0.392; $p_{2,4}$=0.458; $p_{2,5}$=0.184; $p_{3,4}$=0.730; $p_{3,5}$=0.091; $p_{4,5}$=0.173; p_{mc}=0.340).

On the whole, patients with COVID-19, and in particular pregnant women from the group with extremely severe course of the infection, had Cesarean delivery in the past medical history statistically significantly more often – 81 (16.8%), 153 (21.3%), 35 (23.8%), 10 (47.6%), 4 (4.4%) cases in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$=0.054; $p_{1,3}$=0.055; $p_{1,4}$=0.001; $p_{1,5}$=0.002; $p_{2,3}$=0.503; $p_{2,4}$=0.013; $p_{2,5}$<0.001; $p_{3,4}$=0.021; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}<0.001).

Patients with COVID-19, in particular those from group 2 and 3 of the study, had therapeutic abortions in the past medical history statistically significantly more often – 119 (24.7%), 226 (31.5%), 50 (34.0%), 6 (28.6%), 16 (17.8%) pregnant women in group 1-5, respectively (p_{1-5}=0.008; $p_{1,2}$=0.011; $p_{1,3}$=0.026; $p_{1,4}$=0.687; $p_{1,5}$=0.156; $p_{2,3}$=0.548; $p_{2,4}$=0.777; $p_{2,5}$=0.007; $p_{3,4}$=0.621; $p_{3,5}$=0.007; $p_{4,5}$=0.360; p_{mc}=0.019). As for the frequency of various gynecological pathologies, then, in general, there were no statistically significant differences in the studied groups (p_{1-5}=0.799; p_{mc}=0.604).

Conclusion. Thus, increase in the median age with increasing infection severity is typical of the pregnant women with COVID-19 in comparison to pregnant women without COVID-19. Pregnant women with severe and extremely sever course of COVID-19 are statistically significantly more often have legal marriage and reside in big industrial cities. Smoking is statistically significantly more often registered among pregnant women with mild and moderate COVID-19. As for the somatic diseases, then pregnant women with COVID-19 in general, and pregnant women with severe and extremely severs course of the infection more often have circulatory system diseases (CAH, VVLE), endocrine system diseases, nutrition and metabolic disorders (DM, obesity, excess body weight), chronic anemia.

The increase in the frequency of obesity correlated statistically significantly with the increase in the severity of COVID-19. SLE is observed statistically significantly more often in pregnant women with extremely severe COVID-19. High frequency of the polypathia is a specific feature of the extremely severe course of the infection in pregnant women. The number of multigravida, multiparous women increases statistically significantly with the severity of COVID-19. On the whole, patients with COVID-19 statistically significantly more often have Cesarean delivery in the past medical history. Women with moderate and severe COVID-19 statistically significantly more often have therapeutic abortions in past medical history.

Increase in the median age, frequency of somatic pathology (CAH, VVLE, excess body weight, obesity, hypothyroidism, SLE) and polypathia is charac-

teristic of the increase in the COVID-19 severity in pregnant women. Mild course of the infection occurs more frequently in primigravidas, moderate and severe ones – in pregnant women with deliveries and abortions in the past medical history, extremely severe – in multiparous women.

References

1. Voropaeva EE, et al. Blagopriyatnyj iskhod krajne tyazhelogo techeniya novoj koronavirusnoj infekcii COVID-19 pri beremennosti s total'nym porazheniem legkih, ostrym miokarditom i infarktom miokarda [Favorable outcome of the extremely severe course of the new coronavirus infection COVID-19 during pregnancy in the presence of overall lung damage, acute myocarditis, and myocardial infarction]. Akusherstvo i ginekologiya [Obstetrics and Gynecology. 2021; 10:179-186 (In Russ.).] DOI: 10.18565/aig.2021.10.179-186.

2. Itogovoe zayavlenie o rabote pyatnadcatogo soveshchaniya Komiteta Mezhdunarodnyh mediko-sanitarnyh pravil (2005 g.) po chrezvychajnoj situacii v svyazi s pandemiej [Internet]. URL: https://www.who.int/ru/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic [Final statement on the work of the fifteenth meeting of the International Health Regulations Committee (2005) on the pandemic emergency [Internet]. URL: https://www.who.int/ru/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic]

3. Voropaeva EE, et al. Kliniko-laboratornye osobennosti i materinskie iskhody u beremennyh s kriticheskim porazheniem legkih pri COVID-19 [Clinical and laboratory features and maternal outcomes in pregnant women with critical lung damage in the COVID-19]. Ural'skij medicinskij zhurnal [Ural Medical Journal. 2024; 1: 90-103 (In Russ.).] DOI: 10.52420/2071-5943-2024-23-1-90-103.

4. Belokrinitskaya TE, et al. Materinskaya smertnost' i near miss pri novoj koronavirusnoj infekcii (COVID-19) u beremennyh Sibiri i Dal'nego Vostoka [Maternal mortality and critical conditions (near miss) in COVID-19 in pregnant women of Siberia and the Far East]. Problemy reprodukcii [Russian Journal of Human Reproduction. 2021; 5: 114-120 (In Russ.).] DOI: 10.17116/repro202127051114.

5. Morozov SP, et al. Prognozirovanie letal'nyh iskhodov pri COVID-19 po dannym komp'yuternoj tomografii organov grudnoj kletki [Prediction of lethal outcomes in COVID-19 cases based on the results chest computed tomography]. Tuberkulez i bolezni legkih [Tuberculosis and Lung Diseases. 2020; 6: 7-14 (In Russ.).] DOI: 10.21292/2075-1230-2020-98-6-7-14.

6. Sinchikhin SP, et al. Svyaz' mezhdu COVID-19 i zhelezodeficitnoj anemiej u beremennyh [Relationship between COVID-19 and iron deficiency anemia in pregnant women]. Ginekologiya [Gynecology. 2021; 6: 592-596 (In Russ.).] DOI: 10.26442/20795696.2021.6.201340.

7. Fus A.V., Podolinny G.I. Polipatii: v poiske faktorov etiopatogeneticheskih riskov [Polypathy: searching for etiopathogenetic risks factors]. Vestnik Rossijskogo universiteta druzhby narodov. Seriya: Medicina [RUDN Journal of Medicine. 2020; 2: 135-144 (In Russ.).] DOI: 10.22363/2313-0245-2020-24-2-135-144.

8. Ishchenko LS, et al. Chastota i iskhody ekstremal'no rannih prezhdevremennyh rodov u beremennyh zhenshchin s novoj koronavirusnoj infekciej COVID-19 [Frequency and outcomes of extremely early preterm birth in pregnant women with new coronavirus infection COVID-19]. Yakut Medical Journal. 2023; 1: 80-83 (In Russ.).] DOI: 10.25789/YMJ.2023.81.20.

9. Belokrinitskaya TE, et al. COVID-19 u beremennyh Sibiri i Dal'nego Vostoka: itogi 2 let pandemii [COVID-19 in pregnant women of Siberia and the Russian Far East: 2-year results of the pandemic]. Akusherstvo i ginekologiya [Obstetrics and Gynecology. 2022; 4: 47-54 (In Russ.).] DOI: 10.18565/aig.2022.4.47-54.

10. Smith ER, et al. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis. BMJ Glob Health. 2023; 8(1): e009495. DOI: 10.1136/bmjgh-2022-009495.

11. Jafari M, et al. Clinical characteristics and-outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. Rev Med Virol. 2021; 31(5): 1-16. DOI: 10.1002/rmv.2208.

12. Allotey J, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020; 370: m3320. DOI: 10.1136/bmj.m3320.

13. La Verde M, et al. Maternal death related to COVID-19: A systematic review and meta-analysis focused on maternal co-morbidities and clinical characteristics. Int J Gynaecol Obstet. 2021; 154(2): 212-219. DOI: 10.1002/ijgo.13726.

14. Simons D, et al. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). Addiction. 2021; 116(6): 1319-1368. DOI: 10.1111/add.15276.

15. Gallus S, et al. The role of smoking in COVID-19 progression: a comprehensive meta-analysis. Eur Respir Rev. 2023; 32 (167): 220191. DOI: 10.1183/16000617.0191-2022.

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IMPACT OF COVID-19 ON REMOTE CARDIOVASCULAR ENDPOINTS IN PATIENTS WITH SICK SINUS SYNDROME AND IMPLANTED PACEMAKER

SARS-CoV2, responsible for the COVID-19 pandemic, is still relevant for the medical system throughout the world. In addition to the effect on the respiratory system, cardiac manifestations of COVID-19 are also known in the acute and post-COVID-19 period, including known coronary heart disease, proarrhythmogenic effects including impact on sick sinus syndrome (SSS). Cardiovascular diseases including myocarditis, heart failure, tachyarrhythmias and myocardial infarction, where arrhythmias are widespread were detected among hospitalized patients with COVID-19.

Objective: To investigate the impact of COVID-19 incidence on long-term cardiovascular endpoints in patients with SSS with implanted pacemaker. Methods. In a retrospective, non-randomized, uncontrolled study, 447 patients with SSS were examined, of which 205 patients experienced and 242 - did not have COVID-19. The follow-up period was 30 months and the endpoints were cardiovascular death, myocardial infarction, stroke and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the "Promed" electronic medical record system, as well as during follow-up examinations at the consultative and diagnostic clinic. **Results.** Comparison of the incidence of adverse cardiovascular endpoints in the COVID-19 and control groups showed no differences in all endpoints according to the Chi-square test ($p>0.1$), with the exception of frequency of myocardial infarction in the "COVID-19" ($p=0.040$). The close relationship between tachy-bradicardia, microvascular dysfunction and coronary artery disease, and at the same time the impossibility of modulating the heart rhythm in the presence of vegetative dysfunction and an established pacemaker assumed that autonomic dysfunction in post-COVID patients caused myocardial ischemia and, as a result, an increase of myocardial infarction rate. Conclusion. During long-term follow-up, COVID-19 in patients with SSS increased the risk of myocardial infarction.

Keywords: sinus node weakness syndrome, COVID-19, pacemaker, coronary artery disease, cardiovascular endpoints.

Introduction. SARS-CoV2, the well-known coronavirus responsible for the COVID-19 pandemic, continues to be relevant worldwide. Along with the impact of the disease on the respiratory system, there are also known cardiac manifestations of COVID-19. In addition to other cardiovascular diseases, including myocarditis, heart failure, tachyarrhythmias, and myocardial infarction (MI) [3,13], arrhythmias are widespread among hospitalized patients with COVID-19 [8]. Tachyarrhythmias are the most common rhythm disorders. Scientific publications about bradyarrhythmia, including sinus and atrioventricular node dysfunctions are much less common, despite the fact that they are associated with a worser prognosis. Several observational studies and clinical cases have been published that do not provide data on the long-term prognosis of bradyarrhythmia and sinus node dysfunction in COVID-19 [3]. Recently published reports indicate the involvement of COVID-19 in heart's conduction system damage, especially in the sinoatrial node and atrioventricular node. Although the exact mechanism remains unclear, it is thought to be the result of hypoxemia, inflammation, or direct viral infiltration leading to impaired myocardial function [1-11]. Methods for treating bradyarrhythmia in patients with COVID, especially with regard to the reversibility of the process and the need for constant pacing, are not properly investigated. Despite implantation of pacemaker, mortality in patients with SSS remains high [6]. The clinical consequences of first-time bradyarrhythmia in patients with COVID-19 are unknown, and the treatment approach is controversial without understanding the short-and long-term outcomes [3].

Sinus sick syndrome syndrome (also known as sinus node dysfunction) is a medical condition characterized by a malfunction of the sinus node. This dysfunction can lead to heart failure and bradycardia. Sinus node weakness syndrome most often affects the elderly, but can affect all age groups. Causal factors can be divided into internal and external. Internal factors include idiopathic degenerative fibrosis, cardiomyopathy, and ischemia. External factors include medications, hypothyroidism, autonomic dysfunction, and electrolyte disturbances. Patients usually experience fainting or pre-fainting states, palpitations, dizziness, and fatigue. Treatment consists of eliminating the underlying causes and installing a pacemaker [1].

The aim of the study was to identify the impact COVID of COVID-19 morbidity on long-term cardiovascular endpoints in patients with sick sinus syndrome and an implanted pacemaker.

Materials and methods. In a retrospective longterm controlled study, a comparison of longterm cardiovascular endpoints was performed in patients with SSS and implanted pacemaker in the period from April 2020 по to December 2020. Implantation of the pacemaker was performed in the Department of Arrythmology in the Republic Cardiological Center (Ufa).

Inclusion criteria: established diagnosis of SSS, no indications for permanent

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pacemaker implantation, according to the Clinical Recommendations of Bradiarrhythmias and Conduction Disorders (2020) [2], voluntary informed consent, age 40-85 years old, absence of decompensation. Non-inclusion criteria: unstable coronary heart disease (CHD), MI for 3 months, and stroke for 3 months, chronic heart failure of the IV degree according to the NYHA classification, ejection fraction <35%, severe chronic concomitant diseases, and the presence of a malignant tumor for 5 years. The criterion for exclusion from the study was the patient's refusal to participate in the study.

A total of 607 patients were selected who were admitted during the COVID-19 pandemic and developed severe bradiarrhythmias requiring pacemaker implantation. For the analysis, two groups of patients with SSS were identified: the "COVID-19" group (*n*=205) and the "Control" group (*n*=242), which included patients who did not tolerate COVID-19 during the follow-up period. 160 patients were later completely excluded from the study with a diagnosis of acute respiratory viral infections, without confirmed COVID-19.

The diagnosis of COVID-19 was established based on the presence of detected SARS-CoV-2 RNA using nucleic acid amplification methods and / or detected SARS-CoV-2 class M and G immunoglobulins, in accordance with the current recommendations on COVID-19 of the Ministry of Health of the Russian Federation at the time of the study.

The following unfavorable events were selected as endpoints: MI, stroke, pulmonary embolism (PE), death, and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the “Promed” electronic medical record system, as well as during follow-up examinations in the consultative and diagnostic polyclinic of the Republic Cardiologic Center for the period of 30 months from April 2020 to June 2024.

To analyze the main clinical and demographic characteristics of SSS patients, continuous numerical features were presented in the form of median *Me* and interquartile range (Q1-Q3), for nominal features in the form of absolute and relative frequency (%). Frequency differences were evaluated using nonparametric criteria: for continuous numerical features – the Mann-Whitney criterion, for categorical features – the "Chi-square" criterion with the Yates correction for the rarity of events (if necessary). Differences were considered statistically significant if the significance level of rejecting the null hypothesis of no differences in

Table 1

Clinical and instrumental characteristics of patients with SSS

Sign	of COVID-19 (*n*=205)	Control (*n*=242)	*p*-level of differences
Representation of continuous features: median and interquartile range interquartile			
range of LV EF	62 (58. 64)	62 (58. 64)	0.637
LA	39 (37. 42)	39 (37. 42)	0.879
RV	23 (22. 25)	24 (22. 25)	0.878
BMI	28.2 (25.1 – 32.1)	27.7 (24.7 -30.6)	0.176
Representation of categorical features: absolute frequency and relative frequency (%)			
AH	193 (94.2)	230 (95)	0.988
AF	87 (42.4)	93 (38.4)	0.390
DM	37 (18.1)	38 (15.7)	0.509
CKD	32 (15.6)	35 (14.5)	0.735
IHD	199 (96.6)	238 (98.3)	0.558†
PMIC	40 (19.5)	47 (19.4)	0.981
CHF	198 (96.6)	234 (96.7)	0.842†
stroke in history	19 (9.3)	25 (10.3)	0.708
COPD+ Bronchial Asthma	10 (4.9)	7 (2.9)	0.275
stenting	53 (25.8)	47 (19.4)	0.104

Note: AH – arterial hypertension, CHD – coronary heart disease, BMI – body mass index, LA – anterior-posterior size of the left atrium, - acute cerebrovascular мозгового accident, RV-basal diameter of the right ventricle, PMIC - postmyocardial infarction cardiosclerosis, DM - diabetes mellitus, LV EF-left ventricular ejection fraction, AF – atrial fibrillation, CKD - chronic kidney disease, COPD-chronic obstructive pulmonary disease, CHF-chronic heart failure; † - the "chi-square" test was performed with the Yates correction.

Table 2

Comparison of end point frequencies in patients in the study groups

End point	COVID-19 endpoint (n=205), %	Control (n=242), %	p
Death All-cause death	26 (12.7)	27 (11.2)	0.620
CV death	15 (7.3)	19 (7.9)	0.832
CV hospitalization	71 (34.6)	94 (38.8)	0.359
MI	**24 (11.7)**	**15 (6.2)**	**0.040***
Stroke	14 (6.8)	18 (7.4)	0.804
AF	34 (16.6)	38 (15.7)	0.801
PE	0 (0)	1 (0.4)	0.934†

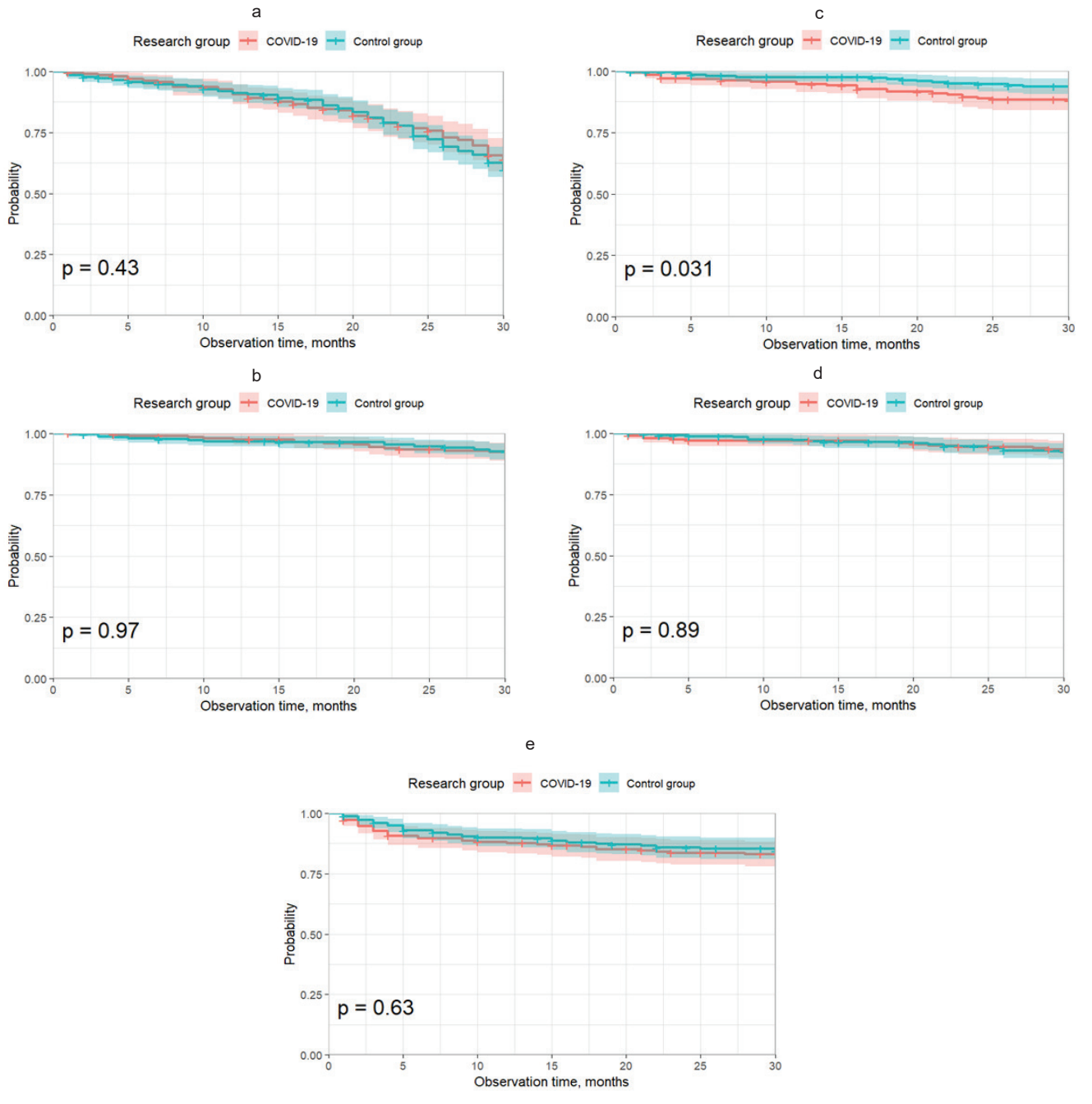
Note: MI – myocardial infarction, PE – pulmonary embolism, AF- new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death;† - the chi-square test was performed with the Yates correction. * - differences are statistically significant at p<0.05

Table 3

Results of the Gehan-Wilcoxon test comparing the duration of the period before the end point in patients in the study groups

Endpoint	Number of censored observations		*p*-level
	of COVID-19 differences (*n*=205)	Control (*n*=242)	
CV death	11	8	0.431
CV hospitalization	17	20	0.968
MI	**9**	**10**	**0.031***
Stroke	11	11	0.890
AF	6	8	0.627

Note: MI – myocardial infarction, AF-new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death; * - differences are statistically significant at p<0.05.



Kaplan-Meier curves with confidence intervals according to the Greenwood form for end points: a - cardiovascular hospitalization; b - death due to cardiovascular causes; c - myocardial infarction; g - stroke; e - newly diagnosed atrial fibrillation for patients with CVS in the COVID-19 group and the control group during an observation period of 30 months

the study groups was $p<0.05$. The study of differences in the duration of the period before the onset of adverse cardiovascular endpoints in patients with SSS, depending on the presence of a history of COVID-19, was carried out using a survival analysis. In particular, we used Kaplan-Meier multiplication scores with an estimate of the confidence interval for them using the Greenwood formula, and also performed the Gehan-Wilcoxon test for differences in survival. When finding Kaplan-Meier estimates for the endpoints of cardiovascular hospitalization, MI, stroke, atrial fibrillation, censored events were the patient's death before the follow-up period (30 months), for cardiovascular mortality, censored events were deaths from other causes before the end of the follow-up period.

The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the Bashkir State Medical University of the Ministry of Health of the Russian Federation, Meeting No. 9 of 17.12.2021. Prior to inclusion in the study, all participants received written voluntary informed consent.

Results. Table 1 shows the results of the analysis of clinical and demographic characteristics of patients with SSS in the "COVID-19" (n=205) and "Control" (n=242) groups. As can be seen, the groups did not differ in gender and age composition, the age of patients in the COVID-19 group was 73 (66, 80) years, and in the Control group - 73 (67, 81), according to the main indicators of the structure and functions of the heart

chambers, and the frequency of concomitant diseases (p>0.1).

Comparison of the frequency of occurrence of unfavorable cardiovascular endpoints in the COVID-19 and control groups in patients with SSS over the 30-month follow-up period showed no differences in all endpoints according to the "Chi – square" criterion (p>0.1), with the exception of MI in the "COVID-19" group, it occurred more often (p=0.040), Table 2.

Table 3 shows the results of the Gehan-Wilcoxon test comparing the duration of the period before the onset of various adverse cardiovascular endpoints in the COVID-19 and control groups in patients with SSS over a 30-month follow-up period. The table shows how many observations were censored in each group during the survival analysis for different endpoints. That is, for example, in the group of patients with SSS who experienced COVID-19, 9 persons died before the end of the 30-month follow-up period, while they did not have MI during the follow-up period before death. As can be seen from the test results, significant differences in the duration of the period before the onset of unfavorable endpoints were observed only for MI (p=0.031). For the pulmonary embolism (PE), the Gehan-Wilkoskon test was not performed, as COVID was not observed in the COVID-19 group of patients.

Figures 1-5 show Kaplan-Meier curves with confidence intervals for the endpoints of cardiovascular hospitalization, cardiovascular death, MI, stroke, and new-onset atrial fibrillation, respectively, for patients with SSS in the «COVID-19» and «Control» groups during the 30-month follow-up period. Censored observations were marked with a " + " sign on the graphs, and the confidence intervals of Greenwood-shaped survival curves at 95% confidence are highlighted with a blurred shadow of the corresponding color curve.

Discussion. More than 6 billion patients were infected during the COVID-19 pandemic, including those with atrial arrhythmias, the presence of SSS with an implanted pacemaker [12]. A number of studies have shown clinical cases of a combination of SSS and COVID-19 [3, 8, 11].

Comparison of the frequency of occurrence of adverse cardiovascular endpoints in the COVID-19 and control groups in patients with SSS 30 months of follow-up showed no differences in all endpoints according to the "chi-square" criterion (p>0.1), with the exception of MI – in the "COVID-19" group-it occurred significantly more often (p<0.05). Patients with SSS and COVID-19, the frequency of MI was higher than in the group without COVID-19, despite the correction of bradycardia by pacing. This is consistent with the results of a large study by Yan Xie et al. (2022), which included 153153,760 persons with COVID-19 and showed that patients with COVID-19 in 12 months long-term follow-up had an increased risk of cardiovascular diseases, including CHD and MI [10]. Cardiovascular symptoms such as tachycardia, arterial hypertension, and cardialgia are important component of post-COVID-19 syndrome and can affect up to a third of patients with COVID-19 [4]. Currently, post-COVID syndrome, which is observed in 20% of the population, is largely associated with symptoms of cardiovascular autonomic dysfunction (CVAD) [5]. The consequences of CVAD are usually manifested in the form of microvascular dysfunction, which can lead to type 2 MI. CVAD can also manifest with arterial hypotension, such as orthostatic or postprandial hypotension, and recurrent reflex syncope [5]. Asarcikli L. D. et al. [9] when examining COVID-19 convalescents, showed significantly higher values of RMSSD, pNN50 and HF indicators of heart rate variability in regard to CVAD in the group with COVID-19 compared to the control in the period up to 3 months after viral infection [7].

Conclusion. Early-onset of COVID-19 in patients with SSS increases the risk of MI during long-term follow-up, which is probably associated with cardiovascular autonomic dysfunction. Given the close relationship between CVAD, microvascular dysfunction, and CHD [5], and at the same time, the inability to modulate the heart rate in the presence of SSS and an established pacemaker, it can be assumed that autonomic dysfunction in post-COVID patients with SSS and implanted pacemaker causes myocardial ischemia and, as a consequence, an increase in the probability of MI. There is currently no available literature data on the long-term impact of COVID-19 on adverse cardiovascular events in patients with SSS.

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References

1. Badykov MR, Plechev VV, Sagitov IS, Lakman IA, Zagidullin NS. Analiz otdalyonnyh serdechno-sosudistyh sobytij u pacientov s disfunkciej sinusovogo uzla i implantirovannym elektrokardiostimulyatorom [Cardiovascular events follow-up analysis in patients with sinus node dysfunction and implanted pacemaker]. Rossijskij kardiologicheskij zhurnal [Russian Journal of Cardiology. 2019;(2):53-57 (In Russ.).] doi: 10.15829/1560-4071-2019-2-53-57.

2. Revishvili ASh, et al. Bradiaritmii i narusheniya provodimosti [Clinical practice guidelines for Bradyarrhythmias and conduction disorders]. Rossijskij kardiologicheskij zhurnal [Russian Journal of Cardiology. 2021;(4):203-24 (In Russ).] doi: 10.15829/1560-4071--2021-4448.

3. Chinitz, JS, et al. Bradyarrhythmias in patients with COVID-19: marker of poor prognosis? Pacing Clin Electrophysiol. 2020;43:1199–1204. doi:10.1111/pace.14042.

4. Brogi E, et al. Cardiac complications in patients with COVID-19: A systematic review. J Anesth Analg Cri. Care. 2022;2:18. doi:10.1186/s44158-022-00046-7

5. Fedorowski A, et al. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. Nat Rev Cardiol. 2024 Jun;21(6):379-395. doi: 10.1038/s41569-023-00962-3.

6. Nagamine T, et al. Characteristics of bradyarrhythmia in patients with COVID-19: Systematic scoping review. Pacing Clin Electrophysiol. 2022;45(4):556-566. doi: 10.1111/pace.14466.

7. Kaliyaperumal D, et al. Characterization of Cardiac Autonomic Function in COVID-19 Using Heart Rate Variability: A Hospital Based Preliminary Observational Study. J Basic Clin Physiol Pharmacol. 2021;32:247–253. doi: 10.1515/jbcpp-2020-0378.

8. Gopinathannair R, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. J Interv Card Electrophysiol. 2020; 59: 329-336. doi: 10.1007/s10840-020-00789-9.

9. Asarcikli LD, et al. Heart Rate Variability and Cardiac Autonomic Functions in Post-COVID. Period J Interv Card Electrophysiol. 2022;63:715-721. doi: 10.1007/s10840-022-01138-8.

10. Xie Y, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-590. doi: 10.1038/s41591-022-01689-3.

11. Gm Peigh, et al. Novel coronavirus 19 (COVID-19) associated sinus node dysfunction: a case series. 2020 May 8;4(FI1):1-6. doi: 10.1093/ehjcr/ytaa132.

12. Sundaram Ch, et al. Reversible sinus node dysfunction in novel COVID-19 infection: two years of follow-up. IHJ Cardiovascular Case Reports (CVCR). 2023;7(3-4):89-91. doi:10.1016/j.ihjccr.2023.11.001.

13. Fried JA, et. al. The variety of cardiovascular presentations of COVID-19. Circulation. 2020;141(23):1930–1936. doi: 10.1161/ CIRCULATIONAHA.120.047164.

YU.N. Mikhailov, E.V. Filippov, G.V. Filippova, F.G. Ivanova, T.I. Nikolaeva, P.V. Nikiforov, L.N. Afanasyeva

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EGFR MUTATIONS (DEL19/L858R) IN LUNG ADENOCARCINOMA IN PATIENTS OF THE YAKUT REPUBLICAN ONCOLOGICAL DISPENSARY

The frequency of Del 19 and L858R mutations of the EGFR gene was studied among patients of the Yakut Republican Oncology Dispensary with lung adenocarcinoma (n=177). Mutations were found 3.8 times more commonly in female population than in male. Mutations were detected 2.8 times more regularly among patients with stages I and II of the disease in compare with stages III and IV. The mutation frequency was 3.4 times over in the Sakha (Yakut) ethnic group patients as opposed to Russian ethnic group. In addition the mutation frequency was 9.6 times higher in the Sakha (Yakut) ethnic group male patients as opposed to Russian ethnic group. It was shown that the overall 36-month survival of patients with a positive status of EGFR mutations increases by 2.5 times (from 29.3% to 74.1%). Moreover in patients with stages I and II of the disease, survival rate increases by 1.4 times, in patients over 65 years old in 2.9 times, in female patients in 2.4 times.

Keywords: non-small cell lung cancer, adenocarcinoma, EGFR gene mutations, survival.

Introduction. Lung cancer is one of the most common types of malignant neoplasms (MN) in the world [10]. In the structure of mortality from MN in Russia, it is 16.8%, in the Republic of Sakha (Yakutia) it reaches 18.5% [3]. Lung cancer is characterized by late detection, rapid and aggressive course and high mortality [16, 18]. A regional feature of the nosology is that among the female population of Yakutia, the primary incidence rates of MN of the trachea, bronchi, lung (C33, 34) are 1.9 times higher than the Russian average [1]. The most common form (80-85%) is non-small cell lung cancer (NSCLC) [16]. Molecular genetic studies have shown that in 60-70% of cases (30-45% of which are adenocarcinomas), EGFR gene hyperexpression is detected in tumor cells due to the presence of activating mutations [13, 15]. This discovery was a key moment in the development of an effective strategy for the treatment of NSCLC and led to the emergence of a new molecular indicator of lung tumor sensitivity to low-molecular-weight EGFR tyrosine kinase inhibitors (TKIs).

Currently, the study of EGFR gene mutations in tumors is standard in the diagnosis of patients with NSCLC and is included in Clinical Guidelines for determining indications for targeted therapy. For patients with locally advanced or metastatic NSCLC with EGFR gene mutations in exons 19 or 21, EGFR tyrosine kinase inhibitors are recommended as first-line therapy: gefitinib, erlotinib, afatinib, or osimertinib [5]. Since TKIs have become common in the treatment of NSCLC in Russia, information on the incidence of EGFR mutations is important. It is known that the incidence of EGFR mutations in patients with lung adenocarcinoma may depend on race, smoking status, and gender of the patient [9, 11, 14]. Thus, EGFR mutations are found in 35-62% of NSCLC cases in East Asians and only in 10% of NSCLC cases in Europeans and North Americans [12]. In Russia, EGFR gene mutations are found in 13-29% of patients with NSCLC adenocarcinoma [4, 7]. There are no data on the frequency of EGFR oncogene mutations in patients with NSCLC in the Republic of Sakha (Yakutia), where the majority of the population are indigenous people - "Sakha (Yakuts)", who have Turkic-Mongolian (Asian) origin with high genetic homogeneity [17, 19]. However, these data are important in determining indications for targeted therapy, prognosis of treatment and planning, as well as in obtaining new information in oncological studies of the frequency of driver mutations in Russia. The aim of this work is to study the frequency of Del 19 and L858R mutations of the EGFR gene and to assess the prognostic significance of its diagnosis in patients of the Yakut Republican Oncology Dispensary with lung adenocarcinoma.

Materials and research methods. The study included patients whose tumor material was tested for mutations in the EGFR gene (Del 19 and L858R) and who received treatment at the Yakutsk Republican Oncology Dispensary (YROD) from

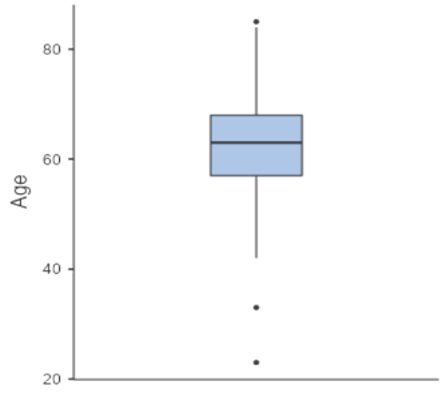

Fig. 1. Average age of examined patients (years)

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2018 to 2020. Data for a longer period of time were not available due to the start of using research data in the dispensary, with appropriate therapy, since 2018. The study included 177 patients with a verified diagnosis of non-small cell lung cancer, with a histological tumor type of adenocarcinoma. The clinical part of the study was carried out at the Department of Antitumor Drug Therapy, and studies for the presence of mutations were carried out in the molecular biology laboratory of the dispensary. Patients with a positive status of EGFR gene mutations received therapeutic targeted therapy using first- and third-generation tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib, osimertinib). Patients in whom EGFR mutations were not detected received other types of therapy prescribed individually according to treatment regimens, according to Clinical Guidelines [5]. DNA was isolated from tumor cells of paraffin block sections containing formalin-fixed postoperative or biopsy material. DNA isolation was performed after deparaffinization, using QIAmp DNA FFPE Tissue Kit reagent kits (Qiagen, Germany) in accordance with the protocol, according to the principle of proteinase treatment with rehydration and sorption on a membrane, followed by elution. To determine mutations in exons 19 and 21 of the EGFR gene (Del 19 and L858R), DNA amplification with Real-Time detection was performed on BioRad CFX 96 devices (BioRad, USA).

Information on smoking status was not available for most patients, and therefore was not taken into account in the study.

The study included 177 patients aged 42 to 83 years. The average age of patients was 62.8 ± 9.1 years (Fig. 1).

