

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

2(70) `2020

YAKUT MEDICAL JOURNAL



YAKUT MEDICAL JOURNAL

The founder
The Yakut Science Centre
of Complex Medical Problems

Editor-in-chief
Romanova A.N., MD

Editorial Board:
Deputy Chief Editor
and Executive secretary
Nikolaev V.P., MD
Scientific editor
Platonov F.A. MD

Editorial Council:
Aftanas L.I., MD, Professor, acad. RAMS
(Novosibirsk)
Voevoda M.I., MD, Professor, Corresponding
Member RAMS (Novosibirsk)
Ivanov P.M., MD, Professor (Yakutsk)
Kryubezi Eric, MD, Professor (France)
Maksimova N.R., MD (Yakutsk)
Nelson Debora, MD, Professor (USA)
Nikitin Yu.P., MD, Professor, Acad. RAMS
(Novosibirsk)
Odland John, MD, Professor (Norway)
Puzyrev V.P., MD, Professor, Acad. RAMS (Tomsk)
Reutio Arya, MD, PhD, Professor (Finland)
Sleptsova S.S., MD, Professor (Yakutsk)
Fedorova S.A., Doctor of Biology (Yakutsk)
Husebek Anne, MD, Professor (Norway)
Khusnutdinova E.K., Doctor of Biology, Professor
(Ufa)
Chasnyk V.G., MD, Professor (Saint Petersburg)

Editors:
Chuvashova I.I.,
Kononova S.I.
Semenova T.F. (English)

Computer design
Sannikova M.I. (English)

Address:
Sergelyakhskoe Highway, 4, Yakutsk Republic
Sakha (Yakutia) Russian Federation 677019
Fax: +7 (4112) 32-19-81;
Phone: +7 (4112) 39-55-52
yscredactor@mail.ru
e-mail: ymj-red@mail.ru
http: // www.ymj.mednauka.com

The articles are given
in the authors' translation

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

Quarterly

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

Registration number PI No.TU 14-00475

*Subscription index: 78781
Free price*

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

*The journal is included in the international directory
system under periodic and proceeding editions "Ulrich's
International Periodicals Directory"*

CONTENTS

5 Editor-in-Chief column

Original research

- 6 Staborov V.A., Dobrodeeva L.K., Patrakeeva V.P.
Migration activity of immunocompetent cells in various pathologies of the gastrointestinal tract
- 10 Dovzhikova I.V., Andrievskaya I.A., Petrova K.K.
Changes in the progesterone synthetic function of the villous chorion in cytomegalovirus infection as one of the factors of the threatened miscarriage in early pregnancy
- 13 Egorova M.V., Mordovskaya L.I., Klimova T.M., Alekseeva S.D.
Vitamin D status in patients with tuberculosis in Yakutia
- 15 Tobokhov A.V., Nikolaev V.N.
Immunocorrective therapy in combined treatment of patients after simultaneous surgery on the abdominal organs during the early postoperative period

Diagnostic and treatment methods

- 18 Kirillina M.P., Sofronova S.I., Kononova I.V., Ivanova A.K., Vorontsova V.A., Lushnikova E.L.
Liquid cytology in comparison with traditional in the diagnosis of cervical diseases
Korostelev A.S., Potapov A.F., Ivanova A.A., Zakharov P.I., Bulatov A.V.
- 21 Predicting acute kidney injury in CAD patients undergoing coronary artery bypass grafting
- 24 Nikitina M.A., Brazovskaya N.G., Zhukova N.G., Bragina E.Yu., Alifirova V.M.
Apathy as a non-motor symptom of Parkinson's disease and Huntington's chorea
- 28 Bedina S.A., Trofimenko A.S., Mozgovaya E.E., Spitsina S.S., Mamus M.A., Tikhomirova E.A.
Activity of prooxidant and antioxidant systems enzymes in plasma of rheumatoid arthritis patients
- 31 Vasilieva O.L., Rudykh Z.A., Sofronova A.V., Starostina N.G., Tarabukina S.M., Tatarinova O.V., Chertovskikh Y.V., Sychev D.A.
The impact of polypharmacy, compliance with the STOP/START criteria on the risk of falls in elderly patients in a hospital

Healthy lifestyle. Prevention

- 34 Savvina M.S., Nelunova T.I., Burtseva T.E., Obratsova G.I., Chasnyk V.G., Evseeva S.A., Klimova T.M., Slobodchikova M.P.
Congenital heart diseases in indigenous children of the Republic Sakha (Yakutia)
- 37 Okhlopko E.D., Alekseeva Z.N., Efremova S.D., Mironova G.E., Grigoryeva A.A., Vinokurova F.V., Rummyantsev E.K., Semenova E.I., Yakovleva A.I., Olesova L.D., Efremova A.V., Konstantinova L.I., Romanova M.M., Filippov A.A., Romanova A.N.
Assessment of the psychoemotional state and level of cortisol and testosterone in the pre-competition period in athletes of Yakutia



Organization of Health, Medical Science and Education

- 41 Timofeev L.F., Petrova P.G., Borisova N.V., Turkebaeva L.K., Timofeev A.L.
Resource provision of healthcare in the Central Economic Zone of the Sakha Republic (Yakutia) and its relationship with population health indicators

Hygiene, sanitation, epidemiology and medical ecology

- 44 Gribova V.V., Okun D.B., Shalfeeva E.A., Scheglov B.O., Shchelkanov M.Yu.
Cloud service for the differential clinical diagnostics of acute respiratory viral diseases (including those associated with highly contagious coronaviruses) with an application of methods of artificial intelligence
- 47 Akhremenko Ya.A., Goncharov A.E., Kolodzhieva V.V., Belonogova E.Yu., Kolesnik D.S., Mokhov A.S., Ilarova V.I., Tarasova L.A.
Microbiological characteristics of *Streptococcus pneumoniae* strains isolated in Yakutsk
- 50 Nikitina A.A., Pavlova A.I., Gulyaev T.T., Chernyavsky V.F., Nikiforov O.I., Romanova I.A., Sofronova O.N.
Modern epizootiological and epidemiological characteristics of leptospirosis in the Republic Sakha (Yakutia)
- 54 Klimova T.M., Egorova A.G., Fedulova A.G., Kuzmina A.A., Malogulova I.Sh., Novikova M.S., Gorshenin N.I.
Behavioral determinants of diphyllbothriasis in the population of Yakutia

Topical issue

- 57 Siahidi M. Kh., Savvina N.V., Timofeev L.F., Bessonova O.G.
Mortality and lost years of life (YLL) due to breast, cervical and ovarian cancer in the Republic Sakha (Yakutia) in 2006-2016
- 59 Yakovleva L.P., Kondratyeva O.D., Kondratyeva M.N.
Main trends in the incidence of tuberculosis in the Sakha Republic (Yakutia) over the period from 2013 to 2018
- 62 Galkin S.A., Peshkovskaya A.G., Roshchina O.V., Kisel N.I., Ivanova S.A., Bohan N.A.
Relationship of cognitive disorders with clinical features of alcohol dependence

Arctic medicine

- 65 Sofronova S.I., Romanova A.N., Kirillina M.P.
Association of *IL-6* gene polymorphism with arterial hypertension and its risk factors in indigenous peoples of Yakutia
- 69 Evseeva S.A., Burtseva T.E., Egorova A.G., Makarova A.M., Savvina M.S., Slobodchikova M.P.
Causes and mortality indicators of child population in the arctic regions of the Republic Sakha (Yakutia)
- 72 Mikhaylichenko M.I., Shapovalov K.G., Mudrov V.A., Gruzdeva O.S.
The role of matrix metalloproteinases and their inhibitors in patients with local cold injury



- 77 Molodovskaya I.N., Tipisova E.V., Popkova V.A.,
Elfimova A.E., Potutkin D.S.
Photoperiodic variation of thyroid hormones and autoantibodies
in males of the European North

Scientific reviews and lectures

- 80 Danilov N.A., Burtseva T.E., Munkhalova Ya.A.,
Slobodchikova M.P.
Metabolic syndrome in children and adolescents

Point of view

- 84 Tabikhanova L.E., Osipova L.P., Kovalev S.S., Kawai-ool U.N.,
Saryglar A.N., Churkina T.V., Khantemirova M.R.
Features of the gene pool of the Tuvinian ethnos based on the study
of blood group antigens in comparative perspective
- 88 Polivanova T.V., Vshivkov V.A.
The relationship of family predisposition for gastric pathology
with GERD and erosive-ulcerative lesions of the gastroduodenal zone
in schoolchildren in Siberia
- 92 Akhmedinova Yu.R., Evert L.S., Potupchik T.V.
Brain neurotrophic BDNF level at teenagers
with syncopal conditions
- 96 Ferubko E.V.
Investigation of the role of phenolic compounds in the mechanism
of action of the new agent for prevention and treatment
of digestive diseases
- 99 Barilo A.A., Smirnova S.V., Borisova I.V.
Features of the sensitization spectrum in dermato-respiratory
manifestations of allergy in children of Khakassia

Clinical Case

- 102 Filippova R.D., Pavlova T.Yu., Danilova S.I., Maslova M.V.
Pregnancy and childbirth in a patient with Swyer syndrome
- 104 Ivanova O.N., Burtseva T.E., Protopopova N.N.,
Kondratyeva S.A., Furman D.M., Slobodchikova M.P.
A clinical case of Wiskott-Aldrich syndrome
- 106 Popova K.E., Popova T.E.
Psoriatic arthritis: clinical observation



EDITOR-IN-CHIEF COLUMN

**Dear Colleagues!**

The pandemic of the new coronavirus infection COVID-19, announced by the World Health Organization (WHO) on March 11, 2020, continues. It was first identified in late 2019 in Wuhan, China, Hubei Province. More than 6.1 million confirmed cases of COVID-19 have been reported worldwide. The United States of America, Brazil, Russia, Great Britain, Spain, Italy, Germany, Turkey, France, India, Iran and Peru became the most affected countries by the pandemic. On May 25, 2020, WHO noted that the pandemic of a new coronavirus infection is on the first wave and one needs to be prepared for the second. In Russia, as in many countries of the world, measures were taken to protect health and prevent the spread of COVID-19, which led to

certain successes. In the Sakha (Yakutia) Republic, despite taken restrictive measures, the epidemiological situation regarding COVID-19 remains to be tense. It is currently difficult to talk about the timing of the end of the pandemic and make predictions for the future.

The 2020 pandemic set the world scientific and medical community a number of new tasks for the diagnosis, treatment and prevention of new coronavirus infection. The pandemic has made adjustments to all sectors and activities of our lives. In the new online format, the 75th anniversary of the Victory in the Great Patriotic War was celebrated.

In the context of the pandemic, the work of scientists did not stop for a minute, including those who worked in a remote mode. The editors of the journal, as well as in the "pre-coronavirus" time, received a large amount of interesting material from the authors.

In the 70th issue of the magazine, as always, different regions of our country are presented - Central Russia, Siberia, the Far East and, of course, the Sakha (Yakutia) Republic. Researchers are interested in such issues as the functional activity of immunocompetent cells in various pathologies of the gastrointestinal tract (Staborov V.A. et al.) and in the complex treatment of patients after simultaneous operations on the abdominal organs (Tobokhov A.V., Nikolaev V.N.). The constant heading "Hygiene, Sanitation, Epidemiology and Medical Ecology" offers our users interesting materials that have become relevant in connection with the COVID-19 pandemic. So, the article of V.V. Gribova et al. "Cloud service for the differential clinical diagnostics of acute respiratory viral diseases (including those associated

with highly contagious coronaviruses) with an application of methods of artificial intelligence" will cause undoubted theoretical and practical interest. The authors presented a cloud service that allows accumulating data on the clinical manifestations of acute respiratory viral infections (including those associated with especially dangerous coronaviruses MERS-CoV, SARS-CoV, SARS-CoV-2) and, using artificial intelligence methods, significantly simplify and speed up the preliminary diagnosis. Actual issues of microbiology, epizootology in the region of Yakutia are covered in papers of Akhremenko Ya.A. et al., A.A. Nikitina et al., Klimova T.M. et al.

The problems of Arctic medicine are one of the important scientific directions, so the journal highlights them as well. This issue presents the results of molecular genetic studies in indigenous peoples of Yakutia with arterial hypertension (Sofronova S.I. et al.), mortality problems in the child population of the Arctic regions of the Sakha (Yakutia) Republic (Evseva S.A. et al.) etc.

A group of authors from Tuva (L.E. Tabikhanova et al.) presented an article entitled "Features of the gene pool of the Tuvianian ethnos based on the study of blood group antigens in comparative perspective", which submits materials on modern Siberian populations, which will undoubtedly arouse the interest of specialists in various fields.

I would like to believe that life will gradually return to normal and that the papers published on the pages of this issue will be interesting to our dear readers and useful in your professional activity.

Dear colleagues, enjoy your reading and see you in the next issue of our journal.

Editor-in-chief Anna Romanova



ORIGINAL RESEARCH

V.A. Schtaborov, L.K. Dobrodeeva, V.P. Patrakeeva

MIGRATION ACTIVITY OF IMMUNOCOMPETENT CELLS WITH DIFFERENT GASTROINTESTINAL TRACT PATHOLOGIES

DOI 10.25789/YMJ.2020.70.01

УДК 612.017.1:616.34

This study focuses on the migration and functional activity of immunocompetent cells in the intestinal contents in people with various pathologies of the gastrointestinal tract and in practically healthy people. Actively phagocytic neutrophilic granulocytes and monocytes, as well as lymphocytes without signs of degeneration and plasma cells, were recorded in the intestinal contents. Differences in the migration activity of cells depended on the pathology of the gastrointestinal tract. The levels of immunocompetent cells in the contents of the intestine in practically healthy people were determined. In gastrointestinal diseases, abnormal concentrations of pro-inflammatory cytokines are detected at a high frequency, the highest content of these cytokines have been recorded in malignant intestinal neoplasms.

Objective is to identify the features of the migration and functional activity of immunocompetent cells of the intestinal contents in norm and gastrointestinal pathology.

Keywords: local immunity, mucous membrane, lymphocyte, neutrophilic granulocyte.

The gut-associated lymphoid tissue (GALT) is the largest organ of the lymphatic system and contains all the cells involved in immune response. The lymphoid tissue of the gastrointestinal tract is represented by individual cellular elements (intraepithelial lymphocytes, plasma cells, macrophages, mast cells and granulocytes) and organized structures (Peyer's plaques, appendix, tonsils and lymph nodes). However, the presence and functional activity of immunocompetent cells in the intestinal contents remains unclear. The participation of lymphatic formations in the functional activity of the gastrointestinal tract is predetermined phylogenetically since, throughout the evolution of vertebrates, lymphatic tissue is associated with the digestive canal. Lymphocytes enter the intestinal lumen during digestion [4]. However, there is no cytogram data on the structure of intestinal contents and the presence of functionally active white blood cells. There is also no information about comparative levels of migration and changes in haemogram indicators in normal and pathological conditions. The body normally produces IgA for intestinal microbes and most bacteria in the stool are covered in IgA, but there is little evidence that IgA prevents normal bacteria from entering tissues. To date, IgA secretion remains controversial; it is not fully understood whether IgA is redistributed only

by migration from the peripheral blood to the mucosa or can be secreted locally. The output of cells into the intestinal lumen is influenced by factors including the state of the epithelium, the presence of adhesive molecules and the cohesion of epithelial cells. Violations of intercellular contacts and intestinal permeability are found in pathological conditions; instability of intercellular contacts can determine a predisposition for tumour transformation. Tumour cells form weaker bonds with each other than normal tissues, although some transformed tissues retain the ability for contact inhibition [4].

In this regard, this study addressed the activity of local immune responses, the activity of leukocyte migration and lymphocyte recycling in people with various gastrointestinal tract pathologies including inflammatory (colitis, gastroduodenitis), autoimmune (Crohn's colitis) and tumour (rectal cancer, colon cancer, stomach cancer) processes.

Materials and methods. In total, 581 people with chronic gastrointestinal tract pathologies who applied to the medical company «Biocor» were examined, including 106 people with Crohn's colitis, 135 people with non-specific colitis, 123 people with gastroduodenitis, 105 people with colon cancer and 112 people with rectal cancer. As a comparison group, 154 otherwise healthy people living in the city of Arkhangelsk, Russia were examined. The study consisted of peripheral venous blood, mucosal discharge (intestines) and faeces. Citogramma and phagocytosis were studied in smears gram-stained by Romanovsky-Giemsa; the calculation was made at the rate of 100 cells. The expression of markers for T-helper cells and NK cells was determined using indirect immunoperoxidase reaction on lym-

phocytes. The serum content of cancer markers REA, CA19-9, CA72-4 (CanAg Diagnostica, Sweden), cytokines IL-6, IL-4, TNF- α , IL-10 (Bender MedSystems, Austria), IgA and IgE (Seramun Diagnostica GmbH (Germany), Monobind Inc. (USA)) was determined by enzyme immunoassay on the analyser «Multiscan MC» and automatic «Evolis» analyser of the company «Bio-Rad» (USA). Levels of less than 1.2 g/l were considered IgA deficits. For high levels of IgE > 100 IU/ml was taken. Elevated levels of cytokines were considered for IL-1 β > 5 pg/ml, IL-4 > 20 pg/ml, IL-6 > 20 pg/ml, TNF- α > 20 pg/ml, IL-10 > 20 pg/ml. The lymphocytogram was studied by the method of I.A. Kassirsky, 1970 [3]. The research results were processed using the Statistica 6 application software package (StatSoft, USA). The Shapiro-Wilka test was used to determine the statistical difference in values. Differences were accepted at a statistical significance of $p < 0.017$.

Results and discussion. Table 1 shows data on the content of the cytogram of intestinal contents of healthy adults. The limits of neutrophils were 7.11–9.93%, lymphocytes were 17.76–22.5%, monocytes were 1.35–2.49% and plasma cells were 4.41–10.86%. That the results suggest that inflammatory, autoimmune processes and oncological diseases cause an increase in the content of neutrophils, monocytes and lymphocytes in the intestinal lumen (Fig. 1-3). The structure of intestinal content cytograms differs depending on the nature of the disease (Table 1). Inflammatory processes (gastroduodenitis, colitis), including autoimmune (Crohn's colitis) and intestinal malignancies, migration and flushing of neutrophils into the intestinal lumen is activated. Neutrophils are

N. Laverov Federal Center for Integrated Arctic Research, Arkhangelsk, Russian Federation: **SHTABOROV Vyacheslav Anatol'evich** – PhD (Biology), Senior Researcher, schtaborov@mail.ru; **DOBRODEEVA Liliya Konstantinovna** – MD, prof., Director, Chief Researcher; **PATRAKEEVA Veronika Pavlovna** – PhD (Biology), Head of lab., Leading Researcher.

immunocompetent cells that migrate to the centres of trouble first; they phagocytize, form traps, and secrete all known cytokines [5, 8]. Neutrophil migration is most significant in non-specific colitis ($22.84 \pm 0.77\%$). Crohn's autoimmune colitis is characterised by a higher content of monocytes in the cytogram ($10.86 \pm 1.22\%$). In intestinal tumours, specific features of the cytogram have not been established. The main part of monocytes is found in tissues, so even minor changes to the content of monocytes in the blood indicate a significant reaction on the part of the monocyte system. Monocytes phagocyte, form traps, and secrete cytokines and colony-stimulating factors [2]. Monocytes migrate to the inflammation area after neutrophil granulocytes to ensure the elimination of decay products. Migration of monocytes to the mucosa and intestinal lumen is associated with a lack of natural killer cells in the blood. The origin of natural killers is not clear; there are cells that do not have T-lymphocyte antigen (CD3-CD16+CD56+). There are also NK cells with the T-lymphocyte antigen, the thymus-dependent NK cells (CD3+CD16+CD56+), involved in specific immune reactions with antibody formation. The most pronounced reaction of monocytes was found in Crohn's colitis, which is associated with a deficiency in the blood of natural killers in 54.72%. The largest group of cells in the intestinal contents were lymphocytes; their levels did not differ depending on the pathology. In patients with Crohn's colitis, the number of plasma cells increases. The presence of a plasma cell reaction in the intestine of patients with Crohn's colitis confirms local antibody synthesis [7].

In the structure of the lymphocytogram, the level of cells with signs of degeneration is minimal and does not exceed 10% of the total content of small lymphocytes

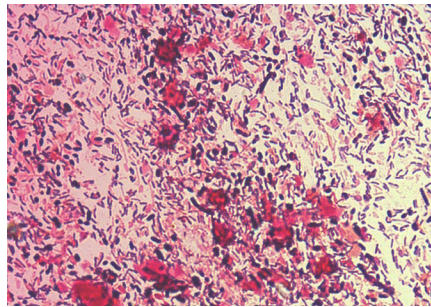


Fig. 1. A smear of feces at nonspecific colitis. Gram stain $\times 1000$. Migration of cells, mainly neutrophils, phagocytosis

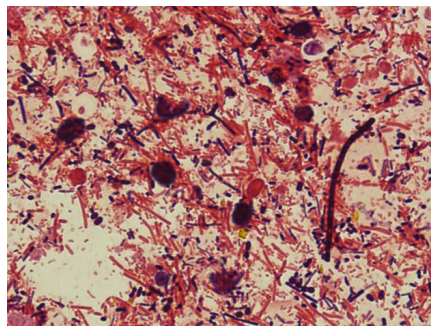


Fig. 2. A smear of feces at nonspecific colitis. Gram stain $\times 1000$. Lymphocytes, plasma cells

in the intestinal lumen; however, the frequency of detecting medium-sized lymphocytes with signs of degeneration is 3-3.5 times higher (24–42%). Migration of lymphocytes is not unilateral; lymphocytes, unlike other immunocompetent cells, are capable of recycling [12, 13, 19]. Among lymphocytes in the composition of the lymphocytogram, 17.46–20.17% are small lymphocytes, which reflect the processes of recycling these cells from tissues to lymphoid organs [12, 13, 19]. Most intraepithelial lymphocytes were identified as CD3+ mature T cells,

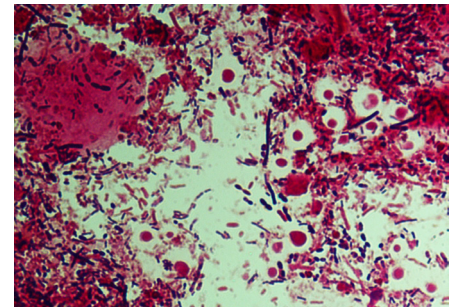


Fig. 3. A smear of feces at Crohn's colitis. Gram stain $\times 1000$. Plasma cells, sorption activity of the epithelium

but 5% and 15% of patients had CD4 or CD8 on the membrane, respectively; the predominance of CD8+ is characteristic of the lamina propria lymphoid pool. Intraepithelial lymphocytes exhibit cytotoxic effects, secrete lymphokines, regulate the regeneration of the mucosal epithelium, and ensure tolerance to food antigens [1]. Almost 50% of the population of intraepithelial lymphocytes consists of regulatory $\gamma\delta$ T-lymphocytes [14]. A large population of intraepithelial lymphocytes is CD4+CD25+; however, it has been previously demonstrated that they are not capable of proliferation in response to stimulation by a thymus-dependent antigen in vitro [16]. Intraepithelial lymphocytes have receptors for IL-2 but do not secrete it; they instead produce proinflammatory cytokine IL-10 and transforming growth factor- β in large amounts [11]. Lymphocytes CD4+CD25+ participate in tolerance when low doses of protein are administered but do not have a significant effect at high doses [9, 10]. It can be assumed that small lymphocytes, performing an informational role, migrate from the nearest lymphatic formation. In response to the migration of lymphocytes from the intestine to Peyer's plaques,

Table 1

Cytograms of intestinal contents (%)

index	apparently healthy (n=154)	Gastroduodenitis (n=123)	Colitis (n=135)	Colitis Crohn (n=106)	Colon cancer (n=105)	Rectal cancer (n=112)
Neutrophilic granulocytes	8.52 \pm 0.47	12.72 \pm 0.31	22.84 \pm 0.77	13.52 \pm 0.19	11.06 \pm 0.28	12.2 \pm 0.30
Monocytes / macrophages	1.92 \pm 0.19	7.58 \pm 1.02	6.75 \pm 0.85	10.86 \pm 1.22	8.81 \pm 1.33	8.79 \pm 1.32
Lymphocytes	20.13 \pm 0.79	28.35 \pm 0.58	24.94 \pm 0.43	34.36 \pm 0.96	32.99 \pm 0.96	33.71 \pm 0.82
Small lymphocytes	7.09 \pm 0.11	17.46 \pm 0.34	17.49 \pm 0.52	16.41 \pm 0.23	17.46 \pm 0.36	20.17 \pm 0.48
Medium Lymphocytes	13.04 \pm 0.23	11.39 \pm 0.37	6.62 \pm 0.18	17.87 \pm 0.36	15.45 \pm 0.48	12.4 \pm 0.43
Plasma cells	7.50 \pm 1.12	5.06 \pm 2.41	3.89 \pm 2.50	12.95 \pm 3.07	7.36 \pm 2.83	5.25 \pm 2.79
Sorption activity of epithelial cells	58.39 \pm 7.39	87.5 \pm 2.31	95.32 \pm 2.59	126.53 \pm 4.73	90.09 \pm 3.05	114 \pm 4.86
% active phagocytes	49.96 \pm 1.21	52.93 \pm 0.47	52.42 \pm 0.41	58.02 \pm 0.09	54.99 \pm 0.43	52.12 \pm 0.40
Phagocytosis deficiency	47.83	42.28	50.37	50.94	51.43	61.61

mass death of large lymphocytes in the centres of reproduction of lymphoid formation has been observed (6, 17, 20). This, in our opinion, indicates the involvement of these reactions in the formation of tolerance to food antigens and products of the intestinal microflora.

Cytokines are powerful regulators of cell migration and recycling. In healthy people, the frequency of elevated concentrations of pro-inflammatory cytokines in the blood was low, ranging from 1.19–8.43%. IgA deficiency in the blood was found to be within 14.55% and elevated IgE concentrations were 21.59%. In diseases of the gastrointestinal tract, the level of detection of abnormally high reactions from the studied immunological parameters increases; the highest concentrations of proinflammatory cytokines appeared in intestinal malignancies (Table 2).

The highest levels of elevated IL-1 β (59.05%) and IL-10 (23.81%) were found in patients with colon cancer. In patients with Crohn's colitis, the highest concentrations of IL-4 in venous blood was 26.32 ± 0.14 pg/ml; elevated levels were observed in 23.58% of the patients. Patients with Chron's colitis also presented the lowest levels of IL-1 β (4.58 ± 0.08 pg/ml) with a frequency of elevated concentrations at 36.9%. In non-specific colitis, the cytokine reaction is characterised by a moderate increase in pro-inflammatory cytokines against the background of low levels of anti-inflammatory IL-10, whose content in peripheral blood was 11.32 ± 0.07 PG/ml. The anti-inflammatory cytokine IL-10 causes a decrease in the expression of activating genes and a reduction in the number of receptor structures [15]. In Crohn's colitis and malignancies, elevated IgE concentrations were most often detected (62.19% and 55.24%, respectively). The highest concentrations of reagens (169.71 ± 0.56 IU/ml) were observed in malignant neoplasms. Serum IgA deficiency was reported in 65.71% of

patients with rectal cancer. In non-specific colitis, IgA deficiency was detected in 31.71% of the examined patients, twice as often as in healthy patients. Cancer patients presented a high frequency of natural killer (NK) and T-helper (CD4+) deficits, respectively; T-helper deficits were registered in 74.29% of cancer cases and natural killer deficits were registered in 60.71% of the examined cancer patients.

Conclusion. In the composition of the intestinal contents, actively phagocytic neutrophilic granulocytes and monocytes, lymphocytes without signs of degeneration and plasma cells were registered. Neutrophil granulocytes in the intestinal lumen actively phagocytize ($49.96 \pm 1.21 - 58.02 \pm 0.09\%$), phagocytic activity of neutrophil granulocytes in gastrointestinal pathology is noticeably higher than in healthy individuals. The exception is cases of malignant neoplasms when the deficit of phagocytic activity of neutrophils reached 61.61%. The cytokine reaction in inflammatory processes of the gastrointestinal tract is moderate and relatively uniform compared to that in autoimmune inflammation and tumours.

The most pronounced reaction of monocytes was found in patients with Crohn's colitis; this was associated with a deficiency in the blood of natural killer cells in 54.72% of examined patients. Perhaps the most pronounced migration of monocytes into the intestinal lumen in Crohn's colitis is related to the local variant of antibody formation and the appearance of plasma cells. Eviction of lymphocytes in the lumen of the intestine increases in the pathology of the gastrointestinal tract and reflects the activity of local immune responses. Almost 50% of lymphocytes are represented by medial cells and large lymphocytes; large lymphocytes make up 2–5%. The low level of death of large lymphocytes (1–2%) confirms the development of a local immune response with potential for lymphoprolif-

eration. The features of migration activity in the intestine in malignant neoplasms, compared with other inflammatory processes, could not be identified. The most characteristic features of colon cancer are extremely low phagocytic activity of neutrophil granulocytes in the blood, a high rate of registration of T-helper deficiency (74.29%) and elevated concentrations of IL-10 (23.81%). The highest frequency of elevated blood concentrations of IL-10 was recorded in malignant neoplasms, indicating a significant role of immunosuppression in this pathology.

This work was carried out as part of a fundamental research program on the topic of the laboratory of environmental immunology by the FCIARctic project № AAAA-A17-117033010124-7.

References

1. Бурмистрова А.Л. Иммунный гомеостаз и микросимбиоз. Метаморфозы и пути развития воспалительных заболеваний кишечника. Челябинск: Челябинский дом печати; 1997. [Burmistrova AL. Immune homeostasis and microsimbiocenosis. Metamorphoses and the development of inflammatory bowel diseases. Chelyabinsk: Chelyabinskij dom pechati; 1997. (In Russ.).]
2. Григорова О.П. Роль моноцитарной системы в реактивности человека. Москва: Медицина; 1956. [Grigороva OP. The role of the monocyctic system in human reactivity. Moscow: Medicina; 1956. (In Russ.).]
3. Кассирский Н.А., Алексеев Г.А. Клиническая гематология. Москва: Медицина; 1970. [Kassirsky NA, Alekseev GA. Clinical Hematology. Moscow: Medicina; 1970. (In Russ.).]
4. Маленков А.Г., Чуич Г.А. Межклеточные контакты и реакции тканей. Москва: Медицина; 1979. [Malenkov AG, Chuich GA. Intercellular contacts and tissue reactions. Moscow: Medicina; 1979. (In Russ.).]
5. Нехаев С.Г. Григорьев Ю.И. Полиморфноядерные лейкоциты как система антиэндотоксицианной защиты организма. *Иммунология*. 2010; 31(3):116-8. [Nekhaev S.G. Grigor'ev YU.I. Polymorphonuclear leukocytes as a system of anti-endotoxic defense of the body. *Immunologiya*. 2010; 31(3):116-8. (In Russ.).]
6. Пономарева Т.В. Лимфоидный аппарат кишечника кролика в норме и при искусственной сенсбилизации. *Архив анатомии, гистологии и эмбриологии*. 1965; 48(4):67-74. [Ponomareva TV. The lymphoid apparatus of the intestine of the rabbit in norm and with artificial sensitization. *Arhiv anatomii, gistologii i embriologii*. 1965; 48(4):67-74. (In Russ.).]
7. Шварцман Я.С., Хазенсон Л.Б. Местный иммунитет. Ленинград: Медицина; 1978. [Schwartzman YS, Hazenson LB. Local immunity. Leningrad: Medicine; 1978. (In Russ.).]
8. Cascao R, Rosario HS, Fonseca JE. Neutrophils: Warriors and commanders in immune mediated inflammatory diseases. *Acta reumatol. port*. 2009; 34(2B): 313-26.
9. Chung Y, Lee SH, Kim DH et al. Complementary role of CD4+CD25+ regulatory T cells and TGF- β in oral tolerance. *Journal of Leukocyte Biology*. 2005; 77:906-13.
10. Chung Y, Chang SY, Kang CY. Kinetic

Table 2

The frequency of registration of high levels of parameters of the immune defense of people (%)

index	apparently healthy	Gastroduodenitis (n=123)	Colitis (n=135)	Colitis Crohn (n=106)	Colon cancer (n=105)
IL-1 β > 5 pg / ml	1.19		22.96	36.79	59.05
IL-4. > 20 pg / ml	4.34		10.37	23.58	18.09
IL-6 >20 pg / ml	8.43	17.89	14.07	29.25	32.38
TNF α . > 20 pg / ml	5.47		11.85	17.92	20.95
IL-10. > 20 pg / ml	1.14		8.89	16.98	23.81
IgE >100 IU / ml	21.59	41.46	15.56	62.19	55.24
CEA. > 5 pg / ml	4.44	39.84	51.85	36.79	70.48

analysis of oral tolerance: memory lymphocytes refractory to oral tolerance. *J. Immunol.* 1999; 163:3692-8.э

11. Dubois B, Chapat L, Goubier A et al. Innate CD4+CD25+ regulatory T cells are required for oral tolerance and inhibition of CD8+ T cells mediating skin inflammation. *Blood.* 2003; 102:3295-301. DOI: 10.1182/blood-2003-03-0727

12. Field EO, Sharpe HBA, Dawson KB et al. Turnover rate of normal blood lymphocytes and exchangeable pool size in man, calculated from analysis of chromosomal aberrations sustained during extracorporeal irradiation of the blood. *Blood.* 1972; 39:39-56. DOI:10.1182/blood.V39.1.39.39

13. Ford WL, Gowans JL. The traffic of lymphocytes. *Seminars in hematology.* 1969; 6(1):67-83.

14. Fujihashi K, Dohi T, Rennert P et al. Peyer's patches are required for oral tolerance to proteins. *Proc. Natl. Acad. Sci. USA.* 2001; 98:3310-15. DOI: 10.1073/pnas.061412598

15. Hebeda CB, Teixeira SA, Tamura EK et al. Nitric oxide modulates lipopolysaccharide-induced endothelial platelet endothelial cell adhesion molecule expression via interleukin-10. *Clin. and Exp. Immunol.* 2011; 165(2):172-6. DOI: 10.1111/j.1365-2249.2011.04396.x

16. Itoh M, Takahashi T, Sakaguchi N et al. Thymus and autoimmunity: production of CD4+CD25+ naturally anergic and suppressive T cells as a key function of thymus in maintaining immunologic self-tolerance. *J. Immunol.* 1999; 162(9):5317-26.

17. Normane A, Sasaki MS, Ottoman RE et al. Lymphocyte lifetime in women. *Science.*

1965; 147(3659):745-53. DOI: 10.1126/science.147.3659.745

18. Pitt JM, Stavropoulos E, Redford PS et al. Blockade of IL-10 signaling during bacillus Calmette-Guerin vaccination enhances and sustains Th1, Th17 and innate lymphoid IFN- γ and IL-17 responses and increases protection to Mycobacterium tuberculosis infection. *J. Immunol.* 2012; 189(8):4079-87. DOI: 10.4049/jimmunol.1201061

19. Springer T.A. Traffic signals for lymphocytes recirculation and leukocyte emigration: the multistep paradigm. *Cell.* 1994; 76(2):301-14. DOI: 10.1016/0092-8674(94)90337-9

20. Waksman BH, Arnason BG, Jankovic BD. Role of the thymus in immune reactions in rats. III. Changes in the lymphoid organs of thymectomized rats. *J. Exp. Med.* 1962; 116:187-206. DOI: 10.1084/jem.116.2.187



I.V. Dovzhikova, I.A. Andriyevskaya, K.K. Petrova

CHANGES IN THE PROGESTERONE SYNTHETIC FUNCTION OF THE VILLOUS CHORION IN CYTOMEGALOVIRUS INFECTION AS ONE OF THE FACTORS OF THE THREATENED MISSCARRIAGE IN EARLY PREGNANCY

DOI 10.25789/YMJ.2020.70.02

УДК 577.175.632:618.36-06:616-076.5
(618.344+611-018.54):618.39]
578.825.12

The **aim** of the study was to identify the relationship between the indicators of progesterone synthetic activity of the fetoplacental complex being formed and the nature of clinical and echographic manifestations of the threatened miscarriage in groups of women with different course of cytomegalovirus (CMV) infection. A study of villous chorions at 9-12 weeks of pregnancy was carried out, of which 65 were obtained from women without infection (control group, n=30) and its latent form (comparison group, n=35) during medical abortion, from women with exacerbation of infection and spontaneous miscarriage (main group, n=35). The activity of 3 β -hydroxy-5-pregnen-20-one-dehydrogenase was determined by histochemical method, progesterone in blood serum and villous chorion was determined by enzyme immunoassay. The course of pregnancy and echographic indicators of the threatened miscarriage were evaluated. The results of the analysis revealed a significant dependence of the incidence of threatened miscarriage ($\chi^2=31,386$, $p<0,001$), decline of progesterone and 3 β -hydroxy-5-pregnen-20-one-dehydrogenase from the exacerbation of the infection ($\chi^2=31,869$, $p<0,001$). The results of the correlation analysis revealed a direct strong correlation between progesterone and 3 β -hydroxy-5-pregnen-20-one-dehydrogenase ($r=0,82$ and $r=0,75$, $p<0,001$), which indicated the pathogenetic role of infection in the metabolic deactivation of the enzyme that determines the insufficiency of progesterone synthesis. At the same time, there was no correlation between progesterone levels in blood serum and villous chorion. The results obtained allow us to conclude that presence of CMV infection in past medical history of woman and violation of progesterone synthetic function of trophoblast activity are significant risk factors for the threatened miscarriage in the first trimester of pregnancy, the outcome of which depends on the activity of the virus and the level of progesterone.

Keywords: progesterone, 3 β -hydroxy-5-pregnen-20-one, villous chorion, cytomegalovirus infection, pregnancy.

The miscarriage of early pregnancy is one of the most important problems of obstetrics. The frequency of spontaneous miscarriages in the first trimester of pregnancy has remained consistently high over the past years, accounting for 15-20% of all pregnancies [1].

Factors such as infectious and endocrine pathologies in women are directly involved in the pathogenesis of spontaneous miscarriages [4,7,11]. Among infections that have a direct abortifacient effect due to the toxicity of the virus and its cytopathic effect on embryonic and

provisional organs, cytomegalovirus (CMV) infection is pointed out. The main hormones necessary to the sustentation of pregnancy are progesterone and its precursor pregnenolone (3 β -hydroxy-5-pregnen-20-one) [8,10]. Tocolytic, gestagenic, and immunomodulatory effects are significant for the normal course of gestation [3]. It is shown that progesterone system indicators decrease in the risk of miscarriage and premature birth, placental insufficiency [2].

However, there is no comparative analysis of the clinical course of the first trimester of pregnancy in women with different forms of CMV infection, echographic markers of the threatened miscarriage and their relationship with the state of progesterone synthesis function of the formed fetoplacental complex.

The aim of the study was to identify the relationship between the indicators of progesterone synthetic activity of the fetoplacental complex being formed and the nature of clinical and echographic manifestations of the threatened miscarriage in groups of women with different state of CMV infection.

Materials and methods. A study of villous chorions at 9-12 weeks of pregnancy was conducted, of which 65 were obtained during medical abortion from women with no CMV infection in past medical history (control group, n=30) and from women with latent course of CMV

infection (comparison group, n=35), and during instrumental revision of the uterine cavity from women with exacerbation of CMV infection and spontaneous miscarriage (main group, n=35).

Histochemical analysis of cryostatic sections of villous chorion was performed using the Lojda method to study an enzyme that catalyzes the synthesis of progesterone. A 2 mM solution of 3 β -hydroxy-5-pregnen-20-one (Sigma-Aldrich) was used as the substrate. To quantify the expression of the enzyme, a system of computer analysis of microscopic images was used, consisting of a MEIJI microscope (Japan), a Canon digital camera (Japan), and Scion Image software (USA).

The level of progesterone was determined in the homogenate of villous chorions and peripheral blood serum taken on an empty stomach in the morning by the method of enzyme immunoassay using standard test kits of «Hema-Medica» Ltd. (Russia).

In order to detect of immunoglobulins (Ig) of classes M and G to CMV, as well as avidity of IgG antibodies, we used enzyme immunoassay and corresponding test systems manufactured by Vector-best SC (Russia). Determination of CMV in peripheral blood, buccal epithelium scraping, and cervical canal contents was performed by polymerase chain reaction. The diagnosis of exacerbation of

Inna V. DOVZHKOVA – PhD, D.Sc. (Biol.), Leading Staff Scientist of Laboratory of Mechanisms of Etiopathogenesis and Recovery Processes of the Respiratory System at Non-Specific Lung Diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration, 22 Kalinina Str., Blagoveshchensk, 675000, Russian Federation. e-mail: dov_kova100@rambler.ru, **Irina A. ANDRIYEVSKAYA** – PhD, D.Sc. (Biol.), Professor RAS, Head of Laboratory of Mechanisms of Etiopathogenesis and Recovery Processes of the Respiratory System at Non-Specific Lung Diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration, 22 Kalinina Str., Blagoveshchensk, 675000, Russian Federation. e-mail: irina-andriyevskaja@rambler.ru, **Kseniya K. Petrova** – MD, obstetrician-gynecologist of the paid medical services department FESC PPR, 22 Kalinina Str., Blagoveshchensk, 675000

chronic CMV infection was established on the basis of laboratory and clinical and anamnestic data.

The echographic study was performed on the SonoScape S6 ultrasound diagnostic device (China) in the mode of pulse and color Doppler mapping.

Statistical analysis and data processing were performed using the Statistica 10.0 (StatSoftInc., USA) in compliance with the General recommendations for medical and biological research. The Lilliefors and Kolmogorov–Smirnov tests were used to assess the distribution in the aggregate using sample data. In order to check the equality of the average values in samples with normal distribution, the Student's t-test was used. The Fisher criterion was used to evaluate the equality of variances between independent samples. The differences were considered significant at a significance level of $p < 0,05$. Analysis of differences between frequencies in two independent groups was performed using Pearson's χ^2 criterion, when the value of the absolute frequencies in the contingency tables was less than 10, the criterion was adjusted χ^2 Yates. The relative risk analysis (RR) was performed using four-field conjugacy tables with a 95% confidence interval (CI).

Results and discussion. The nature of the course of the first trimester of pregnancy in women with an exacerbation of chronic CMV infection (the main group) was determined by the presence of a significant pain syndrome in all subjects characterized by nagging pains in the lower abdomen and bloody vaginal discharge of different severity. Among the echographic criteria for incipient abortion (table) the most common were: myometrial hypertonicity in 25 (83%), chorion previa in 18 (60%), gain of chorion thickness in 8 (27%), retrochoral hematoma in 16 (53%), gestational sac deformity in 10 (33%), and low location of the gestational sac in 3 (10%). The gain of chorion thickness appears to be the result of an involutive and exudative reaction that occurs in the course of the infection, which was confirmed by PCR analysis. CMV DNA was detected in chorion tissues in 28% of cases.

In the comparison group, clinical signs of a threatened miscarriage were diagnosed in 10 (29%) women. It was accompanied by nagging pains in the lower abdomen in 6 (17%) and spotting bloody vaginal discharge in 2 (6%). Echographically, the most common signs of miscarriage listed in the table were: myometrium hypertonicity in 8 (23%), chorion previa in 6 (17%),

and retrochoral hematoma in 4 (11%).

When evaluating systemic and local progesterone indicators in the main group of women with an exacerbation of CMV infection, they were found to decrease in serum to $63,70 \pm 2,33$ nmol/L ($p < 0,001$), in the villous chorion to $82,49 \pm 1,01$ nmol/L ($p < 0,001$) compared to the control group ($102,11 \pm 3,34$ and $143,83 \pm 2,15$ nmol/L, respectively). Attention was drawn to the detected decrease in cytophotometric parameters of 3β -hydroxy-5-pregnen-20-one-dehydrogenase to $17,2 \pm 1,01$ pixels/ μm^2 (control group – $28,3 \pm 1,97$ pixels/ μm^2 , $p < 0,001$) (Fig. 1,2). In the comparison group, the concentration of progesterone in the blood serum was $87,50 \pm 3,11$ nmol/L ($p < 0,001$), in the villous chorion – $127,23 \pm 1,09$ nmol/L ($p < 0,001$), cytophotometric indicators of 3β -hydroxy-5-pregnen-20-one-dehydrogenase – $22,7 \pm 1,80$ pixels/ μm^2 ($p < 0,01$) (Fig. 3).

In addition, it was carried out a comparative analysis of clinical and echographic parameters and progesterone synthetic activity indicators of the formed fetoplacental complex with risk assessment by the value of χ^2 in the study groups.

The results of the analysis revealed a significant dependence of the frequency of the threatened miscarriage in the first trimester of pregnancy on the exacerbation of CMV infection ($\chi^2 = 31,386$, $p < 0,001$). The probability of its occurrence in the main group of women is 3.5 times higher (RR=3,500; 95% CI: 2,073 – 5,910) than in the comparison group. The dependence of the frequency of nagging pains in the lower abdomen on the exacerbation of CMV infection in early pregnancy is also statistically significant ($\chi^2 = 41,59$, $p < 0,001$), and the risk of its development was 5,83 (RR=5,833; 95% CI: 2,816-12,085). In addition, it was found the statistically significant dependence of spotting bloody vaginal discharge on the exacerbation of CMV infection ($\chi^2 = 53,745$, $p < 0,001$), its risk in the main group was 17,5 (RR=17,500; 95% CI:

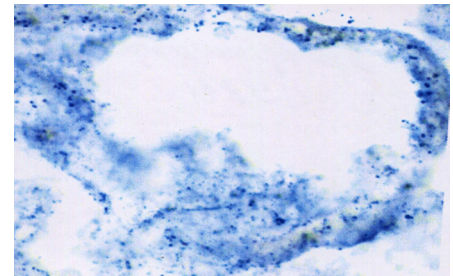


Fig. 1. Villous chorion at 10 weeks of pregnancy. Control group. Histochemical reaction to 3β -hydroxy-5-pregnen-20-one-dehydrogenase. The intensity of the histochemical reaction is $28,3 \pm 1,97$ pixels/ μm^2 . Magnification 40×15 .

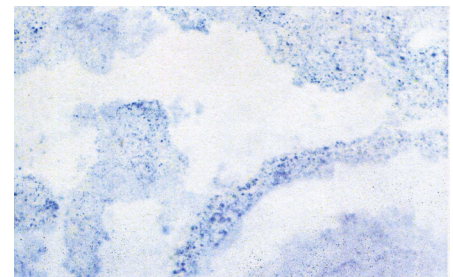


Fig. 2. Villous chorion at 10 weeks of pregnancy. Exacerbation of cytomegalovirus infection. Histochemical reaction to 3β -hydroxy-5-pregnen-20-one-dehydrogenase. There is a decrease in the reaction activity to $17,2 \pm 1,01$ pixels/ μm^2 . Magnification 40×15 .

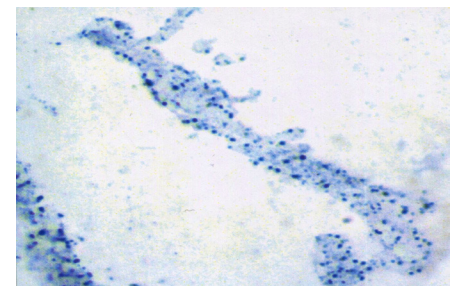


Fig. 3. Villous chorion at 10 weeks of pregnancy. Latent cytomegalovirus infection. Histochemical reaction to 3β -hydroxy-5-pregnen-20-one-dehydrogenase. There is a decrease in the reaction activity to $22,7 \pm 1,80$ pixels/ μm^2 . Magnification 40×15 .

Echographic markers of miscarriage in the first trimester of pregnancy in the study groups. n (%)

Detected change	main group (n=35)	comparison group (n=35)	P
Gain of chorion thickness	8 (27)	-	
Chorion previa	18 (60)	6 (17)	<0.001
Gestational sac deformity	10 (33)	-	
Low location of the gestational sac	3 (10)	-	
Retrochoral hematoma	16 (53)	4 (11)	<0.001
Myometrial hypertonicity	25 (83)	8 (23)	<0.001

Note: P is the significance of differences when comparing women with exacerbation of CMV infection and its latent course.

4,556-67.219) compared with the control group.

When evaluating supersonic markers of the threatened miscarriage, a significant dependence of the detection of myometrial hypertonicity on the exacerbation of CMV infection in the early pregnancy was established ($\chi^2=21,28$, $p<0,001$). The risk of this disorder pathway in the main group of women was 3,646 (RR=3,646; 95% CI: 1,943– 6,841. The dependence of the frequency of chorion previa on the exacerbation of CMV infection ($\chi^2=10,966$, $p<0,001$) is also statistically significant. The odds of chorion previa in pregnant women of the main group was 3,5 times higher (RR=3,500; 95% CI: 1,597 – 7,672) than in the comparison group. In addition, the dependence of the onset of retrochoral hematoma on the exacerbation of CMV infection is also statistically significant ($\chi^2=11,422$, $p<0,001$). The risk of this marker of threatened miscarriage in pregnant women of the main group is 4,667 times higher (RR=4,667; 95% CI: 1,749-12,449) than in pregnant women of the control group.

All women in the main group showed a significant decrease in the level of progesterone and 3 β -hydroxy-5-pregnen-20-one-dehydrogenase, and these indicators changed less pronounced in the comparison subgroup. According to the results of the comparative analysis, a strong dependence of the decrease in the level of progesterone and 3 β -hydroxy-5-pregnen-20-one- dehydrogenase on the exacerbation of CMV infection was established ($\chi^2=31,869$, $p<0,001$). The risk of developing these disorders in the group of women with exacerbation of CMV infection was 3,5 (RR=3,500; 95% CI: 2,073 – 5,910).

The results of the correlation analysis revealed a direct strong correlation between progesterone and 3 β -hydroxy-5-pregnen-20-one-dehydrogenase ($r=0,82$ and $r=0,75$, $p<0,001$), which indicated the pathogenetic role of infection in the metabolic deactivation of the

enzyme that determines the insufficiency of progesterone synthesis. At the same time, there was no correlation between systemic and local progesterone indicators, which indicated the specificity of the sites of production and the effect of the hormone on the target cells of the uterine mucosa and the villous chorion.

Apparently, the reason for the revealed regularities is the development of inflammatory processes in the utero-placental zone caused by an exacerbation of CMV infection in the first trimester of pregnancy, which is accompanied by a violation of implantation and the formation of the fetoplacental complex [4,6,9]. The resulting functional and metabolic disadaptation, as shown by the studies, leads to the formation of enzymatic 3 β -hydroxy-5-pregnen-20-one-dehydrogenase deficiency, which causes a decrease in the production of progesterone by trophoblast. Formed progesterone deficiency increases the manifestations of inflammation by modulating the cytokine response according to Th-1 type, which initiates trophoblast apoptosis, leads to reduction of utero-placental blood circulation and the threatened miscarriage [5].

Conclusion. The occurrence of CMV infection in past medical history of women and violation of progesterone synthetic activity of trophoblast are significant risk factors for the threatening course of the first trimester of pregnancy, the outcome of which, according to the results of the study, depends on the activity of the virus and the level of progesterone.

References

1. Боровкова Е.И., Мартынова И.В. Самопроизвольный выкидыш: состояние изученности вопроса. *Исследования и практика в медицине*. 2014; 1(1): 52-56. [Borovkova EI, Martynova IV. Spontaneous miscarriage: state study questions. *Issledovaniya i praktika v medicine*. 2014; 1(1): 52-56. (in Russ.)]
2. Воскресенский С.Л., Тришина В.Л. Содержание прогестерона в крови беременных в I и во II триместрах гестации при неблагоприятном завершении беременности. *Журнал*

акушерства и женских болезней. 2017;66(4): 32–39. [Voskresenskiy SL, Trishina VL. The contents of progesterone in the blood of pregnant in I and II trimesters of gestation with an unfavorable outcome of the pregnancy. *Zhurnal akusherstva i zhenskikh boleznej*. 2017; 66(4): 32–39. (in Russ.)] doi: 10.17816/JOWD66432-39

3. Довжикова И.В., Луценко М.Т. Современные представления о роли прогестерона (обзор литературы). *Бюллетень физиологии и патологии дыхания*. 2016;60:94-104. [Dovzhikova IV, Lutsenko MT. Modern concepts of progesterone role (review). *Bulleten' fiziologii i patologii dyhanija*. 2016; 60: 94-104. (in Russ.)] doi: 10.12737/20128

4. Потапов В.П., Пекарев О.Г., Надеев А.П. Факторы риска и цитоморфологическая характеристика хориона в генезе самопроизвольного прерывания беременности в первом триместре. *Акушерство, гинекология и репродукция*. 2012;6(3):39-44. [Potapov VP, Pekarev OG, Nadeev AP. Risk factors and cytomorphological characteristics of the chorion in the genesis of spontaneous abortion in first trimester. *Akusherstvo, ginekologija i reprodukcija*. 2012; 6(3):39-44. (in Russ.)]

5. Andrievskaya I.A., Lucenko M.T., Babenko O.P. Specific and non-specific factors of humoral immunity as markers for pregnancy loss in women with cytomegalovirus infection. *International Journal of Biomedicine*. 2015; 5(4):184-187.

6. Maidji E., Nigro G., Tabata T. [et al.]. Antibody treatment promotes compensation for human cytomegalovirus-induced pathogenesis and a hypoxia-like condition in placentas with congenital infection. *Am J Pathol*. 2010; 177(3):1298-1310. doi: 10.2353/ajpath.2010.091210.

7. Cheshik S.G., Kisteneva L.B. Human cytomegalovirus infection and spontaneous abortion in pregnant women of I and II trimester. *Vopr Virusol*. 2016; 61(2):74-78.

8. Chatuphonprasert W., Jarukamjorn K., Ellinger I. Physiology and pathophysiology of steroid biosynthesis, transport and metabolism in the human placenta. *Front Pharmacol*. 2018; 9:1027. doi: 10.3389/fphar.2018.01027

9. Chou D., Ma Y., Zhang J. [et al.]. Cytomegalovirus infection of trophoblast cells elicits an inflammatory response: a possible mechanism of placental dysfunction. *Am J Obstet Gynecol*. 2006; 194(2):535-541. DOI: 10.1016/j.ajog.2005.07.07310. Nigro G., Mazzocco M., Mattia E. [et al.]. Role of the infections in recurrent spontaneous abortion. *J Matern Fetal Neonatal Med*. 2011; 24(8):983-9. doi: 10.3109/14767058.2010.547963.

11. Fraichard C., Bonnet F., Garnier A. [et al.]. Placental production of progestins is fully effective in villous cytotrophoblasts and increases with the syncytiotrophoblast formation. *Mol Cell Endocrinol*. 2020; 499:110586. doi: 10.1016/j.mce.2019.110586.

DOI 10.25789/YMJ.2020.70.03

УДК 616-002.56/.58, 577.161.2 (571.56)

M.V. Egorova, L.I. Mordovskaya, T.M. Klimova, S.D. Alekseeva

VITAMIN D STATUS IN PATIENTS WITH TUBERCULOSIS IN YAKUTIA

Material and methods: Enzyme immunoassay (EIA) concentrations of 25-hydroxycholecalciferol (25(OH)D) were studied in 88 patients with tuberculosis. Serum levels 25(OH)D were assessed using the following criteria: optimal level 30-100 ng/mL; subnormal level 20-30 ng/mL; vitamin D deficiency -10-20 ng/mL; severe deficiency – less than 10 ng/mL. For statistical processing, Student's unpaired t-test, Mann-Whitney, and Kruskal-Wallis tests were used. Cutoff for statistical significance of differences (p) was 5%.