Considering the influence of age on the development of clinical changes, patients were divided into two age groups: under 65 years and 65 years and older. The age category "65 years and older" is distinguished in clinical studies due to the progressive increase in biological changes in the body [2, 6, 8]. Splitting into smaller age groups did not form a representative sample. For the same reason, when dividing patients by disease stages, 2 combined groups were identified: stages I, II and stages III, IV. The majority of the examined patients (68.9%) were men, women - 31.1% (Table 1). The proportion of patients under 65 years of age was 57.1%, 65 years and older - 42.9%. By disease stage, the predominant part (71.8%) were patients with stages III, IV, and 28.2% - with stages I, II of the disease. When analyzing by ethnicity, 2 main groups were identified:

Distribution of the identified mutations in groups by gender, age, stage of the disease, ethnicity of patients

Group	Observed, abs., (%)	EGFR mutations detected, abs., (%)		
		Deletions (del 19)	Spot Replacement (L858R)	Total
Total patients	177 (100.0)	13 (7.3)	14 (7.9)	27 (15.2)
Sex				
male	122 (68.9)	3 (2.5)	7 (5.7)	10 (8.2)
female	55 (31.1)	10 (18.2)	7 (12.7)	17 (30.9)
Age				
up to 65 years		9 (8.9)	6 (5.9)	15 (14.8)
over 65 years old		4 (5.3)	8 (10.5)	12 (15.8)
Stage of the disease				
I, II	50 (28.2)	8 (16.0)	6 (12.0)	14 (28.0)
III, IV	127 (71.8)	5 (3.9)	8 (6.3)	13 (10.2)
Ethnic group				
Russians	74 (41.8)	4 (5.4)	1 (1.4)	5 (6.8)
Sakha (Yakuts)	92 (52.0)	9 (10.9)	11 (11.9)	21 (22.8)
other	11 (6.2)	0	1 (9.1)	1 (9.1)
Male				
Russians	59 (48.4)	1 (1.7)	0	1 (1.7)
Sakha (Yakuts)	55 (45.1)	2 (3.6)	7 (12.7)	9 (16.3)
Female				
Russians	15 (27.3)	3 (20.0)	1 (6.7)	4 (26.7)
Sakha (Yakuts)	37 (67.3)	7 (18.9)	5 (13.5)	12 (32.4)

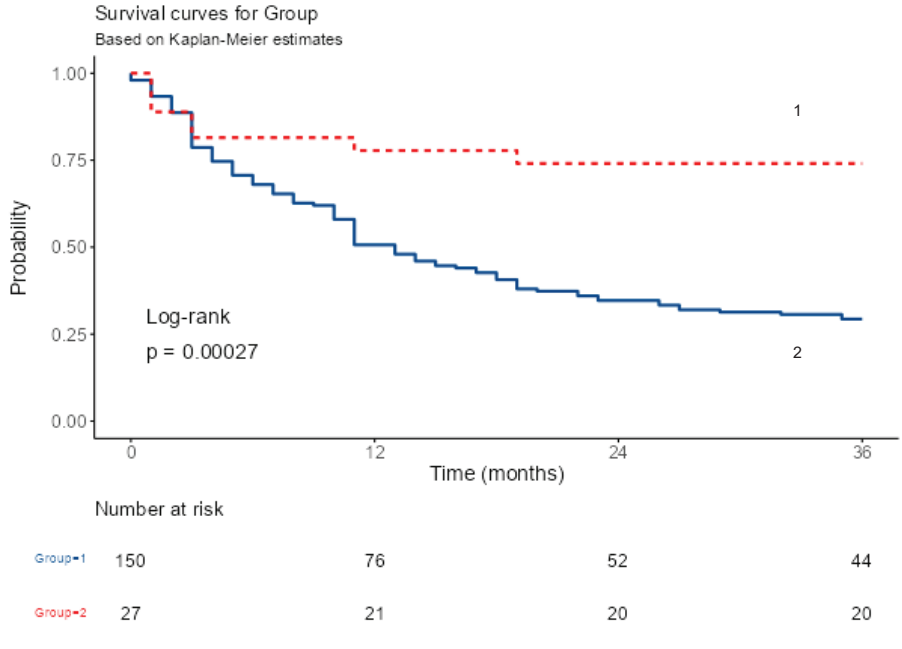
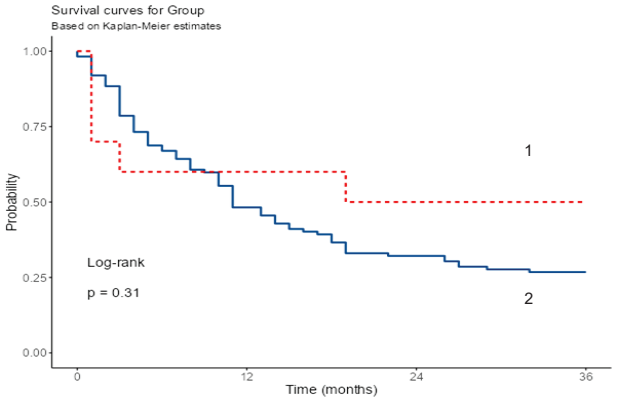
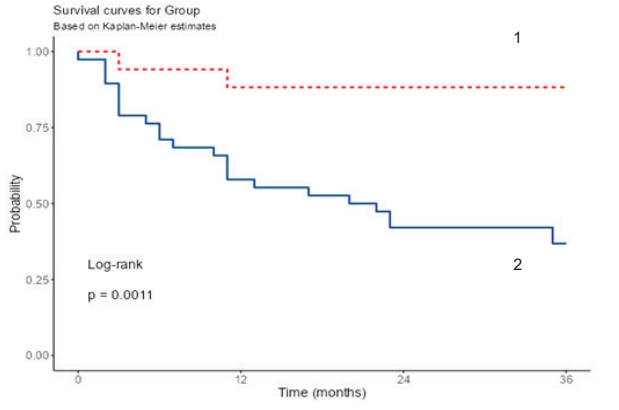


Fig. 2. Overall survival of patients (Kaplan-Meier curve) depending on the EGFR mutation status: 1 – yes; 2 – no

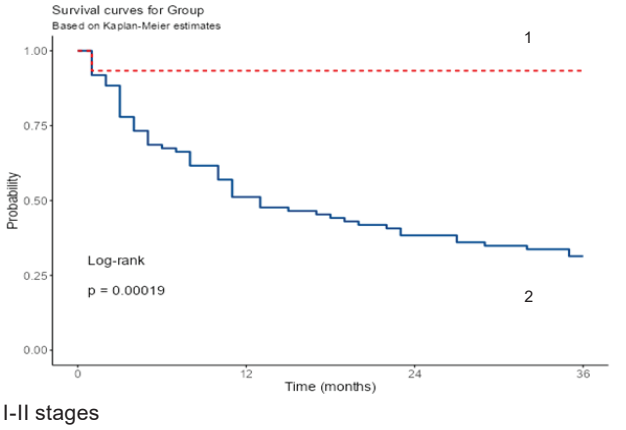
men



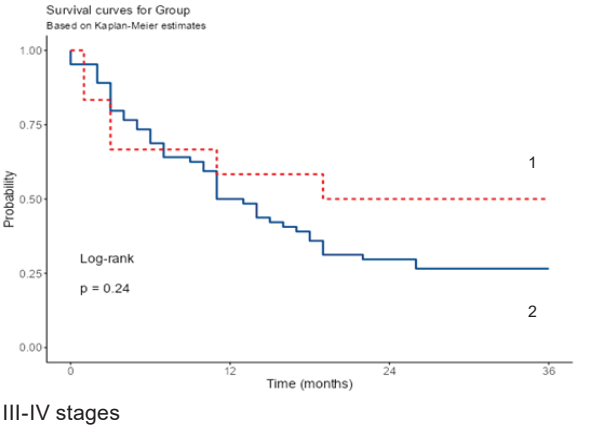
women



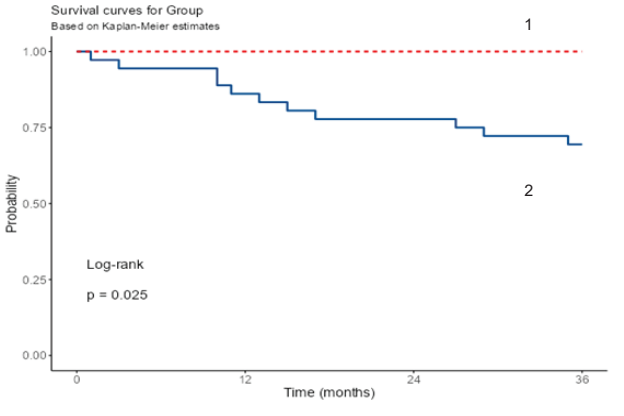
up to 65 years



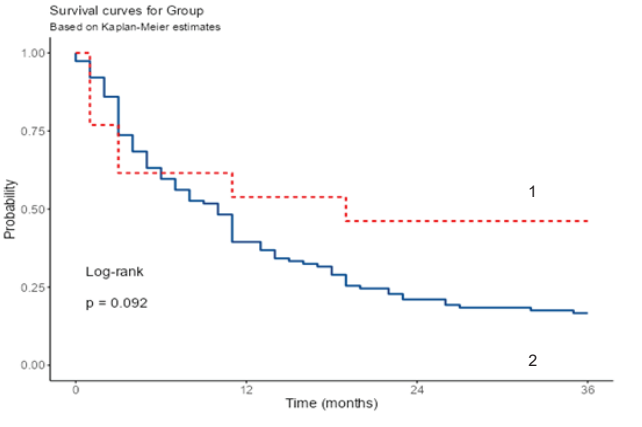
65 years and older



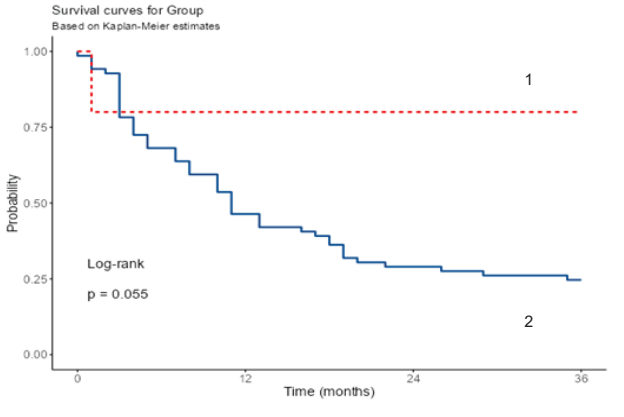
I-II stages



III-IV stages



Russians



Sakha (Yakuts)

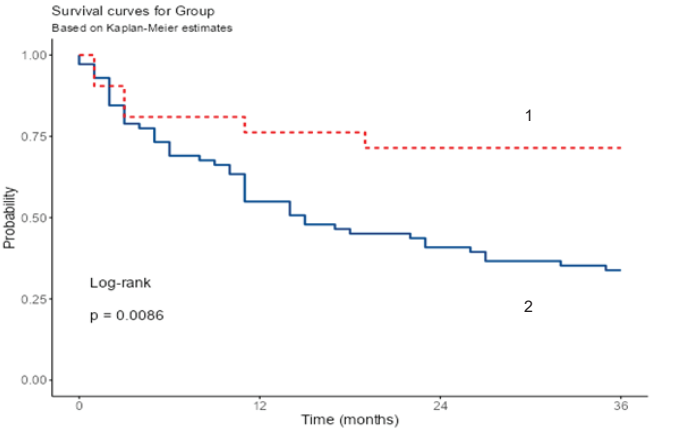


Fig. 3. Subgroup analysis of overall survival of patients depending on the EGFR mutation status: 1 – yes; 2 – no

"Sakha (Yakuts)" 92 examined - 52.0% of patients and "Russians" (41.8%) - 74 patients. The results of analyses of patients of other nationalities (n=11): Armenians (1), Georgians (1), Kyrgyz (1), Tatars (4), Ukrainians (1), Evenks (2) and Evens (1), the total share of which was 6.2% of all examined, were not used in the analysis by ethnicity due to the non-representativeness of the sample. Combining nationalities into groups by racial classification was not carried out for the same reason, as well as to exclude controversial issues of ethnogenesis. The data obtained during the study were subjected to statistical analysis using the free software development environment RStudio and the statistical package Jamovi ($\chi 2$ criterion, Fisher's exact criterion, survival according to the Kaplan-Meier method, median survival, overall survival, log-rank criterion).

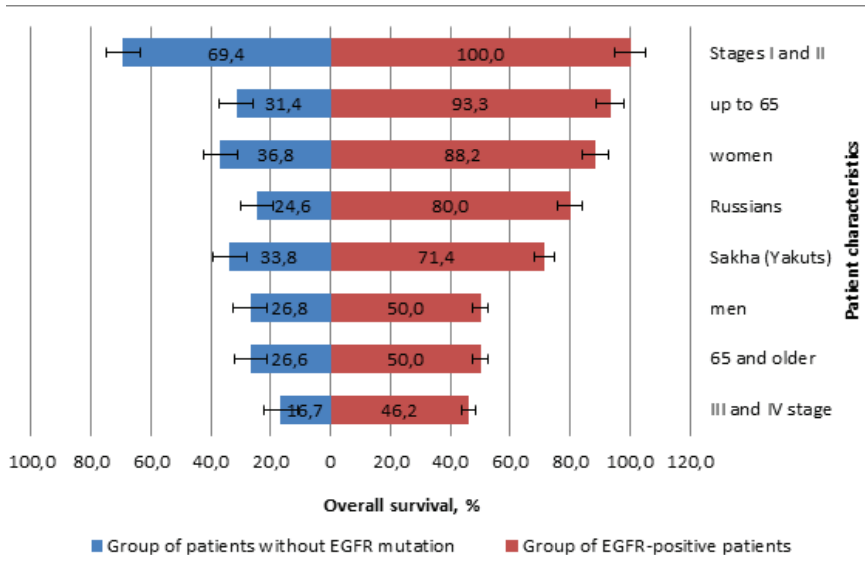


Fig. 4. 3-year survival, subgroup analysis (observation time – 36 months)

Results and discussion. *Mutation frequency.* Data on the presence and types of mutations were analyzed according to the patients' gender, age, nationality, and stage of the disease (Table 1). The total frequency of mutations in exons 19 and 21 of the EGFR gene in NSCLC (adenocarcinoma) in the total sample of patients was 15.2% (27/177). The obtained value corresponds to the frequency range of these mutations in the Russian population (13–29%) [4, 7]. Moreover, the studied mutations were distributed evenly: deletions in exon 19 were detected in 13 patients (7.3%), and L858R substitution in exon 21 was detected in 14 patients (7.9%). Mutations were significantly more common in women (30.9%, 17/55) than in men (8.2%, 10/122), ($p < 0.001$). An assessment of the distribution of mutation rates by age group of patients did not reveal any significant differences: in the "under 65" group, mutations were detected in 14.8% of patients (15/101), in the "65 years and older" group – in 15.8% of patients (12/76), ($p = 0.864$). The differences in the frequency of Del 19 and L858R mutations did not reveal any significant differences.

In patients with stages I and II of the disease, mutations were detected 2.8 times more often (28.0%, 14/50) than in patients with stages III and IV (10.2%, 13/127), ($p = 0.003$). The differences in the frequency of Del 19 and L858R mutations did not reveal any significant differences. In patients of the "Sakha (Yakut)" group, the incidence of mutations was 22.8% (21/92), which is 3.4 times higher than in the "Russian" group (6.8%, 5/74), ($p = 0.005$). It should be noted that the obtained frequency for the "Sakha (Yakut)" group is significantly lower than for residents of East Asian countries (35-62%), and is comparable with the average value in the Russian population (13-29%). In the "Russian" group, the value obtained was also twice lower than expected (6.8%). Here it can be noted that in the "Russian" group, deletions (del 19) were more common - 5.4% and point substitutions (L858R) were less common - 1.4%, while in the "Sakha (Yakut)" group they were distributed approximately equally (10.9/11.9%). For men of the "Sakha (Yakut)" ethnic group, the incidence of EGFR gene mutations was 16.3% (9/55), which is 9.6 times higher than in men of the "Russian" group (1.7%, 1/59), ($p = 0.006$). In women of the "Sakha (Yakut)" and "Russian" ethnic groups, mutations were detected in 32.4% (12/37) and 26.7% (4/15), respectively, the differences are not significant ($p = 0.683$). Thus, in contrast to men, in women, no reliable significant differences in the frequency of the studied EGFR mutations were found in the "Sakha (Yakut)" and "Russian" groups.

Survival assessment. Overall survival in the entire patient sample after 36 months of follow-up was 36.2% (64/177), with a median survival of 16 months. In patients with NSCLC with a positive EGFR mutation status, 36-month survival is 2.5 times higher (Fig. 2). Thus, in treated patients with the wild type EGFR (wt), overall survival was 29.3% (44/150), with the mutant type (mt) of the gene - 74.1% (20/27), respectively. Differences in survival between patients with EGFR-wt and patients with mt-EGFR NSCLC are statistically significant ($p = 0.0003$). The median survival for patients without mutations was 13 months, in patients with the EGFR-mutant type, the median was more than 36 months, the event corresponding to the median value did not occur. The obtained data confirm the fact that the presence of EGFR gene mutation is a reliably significant positive prognostic factor for increased survival.

Gender. In the patient groups by gender, survival in men and women differed (Figs. 3 and 4). Thus, in men with the wild type of EGFR, the overall survival was 26.8% (30/112), with the mutant type of the gene 50.0% (5/10), the differences were insignificant ($p = 0.31$). The median survival, in this case, was 11 and 19 months, respectively. In women, in the presence of mutations, the overall survival significantly increased by 2.4 times. Thus, with a negative status of the EGFR gene, survival was 36.8% (14/38), with a positive one - 88.2% (15/17), ($p = 0.001$). The median survival in the absence of mutations is 11 months. In patients with the mutant type of the EGFR gene, the event corresponding to the median value of three-year overall survival did not occur.

Age. In the cohort of patients divided by age, survival also differed. In the group of patients under 65 years old, three-year overall survival, in the presence of mutations, was significantly 3 times higher. Thus, in the group of patients without mutations, it was 31.4% (27/86), in patients with mutation - 93.3% (14/15), the differences are significant ($p = 0.0002$). The median survival in the absence of mutations is 13 months. In patients under 65 years old with a mutant type of the EGFR gene, the event corresponding to the median value of three-year overall survival did not occur. In the group of patients 65 years and older, EGFR-wt status corresponded to survival of 26.6% (17/64), EG-

FR-mt - 50.0% (6/12), the differences are insignificant (p = 0.24). The median survival is 12 and 19 months, respectively.

Disease stages. Patient survival also differed depending on the disease stage. Thus, in the group with stages I and II, in the absence of mutations, the survival rate was 69.4% (25/36), with the mutant type, all 14 patients were alive at the time of observation (p = 0.025). In patients with stages I and II of the disease with both types of the EGFR gene, the event corresponding to the median value of three-year overall survival did not occur. In the group of patients with stages III and IV of the disease, survival is lower. In patients without mutations, survival is 16.7% (19/114), with a mutation it is 2.8 times higher - 46.2% (6/13), the differences are insignificant (p = 0.09). The median survival was 10 and 19 months, respectively.

Nationality. Patient survival did not show significant differences depending on ethnicity; the presence of the mutation increased survival in both national groups. Thus, in the "Russian" group, survival increased by 3.2 times from 24.6% (17/69) to 80% (4/5), (p=0.055) and by 2.1 times in the "Sakha (Yakut)" group, from 33.8% (24/84) to 71.4% (15/21), (p=0.009). The median survival in the absence of mutations was 11 and 15 months, respectively. With the mutant type of the gene, the event corresponding to the median value of three-year overall survival did not occur in both national groups.

As a result of the subgroup analysis of overall survival data, a number of prognostic factors for the survival of patients with NSCLC adenocarcinoma were constructed (Fig. 4). In all studied patient groups, the presence of EGFR mutations resulted in increased overall survival. Taking into account statistical significance, the following can be distinguished, arranged in descending order of significance: early stage of the disease (I and II), patient age under 65, female gender. In patients without EGFR mutations, the early stage of the disease (stages I and II) is reliably significant as a positive prognostic factor.

Conclusion. The total frequency of Del 19 and L858R mutations of the EGFR gene in the total sample of examined patients (15.2%) generally corresponds to the frequency range of these mutations in the Russian population (13-29%). In women, mutations were significantly 3.8 times more common (30.9%) than in men (8.2%). In patients with stages I and II of the disease, mutations were detected 2.8 times more often (28.0%) than in patients with stages III and IV (10.2%). In patients in the "Sakha (Yakut)" group, the frequency of mutations is 3.4 times higher than in the "Russians" group (22.8/6.8%). In the "Russian" group, deletions (del 19) were more common - 5.4% and point substitutions (L858R) were less common - 1.4%, while in the "Sakha (Yakut)" group they were distributed approximately equally. In "Sakha (Yakut)" men, the incidence of EGFR gene mutations was 9.6 times higher than in men in the "Russian" group (16.3/1.7%). In women in the "Sakha (Yakut)" and "Russian" ethnic groups, the frequency of mutations did not differ significantly. Evaluation by age groups of patients did not show significant differences in the frequency of EGFR gene mutations.

With a positive status of EGFR mutations in patients with NSCLC adenocarcinoma, 36-month survival increases by 2.5 times from 29.3% to 74.1%. Subgroup analysis allowed us to additionally identify stages I and II of the disease, age up to 65 years and female gender as positive prognostic factors, in which patient survival is higher by 1.4/2.9/2.4 times, respectively.

Data on the frequency of EGFR gene mutations in patients with NSCLC adenocarcinoma in the Yakutsk Republican Oncology Dispensary were obtained for the first time and may be important for filling the "blank spots" of the frequency map of driver oncomutations in Russia and the world. Analysis of the results of the work showed that the presence of EGFR gene mutation is a significant positive prognostic factor for diagnosis, and the data obtained are important in determining treatment tactics and planning medical care in oncology.

References

1. Afanasyeva LN. Nauchnoye obosnovaniye mediko-organizatsionnykh meropriyatiy po sovershenstvovaniyu meditsinskoy pomoshchi pri zlokachestvennykh novoobrazovaniyakh v regione Arkticheskoy zony Rossiyskoy Federatsii: dis.doktor nauk. FGBNU «NII obshchestvennogo zdorov'ya im. N.A.Semashko» [Scientific substantiation of medical and organizational measures to improve medical care for malignant neoplasms in the Arctic zone of the Russian Federation: dis. doctor of sciences. Federal State Budgetary Scientific Institution N.A. Semashko Research Institute of Public Health, 2023. 371 p. (In Russ.).]

2. Vozrast. V kn.: Malaya meditsinskaya entsiklopediya. M.: Meditsinskaya entsiklopediya [Age. In the book: Small Medical Encyclopedia. Moscow: Medical Encyclopedia; 1991-96 (In Russ.).]

3. Kaprin AD, Starinsky VV, Shakhzadova AO. Zlokachestvennyye novoobrazovaniya v Rossii v 2021 godu (zabolevayemost' i smertnost'). – M.: MNIOI im. P.A. Gertsena − filial FGBU «NMITS radiologii» Minzdrava Rossii [Malignant neoplasms in Russia in 2021 (morbidity and mortality). M.: Herzen Moscow Oncology Research Institute − branch of the National Medical Research Center of Radiology of the Ministry of Health of the Russian Federation. 2022. 252 p. (Russ.).]

4. Klinicheskiye rekomendatsii Ministerstva zdravookhraneniya Rossiyskoy Federatsii «Zlokachestvennyye novoobrazovaniya bronkhov i legkogo». – 2022. – Tekst : elektronnyy [Clinical guidelines of the Ministry of Health of the Russian Federation "Malignant neoplasms of the bronchi and lung]. Rubrikator klinicheskikh rekomendatsiy: sayt [Rubricator of clinical guidelines: website. URL: https://cr.minzdrav.gov.ru/recomend/30_4 (date of access: 05/20/2024) (In Russ.).]

5. Milyukov VYe, Zharikova TS. Kriteriy formirovaniya vozrastnykh grupp patsiyentov v meditsinskikh issledovaniyakh [Criterion for the formation of age groups of patients in medical research]. Clinical Medicine, 2015; 93 (11): 5-11 (In Russ.).]

6. Ognerubov NA, Sychev VD, Kozlova NA, Chang VL. Molekulyarno-geneticheskij portret nemelkokletochnogo raka legkih v Tambovskoj oblasti: regional'nyj opyt [Molecular genetic portrait of non-small cell lung cancer in the Tambov region: regional experience]. Sovremennaya onkologiya [Modern Oncology. 2020; 22 (3): 88–93 (In Russ.).] DOI: 10.26442/18151434.2020.3.200393.

7. Pogodina AB., Gazimov AKh. Osnovy gerontologii i geriatrii [Fundamentals of gerontology and geriatrics. Rostov on Don: Phoenix; 2007 (In Russ.).]

8. Elez-Burnjakovic N, Ugrin N, Obradovic J, et al. “Distribution of EGFR SNPs -191C/A and 181946G/A in patients with lung cancer depending on smoking status in the Republic of Srpska, Bosnia and Herzegovina,” Journal of BU ON, vol. 23, no. 2, pp. 384–390, 2018

9. Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. – 2018; 68(6): 394-424.

10. Jurišić V., Obradovic J., et al., "Epidermal Growth Factor Receptor Gene in Non-Small-Cell Lung Cancer: The Importance of Promoter Polymorphism Investigation", Analytical Cellular Pathology, vol. 2018, Article ID 6192187, 9 pages, 2018. https://doi.org/10.1155/2018/6192187

11. Liang H, Li C, Zhao Y, et. al. / Concomitant Mutations in EGFR 19Del/L858R Mutation and Their Association with Response to EGFR-TKIs in NSCLC Patients. Cancer Manag Res. 2020 Sep 18;12:8653-8662. doi: 10.2147/CMAR.S255967. PMID: 32982456; PMCID: PMC7509478.

12. Lynch T, Bell DW. Sordella Retal. N Engl J Med. 2004 May 20; 350(21): 2129-3.

13. Seow W.J., Matsuo K., Hsiung C.A. et al., “Association between GWAS-identified lung adenocarcinoma susceptibility loci and EGFR mutations in never-smoking Asian women, and comparison with findings from Western populations,” Human Molecular Genetics, vol. 26, no. 2, pp. 454–465, 2016.].

14. Sequist L, et al. J Clin Oncol 2013; 31: 3327-3334.

15. Small Cell Lung Carcinoma: Staging, Imaging, and Treatment Considerations / B.W. Carter [et al.] // RadioGraphics. 2014. Vol. 34. № 6. P. 1707-1721.

16. Stepanov V.A. «Origin of Sakha: Analysis of Y-chromosome Haplotypes». Molecular Biology. 2008; 42(2): 226—237, 2008.

17. Thatcher N. First- and second-line treatment of advanced metastatic non-small-cell lung

cancer: a global view. BMC Proceedings. 2008; 2 (Suppl 2):S3: S3.
18. Tikhonov D.G., Gurkan C., Demirdov K. D., et al. On the origins of the Sakhas' paternal lineages: Reconciliation of population genetic / ancient DNA data, archaeological findings and historical narratives. Siberian Research. 2019; 1(1): 91 -111. http://doi.org/10.33384/26587270.2019.01.004e

ARCTIC MEDICINE

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STUDY OF DOPAMINE LEVELS IN PERIPHERAL VENOUS BLOOD AND IMMUNE PROTECTION STATUS IN RESIDENTS OF NORTHERN TERRITORIES OF THE RUSSIAN FEDERATION ACCORDING TO HEALTH STATUS

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The correlation between the dopamine concentration in the peripheralblood and the level of immune protection in Northerners was studied. 70 practically healthy people and 172 patients (including 67 people with cancer of the large intestine) were examined to study the level of dopamine in peripheral venous blood and the state of immune protection in residents of the northern territories of the Russian Federation, depending on their state of health. Thus, for the first time, it was established that the level of registration of the frequency of elevated dopamine concentrations in peripheral venous blood in practically healthy residents of the northern territories of the Russian Federation is high and amounts to 7.14±0.38%, the level of registration of the frequency of elevated dopamine concentrations in peripheral venous blood in sick people was recorded much more often (59.21±1.7%). A high level of registration of elevated concentrations of IL-10 and TNF-α was also established, both in practically healthy people and in people with oncologicaldiseases. There was an increase in the frequency of registration of phagocytic activity deficiency, circulating mature, activated lymphocytes, natural killers, and lymphocyte phenotypeswithцепторами к transferrin and IL-2 receptors. In cancer pathology, there was a high frequency of neutrophil deficiency, phagocytic activity, NK, mature, activated T cells, and lymphocyte phenotypes with transferrin and IL-2 receptors.

Keywords: dopamine, cortisol, thyroxine, T-lymphocytes, natural killers, T-helpers, cytokines, IL-10, TNF-α, phagocytes.

The correlation of dopamine concentration in peripheral blood with the level of immune protection in Northerners was studied. 70 practically healthy people and 172 patients (including 67 people with oncological pathology of the large intestine) were examined to study the level of dopamine in peripheral venous blood and the state of immune protection in residents of the northern territories of the Russian Federation, depending on the state of health. Thus, it was established for the first time that the level of registration of the frequency of elevated concentrations of dopamine in peripheral venous blood in practically healthy residents of the northern territories of the Russian Federation is high and amounts to 7.14±0.38%, the level of registration of the frequency of elevated concentrations of dopamine in peripheral venous blood in sick people was recorded much more often (59.21±1.7%). A high level of registration of elevated concentrations of IL-10 and TNF-α was also established, both in practically healthy people and in people with oncological diseases. There was an increase in the frequency of registration of deficiency of phagocytic activity, circulating mature, activated lymphocytes, natural killers and phenotypes of lymphocytes with transferrin and IL-2 receptors. In oncological pathology, there was a high incidence of deficiency of neutrophils, phagocytic activity, NK, mature, activated T cells, lymphocyte phenotypes with transferrin and IL-2 receptors.

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Introduction. The mechanisms of the effects of norepinephrine and epinephrine are well known, but the available data on the effects of dopamine are contradictory [5]. Dopamine, an intermediate precursor of norepinephrine and epinephrine, is secreted by the chromaffin cells of the adrenal medulla. Regulation of the activity of the adrenal medulla is carried out by sympathetic impulses. Each chromaffin cell at one end is in contact with the arterial capillary, and the other is turned to the venous sinusoid, where synthesized catecholamines are released. Sinusoids form the central vein of the adrenal gland, which flows into the inferior vena cava. This ensures simultaneous entry of both glucocorticoids and catecholamines into the circulation, which makes it possible for them to act together on effector organs.

It is known that dopamine can inhibit the secretion of thyroid-stimulating hormone and prolactin in hyperthyroidism. There is evidence that dopamine is involved in the regulation of arousal and inhibition in the central nervous system. The effect of dopamine on the state of the immune system can vary, from stimulation to a sharp suppression of activity. In

oncological diseases, there is a violation of the immune defense [2]. It was interesting to compare the results of studying elevated dopamine concentrations and associated changes in immune status in practically healthy people in comparison with sick people with malignant neoplasms of the intestinal tract in residents of the northern territories of the Russian Federation [1, 9].Current data on dopamine levels indicate that a lack of dopamine plays an important role in stress, aging of the body, and also restricts the growth and development of tumors [4]. From the literature sources of foreign authors, it is knownthat studies of the level of dopamine in various diseases пwere conducted in Scandinavian residents and the level of its content changed, relative to one or another pathology, but not in-all cases. At what level and whatcauses changes in dopamine levels, is of some interest [11].

Objective: to identify the level of dopamine in peripheral venous blood and the state of immune defense in residents of the northern territories of the Russian Federation, depending on their health status.

Materials and methods. The article analyzes the material carried out over the past ten years by employees of the laboratories of the Institute of Physiology of Natural Adaptations of the Russian Academy of Sciences named after Academician N. P. Laverov, including the examination of 70 practically healthy people who did not have a history of acute and chronic pathology at the time of examination for dopamine, cortisol, thyroxine, neutrophil granulocytes, % of active phagocytes, natural killer cells, T-lymphocytes, cytokines in peripheral venous blood. As a comparison group, 172 people with malignant neoplasms of the intestinal tract were taken. The examination was conducted in the medical company "Biokor", Arkhangelsk. The age of the subjects ranged from 21 to 75 years. The survey was conducted with the written consent of respondents in compliance with the basic norms of biomedical ethics in accordance with the document "Ethical principles for conducting medical research involving people as research subjects" (World Medical Association Declaration of Helsinki 1964 (as amended in 2008)). Blood sampling for the study was performed from the ulnar vein at 8-10 o'clock in the morning, on an empty stomach. The serum was separated from the formed blood elements (erythrocytes) by the method of centrifugation-separation of the liquid part of the blood from the cells in order to prepare the biomaterial for subsequent analysis. The complex of immunological research included the study of hemograms in blood smears stained according to the Romanovsky-Giemse method, the preparation of lymph suspension, and the phagocytic activity of neutrophil granulocytes. To detect the phagocytic activity of neutrophils, the following method was used: a mixture of 100 μl of latex was taken (the latex suspension was prepared by injecting 2 ml of buffer solution into a Latex bottle, shaking intensively for 2 minutes) and 100 μl of blood with heparin, mixed and put in a thermostat for 30 minutes, the temperature of the device was set to 37°C. Then the supernatant was sucked out of the test tube, mixed and a blood smear was made from it. Slides with smears were dried at room temperature. Then it was fixed in the Nikiforov mixture for 20 minut, stained according to Romanovsky-Giemsa for 40 minutes. Washed and dried slides were examined under a microscope at magnification of the x90 lens and the x7 eyepiece. The results obtained were evaluated using the phagocytic index, i.e., the percentage of phagocytic cells from the number of counted neutrophils, and the phagocytic number, i.e., the number of particles absorbed by one active neutrophil.

The level of T-cells (CD3+), T-helper cells (CD3+ CD4+), natural killer cells (CD3-CD16+CD56+), activated lymphocytes with transferrinreceptors трансферрину(CD71+) and IL-2 (CD25+) was evaluated using the indirect immunoperoxidase reaction method using monoclonal cells. antibodies (Sorbent, Moscow) and flow cytometry on цитометре «an Epics XL flow cytometer (Beckman Coulter, USA). HamburgThe content of dopamine (IBL Hamburg, Germany)пг, cortisol (DBC, Canada), thyroxine (Human GmbH, Germany), интерлейкинovand interleukins (IL) 1b, 4, and 6 was studied by enzyme - linked immunosorbent assay in peripheral venous blood serum., 10, 13 ("BIOSOURSE", USA). Statistical analysis of the research results was carried out using the application software package "Microsoft Excel 2010" and "Statistica 7.0" (StatSoft, USA). The boundaries of the normal distribution of indicators were determined. Сравнение расThe data distribution was compared with the normaldistribution and выполняwas performed using the Shapiro–Wilk criterionУилка. The distributions of the results turned out to be similar to the normal one, sothe arithmetic mean (M) and standard error of the mean (m) were calculated to describe the data.

Table 1

Frequency of registration of elevated concentrations of dopamine, cortisol, thyroxine and cytokines in peripheral venous blood in normal and oncological pathology of the large intestine in residents of the northern territories of the Russian Federation, depending on the state of health, %

Parameters studied	Frequency of registration of elevated concentrations in practically healthy people, n=70, %	Frequency of registration of elevated concentrations in patients with colon cancer, n=172, %	Physiological limits
Dopamine	7.14±0.38	59.21±1.7 ***	>30 pg/ ml
Cortisol	7.82±0.41	17.65±0.55 ***	>600 nmol/ L
Thyroxine (T4)	7.36±2.11	9.2±0.35*	10-25 pmol/ l
IL-1β	22.92±0.99	24.56±0.87*	>5 pg/ ml
IL-4	7.55±0.52	9.38±0.48*	>5 pg/ ml
IL-6	1.92±0.27	3.33±0.38*	>20 pg/ ml
of IL-10	8.93±0.53	17.86±0.75***	>10 pg/ ml
of IL-13	2.44±0.38	4.08±0.41*	>20 pg/ ml
TNF-α	1.89±0.08	42.11±0.38 ***	>20 pg/ml

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

Table 2

Frequency of registration of low concentrations of neutrophilic granulocytes, % of active phagocytes, natural killers and T-lymphocytes in peripheral venous blood with normal and elevated dopamine levels in residents of the northern territories of the Russian Federation, depending on the state of health, %

Studied parameters and physiological limits	Frequency of registration of low concentrations in practically healthy people, n=70		Frequency of registration of low concentrations in patients with small bowel cancer, n=172	
	With normal dopamine content, n=70	With increased dopamine content, n=70	With normal dopamine content, n=172	With increased dopamine content, n=172
Neutrophil granulocytes,<2×10^9 cells/l	2.86±0.24	5.71±0.34**	6.9±0.32	8.2±0.47*
% active phagocytes, <50	20.86±0.65	24.29±0.7*	72.41±0.97	84.62±1.66**
Natural killers CD3-CD16+CD56+,<0.4×10^9 cells/l	1.43±0.17	2.86±0.24***	63.95±1.45	76.92±1.34**
T-helper cells, CD3+ CD4+, <0.4×10^9 cells/l	4.29±0.29	5.71±0.34**	13.79±0.42	17.44±1.39**
CD3+, <1×10^9 cells/l	13.19±1.97	14.29±0.54*	40.23±0.73	45.92±0.95*
CD25+, <0.5×10^9 cells/l	15.27±2.83	17.14±0.59*	50.02±17.59	55.56±1.65*
CD71+, <0.4×10^9 cells/l	11.97±2.32	12.99±0.51*	42.86±3.13	54.88±0.90**

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

Quantitativevalues between groups were comparedusing *t*the Student's t-test. The differences were considered statistically significant at the significance level of the t-test p< 0.05-0.001.

Results and discussion. A high level of registration of elevated concentrations of dopamine, IL-10, and TNF-α in peripheral venous blood has been established both in practically healthy people and in individuals with colon cancer (Table 1). High levels of cortisol can negatively affect the stateof the human immune system. Cortisol controls cell proliferation and antiproliferative activity against cancer cells, which is of interest. Thyroxine is the most influential thyroid hormone of the thyroid gland, regulating metabolism and energy. Increasing its concentration in the blood affects many functions in the body. Elevated levels of IL-1b may reflect the activity of the tumor microenvironment and the development of immunosuppression. IL-4 affects the growth and development of the tumor, and an increase in its production accelerates the development of pathological processes. High levels of IL-6 are associated with many diseases, including cancer, which are associated with disorders of the immune system. IL-6 can be produced by malignant cells of tumor formations, and when the production of this cytokine is activated, transcriptional mechanisms are triggered and active division of cancer cells occurs. IL-10 is a natural immunosuppressant, the main anti-inflammatory cytokine. Its special function is to prevent an excessive inflammatory reaction, because even with this reaction, not a physiological, but a pathological effect is observed. And, as a result, excessive inflammation damages healthy cells and tissues of the body. IL-13 plays an important role in cancer pathology, because its receptors are overexpressed and affect cell proliferation. It is also an autocrine cytokine growth factor of malignant cells. The tumor necrosis factor activates the receptors that recognize the malignant cell and prevents its further development. TNF-α, along with cytokines, enhances the inflammatory process in order to protect against foreign antigens [8]. Dysregulation of TNF-α is associated with many diseases, including ccancer.

As can be seen from the data in Table 1, patients with malignant neoplasms of the large intestine, compared with practically healthy individuals, as well as with physiological limits, are significantly more likely to detect elevated levels of dopamine, cortisol and cytokines (IL-10 and TNF-α). It is known that 75-90% of blood dopamine is mainlysecreted in the intestine [10, 12]. The development of a malignant neoplasm in the gastrointestinal tract is accompanied by an increase in the blood concentration of TNF-α with a parallel decrease in the migration of immunocompetent cells to the affected area [3]. In the gastrointestinal tract, dopamine provides vasodilation, increased blood flow in the mesenteric vessels against the background of reduced peristalsis [6].

Since dopamine is produced by cells of the diffuse endocrine system, it can be assumed that an increase in dopamine concentrations in the blood occurs by increasing its secretion by APUD cells, although no one excludes the possibility of dopamine secretion by endotheliocytes. The relationship between elevated levels of dopamine and TNF-α in the blood may be mediated by the effect of the source of distress on cortisol secretion.

An increase in the concentration of dopamine in peripheral venous blood occurs due to dopamine sulfate. Once in the peripheral blood, dopamine in high concentrations naturally affects hemodynamics. There is reason to believe that dopamine inhibits the development and activity of a wide variety of reactions through direct effects on the membrane and mainly through the regulation of the autonomous system. It was of interest to study the content of dopamine in the blood of patients with diseases of the intestinal tract, since it is known that blood dopamine is mainly represented by an amine synthesized in the intestinal tract. After a meal, the content of dopamine in the blood of mesenteric vessels increases by 50 times, and even prolonged fasting reduces its concentration very slightly. In addition, significant concentrations of dopamine secrete APUD cells of the kidneys and adrenal glands, reduce the resistance of renin and aldosterone.

Установлены Elevated dopamine concentrations were found, концентрации , and blood concentrations of cortisol and thyroxine в крови were also sig-

nificantly increased. Thus, the obtained data confirm the revealed regularity of dopamine involvement in interoceptive visceral signaling about the presence of elevated cortisol and thyroxine concentrations. Given that dopamine secreted in the central nervous system does not enter the blood, it can be assumed that an increase in dopamine content is one of the stages in the implementation of interoceptive signaling to the brain about these changes.

The frequency of registration of reduced concentrations of neutrophilic granulocytes, active phagocytes, natural killercells, T-lymphocytes, and lymphocyte phenotypes with transferrin and IL-2 receptors in the blood was determined depending on the level of dopamine in practically healthy people and cancer patients. The studied parameters were compared with physiological limits (Table 2). Отмечалось There was an increase in the frequency of registration of phagocytic activity deficiency, circulating matureых T-lymphocytes, T-helpers, natural killers, and lymphocyte phenotypes with transferrin and IL-2 receptors, and an increased level of dopamine in the blood in practically healthy people. Inacute pathology, there was a high frequency of neutrophil deficiency, phagocytic activity, NK, T helper cells, mature forms of T cells, lymphocyte phenotypes with transferrin and IL-2 receptors, as well as an increased level of dopamine.

The decrease in the concentration of circulating immunocompetent cells at elevated levels of dopamine in the blood can be explained by the peculiarities of the effect of dopamine on hemodynamics. The action of dopamine injected into the vein occurs quickly and ends in 5-10 minutes. Administration of dopamine by intravenous drip in low concentrations leads to an improvement in coronary blood supply by dilating the coronary vessels, increasing the volume of systolic blood output of the heart, reducing the resistance of peripheral vessels, and sharply dilating the vessels of the mesentery [7].

It is possible that the decrease in the concentration of immunocompetent cells in the venous blood from the ulnar vein is caused by the redistribution of cells in the vessels of the gastrointestinal tract from the circulating to the marginal pool.

Thus, an increase in the concentration of dopamine in peripheral venous blood in patientswith intestinal diseases was found. A very high level of deficiency in the activity of effector cells, namely phagocytes, natural killers, mature forms of T-lymphocytes and activated lymphocytes with transferrin and IL-2 receptors, was revealed. It is of interest for further scientific research to study changes in the level of dopamine depending on gender and age in residents of the northern territories of the Russian Federation, since the probability of its change from age and gender characteristics of blood parameters depending on the state of health is not excluded.

Conclusion. So, when examining practically healthy residents of the northern territories of the Russian Federation, the frequency of elevated dopamine concentrations is 7.14±0.38%, in patients with elevated dopamine concentrations in the blood are recorded 7 times more often (59.21±1.7%). Elevated concentrations of cortisol, thyroxine, IL-10, and TNF-α were found in healthy subjects. There was a slight increase in other pro-inflammatory and anti-inflammatory cytokines. This pattern is more pronounced when examining patients. Elevated dopamine concentrations inthe peripheral blood cause a decrease in the level of activated, differentiated T-lymphocytes and natural killers, which is most pronounced in cancer pathology. A decrease in the concentration of immunocompetent cells at elevated dopamine concentrations is possible as a result of their redistribution from the circulating to the marginal pool.

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References

1. Ulyanovskaya SA, Bazhenov DV, Shestakova VG, Kalinkin MN. Vliyanie klimatogeograficheskih faktorov Severa na adaptivnye reakcii organizma cheloveka [The influence of climatic and geographical factors of the North on adaptive reactions of the human body]. Patologicheskaya fiziologiya i eksperimental'naya terapiya [Pathological physiology and experimental therapy. 2020; 64(1): 147-154 (In Russ.).] DOI: 10.25557/0031-2991.2020.01.147-154.

2. Dobrodeeva LK, Samodova AV. Adgezivnaya aktivnost' lejkocitov venoznoj perifericheskoj krovi v usloviyah in vitro u bol'nyh zlokachestvennymi novoobrazovaniyami [Adhesive activity of leukocytes of venous peripheral blood in in vitro conditions in patients with malignant neoplasms]. Voprosy onkologii [Issues of oncology. 2023; 69(4): 665-675 (In Russ.).] DOI: 10.37469/0507-3758-2023-69-4-665-675.

3. Dobrodeeva LK, Patrakeeva VP. Vliyanie migracionnyh i proliferativnyh processov limfocitov na sostoyanie immunnogo fona cheloveka, prozhivayushchego v usloviyah vysokih shirot [The influence of migratory and proliferative processes of lymphocytes on the state of the immune background of a person living in high latitudes. Yekaterinburg: UrORAN, 2018. P. 203 (In Russ.).]

4. Dobrodeeva LK, Patrakeeva VP. Dofaminergicheskaya sistema: stress, depressiya, rak (chast' 2) [Dopaminergic system: stress, depression, cancer (part 2)]. Rossijskij bioterapevticheskij zhurnal [Russian Biotherapeutic Journal. 2019; 18(14): 18. DOI: 10.17650/1726-9784-2019-18-4-25-33.

5. Molodovskaya IN. Dofaminergicheskaya sistema i ee vzaimosvyaz' s gipotalamo-gipofizarno-gonadnoj i gipotalamo-gipofizarno-tireoidnoj sistemami (obzor literatury) [Dopaminergic system and its relationship with hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid systems (literature review)]. Sibirskij nauchnyj medicinskij zhurnal [Siberian Scientific Medical Journal. 2020; 40 (6): 34-43 (Un Russ.).] DOI: 10.15372/SSMJ20200604.

6. Dobrodeeva LK, Samodova AV, Balashova SN, Pashinskaya KO. Osobennosti vzaimosvyazi regulyacii gemodinamiki i aktivnosti immunnyh reakcij u zdorovyh i bol'nyh ishemicheskoj bolezn'yu serdca, prozhivayushchih na Evropejskom severe i v Arktike RF [Features of the relationship between the regulation of hemodynamics and the activity of immune reactions in healthy and patients with coronary heart disease living in the European north and in the Arctic of the Russian Federation]. Klinicheskaya medicina [Clinical medicine. 2023; 101 (2-3): 116-122 (In Russ.).] DOI: 10.30629/0023-2149-2023-101-2-3-116-122.

7. Neiman J, Hofmann B, Dane S, Gergs U. Rol' dofamina v serdce v zdorov'e i boleznyah [The role of dopamine in the heart in health and diseases]. Mezhdunarodnaya konferenciya po nauke [International Conference on Science. 2023; 24 (5):5042 (In Russ.).] DOI: 10.3390/ijms24055042.

8. Topolyanskaya SV. Faktor nekroza opuholi-al'fa i vozrast-associirovannaya patologiya [Tumor necrosis factor-alpha and age-associated pathology]. Arhiv" vnutrennej mediciny [Archive of Internal Medicine. 2020; 10(6): 414-421 (In Russ.).] DOI: 10.20514/2226-6704-2020-10-6-414-421.

9. Molodovskaya IN, Tipisova EV, Popkova VA, Elfimova AE, Potutkin DS. Fotoperiodicheskaya variaciya gormonov shchitovidnoj zhelezy i autoantitel u muzhchin Evropejskogo Severa [Photoperiodic variation of thyroid hormones and autoantibodies in men of the European North]. Yakutskij medicinskij zhurnal [Yakut Medical Journal. 2020; 2: 77-80 (In Russ.).] DOI: 10.25789/YMJ.2020.70.23.

10. Liu CZ, Zhu JX. Source, metabolism, and function of dopamine in the digestive tract. 2020; 72 (3): 336-346.

Liu CZ, Zhu JX. The source, metabolism and function of dopamine in the digestive tract. 2020; 72 (3): 336-346.

11. Geijer T, Neiman J, Rydberg U., Gyllander A., Jönsson E., Sedvall G., Valverius P., Terenius L. Dopamine D2-receptor gene polymorphisms in Scandinavian chronic alcoholics. Eur Arch Psychiatry Clin Neurosci. 1994;244(1):26-32. DOI: 10.1007/BF02279808.

12. Xue. R., Zhang H., Pan J., Du Z., Zhou W., Zhang Z., Tian Z., Zhoum R., Baim L. Peripheral Dopamine Controlled by Gut Microbes Inhibits Invariant Natural Killer T Cell-Mediated Hepatitis. Front. Immunol. 2018, 9, 2398.

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CURRENT HEALTH ISSUES IN THE ARCTIC ZONE OF THE REPUBLIC OF SAKHA (YAKUTIA)

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Introduction. Despite the important strategic importance of the Arctic zone of the Republic of Sakha (Yakutia), it has been experiencing negative population dynamics for more than a quarter of a century. This fact has increased the costs of social and medical services, education, and has threatened the traditional economic activities of indigenous peoples. Moreover, there is a widespread shortage of highly qualified personnel, including medical personnel, in the Arctic, which is an additional trigger for population outflow.

Objective. To analyze the problems of modern health care in the Arctic zone of RS(Ya) as a territory with extremely specific socio-ecological conditions.

Methods. The research methodology was based on the data of the State Statistics Committee, reporting materials of district and seconded medical workers, as well as the educational and methodological department of the Medical Institute of the North-Eastern Federal University.

Results. A comprehensive analysis of the problems of modern healthcare in the region with specific socio-ecological conditions is presented, and practical recommendations for their resolution to improve medical services for the population of the Arctic zone of Yakutia are proposed. Much attention is paid to the problem of shortage of qualified personnel, material and technical provision of health care. The work of the Ministry of Health of the Republic of Sakha (Yakutia) to resolve some of the most pressing issues is shown.

Conclusion. One of the main unsolved problems of the Arctic health care is the low staffing of doctors, including graduates of the NEFU Medical Institute. It is a complex problem and to solve it it is necessary to strengthen the work on improving working and living conditions for medical workers and material and technical base of medical institutions, introduction of new technologies. It is important to pay attention to vocational guidance of graduates of schools of AZ RS(Ya). Taking into account the temporary effect of the programs "Zemsky Doctor" and "Zemsky Feldsher", we consider it necessary to provide preferential conditions for assignment of labor pension for medical workers working in the Arctic zone. Integration of new technologies, improvement of infrastructure and creation of programs to retain and attract medical workers are important steps not only to improve the health care system in the Arctic zone of the RS(Ya), but should also contribute to reducing the outflow of population.

Keywords. Arctic zone; health care organization; population dynamics, staff shortage, Yakutia.

Introduction. The Arctic zone of the Republic of Sakha (Yakutia) (AZ RS(Ya)) occupies more than 40% of the Arctic zone of Russia and more than half of the region's area. This vast area, divided into 3 time zones, is not only a strategically important territory of the Russian Federation, but also a settlement area for the indigenous peoples of the North, where their language and original culture are preserved due to their traditional way of life and economic activities. AZ RS(Ya) is also rich in mineral resources and has an impressive recreational potential due to its diverse natural conditions**.** However, remoteness from the center, dispersed settlement of residents, a significant number of small and medium-sized rural settlements, focal character of industrial and economic development and poorly developed social and transport infrastructure against the background of extreme climate cause its significant dependence on the "big earth", high resource intensity, dependence on supplies from other regions and low living standards of the local population. As a result of the above, the population of AZ RS(Ya) has decreased by more than a quarter in the last two decades alone. The loss of people has increased the costs of social and medical services, education, created a shortage of personnel (especially highly qualified) and a threat to traditional economic activities, as well as created a noticeable imbalance in the capital of the region, where the economically active part of the Far North residents mainly resettle.

Objective. To analyze the problems of modern public health care in AZ RS(Ya) as a territory with extremely specific socio-ecological conditions.

Materials and methods. To analyze the long-term population dynamics in the Yakut Arctic, the authors used data from the Federal State Statistics Service of the Republic of Sakha (Yakutia), including materials from the 2002 and 2020 All-Russian Population Censuses (ARPC). Information on the number and technical condition of buildings of medical institutions, staffing with doctors and nurses, the most common problems encountered in the course of work of the Arctic medical institutions of Yakutia was obtained from the heads of central district hospitals of AZ RS(Ya). Data on applicants enrolled in the NEFU Medical Institute and their academic performance were provided by the educational and methodological department of the mentioned educational institution. The results of the work of mobile medical teams and sanaviation are presented by the Yakutsk Republican Oncological Dispensary (YAROD), the Regional Center of the RS(Ya) (YAROD), the Regional Center for Mobile Brigades and the Republican Center for Disaster Medicine of the Ministry of Health of the RS(Ya).

Results and discussion. As can be seen from Table 1, from 2002 to 2020, the number of children in AZ RS(Ya) de-

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creased by 31.4% (from 24407 to 16748 people), while the number of citizens over 60 years old increased by 57.7% (from 6271 to 9888 people). In the region as a whole, the number of children decreased insignificantly (-5.0%), while the number of the elderly increased by 88.4%. additional evidence of the outflow of young people from AZ RS(Ya) is evidenced by a direct correlation (r = +0.7) between the population outflow indicator by ulus (%) and the share of Arctic residents over 60 years old in 2020.

When analyzing the national composition of the population, it is clearly seen that the loss of Arctic residents (in some areas up to 1/3 and higher, for example, Verkhnekolymsky or Ust-Yansky uluses) is due to the departure of the non-indigenous population. Thus, if in 2002 their share in the total structure of AZ residents was 32.3%, by 2020 this figure is 20.9% (tab. 2).

Due to remoteness and lack of year-round land communication with the central part of the region, one of the pressing problems of the residents of AZ RS(Ya) is high prices for all goods and air tickets, so not all residents have the opportunity to travel to Yakutsk every year. In addition, due to climatic conditions almost throughout the territory of AZ RS(Ya), the population has no opportunity to fully engage in crop production. Undoubtedly, the extremely specific conditions of the Arctic have a significant impact on the human body - the lack of biologically active ultraviolet radiation, increased electromagnetic activity, winds, low air temperatures and other features of the North can lead to exacerbation of chronic diseases, the appearance of the so-called polar stress syndrome and other serious health disorders, as well as an increase in mortality from external causes [3, 7, 13-15]. Moreover, according to a number of researchers, due to the small indigenous population and the peculiarities of their settlement, Yakutia has a high incidence of hereditary diseases [2, 11, 16]. It should be emphasized that the climatic changes observed in recent decades lead to the destruction of permafrost, which in turn increases methane emissions, which is a catalyst of global warming [1]. This is not only a direct threat to the entire infrastructure of the Arctic, but also new environmental problems, including prerequisites for expanding the range of vectors and pathogens of various diseases and carrying dangerous infections of the past from permafrost soils [8].

Analysis of literature data shows that a significant part of the population of the Arctic zone of Russia is dissatisfied with the quality of medical care received. Thus, in the research conducted in 2017 in the Murmansk Oblast, the activity of the regional health care system was rated "unsatisfactory" by 34.9% [10]. In 2019 in the Yamalo-Nenets Autonomous District, only 16.9% of respondents were satisfied with the quality of medical services provided [9]. This is despite the fact that a significant proportion of respondents in these regions were residents of cities. Unfortunately, no such surveys have been conducted in remote areas of Yakutia in recent years, except for Oymyakonsky ulus, the question of including it in the AS of RS(Ya) is still open [4-6]. Thus, in the course of the medical and social survey conducted in the spring of 2023, it was found that 9.3% of the district residents were fully satisfied with the work of doctors, 22.4% with the work of nursing staff, and 4.1% with the quality of medical care In general, more than 40% of the surveyed Oymyakon residents planned to change their place of residence. And it was dissatisfaction with the quality of medical services that was the most significant reason for the proposed departure, while harsh climatic conditions and unemployment were only secondary predictors [12].

It can be confidently stated that a similar situation is observed in all Arctic uluses, because out of 84 settlements of AZ RS(Ya) about half of them are located at a distance of more than 100 km (by air) from their ulunar centers, and more than 80% have no land communication with them for six months and more. For example, the village of. Kharyyalakh village of Olenek ulus, located only 2 kilometers from the ulus center in the spring and autumn period remains cut off from the Central Regional Hospital. That is, given the sparsely populated AZ RS(Ya), it is obvious that the generally accepted indicators of provision of the population with medical workers or beds (people/10 thousand people) should not be used as an indicator of the state of health care in this area. For the same reason, due to the law of small numbers, even insignif-

Table 1

Age structure of residents of AZ RS(Ya) according to the 2002 and 2020 National Population Census

District/Ulus	Total. people.	up to 15 years		60 +		Old age index	Total. people.	up to 15 years		60 +		Old age index
		people.	%	people.	%			people.	%	people.	%	
	2002						2020					
Abyisky	4750	1400	29.5	456	9.6	32.6	3838	900	23.4	654	17.0	72.7
Allanhovsky	3421	1013	29.6	263	7.7	26.0	2379	612	25.7	432	18.2	70.6
Anabarsky	4024	1386	34.4	193	4.8	13.9	3479	1095	31.5	321	9.2	29.3
Bulunsky	9775	2657	27.2	565	5.8	21.3	7706	1892	24.6	888	11.5	46.9
Verhnecolymsky.	5653	1366	24.2	542	9.6	39.7	3803	846	22.2	797	21.0	94.2
Verkhoyansky.	13666	4332	31.7	1108	8.1	25.6	10037	2408	24.0	1614	16.1	67.0
Zhigansky	4312	1352	31.4	359	8.3	26.6	4177	1246	29.8	599	14.3	48.1
Momsky	4699	1592	33.9	385	8.2	24.2	3733	1098	29.4	588	15.8	53.6
Nizhnekolymsky	5932	1581	26.7	490	8.3	31.0	4214	1059	25.1	705	16.7	66.6
Olenek	4091	1465	35.8	295	7.2	20.1	4313	1386	32.1	482	11.2	34.8
Srednekolymsky.	8353	2637	31.6	811	9.7	30.8	6805	1770	26.0	1310	19.3	74.0
Ust-Yansky	10009	2724	27.2	583	5.8	21.4	6810	1595	23.4	1108	16.3	69.5
En. -Bytantai	2761	902	32.7	221	8.0	24.5	2913	841	28.9	390	13.4	46.4
Total/average*	81446	24407	30.0*	6271	7.7*	25.7	64 207	16748	26.1*	9888	15.4*	59.0
for RS(Ya)	949280	251880	26.5	79109	8.3	31.4	995686	239300	24.0	149046	15.0	62.3

icant annual changes in the number of sick or dead people per 100 thousand population show significant fluctuations in the context of districts. By the way, the data on the number of population presented in official sources actually differ greatly from the real figures to a lesser extent. For example, in rural settlements of Nizhnekolymsky ulus there are currently 844 people (including 254 children), while in the data of the ERP-2020 there are 1591 people. In Utaya village of Verkhnekolymsky ulus, no more than 25 people actually live in the winter period, i.e. 4 times less than indicated in the WHI data.

Thus, for the average Arctic resident living outside the district center, which is about half of the population, the first priority issue is to overcome the road to the Central Regional Hospital. Similar difficulties arise for health care workers traveling to the districts. In addition, many local medical institutions have problems due to the lack or malfunction of transportation, diagnostic and treatment equipment necessary for the area. As a rule, high tariffs for public utilities are noted everywhere. Often there are difficulties with delivery of medicines. Low speed and instability of Internet connection, as well as high prices for communication services, create significant interference in the activities of medical institutions, do not allow to fully use modern technologies.

Particular attention should be paid to the high level of deterioration of buildings at the CRBs. For example, as of 2024, 4 out of 10 buildings at the Abyisk CRH are in emergency condition, in Verkhnekolymskiy ulus - 7 out of 15, and in Srednekolymskiy ulus 8 out of 12 buildings were built more than 30 years ago (Table 3). In total, as of the first half of 2024, 65% of all buildings in the CDBs either require major repairs or are in emergency condition. However, it should be noted that over the last 2-3 years there have been significant positive changes in improving the material and technical base of district medical institutions. Thus, within the framework of the national project "Health Care", which envisages measures to improve the material and technical base of district medical institutions, new FAPs appeared in Bykovsky village of Bulunsky ulus (2022), in Chkalov village of Allaihovsky ulus (2023) and in Khayyr village of Ust-Yansky ulus (2023). In 2021, medical outpatient clinics will be commissioned in Aleko-Kyuel village of Srednekolymsky ulus and Kuberganya village of Abyisky ulus, and in 2022, in Nalimsk village of Srednekolymsky ulus. - in Nalimsk village of Srednekolymsky

Table 2

Data on the number and composition of the population in AZ RS(Ya)

District/Ulus	Population, thousand people		National composition, % (according to National Population Census data)					
			2002			2020		
	2000	2023	КМНС	саха	другие	КМНС	саха	другие
Abyisky	5.1	3.8	5.9	80.9	13.2	10.3	80.2	9.5
Allanhovsky	3.7	2.3	20.7	39.9	39.4	26.4	38.2	35.4
Anabarsky	3.9	3.5	45.4	27.3	27.3	76.3	19.2	4.5
Bulunsky	9.9	8.0	30.3	23.2	46.5	40.8	24.4	34.8
Verhnecolymsky.	6.1	3.7	10.3	25.9	63.8	16.7	28.3	55.0
Verkhoyansky	15.2	10.0	3.2	70.2	26.6	5.2	78.7	16.1
Zhigansky	4.5	4.1	49.1	33.5	17.4	63.5	25.0	11.5
Momsky	4.7	3.8	17.9	70.0	12.1	31.0	62.1	6.9
Nizhnekolymsky.	6.7	4.2	22.9	18.7	58.4	37.2	17.5	45.3
Olenyoksky	4.1	4.4	64.0	30.5	5.5	83.4	13.9	2.7
Srednekolymsky.	8.4	6.7	5.6	80.8	13.6	8.8	79.8	11.4
Ust-Yansky	11.9	6.8	11.6	37.7	50.7	22.2	46.7	31.1
En. -Bytantai	2.7	2.9	43.6	53.4	3.0	59.4	39.0	1.6
Total/average*	86.9	64.2	20.3*	47.5*	32.2*	32.4*	46.7*	20.9*
Average for RS(Ya)	…	…	3.5	45.5	51.0	4.2	47.1	48.7

Table 3

Number and technical condition of medical buildings in AZ RS(Ya) as of the first half of 2024

Hospital facilities	Район/улус													Total
	Abyisky	Allanhovsky	Anabarsky	Bulunsky	Verhnecolymsky.	Verkhoyansky	Zhigansky	Momsky	Nizhnekolymsky.	Olenyoksky	Srednekolymsky.	Ust-Yansky	Eveno-Bytantai	
CDP	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Community hospitals	-	-	-	-	-	-	-	-	1	-	-	-	-	1
City hospitals	-	-	-	-	-	1	-	-	-	-	-	-	-	1
Doctor's clinics	5	-	1	5	3	7	1	1	1	3	9	4	1	41
Antitussive dispensaries		-	-	-	-	1	1	-	1	-	-	-	-	3
FAP	1	4	-	2	2	11	2	4	-	-	-	5	1	32
FP	-	-	-	-	-	-	-	-	1	-	-	-	-	1
Total	7	5	2	8	6	21	5	6	5	4	10	10	3	92
Number of CRB buildings	10	7	3	10	15	40	5	6	8	6	12	14	6	142
including emergency	4	2	1	4	7	17	1	3	4	2	5	4	2	56
overhaul	4	2	0	2	2	16	1	-	2	0	2	4	1	36
Number of CRB buildings commissioned in 2014-2024	1	1	0	1	1	5	1	2	2	0	3	4	1	22

ulus, Nelemnoye village of Verkhnekolymsky ulus, Saidy village of Verkhoyansk ulus, Kustur village of Eveno-Bytantai ulus and Ust-Kuiga village of Ust-Ya ulus; in 2023 - in Kyusyur village of Bulunsky ulus and Andryushkino village of Nizhnekolymsky ulus. Andryushkino village of Nizhnekolymsky ulus, and in 2024 - in Sasyr village of Momsky ulus. Also in Moma ulus (Khonuu village), a three-storey hospital complex with adult and children's polyclinics was inaugurated on March 12, 2024.

Although a number of uluses actively practice social support measures for newly arrived medical workers, living conditions do not always meet the needs of specialists, especially in the cold season. Moreover, with the exception of participants of the "Zemsky Doctor/"Zemsky Feldsher" program, newly arrived medical workers do not have permanent res-

idence registration, which deprives them of the benefits provided for residents of AZ RS(Ya), for example, the purchase of air tickets at subsidized prices. All the described problems cause a high turnover of migrant staff. This was observed during the COVID-19 pandemic - there were cases when specialists left uluses in pursuit of "covid payments". The shortage of highly specialized doctors, including infectious disease specialists, psychiatrists-drug specialists, ophthalmologists, neurologists, etc. should be considered a separate problem. Unfortunately, due to the small number of the Arctic population it is not possible to organize a full-fledged geriatric service, although over the last two decades the number of people in the AS of RS(Ya) over 60 years of age has increased significantly.

In general, the staffing levels of doctors (59.7%) and EMTs (69.7%) are low throughout the Arctic, which means that in some areas specialists are forced to combine 2-3 positions. It should also be recognized that the effect of the "Zemsky Doctor" and "Zemsky Feldsher" programs implemented since 2012 is only temporary - in the vast majority of cases, specialists are initially set up for a short period of work.

It is important to emphasize that among newly arrived medical workers, the share of graduates of the NEFU Medical Institute remains low (54.8%), while it is this educational institution that should be the main forge of the medical elite of the republic (tab. 4). By the way, in the period from 2018 to 2023, from the total number of those admitted to the MI NEFU (n = 2451), only 3.8% are natives of AZ RS(Ya). At the same time, even after passing the competitive selection, graduates of northern schools are much more likely to drop out than other students. Thus, according to the data of the educational and methodological department of MI NEFU, out of 269 natives of AZ RS(Ya), enrolled in the specialties "Medicine", "Dentistry" and "Pediatrics" in the period from 2010 to 2023, 33.8% (91 people) received a diploma of graduation, 29.7% (80 people) are studying or are on leave of absence, 36.4% (98 people) were expelled. Most of the total number of students on leave of absence and expelled dropped out due to the low level of basic secondary education, primarily in the subjects "chemistry" and "biology". This is another clear evidence that the problem of shortage of medical personnel in the North is complex and should not be placed solely on the shoulders of higher education or the Ministry of Health.

Table 4

Information on the number of medical workers and staffing of medical institutions in AZ RS(Ya) as of the first half of 2024

Ulus												
Abyisky	Allanhovsky	Anabarsky	Bulunsky	Verhnecolymsky.	Verkhoyansky	Zhigansky	Momsky	Nizhnekolymsky.	Olenek	Srednekolymsky.	Ust-Yansky	Eveno-Bytantai
Absolute number of doctors/including NEFU graduates, people												
15/9	12/3	9/6	33/20	19/5	38/18	19/14	12/9	15/4	16/12	24/19	28/9	10/9
Absolute number of nursing staff/including graduates of Yakutia's educational institutions, people												
54/52	27/27	30/29	72/68	39/28	128/114	48/48	50/48	35/14	39/27	79/75	71/31	30/30
Physician staffing, %												
51,7	55,8	58,7	63,5	69,1	58,5	71,6	55,8	42,5	54,0	63,5	54,9	76,9
Staffing of nursing staff, %												
78,8	60,0	71,8	58,8	73,5	61,1	84,2	78,1	47,2	69,0	72,5	57,7	93,9

Table 5

Performance indicators of IMBs in the Arctic uluses of the RS(Ya) for 2023

Район/улус	Quantity of medical team sorties per year	Total length of stay, days	Settlements visited	Persons examined		Coverage (of the total number of inhabitants on the	Diseases detected for the first time, cases	Taken from Dispensary registration, people	Referred to republican medical institutions, persons
				total	including children				
Abyisky	3	42	7	2440	870	64,4	365	60	117
Allanhovsky	3	30	5	1396	453	59,4	282	76	203
Anabarsky	3	30	2	1938	673	56,1	442	289	286
Bulunsky	4	52	8	2983	1006	37,3	873	29	201
Verhnecolymsky.	3	39	6	1749	410	46,7	342	73	285
Verkhoyansky	4	80	19	5522	2407	55,2	1158	191	681
Zhigansky	4	31	4	2327	1090	57,0	713	88	370
Momsky	3	33	7	2371	817	62,7	641	249	342
Nizhnekolymsky.	4	46	4	2132	882	50,6	405	27	151
Olenek	3	29	4	1683	434	38,6	440	125	241
Srednekolymsky.	5	66	10	4172	1632	61,9	861	148	507
Ust-Yansky	4	60	10	3157	787	46,4	812	318	324
En. -Bytantai	3	26	3	1356	423	46,0	279	113	188
Total	46	564	89	33226	11884	51,7	7613	1786	3896

Taking into account all the above-mentioned, in order to retain doctors in rural areas it is necessary not only to improve working and living conditions of doctors, to strengthen the work on target distribution of young specialists, but also to pay special attention to vocational guidance of entrants starting from school, as well as to strengthen the subject training of graduates in specialized subjects. In addition, in our opinion, an effective lever for attracting new personnel to remote uluses would be the introduction of additions to the RF Government Decree of

September 22, 1999 N 1066 on the provision of preferential conditions for the appointment of labor pensions for medical workers working in the Arctic zone.

Nevertheless, despite the numerous difficulties in work, the republic continues active activities on medical examination of the population of remote areas of the republic. For example, one of the achievements of regional healthcare is the creation of a mobile multidisciplinary brigade "Oncodesant", consisting of oncologists from YaRD. In the period from 2020 to 2023, working in close connection with ulu medical institutions, the specialists visited almost all Arctic uluses, except Bulunsky, where they examined 3,841 people. In the course of research, 33 cases of cancer were identified, and 169 people were sent to Yakutsk for further examination.

It was possible to significantly improve the provision of comprehensive medical care to the residents of AZ RS(Ya) thanks to the implementation of a large-scale project of the Ministry of Health of the RS(Ya), developed and implemented with the active support of a number of other regional bodies - the Ministry of Arctic Development of the RS(Ya), the Ministry of Transport of the RS(Ya) and the Ministry of Innovation of the RS(Ya). Thus, on January 30, 2023[1] a Regional Center of Mobile Brigades was established on the basis of the Republican Center of Public Health and Medical Prevention. At present, the center unites 7 multidisciplinary teams (including one pediatric team), staffed with specialists of narrow focus and all necessary equipment. During the first year of operation, the mobile multidisciplinary teams visited each of the Arctic uluses at least 3 times. The total time spent in each district averaged 1.5 months (Table 5). During this period, the doctors traveled to all settlements of the Yakut Arctic and examined 33226 people, including 11884 children. In addition to scheduled examinations, 359 patients received home care and 159 received emergency care. Also 72 small surgical interventions were performed. Unfortunately, a psychiatrist-narcologist and a clinical psychologist were present only during the visit to Ust-Yansky ulus. In general, the results of the IMB's activities have shown the best side, and therefore, from 2024, the area of their activities began to cover 5 more industrial uluses - Mirny, Neryungri, Lensk, Aldan and Oymyakonsk.

Introduction of such projects into practical healthcare not only increases the quality of medical care, promotes timely diagnosis of diseases, forms a culture of public health, but also obviously significantly reduces financial costs for residents of remote uluses. As for prompt medical assistance in AZ RS(Ya), the activities of sanaviation undoubtedly play an invaluable role here. According to the data of the Republican Center for Disaster Medicine, in 2020-2023, 2510 sanaviation missions were carried out in the Yakut Arctic, 3,833 patients were assisted, including 742 with COVID-19[2] .

All the above-mentioned expeditions provide invaluable assistance to uluses medical institutions. Therefore, it is obvious that all this work will continue. In this regard, we consider it expedient to find funds for the construction of additional residential modular comfortable premises at the Arctic CRBs both for medical workers arriving for permanent work and for the rest of seconded specialists.

Conclusion. The study of the current state of health care in AZ RS(Ya) reveals serious challenges and problems arising in the unique socio-ecological conditions of this region. The mass outflow of people from this territory is associated with a number of factors, among which dissatisfaction of the population with medical care takes one of the leading places. To address this problem, under the auspices of the Ministry of Health of the RS(Ya), mobile teams of doctors have been created since 2020 to serve residents of hard-to-reach settlements in the Arctic and industrial areas. It is important to emphasize that a significant contribution to strengthening the material and technical base of the Arctic CDCs was made by the implementation of the national project "Health Care", thanks to which 14 health care facilities were built in AZ RS(Ya) in 2021-2024.

However, the problem of low staffing of physicians in RS(Ya) AH, including graduates of the Medical Institute of the North-Eastern Federal University (NEFU) currently requires close attention. It is a complex problem and its solution requires consolidation of various regional agencies. It is necessary to strengthen work on improving working and living conditions for medical workers and the material and technical base of medical institutions, to introduce new technologies, to focus on career guidance for schoolchildren, to strengthen scientific research and medical and social projects in the field of Arctic medicine. Taking into account the temporary effect of the programs "Zemsky Doctor" and "Zemsky Feldsher", we consider it necessary to provide preferential conditions for the appointment of labor pensions for medical workers working in the Arctic zone.

[1] Order of the Ministry of Health of the RS(Ya) No. 01-07/163 dated January 30, 2023.

[2] Reference from the Republican Center for Disaster Medicine of the Ministry of Health of the RS(Ya) dated 26.03.2024 No. 0118/180.

References

1. Arustamova IS, Isaeva LO, Ostapenko PR. Ekologicheskie posledstviya vy`brosov metana v atmosferu [Environmental consequences of methane emissions into the atmosphere]. Nauchny`e chteniya imeni professora N.E. Zhukovskogo: Sb. nauch. st. XIII Mezhdunar. nauch.-prakt. konf., Krasnodar, 21-22 dekabrya 2022 g. [Scientific readings named after Professor N.E. Zhukovsky: Sat. scientific Art. XIII Int. scientific-practical Conf., Krasnodar, December 21-22, 2022. Krasnodar, 2023:186-190 (In Russ.).]

2. Aftanas LI, Voevoda MI, Puzyryov VP, et al. Arkticheskaya medicina v XXI veke [Arctic medicine in the XXI century]. Vestnik Rossijskoj akademii nauk [Bulletin of the Russian Academy of Sciences. 2015; 85 (5-6): 501-506 (In Russ.).] doi: 10.7868/S086958731506002X

3. Gmoshinsky IV, Nikityuk DB. Polyarny`j stress: mexanizmy` i modelirovanie v e`ksperimente [Polar stress: mechanisms and experimental modeling]. Vestnik Rossijskoj akademii medicinskix nauk [Bulletin of the Russian Academy of Medical Sciences. 2022; 77 (6): 447-457 (In Russ.).] doi: 10.15690/vramn2209

4. Polar stress: mechanisms and experimental modeling //. 2022. T. 77, no. 6. pp. 447-457. (In Russ.) doi: 10.15690/vramn220911

5. Danilov YuG. Fiziko-geograficheskij podxod k vy`deleniyu Arkticheskoj zony` v Yakutii [Physiographic approach to the identification of the Arctic zone in Yakutia]. Arktika XXI vek. Estestvenny`e nauki [Arctic XXI century. Natural Sciences. 2016; 1: 4-9 (In Russ.).]

6. Ivanova RN. Klimat Ojmyakon`ya kak faktor otneseniya k territorii arkticheskoj zony` Rossijskoj Federacii [Climate of Oymyakon as a factor of classification as a territory of the Arctic zone of the Russian Federation]. Voprosy` geografii Yakutii. Vy`p. 12. Prirodno-klimaticheskie usloviya Severo-Vostochnoj Yakutii. Sbornik nauchny`x trudov [Issues of geography of Yakutia. Vol. 12. Natural and climatic conditions of North-Eastern Yakutia. Collection of scientific papers. Novosibirsk: Nauka, 2017: 32-37 (In Russ.).]

7. Ivanova TS. K voprosu o vklyuchenii Ojmyakonskogo ulusa Respubliki Saxa (Yakutiya) v sostav Arkticheskoj zony` Rossijskoj Federacii [On the issue of including the Oymyakonsky ulus of the Republic of Sakha (Yakutia) in the Arctic zone of the Russian Federation]. Xolod i zdorov`e: Sbornik materialov mezhdisciplinarnogo mobil`nogo nauchno-prakticheskogo seminara (24–29 marta 2021 g.) / Pod red. S.S. Slepczova. Novosibirsk: Nauka [Cold and health: Collection of materials from an interdisciplinary mobile scientific and practical seminar (March 24–29, 2021) / Ed. S.S. Sleptsov. Novosibirsk: Nauka, 2023: 24-33 (In Russ.).] doi 10.7868/978-5-02-041524-9(3)

8. Konnova LA, Lvova YuV, Rudnev EV. O vliyanii polyarnogo siyaniya i geomagnitny`x bur` na texnosferu i naselenie v Arkticheskom regione [On the influence of the aurora and geomagnetic storms on the technosphere and population in the Arctic region]. Vestnik Sankt-Peterburgskogo universiteta Gosudarstvennoj

protivopozharnoj sluzhby` MChS Rossii [Bulletin of the St. Petersburg University of the State Fire Service of the Ministry of Emergency Situations of Russia. 2020; 3: 1-5 (In Russ.).]

9. Malkhazova SM, Mironova VA, Bashmakova IKh. Prirodnoochagovy`e bolezni v Arktike v usloviyax menyayushhegosya klimata [Natural focal diseases in the Arctic in a changing climate]. Vestnik Moskovskogo universiteta. Seriya 5: Geografiya [Bulletin of Moscow University. Episode 5: Geography. 2022; 1:43-57 (In Russ.).]

10. Markin VV, Silin AN, Vershinin IS. Zdorov`e lyudej v Arktike: social`no-prostranstvenny`j diskurs (na primere Yamalo-Neneczkogo avtonomnogo okruga) [Human health in the Arctic: socio-spatial discourse (using the example of the Yamalo-Nenets Autonomous Okrug)]. E`konomicheskie i social`ny`e peremeny`: fakty`, tendencii, prognoz [Economic and social changes: facts, trends, forecast. 2020; 13 (5): 182–199 (In Russ.).] doi: 10.15838/esc.2020.5.71.11

11. Polozhentseva OA. Uroven` i kachestvo zhizni kak faktor samorazvitiya mestny`x soobshhestv Murmanskoj oblasti [Level and quality of life as a factor in the self-development of local communities in the Murmansk region]. Vestnik Altajskoj akademii e`konomiki i prava [Bulletin of the Altai Academy of Economics and Law. 2020; 10-1:69-75; URL: https://vaael.ru/ru/article/view?id=1348 (date of access: 02/29/2024) (In Russ.).]

12. Savvina MT, Maksimova NR, Sukhomyasova AL, et al. Nasledstvenny`e bolezni i programmy` molekulyarno-geneticheskogo skrininga v geneticheski izolirovanny`x popu1yaciyax [Hereditary diseases and carrier's screening programs in genetically isolated populations]. Medicinskaya genetika [Medical Genetics. 2022; 21(1):3-13 (In Russ.).] https://doi.org/10.25557/2073-7998.2022.01.3-13

13. Sleptsov SS, Andreev MN, Sleptsova SS. Vliyanie kachestva zdravooxraneniya na ottok naseleniya iz otdalenny`x rajonov Yakutii (na primere Ojmyakonskogo ulusa) [The influence of the quality of healthcare on the outflow of the population from remote areas of Yakutia (on the example of the Oymyakonsky ulus)]. Uspexi sovremennogo estestvoznaniya [Advances in modern natural science. 2023; 7: 42-48 (In Russ.).] doi: 10.17513/use.38069.

14. Solonin YuG, Boyko ER. Mediko-fiziologicheskie problemy` v Arktike [Medical and physiological problems in the Arctic]. Izvestiya Komi nauchnogo centra UrO RAN [News of the Komi Scientific Center of the Ural Branch of the Russian Academy of Sciences. 2017; 4(32): 33-40 (In Russ.).]

15. Tikhonov DG. Arkticheskaya medicina [Arctic medicine. Ed. V.A. Galkina, M.I. Tomsky; RAMS, SO, YSC CMP. Yakutsk: Publishing house YSC SB RAS, 2010: 313 (In Russ.).]

16. Tomsky MI. Naselenie promy`shlenny`x rajonov Yakutii i «sindrom polyarnogo napryazheniya [Population of industrial regions of Yakutia and the "polar voltage syndrome]. E`konomika Vostoka Rossii [Economics of the East of Russia. 2015; 1:78-81 (In Russ.).]

17. 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): 29-30 (In Russ.).] doi: 10.25557/2073-7998.2020.07.29-30.

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ANALYSIS OF CORTISOL AND DEHYDROEPIANDROSTERONE-SULFATE LEVELS IN MALE NORTHERNERS: THE INFLUENCE OF GENERATION LIVING IN THE NORTH

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Relevance. The body's ability to resist the effects of harsh climatic and geographical conditions is determined by characteristics of adaptive mechanisms and the process of their change based on the hypothalamic-pituitary-adrenal axis and depending on the length of residence in the North.

Purpose. This study examined male Northerners to assess fluctuations in their cortisol and dehydroepiandrosterone-sulfate mean levels in the increasing reliance on the generation of residence in the North.

Methods. Seventy male residents of the Magadan Region (mean age 40.0±0.8 yrs) participated in the survey and made up subgroups varying with the length (generation) of residence in the North: the 0th generation (n=15), the 1st generation (n=35), and the 2nd-3rd generation (n=20). Immunochromatographic and immune enzyme analyses were applied in the research.

Results. Subjective mean levels of serum cortisol and dehydroepiandrosterone-sulfate and their ratio tended to significantly fluctuate based on the generation of residence in the North: the highest values were observed in examinees with the longest period of residence (2nd-3rd generation), and the lowest – in representatives with a shorter period of adaptation to the North extremes (0th generation). In addition, the cortisol concentrations in the evening saliva test were optimized according as we traced them in representatives of 0th to 2nd-3rd generations.

Conclusion. The study has resulted in referring serum cortisol and dehydroepiandrosterone-sulfate concentrations, their ratio, as well as cortisol concentrations in the evening saliva tests to significant markers that reflect readjustments in the endocrine picture with increasing length of residence in the North, thus confirming the generally recognized role of glucocorticoids in hormonal support of the body adaptation to extreme factors including climatic environments.

Keywords: North, middle-aged men, cortisol, DHEA-S, the generation of residence

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Introduction. The issue of the mechanisms of newcomers' long-term adaptation to the harsh conditions of the north remains relevant and requires further study. Currently, in addition to the indigenous peoples in the Magadan Region, the permanent residents are made up of quite numerous ethnic groups of Caucasians: migrants and those born to them in the north in different generations [1]. In the course of our long physiological research, we found that migrants and north-born Caucasians have their own specific characteristics and also much in common in their body functional adaptive readjustments. As we were examining young male adults from Caucasian migrants and those born to migrants in the 1st-3rd generations, all being residents of the Magadan Region, we identified the main components of the adaptation strategy according as the examinees be-

longed to a particular generation. Those components showed optimization in the studied body functional performance as effectiveness of adaptive changes to the harsh impact of natural and climatic environments and were characteristic of generation-related subjects in the range from 0th generation to 2nd and 3rd generations: increased contribution of the parasympathetic component with a fall in the hypertensive focus in the cardiovascular system, reduced total energy costs, and lowered atherogenicity of the lipid picture [1].

It is known that successful adaptation of a human body to extreme climatic and geographical conditions varies with the state of adaptive mechanisms which are based on the hypothalamic-pituitary-adrenal axis (HPA). The structure of adaptive neurohormonal and endocrine reactions is quite plastic and is subject to changes depending on the duration of residence in the northern regions [7, 26]. Cortisol and dehydroepiandrosterone (DHEA) are considered valuable markers of the hypothalamus-pituitary-adrenal axis [19] with cortisol as the main biomarker of its activity [14] and the hormone that performs to ensure physiological homeostasis and adaptation to stressful situations. However, maintaining high levels of these hormones is energetically inefficient and prevents other physiological processes [32, 29]. Measuring the cortisol level provides important information on a person's capability to adapt to various environmental requirements [17] since its concentration is influenced by psychological and physiological stress factors [28]. To keep the energy balanced when exposed to hormones of the HPA axis, various mechanisms of adaptation of their levels to environmental conditions work at different time scales, i.e. through generations, between parents and their descendants, and during the life of an individual [21]. Dehydroepiandrosterone (DHEA) is mainly present as sulfated ether (DHEA-S); it shows an anti-glucocorticoid effect in vitro and can protect against the side effects of elevated circulating cortisol [19].

We have considered the wide range of physiological effects of the above hormones, as well as the concept of optimization that occurs in the main physiological systems with the increasing duration of residence in the north. Based on this, we defined the aim of the present research as the analysis of saliva and serum cortisol, assessment of the DHEA-S level in the blood as well as the f DHEA-S/cortisol ratio in the population of male northerners in reliance on belonging to a particular generation.

Materials and Methods. During the scientific monitoring program for northerners entitled "The Arctic. Man. Adaptation" which is being implemented with the "Arktika" Scientific Research Center, the Far Eastern Branch of the Russian Academy of Sciences (the city of Magadan), we have studied the main hypothalamic-pituitary-adrenal system's indicators in northern men, all being permanent residents of the Magadan Region, and assessed the variables based on different periods of subjective living under the north conditions. The total sample involved 70 men (mean age 40.0±0.8 years) with the following anthropometric indicators: body height – 180.7±0.9 cm, body mass 87.5±2.1 kg, body mass index – 26.8±0.6 kg/m^2. The examined subjects made up two subgroups based on their generation of living in the north (0 generation (n=15), 1st generation (n=35), 2nd and 3rd generations (n=20). Subjects' venous blood was taken with a vacuum system in the laboratory of Unilab-Khabarovsk LLC. Saliva cortisol (ng/ml) was evaluated twice (morning and evening) using the IFA method on the Muitiscan FS immune enzyme analyzer (reader). Dehydroepiandrosterone sulfate (DHEA-S) (ng/ml) and cortisol (nmol/L) in serum were determined by the IHA method using an automatic immunochemiluminescence analyzer of Mindray CL 6000i. The index for DHEA-S (mmol/l) / cortisol (nmol/l) was calculated from the obtained data [6]. The numerical values of the ratio reflect various stages of adaptation (< 1.1 – adaptive reserves are depleted; from 1.1 to 2.1 – adaptive reserves are consumed; > 2.1 – adaptive reserves are preserved). The research protocol was approved by the Local Ethics Committee of the Federal State Budgetary Institution of Science of the Scientific Research Center "Arktika" of the Far Eastern Branch of the Russian Academy of Sciences (conclusion No. 002/021 dated 11/26/2021). The study was performed in accordance with the principles of the Helsinki Declaration (2013). Prior to inclusion in the study, all participants provided their written informed consent. The criterion for inclusion in the study was absence of chronic diseases in the acute stage and complaints about the state of health. All subjects were permanent residents of the Magadan Region living in comparable conditions and having the same mode of physical activity. The following subjective items were monitored: morning activity, caffeine intake, and smoking – factors that can affect morning cortisol and DHEA-S levels. Blood sampling was performed on an empty stomach before 10 a.m. The subjects were instructed to avoid unusual physical activity or stress for 24 hours before the blood tests. Samples of the morning saliva cortisol were taken by the subjects immediately after awakening, the evening saliva cortisol – before going to bed, independently, according to the instructions. Hormone levels in all samples were measured simultaneously to avoid variability among tests.