Results: Mean age of patients was 40,7 (16,1) years. Proportion of male patients was significantly larger (p=0.035). Levels of 25(OH)D in men were somewhat lower than in women, but the differences were statistically negligible. No statistically significant correlation was established between age and level of 25(OH)D (r=-0.037; p=0.729). Assessment of distributions of vitamin D levels against laboratory reference showed, that serum vitamin D level was optimal in 4.5% of patients, and 12.5% had subnormal levels of vitamin D (20 to 30 ng/mL). In 34% of patients, vitamin D level was graded as 'vitamin d deficiency' (10 to 19.9 ng/mL); 49% had 'severe vitamin D deficiency' (below 10 ng/mL).

Conclusions: Results of this pilot study demonstrated the presence of marked vitamin D deficiency in patients with TB. Due to absence of control group, no comparisons of vitamin D levels between TB patients and general population could be made. Considering the role of vitamin D in the induction of innate antimicrobial immune response, further investigation is needed into the causes of deficiencies, opportunities to correct deficiencies in patients with TB, role of vitamin D in therapy of TB, and a role of vitamin D receptor gene polymorphism in Yakut ethnic group.

Keywords: vitamin D, tuberculosis, 25(OH) D, calcidiol, Yakutia.

Tuberculosis (TB) is one of the most urgent and underappreciated problems in world healthcare, and, at the same time, a sociomedical problem in virtually all countries [6]. Based on WHO reports, in 2017, as much as 1 million were diagnosed with TB, and 1.3 million died of it. Russia is currently among the 22 countries with the highest TB burden [1].

TB often goes along with nutritional deficiency, including deficiency in vitamin D. Vitamin D has an important role in innate host defense mechanisms against infection, by facilitating macrophage and monocyte activation, which is of significance in disease development. In the event of host infection with M.tuberculo-

sis, calcidiol, key circulating metabolite of vitamin D, preserves induction of the innate antimicrobial immune response, curbing the growth of tubercle bacilli [16]. Vitamin D deficiency in patients with TB is interrelated with M.tuberculosis drug sensitivity. In pre-antibiotic era, high doses of vitamin D were widely used for treating patients with TB [8].

Hence, there may be a place for vitamin D in therapy of TB, which calls for further studies.

Objective: to study the availability of vitamin D in patients with tuberculosis in Yakutia.

Material and methods: This study was conducted among 88 patients, who had been hospitalized in the Phthisiatry Research-Practice Center in 2017 to 2018, with the confirmed diagnosis of

TB (51 male; 37 females). No one was under medication with vitamin D during the study period. Serum concentrations of 25-hydroxycholecalciferol (25(OH)D) were determined, using enzyme immunoassay (EIA) kit from Euroimmun, Germany. The following criteria were used to estimate serum level of 25(OH)D: optimal level 30-100 ng/mL; subnormal level 20-30 ng/mL; vitamin D deficiency -10-20 ng/mL; severe deficiency – less than 10 ng/mL.

Statistical processing was performed using IBM SPSS Statistics 22 software suite. To compare patient groups, we used unpaired t-test, Mann-Whitney, and Kruskal-Wallis tests. Cutoff for statistical significance of differences (p) was 5%.

Results and discussion: Main characteristics of the patients studied are

Table 1

Main characteristics of patients

Indicator	Both genders n=88	Males n=51	Females n=37	p
Mean age, years	40.7 (16.1)	43.9 (13.6)	36.3 (18.2)	0.035
Tuberculosis (TB) clinical forms, n (%)				
Disseminated TB	17 (19.3)	14 (27.5)	3 (8.1)	0.023
Infiltrative TB	48 (54.5)	29 (56.9)	19 (51.4)	
Focal TB	8 (9.1)	1 (2.0)	7 (18.7)	
Tuberculoma	4 (4.5)	3 (5.9)	1 (2.7)	
Caseous pneumonia	3 (3.4)	2 (3.9)	1 (2.7)	
Thoracic lymph node TB	3 (3.4)	0 (0)	3 (8.1)	
Primary TB complex	2 (2.3)	1 (2.0)	1 (2.7)	
Other forms	3 (3.4)	1 (2.0)	2(5.4)	

Note. Data are presented as mean and standard deviation, M (SD); p - statistical significance of differences between males and females.

EGOROVA Marina Vasilievna – clinical Immunological laboratory specialist, Phthisiatry Research-Practice Center, 677005, Yakutsk, P. Alekseeva 87/5, email: romari86@mail.ru, phone (office): +7 (411) 240-24-43. **MORDOVSKAIA Larisa Ivanovna** – Doctor of Medical Sciences, Professor, Department of Public Health and Health Care, General Hygiene and Bioethics, Medical Institute of the North-Eastern Federal University named after M.K. Ammosova Head of the Immunological laboratory, Phthisiatry Research-Practice Center, 677005, Yakutsk, P. Alekseeva 87/5, email: limordovskaya@mail.ru, phone (office): +7 (411) 240-24-43. **KLIMOVA Tatiana Mikhailovna** – Associate Professor, Department of Pharmacology and Pharmacy, Medical Institute of the M.K. Ammosov North-East Federal University, 677013, Yakutsk, Oyunskogo 27, e-mail: biomedyk@mail.ru, phone (office): +7 (411) 249-66-23. **ALEKSEEVA Svetlana Dmitrievna** – clinical immunological laboratory specialist, Phthisiatry Research-Practice Center, 677005, Yakutsk, P. Alekseeva 87/5, email: immlab@mail.ru, phone (office): +7 (411) 240-24-43.

summarized in Table 1. Mean age of the patients was 40,7 (16,1) years. Male proportion was significantly larger than female ($p=0.035$). Infiltrative or disseminated TB were the two most frequent clinical forms of TB.

In both groups, distributions of 25(OH) D levels were deviating from normal distribution, therefore quartiles were calculated, to describe measures of central tendency and scatter. Levels of 25(OH) D in men were somewhat lower than in women, but the differences were statistically negligible. Considering a generally older age of men, compared to women, rank correlation analysis was performed. No statistically significant correlation was established between age and level of 25(OH) D ($r=-0.037$; $p=0.729$).

Assessment of distributions of vitamin D levels against laboratory reference showed, that serum vitamin D level was optimal in 4.5% of patients, while 12.5% had subnormal levels of vitamin D (20 to 30 ng/mL). In 34% of patients, vitamin D level was graded as 'vitamin d deficiency' (10 to 19.9 ng/mL), and in 49% – as 'severe vitamin D deficiency' (below 10 ng/mL) (Table 2).

Currently, an estimated 1 billion people have vitamin D deficiency. The recent large-scale studies have elicited a statistically significant correlation between vitamin D deficiency and the prevalence of a number of chronic diseases, including lung diseases, and TB as one of them [5,10,12,13,15]. Some long-lasting conjectures can be found in works of classical scholars in pediatrics, linking the disturbances in vitamin D metabolism with decreased immunity: namely, Tur A.F. emphasized that rickets and infections, and TB in particular, accompany one another [3]. Sufficiency of vitamin D in patients with TB infection is an under-investigated topic, except for several studies.

A study in the Province of Castellon, Spain, included 42 patients with TB and 202 contacts. Only 20.3% of them had

sufficient serum levels of 25(OH)D (≥ 30 ng/mL) [7]. Study of vitamin D levels in patients with TB in Mwanza, Tanzania, showed hypovitaminosis in 39.6% of patients, of them, vitamin D deficiency in 4.3% [9]. Study in Vietnam comprised 166 patients, and found that vitamin D deficiency in men was 35.4%, and 45.3% in women [11].

Study on the effect of mean therapeutic doses of vitamin D, administered as part of multimodality therapy for multidrug and extensively drug resistant TB in Belarus, showed that serum level of 25(OH) D was 12.3 ± 0.3 before therapy, and 19.8 ± 0.2 after 6 months of therapy. Mean course of vitamin D administration was 184.5 ± 3.5 days. Patients receiving vitamin D on top of polychemotherapy displayed positive response on their x-rays and microbiological tests. Also, administration of mean therapeutic doses of vitamin D on top of chemotherapy resulted in less proportion of patients who did not convert from positive to negative (57.9%), compared to patients who received chemotherapy without vitamin D (72.7%) [4].

Similar study was conducted in London, assessing the effect of high doses of vitamin D in patients with sputum-positive TB. Vitamin D supplement reduced time to sputum conversion by 1 week (from 43.5 to 36 days). Mean time to sputum culture conversion was 36 days for intervention group, and 43.5 for placebo group [14].

Sharply decreased levels of 25(OH)D in patients with TB (compared to healthy donors) were observed in the study in Saint-Petersburg, Russia (8.2 ± 1.4 ng/mL of calcidiol in fibrocavitary TB vs. 19.3 ± 1.4 ng/mL in healthy donors) [2].

In Yakutia, to date, no studies have been undertaken yet exploring the effect of vitamin D on treatment of patients with TB. As it appears from the studies conducted in other cities, reduced level of vitamin D is widely observed, even in

healthy people. In view of potential effect of vitamin D prescription on sputum culture conversion, and on progression of TB disease, there is a need in studies in a region of Yakutia.

Conclusions. Results of this pilot study demonstrated the presence of marked vitamin D deficiency in patients with TB. Due to absence of control group, no comparisons of vitamin D levels between TB patients and general population could be made. Considering the role of vitamin D in the induction of innate antimicrobial immune response, further investigation is needed into the causes of deficiencies, opportunities to correct deficiencies in patients with TB, role of vitamin D in therapy of TB, and a role of vitamin D receptor gene polymorphism in Yakut ethnic group.

References

1. Арчакова Л.И., Гришко А.Н. Туберкулез в России. *Здоровье – основа человеческого потенциала: проблемы и пути их решения*. 2009; 4(1): 97-98. [Archakova L.I., Grishko A.N. Tuberculosis in Russia. *Zdorov'e – osnova chelovecheskogo potenciala: problemy i puti ih resheniya*. 2009; 4(1): 97-98 (In Russ.).]
2. Беляева И.В., Чурилов Л.П., Михайлова Л.П. Иммунологическое зеркало туберкулеза. *Медицина: теория и практика*. 2019; 4(S): 95-96. [Belyaeva I.V., Churilov L.P., Mihajlova L.R. Immunological mirror of tuberculosis. *Medicina: teoriya i praktika*. 2019; 4(S): 95-96. (In Russ.).]
3. Доан Т.М., Александрова В.А., Чурилов Л.П. Дефицит витамина D в тропиках и субтропиках. *Крымский журнал экспериментальной и клинической медицины*. 2017 7:1: 80-88. [Doan T.M., Aleksandrova V.A., Churilov L.P. Vitamin D deficiency in the tropics and subtropics. *Krymskij zhurnal eksperimental'noj i klinicheskoy mediciny*. 2017; 7(1): 80-88. (In Russ.).]
4. Кралькова В.Я., Скрягина Е.М., Дюсьмикеева М.И., Скрягин А.Е. Витамин D в комплексной терапии лекарственно-устойчивого туберкулеза. *Рецепт*. 2018; 21:2: 179-189. [Kral'ko V.Ya. Skryagina E.M., Dyus'mikeeva M.I., Skryagin A.E. Vitamin D in the complex treatment of drug-resistant tuberculosis. *Recept*. 2018; 21:2: 179-189. (In Russ.).]
5. Угай Л.Г., Кочеткова Е.А., Невзорова В.А. Витамин D и болезни органов дыхания: молекулярные и клинические аспекты. *Дальневосточный медицинский журнал*. 2012; 3: 115-119. [Ugai L.G., Kochetkova E.A., Nevzorova V.A. Vitamin D and respiratory diseases: molecular and clinical aspects. *Dal'nevostochnyj medicinskij zhurnal*. 2012; 3: 115-119. (In Russ.).]
6. Шелкова Е.С., Романенко В. В. Туберкулез вчера, сегодня, завтра. *Медицинский алфавит*. 2015; 6(1): 34-43. [Shelkova E.S., Romanenko V.V. Tuberculosis yesterday, today, tomorrow. *Medicinskij alfavit*. 2015; 6(1): 34-43. (In Russ.).]
7. Arnedo-Pena A. Latent tuberculosis infection, tuberculin skin test and vitamin D status in contacts of tuberculosis patients: a cross-sectional and case-control study / A. Arnedo-Pena, J. V. Juan-Cerdán, A. Romeu-García // *Infectious Diseases*. – 2011. - №11. - P. 349.

Table 2

Serum vitamin D levels

Indicator	Both genders n=88	Males n=51	Females n=37	p
Level of 25(OH)D ²	10.0 (9.2; 18.2)	9.8 (8.7; 13.5)	15.0 (9.3; 19.2)	0.056
Distributions of vitamin D levels, n (%)				
Optimal (30-50 ng/mL)	4 (4.5)	3 (5.9)	1 (2.7)	0.085
Subnormal level (20-29.9 ng/mL)	11 (12.5)	4 (7.8)	7 (18.9)	
Deficiency (10-19.9 ng/mL)	30 (34.1)	14 (27.5)	16 (43.2)	
Severe deficiency (0-9.9 ng/mL)	43 (48.9)	30 (58.8)	13 (35.1)	

Note. Data are presented as mean and standard deviation, M(SD); data are presented as quartiles, Me (Q1; Q3); p - statistical significance of differences between males and females.

8. Brighenti S., Brighenti S., Bergman P., Martineau A. R. Vitamin D and tuberculosis: where next? *Journal of Internal Medicine*. 2018; 284: 145–162.
9. Friis H., Range N., Chungalucha J. Vitamin D status among pulmonary TB patients and non-TB controls: a cross-sectional study from Mwanza, Tanzania. *Plos one*. 2013; 8: 12.
10. Gilbert C.R., Arum S.M., Smith C.M. Vitamin D deficiency and chronic lung disease. *Can Respir. J*. 2009; 6 (3): 75–80.
11. Ho-Pham L.T., Nguyen N.D., Nguyen T.T. Association between vitamin D insufficiency and tuberculosis in a vietnamese population. *Infectious Diseases*. 2010; 10: 306.
12. Holick M.F. Vitamin D deficiency. *New Engl. J. Med*. 2007; 357(6): 266–281.
13. Hughes D.A., Norton R. Vitamin D and respiratory health. *Clinical and Experimental Immunology*. 2009; 158 (3)6: 20–25.
14. Martineau A. High-dose vitamin D failed to increase recovery rate in patients with TB. *Infectious Diseases*. 2011; DOI: 10.1016/S0140-6736(10)61889-2.
15. Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. *J. Neurol*. 2009; 256(8): 1468–1479.
16. Soeharto D.A., Rifai D.A., Marsudidjadja S. [et al.] Vitamin D as an Adjunctive Treatment to Standard Drugs in Pulmonary Tuberculosis Patients: An Evidence-Based Case Report. *Advances in Preventive Medicine*. 2019; 5181847. DOI: 10.1155/2019/5181847

A. Tobokhov, V. Nikolaev

IMMUNOCORRECTIVE THERAPY IN COMBINED TREATMENT OF PATIENTS AFTER SIMULTANEOUS SURGERY ON THE ABDOMINAL ORGANS DURING THE EARLY POSTOPERATIVE PERIOD

DOI 10.25789/YMJ.2020.70.04

УДК 615.37:617.55-089

The article analyzes results of the combined treatment at 452 patients, aged 16 to 64, after the simultaneous surgery on the abdominal organs for visceroptosis, during the early postoperative period. In 280 (61.9%) of them, studies of the immune status were conducted against the background of immunocorrective therapy. Thymogen and polyoxidonium were used as immunocorrectors. The drugs were injected to patients during surgery intravenously: the thymogen by 2 ml. of 0.01% solution, the polyoxidonium-12 mg in solution. In the postoperative period, the drugs were injected intramuscularly for 8 days: the thymogen by 1 ml of 0.01% solution, the polyoxidonium 6 mg in solution. Use of the immunocorrective therapy allowed to achieve a significant improvement in the dynamics of immune indicators in patients compared to a control group. The polyoxidonium effect on immunological parameters was strongly pronounced and significantly exceeded the effect of thymogen.

Keywords: visceroptosis, simultaneous operations, immunocorrective therapy.

Combined surgical correction for visceroptosis is characterized by the postoperative period severity and treatment complication, which is due to simultaneous surgery on the abdominal organs. Research met in the scientific literature on the surgery problem of the digestive system diseases mainly raises questions on new types of surgical approaches, methods of operation, methods of hemostasis, etc., and treatment of this category of patients in the postoperative period is not fully covered, which determines the need for a deeper study of this stage of treatment.

Materials and research methods. We performed surgical treatment of 452 patients aged 16 to 64 years. 421 (93.1%) patients were operated at the age of 21 to 60 years, i.e. at the most active working age. Patients older than 60 years were admitted for surgical treatment from other medical institutions, where due to the chronic intestinal obstruction and progressive weight loss, they were examined with suspicion of colon cancer. Pa-

tients operated at the age of 20 years, as a rule, belonged to the group of patients with a form of visceroptosis, occurring with a pronounced pain syndrome, and 19 of them had daily defecation.

To treat patients with visceroptosis, we applied methods of combined surgical correction depending on variants of the pathological process, operational findings and verification with the data of a comprehensive clinical study. In this case, simultaneous surgical treatment of all changes detected in the preoperative period and requiring surgical correction is performed. Many authors indicate causal relationship and interdependence between changes in one organ and development of painful processes in another, and in this regard, they support expansion of indications for combined surgical interventions. Our experience of simultaneous operations at patients with visceroptosis confirms correctness of these assumptions.

The combined surgical treatment includes both well-known methods of operations on the gastrointestinal tract, and techniques developed in our clinic (Table 1).

1718 operations were performed at 452 patients. On average, each patient had 3-4 simultaneous operations.

Rehabilitation of patients after oper-

ations on organs of the gastrointestinal tract (GIT) has the main goal to restore the motor-evacuation function of the gastrointestinal tract that was disrupted during surgery, as well as normalization of the digestive conveyor. Especially severe postoperative disorders occur in the organs of nervous and endocrine regulation, in the process of metabolism. In the early postoperative period, combined therapy is performed aimed at stabilizing the condition of patients and preventing the development of early complications: failure of anastomosis, development of infectious complications and pneumonia.

Traumatic and operational stress have a depressing effect on the functional state of vital organs and systems in the postoperative period, and especially the immune system, which leads to an increase in the frequency of postoperative complications and fatalities. The use of immunocorrective therapy in the combined treatment of patients with various surgical pathologies allows us to improve the results of treatment, reduce frequency of postoperative complications.

In patients with visceroptosis complicated by CTS, before surgery, we observed a moderate decrease in concentration of IgA and a marked increase in IgG compared to the control group, which indicates a greater tension of the immune

Table 1

The nature of the held surgery

Type of surgery	n=452	%
Nissen fundoplication	91	20.1
Toupet fundoplication	12	2.7
Round ligament of liver gastropexy	148	32.7
Bay gastropexy	11	2.4
Billroth operation I	4	0.9
Dorsal stem selective vagotomy	4	0.9
SPV with Onopriev duodenoplasty	2	0.4
Pyloroplasty	4	0.9
Surgery by Strong	29	6.4
Duodenojejunostomy by Vitebski	3	0.7
Ileocecostomy	49	10.8
Appendectomy	168	37.2
Resection of the colon left flank	440	97.3
Bilateral colonopexia	443	98.0
Right colonopexia	5	1.1
Left colonopexia	4	0.9
Sigmoid colectomy	9	2.0
Sigmoid reduction	3	0.7
Cholecystectomy	101	22.3
Cholecystolithotomy	4	0.9
Nephropexy	73	16.1
Splenectomy	3	0.7
Pelvic floor plastics	41	9.1
Omentum resection	28	6.2
Ovary resection	36	7.9
Removal of uterine fibroids	3	0.7

system, activation of humoral immune factors, in particular, an increase in IgG production. The data obtained are consistent with the work of a number of authors who noted a tendency to increase the number of immunoglobulins in the blood of patients with chronic inflammatory bowel diseases. The authors believe that bacteria and their toxins, food proteins and medications that are constantly present in the gastrointestinal tract in patients with colitis are of crucial importance in formation of hyperimmunoglobulinemia.

After the combined surgical correction of visceroptosis, the state of the immune system was studied in 280 (61.9%) patients, who were divided into 3 groups. The control group included 90 people who received traditional treatment without immunocorrective therapy. In the second one 90 patients were immunocorrected with the thymogen, the third group formed 90 patients who had polyoxidonium used as an immunocorrector. All groups were comparable by gender, age and volume of surgery. The drugs were injected to patients during the surgery intravenously: the thymogen in a dose of 2 ml. 0.01% of the solution, the polyoxidonium - 12 mg in solution. In the postoper-

ative period, the drugs were administered intramuscularly for 8 days: the thymogen by 1 ml of 0.01% solution, the polyoxidonium - 6 mg in solution. To objectively assess changes in the complex immune system, the immune status indicator (ISI) [2] was used taking into account the extent and nature of the changes in leading parameters of the immune system – the level of T-lymphocytes with helper and suppressor activity, as the main regulatory factors of the immune system activity of T-lymphocytes, the level of IgG, the main opsonin of the immune system and also the phagocytosis activity.

The immune status indicator was calculated using the formula: $ISI = (H + S + T + G + P) : 5 \times 100\%$, where X is the indicator of T – lymphocytes with helper ac-

tivity, C is the indicator of T-lymphocytes with suppressor activity, T is the indicator of lymphocyte activity, G is the indicator of IgG immunoglobulin level, and f is the indicator of phagocytosis. Values of the immune status indicator can range from (-100%) to (+100%). An interval from (-10%) to (+10%) was considered to be the norm for ISI. Under the USI values from (-10%) to (-20%) and from (+10%) to (+20%), immune disorders were considered light, from (-20%) to (-30%) and from (+20%) to (+30%) moderate, and at values less than (-30%) and more (+30%) severe. Study of the immunity indicators was carried out on the 1, 3-4, 7-8 days after surgery and before discharge from the hospital on the 10-12 days.

Results and discussion. Changes in the immune system indicators during the early postoperative period are shown in the Table 2.

In patients of the control group, immune disorders appeared on the 1st day after the operation. ISI in these terms was $(-37.8 \pm 2.4\%)$. On day 3-4, the immunodeficiency progressed and the ISI was equal to $(-46.7 \pm 3.2\%)$. On day 7-8, there was a tendency to stabilize the immune status and the ISI was equal to $(-35.4 \pm 3.1\%)$. During the 10-12 days term, the indicators improve, but the numbers remain extremely low. ISI in these terms is equal to $(-22.4 \pm 2.8\%)$. The analysis shows that the control group patients develop secondary immunodeficiency from the first day, reaching a maximum on the 3-4 days, and only by the end of treatment, before discharge from the hospital, they stabilized and corresponded to a moderate degree.

In the second group, where immunocorrection was performed with thymogen on the 1st day, ISI indicators $(-35.9 \pm 3.9\%)$, which indicated an increase in immunodeficiency, but the indicators are lower than in the control group. On the 3-4 days, the growth of indicators was not observed and the ISI was $(-35.1 \pm 2.3\%)$. On the 7-8 day, there was a tendency to normalize in the indicators of the immune status. ISI was equal to $(-23.2 \pm 2.1\%)$, and on the 10-12 days the

Table 2

Indicators of the patients' immune status during the postsurgery period
The control group

Groups of patients	Terms of postsurgery period			
	1 day	3-4 days	7-8 days	10-12
The control group	-37.8 ± 2.4	-46.7 ± 3.2	-35.4 ± 3.1	-22.4 ± 2.8
Thymogen treatment	-35.9 ± 3.9	-35.1 ± 2.3	-23.2 ± 2.1	-12.4 ± 2.5
Polyoxidonium treatment	-32.4 ± 4.1	-27.6 ± 3.6	-14.7 ± 2.4	-1.7 ± 1.1

indicators were approaching normal and ISI was $(-12.4 \pm 2.5\%)$. Against the background of the thymogen use on the 1st day after surgery, immune disorders were severe, but by the 3-4 days they stabilized. On the 7-8 days, the indicators improved and became medium-heavy, and by the 10-12 days after the operation, they were light and close to normal.

In the third group, where the patients received polyoxidonium on the day 1, PI was equal to $(-32.4 \pm 4.1\%)$, which was significantly lower than in the control group. By the 3-4 days of the postoperative period, the indicators stabilized, and the ISI was $(-27.6 \pm 3.6\%)$, on the 7-8 days $(-14.7 \pm 2.4\%)$, and on the 10-12 days $(-1.7 \pm 1.1\%)$. The analysis shows that the use of polyoxidonium allowed to achieve stabilization of the immune system at the level of mild disorders by the 7-8 days after surgery, and complete normalization of the immune system by the 10-12 days. The effect of polyoxidonium was expressed in the activation of the phagocytic link of immunity and an increase in the number of B-lymphocytes.

Thus, the use of immunocorrective therapy allowed achieving a significant improvement in the dynamics of immune indicators in patients after simultaneous operations on the gastrointestinal tract for visceroptosis in comparison with the control group. The effect of the polyox-

idonium on immunological parameters was strong and significantly exceeded the effect of thymogen. It should be noted that against the background of immunocorrective therapy, the indicators of general and biochemical blood tests stabilized much faster. Already on the 7-8 day, these indicators were within the norm.

The operations performed using the methods developed by us for combined correction of visceroptosis in the immediate postoperative period gave good results. There were no such complications as anastomosis, insolvency of the colon anastomosis and fatal outcomes. Of the 452 patients operated, 372 (82.3%) had no abdominal pain, and regular daily or in 1 day defecation was established. When discharged from the hospital, they were concerned about minor pain in the places of fixation. Sleep and appetite were restored. 69 (15.2%) patients' results were assessed as satisfactory. In this group of patients, at discharge, constipation remained, but their duration was reduced to 2-3 days, abdominal and lumbar pain decreased. 11 (2.4%) patients had no effect from the operation. The cause of poor results we see in insufficiently of the colon radical resection in 8 (1.7%) patients and at 3 (0.7%), there a tactical error was committed - a restriction by only the plastics of gastrointestinal ligament and mesosigmapplication under elongation of transverse colon or sigmoid colon.

It should be noted that the best results of the postoperative treatment were obtained in patients using immunocorrective therapy.

Thus, carrying out the combined therapy in the early postoperative period, including in addition to traditional treatment and immunocorrective therapy, allowed avoiding fatal outcomes and achieving good results of surgical treatment in the majority of cases.

References

1. Восстановительное лечение больных после операций на органах пищеварения / под редакцией А.Ю. Барановского. СПб. ФОЛИАНТ, 2002: 576. [Rehabilitation treatment of patients after operations on the digestive organs / Edited by A. Yu. Baranovsky. St. Petersburg, FO-LIANT, 2002: 576 (In Russ.).]
2. Петров Р.В. Иммунокорригирующая терапия в комплексном лечении больных с повреждениями печени (экспериментально-клиническое исследование). *Дисс...канд. мед. наук.* М., 1999:130. [Petrov R.V. Immunocorrective therapy in the combined treatment of patients with liver damage (experimental and clinical study). *Diss...kand. med. nauk.* М., 1999:130 (In Russ.).]
3. Орлов С.В. Современные методы детоксикации и иммунокоррекции в профилактике и лечении гнойно-деструктивных заболеваний легких, плевры и средостения. *Дисс...докт. мед. наук.* СПб., 2000: 260 [Orlov S.V. Modern methods of detoxification and immunocorrection in the prevention and treatment of purulent-destructive diseases of the lungs, pleura and mediastinum. *Diss...kand. med. nauk.* Saint Petersburg, 2000: 260 (In Russ.).]



DIAGNOSTIC AND TREATMENT METHODS

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

LIQUID CYTOLOGY IN COMPARISON WITH TRADITIONAL IN THE DIAGNOSIS OF CERVICAL DISEASES

DOI 10.25789/YMJ.2020.70.05

УДК 618.146-002

This paper presents the results of a cytological study of patients with pathology of the cervix uteri (CU) based on traditional cytology (TC) and on liquid-based cytology (LBC).