Statistical data processing was carried out using the standard statistical software package StatSoft Statistica 7.0. Checking for the normality of the distribution of measured variables was carried out based on the Shapiro-Wilk test. The results of parametric processing methods are presented in the form of an average value (M) and an arithmetic mean error (±m). In multiple comparisons, parametric one-factor analysis of variance (ANOVA) was used. To identify statistically significant differences between specific groups, a posteriori analysis using the Scheffe test for multiple comparisons was applied. The critical significance level (p) in the work was assumed to be 0.05.

Results. Table 1 presents blood serum cortisol and DHEA-S levels, as well as their ratio depending on the generation of residence in the north. The data obtained show raised levels of serum cortisol with the increasing period of residence, from representatives of the 0th to the 2nd-3rd generations. We can see the average value of the indicators in each group significantly exceeded the upper reference limit typical for residents of the north who had no pathologies (314 nmol/l) [10]. The DHEA-S level assessment revealed optimal concentration of this indicator with its significant growth in the next generations of residence in the north. A similar picture could be seen in the ratio of DHEA-S/cortisol. Based on the classification criteria, men of the 0th generation demonstrated the stage of depletion of adaptive reserves whereas subjects of the 1st, 2nd, and 3rd generations tended to preserve the adaptive reserves.

We also analyzed the saliva cortisol levels shown in Table. 2 and found the multidirectional trends in its concentration at different times during the day. We noticed that the content of the morning saliva cortisol remained unchanged with the increasing length of residence in the north, with its average values significantly exceeding the upper reference typical for this indicator, whereas the evening saliva cortisol significantly reduced in the row from representatives of the 0th to the 2nd and 3rd generations with the approach to the normal range. It is worth mention-

Table 1

Concentration of serum cortisol, DHEA-S and DHEA-S/cortisol ratio depending on the generation of residence in the north

Indicator	Generation			Level of significance of differences		
	0	1	2-3	0-1	1-(2-3)	0-(2-3)
Cortisol, nmol/l	383.6±28.0	397.7±15.3	450.8±23.9	p=0.47	p=0.04	p<0.001
DHEA-S, mcg/dl	275.2±21.9	370±20.4	419.0±23.3	p<0.001	p=0.06	p<0.001
DHEA-S mmol/l	7.47±0.59	10.04±0.55	11.37±0.63	p<0.001	p=0.06	p<0.001
DHEA-S, mmol/l / Cortisol, nmol/l	1.80±0.11	2.37±0.14	2.59±0.18	p<0.001	p=0.17	p<0.001

ing that daily fluctuations in saliva cortisol levels that vary with the generation of residence in the north conditions show the preservation of daily biorhythmology.

Discussion. In our study, we observed high blood cortisol levels in northern residents with an increase in mean values from representatives of the 0th to the 2nd-3rd generations, which indicate the signs of hypercortisolism reported in earlier studies performed in the northern territories [8, 9, 5, 2.]. It is believed that such increased activation of hormones of the hypothalamic-pituitary-adrenal axis is part of adaptive adjustments to adverse northern conditions aimed at maintaining basal metabolic parameters to compensate for the cold factor [9]. In previous (the 90s of the twentieth century) assessment studies on hormonal status of those living in the north (the Magadan Region) [5], the authors also observed increased blood cortisol concentrations characteristic of new coming people with its significant fluctuations during the first 15 years of living in harsh conditions. Interestingly, no significant differences between migrants and the north born were revealed.

This research has presented cortisol levels that are significantly lower than those obtained earlier [5]: for example, the mean values of serum cortisol in new coming Magadan residents ranged from 489.9±18.8 to 604.8±25.0 nmol/l varying with periods of residence in the north (under 3 years, from 3 to 10 years and more than 10 years), which was significantly higher than in modern residents who migrated to the territory as the 0th generation. Similar differences were exhibited by the north born population of the last century in comparison with modern representatives of the 1st generation. As we studied modern residents of the Magadan Region, only representatives of the 2nd and 3rd generations demonstrated significantly high values of blood cortisol levels. Some authors consider cortisol as the hormone that preserves energy resources and ensures long-term reactions to stimuli of various etiologies [32]. Following on from that, we can see raised cortisol concentration with longer residence in the north as a normal reaction to acute stressors to maintain survival functions. [23, 32].

Table 2

Concentration of saliva cortisol depending on the generation of residence in the north

	Generation			Level of significance of differences		
	0	1	2-3	0-1	1-2	0-(2-3)
Morning	42.9±3.1	44.0±2.6	41.0±4.1	p=0.39	p=0.27	p=0.57
Evening	11.8±1.2	10.4±1.3	8.3±0.9	p=0.21	p=0.09	p<0.01

For the first time in the Magadan Region, the saliva cortisol level in men was suggested a predictor of the intensed functional reserves, and its daily biorhythmology was assessed as an informative factor on the imbalance which occurs in chronobiological rhythms owing to the specific light periodicity of our region. Saliva cortisol level has long been used as a marker of stress system activity and often assumed to quantify the effects of "biological stress" [20]. However, tracking cortisol daily curves – peak values 30 minutes after awakening and decreasing values to a nighttime minimum – is obviously more valuable than single-point levels, which is necessary to identify characteristics of the HPA function [15].

Currently, the fact that a daily cortisol level comes down by the evening time is considered as a fairly informative biomarker of inhibition of feedback in the HPA axis caused by cortisol, whereas its level upon awakening shows the sensitivity of adrenal receptors and their reactivity to the effects of adrenocorticotropic hormone (ACTH) [20]. The data in Table 2 confirm rather high mean values of the subjective morning saliva cortisol concentration through all the examined groups, which prove to not change in any reliance on a generation of residence in the north, thereby demonstrating the link to the increasing sensitivity of adrenal receptors.

Circadian fluctuations in cortisol, usually measured as the difference between the cortisol level at awakening and before bedtime, as well as cortisol reactivity to stress factors, are associated with the body health condition [11]. The smaller the difference between morning-evening cortisol levels, the worse the physical and mental health indicators [18]. The lowest variables of the difference were exhibited by the 0th generation men.

On the whole, the comparison study on the morning and evening saliva cortisol indicated that each examined group (0th, 1st, 2nd and 3rd generations) kept the circadian rhythm staying unchanged, despite the cortisol hypersecretion in the morning saliva test. The smallest cortisol levels in the evening sample were typical for men of the 2nd and 3rd generations, thereby showing an optimization of sensitivity to inhibition of the feedback of the HPA axis in men characterized by the longest residing experience in the northern conditions. The HPA axis performing activity is known to aim at relieving the adaptation of behavior over time, using past experience to prepare for expected challenges by changing system control points, shifting regulatory control and programming behavioral tendencies [25], as well as keeping hormonal levels within the safe limits by suppressing feedback [31, 24], which conforms with the evening cortisol test results in the examined men of the 2nd and 3rd generations.

It is believed that the universal mechanism of adaptation is the switching of steroidogenesis in the adrenal glands from the production of glucocorticoids to the secretion of androgens, in particular, DHEA-S [4] in order to provide a functional balance of catabolic and anabolic vectors of exchange; they are the stages of adaptive response [3]. The anti-stress mechanisms of DHEA-S include changes

in the metabolism of cortisol to its inactive metabolite cortisone, the resulting ratio of which redistributes energy and restores homeostasis [22]. In this research, the DHEA-S secretion tended to grow up in the increasing reliance on the period of the north residence, from the 0th to the 2nd and 3rd generations, which was probably a response to the raised blood cortisol concentration depending on the generation.

DHEA-S and cortisol have different and often antagonistic effects on each other [13] since these two hormones jointly regulate each other and their joint increase or imbalance determine the total effect on tissues; therefore the DHEA-S/cortisol ratio must be given emphasis in addition to absolute concentrations of both steroids [27]. The emphasis necessity is also backed up by the concept of anabolic balance which takes into account the ratio of anabolic and catabolic hormones and may indicate a susceptibility to diseases associated with stress and aging [13]. Nowadays, the ratio of the sulfated metabolite of DHEA and cortisol is used as an indicator of catabolic/anabolic balance [33]. High values of the ratio suggest an optimal anabolic balance, whereas low values are associated with chronic stress and declining health [33], with mortality [16, dementia [12], metabolic syndrome [16], and decrease in immunity after physical stress [30].

It is worth emphasizing the ratio of cortisol-DHEA as a key marker of human resistance to stress, because for adequate protection against stress, DHEA that works as a protector for the central nervous system must always prevail over cortisol which has a destructive effect on the hippocampus [22]. Calculation and interpretation of the DHEA-S/cortisol index based on the levels of the two antagonist hormones in the blood serum varying with the length of of residence in the north, have revealed that the 0th generation experience tension in the hypothalamus-pituitary-adrenal glands system, and the value of this index shows the expenditure of adaptive reserves whereas the 1st and 2nd-3rd generations exhibit the optimization of this system and keep their adaptive reserves.

Conclusion. Serum cortisol and dehydroepiandrosterone sulfate, their ratio, as well as evening saliva cortisol test have proved to be significant markers that reflect readjustments in a person's endocrine profile with the increasing length of residence in the north, which confirms the generally approved role of glucocorticoids in human adaptation to severe factors including climate extremes. This study has found pronounced tendency of activation of the hypothalamic-pituitary-adrenal axis in northern men who develop excessive cortisol production, report high mean values of DHEA-S and the ratio of DHEA-S/cortisol growing with the next generations of residence in the north. The numerical values of the DHEA-S/cortisol ratio indicate the stage of depletion of adaptive reserves experienced by male subjects of the 0th generation whereas representatives of the 1st, 2nd and 3rd generations tend to keep their adaptive reserves. In the process of adaptation to continuously unfavourable factors of the north, the cortisol hyper production promotes increased catabolic reactions that grow more intense with longer periods of adaptation. At the same time, powerful restorative anabolic processes are activated owing to the driving effect of DHEA-S in the population of northern men. This phenomenon requires further research for better understanding. It is worthy of note that the values of the DHEA-S/cortisol ratio growing from the representatives of the 0th generation to residents with longer residing experience in the north agree with the early identified optimization in physiological performance showing a strong link to the next generations, which allows us to consider the DHEA-S/cortisol indicator as a new criterion for the degree of adaptability.

For the first time, the assessment study on morning and evening saliva cortisol levels has been conducted in northern residents. Despite the morning cortisol hypersecretion, the subjective circadian rhythm in each examined group remained unchanged, which was observed along with a significant fall in the evening cortisol level in men of the 2nd and 3rd generations. That was caused by the pronounced sensitivity of adrenal receptors in the entire population and the changes for optimization of sensitivity to inhibiting the feedback of the HPA axis in men who experienced the longest residing in the north conditions.

Thus, adaptive adjustments to the living conditions of the north develop with the activation of the pituitary-adrenal cortex system and vary with the generation depending on the duration of residence in harsh climate conditions and weather extremes.

We have considered all other equal things and concluded that analysis of the DHEA-S/cortisol ratio indicator can be valuable since its variables identify specific adaptation readjustments that northerners report in the increasing reliance on their duration of residence in severe climatic and natural conditions. In general, this ratio serves as a marker of the degree of adaptation, as well as a highly informative criterion when selecting volunteers to work in extreme living conditions in the Arctic regions.

References

1. Averyanova IV, Maksimov AL Strategija adaptivnyh perestroek funkcional'nyh sistem ukorenjonnyh evropeoidov – urozhencev razlichnyh pokolenij Severo-Vostoka Rossii [Adaptation of functional systems in different generations of Caucasians in the North-East of Russia]. Ekologiya cheloveka [Human Ecology. 2023;30(4): 259-273. DOI: https://doi.org/10.17816/humeco321856 (In Russ.).]

2. Volkova NI, Bichkaeva FA. Analiz soderzhanija kortizola i gljukozy v syvorotke krovi u zhitelej arkticheskogo i priarkticheskogo regionov Severa zrelogo vozrasta [Analysis of the blood serum content of adult Arctic and Arctic North]. V sbornike: Global'nye problemy Arktiki i Antarktiki. Sbornik nauchnyh materialov Vserossijskoj konferencii s mezhdunarodnym uchastiem, posvjashhennoj 90-letiju so dnja rozhdenija akad. Nikolaja Pavlovicha Lavjorova [In the collection: Global Problems of the Arctic and Antarctic. Collection of scientific materials of All-Russia conference with international participation, dedicated to the 90th anniversary of academician Nikolay Pavlovich Laverov. 2020; 956–961 (In Russ.).]

3. Goncharov NP, Katsiya GV Degidrojepiandrosteron: biosintez, metabolizm, biologicheskoe dejstvie i klinicheskoe primenenie (analiticheskij obzor) [Dehydroepiandrosterone biosynthesis, metabolism, biological effects, and clinical use (analytical review). Andrologija i genital'naja hirurgija [Andrology and Genital Surgery. 2015;16(1): 13–22 (In Russ.).] doi: 10.17650/2070-9781-2015-1-13-22.

4. Zaychik ASh, Churilov LP Obshhaja patofiziologija (s osnovami immunopatologii): Patofiziologija. V 3-h tomah [General pathophysiology (with the basics of immunopathology): Pathophysiology. In 3 volumes. Ed. 4th. SPb: JeLBI-SPb. 2008 (In Russ.).]

5. Maksimov AL, Bartosh TP Invarianty normy gormonal'nogo statusa cheloveka na Severo-Vostoke Rossii: nauchn.-prakt. Rekomendacii [Invarianty normy gormonal'nogo statusa cheloveka na Severo-Vostoke Rossii: nauchn.-prakt. Rekomendacii. Magadan: SVNC DVO RAN, 1995. (In Russ.).]

6. Aleksanin SS, et al. Ocenka adaptacionnyh rezervov organizma muzhchin: teoreticheskie osnovy, tehnologija: metodicheskie im. A.M. Nikiforova MChS Rossii Variations of the norm of human hormonal status in the North-East of Russia: scientific –practical recommendations]. SPb.: IPC Izmajlovsky, 2022; 19 (In Russ.).]

7. Pirogov AB Nejrojendokrinnaja organizacija adaptacii zhitelej Severo-Vostoka Rossii [Neuroendocrine structure of adaptation of Russian north-eastern population] Bûlleten' fiziologii i patologii dyhaniâ [Bulletin of physiology and pathology of respiration] 1998;1:14-27. (In Russ.).]

8. Dogadin SA, et al. Soderzhanie insulina, S-peptida i kortizola v dinamike testa tolerantnosti k gljukoze u korennyh i prishlyh zhitelej Krajnego Severa [Levels of insulin, C-peptide, and hydrocortisone in the course of glucose tolerance test in indigenous population of the Extreme North and in newcomers]. Problemy jendokrinologii [Problems of Endocrinology]. 1997;43(2):7–10 (In Russ.).]

9. Hasnulin VI. Osobennosti psihojemocional'nogo stressa u zhitelej regionov severa i Sibiri s diskomfortnym klimatom pri vysokom i nizkom soderzhanii gormonov stressa v krovi [Features of emotional stress in the residents of the north and siberian regions with discomfortable climate at high or low content of hormones in the blood]. Mir nauki, kul'tury, obrazovanija [The world of science, culture, and education. 2012;5(36): 32–35 (In Russ.).]

10. Hasnulin VI, Hasnulin PV. Sovremennye predstavlenija o mehanizmah formirovanija severnogo stressa u cheloveka v vysokih shirotah [Modern concepts of the mechanisms forming northern stress in humans in high latitudes]. Jekologija cheloveka [Human ecology]. 2012;1:3–11 (In Russ.).]

11. Adam EK, Kumari M Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology. 2009;34:1423-1436. DOI: 10.1016/j.psyneuen.2009.06.011

12. Ferrari E, et al. Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. Eur J Endocrinol. 2001;144(4):319–329. DOI:10.1530/eje.0.1440319

13. Aldwin CM, Park CL, Spior. A Handbook of Health Psychology and Aging, Guilford Publications, Inc, New York. 2007: 119-141 DOI:10.1348/000712607X246

14. Ghiciuc CM, et al. Awakening responses and diurnal fluctuations of salivary cortisol, DHEA-S and α-amylase in healthy male subjects. Neuroendocrinol Lett. 2011; 32(4): 475–480.

15. Stalder T, et al. Clow Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology. 2016;63:414-432. DOI: 10.1016/j.psyneuen.2015.10.010

16. Phillips AC, et al. Cortisol, DHEA sulphate, their ratio, and all-cause and cause-specific mortality in the Vietnam Experience Study. Eur J Endocrinol. 2010;163(2):285–292. DOI: 10.1530/EJE-10-0299

17. de Bruijn R, Romero LM. The role of glucocorticoids in the vertebrate response to weather. General and Comparative Endocrinology. 2018;269:11-32, https://doi.org/10.1016/j.ygcen.2018.07.007.

18. Adam EK, et al. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. Psychoneuroendocrinology. 2017;83: 25-41. DOI: 10.1016/j.psyneuen.2017.05.018

19. Wilcox RR, et al. Diurnal patterns and associations among salivary cortisol, DHEA and alpha-amylase in older adults. Physiology & Behavior. 2014;129:11-16, https://doi.org/10.1016/j.physbeh.2014.02.012.

20. Abelson JL, et al. Do diurnal salivary cortisol curves carry meaningful information about the regulatory biology of the HPA axis in healthy humans? Psychoneuroendocrinology. 2023;150. https://doi.org/10.1016/j.psyneuen.2023.106031.

21. Homberger B, Jenni-Eiermann S, Jenni L Distinct responses of baseline and stress-induced corticosterone levels to genetic and environmental factors. General and Comparative Endocrinology. 2015;210: 46-54. https://doi.org/10.1016/j.ygcen.2014.09.020.

22. Kamin HS, Kertes DA Cortisol and DHEA in development and psychopathology. Horm. Behav. 2017;89: 69–85. doi: 10.1016/ j.yhbeh.2016.11.018.

23. King SL, Hegadoren KM Stress hormones: how do they measure up? Biol Res Nurs 2002;4: 92–103.

24. McEwen BS. Protective and damaging effects of stress mediators. N. Engl. J. Med. 1998;338:171-179. DOI:10.1056/NEJM199801153380307

25. McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. J. Neurosci. 2020;40:12-21. DOI:10.1523/JNEUROSCI.0733-19.2019

26. Møller N, Jørgensen JOL. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev. 2009;30:152-177. DOI:10.1210/ er.2008-0027

27. Maninger N, et al. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Frontiers in Neuroendocrinology. 2009;30(1): 65-91. https://doi.org/10.1016/j.yfrne.2008.11.002.

28. Obayashi K. Salivary mental stress proteins. Clin Chim Acta. 2013;425:196–201. doi: 10.1016/j.cca.2013.07.028

29. Oyola MG, Handa RJ. Hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes: sex differences in regulation of stress responsivity. The International Journal on the Biology of Stress. 2017;20: 1-19. DOI:10.1080/10253890.2017.1369523

30. Butcher SK, et al. Raised cortisol:DHEAS ratios in the elderly after injury: potential impact upon neutrophil function and immunity. Aging Cell. 2005;4(6):319–324. DOI:10.1111/j.1474-9726.2005.00178.x

31. Herman JP, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr. Physiol. 2016;6:603-621. DOI:10.1002/cphy.c150015

32. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress-responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrinol. Rev. 2000;21:55-89. DOI:10.1210/edrv.21.1.0389

33. Wolkowitz OM, Epel ES, Reus VI. Stress hormone-related psychopathology: pathophysiological and treatment implications. World J. Biol. Psychiatry. 2001;2:115-143. 10.3109/15622970109026799

SCIENTIFIC REVIEWS

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ACUTE ENDOTHELIAL CELL INJURY IN CARDIAC SURGERY PATIENTS UNDER ARTIFICIAL BLOOD CIRCULATION: THE CURRENT STATE OF THE PROBLEM

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This study summarizes the existing literature data on endothelial damage and its etiology, pathophysiology, and diagnosis in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Data on endothelial dysfunction and the history of its study were obtained from various medical databases, including PubMed, Cochrane, Elibrary, and Cyberleninka. We suggest that endothelial injury that occurs during and after the surgery predicts poor clinical outcomes, and should therefore be considered by anesthesiologists, intensivists, cardiac surgeons, and transfusion medicine specialists.

Keywords: endothelium, endothelial dysfunction, cardiopulmonary bypass (CPB), endothelial glycocalyx (eGCX).

Introduction. Numerous studies conducted in recent decades have demonstrated the crucial role of endothelium in physiological and pathological processes in the body. The endothelium constantly counteracts the effects of damaging factors and produces multiple biologically active substances thus preventing negative impacts of these factors on the vascular wall and regulating its functions.

However, in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), acute endothelial cell injury occurs, which significantly impairs vascular function and serves as a predictor of postoperative complications.

Over the past seven decades, there have been significant changes in the CPB technologies. CPB is a crucial component of open-heart surgery. New equipment and circuits made from biocompatible materials with minimal priming volumes have been developed, and techniques such as hemodilution, hypothermia, and myocardial protection have been implemented [1]. However, despite undeniable advances, CPB remains a non-physiological procedure that disrupts the homeostasis. This increases the risk of postoperative complications associated not only with blood coagulation disorders but also with damage to the functional vascular layer, i.e. the endothelium. Numerous experiments aimed at improving and enhancing the quality of perfusion involve modifications to available devices as well as the timely diagnosis of disorders that develop during and after perfusion.

General functions of endothelial cells, such as the regulation of vascular tone, hemostasis, adhesion, and angiogenesis, depend on the location of the blood vessels and the specific characteristics of their cells [3]. The morphological and physiological diversity of endothelial cells throughout the vascular tree is driven by their heterogeneity. Another factor contributing to the variation in structure and function of the endothelium is the endothelial glycocalyx (eGCX).

Our current understanding of the pathophysiology of certain disorders (including cardiovascular diseases, atherosclerosis, systemic autoimmune diseases, chronic kidney disease, diabetes mellitus, and multiple other conditions) recognizes endothelial dysfunction as a critical factor in the pathological process [4,5].

Patients undergoing heart surgery usually have pre-existing chronic vascular damage as a result of cardiovascular diseases, putting them at particularly high risk. Moreover, cardiovascular surgery itself results in acute endothelial injury, which contributes to the development of perioperative or postoperative multiple organ dysfunction syndrome (MODS). Mortality rates in patients with MODS exceed 50-80%, and this parameter does not tend to decrease over time [9].

The effects of acute endothelial cell injury associated with the use of cardiopulmonary bypass on the functions of organs and systems. Many researchers believe that markers of endothelial dysfunction in patients undergoing heart surgery are predictors of postoperative complications and poor clinical outcomes as a result of damage to various systems and organs [8, 12]. The endothelium has been shown to affect the vascular tone directly via the release of vasodilators and vasoconstrictors such as endothelin-1, which is the most potent vasoconstrictor. Ilker Mercan et al. (2020) showed that endothelin-1 levels were elevated in all patients who had undergone cardiac surgery with the use of CPB, which, in the authors' opinion, was a factor contributing to the development of endothelial cell injury [17]. Similar results were obtained in another study (Dorman et al., 2004) that demonstrated significantly elevated endothelin levels in a comparable patient cohort. Thus, plasma endothelin levels in patients recovering after coronary artery bypass grafting (CABG) with CPB increased to 200%. Meanwhile, in patients who underwent surgery without the use of CPB, the concentration of endothelin increased by no more than 50%. The authors believe that the significant elevation of endothelin as one of the markers of endothelial injury occurs for a number of reasons, such as platelet activation, myocardial reperfusion injury, endothelial injury associated with *pulsatile flow during CPB, as well as atrial and aortic cannulation. Moreover, a multiple-fold increase in the endothelin concentrations results in vasoconstriction of the pulmonary and graft vessels and is associated with a higher risk of complications during the postoperative period* [15]. These conclusions are supported by the study conducted by Mikheev et al. (2017) evaluating the endothelin-1 levels in patients who underwent CABG with CPB before and after surgical procedures. The authors revealed a direct correlation between plasma endothelin-1 levels and the severity of postoperative complications. It should be noted that patients who developed MODS after the surgery had a high level of endothelin before the surgery and maintained this high level in the postoperative period. According to the researchers, this correlation could indicate that high concentrations of endothelin-1 was a predictor for postoperative complications [7,8].

Another technique used to assess acute endothelial injury is the evaluation of endothelial vasomotor function after exposure to various vasoactive substances, most commonly acetylcholine and adenosine that cause NO-mediated vasodilation. Reduced vasodilation indicates the presence of endothelial dysfunction. Similar findings were observed in a study by Krispinsky et al. (2019), which included infants who had undergone surgical procedures with the use of CPB for their congenital heart defects. The authors applied acetylcholine and sodium nitroprusside delivered via iontophoresis. Immediately after surgery with CPB, vasodilation in response to acetylcholine administration was significantly decreased. Interestingly, no changes were observed in response to sodium nitroprusside administration in the postoperative period. The authors suggested that acetylcholine affected the endothelium, while nitric oxide (NO) acted on the vascular smooth muscle cells, whose function remained unchanged after the surgery. The researchers also measured blood creatinine levels in the postoperative period: they were elevated in all patients indicating the development of acute kidney injury (AKI), which was thought to be related to impaired renal vascular endothelial barrier [20].

Fouquet et al. (2020) obtained contrasting results, finding that endothelium-dependent vasodilation in response to intra-arterial administration of acetylcholine was maintained. Vasodilation was assessed using myography: a tungstyen introducer was placed intraoperatively inside the internal thoracic artery. The authors also investigated whether the pump type (roller or centrifugal) affected the acetylcholine-dependent vasodilation; however, the analysis showed no differences between two groups. The researchers also suggested that these results are related to the absence of a local inflammatory response despite the development of systemic inflammatory response during surgery with CPB [16].

Scientific literature described different methods for studying endothelial dysfunction by examining histological specimens and cell cultures. For example, a study by Marc Ruel et al. (2005) investigated patients who underwent CABG with or without CPB. For this purpose, endothelial progenitor cells were isolated and cultured from peripheral blood before and 24 hours after the surgery. The cells were then identified using double fluorescent lectin and lipoprotein staining and examined under a microscope. The researchers concluded that CABG with or without CBP resulted in an increased number of endothelial progenitor cells with equivalent proliferative activity. However, both the migratory activity of endothelial progenitor cells and the postoperative viability of endothelial

progenitor cells (adjusted for the baseline preoperative level) were higher in patients who underwent CABG without CPB compared to those who underwent CABG with CPB. Endothelial progenitor cells in patients who underwent CABG with CPB were less viable after the surgery compared to baseline, whereas the patients who underwent CABG without CPB demonstrated the opposite results. The authors concluded that CABG without CPB resulted in fewer cardiovascular complications compared to CABG with CPB [19]. N. Dekker et al. also conducted a cell culture study. Renal and pulmonary microvascular cells were incubated with patient plasma, and the endothelial barrier function was assessed in vitro using electric cell-substrate impedance sensing. The researchers demonstrated that the decrease in the renal and pulmonary endothelial barrier function (i.e. hyperpermeability) was significantly more pronounced in patients who underwent surgical procedures with CPB and was maintained for at least 72 hours after the surgery. According to the authors, this abnormal endothelial hyperpermeability was associated with increased levels of circulating angiopoietin-2 in this patient cohort. The study proved that the angiopoietin/tyrosine kinase-2 system was involved in the development of endothelial dysfunction in patients who had undergone surgical procedures with CBP, which represents a new step of scientific research in this field [22,23].

The function and state and endothelial glycocalyx in patients undergoing surgery with CPB. On the surface of the endothelium, there is a complex multicomponent system called the glycocalyx. In healthy subjects, the blood contains low concentrations of endothelial glycocalyx (eGCX) molecules; however, under pathological conditions, this structure can be partially or completely lost, causing its components to be released into the bloodstream in large quantities. Such molecules include syndecan-1, hyaluronan, heparan sulfate, VE-cadherin, and endocan [13]. Wu Qiaolin et al. (2019) assessed plasma concentrations of syndecan-1, heparan sulfate, and hyaluronan as markers of glycocalyx damage before and after surgery using CPB. The researchers came to an unambiguous conclusion regarding a significant increase in these biochemical markers as a sign of endothelial glycocalyx degradation [18]. A study conducted by Florian Brettnera (2017) also evaluated the markers of eGCX damage in patients undergoing surgery with and without CPB. The results showed that in both groups, the concentration of these markers increased regardless of the type of surgical procedures and the use of CPB. However, the patients in the CPB group had higher plasma levels of these markers. The researchers attributed this increase not only to the negative impact of CPB on eGCX but also to the presence of chronic comorbidities in this cohort, which is an important factor influencing the postoperative recovery [28]. Robich M. et al. obtained similar data when investigating the impact of CPB time on the endothelial glycocalyx degradation. The study revealed a significant correlation between the duration of CPB exposure and blood levels of syndecan-1 using correlation analysis. The scientists also pointed out that patients undergoing surgical procedures with CPB could benefit from the development of therapy aimed at removing endothelial glycocalyx degradation products from the blood [25]. Moreover, the measurement of blood levels of syndecan-1 will help predict the development of early postoperative complications, which was demonstrated by Hye-Bin Kim et al. who investigated the connection between blood syndecan-1 concentrations and the development of acute kidney injury (AKI) during the early postoperative period in patients undergoing valve replacement surgery using CPB. The study showed that the syndecan-1 levels over 90 ng/mL could reliably predict the development of AKI in this patient cohort [21].

There have been studies of eGCX using dark-field microscopy, is one of the main non-invasive techniques used for *in vivo* studies of glycocalyx in humans. In a study by Claudia Nussbaum et al., 2015, this method was used in children who underwent heart surgery with and without CPB. The glycocalyx thickness was assessed by measuring the perfused boundary region of the sublingual microvessels before and after the surgery. Additionally, the microcirculatory flow index and the vessel density were assessed. After the surgery using CPB, the thickness of the glycocalyx significantly decreased, gradually returning to baseline values in the postoperative period. The authors also reported a transient decrease in microcirculatory parameters [24]. Similarly, Dekker [29] used this method to assess eGCX in a study of adult patients who underwent CABG with CPB. Perfusion of the sublingual micro-vessels was measured before, during, and after CPB, followed by an analysis of the perfused vessel density and the perfused boundary region (the parameter inversely related to the glycocalyx thickness). This study revealed that the use of *phosphorylcholine* coating of extracorporeal *circuits was associated with better* preservation of the endothelial glycocalyx compared to heparin-coated circuits, while the microcirculatory perfusion was impaired to an equal extent in both groups. Therefore, microcirculatory perfusion disorders caused by CPB do not seem to depend on the coating type.

Our literature review suggests that endothelial dysfunction, as well as eGCX degradation, may predispose patients undergoing cardiac surgery to postoperative complications, and also serve as markers of progressive organ damage associated with the use of CPB.

Conclusion: The analysis of scientific publications indicate that endothelial injury is a primary abnormality associated with the use of CPB is endothelial injury. Factors affecting the endothelial function include hemodynamic factors (such as blood pressure and shear rate), along with blood gas composition, hormones, and mediators (such as catecholamines, vasopressin, acetylcholine, endothelin, bradykinin, angiotensin II, thrombin, cytokines, lipoproteins, endotoxins, and other molecules).

Thus, despite the essential role of CPB in heart surgery practice, this method produces certain negative effects on the body. These effects include contact activation of white blood cells and the blood coagulation system, blood cell damage, hyperoxia, hypothermia, and hemodilution. The non-pulsatile blood flow is also one of the additional damaging factors associated with CPB. Pulsatile blood flow is of constant interest in clinical perfusion science because, according to current concepts, it contributes to the normalization of total peripheral vascular resistance, improves tissue perfusion, increases oxygen extraction, and reduces the level of stress hormones, and produces a beneficial effect on renal and cerebral blood flow [10,26]. However, it is not always possible to choose a blood flow mode in surgical practice or to rule out the influence of other adverse factors on the patient's body. Therefore, researchers are evaluating possible ways to improve clinical outcomes by studying important pathophysiological patterns and methods to influence them. This explains the numerous studies of endothelial dysfunction in patients undergoing heart surgery with or without CPB [6; 11].

Despite the growing number of clinical studies evaluating the number of circulating markers of endothelial cell injury, evidence of a causal relationship between endothelial barrier dysfunction and the development of postoperative compli-

cations is scarce and mainly limited to experimental models [27,23]. However, patients with evident endothelial injury must receive pharmaceutical therapy in the postoperative period. Thus, a study by Yakubtsevich et al. [14] demonstrated the positive effects of therapy with angiotensin-converting enzyme inhibitors, calcium sensitizers, phosphodiesterase-3 inhibitors, and beta-blockers on the endothelial function in patients underdoing heart surgery.

Patients undergoing off-pump CABG are also prone to the development of endothelial dysfunction, as was shown in a study by Shlyk I.F. However, CABG with CPB is a risk factor for more severe intra- and postoperative complications compared to off-pump CABG [2, 11]. Endothelial dysfunction developing during heart surgery requires more thorough evaluation and treatment. Thus, Kornev et al. reported that minimally invasive CPB was associated with less pronounced endothelial dysfunction compared to that occurring when using the conventional extracorporeal circuit. Therefore, the use of minimally invasive CPB systems or the choice of off-pump surgical techniques significantly reduces the risk of developing ED in the postoperative period.

Endothelial dysfunction is closely linked to the development of complications during and after heart surgery. Such diagnostic methods as assessment of endothelial vasomotor function using Doppler color flow imaging, evaluation of endothelial glycocalyx using *dark-field* imaging, laboratory tests and histological examination can be used since they help reliably evaluate the condition of the vascular wall. These tests expand our understanding of microcirculatory dysfunction that occurs in patients receiving surgical care with and without CPB. Early diagnosis of this disorder can contribute to a more thorough approach to choosing the surgical technique. Raising awareness among healthcare providers (especially anesthesiologists and critical care specialists) about the importance and the diagnostic methods to evaluate endothelial dysfunction is necessary since even mild endothelial injury may have serious consequences (i.e. multiple organ failure). The implementation of methods for evaluation of the endothelial structure and function (including those of the eGCX) will aid in the search for markers and predictors of poor clinical outcomes in patients undergoing cardiac surgery with CPB. This will help assess the patient's condition during the perioperative period and predict the development of postoperative complications.

References

1. Averina TB. Iskusstvennoe krovoobrashhenie [Extracorporeal circulation]. Annaly` xirurgii [Annals of surgery. 2013; 2: 5-12 (In Russ.).]

2. Bokeria LA, Milievskaya EB, Skopin AI. Serdechno-sosudistaya xirurgiya. Iskusstvennoe krovoobrashhenie v Rossijskoj Federacii – 2018 god. [Cardiovascular surgery. Extracorporeal circulation in Russian Federation – 2018]. Grudnaya i serdechno-sosudistaya xirurgiya [Russian Journal of Thoracic and Cardiovascular Surgery. 2019; 61(4): 255–264 (In Russ.).] doi: 10.24022/0236-2791-2019-61-4-255-264

3. Vasina LV, Vlasov TD, Petrishhev NN. Funkcional`naya geterogennost` e`ndoteliya (obzor) [Functional heterogeneity of the endothelium (the review)]. Arterial`naya gipertenziya [Arterial hypertension. 2017; 23(2): 88-102 (In Russ.).] doi.org/10.18705/1607-419X-2017-23-2-88-102

4. Vasina LV, Petrishhev NN, Vlasov TD. E`ndotelial`naya disfunkciya i ee osnovny`e marker [Markers of endothelial dysfunction]. Regionar. krovoobrashhenie i mikrocirkulyaciya [Regional blood circulation and microcirculation. 2017; 16 (1): 4–15 (In Russ.).] doi: 10.24884/1682-6655-2017-16-1-4-15.

5. Vlasov TD, Nesterovich II, Shiman`ski DA. E`ndotelial`naya disfunkciya: ot chastnogo k obshhemu. Vozvrat k «staroj paradigme»? [Endothelial dysfunction: from the particular to the general. Return to the «Old Paradigm»?]. Regionar. krovoobrashhenie i mikrocirkulyaciya [Regional blood circulation and microcirculation. 2019; 18(2): 19–27 (In Russ.).] doi: 10.24884/1682-6655-2019-18-2-19-27.

6. Kornev VI, Kalinina NM, Startseva ON. Vliyanie mini-invazivnogo iskusstvennogo krovoobrashheniya na pokazateli e`ndotelial`noj disfunkcii u kardioxirurgicheskix bol`ny`x [Effect of minimally invasive extracorporeal circulation on endothelial dysfunction in cardiac surgery patients]. Kazanskij medicinskij zhurnal [Kazan medical journal. 2020; 101(2): 279–283 (In Russ.).] doi: 10.17816/KMJ2020-279.

7. Mikheev SL, et al. Kompleksnaya ocenka markyorov disfunkcii e`ndoteliya v prognozirovanii isxoda operacij v koronarnoj xirurgii [Complex evaluation of endothelial dysfuncion markers for prediction of outcomes in coronary surgery]. Klinicheskaya medicina [Clinical medicine. 2017; 95(11): 1026-1034 (In Russ.).] doi. org/10.18821/0023-2149-2017-95-11-1026-1034

8. Mikheev SL, et al. Rol` markerov e`ndotelial`noj disfunkcii v prognozirovanii isxodov kardioxirurgicheskix vmeshatel`stv u pacientov s ishemicheskoj kardiomiopatiej [The role of markers of endothelial dysfunction in predicting the outcomes of cardiac surgery in patients with ischemic cardiomyopathy]. Tezisy` IV Evrazijskogo kongressa kardiologov [Abstracts of the IV Eurasian Congress of Cardiologists. 2016; 3:155-156 (In Russ.).]

9. Babaev MA, et al. Sindrom poliorgannoj nedostatochnosti u bol`ny`x posle operacij v usloviyax iskusstvennogo krovoobrashheniya [The multiple organ failure syndrome after cardiac surgery with artificial blood circulate]. Xirurgiya. Zhurnal im. N.I. Pirogova [Pirogov Russian Journal of Surgery. 2013; 2:119-123 (In Russ.).]

10. Shiganov MYu, et al. Sravnenie pul`siruyushhego i nepul`siruyushhego rezhimov iskusstvennogo krovoobrashheniya pri operaciyax aortokoronarnogo shuntirovaniya [Comparison of pulsating and non-pulsating modes of artificial blood circulation during coronary artery bypass surgery]. Vestnik xirurgii [Bulletin of surgery. 2008; 4: 26-29 (In Russ.).]

11. Shlyk IF. Citokinovy`j profil` i sostoyanie e`ndoteliya u pacientov s ishemicheskoj bolezn`yu serdcza i razlichny`m isxodom koronarnogo shuntirovaniya. // Kubanskij nauchny`j medicinskij vestnik. 2019. T. 26, №5. S. 96–104. doi. org/10.25207/1608-6228-2019-26-5-96-104.

Shlyk I.F. Cytokine profile and endothelial condition in patients with coronary artery disease and different outcomes of coronary bypass surgery. // Kuban Scientific Medical Bulletin. 2019. V. 26. N.5. P. 96-104. doi. org/10.25207/1608-6228-2019-26-5-96-104.

12. Martynov AI, et al. E`ndotelial`naya disfunkciya i metody` ee opredeleniya [Endothelial dysfunction and methods of its determination. RKZH. 2005; 4 (In Russ.).]

13. Vlasov TD, et al. E`ndotelial`ny`j glikokaliks: metody` issledovaniya i perspektivy` ix primeneniya pri ocenke disfunkcii e`ndoteliya [The endothelial glycocalyx: research methods and prospects for their use in endothelial dysfunction assessment]. Regionarnoe krovoobrashhenie i mikrocirkulyaciya [Regional blood circulation and microcirculation. 2020; 19 (1): 5-16 (In Russ.).] doi: 10.24884/1682-6655-2020-19-1-5-16.

14. Yakubtsevich RE, Krotkov KO. Sovremeny`e vozmozhnosti medikamentoznoj korrekcii e`ndotelial`noj disfunkcii u pacientov s ishemicheskoj bolezn`yu serdcza v intraoperacionnom i rannem posleoperacionnom periode posle revaskulyarizacii miokarda [Modern possibilities of drug correction of endothelial dysfunction in patients with coronary artery disease in the intraoperative and early postoperative period after myocardial revascularization]. Zhurnal Grodnenskogo gosudarstvennogo medicinskogo universiteta [Journal of Grodno State Medical University. 2022; 20 (1): 13-20 (In Russ.).] https://doi.org/10.25298/2221-8785-2022-20-1-13-

15. Fouquet O, et al. Cardiopulmonary bypass and internal thoracic artery: Can roller or centrifugal pumps change vascular reactivity of the graft? The IPITA study: A randomized controlled clinical trial. PLOS ONE 2020. V.15(7). doi:10.1371/journal.pone.0235604

16. Braz J, Mercan I. et al. Comparison between the Effects of Bretschneider's HTK Solution and Cold Blood Cardioplegia on Systemic Endothelial Functions in Patients who Undergo Coronary Artery Bypass Surgery: a Prospective Randomized and Controlled Trial. Cardiovasc. Surg. 2020;1;35(5):634-643. doi: 10.21470/1678-9741-2019-0327.

17. Qiaolin W, et al. Correlation between acute degradation of the endothelial glycocalyx and microcirculation dysfunction during cardiopulmonary bypass in cardiac surgery. Microvascular Research 2019; 124(37-42). doi:10.1016/j.mvr.2019.02.004]

18. Ruel M, et al.]Effects of off-pump versus on-pump coronary artery bypass grafting on function and viability of circulating endothelial progenitor cells./ // J. Thorac. Cardiovasc. Surg. 2005 V.130(3):633-9. doi: 10.1016/j.jtcvs.2005.01.013.

19. Krispinsky LT, et al. Endothelial-Dependent Vasomotor Dysfunction in Infants After Cardiopulmonary Bypass. Pediatr Crit Care Med. 2020; 21(1):42-49. doi: 10.1097/PCC.0000000000002049

20. Kim HB, et al. High Preoperative Serum Syndecan-1, a Marker of Endothelial Glycocalyx Degradation, and Severe Acute Kidney Injury after Valvular Heart Surgery. J Clin Med. V. 2020 Jun 10;9(6):1803. doi: 10.3390/jcm9061803.

21. Dekker N, et al. Microcirculatory perfusion disturbances following cardiac surgery with cardiopulmonary bypass are associated with in vitro endothelial hyperpermeability and increased angiopoietin-2 levels. Crit Care.

2019; 117. doi.org/10.1186/s13054-019-2418-5.
22. Dekker N, et al. Microvascular Alterations During Cardiac Surgery Using a Heparin or Phosphorylcholine-Coated Circuit. Journal of Cardiothoracic and Vascular Anesthesia V. 34. 2019. doi:10.1053/j.jvca.2019.10.012
23. Perturbation of the microvascular glycocalyx and perfusion in infants after cardiopulmonary bypass. / C. Nussbaum [et al.] // The Journal of Thoracic and Cardiovascular Surgery. 2015. V. 150(6). P.1474-1481. doi.org/10.1016/j.jtcvs.2015.08.050.
24. Robich M, et al. Prolonged Cardiopulmonary Bypass is Associated With Endothelial Glycocalyx Degradation. J. Surg. Res. 2020 V. 251:287-295. doi: 10.1016/j.jss.2020.02.011.
25. Ugenti V, et al. Reduced Systemic Nitric Oxide Bioavailability Parallels Microvascular Endothelial Dysfunction during Cardiopulmonary Bypass. Arq. Bras. Cardiol. 2021 V.117(3):554-7
26. Koning NJ, et al. Reduction of vascular leakage by imatinib is associated with preserved microcirculatory perfusion and reduced renal injury in a rat model of cardiopulmonary bypass. Br. J. Anaesth. 2018 V. 120(6):1165-75.
27. Brettner F, et al. Vascular Endothelial Dysfunction during Cardiac Surgery: On-Pump versus Off-Pump Coronary Surgery. Eur Surg Res. 2017; 58(5-6): 354-368. doi: 10.1159/000480431.
28. Dekker N, et al.] Vasculotide, an angiopoietin-1 mimetic, reduces pulmonary vascular leakage and preserves microcirculatory perfusion during cardiopulmonary bypass in rats. Br J Anaesth. 2018; 121(5): 1041-1051. doi.org/10.1016/j.bja.2018.05.049

POINT OF VIEW

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RESULTS OF PRIMARY DRAINAGE OF THE ABDOMINAL CAVITY IN PREMATURE INFANTS WITH NECROTIZING ENTEROCOLITIS

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For newborns with severe stages of necrotizing enterocolitis, peritoneal drainage should be used as initial treatment, as peritoneal drainage can provide initial stabilization; most of these infants will require subsequent laparotomy. In premature infants with necrotic enterocolitis, peritoneal drainage, reducing intra-abdominal pressure, improves lung and liver function and stabilizes the position, performs a kind of detoxification by reducing the level of toxic fluid accumulated in the abdominal cavity; determines the nature of the effusion, that is, the presence of odorous, fibrous secretions indicating necrobiosis of the intestinal wall, thereby definitively diagnoses the perforation. The overall survival rate when using peritoneal drainage appears to be higher, and it should be assumed that it is preferable to use peritoneal drainage in severe stages of necrotizing enterocolitis before laparotomy to reduce intra-abdominal pressure and sanitize the abdominal cavity, thus avoiding complications associated with direct laparotomies.

Keywords: premature newborns, necrotic enterocolitis, primary peritoneal drainage, intra-abdominal pressure.

Introduction. Percutaneous injection of Penrose drainage into the abdominal cavity of newborns with intestinal perforation was first described by Ein SH et al. [7].

Initially, this procedure was recommended as a temporary measure for premature infants (PI) in critical condition with perforation of the intestinal wall caused by necrotizing enterocolitis. It was hoped that the drainage of air and feces collected in the abdominal cavity as a result of perforation would alleviate the symptoms of abdominal syndrome and sepsis and allow the child to better tolerate subsequent laparotomy [5]. Back in 2000, Cass DL and co-authors reported the use of peritoneal drainage (PD) for 15 years in PI with very light weight as an initial treatment measure for isolated or complicated intestinal perforation caused by necrotic enterocolitis (NEC) [6]. The results of NEC treatment using PD turned out to be unexpected - they were the same, and possibly more effective than when treated with immediate laparotomy [3.19]. Some researchers recommend PD primarily at the stages of NEC, when perforation is noted with extremely low weight of PI. In general, clinicians attach great importance to PD in severe forms of NEC. PD, even in the severe stage of NEC at an early stage, can help in the resuscitation and recovery of a seriously ill child, and in some cases can become a decisive surgical intervention [8,9].

In the UK, surgeons use PD to stabilize the general condition in 95% of patients and as a radical treatment in 58%. Most surgeons use PD in newborns of any weight, while others do not recommend it in newborns with a body weight of less than 1000 g [14].

Other recent studies in the literature have not found significant benefits or harms of PD compared to laparotomy [16].

Thus, there is no consensus in the literature on whether laparotomy should be performed after PD or without it.

The aim of the study was to use a randomized clinical trial to determine how primary peritoneal drainage affects the dynamics of intra-abdominal pressure and the outcome of treatment of premature newborns with severe necrotizing enterocolitis with very low birth weight.

Materials and methods. The prospective study included 87 premature newborns (PN) who were examined and treated with a diagnosis of necrotic enterocolitis in the intensive care unit of the Farajeva Research Institute of Pediatrics (Baku, Azerbaijan Republic) in the period from 2010 to 2021. Among them, 13 (14.95%) had extremely low body weight, 22 (25.29%) had very low body weight and 44 (50.57%) had low body weight (the minimum body weight averaged 650 g). Only 8 (9.19%) PN had a maximum body weight of 4,200 g.

Of the total number of newborn boys, there were 68 (78.16%), girls – 19 (21.84%). The criteria for inclusion in the study were pathology of the gastrointestinal tract and clinical manifestations of necrotizing enterocolitis.

The presence of NEC was established by anamnestic, clinical, laboratory, mi-

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crobiological, instrumental and radiation (X-ray, sonography) research methods. Data on the number of platelets and leukocytes per day of perforation and X-ray data on intestinal bloating, intestinal pneumatosis, gas in the portal vein, "gasless abdomen" and pneumoperitoneum were also collected. The outcome variables studied included: physiological improvement during the first 24 hours, 30-day period, survival and long-term survival. Based on the results of the studies, infants were divided into 2 groups: group 1 – with suspected NEC perforation – 57 (65.52%) patients and group 2 – with an established diagnosis of intestinal perforation – 30 (34.48%) patients; PD was performed in group 1, laparotomy in group 2. According to the prevalence of the disease during intraoperative examination, we determined focal damage in 43 patients, multifocal damage in 27 patients, damage to all loops (pancreatic) in 17 patients. Some preoperative indicators of patients with NEC are shown in Table 1.

Intraperitoneal pressure was measured using a catheter inserted into the bladder using the ND 500/75 device (Triton, Russia) RM304.00.000RE (invasive low pressure device "Meter").In the case of pneumoperitoneum, if the patient was in a serious physiological condition and was not suitable for laparotomy, we performed emergency laparocentesis (peritoneal drainage) with peritoneal dialysis and performed laparotomy after stabilization.

We determined the day of life on which abdominal pathology was suspected and on which the PD procedure was performed, the duration of the installation of peritoneal drains and the time from PD to the beginning and achievement of full feeding. To perform laparocentesis, a 5 mm long skin incision was made after treatment of the surgical field at a point 0.5-1.0 cm above the iliac wing in the right or left inguinal region under local anesthesia with 0.25% novocaine solution. All patients underwent peritoneal drainage in the neonatal intensive care unit. In all patients, air and intestinal contents were evacuated through the wound and Penrose drainage with a diameter of 6 mm was inserted into the abdominal cavity and fixed on the skin of the abdomen. During the next 24-48 hours, the patients were closely monitored. Laparotomy was performed with any signs of clinical deterioration.

The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study was approved by the Regional Ethics Committee of the K. Faradzhova Research Institute of Pediatrics. All parents of sick children received full information about the study and signed an informed consent for voluntary participation in it.

Statistical comparisons between the groups were carried out using the Student's two-way t-test and Fisher's exact test, where necessary, and a p value of less than 0.05 was considered significant.

The results of the study and their discussion. Among 87 infants with NEC 2B, 3A and 3B, peritoneal drainage with peritoneal dialysis was performed in 57 cases; 30 premature infants with severe NEC were operated without PD.

Table 2 shows the effect of PD on the dynamics of intra-abdominal pressure (IAP) among premature infants at various stages of NEC severity.

As can be seen from Table 2, as the severity of NEC increased, the level of IAP continued to rise: 22 cmWC at NEC 2B, 37 cmWC at NEC 3A and 50 cmWC at NEC 3B.

Peritoneal drainage and constant direct monitoring of intra-abdominal pressure were performed in 20 cases among premature infants at the NEC 2B stage, in patients with NEC 3A - in 25 cases and in patients with NEC 3B – in 18 cases.

Among 87 PN diagnosed with NEC in 30 (34.48%) cases, infants underwent laparotomy without performing a preliminary PD. Table 3 shows the nature of the

Table 1

Some preoperative indicators of patients with NEC (n=87)

Preoperative indicators	Premature infants with NEC with suspected perforation	Premature infants with NEC with a confirmed diagnosis of perforation	p
Baby's body weight (g)	949 ± 330 (550-1.465)	708 ± 187 (320-910)	< 0. 05
Gestational age (weeks)	27.8 ± 2.2 (24-30)	25.6 ± 1.6 (24-27)	< 0.05
Cumulative Apgar scores	15.2 ± 2.1	12.9 ± 2.6	< 0.05

Table 2

The influence of PD on the dynamics of IAP among premature infants at various stages of NEC severity

NEC stages (n=87)	The number of PD, 57 (%)	Intra-abdominal pressure (cmWC)	
		Before PD	After PD
2B n=40	20(50)	22.3±5.1	16.2±4.1
3A n=29	25(86.2)	37.0± 3.2	22.0± 2.2
3B n=1 8	12(66.67)	50.0±4.5	37.0± 3.3

Table 3

The nature of the surgical methods used and mortality in premature infants with NEC

Methods of operations (n=87)	PD+laparotomy n=57			Laparotomy without prior PD n= 30		
	NEC 3A n=25	NEC 2B n=20	NEC 3B n=12	NEC 3A n=4	NEC 2B n=20	NEC 3B n=6
Intestinal resection+anastomosis (т=9)	1	5	1		2	
Intestinal resection + enterostomy (п=14)	2	5	2	1	2	2
Intestinal resection+ colostomy (п=8)	1	-	1	1	3	2
Intestinal resection + T.anastomosis + ileostomy (п=6)	3	2	1			
ileostomy (п=43)	17	8	6	1	9	2
Jejunostomy (п=7)	1	-	1	1	4	
Lethality n=19(21,84%)	3(12%)	3(15%)	4(33.3%)	4(100%)	5(25%)	3(50%)

operations performed and the mortality rate.

As can be seen from Table 3, among 29 patients with NEC 3A, IAP was at the level of 37.0± 3.2 cm; of these, 25 (86.2%) premature infants had PD before laparotomy, after which it was possible to reduce IAP to 22.0± 2.2 cm followed by laparotomy; in the postoperative period, 25 of these infants died 3 (12%) patients. 4 (13.8%) newborns with NEC 3A were operated without prior PD, and all of them died.

PD was applied in 40 patients with NEC 2B in 20 (50%) cases due to high IAP (22.3±5.1 cm), after which IAP decreased to 16.2±4.1 cm, which allowed laparotomy to be performed in more favorable conditions; postoperative mortality among these 20 infants with NEC 2B was 15% (3 babies). Of this group, in 20 cases, premature infants with NEC 2B were taken for surgery without prior PD; 5 of them died after surgery ((25%) children

In patients with NEC 3B, IAP reached 50.0± 4.5 cm before surgery. In 6 cases, they were taken for surgery for a perforated NEC without prior PD and 3 (50%) of the patients died after the operation. In the remaining 12 cases with NEC 3B, PD was used, which contributed to a decrease in IAP to 37.0± 3.3 cm; 4 (33.3%) of these 12 patients died after laparotomy.

Thus, the mortality rate among 57 premature infants with NEC who received primary peritoneal drainage followed by laparotomy was 21.05% (12 patients), whereas in those operated without prior peritoneal drainage, the mortality rate was 23.33% (7 patients). Necrotic enterocolitis (NEC) is a life—threatening disease of the digestive system that occurs in the neonatal period. NEC is difficult to diagnose at an early stage, and the prognosis is unfavorable [20].In premature infants with low body weight, when symptoms related to necrotic enterocolitis appear, the primary task is to determine the severity of the pathological process and the tactics of the treatment method. Since such children, due to prematurity, along with the underlying disease, have impaired lung function, circulatory and adrenal insufficiency, as well as other immaturity diseases, the risks of laparotomy are significant. When deciding on the need for a surgical treatment method, in addition to anesthesiological problems in such newborns, it is necessary to maintain body temperature, fluid balance and gas exchange; In addition, these patients have surgical problems in solving the elimination of the source of peritonitis, creating intestinal anastomoses or stomas and avoiding damage to the abdominal organs. [11,21]. Surgical stages of NEC occur on average in 50% of sick children. The mortality rate varies from 20 to 30%; in the group of children who underwent surgery, it is up to 50% [1,11]. The progressive course of the disease is considered to be the clinical and laboratory deterioration of the condition of a child with a previously diagnosed NEC (stage I and II), as well as the lack of clinical and laboratory effect of the therapy and the appearance of signs of transmural infarction / perforation of the intestinal wall. In these cases, such signs of transmural infarction of the intestinal wall as edema, hyperemia and (or) cyanosis of the anterior abdominal wall; pronounced/ increasing bloating; increasing and (or) refractory to intensive care metabolic acidosis; severe thrombocytopenia and repeated positive blood cultures; static bowel loop on a series of radiographs; an increase in ascites should be carefully weighed, gas along the course of the portal vessels of the liver according to the results of ultrasound. When detecting free gas in the abdominal cavity against the background of these symptoms, perforation of the intestinal wall should be recognized. It is for the adequate treatment of premature infants with the presence of the above-mentioned symptom complexes that Ein SH, et al. proposed peritoneal drainage as an alternative method to therapeutic ones. After the use of PD in some patients with moderate NEC severity against the background of conservative therapy, the condition progressively improved and in patients with severe NEC it was possible to achieve adequate indicators of the cardiovascular system for surgical interventions. [7]

In most institutions, the procedure was selectively applied to the youngest premature infants (from 750 to 1000 g) who cannot undergo laparotomy immediately[4].

Roy A. and the co-authors note that pneumoperitoneum, although it is the only absolute proof of intestinal perforation, cannot predict the degree of the disease. PD is a useful stabilizing procedure, but the presence of any of the NEC criteria associated with severe disease requires a quick decision in favor of laparotomy. However, the absence of these signs cannot exclude extensive or progressive NEC, and the lack of improvement after peritoneal drainage also requires emergency laparotomy, regardless of birth weight or gestational age [18].

According to Ein SH, et al., of 77 premature infants diagnosed with NEC, thirty-seven patients were treated with peritoneal drainage, and 40 with primary laparotomy. Among patients treated with PD, almost one third recovered completely without the need for laparotomy, and the overall survival rate was 56%. Ein SH, et al. concluded that PD should only be used in premature infants weighing less than 1,500 g and with radiologically confirmed NEC; they also warned that PD may be useless in phlegmon and that laparatomy should be performed in the absence of improvement within 24 hours after PD.[7]

Subsequently, other clinicians showed similar results. However, intestinal perforation in newborns may occur without signs of NEC [12, 20].

Compared with NEC-related perforation, isolated intestinal perforation is more common in most premature infants with the lowest index on the Apgar scale.

Cass DL,et al. report that in newborns who have undergone PD, the course of isolated perforation usually improves and subsequent laparotomy is required only in rare cases for resection of stricture or persistent fistula. However, for another group of patients who underwent PD for NEC perforation, the results were much worse. Although PD allowed many of these infants to survive for a month, most of them eventually died due to complications from the lungs, liver, and ongoing sepsis. Although some may object that it might have been better to help these newborns at an early age, to have laparotomy and sanitation of necrotic tissues, but most of these patients had pancreatic necrosis, and the survival rate does not differ much from that reported by others with similar pancreatic diseases[6].

For newborns with perforation caused by necrotizing enterocolitis, peritoneal drainage can provide initial stabilization. However, most of these infants will require subsequent laparotomy, and their long-term survival remains low. We conclude that peritoneal drainage should be used as an initial treatment for all newborns with low birth weight and isolated intestinal perforation.

According to Li W et al (2022), there is no significant difference in mortality between peritoneal drainage and laparotomy as an initial surgical intervention[10].

Rao SC, et al. believe that the standard surgical treatment for young children with perforative necrotic enterocolitis (NEC) or spontaneous intestinal perforation (SIP) is laparotomy with resection of a necrotic or perforated segment of the intestine[17]. Peritoneal drainage is an alternative approach to the management of such children.

Other clinicians used peritoneal drainage more often as an initial surgical procedure for the treatment of spontaneous intestinal perforation compared with surgical NEC; mortality was higher in infants who initially underwent peritoneal drainage compared with those who underwent primary laparotomy[15].

According to Mishra P, co-authors (2015), primary PD is still useful for patients without signs of necrotizing enterocolitis [13].

Argumosa Salazar Y, et al. performed primary laparotomy on two patients, 10 patients underwent peritoneal drainage followed by laparotomy, and 3 patients underwent peritoneal drainage. They found that survival was higher in the group that underwent the first laparotomy with an overall mortality rate of 32% [2].

We analyzed the results of the examination and treatment of 87 premature infants with severe forms of NEC 2B, 3A and 3B (according to the classification of J.M. Bell and co-authors in the modification of M. S. Walsh and R.M. Kliegman).

In the diagnosis and selection of treatment methods for premature infants with suspected NEC, we followed the generally accepted protocol for this pathology, paying special attention to intra-abdominal pressure indicators, which are one of the etiopathological factors of the development of a severe stage of NEC.

During PD, we tried not only to reduce intra-abdominal pressure and stabilize the condition, but also to determine the nature of the effusion, that is, the presence of a smelling fibrous secretion, which indicates necrobiosis of the intestinal wall. The air and pathological contents were evacuated through a drainage tube placed in the abdominal cavity. The resulting liquid made it possible to assess the nature of the exudate, reduce intra-abdominal pressure, to some extent reduce the development of pathological pressure and prepare the patient for surgery. Laparocentesis and drainage of the peritoneum during perforation of the gastrointestinal tract are pathogenetically justified treatment methods that increase clinical efficacy. The appearance of at least 1 ml of a yellow-brown or green cloudy solution from the abdominal cavity during aspiration, as well as the release of gas, indicated intestinal necrosis, perforation of the intestinal wall and peritonitis, depending on which we chose further treatment tactics.

In our opinion, it is necessary to drain the peritoneum and flush the abdominal cavity (through a double-light tube inserted by laparocentesis) with aspiration of pathological fluid from the laparocentesis tube. Using this method allows you to remove free air, inflammatory fluid and endotoxin from the abdominal cavity, improve heart function and lung ventilation by reducing intra-abdominal pressure. The clinical effect of laparocentesis and drainage of the abdominal cavity is associated with the elimination of high intra-abdominal pressure, the pathophysiological manifestations of which are acute respiratory failure, acute liver failure, impaired ventilation of the lungs up to the development of acute liver failure.

In some cases, PD contributes to the regression of the pathological process even in patients who have not had laparotomy.

Conclusions.

1. For newborns with severe stages of necrotizing enterocolitis, peritoneal drainage should be used as initial treatment, as PD can provide initial stabilization; most of these infants will require subsequent laparotomy.

2. In premature infants with necrotic enterocolitis, peritoneal drainage, reducing intra-abdominal pressure, improves lung and liver function and stabilizes the condition, performs a kind of detoxification by reducing the level of toxic fluid accumulated in the abdominal cavity; determines the nature of effusion, that is, the presence of odorous, fibrous secretions indicating necrobiosis of the intestinal wall, thereby definitively diagnoses perforation.

3. Peritoneal drainage allows laparotomy for intestinal necrosis against a background of more favorable indications, saving time for correction of vital functions. In some cases, peritoneal drainage confirms the absence of indications for laparotomy and confidently justifies the continuation of conservative therapy.

4. The overall survival rate when using PD appears to be higher, and it should be assumed that it is preferable to use PD in severe stages of NEC before laparotomy in order to reduce IAP and sanitize the abdominal cavity, thus avoiding complications associated with direct laparotomies.

5. However, despite the success that we and others have achieved with PD in the management of premature infants with severe forms of NEC, it is difficult to say how much more effective primary PD is than laparotomy without prior PD.

References

1. Abolina TB, Tsap NA, Chudakov VB. Hirurgicheskie rezul'taty lecheniya nekrotich-eskogo enterokolita u nedonoshennyh detej s ekstremal'no nizkoj massoj tela [Surgical results of treatment of necrotic enterocolitis in premature infants with extremely low body weight]. Rossijskij vestnik detskoj hirurgii, anesteziologii i reanimatologii. 2018;8 ,st1.(Prilozhenie) [Russian Bulletin of Pediatric Surgery, Anesthesiology and Intensive Care. 2018;8 ,st1.(Appendix) 1 (In Russ.).]

2. Argumosa Salazar Y, Fernández Córdoba MS, Gonzálvez Piñiera J, et al. [Necrotizing entercolitis and intestinal perforation in very low weight premature infants: which is the best surgical option?]. Cir Pediatr. 2011 Aug;24(3):142-5. (In Spanish).

3. Azarow KS, Ein SH, Shandling B, et al. Laparotomy or drain for perforated necrotizing enterocolitis: Who gets what and why? Pediatr Surg Int 12:137-139, 1997

4. Blakely ML, Tyson JE, Lally KP, et all. Initial Laparotomy Versus Peritoneal Drainage in Extremely Low Birthweight Infants With Surgical Necrotizing Enterocolitis or Isolated Intestinal Perforation: A Multicenter Randomized Clinical Trial. Ann Surg. 2021 Oct 1;274(4):e370-e380. doi: 10.1097/SLA.0000000000005099.

5. Carpenter JL, Fallon SC, Swartz SJ, et al. Outcomes after peritoneal dialysis catheter placement. J Pediatr Surg. 2016 May;51(5):730-3. doi: 10.1016/j.jpedsurg.2016.02.011.

6. Cass DL, Brandt ML, Patel DL, Nuchtern JG, Minifee PK, Wesson DE. Peritoneal drainage as definitive treatment for neonates with isolated intestinal perforation. J Pediatr Surg. 2000 Nov;35(11):1531-6. doi: 10.1053/jpsu.2000.18299.

7. Ein SH, Marshall DG, Girvan D. Peritoneal drainage under local anesthesia for perforations from necrotizing enterocolitis. J Pediatr Surg. 1977 Dec;12(6):963-7. doi: 10.1016/0022-3468(77)90607-8.

8. Jakaitis BM, Bhatia AM. Definitive peritoneal drainage in the extremely low birth weight infant with spontaneous intestinal perforation: predictors and hospital outcomes. J Perinatol. 2015 Aug;35(8):607-11. doi: 10.1038/jp.2015.23.

9. Lessin MS, Luks FI, Wesselhoeft CW, et al. Peritoneal drainage as definitive treatment for intestinal perforation in infants with extremely low birth weight (<750 g). J Pediatr Surg. 1998 Feb;33(2):370-2. doi: 10.1016/s0022-3468(98)90465-1.

10. Li W, Tang J, Zhu Z, Tang W. Initial surgical treatment of necrotizing enterocolitis: a meta-analysis of peritoneal drainage versus laparotomy. Eur J Pediatr. 2022 Jul;181(7):2593-2601. doi: 10.1007/s00431-022-04454-3.

11. Luig M, Lui K; NSW & ACT NICUS Group. Epidemiology of necrotizing enterocolitis - Part I: Changing regional trends in extremely preterm infants over 14 years // J Paediatr Child Health. 2005 Apr;41(4):169-73. doi: 10.1111/j.1440-1754.2005.00582.x.

12. Mao W, Jiang S, Shen C, Zhu H, Wang Y, Zeng L, et al. Spontaneous intestinal perforation among very preterm infants in China: a multicenter cohort study. Transl Pediatr. 2024 Apr 30;13(4):542-554. doi: 10.21037/tp-23-584.

13. Mishra P, Foley D, Purdie G, Pringle KC. Intestinal perforation in premature neonates: The need for subsequent laparotomy after placement of peritoneal drains. J Paediatr Child Health. 2016 Mar;52(3):272-7. doi: 10.1111/jpc.13013.

14. Moss RL, Dimmitt RA, Barnhart DC, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. N Engl J Med. 2006 May 25;354(21):2225-34. doi: 10.1056/NEJMoa054605.

15. Raba AA, Coleman J, Cunningham K. Evaluation of the management of intestinal perforation in very low birth infants, a 10-year review.

Acta Paediatr. 2024 Apr;113(4):733-738. doi: 10.1111/apa.17069.

16. Ramaswamy R., Hegab S.M., Mugheri A., Mukattash, Gh. Surgical treatment of necrotizing enterocolitis: single-centre experience from Saudi Arabia. Annals of Pediatric Surgery: April 2016 ;12 (2): 43-46 DOI: 10.1097/01.XPS.0000481343.28971.ad

17. Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database Syst Rev. 2011 Jun 15;(6):CD006182. doi:10.1002/14651858.

18. Roy A, Tayeb M, Khogeer SS, Al-Salem AH. Predictors of gangrenous necrotizing enterocolitis and extent of disease. Early laparotomy versus peritoneal drainage. Saudi Med J. 2005 Mar;26(3):447-52.

19. Sola JE, Tepas JJ 3rd, Koniaris LG. Peritoneal drainage versus laparotomy for necrotizing enterocolitis and intestinal perforation: a meta-analysis. J Surg Res. 2010 Jun 1;161(1):95-100. doi: 10.1016/j.jss.2009.05.007.

20. Solis-Garcia G, Pierro A, Jasani B. Laparotomy versus Peritoneal Drainage as Primary Treatment for Surgical Necrotizing Enterocolitis or Spontaneous Intestinal Perforation in Preterm Neonates: A Systematic Review and Meta-Analysis. Children (Basel). 2023 Jul 6;10(7):1170. doi: 10.3390/children10071170.

21. Wu S, Di S, Liu T, Shi Y. Emerging prediction methods for early diagnosis of necrotizing enterocolitis. Front Med (Lausanne). 2022 Sep 16;9:985219. doi: 10.3389/fmed.2022.985219.

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In recent decades, a new interdisciplinary direction of research in the field of neurobiology has been formed – neuroethics. The aim of the article is to discuss the possibility of introducing neuroethics into clinical practice, since complex methods that differ from traditional ones are used for examination, treatment, rehabilitation and prevention of neuropathology. At the stages of treatment, rehabilitation and prevention of neurodegenerative diseases, ethical questions and dilemmas arise that force health professionals to make decisions, reflecting on the moral problems that arise in the process.

Keywords: bioethics, neuroethics, neuropathology, neurodegenerative diseases, Republic of Sakha (Yakutia)

Introduction. *Bioethical research in Yakutia.* The use of genomic technologies in the clinical practice of medical and genetic consultation of the Republican Hospital No. 1 - National Center of Medicine (MGC RB No. 1-NCM) was several years ahead of scientific molecular genetic research, in particular, the genetic study of the populations of the Republic of Sakha (Yakutia) and the genomic analysis of certain hereditary diseases common among indigenous people. The introduction of molecular methods to the MGC was associated with methodological and ethical issues of DNA diagnostics as a routine analysis to detect gene mutations in patients seeking medical and genetic care. The first were patients with neurodegenerative hereditary diseases (NDD), in particular with spinocerebellar ataxia type 1 (SCA1), which occurs in Yakutia with a frequency of 46 : 100000 [3] and with myotonic dystrophy (MD) - 21.3:100000 [1]. Until the year 2000, the MGC of Yakutia did not have its own molecular genetic laboratory, so it had no experience of conducting genetic analyses and no knowledge of principles of medical genetic counseling related to DNA testing of hereditary diseases.

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Moral issues related to the autonomy of the individual, confidentiality, accessibility of genetic information to the patient were discussed by us collegially, decisions were made in accordance with international standards of bioethical regulation of medical genetic counseling and genetic research involving humans.

We needed to establish algorithms for the relationship between the doctor and the patient when referring for DNA testing, taking into account the ethnospecific and psychological aspects of genetic counseling; provide the patient with a voluntary informed consent (VIC) form for presymptomatic DNA testing, develop a procedure for medical personnel when referring a patient for prenatal diagnosis of monogenic diseases diagnosed at the MGC RB No.1-NCM.

Bioethical research in Yakutia was conducted in parallel with the introduction of molecular genetic methods for diagnosing hereditary diseases into clinical practice, as a result of which ethical rules and principles were adopted, in accordance with our local working conditions [2,4].

Prerequisites for the development of neuroethics based on bioethical research in Yakutia. In recent decades, a new interdisciplinary direction of research in the field of neurobiology has been formed – neuroethics [20,23,32]. The most intensively innovative neurotechnologies are developed at the National Institutes of Health (USA), also its own professional community was founded there (International Neuroethics Society), which deals with ethical and social contradictions and professional problems of specialists in the field of neurology, including neuroscience [11, 13, 16, 32].

It is important for neurologists to develop familiarity with the analysis of the ethical problems of neurobiological research and the regulatory challenges arising from experience with patients with neurological diseases and caregivers to ensure quality medical practice [11,32].

This article discusses the main issues of neuroethics and the possibility of introducing neuroethics into the clinical practice of Yakutia.

The activity of the Center for Neurodegenerative Diseases in the clinic of the Yakut Science Center of Complex Medical Problems (CNDD YSC CMP) has prerequisites for the development of neuroethics, since:

- neuroscience is one of the main priorities of the YSC CMP;
- a feature of the scientific activity of the clinic is the study of a certain contingent of patients with neuropathology, including those with rare and unexplored forms of the disease;
- neurodegenerative diseases common in Yakutia are the most important medical and social problem of our time;

- for the examination, treatment, rehabilitation and prevention of neuropathology, complex methods are used that differ from traditional ones;

- at the stages of treatment, rehabilitation and prevention of neurodegenerative diseases, ethical questions and dilemmas arise that force health professionals to make decisions, reflecting on the moral problems that arise in the process.

Problems of neuroethics in clinical practice. *Joint decision-making.* In patient-centered care, collaborative decision-making is seen as the preferred form of medical decision-making [24,25]. It is a partnership that allows clinicians and patients to make decisions related to health and care, treatment, management or support, based on the best available clinical data and the patient's own values and preferences [31].

The most important category of this issue is the communication process, which consists of five stages: separation of goals, exchange of information, discussion, mutual agreement and follow-up actions. Depending on the conditions, treatment, care planning or rehabilitation options are available. Individual desires and expectations for treatment / care are taken into account, including information needs, own opinions, preferences / values containing what is most important for the patient. Clinicians supplement the recommendations by sharing their clinical experience with examples from previous experience related to the disease and its treatment [5]. For a deeper understanding, healthcare professionals give patients and their relatives enough time to dwell on this in more detail and even collect additional information at home without any stress or pressure [26].

The patient's representatives, the patient himself, and the physician discuss and ultimately reach a consensus on diagnostic decisions and further treatment plans [27]. They make decisions together and jointly agree on them [6,7].

In clinics related to research activities, there is a need to include persons with cognitive impairments in the research project, for which VIC registration is required. In this regard, prerequisites may arise for various kinds of violations of the patient's rights. The patient belongs to a vulnerable group of research participants, these persons are often incapacitated and unable to understand a large amount of complex information and are unable to express their consent. In cases of senile dementia, cognitive impairment, Alzheimer's disease, etc., it is possible to involve close relatives or caregivers to collect VIC [17]. Ethical commissions and committees of various levels play an important role in the ethical examination of scientific projects and the protection of patients' rights.

Patients with NDD can have cognitive and mental impairments of varying degrees, so the problem of VIC will be as important for them. Physicians, neuroscientists will need to learn to disclose sufficient information in an accessible form and receive confirmation from patients of the ability to voluntarily choose between consent or other options [31,22,30].

Difficulties in disclosing family history. Discussing family history is a vulnerable experience for some patients with hereditary, neurological, mental illnesses. There may be scenarios of limited awareness of their family members' health history or a patient's lack of interest in discussing family history [19,21].

But this should not be an obstacle to patients' participation in the studies. It is possible to interest the patient in the joint recreation of their family tree, as an opportunity to talk unpretentiously about family history and help to recognize the generations affected by the disease.

Respectful and inclusive attitude to the patient expands his/her decision-making opportunities and builds a relationship in the field of health care, in which the patient and the neurologist work together as a team to ensure maximum efficiency of medical care [33].

In addition, for example, genetic testing in clinical neurology may accidentally reveal unforeseen genetic information completely unrelated to the study, which has potential adverse consequences for both the patient and the family [9].

Genetic testing can also affect family members by inadvertently identifying mutations in asymptomatic at-risk individuals who previously chose to avoid this knowledge (or did not consent to testing) and who may be subject to psychological harm or discrimination. Similarly, genetic testing can affect family relationships by accidentally revealing incorrectly established paternity. The risk of accidental genetic findings may be particularly important for paediatric research participants and others with disabilities. Such participants may find that their future lives have changed significantly or are limited as a result of decisions by parents or guardians to direct them to genetic testing [9].

Use of pharmaceuticals that affect cognitive and behavioral functions. The prospect of developing pharmaceuticals designed specifically to improve cognitive, affective and motivational processes has raised a number of ethical questions. They raise serious concerns, since it is possible that these pharmaceuticals can be used to improve human health in unacceptable ways, and they can also contradict the very nature of man, because they can have serious side effects (Table).

Drugs used for treatment and their side effects [18]

Drug	Usage	Possible effect
Glucocorticoid	Relief of asthma symptoms, reduction of adrenal insufficiency, autoimmune conditions	Improved concentration, psychosis, memory decline, mood changes, memory improvement, especially for emotionally stimulating events
L-dopa	Treatment of PD	Excitement, confusion, psychosis, agitation and anxiety
Lithium	Treatment of mental illness, bipolar disorder	Possible increase in motivation due to prevention of signs of depression, reduction of paranoia, pomposity and risk appetite
Methylphenidate	Treatment of ADHD, hyperactivity, narcolepsy	Irritability, psychosis, signs of increased attention, confusion, improvement of working memory
Modafinil	Treatment of sleep disorders, improvement of cognitive functions in narcolepsy	Signs of aggression or anxiety, increased vigilance and attention, improved working memory
Pramipexole	Treatment of PD	Pathological gambling, hypersexuality, paraphilias (e.g., pedophilia), compulsive behaviors (e.g., compulsive shopping and dressing up)

Millions of doses of pharmaceuticals affecting cognitive abilities and affects are consumed annually, an empirical and philosophical analysis of their effects is the objective of neuroethics [18].

Pharmaceuticals influence important elements of moral decision-making and human behavior. Some dopamine agonists (pramipexole, etc.) used to treat Parkinson's disease (PD) may be examples of drugs with possible morally important behavioral effects (consequences). Publications discuss cases that these drugs caused gambling addiction and hypersexuality in some people [28,12].

Anxiolytics – drugs used to treat disorders associated with excessive anxiety can also have a morally significant effect, given that anxiety can cloud decision-making, including moral [10].

Thus, the assessment of the effect of pharmaceuticals on cognitive and behavioral functions requires not only further scientific research, but also important moral conclusions.

Application of advanced neurotechnologies. Several generations ago, it was impossible to imagine such technologies as neuroimaging, brain stimulation, neural implants, brain structures and areas, mobile technologies, improvement of cognitive functions, brain-computer interfaces, robotics, exoskeletons, artificial intelligence, etc. For example, studies of functional MRI gradually raise new ethical problems, as studies of neural models related to decision-making, memory recovery, personality traits, behavior, perception of surrounding stimuli multiply [29]. Various mental states and processes with neuronal activity in certain areas of the brain, once used to decipher mental activity, may find applications unrelated to medicine or biology, a potential abuse aimed at gathering information that is normally prohibited by law [32]. Significant progress has been made in the field of neurobiological research, for example, it has become clear that the results of studying the cells and mechanisms of brain activity in experimental animals and humans differ significantly [8]. A recent publication by Gidon,et al., 2020 in Science investigated the dendrites of pyramidal neurons of layers 2 and 3 (L2/3) of the human cerebral cortex ex vivo in slices of surgically removed human neocortical brain tissue in patients with epilepsy and tumors. For the first time, the subtle mechanisms of dendritic Ca2+ axonal action potentials in human neurons, as well as previously unknown dendrites that are not characteristic of animal neurons, which may be responsible for human mental activity, have been described [14,15]. In "J Clin Invest", Fernández, et al.,2021, published a successful case in implanting an intracortical matrix (consisting of 96 electrodes) into the visual cortex of a 57-year-old woman with complete blindness for a 6-month period. The results allowed the participant to identify some letters and recognize the boundaries of objects [14,15].

Society should be prepared to examine the ethical considerations surrounding neural modifiers on a case-by-case basis and consider the intervention, its purpose, who chooses it, who may benefit from it and who may be harmed. For example, DBS (deep brain stimulation) to improve symptoms of a mental disorder such as depression can be ethical if it is proven to be safe and effective, and if it is freely chosen by a fully informed adult. However, DBS would be ethically problematic if an adult were coerced into taking it.

Guidelines developed by professional organizations such as neurological associations could be of great help in informing the public and assisting health professionals and other stakeholders in understanding neural modifiers and their potential benefits and risks in different circumstances.

Conclusion. A growing awareness of the ethical implications of neuroscience research in the world has shaped the field that has come to be known as neuroethics.

Neuroethics intersects with biomedical ethics in the sense that neuroethics also deals with the ethical, legal, and social implications of neuroscience findings, as well as the nature of the research itself.

The importance of the properties of the nervous system, the special relationship between the personality and the brain, the influence of human life itself on its neurological functions give rise to more and more novel ethical and philosophical problems.

Neuroscientists can collaborate with neuroethics researchers to advance clinical neuroethics. Neuroethics can also be successfully combined with other specializations in neurology, in particular, synergistic specializations such as neurocritical therapy, cognitive-behavioral neurology, stroke, neurorehabilitation, neurogenetics, global neurology, neurophysiology, and neuropalliative care.

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References

1. Sukhomyasova AL, et al. Miotonicheskaya distrofiya v RS(Ya): populyacionnye osobennosti i podhody v DNK-diagnostike [Myotonic dystrophy in MS(I): population features and approaches in DNA diagnostics. Yakut Medical Journal. 2003; 2:12-17 (In Russ.).]

2. Kononova 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 and genetic counseling in Yakutia]. Medicinskaya genetika [Medical genetics. 2006;14-17 (In Russ.).]

3. Fedorov AI, et al. Rasprostranyonnost' spinocerebellyarnoj ataksii 1 tipa v Yakutii: sovremennoe sostoyanie [The 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.