It was found that the combined use of liquid-based cytology and conventional cytology can improve the effectiveness of CU pathology diagnostics. It is recommended to complete the cytological study with testing for human papillomavirus (HPV). The use of these screening methods (cytological and HPV tests) contribute to improving the early diagnosis, monitoring, and prognosis of CU cancer.

Keywords: cervical cancer, diagnostics, liquid-based cytology, screening.

The problem of cervix uteri (CU) diseases is one of the most urgent in modern gynecology and has great importance for preventing the occurrence and development of malignant neoplasms. CU pathology is the background for the development of precancerous changes and cervical cancer (CC) among gynecological disorders that occur in women of reproductive age [7]. The time of active, rapid development and use of new technologies in medicine dictates the need and shows the importance of changes in traditionally used methods. The question of improving and optimizing the quality of cytological diagnostics is the most prevalent issue. Liquid-based cytology (LBC) plays an important role in solving this issue. LBC is introduced in order to overcome the disadvantages

of traditional methods and thereby to increase the effectiveness of cytological diagnostics [1]. The main feature of the LBC is the production of thin-layer (monolayer) preparations (in which cells are located almost in one layer) from a liquid cell suspension using special cytopspins. The difference between this method and the traditional one is that the substance is not applied directly to the glass, but it is placed in a bottle with a stabilizing solution. Rapid conservation of the substance allows preventing the bacterial contamination of the sample, and the damage of the cells due to their drying that preserves the sample in optimal conditions for further transportation to the laboratory and research. The stabilizing solution ensures the preservation of morphological, immunocytochemical and genetic properties of cells [4]. The sensitivity of the cytological method in using LBC increases to 85% [5]. A feature of the LBC is also that up to 6 "serial" smears can be obtained from a single sample of the substance, that is, identical in cell composition, which makes it possible to use additional research methods, for example, HPV testing, immunocytochemical determination of cancer markers [6]. The LBC with a high specificity should be supplemented with molecular diagnostic methods. Currently, it is considered proven that the main etiological factor of CU cancer is papillomavirus infection [2, 3, 8]. Two major meta-analyses of data from European and American studies have found that the human papillomavirus (HPV) test is more sensitive than cytological screening [11, 15]. The combination of the HPV test and the cytological method has a higher predictive value for detecting CIN (cervical intraepithelial neoplasia) compared to a single HPV test [9, 10, 13] which makes it possible to detect precancerous changes in CU early and, consequently, reduces

the risk of developing CC [12, 14].

Purpose of research: to study the frequency of background and precancerous pathology of CU by conventional cytology and LBC, and compare their results. Evaluate the effectiveness of TC and LBC, as well as establish the HPV genotype in the examined women.

Materials and methods. The study was conducted in the clinical laboratory of pathomorphology, histology, and cytology on the basis of North-Eastern Federal University named after M.K. Ammosov, Federal State Autonomous Educational Institution of Higher Education. The material was taken from CU and cervical canal scraping from the patients (100 people aged 22-60) after examination and extended colposcopy in the OOO "Malex" clinic (Yakutsk, Russia). The sample was obtained from every patient was conducted by traditional cytology and liquid-based cytology on the automated system CellPrep Plus (Korea), as an independent highly informative method that contributes improvement and standardization of cytological examination of all stages. The Romanovskiy - Gimza stain method was used. The presence of endocervical, flat, and metaplastic epithelium cells makes the material adequate for the study. It is very important to take into account that such material should be obtained from the transformation zone – the area where the tumor most often occurs. If the material is represented by a very small number of cells, a large number of blood elements, mucus, and the presence of artifacts, which makes impossible to properly assess the cytological picture, it is considered inadequate.

Cytological decision was made in accordance with the clinicopathologic classification of J. V. Bokhman (1976), and with the commonly accepted

KIRILLINA Maria Petrovna – Candidate of Biological Sciences, Senior Research Scientist, Head of Yakut Science Centre of Complex Medical Problems Laboratory, Head of NEFU Medical Institute Clinic Laboratory, kirillina.namp@mail.ru, 89142716881;

SOFRONOVA Sargylana Ivanovna – Candidate of Medicine, Senior Research Associate, Head of Scientific and Organizational Department of Yakut Science Centre of Complex Medical Problems Laboratory, sara2208@mail.ru 89841094825; **KONONOVA Irina Vasilievna** – Candidate of Medical Science, Research Worker of Yakut Science Centre of Complex Medical Problems Laboratory, irinakon.07@mail.ru 89243683673; **IVANOVA Anna Konstantinovna** – Clinical pathologist (cytology) of diagnostic center "National hospital №1- National medical center", Clinical Pathologist of NEFU Medical Institute Clinic, ivanova.ak11@gmail.com, 89248647588;

LUSHNIKOVA Elena Leonidovna – Doctor of Biological Science, professor, the head of FSBIS Institute of Molecular Pathology and Pathomorphology "Federal Research Center of Fundamental and Translational Medicine" 630117, Novosibirsk, Timakova st., 2, pathol@inbox.ru 8(383)334-80-03

criteria for assessing the state of the epithelium by Bethesda System (2015) [16]. It is based on the introduction of the term SIL (Squamous Intraepithelial Lesion) - squamous intraepithelial lesion. The main categories of the Bethesda classification: NILM- intraepithelial lesions and malignant processes are absent. LSIL- Low Grade Squamous Intraepithelial Lesions. (Mild changes in squamous epithelial cells corresponding to a low risk of cancer), the group covers changes typical of HPV infection and mild dysplasia CIN I. HSIL-High Grade Squamous Intraepithelial Lesions (marked changes in squamous epithelial cells corresponding to a high risk of cancer), the group involves moderate and severe dysplasia - CIN-II, CIN-III and CIS. The Bethesda classification separately identifies the following categories: • "atypical squamous cells of undetermined significant"- ASC-US-cell changes that are more significant than reactive, but quantitatively or qualitatively insufficient to establish a diagnosis of CIN. • Non-exclusive HSIL (ASC-H) — a category that takes middle position between ASC-US and HSIL.

Detection, typing (co-testing) of human papilloma virus (HPV) (6, 11, 44, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 serotypes) by PCR was performed on the basis of microbiological laboratory of the Medical Institute clinic based on NEFU.

Results and discussion. The comparative analysis of cytological samples of 100 women was conducted to evaluate the effectiveness of the liquid-based cytology and traditional cytological screening in the early diagnosis of CU cancer. The patients were aged from 23 to 60 years. The average age of all women surveyed was 38.9+9.2 years.. The percentage of detected background and precancerous pathology was estimated (Fig. 1).

By TC method the absence of intracellular damage (no findings cytogram) was detected in 16 samples (16%). By LBC method (NILM - intraepithelial changes and malignant processes are absent) it was detected in 66 (66% of the entire group) samples, and among all of the samples 26 (26%) have no pathology and 40 (40%) have reactive (background) changes (squamous metaplasia, inflammation, moderate hyperplasia). Generally, according to these data cervical pathologies during routine cytology were detected in 84% of cases, and during liquid-based cytology - in 74 %. Reactive (background) changes in the TC are 53% of cases,

while the LBC are 40% of cases. Cervical dysplasia of varying severity in TC was detected in 31 cases, which was 31% of the total number of samples. Among it, 23 women (74.1% of the total number of samples with detected cervical dysplasia of various severity) had I grade dysplasia (mild), 7 women (22.5%) had II grade dysplasia (moderate) and III grade (severe) dysplasia was diagnosed in 1 woman, which was 3.2% of all cervical dysplasia in the study group. Among it, 23 women (74.1% of the total number of samples with detected cervical dysplasia of various severity) had I grade dysplasia (mild), 7 women (22.5%) had II grade dysplasia (moderate) and III grade (severe) dysplasia was found in 1 woman, which was 3.2% of all cervical dysplasia in the study group. LSIL was detected in 27 cases (79.4%), of which CIN I – 20 (58.8%) cases, CIN I with koilocytes – 7 (20.6%) cases. HSIL was found in 6 cases and accounted for 17.6% of the total number of dysplasias in the study group. In 1 (2.9%) case was diagnosed atypia of unknown origin (ASCUS) (Fig.2).

As seen, even a small difference in the cytological diagnosis in traditional smears compared to smears obtained by LBC indicates that each of these methods showed effectiveness depending on the type of CU pathology.

47 (47%) women were tested for HPV, among them, 19(40%) women were confirmed to have HPV. The presence of oncogenic types of high-risk HPV was detected in 17 women (89.4%), of which 26.3% (5 women) were diagnosed with LSIL, 15.8% (3 women) with HSIL, 5.2% (1 woman) with ASCUS, and 42.1% (8 women) with NILM. HPV type 16 was found in 7 patients (36.8%), the next most common type was HPV type 51 – 4 women (21%). The frequency of

other genotypes distribution (39, 68, 31, 52, 73, 58, 18) varies from 4.2-2.1%. 3 negative cases of LSIL and 2 negative cases in HSIL which were detected in the diagnosis can indicate the beginning of viral damage or other causes of dysplasia.

In conclusion, based on our results, we would like to note that each stage of morphological research has not only certain opportunities but also limitations. This requires the use of complex diagnostic methods. We recommend using the method of liquid-based cytology with traditional cytology obtained with the analysis of HPV to compare the results. This will significantly increase the value of diagnostic measures, including cytological studies, and will determine

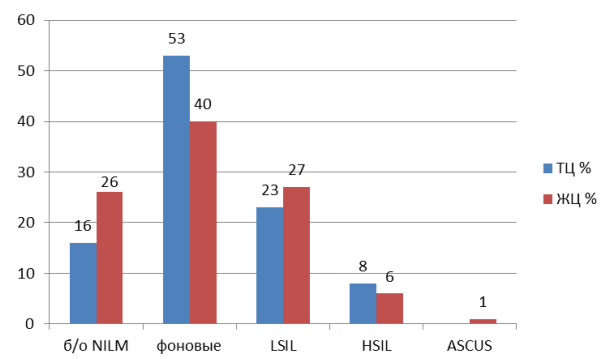


Fig.1. Comparative characteristics of the diagnosis of cervix uteri diseases by traditional and liquid-based cytology

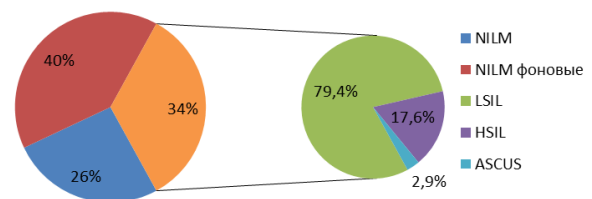


Fig.2. Structure of detected precancerous lesions of the cervix uteri by liquid-based cytology.

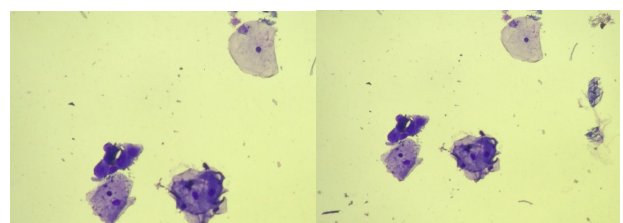


Fig.3. HSIL (CIN III): severe dysplasia. The group of small cells with large hyperchromatic nuclei on the background of flat epithelium surface cells (Romanovsky-Gimza staining method), X400

the most effective therapy for detected cervical pathology.

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

References

1. Бovyкина Г.А. Цитологическое исследование – ранняя диагностика рака шейки матки. *Лабораторная диагностика*. 2015;4(134):35-37. [Bovykina GA Cytological examination - early diagnosis of cervical cancer. *Laboratornaya diagnostika*. 2015;4(134):35-37. (In Russ.)]
2. Чиссов В.И., Старинский В.В., Петрова Г.В. Злокачественные новообразования в России в 2007 году (заболеваемость и смертность). Москва; 2009: 244. [Chissov VI, Starinsky GV, Petrova GV. Malignant neoplasms in Russia in 2007 (morbidity and mortality). Moscow; 2009: 244. (In Russ.)].
3. Коломиец Л.А., Уразова Л.Н, Севастьянова Н.В. и др. Клинико-морфологические аспекты цервикальной папилломавирусной инфекции. *Вопросы онкологии*. 2002;48(1):43–46. [Kolomiets LA, Urazova LN, Sevastyanova NV et al. Clinical and morphological aspects of cervical papillomavirus infection. *Oncology issues*. 2002; 48(1):43–46. (In Russ.)]
4. Касоян К.Т., Джангирова Т.В. Метод жидкостной цитологии в диагностике заболеваний шейки матки: учебно-методическое пособие. 2012:23. [Kasoyan KT, Dzhangirova TV. The method of liquid cytology in the diagnosis of cervical diseases: a training manual. Moscow, 2012:23 (In Russ.)]
5. Казаишвили Т.Н. Ранняя диагностика рака шейки матки методом жидкостной цитологии. Исследования и практика в медицине. *Национальный конгресс «Онкология репродуктивных органов от профилактики и раннего выявления к эффективному лечению»*. 2016:80-81. [Kazaishvili T.N. Early diagnosis of cervical cancer by liquid cytology. Research and practice in medicine. *National Congress "Oncology of reproductive organs from prevention and early detection to effective treatment"*. 2016:80-81 (In Russ.)]
6. Коган Е.А. Файзуллина Н.М., Исраилова А.Х. Мониторинг больных, перенесших операцию конизации шейки матки по поводу цервикальной интраэпителиальной неоплазии (клинико-морфологические и молекулярно-биологические аспекты проблемы). *Акушерство и гинекология*. 2012;1:70-74. [Kogan EA, Fayzullina NM, Israilova A.Kh. Monitoring of patients undergoing cervical conization surgery for cervical intraepithelial neoplasia (clinical, morphological and molecular biological aspects of the problem). *Akusherstvo i ginekologiya*. 2012; 1:70-74 (In Russ.)]
7. Прилепская В.Н. Заболевания шейки матки, влагалища и вульвы. МЕД пре-информ, 2005:432. [Prilepskaya VN. Diseases of the cervix, vagina and vulva. MED pre-inform. 2005:432. (In Russ.)]
8. Евстигнеева Л.А, Бахидзе Е.В., Семиглазов В.В. и др. Роль вирусологических факторов в развитии рака шейки матки у молодых женщин. *Журнал акушерства и женских болезней*. 2007;LVII:153–154. [Evstigneeva LA, Bakhidze EV, Semiglazov VV. et al. Role of virological factors in the development of cervical cancer in young women. *Zhurnal akusherstva i zhenskih boleznej*. 2007; LVII: 153–154. (In Russ.)]
9. Sherman ME, Lorincz AT, Scott DR. et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J. Natl. Cancer Inst*. 2003; 95:46–52.
10. Hoyer H, Scheungraber C, Kuehne-Heid R. et al. Cumulative 5-year diagnoses of CIN2, CIN3 or cervical cancer after concurrent high-risk HPV and cytology testing in a primary screening setting. *Int.J.Cancer*. 2005; 116:136–143.
11. Arbyn M., Sasieni P, Meijer C. et al. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine*. 2006; 24(3):78–89.
12. Ronco G, Giorgi-Rossi, Carozzi F. et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 2010; 11(3):249-257.
13. Petry KU, Menton S, Menton M. et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br. J. Cancer*. 2003; 88:1570–1577.
14. Anttila A. Kotaniemi-Talonen L, Leinonen M. et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomized study within organized screening programme. *BMJ*. 2010; 340:1804.
15. Cuzick J, Terry G, Ho I. et al. Type – specific human papillomavirus DNA in abnormal smears as a predictor of high – grade cervical intraepithelial neoplasia. *Br. J. Cancer*. 1994; 69:167–171.
16. Nayar Ritu, Wilbur David C. The Bethesda System for Reporting Cervical Cytology: Definitions, criteria, and explanatory notes. 3rd Edition. Springer; 2015:321.



A.S. Korostelev, A.F. Potapov, A.A. Ivanova, P.I. Zakharov,
A.V. Bulatov

PREDICTING ACUTE KIDNEY INJURY IN CAD PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

DOI 10.25789/YMJ.2020.70.06

УДК 616-06

The aim of the study was to identify the risk predictors of developing acute kidney injury (AKI) and to create an AKI prognosis chart for patients with coronary artery disease (CAD) undergoing off-pump coronary artery bypass grafting.

The study covered 210 patients with coronary artery disease (mean age of 58.4 ± 6.3 years, 173 (82.4%) men and 37 (17.6%) women) who underwent off-pump coronary artery bypass grafting. The signs of AKI after the surgery were observed in 89 (42.4%) patients. Out of the numerous factors, 17 most significant signs of the risk of developing AKI were selected using the Wald test.

Using the identified signs, we built models (1) and (2) for predicting the probability of developing AKI with the sensitivity of 81% and specificity of 91%.

We also revealed increased probability of developing AKI by 7.83 times (95% CI: 4.2-14.7) in patients with concomitant metabolic syndrome (MS).

Keywords: coronary artery disease, metabolic syndrome, off-pump coronary artery bypass grafting, acute kidney injury, risk predictors, prediction model.

Kidney failure and various degrees of AKI in patients with coronary artery disease undergoing coronary artery bypass grafting remains one of the challenges in cardiac surgery and cardiovascular anesthesiology [4]. The AKI developed in the postoperative period leads to a changed patient treatment tactic, prolonged treatment duration and significantly worse

prognosis, increasing the hospital mortality rate of such patients to 26.3% [1]. In addition, several research results indicate the highest risk of perioperative renal complications in patients with comorbid pathologies, including concomitant MS [3].

With the goal of improving treatment outcomes, the differentiated and patient-oriented approach is a current trend in medicine. From this perspective, the identification of objective prognostic risk criteria for developing AKI is of great applied value.

The aim of the present study was to identify the risk predictors of developing AKI and to create an AKI prognosis chart for patients with CAD undergoing off-pump coronary artery bypass grafting.

Materials and Methods. A retro- and prospective, longitudinal observational study was conducted. The retrospective stage of the study included analysis of medical records of 90 inpatients, prospective - examination and treatment of 210 patients with coronary artery disease (173 (82.4%) men, 37 (17.6 %) women) who underwent myocardial revascularization by coronary artery bypass grafting and mammary coronary artery bypass surgery off-pump. Mean age of patients was 58.4 ± 6.3 years. All surgeries were performed at the Sakha (Yakutia) Republic's Hospital No. 1 - National Center of Medicine in the period 2016-2020.

The diagnostics of the cardiovascular system functional status was carried out in accordance with the 2014 ESC/EACTS Guidelines on Myocardial Revascularization [11]. MS was diagnosed using the criteria from the Clinical Guidelines of the Ministry of Health of the Russian Federation [6].

Under the ASA (American Society of Anesthetists) classification, all the patients were assigned ASAPS Class 3 and Class 4. The anesthetic and postoperative managements were carried out following the management protocols of patients undergoing off-pump coronary artery bypass grafting [5].

The diagnostics of the functional status of kidneys, assessment of the degree of renal dysfunction, AKI and assessment of its severity were carried out following the KDIGO (Kidney Disease Improving Global Outcomes) Clinical Guidelines [12].

The processing of statistical data was performed using SPSS Statistics, version 23, and included: at different stages of the study, calculating the mean value and standard deviation assuming a normal distribution ($M \pm SD$), the median and interquartile range ($Me, IQ RQ3-Q1$); conducting a logistic regression analysis to develop an AKI prediction model; and determining the two-tailed criterion of Student's t-test for comparing mean values of two independent groups, and the Mann-Whitney criteria for a nonparametric test. The statistical significance was set at $p < 0.05$.

Results and Discussion. In the postoperative period, the signs of AKI were observed in 89 (42.4%) patients. To predict postoperative AKI in patients with coronary artery disease, we studied 104 factors that were considered from the perspective of increasing or decreasing the risk of kidney injury. Using a statistical analysis, we identified 72 factors that have a statistically significant relationship with the risk of developing AKI. At the next stage, out of these factors, 17 signs were selected by

KOROSTELEV Aleksandr Sergeevich – anesthesiologist-resuscitator, Department of Anesthesiology, Resuscitation and Intensive Care (Cardiology), State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No. 1 - National Center of Medicine." Address: 677000, Sakha Republic (Yakutia), Yakutsk, ul. Oyunskogo, 27. Tel/fax. +7 (4112) 363489. Mob. +7-924-763-9300. E-mail: bezbazaroff@inbox.ru;
POTAPOV Aleksandr Filippovich – Doctor of Medical Sciences, Head, Department of Anesthesiology, Resuscitation and Intensive Care with Emergency Care Course, Faculty of Post-graduate Studies for Doctors, Institute of Medicine, Federal state educational institution of higher professional education "M.K.Ammosov North-Eastern Federal University".
IVANOVA Albina Ammosovna – Doctor of Medicine, Associate Professor, Department of Anesthesiology, Reanimation and Intensive Care, Institute for Post-graduate Medical Training, Ammosov North-Eastern Federal University.
ZAKHAROV Petr Ivanovich – Doctor of Medical Sciences, chief external expert in cardiovascular surgery, Head, Cardiovascular Surgery Department, Clinical Center, State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No. 1 - National Center of Medicine."
BULATOV Alkviad Valentinovich – Candidate of Medical Sciences Head, Department of Anesthesiology, Resuscitation and Intensive Care (Cardiology), State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No. 1 - National Center of Medicine."

the Wald stepwise backward elimination method (Table 1).

The Table demonstrates that along with the values of blood creatinine, GFR and proteinuria, which are mandatory in assessing renal function [3, 4, 17], we selected the factors whose role in the development and course of AKI has been confirmed by numerous studies. These are anthropometric data [11, 8], smoking [10], a number of hemodynamic parameters [9, 2], blood sugar [11, 14, 15] and lipids [7,10,16,18], as well as the intake of statins, which have nephroprotective effect [18].

The inclusion of the presented risk factors for developing AKI made it possible to create a prediction model (1) for determining the probability of developing AKI in each case:

$$PAKI = 1/(1 + e^{-z}),$$

where: PAKI – the probability of developing AKI, expressed in %; e^{-z} – the natural logarithm base (Euler's number) = 2.71828.

The following risk factors are to be used to calculate z:

$$z = -28.561 + 0.09 \cdot X_{age} + 0.2 \cdot X_{BMI} + 1.5 \cdot X_{smoking} - 1.2 \cdot X_{statins} + 0.07 \cdot X_{EF} - 1.9 \cdot X_{LVEDd} + 0.1 \cdot X_{GFR} + 0.09 \cdot X_{creatinine} +$$

$$2.0 \cdot X_{proteinuria} + 0.3 \cdot X_{HbA1c} + 0.3 \cdot X_{glucose} + 0.09 \cdot X_{Hb} - 0.2 \cdot X_{Ht} - 0.3 \cdot X_{TC} + 1.1 \cdot X_{TG} - 3 \cdot X_{HDL} + 1 \cdot X_{LDL} \quad (1),$$

where: X_{age} – age (years); X_{BMI} – body mass index (kg/m²); $X_{smoking}$ – smoking factor (0 – non-smokers, 1 – smokers); $X_{statins}$ – the intake of statins in therapeutic doses (0 – does not take, 1 – takes); X_{EF} – ejection fraction (%); X_{LVEDd} – left ventricular end diastolic dimension (cm); X_{GFR} – glomerular filtration rate (ml/min/1.73m²); $X_{creatinine}$ – serum creatinine (μmol/l); $X_{proteinuria}$ – proteinuria (mg/d); X_{HbA1c} – glycosylated hemoglobin (%); $X_{glucose}$ – blood glucose level (μmol/l); X_{Hb} – hemoglobin level (g/l); X_{Ht} – hematocrit (%); X_{TC} – total cholesterol (μmol/l); X_{TG} – triglycerides (μmol/l); X_{HDL} – high-density lipoproteins (μmol/l); X_{LDL} – low-density lipoproteins (μmol/l); - 28.561 – a constant.

The assessment of the probability of developing AKI in CAD patients was carried out as follows: with a value of PAKI > 50 %, the patient was assumed the high-risk group of kidney injury, while with PAKI < 50% – the low-risk group. The sensitivity of the obtained model was 81%, specificity – 91%, with the total percentage of diagnostic efficiency at 86.7%.

Based on the values of the regression coefficients, all of the listed factors are directly related to the probability of developing AKI in the postoperative period. The obtained regression model (1) is statistically significant ($p = 0.001$) and, based on the value of the Nigelerk coefficient of determination, it takes into account 73.5% of the factors signaling the probability of developing AKI in the postoperative period.

In order to adapt this model (1) for application in the routine clinical practice, and also taking into account the complex mathematical calculation of logistic regression, we transformed it using the multiple linear regression. The value of the probability of AKI development, expressed as a percentage, served as a dependent variable, and we introduced the same 17 indicators used in model (1) as factor variables. As a result, the following equation was created (Model 2):

$$YAKI (\%) = 0.7 \cdot X_{age} + 2.3 \cdot X_{BMI} + 14 \cdot X_{smoking} - 16 \cdot X_{statins} + 0.1 \cdot X_{EF} - 18.5 \cdot X_{LVEDd} + 0.4 \cdot X_{GFR} + 0.6 \cdot X_{creatinine} + 13 \cdot X_{proteinuria} + 3 \cdot X_{HbA1c} + 2.7 \cdot X_{glucose} + 0.9 \cdot X_{Hb} - 2.4 \cdot X_{Ht} - 2.5 \cdot X_{TC} - 2 \cdot X_{TG} - 24 \cdot X_{HDL} + 12.2 \cdot X_{LDL} - 105 \quad (2),$$

Where: YAKI (%) – the probability of developing AKI in %; - 105 – a constant (baseline probability of AKI without the factors included in the Model); values of 0.7; 2.3; 14; 16, etc. – regression coefficients determining how much the AKI risk will increase with a certain risk factor.

The created prediction regression model (2) was characterized by a direct, statistically significant correlation of the probability of AKI ($p = 0.001$) and had a strong relationship of the factors on the Chaddock scale ($rx_y = 0.940$). Based on the value of the Nigelerk determination coefficient R^2 , Model (2) takes into account 88.3% of the most significant factors determining the probability of AKI in the postoperative period. The sensitivity of the model remained high and made 81%, specificity – 91%.

The conducted ROC (Receiver Operating Characteristic) analysis confirmed high diagnostic value of the created model (2). The area under the ROC – AUC (area under curve) was 0.94 ± 0.14 (95% CI 0.91-0.97), dividing value of prognostic function (cut-off) – 50% (Fig.).

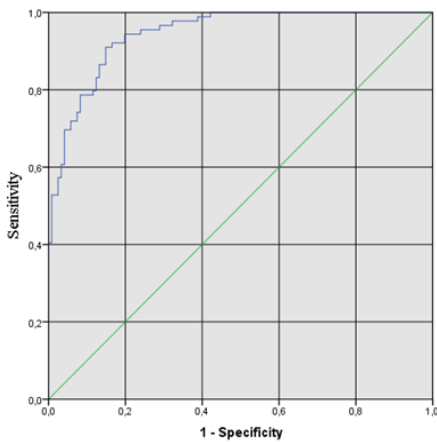
Assuming that the AKI predictors include all the signs characteristic of MS, we carried out a separate analysis of the AKI incidence in patients with concomitant MS. The statistical analysis showed that the probability of developing AKI with concomitant MS increases by 7.83 times (95% CI: 4.2-14.7) (Table 2).