4. Gurinova EE, et al. Sravnenie urovnya trevozhnosti u bol'nyh s monogennymi nasledstvennymi zabolevaniyami nervnoj sistemy / Yakutskij medicinskij zhurnal.-2009.№2(26).S.80-83 [Comparison of anxiety levels in patients with monogenic hereditary diseases of the nervous system. Yakutskij medicinskij zhurnal [Yakut Medical Journal. 2009;2(26):80-83 (In Russ.).]

5. Aoki Y. Shared decision making for adults with severe mental illness: A concept analysis. Jpn J Nurs Sci. 2020;17(4):e12365. doi: 10.1111/jjns.12365.

6. Aoki Y, Yaju Y, Utsumi T, Sanyaolu L [et al] Shared decision-making interventions for people with mental health conditions. Cochrane Database Syst Rev. 2022;11(11):CD007297. doi: 10.1002/14651858.CD007297.pub3.

7. Antoniou R, Hausermann T, Sideman AB [et al] Moral reasoning through the eyes of persons with behavioral variant frontotemporal dementia. Front Neurol. 2023 Jul 10;14:1197213. doi: 10.3389/fneur.2023.1197213.

8. Benavides-Piccione R, Blazquez-Llorca L, Kastanauskaite A [et al] Key morphological features of human pyramidal neurons. Cereb Cortex. 2024; 34(5):bhae180. doi: 10.1093/cercor/bhae180.

9. Byrjalsen A, Tybjærg-Hansen A, Juul K [et al] Actionability and familial uptake following opportunistic genomic screening in a pediatric cancer cohort. Eur J Hum Genet. 2024 ;32(7):846-857. doi: 10.1038/s41431-024-01618-7.

10. Budić M, Galjak M, Rakić V. What drives public attitudes towards moral bioenhancement and why it matters: an exploratory study. BMC Med Ethics. 2021; 22(1):163. doi: 10.1186/s12910-021-00732-1

11. Chiong W. Insiders and Outsiders: Lessons for Neuroethics from the History of Bioethics. AJOB Neurosci. 2020;11(3):155-166. doi: 10.1080/21507740.2020.1778118.

12. Drew DS, Muhammed K, Baig F [et al] Dopamine and reward hypersensitivity in Parkinson's disease with impulse control disorder. Brain. 2020; 143(8):2502-2518. doi: 10.1093/brain/awaa198.

13. Farahany N, Ramos KM. Neuroethics: Fostering Collaborations to Enable Neuroscientific Discovery. AJOB Neurosci. 2020;11(3):148-154. doi: 10.1080/21507740.2020.1778117.

14. Fernández E, Alfaro A, Soto-Sánchez C [et al] Visual percepts evoked with an intracortical 96-channel microelectrode array inserted in human occipital cortex. J Clin Invest. 2021;131(23):e151331. doi: 10.1172/JCI151331.

15. Gidon A, Zolnik TA, Fidzinski P [et al] Dendritic action potentials and computation in human layer 2/3 cortical neurons. Science. 2020; 367(6473):83-87. doi: 10.1126/science.aax6239.

16. Illes J, Bird SJ. Neuroethics: a modern context for ethics in neuroscience. Trends Neurosci. 2006; 29(9):511-7. doi: 10.1016/j.tins.2006.07.002.

17. Lovell K, Bee P, Brooks H [et al] Embedding shared decision-making in the care of patients with severe and enduring mental health problems: The EQUIP pragmatic cluster randomised trial. PLoS One. 2018;13(8):e0201533. doi: 10.1371/journal.pone.0201533.

18. Levy N, Douglas T, Kahane G, Terbeck S, Cowen PJ, Hewstone M, Savulescu J. Are You Morally Modified?: The Moral Effects of Widely Used Pharmaceuticals. Philos Psychiatr Psychol. 2014;21(2):111-125. doi: 10.1353/ppp.2014.0023.

19. LoCastro M, Jensen-Battaglia M, Sanapala C [et al] Exploring the role of the oncologist in promoting shared decision making during treatment planning for older adults with acute myeloid leukemia. J Geriatr Oncol. 2024;15(5):101793. doi: 10.1016/j.jgo.2024.101793.

20. McDonald PJ. It Is Time to Expand the Scope and Reach of Neuroethics. AJOB Neurosci. 2019 Jul-Sep;10(3):128-129. doi: 10.1080/21507740.2019.1632968.

21. Niranjan SJ, Wallace A, Williams BR [et al] Trust but Verify: Exploring the Role of Treatment-Related Information and Patient-Physician Trust in Shared Decision Making Among Patients with Metastatic Breast Cancer. J Cancer Educ. 2020;35(5):885-892. doi: 10.1007/s13187-019-01538-x.

22. Protheroe J, Brooks H, Chew-Graham C [et al] 'Permission to participate?' A qualitative study of participation in patients from differing socio-economic backgrounds. J Health Psychol. 2013;18(8):1046-55. doi: 10.1177/1359105312459876.

23. Ramos KM, Grady C, Greely HT [et al] The NIH BRAIN Initiative: Integrating Neuroethics and Neuroscience. Neuron. 2019 ;101(3):394-398. doi: 10.1016/j.neuron.2019.01.024.

24. Sandman L, Munthe C. Shared decision-making and patient autonomy. Theor Med Bioeth. 2009;30(4):289-310. doi: 10.1007/s11017-009-9114-4

25. Schermer MHN, Richard E. On the reconceptualization of Alzheimer's disease. Bioethics. 2019;33:138–145. https://doi.org/10.1111/bioe.12516

26. Schön UK, Grim K, Wallin L [et al] Psychiatric service staff perceptions of implementing a shared decision-making tool: a process evaluation study. Int J Qual Stud Health Well-being. 2018;13(1):1421352. doi: 10.1080/17482631.2017.1421352.

27. Stacey D, Lewis KB, Smith M [et al] Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2024; 1(1):CD001431. doi: 10.1002/14651858.CD001431.pub6.

28. Soileau LG, Talbot NC, Storey NR [et al] Impulse control disorders in Parkinson's disease patients treated with pramipexole and ropinirole: a systematic review and meta-analysis. Neurol Sci. 2024 Apr;45(4):1399-1408. doi: 10.1007/s10072-023-07254-1

29. Tolchin B, Conwit R, Epstein LG, Russell JA; Ethics, Law, and Humanities Committee, a joint committee of the American Academy of Neurology, American Neurological Association, and Child Neurology Society. AAN position statement: Ethical issues in clinical research in neurology. Neurology. 2020;94(15):661-669. doi: 10.1212/WNL.0000000000009241.

30. Tam NT, Huy NT, Thoa le TB [et al] Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93(3):186-98H. doi: 10.2471/BLT.14.141390.

31. Tate CE, Mami G, McNulty M [et al] Evaluation of a Novel Hospice-Specific Patient Decision Aid. Am J Hosp Palliat Care. 2024 ; 41(4):414-423. doi: 10.1177/10499091231190776.

32. Young MJ, Bernat JL. Emerging Subspecialties in Neurology: Neuroethics: An Emerging Career Path in Neurology. Neurology. 2022; 98(12):505-508. doi: 10.1212/WNL.0000000000200054.

33. Zulman DM, Haverfield MC, Shaw JG [et al] Practices to Foster Physician Presence and Connection With Patients in the Clinical Encounter. JAMA. 2020;323(1):70-81. doi: 10.1001/jama.2019.19003.

CLINICAL CASE

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HYPERTROPHIC PACHYMENINGITIS AS A RARE CAUSE OF HEADACHES: A CLINICAL CASE

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The article presents a description of the clinical case of a 62-year-old woman who had been suffering from headaches for 5 months. MRI of the brain revealed pachymeningeal enhancement, especially in frontal-parietal regions, and tentorium cerebellum. Based on the clinical picture and neuroimaging data, the patient was diagnosed with idiopathic hypertrophic pachymeningitis. Corticosteroid therapy resulted in regression of pain and reduction of MRI changes. The article also discusses the difficulties of differential diagnostics of hypertrophic pachymeningitis with other diseases, which can be imitated by clinical picture and changes on MRI images.

Keywords: hypertrophic pachymeningitis, dura mater, headache, meningeal signs.

Introduction. Hypertrophic pachymeningitis (HPM) is a rare disease resulting from localized or diffuse thickening of the dura mater of the brain and/or spinal cord [9]. The most frequent manifestations of HPM are headaches, cranial neuropathies, and less frequently focal symptoms [5].

According to pathogenesis, HPM can be primary and secondary. Secondary forms of HPM develop in infectious and non-infectious diseases. Infectious causes include tuberculosis, fungal infections, Lyme disease, syphilis; and noninfectious HPM can develop in systemic inflammatory diseases such as granulomatosis, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, IgG4-associated diseases, and neoplastic processes. Primary (idiopathic) HPM is diagnosed in the absence of causative factors [9, 12].

The prevalence of HPM is unknown, and scientific data on the disease are based on single clinical observations.

The aim of the study is to describe our own clinical case of a patient diagnosed with HPM on the basis of clinical and neuroimaging data and to discuss the difficulties of differential diagnosis of this disease.

Clinical part. A 62-year-old woman, accountant, living in a rural area, was hospitalized in the neurological department with complaints of constant severe headaches in the occipital region, right temporal region of compressive, aching, pulsating character (VAS = 5-6 points), non-systemic dizziness, unsteadiness when walking, interrupted sleep and increased fatigability.

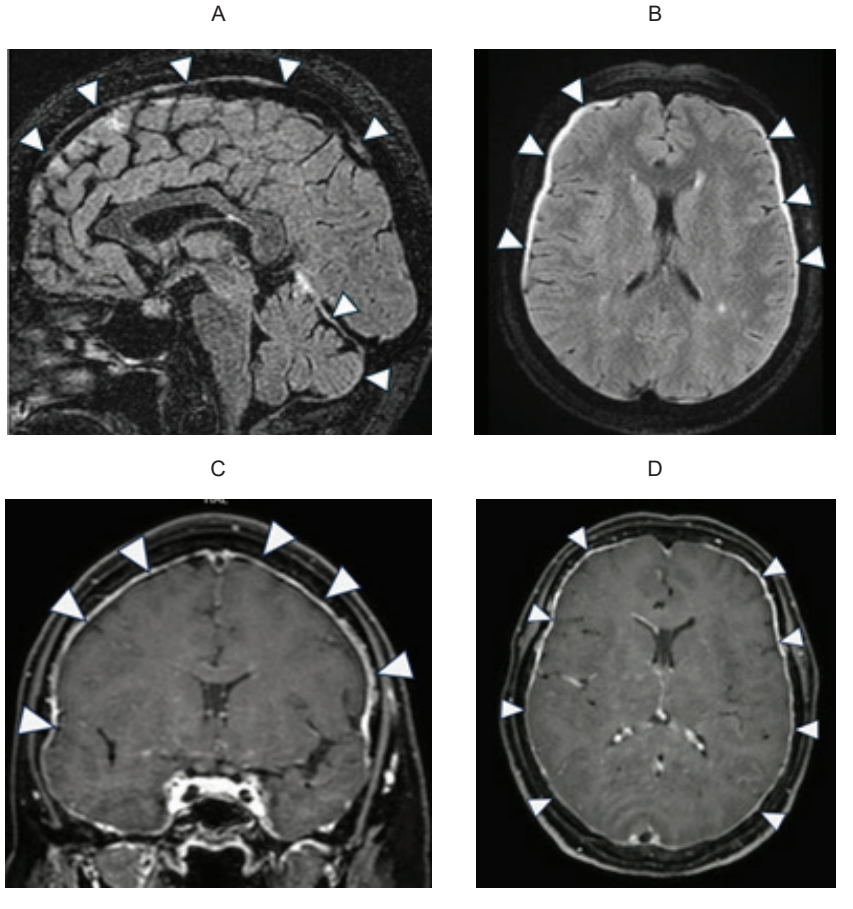

Fig. 1. Brain MRI of the patient (2 months after the onset): A (sagittal), B (axial) – FLAIR images showing higher signal from the dura mater and the tentorium of cerebellum; C, D – post-contrast pachymeningeal enhancement. Arrows indicate the corresponding changes in FLAIR images an increase in the signal from the dura mater is determined, mainly in the fronto-parietal regions, and the tentorium of the cerebellum; C, D – contrast enhancement reveals a uniform accumulation of contrast in the meninges and tentorium of the cerebellum. Arrows indicate the corresponding changes.

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5 months ago, she first felt soreness and stiffness in her neck area, which she attributed to high blood pressure. A few days later she developed severe headaches of compressive character, mainly in the occipital region (VAS = 7-8 points). The woman had not practically suffered from headaches before; she rarely experienced pressing headaches, which were quickly relieved; she attributed them to increased blood pressure, sleep disorders or stress. The real headaches were constant, intensified by turning, head tilting, pushing, not accompanied by nausea, vomiting, but the patient noted photo- and phonophobia. The patient also had disturbed sleep and developed increased fatigue, and her work capacity decreased sharply.

The patient did not receive treatment. After 2 months, she underwent a contrast-enhanced magnetic resonance imaging (MRI) of the brain, which revealed pachymeningeal enhancement (Fig. 1).

Despite the MRI results, the patient consulted a neurologist only one month later, but the clinical manifestations and head MRI changes were associated with vascular encephalopathy. Neurometabolic therapy was prescribed, which did not lead to improvement.

She also underwent an ultrasound examination of the carotid and vertebral arteries, which revealed stenosis of the left common carotid artery up to 32%. She also independently visited an ophthalmologist and was diagnosed with hypertensive retinal angiopathy, myopia, presbyopia.

Due to persisting headaches in the 5th month from the moment of the disease she was referred to the vascular center. After exclusion of stroke, the patient was transferred to the neurological department.

Chronic diseases: hypertension; chronic heart failure; stenotic atherosclerosis of carotid arteries.

Constant intake of medications: amlodipine 5 mg/day, azilsartan medoxomil 20 mg/day.

On objective examination: condition of average severity. The skin is of normal color. Peripheral lymph nodes are not enlarged, painless. Respiration in the lungs is vesicular, no rales. Cardiac tones rhythmic, muffled. Blood pressure 130 / 80 mm Hg, heart rate - 88 beats per min. The abdomen is soft, painless. Urination is regular.

In the neurological status at the time of admission to the department, no focal symptoms were detected, mild rigidity of occipital muscles, Kernig's symptom 60. On the MoCA scale - 28 / 30 points (normal), HADS-D (depression) - 5 points (normal), HADS-A (anxiety) - 7 points (normal).

Laboratory blood tests without inflammatory changes, the biochemical blood test showed signs of dyslipidemia (increase in total cholesterol to 6.66 mmol/L, triglycerides to 2.98 mmol/L, with normal values of LDL and HDL).

MRI of the brain with contrast-enhanced gadolinium revealed previously detected signs of dura mater thickening; it was recommended to differentiate intracranial hypotension, hypertrophic pachymeningitis and neurosarcoidosis.

General and biochemical analyses of cerebrospinal fluid did not reveal pathology.

After lumbar puncture, the patient subjectively noted a short-term improvement, but headaches resumed the next day.

To exclude sarcoidosis and other systemic diseases, a computed tomography (CT) scan of the chest organs was performed, which was normal, and a blood test for C-reactive protein, ASLO, and rheumatoid factor was performed; all parameters were within reference values.

Based on the presence of general cerebral, meningeal symptoms, absence of evidence of infectious and systemic lesions (e.g., fever, cough, lymph node enlargement, normal cerebrospinal fluid and inflammatory markers), taking into account pachymeningeal enhancement, the patient was diagnosed with idiopathic hypertrophic pachymeningitis.

Treatment with prednisolone 90 mg/day for 5 days with subsequent dose reduction was carried out.

Starting from the 2nd day of steroid therapy a significant improvement of the condition in the form of meningeal and general cerebral symptoms was noted.

The control MRI of the brain (20th day of hospitalization) showed a significant decrease in the previously detected pachymeningeal enhancement and reduction of paramagnetic accumulation (Fig. 2).

For oncologic search we analyzed specific markers (alpha-fetoprotein, CA 15-3, CA-125, CA 19-9), ultrasound examination of abdominal and pelvic organs. The results were negative.

The patient was discharged in satisfactory condition with recommendations to gradually reduce the dose of prednisolone until complete withdrawal.

The patient was followed for one year, there was no recurrence of general cerebral and meningeal symptoms, she continues to work professionally.

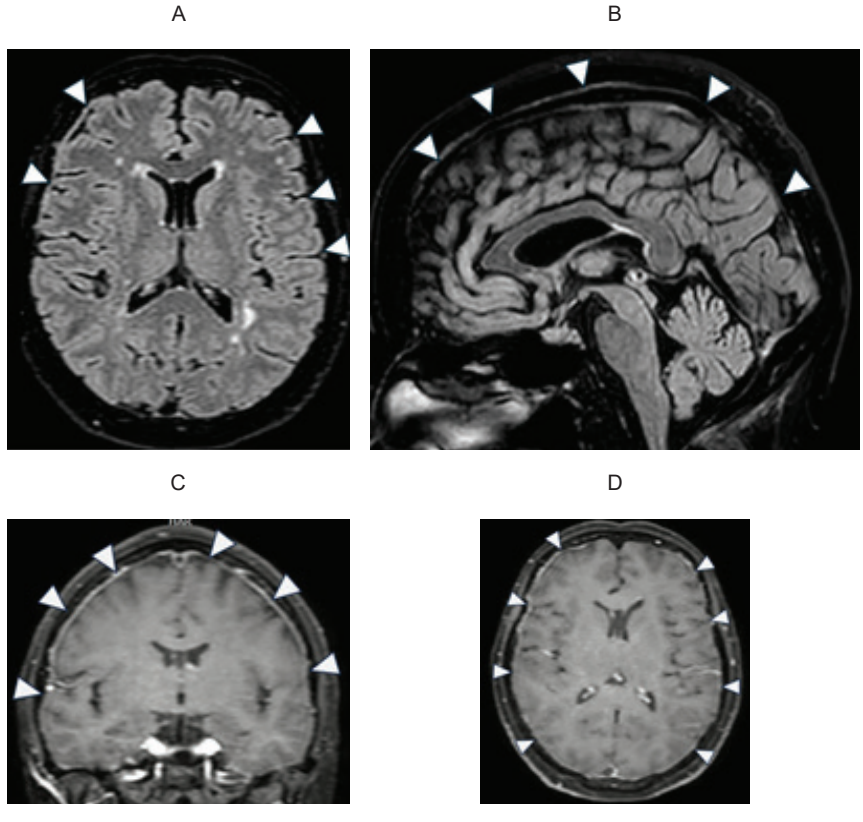

Fig. 2. MRI of the brain after steroid therapy: FLAIR images show a decrease in previously identified pachymeningeal enhancement in axial (A) and sagittal (B) sections; paramagnetic accumulation was reduced in coronal (C) and axial (D) sections

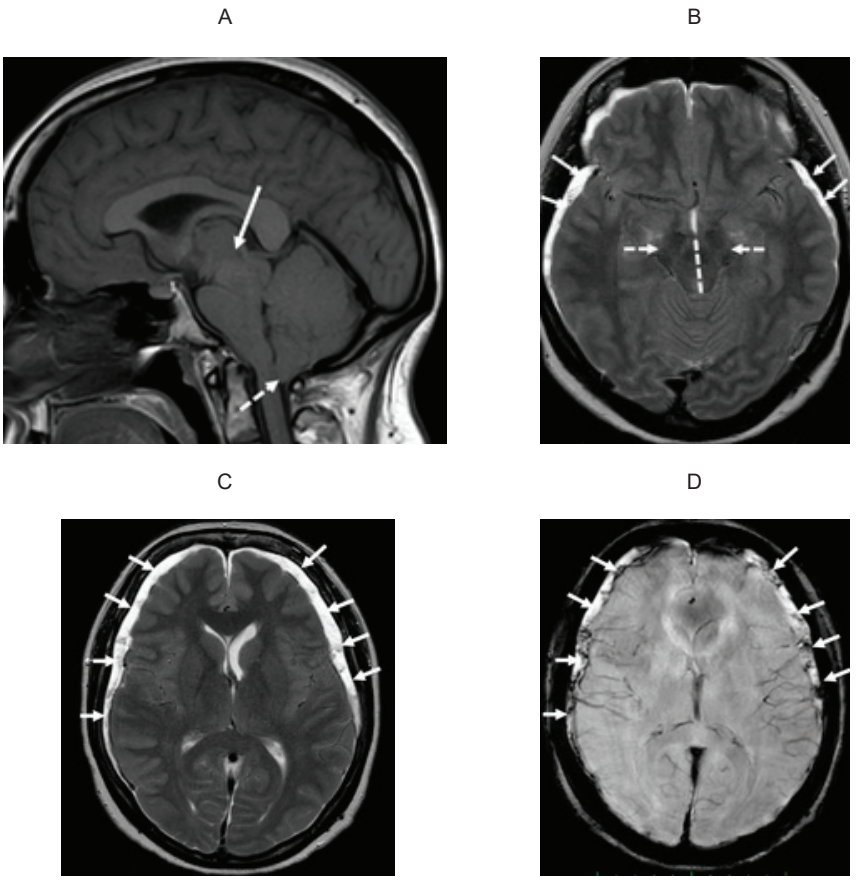

Fig. 3. Barin MRI in intracranial hypotension (own observation): A – caudal displacement of the cerebellum (dashed arrow), stem structures and midbrain, with narrowing of the basal cisterns of the brain, deformation of the pons and cerebral peduncles (solid arrow) on T1-weighted sagittal images; B – subdural hygromas (solid arrows), "flattening" of the midbrain on the lateral sides with an increase in its anteroposterior size (dashed arrows) on T2-weighted axial images; C (T2 images), D (SWI mode) – subdural effusions with a slight accumulation of hemosiderin, which indicates previous subdural hemorrhages; significant narrowing (slit-like shape) of the lateral ventricles on axial images

Discussion. We present a clinical observation of a patient with a rare disease - idiopathic HPM. The patient had "red flags" from the moment of disease debut, which reduce the likelihood of primary headache (primarily migraine and tension headache) and require further evaluation, namely: 1) development of unusual headache after age 50; 2) absence of remissions; 3) meningeal signs; 4) signs of intracranial hypertension (increased headache on pushing) [3]. Neuroimaging performed independently revealed specific signs that required specialized care, but the patient continued to work and turned to a specialist late. The initial examination by the neurologist also missed "red flags" and changes on MRI of the head. These circumstances were the reason for the patient's late hospitalization.

According to a study of HPM in India, 52% of patient cases have primary (idiopathic) form and 48% have secondary form (immune mediated, infectious and neoplastic). The most common cause of secondary HPM was IgG4-associated forms (25%), with sarcoidosis, tuberculosis and fungal infection accounting for 3 cases each (18.75%). Headache occurred in all patients and cranial neuropathies were identified in 73% of cases. Focal symptoms indicated the secondary nature of HPM. MRI showed localized pachymeningeal enhancement in 97% of cases and diffuse enhancement in only one patient (with fungal osteomyelitis of the skull base). Treatment was with glucocorticosteroids, except for cases of fungal etiology. In severe cases, intravenous immunoglobulins, rituximab, cyclophosphamide and azathiaprine were administered [12]

Of particular interest in recent years is IgG4-associated HPM, which, according to some researchers, was previously diagnosed as idiopathic (primary) HPM [6, 10, 13]. Clinically, IgG4-associated HPM does not differ practically from idiopathic HPM: headaches (67%) and signs of cranial nerve damage (33%) are the most common. However, approximately half of patients with IgG4-associated HPM may have systemic manifestations: weight loss, thyroid dysfunction, autoimmune pancreatitis, interstitial pneumonia, and salivary gland enlargement. MRI of the brain reveals pachymeningeal enhancement. Serum IgG4 antibody levels correlate with systemic manifestations of the disease. Antibodies to IgG4, mild protein and cell (lymphocyte) elevation are detected in the cerebrospinal fluid. "The gold standard" for diagnosis is a biopsy of the dura mater, which reveals whirling fibrotic inflammatory reactions. There is no consensus in treatment, but glucocorticosteroids are used, and if they are ineffective, cytostatics (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide) may be used; the use of anti-B-cell therapy with rituximab is promising [11]. Unfortunately, in the Russian Federation, it is not possible to conduct research on IgG4, and probably IgG4-associated forms are hidden under cases of idiopathic HPM. At the same time, there is currently no convincing evidence that the treatment of these two forms is fundamentally different.

In the literature there are descriptions of HPM in combination with Tolosa-Hunt syndrome (HTS). Ivanov V.V. and colleagues reported a successful surgical intervention with decompression of the orbital structures and optic nerve in a 39-year-old patient with HTS and suspected volumetric process of the right orbit, who complained of acute decrease of vision in the right eye and burning pain in the right eye. Intraoperative biopsy made it possible to establish the diagnosis of HPM [2]. No cranial neuropathies were detected in the patient we presented.

There are also rare causes of HPM. For example, a 13-year-old girl who had been bothered by headaches, facial and withdrawal nerve neuropathies for 8 months was found to have contrast enhancement of the dura mater on brain MRI. Subsequently, antibodies to GFAP were detected, characteristic of autoimmune glial fibrillary acidic protein astrocytopathy, a rare inflammatory disease of the nervous system that manifests with steroid-sensitive encephalitis, myelitis, and meningitis. Administration of steroid therapy improved the girl's condition [7]. Mendelevich E.G. and colleagues reported on the development of HPM in a 44-year-old patient in whom the disease debuted with narrowing of the eye slit and only 2 years after the development of ocular symptoms headaches developed, followed by optic atrophy with complete

blindness in the left eye, transient deafness in the left ear, and hypersomnia. According to MRI of the brain and laboratory tests (proteinuria, microhematuria), HPM was diagnosed, probably as part of Wegener's granulomatosis. The patient was treated with corticosteroids (prednisolone 40 mg/day) with positive effect [4].

In 2020, guidelines for idiopathic HPM were issued, the most frequent clinical manifestations are headaches and cranial nerve dysfunction, the cerebrospinal fluid may show increased protein levels and lymphocytic pleocytosis, and MRI with contrast-enhanced gadolinium is the priority method of diagnosis. The pain syndrome is mimicked by chronic daily headache or chronic migraine with typical features (nausea, vomiting), less commonly by SUNA [8].

A similar neuroimaging picture to HPM can be observed in intracranial hypotension. At the same time, intracranial hypotension is also characterized by swelling of venous sinuses, prolapse of cerebellar tonsils into the greater occipital foramen, increased pituitary size, decreased mammillopontine distance, and pontomesencephalic angle, as well as a number of other changes [1, 14]. No such changes were detected in our patient, which reduces the possibility of intracranial hypotension. Figure 3 shows MRI of the brain of our other patient with intracranial hypotension.

References

1. Ramazanov GR, Shevchenko EV, Izmailova AM, et al. Vnutricherepnaya gipotenziya [Intracranial hypotension]. Vestnik Smolenskoj gosudarstvennoj medicinskoj akademii [Bulletin of Smolensk State Medical Academy. 2021; 20 (1): 159-167 (In Russ.).] doi :10.37903/vsgma.2021.1.24

2. Ivanov VV, Shestakov AA, Gorozhanin AV, et al. Gipertroficheskij bazal'nyj pahimeningit, rasprostranennyj na orbitu, v sochetanii s sindromom Tolosa-Hanta: opisanie klinicheskogo sluchaya [Hypertrophic basal pachymeningitis spreading to the orbit in combination with Tolosa-Hunt syndrome: description of a clinical case]. Rossijskij nejrohirurgicheskij zhurnal im. professora A.L. Polenova [Russian neurosurgical journal named after Professor A.L.]. 2022; 14 (4) 111-116 (In Russ.).] doi: 10.56618/20712693_2022_14_4_111.

3. Osipova VV, Filatova EG, Artemenko AG, et al. Diagnostika i lechenie migreni: rekomendacii rossijskih ekspertov [Diagnosis and treatment of migraine: recommendations of Russian experts]. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova [S.S. Korsakov Journal of Neurology and Psychiatry]. 2018; 48 (5): 621-635. doi:10.1007/s11055-018-0608-2

4. Mendelevich EG, Fattakhova CS, Bogdanov EI. Gipertroficheskij pahimeningit: sovremennye kriterii diagnostiki i differenciacii [Hypertrophic pachymeningitis: modern criteria of diagnosis and differentiation (clinical observation and literature review)]. Nevrologiya, nejropsihiatriya, psihosomatika [Neurology, neuropsychiatry, psychosomatics]. 2015; 7(2): 42-46 (In Russ.).] doi: 10.14412/2074-2711-2015-2-42-46

5. Abrantes FF, de Moraes MPM, Rezende Filho FM, et al. A clinical approach to hypertrophic pachymeningitisArquivos de neuro-psiquiatria. 2020; 78 (12) 797-804. doi: 10.1590/0004-282X20200073

6. Rayamajhi S, Shrestha R, Sunuwar N, et al. A rare case report on hypertrophic pachymeningitis: Serum IgG4-related disease. Radiology Case Reports. 2022; 17 (11): 4371-4375. doi: 10.1016/j.radcr.2022.08.044

7. Tan C, Zhong M, Yao Z, et al. Anti-GFAP Antibody-Associated Hypertrophic Pachymeningitis. Neuropediatrics. 2022; 53 (2): 143-145. doi: 10.1055/s-0042-1742718

8. Charleston L, Cooper W. An Update on Idiopathic Hypertrophic Cranial Pachymeningitis for the Headache Practitioner. Current Pain and Headache Reports. 2020; 24 (10). doi: 10.1007/s11916-020-00893-5

9. De Virgilio A, de Vincentiis M, Inghilleri M, et al. Idiopathic hypertrophic pachymeningitis: an autoimmune IgG4-related diseaseImmunologic Research. 2017; 65 (1): 386-394. doi:10.1007/s12026-016-8863-1

10. Sapkota B, Rampure R, Gokden M, Kanuru S. Cureus.IgG4-Related Disease Presenting as Hypertrophic Pachymeningitis. 2022; 14 (2). doi: 10.7759/cureus.21850

11. Lu LX, Della-Torre E, Stone JH, Clark SW. IgG4-Related hypertrophic pachymeningitis clinical features, diagnostic criteria, and treatment. JAMA Neurology. 2014; 71 (6): 785-793. doi:10.1001/jamaneurol.2014.243

12. Jagiasi, K., Barvalia P. Is Hypertrophic Pachymeningitis Really Idiopathic?. Neurology India. 2022; 70 (6): 2422-2426. doi: 10.4103/0028-3886.364052

13. Sergio P, Alejandro R, Cristian F. Hypertrophic pachymeningitis due to IgG4-related disease (RD-IgG4). A case report. Reumatologia clinica. 2023; 19 (6): 338-344. doi: 10.1016/j.reumae.2023.05.001

14. Spontaneous intracranial hypotension: diagnostic and therapeutic workup. Luetzen N., Dovi-Akue P., Fung C. et al. Neuroradiology. 2021; 63 (11): 1765-1772. doi:10.1007/s00234-021-02766-z

E.A. Tkachuk, D.M. Barykova, T.E. Povalko, G.P. Bogonosova, I.J. Seminsky, T.A. Astakhova, D.V. Lubimova, V.V. Sizykh

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CLINICAL CASE OF MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 5 (LEY SYNDROME)

Relevance. Diagnosis of mitochondrial pathology is a difficult practical task. The variability of clinical manifestations of mitochoric diseases is associated with high genetic heterogeneity of mitochondrial pathology. Therefore, the analysis of clinical cases of mitochondrial pathology is an urgent task for early diagnosis.

The aim of this study: to analyze a clinical case of mitochondrial complex deficiency complex I, nuclear type 5 (Ley syndrome).

The result of the study: a description of a clinical case of Ley syndrome was carried out. It is shown that the development of the disease manifested in early preschool age against the background of intercurrent disease. The disease manifested itself by metabolic disorders, degenerative signs from the nervous system, immunological changes and within 9 months led to a fatal outcome.

Conclusion. The absence of specific signs at the initial stage significantly complicates the diagnosis of the disease and leads to difficulties in diagnosis.

Keywords: Ley syndrome; "mitochondrial complex I deficiency, type 5"; NDUFS1 gene.

Relevance. Timely diagnosis of hereditary pathology remains an urgent problem in clinical medicine. Mitochondrial diseases are particularly difficult to diagnose. The genetic heterogeneity of mitochondrial diseases is extremely high, including due to mutations in genes regulating the work of mitochondria, but located in the nucleus. At the same time, there are no obvious correlations between genotype and phenotype, and a conclusion about the etiology based on a clinical or biochemical picture is difficult, and sometimes impossible [7]. In this regard, the analysis of clinical variants of mitochondrial diseases is an important and urgent task.

Introduction. Leigh syndrome (synonyms: Lee, Leigh) is a heterogeneous disease of hereditary genesis associated with mutation of energy metabolism genes (complexes I, II, III, IV, V of the mitochondrial respiratory chain) responsible for oxidative phosphorylation, synthesis of ATP and components of the pyruvate dehydrogenase complex [1]. As a result of a violation of energy metabolism, damage to the substance of the brain occurs [1], accompanied by progressive neurological symptoms (muscle hypotension, loss of previously acquired psychomotor skills, seizures in the form of myoclonus, cerebellar and extrapyramidal disorders) [12]. Along with neurological symptoms, cardiomyopathy and liver failure develop [13], lactic acidosis [8], and a specific X-ray picture of degenerative brain changes. The manifestation of the disease occurs at an early age [8], or preschool [4], even less often – in adolescence [2] and can be provoked by intercurrent diseases [1].

The incidence of Ley syndrome is 1 in 36,000 newborns [1]. The type of inheritance is autosomal recessive [6], but may have mitochondrial or X-linked recessive inheritance (depending on the mutant gene responsible for the formation of the mitochondrial complex) [5].

A clinical case. The child (girl) is 4 years old, urgently admitted to the City Ivano-Matrenenskaya Children's Clinical Hospital (GIMDKB) with complaints of convulsive contractions in the extremities, periodic vomiting, weakness, gait disorder (turns her right leg outwards when walking, bends her knee), lower back pain, soreness in the lower extremities.

Anamnesis. A child from the first pregnancy, the first birth. The pregnancy proceeded without any peculiarities. Delivery on time is 39 weeks, independent, the age of the parents at the time of delivery: mother is 24 years old, father is 61 years old. Birth weight 3200 g, body length at birth 51 cm. She grew and developed according to her age. He is registered at a dispensary with a gastroenterologist with a diagnosis of gastroesophageal reflux disease (GERD) of the 3rd degree, a reactive state of the pancreas. All vaccinations are age-appropriate. There were no blood transfusions. It was not possible to identify the hereditary burden.

The disease began acutely 6 months ago with an increase in body temperature to 40 ° C, treatment did not help, the fever lasted for 3 days.

She was taken to the district hospital with a diagnosis of acute respiratory viral infections, neurotoxicosis. On the same day, she felt worse, lost consciousness, and was transferred to the intensive care unit. PCR (polymerase chain reaction) for COVID-19 is positive. I received ceftriaxone and mannitol. Computed to-

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mography (CT) of the brain revealed no focal changes. The condition is without positive dynamics. She was transferred to the regional clinical children's hospital, where she was diagnosed with grade 3 GERD without esophagitis (vomiting syndrome). Metabolic disorders (hypercholesterolemia), cardiac arrhythmia. A nuclear magnetic resonance imaging of the brain was performed, which revealed gliosis of the brain. She was discharged with improvement.

6 months after discharge, her condition deteriorated sharply, which is why she was hospitalized in the HIMDKB.

Objective status. The condition is serious. The temperature is at normal and subfebrile levels. There is no vomiting upon admission. The child is conscious, answers questions late, correctly. Sluggish, hypodynamic. Visual response is preserved, friendly, horizontal nystagmus. Divergent squint, watching objects. You can't stand on your own. There are no seizures. Hyperesthesia. The skin is pale, the turgor is preserved. There is no swelling. There is hyperemia of the arches in the throat, hypertrophy of the palatine tonsils of the 1st degree, the tongue is overlaid with a yellow plaque along the middle line.

The biochemical blood test increased the level of C-reactive protein (CRP) to 6.9 mg/l.

MSCT of the brain with contrast was performed. Conclusion: signs of partial concretion of C2-C3 vertebrae. Otherwise, no pathological changes were detected.

During the examination by an ophthalmologist, the alleged diagnosis was made – pronounced hypoxic changes in the optic disc with its atrophy.

Tandem mass spectrometry (MS/MS) for the quantitative determination of amino acids, succenylacetone, free carnitine, acylcarnitines revealed no significant deviations. Of the studied parameters, only proline 78.8 mmol/l was below the norm (at a norm of 89.8-305 mmol/l).

Based on anamnestic, clinical, laboratory, and instrumental data, the diagnosis was made: unspecified quadriparesis. Nystagmus. Differential diagnosis: encephalic demyelinating process.

Further, during the next 3 months after hospitalization, there was a deterioration in the general condition and an aggravation of the MRI picture of the brain and spinal cord by the type of acute demyelinating encephalomyelitis. Foci of demyelination appeared in the basal nuclei (pale ball on the right, white matter of the legs of the brain, right cerebellar pedicle, hemispheres of the cerebellum, medulla oblongata, spinal cord to the level of C7, which may correspond to the course of acute demyelinating encephalomyelitis). The picture of the epiphysis cyst, moderate expansion of the internal cerebrospinal spaces (Fig. 1, 2, 3).

Immunological changes were noted: the phagocytic activity of leukocytes was reduced, the level of JgG was reduced (0.611 g/l, norm 4.53 – 9.16 g/l; 0.0526 g/l, norm 5.40-18.22 g/l), bilateral polysegmental pneumonia joined. A toxic allergic reaction developed during immunoglobulin treatment. There were signs of systemic inflammatory response syndrome, generalized edematous syndrome, hypoproteinemia, reactive pericholecystitis, pancreatitis.

Moderate respiratory distress syndrome (RDS), pulmonary hypertension, and increasing cardiovascular insufficiency have joined. Pronounced quadriparesis remained in the neurological status. The level of erythrocytes decreased to 2.92×109, the hemoglobin level was 80 g/l. In the biochemical analysis of blood, hypoalbuminemia, hypoproteinemia were noted, a small-point rash appeared on the trunk, limbs, and the temperature rose to 37.7 ° C. DIC syndrome has developed. A hemotransfusion of erythrocyte mass was performed with a positive effect.

However, the condition worsened further, the patient was immersed in a drug-induced sleep, while the signs of severe RDS persisted, effective breathing could be maintained only on 90% oxygen. By this point, the leading pathogenetic syndrome determining the severity of the condition was cerebral, respiratory and cardiovascular insufficiency.

This was followed by a deterioration of the picture on MSCT: damage to the white matter of the brain (mainly the frontal-parietal lobes symmetrically on both sides, with hemorrhagic impregnation in the right frontal lobe, damage to the knee of the corpus callosum). Signs of widespread lesions of the white matter of the frontal, temporal and occipital lobes on both sides, the white matter of the basal nuclei (outer capsule) on both sides, the corpus callosum with the formation of leukomalacia sites in the frontal lobes with negative MSCT dynamics. Signs of partial concretion of C2, C3 vertebrae.

The main diagnosis was formulated as: Demyelinating CNS disease of unspecified etiology. Multiphase disseminated encephalomyelitis, probably postinfectious, severe progressive course. Bilateral pneumonia of mixed etiology, severe respiratory insufficiency of the 3rd degree, disseminated intravascular coagulation syndrome (DIC syndrome), cardiovascular insufficiency, acute pancreatitis. The immunodeficiency condition is unspecified. Toxic-allergic reaction to immunoglobulin. Common urticaria. Dilation of the esophagus. Non-erosive reflux esophagitis. Insufficiency of the cardia. Superficial gastroduodenitis of the antrum of the stomach. GERD of the 4th degree.

3 months after hospitalization, biological death was diagnosed. Resuscitation measures in full were not effective. Death occurred as a result of cardiac arrest against the background of progressive cerebral insufficiency.

Morphological signs of damage to the brain and spinal cord were posthumously recorded: foci of necrosis of the substance of the brain and spinal astrogliosis, numerous perivascular couplings in the substance of the brain, pronounced dystrophic changes in preserved neurocytes, foci of linear discharge and cellular prolapse in the substance of the brain, foci of a decrease in the number of neurons of the molecular and granular layers

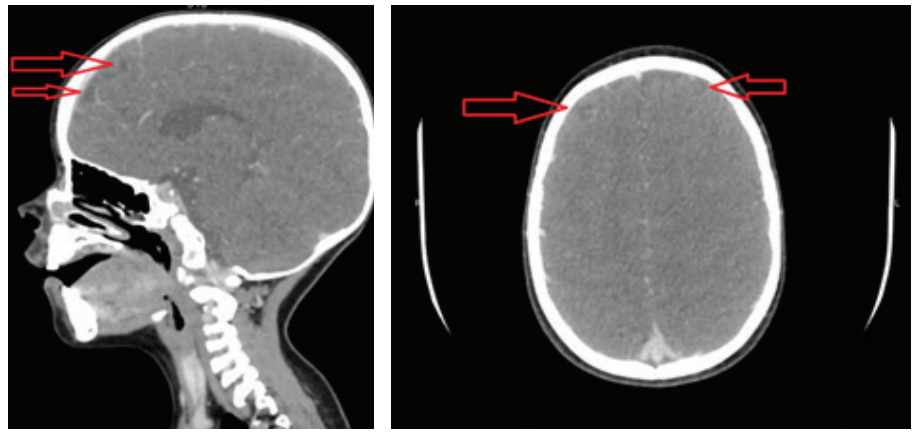

Fig.1. Initial brain changes. 6 months from the beginning of the manifestation of the disease (upon admission to the hospital. The arrows indicate the formation of a cyst

of the cerebellum with focal inclusions of Purkinje cells, fields of gliofibrosis, foci of large-focal encephalomyelolysis, secondary foci of cerebral leukomalacia in the corpus callosum, tissues of the frontal lobe of the right hemisphere, the zone of the central nuclei of the right hemisphere. Postmortem signs of progressive cerebral insufficiency, multiple organ failure syndrome were noted: RDS in the lungs, foci of tubular necrosis in the kidneys, deglycogenesis of the heart, liver, and skeletal muscles. Swelling of the brain and spinal cord. Adrenal adenoma. Morphological signs of secondary immunodeficiency: emptying of follicles of the paratracheal lymph node, as well as lymph nodes of the mesentery and spleen.

Posthumously, full-exome DNA sequencing was performed, which revealed a pathogenic variant of the NDUFS1 gene at position (GRCh37/hg19) chr2:207011681:A>G, position in cDNA c.683T>C with effect p.(Val228Ala). The patient's DNA was analyzed using the Illumina NextSeq550DX genetic analyzer using the pair-terminal reading method (2x151 bp). For sample preparation, the technique of selective capture of DNA sites belonging to the coding regions of human genes (Agilent SureSelect Human All Exon V8 kit) was used, followed by sequencing by synthesis (SBS). The designation of the identified variants was carried out in accordance with the international standards of the HGVS nomenclature (http://varnomen.hgvs.org). Sequencing data processing was carried out using an automated algorithm developed in the Bioinformatics Department of the Federal State Budgetary Budgetary Institution "Medicogenetic Center named afteracademician N.P.Bochkova" (NGS-DATA reg. No. 2021614055, 2021662119, since 2017).

Discussion of the results. Mutations of the NDUFS1 gene cause deficiency of mitochondrial complex I, nuclear type 5. [10]. The mitochondrial complex I (NADH) itself, a multisubunit forming ubiquinone oxidoreductase, is the first enzyme complex in the electron transport chain of mitochondria [10]. It can be fragmented into 3 different fractions: flavoprotein fraction, iron-sulfur protein fraction (IP) and hydrophobic protein fraction (HP). The IP fraction consists of products of *the NDUFS, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6* and *NDUFA5* genes [9]. Functionally, this enzyme is considered to be the first protein to accept electrons from NADH-flavoprotein reductase inside the complex [10].

Other researchers [11] have identified the protein encoded by the NDUFS1 gene as a critical substrate of caspase in mitochondria. When mutated, the protein becomes insoluble, but even with such a protein, the cell is able to maintain mitochondrial transmembrane potential and ATP levels during apoptosis. However, there is a decrease in the production of reactive oxygen species in response to apoptotic stimuli. This did not affect the release of cytochrome C and DNA fragmentation during apoptosis, but the morphology of the mitochondria of apopting cells and the integrity of the plasma membrane were preserved [11].

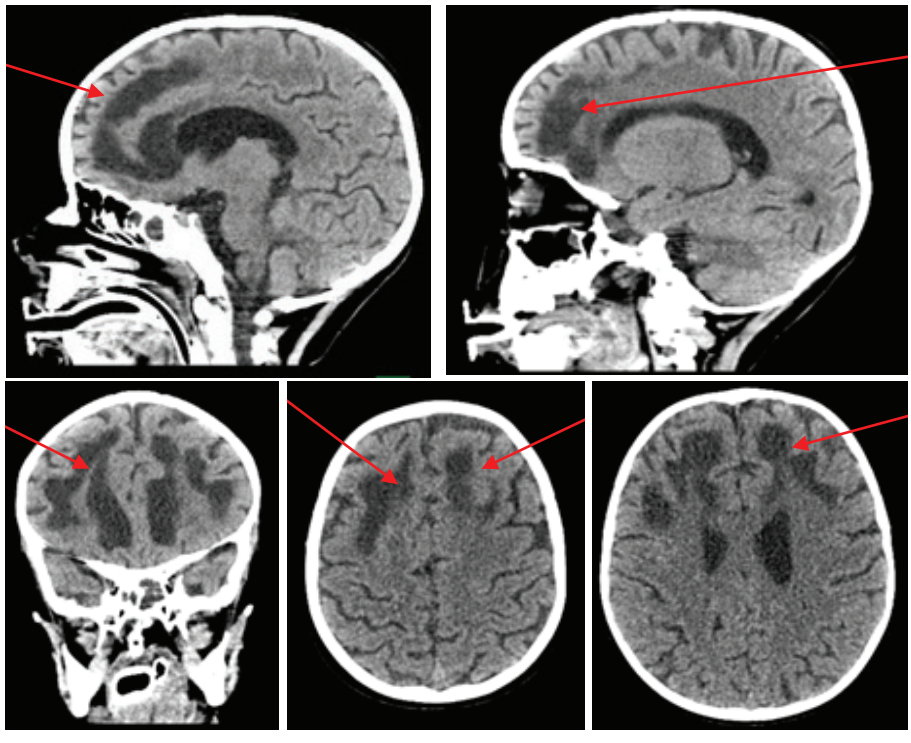

Fig. 2. Brain changes 8 months after the onset of the disease manifestation. Multiple cysts of the brain

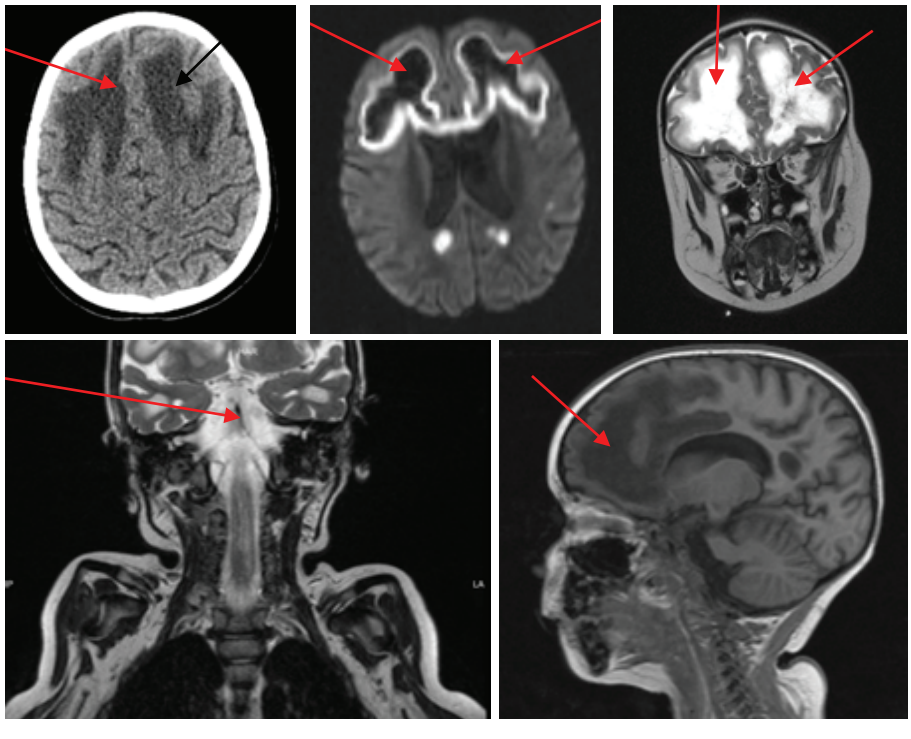

Fig. 3. Brain changes 9 months after the onset of the disease (20 days before the fatal outcome. Multiple cysts of the brain

In general, from the data presented, it can be concluded that the product of the NDUFS1 gene plays an important role in the synthesis of ATP (controlling energy processes), but most importantly regulates the processes of apoptosis (probably triggering autoimmune processes).

Conclusion. At the moment, mitochondrial pathology is difficult to diagnose and has no effective treatment methods. The considered clinical case associated with a deficiency of mitochondrial complex I, nuclear type 5 has severe clinical manifestations and a progressive course. The absence of specific diagnostic markers at the initial stage of development and the rare prevalence of the disease significantly complicates diagnosis. In this regard, it is necessary to pay more attention to the awareness of doctors about hereditary pathology and the role of genetic factors in the structure of general pathology [3].

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Informed consent to publication. The authors received written consent from the patient's legal representative for the analysis and publication of medical data.

References

1. Lepesova MM, Myrzalieva BD, Kurmanbekova NA, Vaisova EM, & Aitbayeva PR. Podostraya nekrotiziruyushchaya encefalomielopatiya – sindrom Li. Slozhnyj klinicheskij sluchaj [Subacute necrotizing encephalomyelopathy – Ley syndrome. A complex clinical case]. Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta [Bulletin of the Kazakh National Medical University. 2016; 2: 116-118 (In Russ.).]

2. Sukhorukov VS. Ocherki mitohondrial'noj patolgii [Sketches of mitochondrial pastoralism. M.: ID «Medpraxis-M», 2011. P 60-68 (In Russ.).]

3. Tkachuk EA, Seminsky IZh. Rol' genetiki v sovremennoj medicine [The role of genetics in modern medicine]. Bajkal'skij medicinskij zhurnal [Baikal Medical Journal. 2022;1(1):81-88 (In Russ.).] https://doi.org/10.57256/2949-0715-2022-1-81-88 .

4. Haack TB, Haberberger B, Frisch EM, Wieland T, Iuso A, Gorza M, Strecker V, Graf E, Mayr JA, Herberg U, Hennermann JB, Klopstock T, Kuhn KA, Ahting U, Sperl W, Wilichowski E, Hoffmann GF, Tesarova M, Hansikova H, Zeman J, Plecko B, Zeviani M, Wittig I, Strom TM, Schuelke M, Freisinger P, Meitinger T, Prokisch H. Molecular diagnosis in mitochondrial complex I deficiency using exome sequencing. J Med Genet. 2012 Apr;49(4):277-83. doi: 10.1136/jmedgenet-2012-100846. PMID: 22499348.

5. van den Heuvel L, Ruitenbeek W, Smeets R, Gelman-Kohan Z, Elpeleg O, Loeffen J, Trijbels F, Mariman E, de Bruijn D, Smeitink J. Demonstration of a new pathogenic mutation in human complex I deficiency: a 5-bp duplication in the nuclear gene encoding the 18-kD (AQDQ) subunit. Am J Hum Genet. 1998 Feb;62(2):262-8. doi: 10.1086/301716. PMID: 9463323; PMCID: PMC1376892.

6. von Kleist-Retzow JC, Cormier-Daire V, de Lonlay P, Parfait B, Chretien D, Rustin P, Feingold J, Rötig A, Munnich A. A high rate (20%-30%) of parental consanguinity in cytochrome-oxidase deficiency. Am J Hum Genet. 1998 Aug;63(2):428-35. doi: 10.1086/301957. PMID: 9683589; PMCID: PMC1377299.

7. Loeffen JL, Smeitink JA, Trijbels JM, Janssen AJ, Triepels RH, Sengers RC, van den Heuvel LP. Isolated complex I deficiency in children: clinical, biochemical and genetic aspects. Hum Mutat. 2000;15(2):123-34. doi: 10.1002/(SICI)1098-1004(200002)15:2<123::AID-HUMU1>3.0.CO;2-P. PMID: 10649489.

8. Bénit P, Chretien D, Kadhom N, de Lonlay-Debeney P, Cormier-Daire V, Cabral A, Peudenier S, Rustin P, Munnich A, Rötig A. Large-scale deletion and point mutations of the nuclear NDUFV1 and NDUFS1 genes in mitochondrial complex I deficiency. Am J Hum Genet. 2001 Jun;68(6):1344-52. doi: 10.1086/320603. Epub 2001 May 7. PMID: 11349233; PMCID: PMC1226121.

9. Ferreira M, Torraco A, Rizza T, Fattori F, Meschini MC, Castana C, Go NE, Nargang FE, Duarte M, Piemonte F, Dionisi-Vici C, Videira A, Vilarinho L, Santorelli FM, Carrozzo R, Bertini E. Progressive cavitating leukoencephalopathy associated with respiratory chain complex I deficiency and a novel mutation in NDUFS1. Neurogenetics. 2011 Feb;12(1):9-17. doi: 10.1007/s10048-010-0265-2. Epub 2011 Jan 4. PMID: 21203893.

10. DiMauro S, De Vivo DC. Genetic heterogeneity in Leigh syndrome. Ann Neurol. 1996 Jul;40(1):5-7. doi: 10.1002/ana.410400104. PMID: 8687192.

11. Ragan, C. I. Structure of NADH-ubiquinone reductase (complex I). Curr. Top. Bioenerg. 15: 1-36, 1987.

12. Loeffen JL, Triepels RH, van den Heuvel LP, Schuelke M, Buskens CA, Smeets RJ, Trijbels JM, Smeitink JA. cDNA of eight nuclear encoded subunits of NADH:ubiquinone oxidoreductase: human complex I cDNA characterization completed. Biochem Biophys Res Commun. 1998 Dec 18;253(2):415-22. doi: 10.1006/bbrc.1998.9786. PMID: 9878551.

13. Ricci JE, Muñoz-Pinedo C, Fitzgerald P, Bailly-Maitre B, Perkins GA, Yadava N, Scheffler IE, Ellisman MH, Green DR. Disruption of mitochondrial function during apoptosis is mediated by caspase cleavage of the p75 subunit of complex I of the electron transport chain. Cell. 2004 Jun 11;117(6):773-86. doi: 10.1016/j.cell.2004.05.008. PMID: 15186778.

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DILATED CARDIOMYOPATHY IN A YOUNG PATIENT

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First identified by decompensation of chronic heart failure (CHF), requires an immediate diagnostic search for the cause of this clinical condition. Dilated cardiomyopathy (DCM) is the 3rd most common cause of CHF in the Russian Federation, as well as one of the main causes leading to heart transplantation. According to statistics, DCM is most often detected in males, more often of working age. Not only a large number of etiological factors can lead to the development of DCM, but also their combinations, which in turn poses a big problem for doctors of practical healthcare due to the difficulty of highly specific diagnosis and establishment of these causes. A special feature of the clinical case presented below is the young age of a male patient who has suffered an acute respiratory viral infection, with the formation of a further clinical picture of rapidly progressing heart failure. Our clinical case focuses the attention of the medical community not only on the complexity of timely diagnosis of possible causes of DCM, but also on the formation of further patient management tactics, with a parallel assessment of further likely consequences, and most importantly, the development of «alertness» among doctors in similar clinical situations..

Keywords: dilated cardiomyopathy, heart failure.

According to the data of the Federal State Statistics Service of the Russian Federation (RF) for 2022, diseases of the circulatory system, established for the first time in life, amounted to 4928.7, which is 33.6 per 1000 people of the population and exceeds the figures for 2021 (4455.7 and 30.3, respectively) [5]. Standardized mortality rates and their shares in the mortality structure are divided into groups: A (chronic coronary heart disease) (CHD) - 17.8±5.8%, B (cognitive impairment) - 13.9±5.9%, C (acute forms of coronary heart disease) - 4.6±2.8%, D (malformations, cardiopathies, endo- and myocarditis - 4.8±2.7%) and group E (acute cerebral circulatory disorders) - 6,1±1,7% [8]. Dilated cardiomyopathy (DCM) is the most common cardiomyopathy. The incidence of DCM is estimated by various authors to be 5 – 7.5 cases per 100,000 population. According to statistics, men are most often ill with DCM (about 2-5 times more often than women), regardless of age. It is known that DCM is the 3rd most common cause of chronic heart failure (CHF) (RF: DCM is the cause of CHF in 0.8% of cases, and CHF of functional class (FC) III-IV – in 5.0%-5.4%), ranks 1st among all causes leading to heart transplantation [3]. Clinical experience shows that determining the etiological factor leading to the development of DCM is a rather difficult question. What could this be related to? The answer lies on the surface. If you look at the etiological classification of DCM, you can understand that it has a huge number of etiological factors from genetic causes, exposure to toxic substances, the infectious process, to autoimmune, auto-inflammatory and endocrine and metabolic disorders-related diseases [4].

In our opinion, the clinical case of a young patient with a clinical manifestation of CHF decompensation deserves special attention in conducting differential diagnosis in real clinical practice and timely treatment.

A clinical case. The patient, a 40-year-old man, was admitted to the cardiology department in August 2023 with complaints of shortness of breath that occurs with minimal physical exertion, swelling of the lower extremities, abdominal enlargement and palpitations.

Anamnesis of the disease. The patient associates the onset of the disease with the development of acute respiratory viral infection, accompanied by pronounced catarrhal phenomena. For the first time, complaints of shortness of breath, frequent and severe cough with sparsely separated sputum, periodic chest pains on inhalation and an increase in temperature to 38-39°C appeared in early November 2017. By the end of the month, against the background of ineffective self-treatment, the patient sought medical help. The chest X-ray revealed signs of right-sided lower lobe pneumonia. With the persistence of complaints of shortness of breath, periodic discomfort in the chest when walking, fatigue, rapid heartbeat – the patient is referred for inpatient treatment. Against the background of therapy, he noted an improvement in his general condition. In early December 2017, the patient again sought medical help with complaints of chest discomfort when walking, shortness of breath and general weakness. An examination was conducted and, based on the data of anamnesis, clinic, instrumental and laboratory diagnostics, the following diagnosis was made: Basic: Coronary heart disease. Postinfarction cardiosclerosis (without date of establishment). Complication: stage I CHF, FC 2 according to NYHA. Concomitant: Community-acquired right-sided lower lobe pneumonia in the convalescence stage. In January 2018, he was hospitalized in the cardiology department, where coronary angiography was performed – no hemodynamically significant coronary artery stenoses were detected. Differential diagnosis was performed and the following diagnosis was made: DCM, treatment was prescribed. On a regular basis, the patient took medications: valsartan/sacubitril, eplerenone, torasemide, clopidogrel, amiodarone, meldonium dihydrate. Over the next 5 years, the patient was repeatedly hospitalized in various medi-

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cal institutions due to the progression of heart failure (HF). He was consulted by a cardiac surgeon, and the patient was offered a heart transplant, which he refused. Due to the deterioration of his general condition due to decompensation of HF, he was hospitalized in the cardiology department.

Anamnesis of life. No heredity. Denies bad habits. Is a disabled person of the 3rd group due to a general disease. Suffers from chronic gouty polyarthritis, intermittent course, activity 1-2 st. Life history. No heredity. Denies bad habits. Is a disabled person of the 3rd group due to a general disease. Suffers from chronic gouty polyarthritis, intermittent course, activity 1-2 st..

Objective data. The patient's condition is serious. Body temperature is 36.7°C . Body weight 90.0 kg, height 175 cm, body mass index 29.39 kg/m^2. The level of consciousness on the Glasgow scale is 15 points. The skin and visible mucous membranes are pale in color, dry, warm, the hairline is without features, there are no rashes/ hemorrhages, the face is puffy. Peripheral edema of the feet and shins. The lymph nodes available for palpation are not enlarged, painless, and not soldered to the surrounding tissue and skin. Musculoskeletal system without pathological changes. During percussion, there is a dulling of the percussion sound in the lower parts. In the lungs: vesicular breathing is weakened, widespread wet wheezing from the basal parts to the middle of the shoulder blades, respiratory rate (BPD) 23 per minute, SpO2 93%. Percutorially, the boundaries of relative cardiac dullness are expanded to the left by 1.5 cm, heart tones: arrhythmic, muted, heart rate (HR) = 110 per 1 minute, blood pressure (BP) 90/40 mmHg.. The tongue is physiologically colored, the papillae are well expressed, soft and elastic on palpation, mobility is preserved in full. Palpation of the abdominal organs is painless. The abdomen is enlarged in size, the liver protrudes from under the edge of the costal arch by 2 cm.

Laboratory diagnostics: General blood test: Hemoglobin – 148 g/l, erythrocytes – 5.07 x 10^{12}/L, platelets – 151 x 10^9 /L, leukocytes – 11.9 x 10^9/L, erythrocyte sedimentation rate – 5 mm/h. Biochemical blood analysis: glucose – 5.3 mmol/L, alanine aminotransferase – 14.1 U/L, aspartate aminotransferase – 27 U/L, creatine phosphokinase – 21.7 U/L, creatinine – 166 mg/L, urea – 22.89 mmol/L, total protein – 72.2 g/L, bilirubin – 51.7 mmol/L, K+ – 5.3 mmol/l, Na+ – 133 mmol/l, Ca – 0.98 mmol/l, pH – 7.320, LDH – 73.0, albumin – 36.4 g/l. General urine analysis: pH – 5.5, protein – 1.87 g/l, specific gravity – 1013 g/l. The dynamics show thrombocytopenia, moderate erythropenia, a progressive increase in the level of liver enzymes, creatinine and urea, as well as increasing proteinuria, uric acid – 799 mmol /l. Coagulogram: RT (sec) – 24.9, PT PT – 42.6, ARTT – 47.5, INR – 1.92. Lipidogram: total cholesterol - 1.95 mmol/L, low-density lipoprotein cholesterol - 0.8 mmol/L, Triglycerides - 0.99 mmol/L.

Instrumental diagnostics. According to the archive of electrocardiograms (ECG) since 2017, there are signs of focal changes in the anterior wall of the left ventricle (LV). In 2019, the following changes were registered for the first time: hypertrophy of the LV and left atrium (LA) with overload and impaired intraventricular conduction. In 2020, incomplete blockade of the right leg of the Gis bundle, atrioventricular blockade of the 1st degree. In May 2023, 3:1 atrial flutter was first recorded with an atrial contraction rate (AR) of 210 beats/min and a ventricular contraction rate (HR) of 70 beats/min. An ECG in August 2023, at the time of hospitalization, recorded atrial flutter 2:1, heart rate 180 beats/min, heart rate 90 beats/min, overload of the right heart, low voltage (Figure No. 1).

Chest X-ray: On the chest X-ray in direct projection, the patient is rotated. Visible pulmonary fields – diffuse areas of heterogeneous infiltration of low intensity are determined in the right pulmonary field in the lower sections. There were no focal infiltrative changes in the left pulmonary field. The pulmonary pattern in the right lung is unevenly reinforced, low-structured, low intensity, deformed. In the left lung, it is not reinforced, low intensity, not deformed. The shadow of the heart is expanded. The shadow of the roots of the lungs: the right root is slightly structured, not expanded, of medium intensity. The left root is not visualized. Sinuses: signs of free fluid in the right pleural cavity up to the level of the middle segment of the 4th rib, the left sinus is not visualized. The contours of the diaphragm on the left are clear and even, on the right they are not visualized. Signs of a paracostal closed hydrothorax on the right in the projection of a small interlobular gap. No bone – traumatic pathology was revealed. Conclusion: infiltrative changes in the right lung are probably of inflammatory etiology. X-ray signs of a right-sided hydrothorax with a liquid volume of 800 ml. X-ray signs of a paracostal obfuscated hydrothorax on the right. Signs of cardiomegaly (Figure No. 2).

Ultrasound examination of abdominal organs: ultrasound signs of moderate changes in the liver, pancreas, kidneys. Hepatosplenomegaly. Ascites. Fluid in the pleural cavity. Instrumental diagnostics.

According to the echocardiography archive (ECHOCG) (2017). Enlargement of the LA. Zones of a-/hypokinesis of the anteroseptal region of the LV. Regurgitation on the mitral valve (MV) 0-1 st. Ejection fraction (EF) of the LV 50%. In mid-2019 - Hypo-, akinesis of the LV in the area of the interatrial septum (IVS), anterolateral wall (ALW) of the LV, anterior wall of the LV, tricuspid valve insufficiency (TVI), mitral valve insufficiency (MVI), dilation of the chambers. LV EF 38%. A year later - dilation of all cavities of the heart. Global contractility of the LV is reduced. Left ventricular diastolic dysfunction (LVD) st. 1 st. LV EF 35%. In 2022 - dilation of all cavities of the heart. Global LV contractility is reduced. LV diastolic dysfunction, diffuse hypo-, akinesis of the anterior septal wall and apex. LVD stage 3. EF 33%. By May 2023 - dilation of all heart cavities. Global LV contractility is reduced. Left ventricular diastolic dysfunction, diffuse hypo-, akinesis of the anterior septal wall and apex. LVD stage 3. EF 33%.

At the time of hospitalization in the

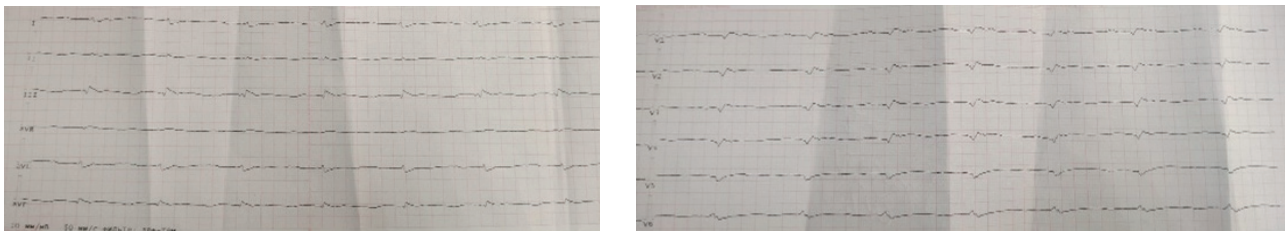

Fig. 1. ECG at the time of hospitalization (August 2023)

cardiology department in August 2023 – LP – 45 mm, end-diastolic size (CDR) LV – 60 mm, end-diastolic volume (CDR) LV – 180 ml, EF (according to Teichgolz) – 30%, interventricular septum (LV) – 11 mm, posterior the wall of the left ventricle (LV) is 10 mm, the right ventricle (RV) is 38 mm, the pulmonary artery (LA) is 22 mm. Dilation of all cavities of the heart. The LV myocardium is not thickened. Diffuse hypokinesis, hypo-, akinesis of the anterior septum wall and apex. Global LV systolic function is drastically reduced. The thoracic aorta is not dilated in all sections. The aortic half-moons are compacted, the opening is sufficient. The wings of the MV are not elongated, not compacted, their opening is sufficient IMV 1.5 st. ITV 3 st. Tricuspid regurgitation. Regurgitation on the pulmonary artery valve. The pressure in the LA is increased (pulmonary hypertension of 1 ct). The inferior vena cava is not dilated, it collapses more than 50% when breathing. At the time of the study, a moderate amount of fluid in the pericardium (up to 500 ml) is determined. Diastolic divergence of pericardial leaflets: behind the posterior wall of the LV up to 16 mm, behind the lateral wall of the LV up to 15 mm, behind the free wall of the pancreas up to 8 mm (Figures No. 3 and No. 4).

The conclusion of the nephrologist. Prerenal acute renal failure (ARF), against the background of chronic renal failure (CRF) stage C3b. The glomerular filtration rate according to CKD-EPI is 37.16 ml/min/1.73 m^2.

Based on complaints, anamnesis data, laboratory and instrumental diagnostic methods, a clinical diagnosis was made: The main one: Dilated cardiomyopathy. Rhythm disturbance according to the type of constant form of atrial flutter 2:1. Complications: stage II B CHF, with reduced systolic function (EF 30%). FC 4 by NYHA. Ascites. Hepatosplenomegaly. MVI 1-2 st. TVI 3 st. Regurgitation on the pulmonary artery valve. Pulmonary hypertension 1 art. Right-hand hydrothorax. Hydropericardium. Prerenal acute renal failure on the background of CRF, CKD C3B, glomerular filtration rate according to CKD-EPI 37.16 ml/min/1.73 m^2. Concomitant: Gout.

Treatment was prescribed: diet No. 10, designed for diseases of the cardiovascular system in order to create favorable conditions for blood circulation, reduce the load on the heart, blood vessels and kidneys, normalize water-salt, ion metabolism, simplify the elimination of toxic products of metabolic processes. Medications: infusion therapy, metabolic therapy, valsartan/sacubitril, dapagliflozin, eplerenone, metoprolol, torasemide, clopidogrel.

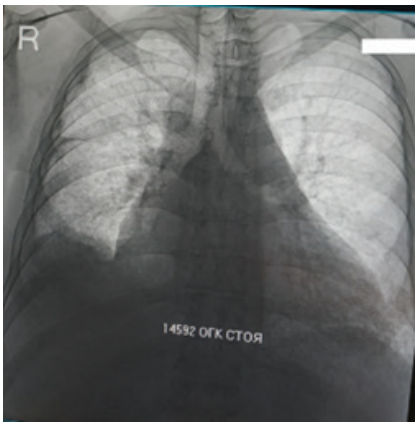

Fig. 2. Chest X-ray

The scales (CHA2 DS2 -VASc) were evaluated - 1 point (LVEF <40%) and (HAS-BLED) - 3 points (creatinine over 200 mg/l – 1 point. Impaired liver function (bilirubin increased by more than 2 times) - 1 point. Labile INR – 1 point) – the patient has indications for anticoagulant therapy, but due to the high hemorrhagic risk, disaggregant therapy is prescribed.

Against the background of the treatment, stabilization of the patient's condition is noted, however, a progressive decrease in PV and the severity of the patient's condition requires urgent consultation with a cardiac surgeon in order to determine indications for heart transplantation. The patient is recommended to: diet No. 10, dynamic monitoring by a cardiologist, nephrologist at the place of residence. At the stage of patient observation, cardiac MRI and Holter ECG monitoring data were not provided. It is recommended to perform echocardiography, daily monitoring of ECG and blood pressure in dynamics, ultrasound Dopplerography of the brachiocephalic arteries on an outpatient basis as planned. Recommended for permanent use: valsartan/sacubitril (under the control of blood pressure, blood electrolytes), dapagliflozin, eplerenone, metoprolol, clopidogrel, torasemide.

Discussion. Taking into account the complaints and anamnesis of the disease of a young man, at the diagnostic stage, the issue of differential diagnosis of diagnoses was solved: postinfarction cardiosclerosis according to ECG data, myocarditis with decompensation of CHF. The revealed scarring of the anterior LV wall on the ECG and the absence of hemodynamic significant stenoses in the coronary arteries according to coronary angiography led to the need for further examination of the patient and differential

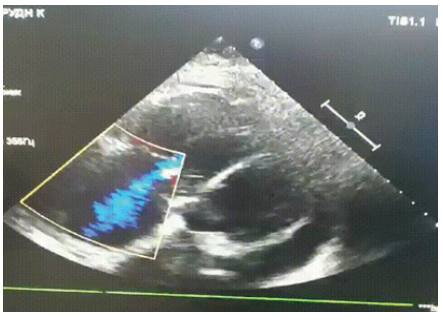

Fig. 3. Echocardiography at the time of admission (August 2023). Dilation of all cavities of the heart, overload of the right parts, regurgitation on the tricuspid valve. Fig. 3. echocardiography at the time of admission (August 2023). Dilation of all cavities of the heart, overload of the right parts, regurgitation on the tricuspid valve

Fig. 4. echocardiography at the time of admission (August 2023). Regurgitation on the pulmonary artery valve

diagnosis.

The problem of diagnosis and treatment of myocarditis in clinical practice stands in a separate place due to the complexity and polyethologicity of the pathological process, the practically absent specific clinical picture limiting pretest diagnosis, the difficulty of conducting a lifetime endomyocardial biopsy (EMB) [1, 6], which is the "gold standard" for the diagnosis of this disease, the basis

for the formation of further tactics patient management [6]. The incidence of myocarditis is 20-30% of all non-coronary heart diseases [1]. With a subacute clinical form not recognized in time, accompanied by latent symptoms at the onset of the disease, with a prolonged course, subsequently leads to the development of structural and functional changes in cardiomyocytes, which causes a further decrease in LV EF and LV dilation [2, 9]

The outcome of all of the above is the transformation into DCM, which, according to clinical observations and autopsies, was detected in a fairly large percentage. There is also evidence of a high percentage of spontaneous recovery (57% on average). According to statistics, morphological signs of myocarditis were not confirmed in patients with DCM who underwent EMB in up to 16% of cases in adults and up to 46% of cases in children. The clinical course of myocarditis described above is important to take into account when making a diagnosis, however, the main and "gold standard" diagnosis that allows you to confirm the diagnosis is the implementation of EMB, performed after an MRI with paramagnetic contrast, to identify the sites of biopsy sampling (at least 3 samples), the data of which are evaluated using the Lake Louise criteria. It should be borne in mind that the sensitivity of this method depends on the number of samples taken (4-5 – 50%, 17 – 79%) [6, 7].

Criteria for the diagnosis of DCM: according to the results of echocardiography, LV dilation or both ventricles of the heart (index of final diastolic volume) LV > 74 ml/ m2 in men and > 61 ml/ m2 in women; significant (EF < 40%) or moderate (EF– 41-49%) decrease in LV EF and the presence of: symptoms and/or signs of CHF; diffuse LV hypokinesia; relative LV wall thickness less than 0.3 (except for diseases with an initially hypertrophic morphofunctional phenotype of the heart); the verified cause of dilation characteristic of DCM (genetic defect, toxic, endocrine, metabolic, alimentary, immune, autoimmune, postinfectious factor, pregnancy). The above criteria are used in the Russian Federation, but there is another classification developed by experts of the World Heart Federation – "MOGE(S)" (Morpho-functional, Organ/system involvement, Genetic, Etiological annotation, Stage, 2013) (Table No. 1), which is based on a combination of letters and numbers that allow you to create each patient has an individual disease code that transmits maximum information about the patient [3].

Classification of cardiomyopathies according to "MOGE(S)"

The key parameter and its letter code	
M – phenotype	**O** – organs and/or systems involved
D - dilated cardiomyopathy	**H** – heart
H – hypertrophic cardiomyopathy	**M** – skeletal muscles
R – restrictive cardiomyopathy	**N** – nervous system
A – Arrhythmogenic dysplasia of the right ventricle	**C** – skin
NC – non–compact myocardium	**E** – eye
NS – non–specific phenotype	**A** – hearing
NA – information is not available	**K** – kidneys
E – previously identified conditions with details (E(D), (E(H), (E(R), (E(A), etc.)	**G** – gastrointestinal tract
	S – skeleton
	Lu – lungs
	Li – liver
	(O) – absence of defeat
G – type of inheritance	**E** – etiology
N – absence of family heredity	**G** - genetic
U - unknown	**G-OC** – is the carrier of the mutation
AD – autosomal dominant	**G-DN** – is a genetic new
AR - autosomal recessive	**G-C** – more than one mutation
XLR – X-chromosome-related recessive	**G-Neg** – no mutations
XLD – X-chromosome-related dominant	**G-NA** – genetic study not available
XL – X-chromosome-related	**G-A** – genetic amyloidosis
M – on the mother's side	**A** –amyloidosis
DN – new mutation	**A-k** – amyloidosis, type K
(O) - absence	**M** – myocarditis
	V – viral infections
	Al – autoimmune
	I – infections other than viral
	T - toxic
	Eo – eosinophilia
	(O) – there is no genetic test
S – stage of heart failure (ACC/AAC:A; B; C; D NYHA class: I; II; III; IV)	

The modern approach to the treatment of patients with DCM has proven its effectiveness in many clinical studies. The tactics of drug management of patients with is based on the principles of therapy of patients with HF with low EF. Quadri therapy is recommended for patients with HF (FC II-IV) and PV less than 40%. This therapy is necessary to reduce the risk of disease progression and includes the use of: angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARA II) or group drugs (ARNI) (valsartan/sacubitril), beta-blockers (BB), ivabradine (in case of intolerance to BB), mineralocorticoid receptor antagonists (AMCR), type 2 sodium-glucose cotransporter inhibitors (iNGLT2, SGLT2 inhibitors), with rapid progression of CHF with the development of edematous syndrome – diuretics. Stable dynamics was achieved against the background of drug support, but the prognosis is more likely unfavorable due to the progression of HF and dilation of all parts of the heart.

A young patient with terminal HF needs not only drug therapy, but also timely resolution of the issue of donor heart transplantation, which is not always available in clinical practice, due to the relatively small percentage of transplants performed. According to statistics from the National Medical Research Center for Transplantation and Artificial Organs named after Academician V.I. Shumakova performed 148 heart transplantations in 2024 [10], but we must not forget that the need for heart transplantation is many times higher than the current statistical indicators of successful operations.

Conclusion. The presented clinical case of a patient with the consequences of an acute respiratory viral infection in a young patient draws the attention of the medical community not only to the need

for timely diagnosis and the choice of the right management tactics, but also to the prediction of possible complications. Assessing the growing proportion of patients with CHF in the population and the socio-economic damage, it is necessary to consider the modernization of the approach to diagnosis and treatment, and most importantly, the prevention of these clinical situations.

References

1. Blagova OV, Moiseeva OM, Paleev FN. Spornye i nereshennye voprosy diagnostiki i lecheniya miokarditov (po materialam obsuzhdeniya Rossijskih nacional'nyh rekomendacij) [Controversial and unresolved issues in the diagnosis and treatment of myocarditis (based on materials from the discussion of Russian national recommendations)]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2021; 26(11): 4655 (In Russ.).] Doi: 10.15829/1560-4071-2021-4655.

2. Blagova OV, Nedostup AV. Sovremennye maski miokardita (ot klinicheskih sindromov k diagnozu) [Modern masks of myocarditis (from clinical syndromes to diagnosis)]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2014; 5(109): 13-22 (In Russ.).]

3. Dilatacionnaya kardiomiopatiya. Proekt klinicheskih rekomendacij [Dilated cardiomyopathy. Project of clinical recommendations). Rossijskoe kardiologicheskoe obshchestvo 2022 (In Russ.).] URL: https://scardio.ru/rekomendacii/proekty_rekomendaciy.

4. Vaikhanskaya TG, Sivitskaya LN, Kurushko TV, et al. Dilatacionnaya kardiomiopatiya: novyj vzglyad na problemu [Dilated cardiomyopathy: a new look at the problem]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2019; 24(4): 35-47 (In Russ.).] Doi: 10.15829/1560-4071-2019-4-35-47

5. Zabolevaemost' naseleniya po osnovnym klassam boleznej, Federal'naya sluzhba gosudarstvennoj statistiki. Naselenie. Zdravoohranenie [Morbidity of the population by main classes of diseases, Federal State Statistics Service. Population. Healthcare (In Russ.).] URL: https://rosstat.gov.ru/folder/13721.

6. Arutyunov GP, Paleev FN, Moiseeva OM, et al. Miokardity u vzroslyh. Klinicheskie rekomendacii 2020 [Myocarditis in adults. Clinical recommendations 2020]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2021; 26(11): 4790 (In Russ.).] Doi: 10.15829/1560-4071-2021-4790.

7. Mitrofanova L.B. Rol' endomiokardial'noj biopsii v diagnostike vospalitel'nyh zabolevanij miokarda [The role of endomyocardial biopsy in the diagnosis of inflammatory myocardial diseases]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2016; 1(129); 73–79 (In Russ.).] Doi: 10.15829/1560-4071-2016-1-73-79.

8. Samorodskaya IV, Starinskaya MA, Boytsov SA. Dinamika regional'nyh pokazatelej smertnosti ot serdechno-sosudistyh zabolevanij i kognitivnye narusheniya v Rossii 2019-2021 godah [Dynamics of regional mortality rates from cardiovascular diseases and cognitive impairment in Russia in 2019-2021]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2023; 28(4): 5256 (In Russ.).] Doi: 10.15829/1560-4071-2023-5256.

9. Titov VA, Ignatieva ES, Mitrofanova LB, et al. Sravnitel'noe issledovanie informativnosti neinvazivnyh metodov diagnostiki vospalitel'nyh zabolevanij miokarda [Comparative study of the information content of non-invasive methods for diagnosing inflammatory myocardial diseases]. Rossijskij kardiologicheskij zhurnal [Russ J Cardiol. 2018; 2(154): 53–59 (In Russ.).] Doi: 10.15829/1560-4071-2018-2-53-59.

10. Publichnyj otchet o rezul'tatah deyatel'nosti FGBU «Nacional'nyj medicinskij issledovatel'skij centr transplantologii i iskusstvennyh organov im. ak. V.I. Shumakova» Minzdrava Rossii i o sostoyanii okazaniya medicinskoj pomoshchi po profilyu «transplantaciya» [Public report on the results of the activities of the Federal State Budgetary Institution "National Medical Research Center for Transplantology and Artificial Organs named after akad. V.I. Shumakov, Ministry of Health of Russia and on the state of medical care in the field of transplantation (In Russ.).] URL: https://transpl.ru/about/statistics.