Table 1

Factor having established relationship with the AKI risk in CAD patients

Characteristics	With AKI (n=89)	Without AKI (n=121)	p
Age, years, (M±SD)	59.1±5.9	57.8±6.6	0.154
BMI, kg/m ² , (M±SD)	31.1±4.1	26.8±5.0	< 0.001*
Smoking, n (%)	63 (70.8%)	26 (29.2%)	< 0.001*
LVED, cm, (M±SD)	4.9 ± 0.4	4.9±0.4	0.159
EF, %	58.5±6.0	59.6±6.24	0.871
GFR/min/1.73m ² , (M±SD)	71.5 ±14.2	77.9 ± 14.1	0.001*
Serum creatinine, μmol/l (Me [Q1-Q3])	101.0 [88.0-122.0]	89.0 [88.0-99.0]	< 0.001*
Proteinuria, mg, (Me [Q1-Q3])	0.3 [0.1-1.0]	0.1 [0-0.2]	< 0.001*
Fasting plasma glucose, μmol/l (Me [Q1-Q3])	8.0 [7.0-9.0]	5.5 [4.5-7.75]	< 0.001*
HbA1c, %	6.5 [5.25-7.0]	4.0 [4.0-4.5]	< 0.001*
Hb, g/l (M±SD)	140.0±8.1	137.1±8.8	0.016*
Ht, %, (Me [Q1-Q3])	35.0 [33.0-38.0]	37.0 [34.0-43.0]	< 0.001*
Total cholesterol, μmol/l, (M±SD)	6.5 [5.25-7.25]	5.5 [4.25-7.0]	0.001*
Triglycerides, μmol/l, (M±SD)	1.63±0.3	1.43±0.3	< 0.001*
HDL cholesterol, μmol/l, (Me [Q1-Q3])	1.36±0.27	1.32±0.29	0.357
LDL cholesterol, μmol/l, (Me [Q1-Q3])	2.35±0.64	1.84±0.7	< 0.001*
Atorvastatin, 20 mg, n (%)	61 (68.5%)	41 (33.9%)	< 0.001*
80 mg, n (%)	28 (31.5%)	80 (66.1%)	

Note: BMI - body mass index; LVED - the final diastolic size of the left ventricle; LVEF - left ventricular ejection fraction; GFR - glomerular filtration rate; TC - total cholesterol; TG - triglycerides; HDL - high density lipoproteins; LDL - low density lipoproteins. In the tables 1-2 * - differences in the indicators are statistically significant ($p < 0.05$).



ROC-curve characterizing the correlation between the probability of developing AKI and the prognostic function Yaki % in Model (2).

serum creatinine of 159 $\mu\text{mol/l}$, and decreased urine output of less than 0.5 ml/kg/h.

Conclusion. Therefore, in our study, signs of AKI were observed in 42.4% of the patients with coronary artery disease, and the probability of its development with concomitant MS increased by 7.83 times. Predicting AKI and assessing the risk of its development should become mandatory for patients with coronary artery disease prior coronary artery bypass grafting. Assessing the probability of developing AKI will allow adjusting the program of preoperative preparation of patients, thereby reducing the number of complications in the postoperative period and improving the results of treating patients of this complex category.

Table 2

Evaluation of the AKI incidence in patients with concomitant MS

Presence/absence of AKI	Patients with MS (n=106)		Patients without MS (n=104)		p*	OR; 95% CI
	Abs.	%	Abs.	%		
Signs of AKI	69	65.1	20	19.2	<0.001	7.83; 4.2-14.7
No signs of AKI	37	34.9	84	80.8		

Upon completion of the study, we created a chart for practitioners "Assessing the risk of developing AKI in patients with coronary artery disease undergoing CABG", including the discussed predictors. Here is a clinical example of calculating the probable risk of AKI in a patient with coronary artery disease and MS:

Patient M., 66, was admitted for a surgery to treat coronary artery disease with concomitant MS. The indicators at admission: BMI – 32 kg/m²; smokes a pack of cigarettes a day; LVEDd – 4.4 cm, EF – 55%; GFR – 71 ml/min/1.73 m², blood creatinine – 126 $\mu\text{mol/l}$, proteinuria – 0.9 mg; HbA1c – 6.4%; blood glucose – 7.2 $\mu\text{mol/l}$; Hb – 124 g/l, Ht – 32%; TC – 6.6 $\mu\text{mol/l}$, HDL – 2.4 $\mu\text{mol/l}$, LDL – 3.1 $\mu\text{mol/l}$, TG – 1.9 $\mu\text{mol/l}$; has been taking Atorvastatin 20 mg for 2 months.

The calculation estimated the risk of AKI in the patient exceeding 50%, which indicated a high risk of developing AKI. The prediction was later confirmed. 48 hours after the surgery, the patient showed signs of AKI: decreased GFR of 59 ml/min/1.73 m², increased

kidney injury after CABG without cardiopulmonary bypass: prediction of outcomes. *Nefrologiya i dializ.* 2014;16(3): 350-358. (In Russ.)]

5. Хенсли А.Ф., Мартин Д.Е., Грэвли Г.П. Практическая кардиоанестезиология. 5-е изд. — М.: «Медицинское информационное агентство», 2017. [Frederick A. Hensley Jr., Donald E. Martin, Glenn P. Gravlee. A practical approach to cardiac anesthesia. *Medicinskoe informacionnoe agentstvo.* 5th ed., transl. version. (In Russ.)]

6. Рекомендации по ведению больных с метаболическим синдромом: клинические рекомендации МЗ РФ; 2013: 42. [Clinical guidelines for the management of patients with metabolic syndrome. *RF Ministry of Health care;* 2013: 42. (In Russ.)]

7. Chen SC, Hung CC, Kuo MC. [et al.] Association of dyslipidemia with renal outcomes in chronic kidney disease. *PLoS One;* 2013; 8(2):556.

8. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. *Clin. Med.* 2005; 5:635–642.

9. Ronco C, McCullough P, Anker S. [et al.] Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur. Heart J.* 2010; 3:703-711.

10. Yamamoto R, Nagasawa Y, Shoji T [et al.] Cigarette smoking and progression of IgA nephropathy. *Am. J. Kidney Dis.* 2010; 56:313–324.

11. Despres J.-P. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. *Eur. Heart J.* - 2006; 8 (suppl. B): 4-12.

12. Windecker S, Kolh P, Alfonso F. [et al.] ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur. Heart J.* 2014;35(37): 619-2541.

13. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int. (Suppl)* 2012; 2:1-138.

14. Chen J, Muntner P, Hamm L. [et al.] Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J. Am. Soc. Nephrol.* 2003;14:469-477.

15. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J. Am. Soc. Nephrol.* 2005;16: 2134-2140.

16. Urazlina CE, Zhdanova TV, Nazarov AV [et al.] Lipid metabolism in patients with chronic renal failure. *Ural Medical Journal.* 2011; 2(80): 6-122.

17. Peterson JC. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann. Intern. Med.* 1995; 123:754–762.

18. Song-jian H. Qiang Liu, Hua-qiu Li, Fang Tian, Shi-yu Chen. Role of statins in preventing cardiac surgery-associated acute kidney injury: an updated meta-analysis of randomized controlled trials. *Ther. Clin. Risk Manag.* 2018; 14: 475–482.

References

1. Искендеров Б. Г., Сисина О.Н. Факторы риска и исходы острого повреждения почек у пациентов с сохранной функцией почек, подвергнутых аорто-коронарному шунтированию. *Нефрология.* 2013;3:7-63. [Iskenderov BG, Sisina ON. Risk factors and outcomes of acute kidney injury in patients with intact renal function underwent coronary artery bypass grafting. *Nefrologiya.* 2013; 3:7- 63. (In Russ.)]

2. Кобалава Ж.Д., Моисеев В.С. Концепция кардиоренальных и метаболических соотношений в современной профилактической кардиологии. *Кардиоваскулярная терапия и профилактика.* 2008;4: 4-7. [Kobalava ZD, Moiseev VS. The concept of cardiorenal and metabolic relationships in modern preventive cardiology. *Kardiovaskulyarnaya terapiya i profilaktika.* 2008; 4: 4-7. (In Russ.)]

3. Мельник А.А. Метаболический синдром и риск хронической болезни почек. *Почки.* – 2017; 6(2): 80-90. [Melnik AA. Metabolic syndrome and risk of chronic kidney disease. *J. Pochki.* 2017; 6(2): 80 – 90. (In Russ.)]

4. Миролюбова О.А., Алексеева М.А., Яковлева А.С., Шонбин А.Н. [и др.] Острое повреждение почек после аортокоронарного шунтирования на работающем сердце: прогнозирование исходов. *Нефрология и диализ.* 2014;16(3): 350-358. [Mirolyubova OA, Alekseeva MA, Yakovleva AS, Shonbin AN. [et al.] Acute

M.A. Nikitina, N.G. Brazovskaya, N.G. Zhukova, E.Yu. Bragina, V.M. Alifirova

APATHY AS THE NON-MOTOR SYMPTOM OF PARKINSON DISEASE AND HUNTINGTON DISEASE

DOI 10.25789/YMJ.2020.70.07

УДК 616.858:616.851-056.7]-07:
616.89-008.484-037

Apathy is one of the most frequent, disabling and difficult to treat non-motor symptoms manifesting in many neurodegenerative diseases, particularly in Parkinson disease and Huntington disease. Aim is to evaluate and compare the clinical profile of apathy in patients with Parkinson disease (PD) and Huntington disease (HD).

Materials and methods. The individual registration card was filled in for each patient containing demographic data, clinical features of the disease, the results of validated scales and questionnaires evaluating motor activity (The Movement Disorder Society-Unified Parkinson's Disease Rating Scale – MDS-UPDRS, the Unified Huntington's Disease Rating Scale – UHDRS), cognitive functions (MoCA-test), anxiety-depressive symptoms (hospital scale for evaluating anxiety and depression, Beck's depression scale-II), apathy (apathy rating scale). Patients with dementia or severe depression were excluded from the study.

Results. The study included 265 patients: 250 with PD and 15 with HD. Apathy was diagnosed in 57.8% of cases in patients with neurodegenerative diseases (139 out of 250 patients with PD and 9 out of 15 patients with HD). In both groups of patients apathy was associated with the severity of motor manifestations. Patients with PD showed a positive correlation of apathy with more severe depression ($r=0.488$; $p<0.0001$), anxiety ($r=0.300$; $p<0.0001$) and drowsiness ($r=0.254$; $p<0.0001$); a negative correlation with a short duration of the disease ($r=-0.160$; $p=0.021$), a lower dose of dopaminergic drugs, LEDD ($r=-0.203$; $p=0.03$). In patients with HD, apathy was associated with disease duration (8 (4; 11) years in patients without apathy and 5 (3;9) years in patients with apathy, $U=3791.5$; $p=0.020$) and cognitive impairment (26 (19;37) points, without apathy – 18 (12;26), $U=3548.5$; $p=0.003$).

Conclusions. Similar frequency of apathy was found in patients with PD and HD, but with different clinical correlations due to the involvement of different brain regions in the pathological process, which requires further research to develop targeted therapy.

Keywords: apathy, Huntington disease, Parkinson disease, cognitive disorders, depression, psychopathological symptoms, non-motor symptoms.

Introduction. Apathy is considered as a disorder of the emotional-volitional sphere, characterized by a lack of emotional manifestations, lethargy, indifference to oneself and relatives, to what is happening around, lack of desires, life motives and inactivity. 3 main components are distinguished in apathy: emotional-affective, cognitive and auto-activity deficit: the first is the apathy associated with impaired emotional-affective processes; the second is the apathy

associated with the violation of cognitive processes; and the third is the apathy associated with the disorder of self-activity process [1].

Each component of apathy is caused by different neuronal connections affecting the basal ganglia, thalamus, and cortical connections. According to research data, the apathy prevalence in cortex and subcortical nuclei lesions ranges from 40 to 60% [4, 7, 12, 14]. Such high rates of apathy in brain diseases are the result of quite frequent involvement of frontal-subcortical neuronal connections between the prefrontal cortex and basal ganglia in the neurodegenerative process, affecting the anterior cingulate gyrus, ventral striatum, pallidum and thalamus [1, 19].

Both PD and HD are motor neurodegenerative disorders caused mainly by lesions of the basal ganglia and manifesting by motor and various non-motor symptoms, including cognitive, behavioral, and emotional-affective manifestations, with apathy among them [19, 20]. In PD, apathy is a frequent neuropsychiatric disorder with prevalence varying from 7 to 70%, and, according to a number of studies, it might even precede motor symptoms with a frequency reaching 36% of cases [7, 8]. The prevalence of apathy usually decreases after the starting of dopaminergic replacement therapy, but it increases again up to 40% in patients without severe cognitive impair-

ment and up to 60% in patients with dementia after 5-10 years of the disease [8]. Apathy in PD is associated with the male sex, old age, the presence of depression and severe motor disorders, deterioration of executive function, and an increased risk of dementia [8, 22].

The prevalence of apathy in HD, according to various literature data, also varies widely: from 11 to 76% [9, 10, 15-17, 21]. One point of view is that apathy is mildly present in almost all patients with HD during the course of the disease, and that its prevalence increases due to the progression of the disease. As a result of the "TRACK-HD" study (UK, 2012-2014), establishing sensitive and reliable biomarkers in identified carriers of the HD gene and in patients with HD at early clinical stages, it was proved that a significant increase in apathy can be detected among patients with HD at the preclinical stage. Apathy in this case was the most reliable psychotic non-motor symptom, which is important for predicting functional disorders at the early stages of HD [9, 16, 18]. According to these studies, apathy in HD was more common in older male patients with a lower overall functional ability score, a higher score of motor function evaluation on the Unified Huntington's Disease Rating Scale – UHDRS, more psychotropic drugs usage, depression, and cognitive impairment.

NIKITINA Maria A. – MD, PhD, Associate Professor, Department of Neurology and Neurosurgery, Siberian State Medical University, Tomsk, Russian Federation, 8-913-865-4918, e-mail: nikitina_ma@mail.ru, ORCID 0000-0002-2614-207X; **BRAZOVSKAYA Natalia G.** – PhD, Associate Professor, Department of Medical and Biological Cybernetics, Siberian State Medical University, Tomsk, Russian Federation, brang@mail.ru, 8-913-884-7333; **ZHUKOVA Natalya G.** – MD, PhD, Professor, Department of Neurology and Neurosurgery, Siberian State Medical University, Tomsk, Russian Federation, znatali@yandex.ru, 8-913-824-6202; **BRAGINA Elena Yu.** – PhD, Senior Researcher, Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk, Russian Federation, elena.bragina72@gmail.com, 8-913-823-4122; **ALIFIROVA Valentina M.** – MD, PhD, Professor, Head of the Department of Neurology and Neurosurgery, Siberian State Medical University, Tomsk, Russian Federation, v_alifirova@mail.ru, 8-913-850-0240

Despite the fact that both PD and HD characterized by severe motor disorders, often manifest by apathy, its profile and correlations with other symptoms differ significantly. The purpose of this study was to evaluate and identify the role of apathy in the clinical picture of PD and HD.

The **aim** of our study was to evaluate non-motor symptoms in patients with PD and HD, on the basis of the apathy presence and its severity.

Materials and methods. The advantage of this work is that a quite large category of patients with neurodegenerative diseases was examined using the same, validated, recommended by the world's leading neurological organizations – «The International Parkinson and Movement Disorder Society (MDS)» and «European Academy of Neurology (EAN)» clinical scales for apathy, cognitive dysfunction and depressive symptoms assessing.

The plan and performing of the study are fully complying with the principles of Good Clinical Practice (GCP) and the Helsinki Declaration (including amendments). The research protocol was approved by the ethics Committee of the Siberian State Medical University (registration number 7813 of may 27, 2019).

265 patients with neurodegenerative disorders were studied: 15 with HD and 250 with PD at different disease stages on base of the department of neurology and neurosurgery Siberian State Medical University, Tomsk, Russian (head of department, professor, MD V.M. Alifirova).

Inclusion criteria: verified diagnosis of idiopathic PD according to the diagnostic Criteria of the United Kingdom Parkinson's Disease Society Brain Bank [13], verified diagnosis of HD with a positive genetic test (the number of trinucleotide CAG repeats in one of the alleles of the HTT gene ≥ 36) and characteristic clinical manifestations in the form of motor symptoms, with UHDRS motor assessment.

Exclusion criteria: the presence of severe depression and dementia, according to the diagnostic criteria of ICD-10; patients with PD who had deep brain stimulation surgery.

The individual registration card was filled in each patient of the study, containing information about demographic data (age, gender, education level), medical history (duration, stage of symptoms development, used drug therapy, the dose of dopaminergic drugs for patients with PD translated into the equivalent daily dose of levodopa (levodopa equivalent daily dose-LEDD) and for both groups,

the analysis of symptomatic therapy); for patients with HD - the number of CAG repeats.

Evaluation of motor disorders in patients with HD was performed using the Unified rating scale for HD manifestations evaluation, the part "motor assessment" (UHDRS-Motor), in patients with PD – using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale – MDS-UPDRS, part III (MDS-UPDRS-III). The analysis of motor and psychoemotional disorders in patients with PD was carried out in the on-phase. Depressive symptoms were studied using the Beck-II depression scale. Cognitive impairment was recorded using the Montreal cognitive assessment scale (MoCA test).

There is an extensive list of psychometric scales published to assess apathy, but for the purposes of this study, we focused on those that could be used in both patients with HD and PD [3]. Apathy was evaluated using the Apathy Scale, which is a self-questionnaire consisting of 14 statements distributed on a 4-point Likert scale (1-not at all, 2-slightly, 3-partially, and 4-to a large extent) and being a modified, abbreviated version of the Marin (Apathy Evaluation Scale - AES) [11]. Answers to questions should contain information about the previous four weeks. The questionnaire has items reflecting various symptoms, according to which you can track their dynamics. Energy, sleep, fatigue, appetite, psychomotor disorders, speed and clarity of thinking, memory, ability to concentrate, the presence of plans and goals for the future, loss of interest and initiative are the main factors for determining the presence and severity of apathy. The main advantages of the scale are the following: ease of use, well-defined score values for apathy screening, high specificity and sensitivity to changes (on the background of treatment). The disadvantages are that this self-questionnaire is not acceptable for patients with moderate to severe dementia.

Statistic results processing was performed using the pack of application programs SPSS 11. 5 for Windows. The critical significance level in our study was 0.05. The description of qualitative features is carried out by specifying absolute and relative (%) frequency of occurrence (Pearson's criterion χ^2 with Yates correction and Fisher's exact criterion). Quantitative characteristics were checked for compliance with the normal distribution law using the Shapiro-Wilk test. The description of quantitative characteristics is presented as the average value and

standard deviation M; σ . Description of quantitative features whose distribution does not correspond to the normal law – in the form of the median and the interquartile range Me (Q1;Q3). We used for comparison of quantitative data criteria Mann-Whitney and Kruskal-Wallace. The relationship between quantitative and ordinal features was evaluated using correlation analysis.

Results. In our sample patients with PD were of average age of 67.2 ± 7.8 years, 130 (52%) were men and 120 (48%) were women, the average duration of education was 9.2 ± 6.3 years, and the average duration of the disease was 7.4 ± 5.1 years. All PwPD received specific antiparkinsonian therapy, 110 (44%) patients were treated with antidepressants, and 2 (0.8%) received neuroleptics.

For patients with HD, the average age was 51.3 ± 7.8 years; there were 6 men and 9 women, the average level of education was 7.2 ± 4.9 years, the average duration of the disease was 7.1 ± 4.2 years, 9 patients received neuroleptic treatment and 10 received antidepressants (4 patients were treated with the combination of these drugs). According to the obtained data, patients with HD were significantly younger than those with PD ($p < 0.001$).

The analysis of the examined groups revealed that patients with PD had a higher average level of education ($p = 0.032$), patients with HD – received neuroleptic treatment more often ($p < 0.001$). In our sample, the average duration of the disease in patients with PD and HD was equivalent, with no significant differences ($p > 0.05$).

High incidence of apathy in patients with various neurodegenerative diseases was found in this study, manifested both by hypokinetic-hypertensive syndrome in PD and hyperkinetic-hypotonic syndrome in HD: 55.6% ($n = 139/250$) and 60.0% ($n = 9/15$), respectively, at $p > 0.05$. Cognitive disorders were observed in all patients with diagnosed apathy in HD ($n = 9$), while in patients with PD – in 44.6% ($n = 62$) of cases, $p < 0.001$. In turn, patients with PD and apathy were more likely to have depressive symptoms – in 93.5% ($n = 130$) of individuals, compared with patients with HD – in 55.5% ($n = 5$), with $p < 0.001$. This data is consistent with the results of international studies [7-10, 15-17]. However, there is a wide variability of the apathy frequency in both diseases in the literature, which is due to various factors, such as the location of the patients' sample (e.g. patients from special clinics for movement disorders in comparison with individuals from the

general population), the inclusion of patients with severe depression and / or dementia, the severity of the disease, different methodological approaches (e.g., assessment of the patient or his relatives) and usage of various diagnostic tools for apathy assessment.

The clinical profile of the studied neurodegenerative disorders is represented by various motor symptoms (in PD – bradykinesia, tremor, hypokinesia and postural instability, in HD – chorea in the form of abnormal short and irregular uncontrolled movements) and non-motor (cognitive, emotional-affective, mental and behavioral) symptoms. Although both diseases are mainly associated with lesions affecting the basal ganglia, the neurodegenerative process in PD and HD develops in different ways. So, the PD manifestation is observed at 70-80% loss of the substantia nigra pars compacta, first in its ventral and then in the dorsal parts, which subsequently leads to a loss of the striatum dopamine content. In HD, the neurodegenerative process is initiated by the loss of striatum neurons [2, 5]. However, despite all these differences, both diseases seem to have an equally high apathy inclination but with features in its profile.

Patients with PD and apathy studied by the MDS-UPDRS-III scale showed a significantly higher level of motor disorders – 38 (30;48), while without apathy – 29 (23;38), ($U=3658.5$; $p=0.003$), a shorter duration of the disease – 6 (4;10) compared with 9 (5;12) points - without emotional-affective disorder, ($U=3793.5$; $p=0.020$), a lower dose of LEDD – 150 (0;350) and 300 (156;375), ($u=3321.5$; $p<0.0001$) and had pronounced depressive symptoms according to BDI-II – 20 (16;27) compared to PD – without apathy – 15 (11;20), ($U=2781.5$; $p<0.0001$).

According to the results of our study, patients with PD and apathy have more severe motor disorders (according to MDS-UPDRS-III), a shorter duration of the disease, and more pronounced symptoms of depression. On this basis it can be assumed that the short duration of clinically expressed neurodegenerative disease and the presence of pronounced motor symptoms might be the apathy predictors in PD.

An interesting result is that the majority of apathy patients with PD and apathy patients with HD had combined depression and / or cognitive disorders, and only 5.6% of those with PD ($n = 14$) and 1 patient with HD (6.7%) had isolated apathy. According to previous studies, apathy is a hypodopaminergic symptom in PD, with the severity decreasing when taking do-

paminergic drugs [5]. In our sample, patients with PD and apathy have a lower total daily dose of levodopa, compared to patients with PD without apathy ($p = 0.05$). Despite the fact that there were no statistically significant differences in dopaminergic drugs dose taken in the group of patients with PD and apathy and without it, there was a trend in which patients who did not suffer from apathy received drugs of dopamine receptor agonists more often.

Moreover, it was found that patients with PD and apathy are significantly more likely to take antidepressants than patients without apathy; however, this can be explained by the fact that apathy is combined with depression in most cases, and patients receive depression pathogenetic treatment that does not affect the severity of such an emotional-affective disorder as apathy.

The connection between apathy and cognitive impairment is contradictory and widely discussed [4, 8, 20]. As a result of neuropsychological testing, it was found that the cognitive profile of patients with apathy in the studied neurodegenerative diseases differs: in patients with HD attention, working memory ($p < 0.001$) and speech ($p = 0.007$) domains are significantly reduced according to the MoCA test compared to patients with PD.

In HD apathy was also significantly associated with the duration of the disease and the presence of cognitive impairments. Thus, in patients without apathy the duration of the disease was 5 (3;9) years, with apathy – 8 (4;11) years, $U = 3791.5$; $p=0.020$.

During the study it was found that all patients with HD had cognitive disorder ($n = 15$). However, patients with clinically expressed apathy had the worst result of cognitive tests of 16 (10;24) points, without apathy – 20 (12;29) points, $U = 3548.5$; $p=0.003$. Our data partially confirm the results received earlier indicating that apathy in HD might be a predictor of cognitive impairment up to dementia [3]. We did not find a predominance of patients taking neuroleptics in the group of patients with apathy. However, this might be connected to the fact that neuroleptics are used at the advanced stage of HD.

As the result of the study it was found that patients with PD have two peaks of apathy in the course of the disease: in the early, before-treatment stages by Hoehn and Yahr (as a rule, they are first-time applying patients of the 1st and 2nd stages by Hoehn and Yahr), when the specific antiparkinsonian therapy, supporting optimal or close to the physi-

ological level of dopamine, has not been prescribed and the second peak is on extensive stages of PD (4th and stage 5th stages) when extensive neurodegenerative process can't be compensated by the drugs and is accompanied by a number of non-motor symptoms. In addition, the association of apathy with hospitalization of the patient was found due to the development of an akinetic crisis, regardless of the PD stage. This might be connected to the constant use of a low dose of dopaminergic drugs, which increases the likelihood of apathy and other associated emotional and affective disorders that contribute to the violation of compliance in this category of patients.

Despite the fact that there are two different disorders of the basal ganglia in the studied diseases, the greater severity of motor symptoms seems to lead to a higher predisposition of apathy in both HD and PD.

Conclusion. As a result of the study, it can be noted that apathy is a frequent and important non-motor manifestation of PD and HD. In the studied neurodegenerative diseases with lesions of the basal ganglia, various neuronal pathways going from the prefrontal cortex to the basal ganglia suffer [2, 6]. Thus, in PD apathy is mostly associated with the emotional component, while in HD it is associated with cognitive areas, that might determine the need for different therapeutic approaches.

According to our data, apathy as a non-motor symptom of the two neurodegenerative pathologies studied in this research, has a similar prevalence, but the clinical profile is different. Apathy in PD is primarily associated with emotional and affective disorders ("emotional apathy"), while in HD it is associated with cognitive functions ("cognitive apathy").

In clinical practice, these results lead us to consider apathy as an independent nosological unit, caused by dysfunction, on the one hand, of different, but at the same time interconnected neuronal projections, which might differ depending on the nosology and even within the same pathology, depending on the stage of the disease. Our study confirms the fact that apathy has a multifactorial nature and depending on the type of neurodegenerative disease might have different points of pharmacotherapy application.

The research was supported by the Grant Council of the President of the Russian Federation (grant № MK-813.2019.7, "Clinical and epidemiological features of neurodegenerative diseases of the Tomsk region").

References

1. Вознесенская Т.Г. Синдром апатии. *Неврологический журнал*. 2013; 18(3): 4-10. DOI: 10.18821/1560-9545-2013-18-3-4-10; [Voznesenskaya TG. Apathy syndrome. *Neurologicheskij zhurnal*. 2013; 18(3): 4-10. DOI: 10.18821/1560-9545-2013-18-3-4-10. (In Russ.)]
2. Таппахов А.А., Николаева Т.Я., Алексеева А.Д., Оконешникова Л.Т. Дифференциальная диагностика мультисистемной атрофии и эссенциального тремора с болезнью Паркинсона. *Якутский медицинский журнал*. 2016; 2(54): 90-93. [Tappakhov AA, Nikolaeva TYa, Alexeeva A.D, Okoneshnikova LT. Differential diagnosis of Multiple system atrophy and essential tremor with Parkinson's disease (clinical cases). *Yakutskij medicinskij zhurnal*. 2016; 2(54): 90-93. (In Russ.)]
3. Иллариошкин С.Н., Ключников С.А., Селиверстов Ю.А. Болезнь Гентингтона: Монография (Серия "Двигательные расстройства"). М.: ООО "Издательское предприятие "Атмосфера", 2018. 472 с., ил. [Illarioshkin S.N., Klushnikov S.A., Seliverstov Y.A. Huntington's Disease: Monograph (Series "Movement Disorders"). Moscow, Publishing house "Atmosphere". 2018: 472. (In Russ.)]
4. Нодель М.Р., Яхно, Н.Н. Апатия при болезни Паркинсона. *Неврологический журнал*. 2014; 19(1): 9-15. DOI: 10.14412/2074-2711-2014-1-80-84 [M.R. Nodel', N.N. Yakhno. Apathy in Parkinson's disease. *Neurologicheskij zhurnal*. 2014; 19(1): 9-15. (In Russ.)] DOI: 10.14412/2074-2711-2014-1-80-84
5. Федорова Н.В., Никитина А.В. Депрессия, апатия и ангедония при болезни Паркинсона: механизмы развития немоторных проявлений и подходы к коррекции. *Нервные болезни*. 2012; (3): 31-36. [Fedorova NV, Nikitina AV. Depression, apathy, and anhedonia in Parkinson's disease: mechanisms of development of non-motor symptoms and approaches to correction. *Nervnye bolezni*. 2012; (3): 31-36. (In Russ.)]
6. Полова Т.Е., Таппахов А.А., Николаева Т.Я., Оконешникова Л.Т. Эпидемиология болезни Паркинсона в Республике Саха (Якутия). *Якутский медицинский журнал*. 2017. 3(59): 98-101. [Popova TE, Tappakhov AA, Nikolaeva TYa, Okoneshnikova LT. Epidemiology of Parkinson's disease in the RS(Ya). *Yakutskij medicinskij zhurnal*. – 2017; 3(59): 98-101. (In Russ.)]
7. Naarding P., Janzing JG., Eling P., van der Werf S., Kremer B. Apathy is not depression in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 2009; 21: 266-270. DOI: 10.1176/jnp.2009.21.3.266
8. Leroi I., David R., Robert P.H. Apathy in Parkinson's disease. In: Edmeier K.P., Obrien J.T., Taylor J.-P., *Psychiatry of in Parkinson's disease. Adv. Biol. Psychiatry. Vol. 27. Basel: Karger*. 2012; 27: 27-40. DOI: http: 10.1159/000331524
9. Pagonabarraga J., Kulisevsky, J., Strafella, A. P., Krack, P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology*. 2015; 14(5): 518–531. DOI: 10.1016/s1474-4422(15)00019-8
10. Camacho M., Barker R.A., Mason S.L. Apathy in Huntington's Disease: A Review of the Current Conceptualization. *J Alzheimer Dis Parkinsonism*. 2018; 8(2): 431. DOI: 10.4172/2161-0460.1000431
11. Drapier D., Drapier S., Sauleau, P., Haegelen C., Raoul S., Biseul I., Lallement F., Rivier I., Reymann J.M., Edan G., Verin M., Millet B. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease. *Journal of neurology*. 2006; 253: 1083-91. DOI: 10.1007/s00415-006-0177-0.
12. Reedeker N., Bouwens J.A., van Duijn E., Giltay E.J., Roos R.A., van der Mast R.C. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. *J Neuropsychiatry Clin Neurosci*. 2011; 23: 434 – 441. DOI: 10.1176/jnp.23.4.jnp434
13. Marsili L., Rizzo G., Colosimo C. Diagnostic Criteria for Parkinson's Disease: From James Parkinson to the Concept of Prodromal Disease. *Front Neurol*. 2018; 9:156. DOI: 10.3389/fneur.2018.00156
14. Guimarães HC., Levy R., Teixeira AL., Beato RG., Caramelli P. Neurobiology of apathy in Alzheimer's disease. *Arq Neuropsiquiatr*. 2008 Jun; 66(2B): 436-43. DOI: 10.1590/s0004-282x2008000300035
15. Paulsen JS., Ready RE., Hamilton JM., Mega MS., Cummings JL. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry*. 2001; 71: 310-314. DOI: 10.1136/jnnp.71.3.310
16. Martinez-Horta S., Perez-Perez J., van Duijn E., Fernandez-Bobadilla R., Carceller M., et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's disease. *Parkinsonism Relat Disord*. 2016; 25: 58-64. DOI: 10.1016/j.parkreldis.2016.02.008
17. van Duijn E., Craufurd D., Hubers AA., Giltay E.J., Bonelli R., et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J Neurol Neurosurg Psychiatry*. 2014; 85: 1411-1418. DOI: 10.1136/jnnp-2013-307343
18. Tabrizi SJ., Scahill RI., Owen G., et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol*. 2013; 12: 637–649. DOI: 10.1016/S1474-4422(13)70088-7
19. Chadwick H., Owens R., McMillan I., Howard E., Craufurd D. Psychiatric symptoms in Huntington's disease: relationship to disease stage in the enroll-HD study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2018; 89: A55. DOI: 10.1136/jnnp-2018-EHDN.147
20. Santangelo G., Vitale C., Trojano L., et al. Relationship between apathy and cognitive dysfunctions in de novo untreated Parkinson's disease: a prospective longitudinal study. *Eur J Neurol* 2015; 22: 253–260. DOI: 10.1111/ene.12467
21. Simpson JA., Lovecky D., Kogan J., Vetter LA., Yohrling G.J. Survey of the Huntington's disease patient and caregiver community reveals most impactful symptoms and treatment needs. *J Huntingtons Dis*. 2016; 5: 395-403. DOI: 10.3233/JHD-160228
22. Aarsland D., Bronnick K., Alves G., et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2009; 80: 928–930. DOI: 10.1136/jnnp.2008.166959

S.A. Bedina, A.S. Trofimenko, E.E. Mozgovaya, S.S. Spitsina, M.A. Mamus, E.A. Tikhomirova

ACTIVITY OF PROOXIDANT AND ANTIOXIDANT SYSTEMS ENZYMES IN PLASMA OF RHEUMATOID ARTHRITIS PATIENTS

DOI 10.25789/YMJ.2020.70.08

УДК 616.72-002.77

The **aim** of our study was to characterize the activity profile of prooxidant and antioxidant systems key enzymes in plasma of rheumatoid arthritis (RA) patients.

Methods. 71 RA patients (46 women and 25 men) were enrolled in the study. The diagnosis was verified with ACR/EULAR criteria (2010). All patients were treated in Municipal Clinical Hospital № 25. The control group consisted of 30 healthy individuals. Disease activity was calculated using DAS 28. 24 (33.8%) patients had low disease activity, moderate and high disease activities were determined in 41 (57.7%) and 6 (8.5%) cases, respectively. Extra-articular manifestations were revealed in 30 (42.2%) patients. Plasma xanthine oxidase (XO), xanthine dehydrogenase (XDH) and superoxide dismutase (SOD) activities were measured using previously described spectrophotometric techniques. XO and XDG activities were expressed as nmol/ml·min, SOD activity – as units of activity.

Results. Reference intervals ($M \pm 2\sigma$) of enzymatic activities were 2.28-5.12 nmol/ml·min (for XO), 3.96-7.24 nmol/ml·min (for XDH), and 3.13-6.58 units (for SOD). We have revealed substantial changes in all the plasma enzymatic activities of RA patients. These changes were independent with the disease activity autoimmune inflammation and presence of extra-articular manifestations. XO and SOD activities were increased in all RA patients. XO activity have been reached its highest values at maximum disease activity with extra-articular involvements, SOD activity – in moderate and high disease activities as well as in patients with articular form of RA. XDG activity was increased at low disease activity and articular form of RA, while moderate, high disease activities and extra-articular manifestations were characterized by decreased activity of this enzyme.

Conclusion. Plasma enzymatic profile in RA patients is characterized by an increase of XO and SOD activities, which indicates the intensification of prooxidant and antioxidant mechanisms. It can be assumed that the excessive generation of reactive oxygen species can stimulate the formation of neutrophil extracellular traps by neutrophil granulocytes as a result of the activation of free radical reactions.

Keywords: rheumatoid arthritis, plasma, enzymatic profile.

Research Institute of Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki street, Volgograd, 400138, Russia; **Svetlana Aleksandrovna BEDINA** – PhD, senior researcher, Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; tel. (8442) 78-90-95 e-mail: clinicalbiochemistry@yandex.ru; **Elena Eduardovna MOZGOVAYA** – PhD, leading researcher, Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; tel. (8442) 78-90-95, e-mail: nauka@pebma.ru; **Andrey Stepanovich TROFIMENKO** – PhD, head of department, Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; assistant, Volgograd State Medical University, 1, Pavshikh Bortsov Sq., Volgograd, 400131, Russia. tel. (8442) 78-90-95 e-mail: a.s.trofimenko@mail.ru; **Svetlana Sergeyevna SPITSYNA** – junior researcher, Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; assistant, Volgograd State Medical University, 1, Pavshikh Bortsov Sq., Volgograd, 400131, Russia; tel. (8442) 78-90-95 e-mail: svetlanahime@yandex.ru; **Mariya Anatolyevna MAMUS** – junior researcher of the Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; tel. (8442) 78-90-95 e-mail: m.mamus@yandex.ru; **Ekaterina Andreyevna TIKHOMIROVA** – junior researcher of the Research Institute for Clinical and Experimental Rheumatology named after A.B. Zborovsky, 76, Zemlyachki str., Volgograd, 400138, Russia; tel. (8442) 78-90-95 e-mail: sezam.luga@mail.ru.

Introduction. Rheumatoid arthritis (RA) is an autoimmune rheumatic disease of unknown etiology which is characterized by chronic erosive arthritis and systemic organ involvement resulting in early disability and shorter life expectancy [6]. Despite significant advances in the diagnostics and treatment of RA over the past 50 years, there still remain unsolved problems. This is due to the fact that RA continues to be one of the most prevalent rheumatic diseases which has significant socioeconomic costs [10]. Moreover, the use of genetically-engineered biological agents frequently leads to RA progression. Therefore, in recent years there has been a growing interest in the molecular and cellular mechanisms of immune-mediated inflammatory pathogenesis of RA. New insights into the mechanisms underpinning RA pathogenesis will lead to improved diagnostics of RA at an early preclinical stage, better assessment of disease activity, prognosis and treatment outcomes, and the development of novel more specific treatment modalities.

At present there is no credible or convincing evidence linking RA with one etiological factor. A combination of genetic and environmental factors has been suggested to cause a cascade of

abnormal cellular and humoral immune responses [12]. These responses cause not only the synovial inflammation leading to the destruction of joints but also internal organ involvement. However, the mechanism underpinning the transition of autoimmune response to joint inflammation still remains uncertain. At the same time, numerous studies have shown that anti-citrullinated protein antibodies appear many years before the clinical onset of joint inflammation [11]. The production of anti-citrullinated protein antibodies is considered to play a key role in the pathogenesis of RA.

Neutrophil granulocytes also play a specific role in the induction and promotion of autoimmune inflammation in RA. It is accounted for by the ability of neutrophils to release neutrophil extracellular traps (NETs) through cell death called NETosis [2, 8, 9, 12, 15].

Anti-citrullinated protein antibodies and inflammatory cytokines (IL-17A, TNF- α and IL-8) can stimulate NETosis, whereas NETs externalize citrullinated autoantigens which are potential anti-citrullinated protein antibody targets, thus perpetuating a cycle of citrullinated autoantigen generation and induction of autoimmune responses in RA [12, 13].

NETs are networks of condensed

chromatin (histones and DNA), components of neutrophil granules (neutrophil elastase, myeloperoxidase, cathepsin G, leucocyte proteinase 3, lactoferrin, gelatinase, lysozyme C, calprotectin, defensins and cathelicidins) and cytoskeletal proteins (actin, tubulin) [1]. NET production is commonly accompanied by neutrophil cell death. According to current data, NETs not only induce RA but also initiate autoaggressive response which underlies chronic autoimmune inflammation in RA [12, 15].

One of the factors triggering the production of NETs is overexpression of reactive oxygen species (ROS) [14]. NADPH-oxidase is considered the main source of ROS. The role of NADPH-oxidase in the initiation of NET production is clearly understood. However, ROS can be formed by other reactions. The enzyme xanthine oxidase/xanthine dehydrogenase complex is the most important source of ROS. These two forms of xanthine oxidoreductase (XOR) may be interconverted. NADPH-oxidase plays a leading role in xanthine dehydrogenase (XDH) and xanthine oxidase (XO) regulation. ROS generated by NADPH may promote the conversion of XOR to oxidase [5]. XO is known to act as a prooxidant. XO activation is accompanied by increased formation of superoxide radicals via oxidation of hypoxanthine and xanthine.

Protection from overproduction of ROS in the body is provided by a complex antioxidant system, with superoxide dismutase being the most important. Healthy individuals tend to have prooxidant-antioxidant balance. A shift in the balance between oxidants and antioxidants is accompanied by increased formation of ROS which can

result in oxidative stress involved in a number of pathological conditions.

As ROS promotes NET generation, the study of oxidant and antioxidant enzyme activity in patients with RA is of great interest.

The aim of our study was to characterize the activity profile of prooxidant and antioxidant systems key enzymes in plasma of rheumatoid arthritis (RA) patients.

Materials and methods. 71 RA patients (46 women and 25 men) were enrolled in the study. Mean age of patients was 43.2±3.6 years, mean RA duration was 11.9±2.6 years. The diagnosis was verified with ACR/EULAR criteria (2010) [7]. All patients were treated in Municipal Clinical Hospital № 25. The control group consisted of 30 healthy individuals. RA patients and healthy individuals were comparable in gender and age. Disease activity was calculated using DAS 28. 24 (33.8%) patients had low disease activity, moderate and high disease activities were determined in 41 (57.7%) and 6 (8.5%) cases, respectively. Extra-articular manifestations were revealed in 30 (42.2%) patients. Mostly, involvement in the pathological process of the heart (30%), lungs (23.3%) and kidneys (23.3%) was diagnosed. 41 patients (57.8%) had an articular form of the disease. The radiological stage of joint involvement was evaluated using Steinbrocker criteria. Most RA patients had II and III stages of joint involvement: 36 (50.7%) and 27 (38.0%), respectively. I stage was determined in 5 (7.0%) cases, IV stage – in 3 cases. Joint functional limitations had 68 (95.8%) patients. 28 (39.4%) of them were related to the first functional class, 35 (49.3%) – to the second functional class, 5 (7.1%) – to

the third functional class. Rheumatoid factor antibodies were revealed in 67.6% cases.

Plasma xanthine oxidase (XO; E.C. 1.17.3.2), xanthine dehydrogenase (XDH; E.C. 1.17.1.4) and superoxide dismutase (SOD; E.C. 1.15.1.1) activities were measured using previously described spectrophotometric techniques. XO and XDG activities were expressed as nmol/ml·min, SOD activity – as units of activity [3, 4].

Statistical analysis was performed using Statistica 6.0 software package. Results were presented as (Me, Q25, Q75). The Mann-Whitney U test was used for statistical analysis. Differences were considered significant when $p < 0.05$.

Results and discussion. All the plasma enzymatic activities of healthy individuals were not dependent on gender and age. These factors were not considered in the enzymatic activities analysis of RA patients. Reference intervals ($M \pm 2\sigma$) of enzymatic activities were 2.28-5.12 nmol/ml·min (for XO), 3.96-7.24 nmol/ml·min (for XDH), and 3.13-6.58 units (for SOD).

We conducted research of the plasma enzymatic activities in RA patients with different clinical manifestations. The dependence of XO, XDG, SOD activities on RA activity and presence of extra-articular manifestations was analyzed. The results are presented in the Table 1.

We have revealed substantial changes in all the plasma enzymatic activities of RA patients. These changes were multidirectional. XO and SOD activities were increased in all RA patients. XO activity have been reached its highest values at maximum disease activity and presence extra-articular involvements, SOD activity – in moderate and high

Activity of enzymes in plasma of rheumatoid arthritis patients (Me (Q25; Q75))

Group	Enzymes			Significance of differences with healthy individuals	Significance of differences between patient's group
	XO	XDG	SOD		
Healthy individuals, n=30	3.7 ^{1,2,3,4,6,8} (3.2; 4.1)	5.6 ^{2,5,7,9} (4.9; 6.1)	4.9 ^{1,2,3,4,6,8} (4.3; 5.1)		
RA patients, n=71	6.3 ¹ (4.8; 9.6)	5.5 (4.8; 6.7)	9.2 ¹ (7.3; 11.6)	¹ p<0.001	
RA activity (degree)					
1, n=24	5.3 ^{2,10,11} (4.1; 6.1)	6.9 ^{2,13,14} (6.3; 7.6)	6.7 ^{2,15,16} (5.3; 7.4)	² p<0.001	¹⁰ p<0.001 ¹¹ p<0.001 ¹² p=0.015
2, n=41	7.2 ^{3,10,12} (5.0; 10.0)	5.2 ¹³ (4.8; 5.8)	9.9 ^{3,15} (9.0; 13.2)	³ p<0.001	¹³ p<0.001 ¹⁴ p<0.001
3, n=6	10.6 ^{4,11,12} (8.3; 11.7)	4.6 ^{5,14} (3.9; 5.2)	11.5 ^{4,16} (9.7; 12.9)	⁴ p<0.001 ⁵ p=0.008	¹⁵ p<0.001 ¹⁶ p<0.001
Форма заболевания					
Articular form, n=41	5.0 ^{6,18} (3.8; 6.2)	6.5 ^{7,19} (5.2; 6.9)	10.5 ^{6,20} (6.7; 13.2)	⁶ p<0.001 ⁷ p=0.011	¹⁸ p<0.001 ¹⁹ p<0.001
Presence of Extra-articular manifestations, n=30	9.7 ^{8,18} (7.5; 10.8)	5.1 ^{9,19} (4.6; 5.5)	8.4 ^{8,20} (7.5; 9.3)	⁸ p<0.001 ⁹ p=0.025	²⁰ p=0.038

disease activities as well as in patients with articular form of RA. XDG activity was increased at low disease activity and articular form of RA, while moderate, high disease activities and extra-articular involvements were characterized by decreased activity of this enzyme.

Plasma enzymatic profile of RA patients is characterized by an increase of XO and SOD activities, which indicates the intensification of prooxidant and antioxidant mechanisms. SOD activity was substantially lower in RA patients with extra-articular manifestations, that confirms the debilitation of the antioxidant protection with disease progression and visceral organs involvement in the autoimmune rheumatoid process. The progressive increase of XO activity against the background of the decreased XDG activity indicates the intensification of free radical oxidation in more severe forms of RA. It can be assumed that the excessive generation of ROS can stimulate the formation of neutrophil extracellular traps by neutrophil granulocytes as a result of the activation of free radical reactions.

Conclusion.

1. RA is characterized by the activation of the prooxidant and antioxidant systems enzymes.
2. The severe forms of RA accompanied by the intensification of free radical oxidation.
3. The visceral organs involvements are accompanied by the debilitation of the antioxidant protection.

References

1. Мамус М.А., Тихомирова Е.А., Бедина С.А., Доценко С.С., Трофименко А.С., Мозговая Е.Э. Внеклеточные нейтрофильные ловушки и их возможная роль в образовании антицитруллиновых антител при ревматоидном артрите. *Актуальные проблемы современной ревматологии: Сб. науч. работ / под ред. И.А. Зборовской.* М.: Планета, 2018; XXXV:202-11. [Mamus MA, Tikhomirova EA, Bedina SA, Dotsenko SS, Trofimenko AS, Mozgovaya EE. Neutrophil extracellular traps and their eventual role in the anti-citrullinated protein antibodies generation in rheumatoid arthritis. *Aktualnyye problemy sovremennoy revmatologii: Sb. nauch. rabot / Zborovskaya I.A., ed. M.: Planet, 2018; XXXV:202-211.* (In Russ.)] DOI: 10.18411/978-5-907109-24-7-2018-xxxx-202-211
2. Воробьева Н.В., Пинегин Б.В. Нейтрофильные внеклеточные ловушки: механизмы образования, роль в норме и при патологии. *Биохимия.* 2014;79(12):1580–91. [Vorobjeva NV, Pinegin BV. Neutrophil extracellular traps: Mechanisms of formation and role in health and disease. *Biokhimiya.* 2014; 79(12):1286-96. (In Russ.)]
3. Дубинина Е.Е., Сальникова Л.А., Ефимова Л.Ф. Активность и изоферментный спектр супероксиддисмутазы эритроцитов и плазмы крови человека. *Лаб. дело.* 1983;10:30-3. [Dubinina EE, Salnikova LA, Efimova LF. Activity and isozyme spectrum of superoxide dismutase human erythrocytes and blood plasma. *Lab. delo.* 1983; 10:30–3. (In Russ.)]
4. Мартемьянов В.Ф., Мозговая Е.Э., Бедина С.А. Клиническое значение исследования активности ферментов и изоферментов пуринового метаболизма в плазме крови больных анкилозирующим спондилитом. *Международный журнал прикладных и фундаментальных исследований.* 2015;12(6):1048-52. [Martemyanov VF, Mozgovaya EE, Bedina SA. Clinical significance of research of the activity of enzymes and isozymes of purine metabolism in the blood plasma of patients with ankylosing spondylitis. *Mezhdunarodnyy zhurnal prikladnykh i fundamentalnykh issledovaniy.* 2015; 12(6):1048-52. (In Russ.)]
5. Надеев А.Д., Гончаров Н.В. Активные формы кислорода в клетках сердечно-сосудистой системы. *Комплексные проблемы сердечно-сосудистых заболеваний.* 2014;4:80-94. [Nadeev AD, Goncharov NV. Reactive oxygen species in the cells of cardiovascular system. *Kompleksnyye problemy serdechno-sosudistykh zabolevaniy* 2014; 4:80-94. (In Russ.)] DOI: 10.17802/2306-1278-2014-4-80-94
6. Насонов Е.Л., ред. Российские клинические рекомендации. Ревматология. М.: ГЭОТАР-Медиа, 2017;464. [Nasonov E.L., ed. Russian Clinical recommendations. *Rheumatology.* M.: GJeOTAR-Media, 2017; 464. (In Russ.)]
7. Aletaha D, Neogri T, Silman AJ [et al.]. 2010 Rheumatoid arthritis classification criteria. An American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010; 62:2569–81. DOI: 10.1136/ard.2010.130310.
8. Angelotti F, Parma A, Cafaro G [et al.]. One year in review 2017: pathogenesis of rheumatoid arthritis. *Clin.Exp.Rheumatol.* 2017; 35(3):368-378.
9. Sur Chowdhury C, Giaglis S, Walker UA [et al.]. Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: analysis of underlying signal transduction pathways and potential diagnostic utility. *Arthritis Res Ther.* 2014; 16:R122. DOI: 10.1186/ar4579
10. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. *Arch Phys Med Rehabil.* 2014; 95(5):986-995. DOI: 10.1016/j.apmr.2013.10.032
11. Catrina AI, Svensson CI, Malmström V [et al.]. Mechanisms lead-ing from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. *Nat Rev Immunol.* 2017; 13(2):79-86. DOI: 10.1038/nrrheum.2016.200.
12. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A [et al.]. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. *Sci Transl Med.* 2013; 5(178):178ra40. DOI: 10.1126/scitranslmed.3005580
13. Corsiero E, Bombardieri M, Carlotti E [et al.]. Single cell cloning and recombinant monoclonal antibodies generation from RA synovial B cells reveal frequent targeting of citrullinated histones of NETs. *Ann Rheum Dis.* 2016; 75:1866-75. DOI: 10.1136/annrheumdis-2015-208356.
14. Stoiber W, Obermayer A, Steinbacher P [et al.]. The Role of Reactive Oxygen Species (ROS) in the Formation of Extracellular Traps (ETs) in Humans. *Biomolecules.* 2015; 5:702-23. DOI: 10.3390/biom5020702.
15. Wright HL, Moots RJ, Edwards SW. The multifactorial role of neutrophils in rheumatoid arthritis. *Nature Reviews Rheumatology.* 2014; 10(10):593-601. DOI: 10.1038/nrrheum.2014.80.

1. Мамус М.А., Тихомирова Е.А., Бедина С.А., Доценко С.С., Трофименко А.С., Мозговая Е.Э. Внеклеточные нейтрофильные ло-



O.L.Vasilyeva, Z.A.Rudykh, A.V.Sofronova, N.G.Starostina,
S.M.Tarabukina, O.V.Tatarinova, Y.V.Chertovskikh, D.A.Sychev

THE IMPACT OF POLYPHARMACY AND COMPLIANCE WITH STOP / START CRITERIA ON THE RISK OF FALLS IN ELDERLY PATIENTS IN HOSPITAL

DOI 10.25789/YMJ.2020.70.09

УДК 615.065

A retrospective analysis of medical records of 100 patients aged 59 years and older, who were on treatment at the Geriatric Centre of Clinical Hospital #3 of the Republic of Sakha, has been done. The study reveals a link between compliance with the STOP / START criteria, polypharmacy, compliance with treatment standards and protocols, and falls in elderly patients.

Keywords: polypharmacy, adverse drug reaction, STOP/START criteria, patient of elderly age, falls in the elderly.

Introduction. Improving the quality of life and increased longevity have led to increased requirements for attending elderly patients. The treatment of patients over 65 years of age requires an indi-

vidual approach due to the physiological characteristics of aging, the burden of diseases accumulated with old age and a modified response to prescribed pharmacotherapy.

According to the UN the dynamics of the rapid growth of number of the elderly in population is expected, who already make up a significant part of the population in most developed countries, and globally could double by 2050 (from 962 million to 2.1 billion) [11]. One of the manifestations of dangerous adverse drug reactions in groups of older age patients is a drug-induced fall [3]. According to the forecasts in the near future the dependency ratio in this country will increase by 8% (from 21% in 2009 to 30% in 2035) [8], therefore, the issue of forecasting the risk of falls and preventing their traumatic effects seems to be topical [5].

World Health Organization (WHO) points out that in many cases the health care system is not ready to meet the needs of the elderly suffering from multiple chronic diseases [1, 2, 4]. The treatment of each elderly or senile patient is always difficult to determine a mandatory risk / benefit assessment due to the large number of mutually affecting and often unpredictable factors [2, 7, 12-13]. Particularly the administration of several drugs leading to a state of polypharmacy greatly increases the risk of developing adverse drug reactions due to inter-drug interactions, reduces adherence to medication in patients, triggers the pathological mechanisms of serious adverse events, contributes to reduced strength and poor health conditions [10]. When prescribing drugs in geriatric practice one must remember that senior citizens tend to have serious adverse drug reactions [5].

As L.B. Lazebnik et al. noticed, simultaneous administration of five drugs increases frequency of drug interactions to 50%, and the risk reaches 100% with tak-

ing 10 drugs or more [4]. STOP/START criteria are used to audit drug prescriptions in order to optimize pharmacotherapy, reduce the development of USE and improve the quality of life in elderly patients in several countries of Europe, Asia, America and Australia. The successful use of these criteria both for research and for practical clinical purposes in a number of countries in Europe, Asia, America and Australia demonstrates that the STOP/START criteria have truly global significance [5].

The Objective of the Study: Improving the quality of life and increasing longevity in the elderly and senile population of the Republic of Sakha (Yakutia) by measures to reduce the risk of falls in this category of patients (compliance with STOP/START criteria, the treatment standards and protocols).

The Materials and Methods. We have undertaken a retrospective analysis of 100 medical records (hereinafter referred to as medical histories) of patients 59 years old and older who were on hospital treatment at the Geriatric Centre of Clinical Hospital #3 of the Republic of Sakha during the 3rd quarter of 2019 to find the relationship between the polypharmacy (prescribing 5 or more drugs [11]) and compliance with the STOP/START criteria (recommendations of the National Health Service of the United Kingdom (NHS), 2014, revised in 2015), as well as to identify the dependence of compliance/inconsistencies of the treatment standards and protocols (account form #313/y «the Map of the Peer Review of Pharmacotherapy Quality» (the Consultation Protocol, dated November, 01, 2003) and the risk of falls. The risk of falls in each patient has been determined upon his/her admission to hospital treatment with the use of the special Morse scale [9].