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CLINICAL CASE OF SEVERE CORONAVIRUS INFECTION COMPLICATED BY BILATERAL HOSPITAL-ACQUIRED PNEUMONIA IN A PREGNANT WOMAN

This article presents a clinical case of a severe course of COVID-19 in a 27-year-old pregnant woman. The infectious process was complicated by bilateral out-of-hospital pneumonia. A woman was admitted to the obstetric infectious disease unit at 39 weeks gestation, complaining of an attack-like cough with scanty sputum, a feeling of tightness in the chest, runny nose, weakness, increased body temperature up to 37.9 C. SARS-Cov-2 virus RNA was diagnosed by PCR. The condition progressively worsened overnight, the pregnant woman was transferred to non-invasive ventilation in the intensive care unit, with lung parenchyma lesions up to 50%.

Against the background of progressing respiratory failure, acute respiratory distress syndrome woman delivered by emergency cesarean section at 39 weeks' gestation. A live, premature baby girl was born, without asphyxia. The patient's condition remained extremely serious. On the 2nd day of the postoperative period sepsis was diagnosed, the lesion of lung parenchyma amounted to 75-100%.

Multicomponent therapy, including recombinant monoclonal antibodies to the interleukin-6 receptor, resulted in improvement.

Keywords: COVID-19, pregnancy, respiratory failure, community-acquired pneumonia, multicomponent therapy

Introduction. The global pandemic of a novel COVID-19 coronavirus infection caused by SARS-CoV-2 virus has had a strong impact on the whole world [3, 4, 8]. Since then, a tremendous breakthrough in science has been made and new diagnostic techniques, prevention, treatment and organizational approaches have been developed in the management of individuals with COVID-19 [5,9].

COVID-19 infection is characterized

by the development of complications from various organs and systems [10,13,14]. Respiratory, cardiovascular, digestive and hemostasis systems are quite often affected [6, 7, 11]. Respiratory system lesions are manifested as viral pneumonia with the development of acute respiratory distress syndrome and respiratory failure [15]. The development of respiratory system lesions leads to the phenomena of general hypoxia, in these conditions there is a violation of homeostasis and adaptive processes of the body, which in turn contributes to the development of pathological conditions of other organs and systems [16, 17, 18].

The incidence of COVID-19 in pregnant women has now been shown to be higher than in the population [1,2]. It has been established that due to unique immune characteristics and susceptibility to respiratory pathogens, pregnant women infected with SARS-CoV-2 should be considered a high-risk group for the development of severe disease and mortality. In pregnant women with COVID-19, a sudden development of a critical condition against the background of a stable course of the disease is possible [12].

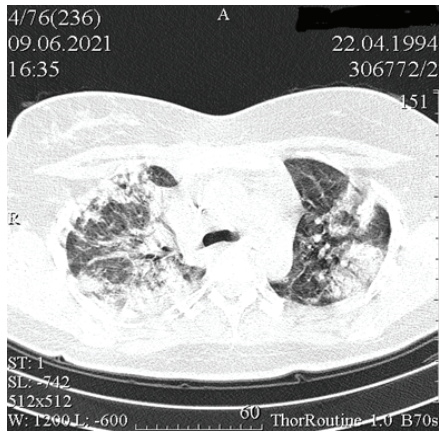
Objective of the study: To analyze a clinical case of a pregnant woman with severe coronavirus infection complicated by bilateral out-of-hospital pneumonia, respiratory failure (RF) of II degree.

Clinical observation: Patient I., 27 years old. The present pregnancy is the second, desired pregnancy. The first pregnancy in 2016 proceeded without complications, ended prematurely by emergency cesarean section due to ineffective treatment of obstetric failure.

Course of the present pregnancy: moderate toxicosis in the first half of the pregnancy, treated as an outpatient; The second half of pregnancy proceeded smoothly. The total weight gain during pregnancy amounted to 6 kg.

The pregnant woman applied on 25/05/2021 at 17h30m to the obstetric infectious disease department of the perinatal center of the Yakutsk Republican Clinical Hospital complaining of an attack-like cough with scanty sputum, a feeling of compression in the chest, runny nose, weakness, increased body temperature up to 37.9C. SARS-Cov-2 RNA was detected by PCR. She was diagnosed with COVID-19, of moderate severity. Pregnancy 39 weeks, cephalic presentation. Aggravated obstetric history - uterine scar.

From the anamnesis: considers herself sick for seven days, when pain in the throat, dry cough appeared. Got sick after coming into contact with a sick friend.



Computed tomography of lungs on the 12th day of the disease. Diffuse lung lesion by type of frosted glass and consolidation combined with reticular changes. Involvement of lung parenchyma more than 80%

On admission, the condition is moderately severe, consciousness is clear. The physique is hypersthenic. The skin and visible mucous membranes are unchanged. Lymph nodes are not enlarged. Body temperature 36.0C, weight 81.4 kg, height 161cm, BMI - 31.4. Heart tones are rhythmic, no murmurs. Heart rate 125d/min, BP 85/66mmHg. Respiration in the lungs is rigid, no rales, HR 22 per min, SpO2 94% (on atmospheric air), 97% (with oxygen support).

CT scan shows signs of interstitial bilateral pneumonia COVID 19. Involvement of lung parenchyma 25-50%- CT-2.

On examination in the general blood test leukocytes 8.34x10^9/l, lymphopenia 0.75x10^9/l, Increased hepatic transaminases ALT 51.2, AST 30.7, increased LDH (lactate dehydrogenase) up to 585ed/l, C reactive protein 88.4 mg/l, urinalysis without features.

According to version №11 of the temporary methodological recommendations dated 07.05.2021 “Prevention, diagnosis and treatment of New coronavirus infection COVID-19”, Antiviral and antibacterial therapy: Interferon alpha 2b 3 capsules 5 times a day nasally, Favipiravir 1800 mg 2 times a day orally, then 800 mg 2 times a day thereafter; Ampicillin and sulbactam 1.0g+0.5g x 3 times a day intravenously from 26/05/21, Azithromycin 0.5 g once a day intravenously from 27/05/21 (№3). Anticoagulants in therapeutic dose - Enoxaparin sodium 0.5 g 2 times a day since 25/06/21 were prescribed. The patient received glucocorticosteroids for preemptive purposes: dexamethasone 12 mg intravenous drip 2 times a day since 26/05/21, methylprednisolone 125 mg 4 times a day intravenously from 27/05/21. Humidified oxygen insufflation was performed at a rate of 10L/min, prone - position on the side for at least 16 hours per day.

On the 2nd day of treatment the pregnant woman with worsening condition was transferred to non-invasive artificial lung ventilation (NIV) by Hamilton C2 apparatus in NIV mode with the parameters of support 17cm of water column, taking into account the level of saturation and blood gases.

During 3 days of intensive treatment the condition continued to worsen, respiratory failure increased, blood oxygen saturation decreased to 88%. Taking into account the grave condition of the pregnant woman, the lack of effect from the therapy, and her premature gestational age, she was delivered by cesarean section. The operation was performed under spinal anesthesia. A live premature baby girl was extracted, without asphyxia, Apgar scale 8-8 points, with a weight of 3366g, length 56cm. Blood loss in labor amounted to 600ml. After delivery, the woman's treatment continued in the intensive care unit. The patient was on non-invasive artificial ventilation for 5 days. The child was observed in the isolation ward, PCR for COVID 19 was negative, discharged home on the 11th day of life.

Against the background of intensive therapy, the patient's condition remained extremely severe. Daily monitoring of blood counts reflected a progressive increase in leukocyte counts to 27.77 (10^9/L), thrombocytosis up to 445(10^9/l),increased CRP level up to 114.7 mg/l, Increase in lactate dehydrogenase to 1120 units/l, interleukin-6 to 27 mg/ml, of presepsin to 732 pg/ml. Sepsis was diagnosed on the 2nd day of the postoperative period, Immunovenin 25ml intravenous micro-jet via syringe pump and Fluconazole 250mg intravenously were added to the treatment. The control computed tomography of lungs on a series of slices revealed negative dynamics: involvement of lung parenchyma 75-100% (photo №1)

During treatment, telemedicine consultation with the Federal State Budgetary Institution “National Medical Research Center of Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov” of the Ministry of Health of the Russian Federation was repeatedly conducted. A drug has been prescribed for treatment Ilcira (levilimumab) 324 mg intravenous drip once 28/05/21 change of antibacterial therapy to drugs from the group of carbopenems and oxazolidines - Meropenem 1 gram 3 times a

day intravenous drip since 28/05/21 was carried out, Linezolid 600 mg 2 times a day intravenous drip. Inotropic support on norepinephrine microjet intravenously 0.2mg/hour, restrictive infusion therapy in the volume of 15 ml/kg/day, correction of water-electrolyte balance, protein enteral nutrition were performed.

On the 10th day of the postoperative period, ultrasound examination revealed lochiometra and podaponeurotic hematoma: uterine cavity expansion up to 33 mm, hematoma with dimensions 68x71x60 mm, volume 153cm3. Surgery was performed: opening and emptying of the hematoma of the anterior abdominal wall, vacuum aspiration of the uterine cavity. Blood loss amounted to 200ml. After surgery - additional change of antibiotic therapy to Cefoperazone and sulbactam 2 g. 2 times a day intravenously since 07/06/21, Levofloxacin 500 mg 2 times a day orally. During further inpatient treatment, dyspnea decreased, cough subsided, and independent breathing without humidified oxygen was restored. Multicomponent therapy led to improvement of the condition, normalization of clinical test parameters on the 21st day of the disease. She spent a total of 16 days in the intensive care unit.

On the background of improvement of clinical and laboratory parameters, on the 36th day, in a condition close to satisfactory, with asthenic syndrome, the patient was discharged for outpatient treatment.

Conclusions:

The clinical interest of the observation lies in the extremely severe course of coronavirus infection in a pregnant woman with multiple complications. In case of worsening of the general condition, increasing dyspnea, reasonable and timely delivery was performed by cesarean section, antibacterial drugs from the reserve group and genetically engineered biological agents were used. The woman has a positive prognosis for further realization of reproductive function.

Delivery at increasing symptoms of respiratory failure, adequate treatment of severe coronavirus infection with total lung damage contributed to the patient's recovery. This clinical case demonstrates the need for an individualized approach in the management of each patient with coronavirus infection.

References

1. Belokrinitskaya TE, Artymuk NV, Filippov OS. Dinamika e`pidemicheskogo processa i techenie novoj koronavirusnoj infekcii COVID-19 u beremenny`x Dal`nevostochnogo i Sibirskogo federal`ny`x okrugov [Dynamics of the epidemic process and course of a new coronavirus infection COVID-19 in pregnant women of the Far Eastern and Siberian Federal Districts]. Gynaecology. 2020; 22 (5): 6-11 (In Russ.).]

2. Belokrinitskaya TE, Artymuk NV, Filippov OS. Klinicheskoe techenie, materinskie i perinatal`ny`e isxody` novoj koronavirusnoj infekcii COVID-19 u beremenny`x Sibiri i Dal`nego Vostoka [Clinical course, maternal and perinatal outcomes of novel COVID-19 coronavirus infection in pregnant women in Siberia and the Far East]. Akusherstvo i ginekologiya [Obstetrics and Gynaecology. 2021; 2: 48-54 (In Russ.).]

3. Ivanova GE. Aktual`ny`evoprosy` reabilitacii pacientov s insul`tom na fone novoj koronavirusnoj infekcii (COVID-19). Rezolyuciya Soveta e`kspertov [Current issues of rehabilitation of stroke patients against the background of a new coronavirus infection (COVID-19). Resolution of the Council of Experts]. Zhurnal nevrologii i psixiatrii im. S.S. Korsakova. Speczvy`puski [Journal of Neurology and Psychiatry named after S.S. Korsakov. Special issues. 2020; 120(8):81-87 (In Russ.).]

4. Prokopenko SV. COVID-19-associirovanny`j insul`t: opy`t Kraevoj klinicheskoj bol`nicy g. Krasnoyarska [COVID-19-associated stroke: experience of the

Krasnoyarsk Krai Clinical Hospital]. Izvestiya Rossijskoj Voenno-medicinskoj akademii [Proceedings of the Russian Military Medical Academy. 2021; 40 (4): 79-85 (In Russ.).]

5. Aslam J, Luqman S, Nazly S, et al. Predictors of fatal neurological complications among admitted COVID-19 patients with their implication in outcome: A Case Control study. PLoS One. 2022; 17(9): e0274485.

6. Bradley BT, Maioli H, Johnston R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020; 396(10247): P.320-332.

7. Choi YH, Laaker C, Hsu M, et al. Molecular Mechanisms of Neuroimmune Crosstalk in the Pathogenesis of Stroke. Int J Mol Sci. 2021; 22(17): 9486.

8. Divani AA, Andalib S, Di Napoli M, et al. Coronavirus Disease 2019 and Stroke: Clinical Manifestations and Pathophysiological Insights. J Stroke Cerebrovasc Dis. 2020; 29(8):104941.

9. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020; 8(12):1201-1208

10.Iwasaki M, Saito J, Zhao H, et al. Inflammation Triggered by SARS-CoV-2 and ACE2 Augment Drives Multiple Organ Failure of Severe COVID-19: Molecular Mechanisms and Implications. Inflammation. 2021; 44(1): 13-34.

11. Johansson A, Mohamed MS, Moulin TC, et al. Neurological manifestations of COVID-19: A comprehensive literature review and discussion of mechanisms. J Neuroimmunol. 2021; 358(577658).

12. Vallejo V, Ilagan JG. A Postpartum Death Due to Coronavirus Disease 2019 (COVID-19) in the United States. Obstet Gynecol. 2020 May 8. doi: 10.1097/AOG.0000000000003950.

13. Remmelink M, De Mendonça R, D'Haene N, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Crit Care. 2020; 24(1): 495.

14. Kiss P, Carcel C, Hockham C, Peters SAE. The impact of the COVID-19 pandemic on the care and management of patients with acute cardiovascular disease: a systematic review. Eur Heart J Qual Care Clin Outcomes. 2021; 7:18–27.

15. Kakarla V, Kaneko N, Nour M, et al. Pathophysiologic mechanisms of cerebral endotheliopathy and stroke due to Sars-CoV-2. J Cereb Blood Flow Metab. 2021; 41(6): 1179-1192.

16. Middeldorp S, Coppens M, van Haaps TF, et al. Middeldorp S. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020; 18(8): 1995-2002.

17. Viguier A, Delamarre L, Duplantier J, et al. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. J Neuroradiol. 2020.

18. Yang AP, Li HM, Tao WQ, et al. Infection with SARS-CoV-2 causes abnormal laboratory results of multiple organs in patients. Aging (Albany NY). 2020; 12(11):10059-10069.

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A CLINICAL CASE OF HYPOPITUITARISM IN AN EIGHT-YEAR PATIENT

A clinical case of hypopituitarism, a rare disease, is diagnosed in an eight-year patient. The early diagnosis of the condition was complicated by specific clinical manifestations. The delayed diagnosis and late replacement therapy resulted in retarded growth of the child.

Keywords: hypopituitarism, retarded growth, hypophisis (pituitary gland), replacement therapy.

Introduction. Hypopituitarism [ICD-10 code: E23.0] is a thyroid disorder resulting from the deficiency of one or several hormones produced by the hypophisis (pituitary gland). It is a rare disease which can be congenital or acquired; thus it can occur in infants, children, teenagers and adults [1,4]. The congenital causes include perinatal traumas (birth asphyxia, birth traumas), disturbed development of the pituitary gland, ectopic position of the neurohypophesis, Pallister-Hall syndrome (hypothalamic hamartoma and polydactyly), genetic disturbances (isolated deficiency of GH, PIT1 and PROP1 mutations, septo-optic dysplasia, gonadotrophin deficiency) and disturbed development of the central nervous system (anencephaly, holoprosencephaly, aplasia or hypoplasia of pituitary gland) [5]. Acquired causes of hypopituitarism include infiltrative disturbances (tuberculosis, sarcoidosis, X-histiocytosis, lymphocytic hypophisis and tumors [7].Most commonly the disease results from PIT1 and PROP1 gene mutations which are caused by transcription factors.

Severe deficiency of somatotropic hormone and prolactin are characterized by PIT1 gene mutation. Deficiency of thyrotrophic hormone may vary by its expression. Retarded growth from the birth, secondary hypothyreoidism and low prolactin level will be diagnosed clinically. Development of adrenal insufficiency and secondary hypogonadism is not characteristic [1,8].

Perinatal signs of hypopituitarism are absent in children with mutation in PROP1. Mean weight and height at birth are within the normal features. Hypoclycemia and long-lasting jaundice of the newborn are not common [1,3,8]. The diagnosis is made when the parents complain of short stature. Deficiency of thyrotrophic hormone can be present at birth and it most commonly occurs together with the deficiency of growth hormone. Hypothyroidism is not expressed. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) deficiencies are revealed at puberty. Insufficient production of adrenocorticotropic hormone (ACTH) is less common, its deficiency is usually revealed at puberty and adulthood [6].

Neuroimaging of hypothalamic-pituitary area commonly reveals hypoplastic or normal anterior and posterior lobes of the pituitary gland [2].

It is known that the early diagnosis of the disease corresponds to expression of the symptoms and thus possible diagnosis of congenital hypopituitarism. In 2019 Child et al declared the median age of hypopituitarism diagnosis to be 11 years [6]. At the same time Boros et al suggested that those patients diagnosed with hypopituitarism after 10 years of age should be referred as late ones when making a final diagnosis [3].

Objectives: The article is aimed at describing the clinical case of hypopituitarism in an eight-year patient.

The research was agreed by the local committee of biomedical ethics in Yakutsk scientific center “Complex medical problems” in accordance with the Helsinki declaration #54, signed in 20.12.2021 #1, declaring ethical responsibility. The legal representatives of the patient signed agreement in a case history, which allows referring to the data anonymously. All the personal data of the patients were deidentified.

In 27.11.2023 the patient M. was admitted to the department of endocrinology and gastroenterology of M.E. Nikolaev Republican hospital #1 of the Republic of Sakha (Yakutia) at the age of 8 years. He complained of short stature, rapid fatigue and constant constipations. The patient is Russian.

Past medical history shows that retarded growth was noticed at the age of 5 years. The patient was referred to the in-patient department for further check-up. The retarded growth was noticed at the age of 4-5 years as his father said.

Past history shows that he was born from the third pregnancy which ran normally. He was born on the 40th week, weight at birth was 3300 gr, and height was 53cm. Nervous and psychological development was not disturbed and corresponded to his age. He rarely was ill with infectious diseases of the respiratory tract, he had chicken-pox. No known allergies were noticed.

Family history: mother’s height – 160 cm, father’s height – 170 cm, brother’s height (12 years) – 150 cm (-1.12 SDS).

Objective examination: Height – 122 cm (-2.32 SDS), weight – 20 kg, BMI – 14.8 kg/m2 SDS BMI (-1.36 SDS).

The condition is satisfactory. General state is normal with clear consciousness. Appetite is not disturbed. No meningeal signs, focal neurological symptoms are absent. The Romberg test is negative. The patient sleep is satisfactory. The body

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habitus type is hyposthenic with moderate diet. The bony and muscular system has no abnormalities. The pharynx is not hyperemic. Mucous membranes of the mouth and pharynx are clear and pale. Nasal breathing is not complicated and free. The osteoarticular system shows no anomalies. The lymphatic nodes are not enlarged. The thoracic cage is regular. On percussion the lungs tone is clear on all sides. Breathing is vesicular, with no rales and wheezes. Cardiac tones are clear and rhythmic. Abdomen is soft and painless. The liver and the spleen are not enlarged. The right foot is swollen. No peripheral swollen areas are noticed. Urination is free and painless. Urine is light and transparent. The outer genitals are formed correctly and have the male type. Puberty corresponds to Tanner stage 1.

The full blood count (28.11.2023): leukocytes – 11.42 (RI 4.27-11.40); lymphocytes – 4.29 (RI 0.97-4.28); eosinophils – 6% (RI 0.00-4.70).

Urine test (28.11.2023): the results correspond to the norm.

Biochemical blood test results (28.11.2023): biochemical blood test results correspond to the norm.

Hormone profile (28.11.2023): Thyroid stimulating hormone (TSH) – 11.00 IU/L (RI: 0.40-7.00), free T4 – 15.17 pmol/L (RI: 8.00-17.00) antibodies to thyroid peroxidase (Ab to TPO) – 0.19 U/mL (RI: 0.00-30.00). Conclusion: high level of thyroid stimulating hormone.

Insulin tolerance test (06.12.2023): 0II – 0.28 ng/mL, 15II – 1.42 ng/mL, 45II – 1.16 ng/mL, 60II – 1.04 ng/mL, 90II – 0.58 ng/mL, 120II – 1.06 ng/mL. Conclusion: insufficient production of somatotropic hormone.

MRI and magnetic resonance angiography of the brain (03.12.2023): No focal and space-occupying lesions in the brain structures were revealed. No hemodinamically significant changes in the vessels of the brain were found out.

X-ray of the wrist with wrist joints (radiocarpal articulations) (28.11.2023): bone age corresponds to 5.5-6 years.

Digital lateral skull X-ray (28.11.2023): Intracranial hypertension. Adenoid hypertrophy grade 2-3.

Discussion. A short stature patient passed a regular check-up at the department of endocrinology. The child was a full-term newborn with normal height and weight in a satisfactory condition. Due to unspecific manifestations of the disease at the early childhood the diagnosis was complicated.

Congenital hypopituitarism is diagnosed after hormone examination. The patient has confirmed deficiency of somatotropic hormone according to glucose intolerance test. Insulin-like growth factor 1 is also examined, as a single identification of somatotropic hormone is incorrect to diagnose a disease because of its high variety.

Taking into account height indices, low concentration of insulin-like growth factor 1 the following diagnosis was made: hypopituitarism with isolated deficiency of somatotropin.

The isolated deficiency of somatotropin is the commonest in most cases. It is a rare case with incidence from 1 per 4,000 to 1 per 10,000. Etiology of most cases remains unknown.

The treatment efficiency depends on early identification of hormone deficiency. This patient is administered a replacement therapy with recombinant somatotropin.

Conclusion. Congenital hypopituitarism is a rare disease with unspecific manifestations which complicates early diagnosis and due time therapy.

The patients with hypopituitarism need a life-long surveillance and replacement therapy.

Early reveal and diagnosis of hypopituitarism in children, administration of adequate replacement therapy with hormone require clinical suspicion and awareness of the local pediatricians. It is important to remember that this disease can be caused not only by isolated somatotropin but also deficiency of other tropic hormones of the pituitary gland resulting in certain clinical picture.

References

1. Vorontsova MV. Gipopituitarizm u detej i podrostkov [Hypopituitarism in children and adolescents]. Trudniy diagnos [Difficult diagnosis]. 2019; 2: 250 – 258 (In Russ.).]
2. Vorotnikova SYu, et al. Endokrinnye narusheniya pri nalichii kisty karmana Ratke: predstavlenie klinicheskogo sluchaya [Endocryne disorders caused by cyst in a Ratke pocket: presentation of a clinical case]. Ozhirenie i metabolism [Obesity and metabolism. 2016; 13(4):45-48 (In Russ.).]
3. Boros E, et al. Delayed diagnosis of congenital hypopituitarism associated with low socio-economic status and / or migration. Eur. J. Pediatr. 2020;179:151 – 155. Doi: 10.1007/S00431-019-03489-3.
4. Khardon R. Pediatric Hypopituitarism. Accessed on 6th May. 2020.
5. Alexandraki KI, et al. Management of Hypopituitarism. J. Clin.med. 2019; 5: 2153. Doi: 10.3390/jcm 8122153.
6. Child CJ, et al. Height Gain and Safety Outcomes in Growth Hormone-Treated children with idiopathic short stature: experience from a prospective observation study. Horm Res. Pediatr. 2019; 91: 241 – 251. Doi: 10.1159/000500087.
7. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Front. Endocrinol. (Lausanne). 2021;12:1–15. Doi: 10.3389/fendo.2021.720419.
8. Yeliosof O., Gangat M. Diagnosis and management of hypopituitarism. Curr. Opin Pediatr. 2019; 31: 531 – 536.

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PRENATAL DIAGNOSIS OF THE 22q11.2 DELETION SYNDROME

Three cases of 22q11.2 deletion syndrome based on prenatally detected fetal anomalies are presented. The possibility of targeted prenatal diagnosis based on identified anomalies is shown.

Microdeletion syndromes are genetic diseases caused by the absence of small sections of chromosomes that are not visible under a microscope (microdeletions). Deletion syndrome (DS) of chromosome 22q11.2 (22q11.2DS) is a chromosomal aberration resulting from submicroscopic deletion (destruction) of a region of 1.5 to 3 megabases (Mb) in the region of the long arm of chromosome 22, which encodes more than 35 genes [1-7]. The incidence of this syndrome ranges from 1:3000 to 1:6000. Mortality in the first year of life is about 4% and exceeds the rates for children with a similar malformation of the cardiovascular system, but without chromosomal microdeletion, aggravated by anomaly of large vessels, hypocalcemia and tracheomalacia. It should be noted that 22q11.2 syndrome was previously classified as separate clinical syndromes: Di George syndrome (DGS), Velocardiofacial syndrome (VCFS), Conotruncal anomalies face syndrome (CTAF), Cayler cardiofacial syndrome [2].

Keywords: prenatal diagnosis, 22q11.2 deletion syndrome, congenital heart disease, fetus

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Pregnant women were consulted in the antenatal fetal care department and in the Medical Genetic Center of the Perinatal Center of the State Autonomous Institution “Republican Hospital No. 1”. Expert ultrasound examinations were carried out using a VolusonE8 (GE) device.

The combined screening was carried out and calculated in the Astraia program in the biochemical laboratory of the Medical Genetics Center. The Astraya program contains an algorithm for calculating the risk of a chromosomal abnormality (CA), developed by the Fetal Medicine Foundation-FMF. BRAHMS Kryptor is used to measure biochemical markers of the 1st trimester PAPP-A and free betahCG.

Pregnant women underwent a molecular cytogenetic study of the fetus: invasive prenatal diagnostics (amniocentesis, cordocentesis) for chromosomal microarray analysis (CMA).

Chromosomal prenatal microarray analysis was carried out in the laboratory of molecular pathology “Genomed” (Moscow). Chromosomal microarray analysis (CMA, molecular cytogenetic study, molecular karyotyping) is a test to determine structural changes in DNA that result in changes in the amount of genetic material - deletions and duplications.

Chromosomal microarray analysis is the recommended first-line test by the medical genetics community for diagnosing the causes of congenital malformations, mental retardation, epilepsy and autism, as well as microdeletion and microduplication syndromes.

Targeted chromosome microarray analysis is performed on a Genoscan 3000 genetic analyzer using low-resolution microarrays.

Results and discussion. In all cases, the first ultrasound examination did not reveal any defects or markers of fetal chromosomal abnormality, and no increase in the thickness of the nuchal translucency was observed. When conducting combined screening, serum markers were within normal limits, individual risks for trisomy were low. Patients were referred for evaluation after the second screening examination with suspected congenital heart defects and multiple malformations.

Pregnant women were diagnosed with various conotruncal heart defects and thymic hypoplasia, characteristic changes accompanying 22q11.2 deletion syndrome. Hypoplasia of the thymus was detected by measuring the thymus; a transverse measurement of the thymus was performed and the thymo-thoracic ratio (TTR) was calculated. These pregnant women showed a decrease in the perimeter of the thymus and a decrease in TTO.

All three pregnant women were diagnosed with 22q11.2 deletion syndrome;

Case Presentation 1. Patient D., 27 years old, this is her first pregnancy. The first screening took place in a private clinic at 12.3 weeks: no markers of fetal

chromosomal abnormality were detected, the thickness of the nuchal translucency was 1.5 mm.

Combined prenatal screening – PAPP-A 2.726, hCG 1.678 MoM, risks for three trisomies are low. At screening in the 2nd trimester with suspected MVD, the patient was sent for examination at 20.2 weeks to the Perinatal Center. An echographic examination of the fetus revealed multiple congenital malformations of the fetus. TPS: Common truncus arteriosus. Ventricular septal defect. Anomaly of facial development: bilateral cleft lip and palate. Hypoplasia of the thymus. Amniocentesis was performed to conduct molecular cytogenetic analysis.

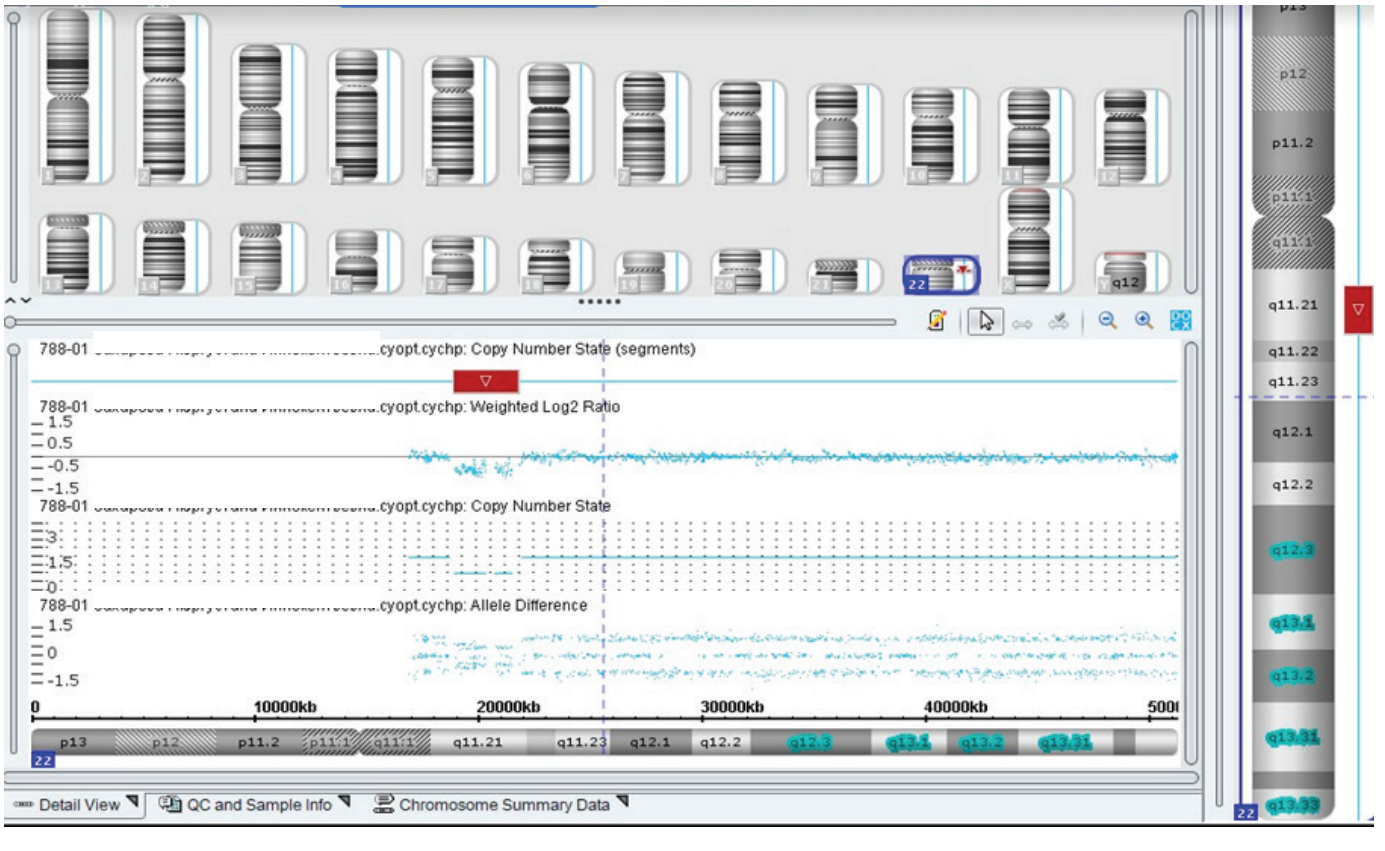
Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(17965842_20177061)x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 17965842 to position 20177061, covering the region 22q11.21. Microdeletion and microduplication syndromes associated with imbalance (OMIM): Chromosome 22q11.2 deletion syndrome (OMIM: 188400). After confirmation of the chromosomal abnormality of the fetus, the prenatal council decided to terminate the pregnancy with pathological verification of the diagnosis.

Case presentation 2. Patient Z., 31 years old. From the anamnesis - 3 marriages, 3 births from previous marriages. The first screening took place at the Central Regional Hospital at 11.6 weeks: the thickness of the nuchal translucency was 1.9 mm, no markers of fetal chromosomal abnormality were identified. Combined screening – PAPP-A 0.775, beta-hCG 0.518 MoM, individual risks for trisomy are low. After the 2nd screening ultrasound, she was sent for examination to the Perinatal Center. An echographic examination at 20.4 weeks revealed multiple congenital malformations. CHD: double origin of vessels from the right ventricle, large high ventricular septal defect. Anomaly of facial development: bilateral cleft of the upper lip and hard palate. Developmental anomaly of the musculoskeletal system: postaxial polydactyly of both hands. Bilateral ventriculomegaly. Hypoplasia of the thymus. Based on the identified changes, cordocentesis was performed for chromosomal microarray analysis. Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(18917030_21804886) x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21. Microdeletion and microduplication imbalance-associated syndromes (OMIM): 22q11.2 deletion syndrome (OMIM: 188400, 192430).

Considering multiple defects and microdeletion syndrome, the pregnancy was terminated by decision of the prenatal consultation. The pathological examination confirmed the diagnosis.

Case Presentation 3. Patient T., 29 years old. From the anamnesis of 3 births, the third birth - early neonatal mortality, 2 medical abortions. The genealogical history is burdened by a congenital facial defect (in a nephew): cleft palate.

The first screening ultrasound examination was carried out at the Central Regional Hospital at 11.3 weeks: the thickness of the nuchal translucency was 1.4 mm. Combined screening – PAPP-A 0.904, beta-hCG 0.401 MoM, low risks for chromosomal pathology. At 26 weeks, with suspected congenital heart disease, she was sent to the Perinatal Center. An ultrasound examination at 26.1 weeks revealed a congenital heart defect: absence of pulmonary valve syndrome (APSV). Expansion of the cavity of the transparent septum. Considering the high risk of 22q11.2 deletion syndrome up to 25% with this combined pathology, amniocentesis was performed.



Microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21

Comparative table of 3 pregnancy observations

Parameters	1 observation	2 observation	3 observation
Nationality	Sakha	Sakha	Sakha
Age	27 years	31 years	29 years
Parity	1st pregnancy	births 3	births 3, termination of pregnancy -2
The 1nd trimester			
CPS	60 mm	53 mm	48 mm
Gestational age	12.3 weeks	11.6 weeks	11.4 weeks
NTT	1.5 mm (95 percentile 2.34 mm)	1.9 mm (95 percentile 2.32 mm)	1.4 mm (95 percentile 2.30 mm)
Nasal bone	visualized	visualized	visualized
PAPPa	2,726 MoM (0,5-2,0 MoM)	0,775 MoM (0,5-2,0 MoM)	0,904 MoM (0,5-2,0 MoM)
hCG	1,678 MoM (0,5-2,0 MoM)	0,518 MoM(0,5-2,0 MoM)	0,401 MoM (0,5-2,0 MoM)
Risks for trisomy (21,18,13)	1:16243; 1:>20000; 1:>20000	1:1653; 1:>20000; 1:>20000	1:137114; 1:>20000; 1:>20000
The 2nd trimester			
Congenital heart defect	common truncus arteriosus, VSD	double outlet of vessels from the right ventricle, VSD	absent pulmonary valve syndrome
Facial abnormalities	bilateral cleft lip, palate	bilateral cleft lip, palate	not identified
Thymus	hypoplasia; transverse diameter of the thymus 8 mm (5th percentile 10 mm)	hypoplasia; transverse diameter of the thymus 6 mm (5th percentile 10 mm)	hypoplasia; transverse diameter of the thymus 11 mm (5th percentile 18 mm)
Additional changes for ultrasound	not identified	ventriculomegaly; postaxial polydactyly of both hands. Microgenia	expansion of the cavity of the septum pellucidi
Invasive diagnostics	study of genomic DNA isolated from amniotic fluid cells	study of genomic DNA isolated from fetal blood	study of genomic DNA isolated from amniotic fluid cells
Chromosomal microarray analysis	microdeletion of a region of the long arm (q) of chromosome 22 from position 17965842 to position 20177061, involving the region 22q11.21 (OMIM: 188400)	microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, involving the region 22q11.21(OMIM: 188400, 192430)	microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, involving the region 22q11.21. (OMIM: 188400, 192430)
Outcome	Termination of pregnancy in the 2nd trimester	Termination of pregnancy in the 2nd trimester	Delivery in the Federal Center

Molecular karyotype (according to ISCN 2016): arr[hg19] 22q11.21(18917030_21804886)x1. There is a microdeletion of a region of the long arm (q) of chromosome 22 from position 18917030 to position 21804886, covering the region 22q11.21. Microdeletion and microduplication syndromes associated with imbalance (OMIM): 22q11.2 deletion syndrome (OMIM: 188400, 192430).

After confirmation of the diagnosis, at the prenatal consultation, the pregnant woman was offered termination of pregnancy, taking into account the identified changes and the unfavorable prognosis for the life of the fetus. The pregnant woman refused to terminate the pregnancy. The birth occurred on time in the Federal Center.

Conclusion: 22q11.2 deletion syndrome is a chromosomal abnormality causing a congenital malformation, the common symptoms of which are heart defects, maxillary defect,facial dysmorphia, growth restriction and immunodeficiency [2].

22q11.2 deletion syndrome in our cases was detected in the 2nd and 3rd trimester of pregnancy. With combined screening, pregnant women were not included in the high-risk group for fetal chromosomal abnormalities.

Prenatal diagnosis for the presence of a deletion of chromosome 22 is mandatory when identifying conotruncal heart defects, in combination with thymic hypoplasia, anomalies of facial development - cleft, facial dysmorphism (chorionic villus biopsy, amniocentesis, cordocentesis).

But at this stage, in the presence of an expert ultrasound machine, corresponding to the qualifications of the ultrasound doctor, and subject to a standardized anatomical protocol, prenatal diagnosis of this microdeletion is in most cases possible during the first screening examination.

References

1. Rumyantsev AG, Maschan AA. Federalnjie i klinicheskie rekomendatsii po diagnostike I lecheniju sindroma deletsii 22 chromosomji [Federal and clinical guidelines for the diagnosis and treatment of chromosome 22 deletion syndrome. 2014; 3-7 (In Russ.).]

2. Namazova-Baranova LS, Ginter OV, Polunina TA, Davydova IV, Savostyanov KV, Pushkov AA, Zhurkova NV, Mospan TYa. Sindrom deletsii 22q11.2: symptomji, diagnostika, leshenie. Voprosji sovremennoi pediatrii [22q11.2 deletion syndrome: symptoms, diagnosis, treatment. Issues of modern pediatrics. 2016; 15(6):590–595 (In Russ.).] doi: 1010.15690/vsp.v15i6.1656.

3. Medvedev MV, Buryakova SI, Zamyatina AI. Prenatalnaja pricelnaja diagnostika syndroma Di Dgordji (sindrom deletsii 22q11.2) [Prenatal targeted diagnosis of DiGeorge syndrome (22q11.2 deletion syndrome)]. Prenatalnaja diagnostika [Prenatal Diagnosis. 2019; 18 (4): 377–382 (In Russ.).] doi: 10.21516/2413-1458-2019-18-4-377-382.

4. Kozlova YuO, Shilova NV, Yudina EV, Minzhenkova ME, Zolotukhina TV. Prenatalnaja diagnostika microdeletii 22q11.2 [Prenatal diagnosis of 22q11.2 microdeletion.] Prenatalnaja diagnostika [Prenatal Diagnosis]. 2012; 11 (4): 311–315.

5. Chaoui R, Heling KS, Zhao Y, Sinkovskaya E, Abuhamad A, Karl K. Dilated cavum septi pellucidi in fetuses with microdeletion 22q11. Prenatal Diagnosis. 2016; 36: 911–915. doi: 10.1002/pd.4911

6. Bataeva R, Bellsham-Revell H, Zidere V, Allan LD. Reliability of fetal thymus measurement in prediction of 22q11.2 deletion: a retrospective study using four-dimensional spatiotemporal image correlation volumes. Ultrasound Obstet. Gynecol. 2013; 41: 172–176.

7. Chaoui R, Kalache KD, Heling KS, Tennstedt C, Bommer C, K rner H. Absent or hypoplastic thymus on ultrasound: a marker for deletion 22q11.2 in fetal cardiac defects. Ultrasound Obstet. Gynecol. 2002; 20 (6): 546–552. doi: 10.1046/j.1469-0705.2002.00864.x

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