Statistical analysis of the results of

VASILIEVA Olga Lukichna – Center for Personalized Medicine, GAU RS (Y) "Republican Clinical Hospital No. 3", Clinical Pharmacologist, Comp. 89142240019, e-mail ol-ga.l.vas@mail.ru, ORCID 0000-0001-9726-5715. **RUDYKH Zoya Aleksandrovna** – Center for Personalized Medicine, GAU RS (Y) "Republican Clinical Hospital No. 3", Clinical Pharmacologist, Comp. 89241656800, e-mail vitae003@rambler.ru, ORCID 0000-0001-8212-0150. **SOFRONOVA Aytalina Valerevna** – Center for Personalized Medicine, GAU RS (Y) "Republican Clinical Hospital No. 3", Clinical Pharmacologist, 89142710744, e-mail naitalina@mail.ru; **STAROSTINA Nadezhda Georgievna** – Center for Personalized Medicine GAU RS (Y) "Republican Clinical Hospital No. 3", Clinical Pharmacologist, St. 89640766454, e-mail starnadezda@mail.ru; **TARABUKINA Sardana Makarovna** – Candidate of Pharmaceutical Sciences, Medical Institute of the Northeast Federal University named after M.K. Ammosova, Associate Professor of the Department of Pharmacology and Pharmacy, S.T. 89246624412, e-mail tcmx@mail.ru, ORCID: 0000-0003-4231-2216; **TATARINOVA Olga Viktorovna** – Doctor of Medical Sciences, GAU RS (Y) "Republican Clinical Hospital No. 3", head physician, senior fellow 89141053471, e-mail tov3568@mail.ru; **CHERTOVSKIKH Yana Valeryevna** – Center for Personalized Medicine, GAU RS (Y) "Republican Clinical Hospital No. 3", head of the CPM, c. 89241741790, e-mail yana_chertovski@mail.ru ORCID 0000-0003-0941-8633. **SYCHEV Dmitry Alekseevich** – Doctor of Medical Sciences, Professor, Professor of the Russian Academy of Sciences, Corresponding Member of the Russian Academy of Sciences, Rector of FSBEI DPO "Russian Medical Academy of Continuing Professional Education", 89104076111, e-mail dmitry.alex.sychev@gmail.com ORCID 0000-0002-4496-3680.

pharmacological expertise has been carried out with the help of the IBM SPSS Statistics 23 application package. Descriptive statistics of the quantity data are given as average values with standard deviation. The quality data are presented in the form of absolute and relative frequencies. The relationships between the studied indicators have been considered with the use of the contingency tables. In order to assess the statistical significance of frequency differences in the studied groups the Pearson Chi-square criterion with significance level has been used. The threshold level of the statistical significance we adopt is 0.05.

Results: The analysis of 100 medical histories has been undertaken: of 61 women (61%) and 39 men (39%). The average age is 75.05 ± 8.143 years. The average age of the women is 74.21 ± 8.335 years, the average age of the men is 76.36 ± 7.758 years. The prescription of 5 or more drugs (polypharmacy) has been noted in 42 cases (42%).

According to the results of the study, violation of the STOP criteria is observed

in 12 cases (12%). When comparing the frequency of detection of non-compliance with the START criteria in the groups of patients with different levels of risk of falls, in cases of non-compliance with the criteria of START-therapy, the proportion of the patients with a high risk of falls increases by 25.1% (Table 3), while the proportion of the patients with no risk of falls is reduced by 35.3%. The significance level is $p = 0.008$, which is statistically significant. Thus, compliance with the criteria of START-therapy leads to a significant reduction in the risk of falls.

According to the results of comparing the frequency of detection of non-compliance with the STOP criteria in the groups of patients with different levels of risk of falls, in cases of non-compliance with the criteria of STOP-therapy, the percentage of the patients with a high risk of falls increases by 5.3% (Table 2), while the significance level is $p = 0.868$, which is statistically insignificant.

According to the results of the analysis of compliance with the treatment stan-

dards and protocols and the risk of falls in elderly patients, in the case of partial non-compliance with the treatment standards and protocols the proportion of the patients with a high risk of falls increases by 9.7% (Table 4) with the significance level $p = 0.328$, which is statistically significant.

According to the results of the study of the occurrence frequency of different levels of risk of falls in the groups of patients with 5 or more drugs, in the patients with polypharmacy, the percentage of the patients with a high risk of falls decreases by 4.3% (Table 1), with the significance level $p = 0.516$, which is statistically insignificant.

Considering the obtained data several conclusions can be drawn about possible causal relationships between age, polypharmacy, compliance with the STOP/START criteria and falls in senile patients: the risk of falls increases with age; there is a connection between the compliance with the START criteria and the risk of falls, this indicator is statistically significant; there is a connection be-

Table 1

START Criteria and the Levels of Risk of Falls in the Elderly Patients

START- therapy	Risk of Falls						X ²	p
	no risk		low risk		high risk			
	frequencies	% in line	frequencies	% in line	frequencies	% in line		
no violation	64 _a	75.3	14 _{a,b}	16.5	7 _b	8.2	9.698	0.008
violation of therapy	6 _a	40.0	4 _{a,b}	26.7	5 _b	33.3		

X² – the Pearson Chi-square criterion. p - significance level Subscripts indicate the presence or absence of statistically significant frequency differences.

Table 2

STOP Criteria and the Levels of Risk of Falls in the Elderly Patients

STOP Criteria	Risk of Falls						X ²	p
	no risk		low risk		high risk			
	frequencies	% in line	frequencies	% in line	frequencies	% in line		
no violation	62 _a	70.5	16 _a	18.2	10 _a	11.4	0.283	0.868
violation of therapy	8 _a	66.7	2 _a	16.7	2 _a	16.7		

Table 3

Compliance with the Treatment Standards and Protocols and the Levels of Risk of Falls in the Elderly Patients

Compliance with the Treatment Standards and Protocols	Risk of Falls						X ²	p
	no risk		low risk		high risk			
	frequencies	% in line	frequencies	% in line	frequencies	% in line		
yes	44 _a	72.1	12 _a	19.7	5 _a	8.2	2.230	0.328
not fully	26 _a	66.7	6 _a	15.4	7 _a	17.9		

Table 4

Polypharmacy and the Levels of Risk of Falls in the Elderly Patients

Polypharmacy (more than 5 drugs)	Risk of Falls						X ²	p
	no risk		low risk		high risk			
	abs.	%	abs.	%	abs.	%		
No	38 _a	65.5	12 _a	20.7	8 _a	13.8	1.321	0.516
Yes	32 _a	76.2	6 _a	14.3	4 _a	9.5		

tween compliance with the STOP criteria and the risk of falls, this indicator is not statistically insignificant due to the small sample of patients; there is a connection between the state of polypharmacy and the risk of falls, this indicator is statistically insignificant due to the small sample of patients; there is a connection between compliance with the treatment standards and protocols and the risk of falls; this indicator is statistically insignificant due to the small sample of patients.

Conclusions: 1. Compliance with the state of polypharmacy, STOP criteria, compliance with the treatment standards and protocols leads to reduction in the risk of falls in elderly and senile patients.

References

1. Всемирная организация здравоохранения. 10 фактов о старении и жизненном пути. Available at: http://www.who.int/features/factfiles/ageing/ageing_facts. [World Health Organization. 10 facts about aging and life path. Available at:

http://www.who.int/features/factfiles/ageing/ageing_facts. (In Russ.)].

2. Ушкалова Е.А., Ткачева О.Н., Рунихина Н.К. и др. Особенности фармакотерапии у пожилых пациентов. Введение в проблему. *Рациональная фармакотерапия в кардиологии*. 2016; 12(1):94-100. [Ushkalova EA, Tkacheva ON, Runikhina NK [et al.]. Features of pharmacotherapy in elderly patients. Introduction to the problem. *Rational pharmacotherapy in cardiology*. 2016; 12(1):94-100. (In Russ.)].

3. Ильина Е.С., Богова О.Т., Синицина И.И., Пузин С.Н., Сычев Д.А.. Падения в стационаре у пациентов старческого возраста с сердечно-сосудистыми заболеваниями и полипрагмазией. *Нервно-мышечные болезни*. 2018; 8(3):19-27. [Ilyina E.S., Bogova O.T., Sinitsina I.I., Puzin S.N., Sychev D.A. In-patient falls in senile patients with cardiovascular disease and polypharmacy. *Neuromuscular Diseases*. 2018; 8(3): 19-27. (In Russ.)].

4. Лазебник Л.Б., Конев Ю.В., Дроздов В.Н., Ефремов Л.И. Полипрагмазия: "герiatricкий аспект" проблемы. *Consilium medicum*. 2007; 12: 29-34. [Lazebnik LB, Konев YuV, Drozdov VN, Efremov LI. Polypharmacy: Geriatric Aspect of the Problem. *Consilium medicum*. 2007; 12: 29-34. (In Russ.)].

5. Сычев Д.А. «Полипрагмазия в клинической практике: проблемы и решения». СПб:

ЦОП «Профессия», 2016. [Sychev DA. Polypharmacy in Clinical Practice: Problems and Solutions. SPb: CCP "Profession". 2016. (In Russ.)].

6. Федеральная служба государственной статистики. Демографический прогноз до 2030 года. Доступно по: http://www.gks.ru/wps/wcm/connect/rosstat_main/rosstat/ru/statistics/population/demography/. [Federal State Statistics. PMID: 24529293].

7. Sibley K.M., Voth J., Munce S.E. [et al.]. Chronic disease and falls in community-dwelling Canadians over 65 years old: a population-based study exploring associations with number and pattern of chronic conditions. *BMC Geriatr*. 2014; 14:22.

8. Garin N., Olaya B., Moneta M.V. [et al.]. Impact of multimorbidity on disability and quality of life in the Spanish older population. *PLoS One*. 2014; 9(11): e111498. DOI: 10.1371/journal.pone.0111498. PMID: 25375890.

9. Morse J. M., Morse R., Tylko S. Development of a scale to identify the fall-prone patient. *Canadian Journal on Aging*. 1989; 8: 366-377.

10. Nobili A., Licata G., Salerno F. [et al.]. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI Study. *Eur J Clin Pharmacol*. 2011; 67 (5): 507-19. DOI: 10.1007/s00228-010-0977-0.

11. United Nations. World Population Prospects. The 2017 Revision. Available at: https://esa.un.org/unpd/wpp/https://esa.un.org/unpd/wpp/Publications/Files/WPP2017_KeyFindings.pdf.

12. Vu T., Finch C.F., Day L. Patterns of comorbidity in community-dwelling older people hospitalized for fall-related injury: a cluster analysis. *BMC Geriatr*. 2011; Aug 18; 11:45. doi: 10.1186/1471-2318-11-45.

13. Wu C., Bell C.M., Wodchis W.P. Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments: a retrospective study. *Drug Saf*. 2012; 35(9):769-81. DOI: 10.2165/11599540-00000000-000000. PMID: 22823502.



HEALTHY LIFESTYLE. PREVENTION

M.S. Savvina, T.I. Nelunova, T.E. Burtseva, G.I. Obratsova,
V.G. Chasnyk, S.A. Evseeva, T.M. Klimova, M.P. Slobodchikova

CONGENITAL HEART DISEASES IN INDIGENOUS CHILDREN OF THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.70.10

УДК 616-053.2(571.56)

The aim of the research was to evaluate the prevalence of congenital heart diseases (CHDs) in children of different ethnic groups of the Republic of Sakha (Yakutia). In a 10-year dynamics of cases in Pediatric center of the Republican hospital №1 (National health center), statistically significant increase of the newborns with CHD associated with severe defects has been noticed. It is revealed that more complicated cases of congenital heart diseases are present in children of indigenous peoples of the Republic of Sakha (Yakutia) (indigenous small-numbered peoples of Russia and the Yakuts) rather than in children of the other ethnic groups.

Keywords: congenital defects, congenital heart disease, the Sakha, indigenous population of the North.

Introduction: Congenital heart diseases are multi-factor diseases that can result from genetic factors, maternal disease during pregnancy and her concomitant somatic disorders, the life level of the family (dietary peculiarities) and etc. [5]. The detection of CHD risk factors and primary prevention of CHD development are most considered as they are associated with possible incapacitating condition, decrease of life quality for a child and with the cost of high-technology medicine.

SAVVINA Maya Semyonovna – Ph.D., senior staff scientist of the laboratory of pediatric health level monitoring, Yakut science center of complex medical problems, maya_savvina@mail.ru; **NELUNOVA Tuyara Ivanovna** – cardiologist of the Perinatal Center of the Republican clinical hospital, postgraduate, St. Petersburg state pediatric medical university; **OBRAZTSOVA Galina Igorevna** – MD, associate professor of the department of childhood diseases, Almazov national medical research center; **BURTSEVA Tatiana Yegorovna** – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, a head of the laboratory of the Yakut science center of complex medical problems, bourtsevat@yandex.ru; **CHASNYK Vyacheslav Grigorievich** – MD, a head of the department of hospital pediatrics, St. Petersburg state pediatric medical university, chasnyk@gmail.com, **EVSEEVA Sardana Anatolievna** – Ph.D., senior staff scientist of the laboratory of pediatric health level monitoring, Yakutsk science center of complex medical problems, sarda79@mail.ru; **KLIMOVA Tatiana Mikhailovna** – Ph.D., associate professor of the Medical institute of the North-Eastern federal university, senior staff scientist of the laboratory of the Yakut science center of complex medical problems; **SLOBODCHIKOVA Maya Pavlovna** – a senior lecturer of the department of foreign languages with the courses of Russian and Latin languages, St. Petersburg state pediatric medical university, slobodchikovamaya@gmail.com

Cardio-vascular system exposures have high prevalence (18.1%) according to the all-national register for CHDs [1]. There were 400.5 cases of CHD per 100 000 of children in 2014, and 439.0 cases in 2015 [3]. The morbidity indices and structure of CHD significantly differ in various regions of the Russian Federation. The regional register has been functioning in the Republic of Sakha (Yakutia) since 2000, all the cases of congenital malformations in newborns, including CHDs, are registered there. The data of the register make the base for scientific and statistic research work for CHD. In 2011 the morbidity rate for CHD was 29.1 per 100 000 children in the Republic of Sakha (Yakutia). The revealed cases of CHD are increasing and CHDs are the second cause of infant mortality for the long time [4].

Genetic factors are often considered as the main cause for CHD development. Perhaps, it is caused by accumulation of the mutated genes in the population, thus genetic disorders can be found in isolated groups of people, where there are many cases of so called homolocal and national families. i.e. families and marriages between those living in the same small geographic area and/or between one ethnic group. According to the data of the 'Yakut Republican medical center of informatics and analysis under the healthcare ministry of the Republic of Sakha (Yakutia)' for the period of 2002-2006, CHD turned to be a second level in mortal prevalence of children under 14 among the Evenks, Evens, Dolgans and Yukagirs. The maximum of CHD occurrence is registered in Olyokminskiy, Ust-Maiskiy and Nizhnekolymskiy regions of the Republic of Sakha (Yakutia) for the period of 1995-2012. The analysis of CHD occurrence reveals considerable number of cases in industrial, Arctic and Viluy regions [4]. The investigation of the

CHD structure shows that 82.2% out of 899 total cases compose the ventricular septal and atrial septal defects; 8.9% are defects of great vessels and 4.67% are combined CHDs. CHD is rather common in indigenous peoples of the North. CHD and other congenital defects are known to be common in the Nenets children in Yamalo-Nenets Autonomous district [4, 2]. The prevalence and risks of CHD in newborns of the indigenous population of the Republic of Sakha (Yakutia) are not investigated in details.

Thus the research is aimed at analysis of CHD dynamics and structure among the newborns of different ethnic groups of the Republic Sakha (Yakutia).

Materials and methods: A retrospective clinical investigation was carried out on the base of the Perinatal center of the Republican hospital №1 (National health center). All the cases of CHD (n=1824) in newborns, born alive in the period of 2001-2003 and 2013-2015, were analyzed. The initial documentation was a statistical medical record of the hospitalized patient (form №066/y-02) and obstetric medical record (form №010y).

The nationality of the patients was registered according to self-identification. The indigenous peoples of Yakutia include the Yakuts and indigenous small-numbered peoples of the North such as the Evens, the Evenks, the Dolgans, the Yukagirs and the Chukchis are analyzed. Besides that, the Russians, the peoples of the Central Asia (the Kirgizes, the Tadzhikis and the Usbeks), the peoples of the Caucasus (the Tchechens, the Ingushes and the Armanians), and the representatives of the other nations (the Kumiks, the Khakasses, the Ukrainians, the Polish, the German, the Tartar and the Buryats) were included in the analysis.

All the cases of CHD were divided into three groups. The first group consisted of the CHD newborns without signs of

cardiac insufficiency (CI); the second group consisted of CHD newborns with the first degree of cardiac insufficiency, according to the 1st class of the NYHA functional classification; in the third class the newborns with CHD with the 1st and 2nd degree of cardiac insufficiency, according to the 2nd and more class the NYHA functional classification. The third group of severe CHD was confirmed with echocardiographic methods, computed tomography angiography (CTA) with contrast material, aortography and selective coronary angiography.

Statistical data are calculated by IBM SPSS Statistics 17 (IBM®, USA). When comparing the groups, the Pearson's criterion (Pearson's chi-squared test (χ^2)) was used. The critical value of the significance in checking the statistical hypothesis was equal to 5%.

The results and discussion: For the both periods there were registered 1824 cases of CHD in newborns. 697 cases were in 2000-2003, and 1127 cases in 2013-2015. When dividing children into

groups according to the class of CHD expression it was determined that 44.5% cases had signs of cardiac insufficiency. The second period (2013-2015) the number of newborns with CHD considerably increased, moreover we noticed the increase of newborns with the signs of decompensated heart failure ($p < 0.001$ when comparing the groups 2 and 3 with 1) (Tab.1).

The Table 2 represents the distribution of the newborns according to the nation-

al identification of the parents. More than 60% of mothers and fathers identified themselves as the Yakuts, approximately 20% the Russians, 5.0% of mothers and 3.4% of fathers were self-identified as indigenous small-numbered peoples of the North.

Two groups of families were identified as mononational and mixed families, when dividing the parents according to their ethnicity (Table 3). Mononational families are the families where a mother's

Table 1

The distribution of children into groups according to CHD and periods of examination

Period	CHD groups			p
	1, n (%)	2, n (%)	3, n (%)	
2001-2003 (n=697)	519 (74.5)	31 (4.4)	147 (21.1)	<0.001
2013-2015 (n=1127)	494 (43.8)	153 (13.6)	480 (42.6)	
Total (n=1824)	1013 (55.5)	184 (10.1)	627 (34.4)	

Note. p – the achieved level of significance in comparison of the both periods.

Table 2

The distribution of CHD newborns (n=1824) according to the parental ethnicity

Ethnicity	Mother's ethnicity		Father's ethnicity	
	n	%	n	%
The Yakuts	1205	66.1	1205	66.1
The Russians	447	24.5	447	24.5
The Evenks and the Evens	62	3.4	31	1.7
Other indigenous small-numbered peoples of the North: the Dolgans, the Yukagirs and the Chukchies	30	1.6	31	1.7
The peoples of the Caucasus	26	1.4	37	2
The peoples of the Central Asia	16	0.9	19	1
Other nations: the Kумыks, the Khakasses, the Ukrainians, the Polish, the German, the Tartar, and the Buryat	36	2	52	2.9
Unidentified	2	0.1	2	0.1

Table 3

Mono- and mixed ethnicities and CHD groups

Parental ethnicity	Всего, N	Группа БИС					
		1-я, n=1013		2-я, n=184		3-я, n=625	
		n	%	n	%	n	%
<i>Mononational families including:</i>	1682	930	55,3	173	10,3	579	34,4
The Yakut / the Yakut	1153	601	52,1	131	11,4	421	36,5
The Russian / the Russian	414	261	63,0	35	8,5	118	28,5
Indigenous small-numbered peoples of the North / Indigenous small numbered peoples of the North	47	22	46,8	5	10,6	20	42,6
Other / other (coinciding nations)	68	46	67,6	2	2,9	20	29,4
<i>Mixed nations, including:</i>	140	83	59,3	11	7,9	46	32,9
The Yakut / the Russian	36	21	58,3	3	8,3	12	33,3
The Yakut / Indigenous small-numbered peoples of the North	45	23	51,1	2	4,4	20	44,4
The Yakut / other	23	18	78,3	2	8,7	3	13,0
The Russian / Indigenous small-numbered peoples of the North	10	3	30,0	1	10,0	6	60,0
Other / Indigenous small-numbered peoples of the North	5	3	60,0	1	20,0	1	20,0
Other mixed families (not coinciding nations)	21	15	71,4	2	9,5	4	19,0

Table 4

The distribution of CHD children within the groups of indigenous and non-indigenous nations of the Republic Sakha (Yakutia)

Groups	Total. N	CHD groups						p
		1 n=1013		2 n=184		3 n=625		
		n	%	n	%	n	%	
Indigenous and non-indigenous nations of the Republic of Sakha (Yakutia)*								
Indigenous	1319	691	52.4	145	11.0	483	36.6	<0.001
Non-indigenous	503	322	64.0	39	7.8	142	28.2	
Indigenous small-numbered peoples of the North and other nations **								
Indigenous small-numbered peoples of the North	107	51	47.7	9	8.4	47	43.9	0.097
Others	1715	962	56.1	175	10.2	578	33.7	

Note. In the Tables 4-5 * - The Yakuts and the indigenous small-numbered peoples of the North are referred to indigenous; non-indigenous – they are represented by the other nations; ** - the Yakuts and the representatives of the other nations are referred to the group “Others”; p – the achieved level of significance. comparison of the both periods.

and a father's ethnicity are the same and in mixed national families both parents belong to different ethnicities. 7.7% of the newborns were born in ethnically mixed families. There were no statistically sig-

($p < 0.001$ when comparing 3rd and 1st groups; $p = 0.004$ when comparing 2nd and 1st groups) (Table 4). When dividing the children into the groups, where one or both parents are represented by the in-

($p < 0.001$), the 3rd group from 23% to 44.5% ($p < 0.001$) respectively. If we look at the indigenous small-numbered peoples of the North separately, there we also notice the increase of number of children in the 2nd group from 0.0% to 11.2%, the 3rd group increased from 14.8% to 53.8% ($p < 0.001$). The analogous numbers for the representatives of the other nations increased from 4.6% to 13.8% in the 2nd group; and from 21.3% to 41.6% in the 3rd group.

Conclusion. The results of the research show the significant increase of CHD newborns, with prevalence of complicated cardiac defects with the signs of decompensation in 10-year dynamics, born in the Perinatal center of the Republican hospital №1 (the National health center). The comparison of parental nationality (those born in mixed or mono-families, i.e. the families, where the parents are of the same nations) did not reveal any significant discrepancies in distribution into CHD groups. The prevalence of complicated CHD cases is more common in newborns of indigenous peoples of Yakutia (the indigenous small-numbered peoples of the North and the Yakuts) than in newborns of the other ethnic groups.

This work was supported by the Budget Projects of YNC CMP “Monitoring the state of children's health of the Republic of Sakha (Yakutia)” (#0120-128-07-98), by the Project of the Ministry of Science and Higher Education of the Russian Federation (basic part of funding to M.K. Ammosov North-Eastern Federal University #FSRG-2020-0016) and by the RFBR grant #18-05-600035_Arctika.

Table 5

The comparison of CHD group distribution in dynamics

Groups	Time periods, years	N	CHD groups, n (%)			p
			1 n=1013	2 n=184	3 n=625	
Indigenous and non-indigenous peoples of Yakutia*						
Non-indigenous	2001-2003	211	171 (81.0)	5 (2.4)	35 (16.6)	<0.001
	2013-2015	292	151 (51.7)	34 (11.6)	107 (36.6)	
Indigenous	2001-2003	486	348 (71.6)	26 (5.3)	112 (23.0)	<0.001
		833	343 (41.2)	119 (14.3)	371 (44.5)	
Indigenous small-numbered peoples of the North and other nations**						
Indigenous small-numbered peoples of the North	2001-2003	27	23 (85.2)	0 (0)	4 (14.8)	<0.001
	2013-2015	80	28 (35.0)	9 (11.2)	43 (53.8)	
Others	2001-2003	670	496 (74.0)	31 (4.6)	143 (21.3)	<0.001
		1045	466 (44.6)	144 (13.8)	435 (41.6)	

nificant differences in distribution into the CHD groups ($p = 0.544$) when comparing mononational families with mixed ones.

For further analyses the children with one or both parents represented by the indigenous small-numbered peoples of the North or the Yakuts were included in one group (Table 4). When comparing this group with the other one, where the children were from parents of different nationalities, the difference between both groups showed statistically significant discrepancies in prevalence of CHD with the signs of cardiac decompensation

indigenous small-numbered nations of the North, the same effects are noticed but the level of differences does not refer to statistically significant data.

The level of the 1st group of CHD has decreased for a 10-year period; increasing the level of the 2nd and 3rd groups CHD in all ethnic groups (table 5). Thus, in a group of non-indigenous peoples the 2nd group increased from 2.4% to 11.6% ($p < 0.001$), the 3rd group increased from 16.6% to 36.6% ($p < 0.001$). In indigenous peoples of the North the numbers of the 2nd group increased from 5.3% to 14.3%

References

- Агаджанян Н.А. Общие и частные вопросы адаптации человека к условиям Севера. *Изд-во: СВНЦ ДВО РАН*, 2007;208. [Aghajanian N.A. General and particular issues of human adaptation to the conditions of the North. *Izd-vo SVNTS DVO RAN*, 2007; 208. (In Russ.)]
- Бойко Е.Р. Проблема адаптации человека к экологическим и социальным условиям Севера. *Политехника-сервис*, 2009;264. [Boyko E.R. The problem of human adaptation to the environmental and social conditions of the North. *Politechnika-servic*, 2009; 264. (In Russ.)]
- Основные показатели деятельности педиатрической службы Республики Саха (Якутия). *ГУ ЯРМИАЦ МЗ РС (Я)*, 2007;153. [Key performance indicators of the pediatric service of the Republic of Sakha (Yakutia). *GU YRMIATS MZ RS(Y)*, 2007; 153. (In Russ.)]
- Полунина Н.В., Разумовский А.Ю., Саввина В.А., Варфоломеев А.Р., Николаев В.Н. Частота врожденных аномалий как составляющая показателя здоровья детского населения региона. *Российский вестник перинатологии и педиатрии*, 2014;5:47-51. [Polunina N.V., Razumovsky A.Yu., Savvina V.A., Varfolomeyev

A.R., Nikolaev V.N. The frequency of congenital anomalies as a component of health of children population of the region. *Rossiiskii vestnik pediatrii*, 2014; 5:47-51. (In Russ..)

5. Черкасов Н.С. Заболевания сердца у новорожденных и детей раннего возраста. *Фенекс*, 2009;268. [Cherkasov N.S. Cardiac diseases in newborns and young children. *Feniks*, 2009; 268. (In Russ..)]

нукс, 2009;268. [Cherkasov N.S. Cardiac diseases in newborns and young children. *Feniks*, 2009; 268. (In Russ..)]

DOI 10.25789/YMJ.2020.70.11

УДК 796.35:159.9.612.018(571.56)

OKHLOPKOVA Elena Dmitriyevna – Leading Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, elena_ohlopkova@mail.ru. **ALEKSEEVA Zinaida Nikolaevna** – researcher of the clinical-population and medical-social research, of the Yakut Science Centre of complex medical problems, gzinaida@mail.ru; **EFREMOVA Svetlana Dmitriyevna** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, esd64@mail.ru; **MIRONOVA Galina Egorovna** – Professor of the Department of Biology of the Institute of Natural Sciences of the M.K. Ammosov North-Eastern Federal university, Doctor of Biological Sciences, Professor, mirogalin@mail.ru. **GRIGORYEVA Anastasia Anatolyevna** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, nastiagrigoryeva@gmail.com. **VINOKUROVA Fekla Vasilievna** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, vfekla@gmail.com; **RUMYANTSEV Egor Konstantinovich** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, tzeentch1993@mail.ru; **SEMENOVA Evgenya Ivanovna** – Senior Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, kunsuntar@mail.ru. **YAKOVLEVA Alexandra Ivanovna** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, sashyak@mail.ru. **OLESOVA Lubov Dygynovna** – Leading Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, oles59@mail.ru. **EFREMOVA Agrafena Vladimirovna** – Senior Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, a.efremova01@mail.ru. **KONSTANTINOVA Lena Ivanovna** – researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, konstanta.l@mail.ru. **ROMANOVA Matrena Mikhailovna** – sports analyst, R.M. Dmitriev Republican College of the Olympic Reserve, 677015, Yakutsk, str. Semen Danilov, 4. romanova.matrena@mail.ru; **FILIPPOV Aleksei Alekseevich** – Director, R.M. Dmitriev Republican College of the Olympic Reserve, 677015, Yakutsk, str. Semen Danilov, 4., filippalex74@mail.ru; **ROMANOVA Anna Nikolaevna** – Director, of the Yakut Science Centre of complex medical problems, Doctor of Medical Sciences, ranik@mail.ru

E.D. Okhlopkova, Z.N. Alekseeva, S.D. Efremova, G.E. Mironova, A.A. Grigoryeva, F.V. Vinokurova, E.K. Rummyantsev, E.I. Semenova, A.I. Yakovleva, L.D. Olesova, A.V. Efremova, L.I. Konstantinova, M.M. Romanova, A.A. Filippov, A.N. Romanova

EVALUATION OF PSYCHOLOGICAL STATUS AND LEVEL OF CORTISOL AND TESTOSTERONE IN THE PRE-COMPETITIVE PERIOD OF YAKUTIA ATHLETES

We examined 37 highly qualified freestyle wrestlers (candidates for master of sports (cms)) of Yakut nationality, aged 17 to 21 years. The control group consisted of 22 young men of students of the same age who are engaged in physical education at least twice a week. The article presents the results of studies of the level of psycho-emotional state in highly qualified martial artists in the pre-competition period. The level of situational and personal anxiety was high in 8 and 11% of athletes and in 23 and 36% of students, respectively. In the group of athletes, low depression was detected in 11, moderate in 6 and high in 7%. The level of depression in the group of students was 32, 9 and 5%, respectively.

The aggressiveness index showed that most young men have a low level of aggression, among athletes 61% - students 73%. In both groups, young men with a high level of aggression were not identified. In the first group of youths with a low and high index of hostility, there were 50 and 34% less than in the second, respectively. The willingness of athletes to compete depends on the psycho-emotional state, which can both contribute to the achievement of high results and prevent it.

Keywords: psycho-emotional state, testosterone, cortisol, athletes, psychological preparedness, Yakutia.

Introduction. The result of the performance of athletes in competitions is determined by the mechanism of behavior and specially directed actions, which are caused by the development of physical qualities, the level of technical preparedness, functional and mental capabilities [5, 7, 9, 16].

In conditions of direct pre-competitive training for a short period of time, it is impossible to significantly develop physical qualities, improve equipment, etc., therefore, at this stage, the athlete's psychological preparedness for competitions is of particular importance [1, 11]. Athlete participation in competitions, especially qualifying or high damage, is stressful. It is known that moderate stress has a positive effect on the effectiveness of training and competitive activity, and excessive stress leads to negative consequences [11].

The effects of stress are due to neurochemical changes in the body. In a state of acute physical and emotional stress in athletes, the hypothalamic-pituitary-adrenal system is activated, which leads to changes in the hormonal profile [5]. Changes in the concentration of

hormones make a significant contribution to the course of physiological processes in the North and help to stabilize the processes of adaptation of the body of athletes to changing environmental conditions and high physical activity [4]. Steroid hormones act on the central nervous system, regulate not only neuroendocrine function, but also behavioral, emotional processes, such as thinking, sleep, perception, as well as emotional states: depression, anxiety, aggression [6; 10]. It is believed that aggressiveness contributes to the implementation of strength and explosive exercises. At the same time, it is associated with testosterone. The question arises of how much emotions of this kind affect the changes in the level of testosterone and cortisol when performing strength exercises. Testosterone provides confidence and motivation, but when there is too much of it, positive qualities are replaced by negative ones. Testosterone activates the subcortical regions of the brain responsible for aggressive behavior, while cortisol and serotonin act as antagonists and reduce the effect of testosterone. Researchers associate aggression in

sports with sports specifics, the athlete's level of training, his individual psychological characteristics, and the research results are very contradictory.

The purpose of this study was to assess the level of psycho-emotional state and steroid hormones in freestyle wrestlers in the pre-competition period.

Materials and methods. A total of 59 young men aged 17 to 23 years were examined. The first group consisted of 37 athletes of freestyle wrestlers, highly qualified (candidates for master of sports (cms)), the Republican College of Olympic Reserve. The second - 22 youth students from the North-Eastern Federal University named after M.K. Ammosov engaged in physical education at least twice a week.

All subjects examined had blood taken from the ulnar vein in the morning (8-10 h) in a state of relative rest, on an empty stomach, from athletes 10-14 days before the competition. An enzyme-linked immuno sorbent assay of hormones (cortisol, testosterone) was performed in serum using AlkorBio kits (Russia), according to the manufacturer's instructions. The results of enzyme immunoassay of hormones were taken into account on a photometer (Picon, Russian Federation).

Psychological examination methods were carried out using the Bass-Dark questionnaire to study aggression, the Beck depression questionnaire, the Spielberg-Khanin anxiety test and the neuro-psychological adaptation questionnaire (NA). The study was approved by the decision of the Local Ethics Committee at the FSBSI YSC CMP and performed with the informed consent of the subjects in accordance with the ethical standards of the Helsinki Declaration (2000).

Statistical processing of the obtained data was carried out using the SPSS Statistics 26 software package. The significance of differences was determined by the Student t-test for independent groups, the Mann-Whitney criterion. The critical value of the level of statistical significance of differences (p) was taken to be 5%.

Results and discussion. The average age of athletes was 18 (18; 19), students-19 (18; 22) years. According to the results of the study, it was found that the indicators of the psycho-emotional state did not have significant differences in the examined groups and varied within the normal range (Table 1).

Moreover, in the first group, lower indices were found for the three studied parameters, compared with the second (the average level (NPA) was lower by 29%, (SA) - 13% and (D) - 47%,) respectively,

which may indicate a better psychological adaptation in this group (Table 1).

Analysis of the level (SA) among the examined individuals showed a predominance of a moderate level in both groups of subjects (Fig. 1). There were 13% more athletes with a "low" level (SA), and 10% fewer with a "high" one (Fig. 1) than in the second. Studies (PA) showed that athletes with a graduation of "moderate" level (PA) were 39% more, "low" and "high" - 54% and 70% less (Fig. 1), compared with students. Increasing feelings of excitement, anxiety, fear of com-

achieve success in the activity performed. However, the price of such success may be the predominance of negative experiences, increased anxiety and sleep disturbance. young men who do not have certain skills of mental self-regulation, having little experience in competitive activity, with a lack of information about rivals in the upcoming competitions, become easily excitable, are not confident in their own abilities, it's enough to simply knock them off of a positive attitude [3].

It is also known that athletes whose anxiety is expressed in aggressive ac-

**Indicators of the psycho-emotional state and level of hormones in athletes in the pre-competition period and students engaged in physical education 2 times a week.
M (25% Q₁-75% Q₃)**

Research indicators	Surveyed groups and size	
	1 group athletes. n=37	2 group students. n=22
Neuro-psychic Adaptation (NPA) points	13.5(6.0; 21.5)	19.0 (11.0; 25.0)
Situational Anxiety (SA) points	34.5(28.5; 37.0)	39.5 (31.0; 43.0)
Personal Anxiety (PA) points	40.5 (35.0; 43.0)	39.5 (32.0; 48.0)
Aggression Index (AI) points	15.0 (13.0;19.5)	12.5 (8.0; 19.0)
Hostility Index (HI) points	5.5 (4.0; 8.0)	6.0 (4.0; 8.0)
Depression (D) points	4.5 (1.5; 9.0)	8.5 (5.0; 12.0)
Cortisol (C)(150-660 nmol/L)	538.48 (485.76;559.72) *p=0.01	591.06 (527.04; 624.73)
Testosterone (T) (12.1-38.3 nmol/L)	26.75 (21.19; 33.60)	30.64 (27.12; 36.83)
Testosterone / Cortisol Index (T / K). conventional	0.057 (0.046; 0.066)	0.052 (0.37; 0.058)

Note: * <0.05 compared with the second group.

petition is a normal reaction of the body. A successful performance requires some optimal level - this is the so-called "useful anxiety". On the other hand, a very high anxiety or indifference "but I do not care" adversely affect the activities of the athlete and can lead to poor results in competitions.

Anxiety performs the function of adaptation, warns of external or internal danger, tells the body that measures must be taken to prevent the danger or mitigate its consequences. These measures may or may not be conscious. Studies show that moderate anxiety, as a personal quality, can increase the ability to

tions usually do not achieve high athletic performance. This also applies to individuals who are not able to control themselves and control their emotional and physical state during stress [2, 17]. The indicator (IA) in the first group was increased (by 17%), compared with the second group, which does not contradict

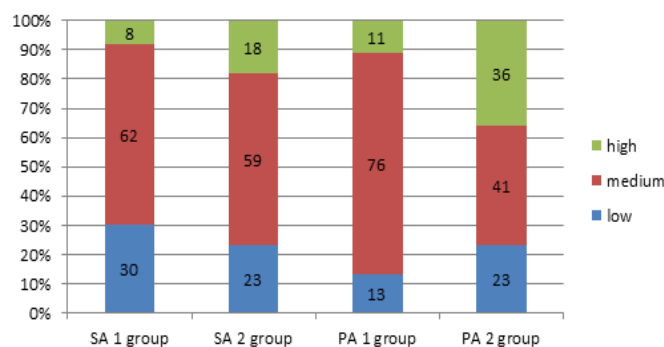


Fig. 1. The level of situational and personal anxiety of athletes in the pre-competition period and among students engaged in physical education 2 times a week, (%).

the literature (Table 1). According to E.P. Ilyin (2009), the aggressiveness and conflict in athletes is slightly higher than in individuals who are not involved in sports. Moreover, the athletes involved in contact martial arts, the aggressiveness is much higher than that of athletes and skiers [7]. In both groups, studies of young men with high (IA) were not detected. There were 31% more athletes with normal (IA). The majority of those examined had a low level (IA) (Fig. 2).

If we talk about aggression and anxiety, then athletes with a predominance of aggression over anxiety are better prepared for competition [14]. In the process of personality socialization, aggression frees people from fear, helps to defend their interests, protects against external threats, and helps to adapt. Often the concept of "aggressiveness" is replaced by the concept of "sports anger." Sport allows you to express aggressive feelings without causing much harm to other people, forming constructive forms of athletes' aggressive behavior. According to the results of the study Petrygin S.B. [15], aggression plays a leading role only at the initial stage of a sports career, and in all subsequent it is a factor in inhibiting the growth and effectiveness of sports indicators. Aggression that occurs in the initial stages of the practice of martial arts is associated with such values as a sports result, victory in competitions, intransigence to shortcomings, the desire to assert oneself at the expense of others. The experience of martial arts influences a decrease in the level of aggression, since there are changes in the individual's value system, causing a shift in the value orientation from the practical result to the process itself.

The hostility index was normal for the majority of young men (Fig. 2), but in the first group of young men with a low and high index of hostility was less by 50 and 34%, compared with the second, respectively. Spearman correlation analysis showed that (IV) had positive cor-

relation in the group of athletes with (SA) ($r = 0.346$; $p = 0.023$), (PA) ($r = 0.420$; $p = 0.021$) and with (AI) ($r = 0.523$; $p = 0.002$), and in the group of students with (NPA) ($r = 0.495$; $p = 0.019$) and with the level (D) ($r = 0.560$; $p = 0.007$).

The level of depression in the first group was 13% (moderate -6, high -7), in the second -14% (moderate -9, high -5) (Fig. 3). However, in the first group of young men with no depression, it was 28% more, and with low depression 66% less (Fig. 3). This is probably due to the fact that normalized physical activity contributes to the production of chemical elements - endorphins, which act on certain neurotransmitter systems in the brain as antidepressants and help improve attitude to life. However, sports can be a source of suffering and many professional athletes suffer from depression, which can be caused by stressful physical and psycho-emotional stress. Going in for sports educate character, self-discipline, hard work, responsibility and other moral and volitional qualities, but few achieve high sports results at the international level [13].

Based on our results, it is clear that the levels of testosterone and cortisol in the blood serum in both examined groups were within the physiological norm (Table 1). The testosterone content did not have statistically significant differences in both groups. The cortisol level in the first group was statistically significantly lower than in the second ($p = 0.01$) (Table 1). Cortisol determines the development of special performance, and therefore an increase in its concentration during different training cycles is accompanied by an improvement in the sportsman's athletic performance. In normal amounts, cortisol is necessary for metabolism, but its chronically elevated level caused by training stress leads to a worsening of the response to stress, which almost always leads to a decrease in testosterone production in endurance athletes. A decrease in testosterone leads to increased

fatigue and depression, which do not allow you to deal with stress. To assess the training status and sports potential, to clarify the course of reactions, anabolic / catabolic processes, we determined the index (T/K). Despite the absence of significant differences in the groups, the group of athletes has a tendency to increase this indicator compared to a group of students, this is ideal, since it shows the predominance of anabolic processes, that the load on the body is adequate and the athletes are in good shape. Correlation analysis showed a weak positive correlation between the level of testosterone c (PA) in the first group ($r = 0.330$; $p = 0.044$), and in the second group the level of cortisol c (HI) ($r = 0.553$; $p = 0.008$). In both groups, testosterone levels correlated with the T/K index, in the first group the correlation coefficient was ($r = 0.700$; $p = 0.000$), in the second ($r = 0.646$; $p = 0.001$). Athletes often ignore the factor of psychological stress, however, this may be the reason for such a wide variability of the training effect on the level of hormones.

Conclusion. Thus, indicators of the psycho-emotional state of fighters in the pre-competition period should be considered as a characteristic of the psychophysiological adaptation of the body and psychological readiness for competition. In order to fully realize the potential capabilities of athletes in competitions and achieve their highest sports result, great attention must be paid to the psychological support system. Conduct individual psycho-diagnostics of personality characteristics, its mental states, to identify athletes experiencing psycho-emotional disorders and teach them the skills of mental self-regulation.

References

1. Апариева Т.Г. Психология предсоревновательной подготовки квалифицированных спортсменов. *Известия ВГПУ*. 2013; 7:159-161. [Aparieva T.G. Psychology of pre-competition training of qualified sportsmen.

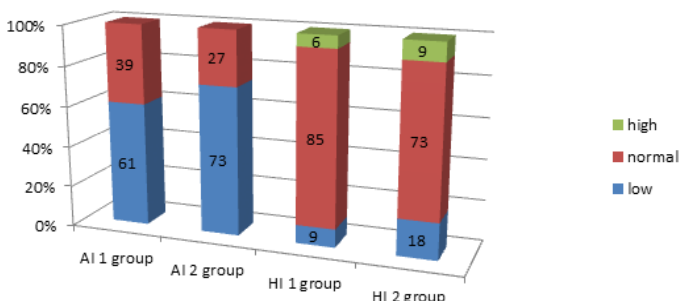


Fig. 2. Indices of aggression and hostility of athletes in the pre-competition period and among students engaged in physical education 2 times a week, %.

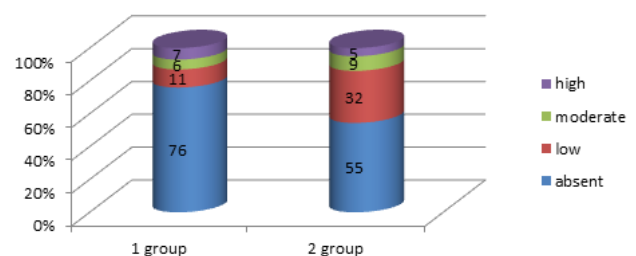


Fig. 3. The level of depression in athletes in the pre-competition period and in students engaged in physical education 2 times a week, %.

Izvestiya VGPU. 2013; 7:159-161. (In Russ.)] URL: <http://cyberleninka.ru/article/n/psihologiya-predsorevovatelnoy-podgotovki-kvalifitsirovannykh-sportsmenov-1>

2. Беспалова Т.А., Царева Н.М. Психологические особенности личности спортсменов. *Влияние физической культуры на формирование картины мира ребенка: международный межвуз. сб. науч. тр.* 2012;102-107 [Bespalova T.A., Tsareva N.M. Psychological characteristics of the personality of athletes. *Vliyaniye fizicheskoy kultury na formirovaniye kartiny mira rebenka: mezhdunarodnyy mezhvuz. sb. nauch. tr.* 2012;102-107 (In Russ.)]

3. Воскресенская Е.В. Психология страха и тревоги в спортивной деятельности (теория и практика): *методические рекомендации*. Витебск: 2015. 53 с. [Voskresenskaya E.V. Psychology of fear and anxiety in sports (theory and practice): *metodicheskiye rekomendatsii*. Vitebsk. 2015. 53 p. (In Russ.)]

4. Губина А.Е., Зуевская Т.В., Аксенов В.В., Павлов П.И., Косаренко Е.С., Гатиятуллина Л.Р. Влияние двигательной активности на функциональное состояние эндокринной системы жителей севера. *Дальневосточный медицинский журнал*. 2018; 12-16 [Gubina A.E., Zuyevskaya T.V., Aksenov V.V., Pavlov P.I., Kosarenko E.S., Gatiyatullina L.R. Effect of motor activity on the functional state of the endocrine system of the inhabitants of the North. *Dal'nevostochnyy meditsinskiy zhurnal*. 2018; 12-16 (In Russ.)]

5. Дубровский В.И. Спортивная медицина. 2-е издание. М.: 2002. 450 с. [Dubrovsky V.I. Sports medicine. 2-ye izdaniye. M.: 2002. 450 p. (In Russ.)]

6. Жуков Д. А. Биологические основы поведения. *Гуморальные механизмы: учебник* М.: 2004. 463 с. [Zhukov D. A. Biological foundations of behavior. *Gumoral'nyye mekhanizmy: uchebnyk*. M.: 2004. 463 p. (In Russ.)]

7. Ильин Е.П. Психология спорта. СПб.: 2008. 352 с. [Ilyin E.P. The psychology of sports. Saint-Petersburg: 2008. 352 p. (In Russ.)]

8. Исмаилов А. И. Психофункциональная подготовка спортсменов: *учебное пособие*. Волгоград: 2001. 116с. [Ismailov A. I. Psycho-functional training of athletes: *uchebnoye posobiye*. Volgograd: 2001. 116p. (In Russ.)]

9. Матвеев Л.П. Интеллектуальная, техническая и тактическая подготовка в спортивной тренировке. М.: 1977; 106 – 139 [Matveev L.P. Intellectual, technical and tactical training in sports training. M.: 1977; 106 – 139 (In Russ.)]

10. Методологические подходы к оценке биологических факторов психической дезадаптации (на примере невротических расстройств): *методические рекомендации* / С.А. Иванова, Е.В. Гуткевич, В.Я. Семке [и др.]. – Томск. - 2006. –33с [S.A. Ivanova, E.V. Gutkevich, V.Ya. Semke [et al.] Methodological approaches to the assessment of biological factors of mental maladaptation (on the example of neurotic disorders): guidelines metodicheskiye rekomendatsii

11. Меньщикова А.Л. Публичность соревнований как фактор психологического воздействия на личность *Спортивная психология в трудах отечественных специалистов : хрестоматия*. СПб.: 2002; 355–361 [Menshchikova A.L. The publicity of competitions as a factor in the psychological impact on the individual. *Sportivnaya psikhologiya v trudakh otechestvennykh spetsialistov : khrestomatiya*. Saint-Petersburg: 2002; 355-361 (In Russ.)]

12. Гудков А.Б., Демин А.В., Долгобородова А.А., Лукманова Н.Б. Особенности уровня тревожности у высококвалифицированных флорболисток в период соревновательной деятельности. *Ученые записки университета имени П.Ф. Лесгафта*. 2016; 3 (133):279-283 [Gudkov A.B., Dyomin A.V., Dolgoborodova A.A., Lukmanova N.B. Features the level of anxiety of high skilled floorball she-players in the period competitive activity. *Uchenyye zapiski universiteta imeni P.F. Lesgafta*. 2016; 3 (133):279-283 (In Russ.)]

13. Лысенко А.В., Таютина Т.В., Лысенко

Д.С., Арутюнов В.А. Оценка влияния физической нагрузки на выраженность тревожно-депрессивных состояний. *Ученые записки университета имени П.Ф. Лесгафта*. 2014;11 (117):218-224 [Lysenko A.V., Tayutina T.V., Lysenko D.S., Arutyunov V.A. Assessment of physical exertion on the expression of anxiety depression. *Uchenyye zapiski universiteta imeni P.F. Lesgafta*. 2014;11 (117):218-224 (In Russ.)]

14. Петрыгин С.Б. Волевая и психологическая подготовка в процессе занятий каратэ. *Российский научный журнал*. 2012; 3/28: 180–187 [Petrygin S.B. Strong-willed and psychological training in the process of karate. *Rossiyskiy nauchnyy zhurnal*. 2012; 3/28: 180–187 (In Russ.)]

15. Петрыгин С.Б. Проявление агрессии у подростков, занимающихся контактными видами единоборств. *Вестник РГУ имени С.А. Есенина*. 2012; 4(37):23–34 [Petrygin S.B. The manifestation of aggression in adolescents involved in contact martial arts. *Vestnik RGU imeni S.A. Yesenina*. 2012; 4(37):23–34 (In Russ.)]

16. Платонов В. Н. Система подготовки спортсменов в олимпийском спорте. *Общая теория и ее практические приложения: учебник тренера высшей квалификации*. М.: 2005. 820 с. [Platonov V. N. The system of training athletes in Olympic sports. *Obshchaya teoriya i yeye prakticheskiye prilozheniya: uchebnyk trenera vysshey kvalifikatsii*. M.: 2005. 820 p. (In Russ.)]

17. Ткачева М.С. Особенности функционирования познавательных психических процессов в различных видах спорта. *Известия Саратовского университета. Новая серия. Акмеология образования. Психология развития*. 2012; 4:65-69 [Tkacheva M.S. Features of the functioning of cognitive mental processes in various sports. *Izvestiya Saratovskogo universiteta. Novaya seriya. Akmeologiya obrazovaniya. Psikhologiya razvitiya*. 2012; 4:65-69 (In Russ.)]



ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

L.F. Timofeev, P.G. Petrova, N.V. Borisova, L.K. Turkeebaeva
A.L. Timofeev

RESOURCE PROVISION OF HEALTH CARE IN THE CENTRAL ECONOMIC ZONE OF THE SAKHA REPUBLIC (YAKUTIA) AND ITS RELATIONSHIP WITH POPULATION HEALTH INDICATORS

DOI 10.25789/YMJ.2020.70.12

УДК 614.2(571.56-191.2)

To achieve the proper level of accessibility and quality of medical care to the population, the provision of the municipalities of the republic with the necessary resources (material, technical, financial, human, information, etc.) is of no small importance. In this work, we analyzed the resource provision in the Central Economic Zone (CEZ) according to the indicators included in the official statistical reporting: the availability of medical personnel (doctors, paramedics), round-the-clock hospital beds (all per 10,000 population) and the capacity of outpatient clinics institutions (OCI, in shift visits). An analysis is made of the relationship of a number of indicators characterizing public health with the resource provision of districts / uluses, by correlation coefficients calculated for the period 2007-2016.

Keywords: health care resources, resource support, medical staffing, medical staff and nursing staff, hospital beds, outpatient facilities, correlation coefficients, the relationship of resource support with the incidence of the population, Republic of Sakha (Yakutia).

Introduction. Earlier (Yakutsk Medical Journal No. 1 for 2018 and No. 1 for 2019), we covered issues related to the medical and demographic situation and the incidence of the population in the Central Economic Zone of the Republic of Sakha (Yakutia). In our opinion, the picture in the CEZ does not seem complete without data on resource provision of health care and their connection with indicators characterizing the health of the population.

Material and methods. The statistical data of Yakutsk and 9 districts / uluses

included in the Central Economic Zone were analyzed. Geographically, all municipalities are included in the central and district group of uluses, and according to the medical and economic zoning, the cities of Yakutsk and Kobyaysky district were assigned to the industrial group, and all the rest to the rural group.

The materials used are official statistics of the republic - the Territorial Authority of the Federal State Statistics Service for the Republic of Sakha (Yakutia) and the Ministry of Health (YRMIAC). To analyze these indicators, the percentile (centile) method was used, which is widely used and used by us in developing the criteria for regionalization of the North of the Russian Federation and in preparing a number of articles. According to this method, areas with indicators up to the 10th percentile belonged to areas with a low level of resource provision, from 10 to the 25th percentile - below the average, from 75 to the 90th - above the average and above the 90th percentile - with a high level. Obviously, with indicators ranging from the 25th to the 75th percentile, the districts belonged to the group with average values of resource provision.

Results and discussion. I. Resource security. According to the results of 2016, the average republican indicator of the availability of medical personnel is 48.4 per 10,000 population (Table 1). Of the 9 districts and the city of Yakutsk considered that are part of the Central Economic Zone, the worst situation is for Namsky (31.1 - below the national average), Amginsky (31.7) and Kobyaysky (31.9) uluses. Throughout the entire period since 1990, there was a shortage of

medical personnel in the Namsky, Ust-Al-dan and Churapchinsky uluses. A favorable situation is noted only in the Gorniy Ulus. But good indicators until 2005 in the city of Yakutsk should be considered critically in view of the ambiguous statistical approach to staffing in the context of republican and city medical institutions. However, this also applies to subsequent calculations starting in 2007.

In 2016, the provision of nurses was higher than the national average (111.7 per 10,000 population), in the Tatta ulus (127.9 per 10,000 population, and this is above average). In the Gorny (97.0) and Namsky (96.1) uluses, the indicators were below the national average, and were in the range below the average. During the period under review, quite good security is observed at Amginsky, Kobyaysky and Tattinsky uluses. The worst situation is noted in the Khangalassky ulus and, taking into account the above, in the city of Yakutsk - since 2007.

Consider the data on the security of municipalities of the CEZ around the clock hospital beds (table. 2). The national average for 2016 was 92.0 per 10,000 people, and only the Kobiai ulus is approaching this level. At the same time, in the Namsky (53.2), Churapchinsky (57.9) uluses and the city of Yakutsk (28.7), indicators on a national scale are low, and in the Tattinsky (68.1) and Khangalassky (67.5) uluses - below average. During the period under review, insufficient security was noted in the same mentioned uluses, with the exception of Tattinsky, where a relatively low level was first registered just in 2016.

As for the provision of outpatient facilities in visits per shift (settlement /

Institute of Medicine, M.K. Ammosov North-Eastern Federal University: **TIMOFEEV Leonid Fedorovich** – Doctor of Medical Sciences, Professor, Chair of Public Health and Health Care, General Hygiene and Bioethics, Institute of Medicine, M.K. Ammosov North-Eastern Federal University, 677016 Yakutsk, ul. Oyunskogo, 27. Tel. +7-914-225-88-45. E-mail: tlfnauka@mail.ru. **PETROVA Palmira Georgievna** – MD, Professor, Head of the Department of Normal and Pathological Physiology of the Medical Institute of NEFU. 677016, Yakutsk, ul. Oyunskogo, 27, cab. 312 Russia. Tel.: + 7-914-272-74-71. E-mail: mira44@mail.ru. **BORISOVA Natalia Vladimirovna** – MD, Professor, Department of Normal and Pathological Physiology, Medical Institute, NEFU. 677016, Yakutsk, ul. Oyunskogo, 27, Tel.: + 7-924-166-96-83. E-mail: Borinat@yandex.ru. **TURKEBAEVA Lena Kimovna** – doctor of Medicine, Associate Professor, Department of Pharmacology and Pharmacy. Address: 677016 Yakutsk, ul. Oyunskogo, 27. Tel: +7-964-415 70 17. E-mail: lk.turkebaeva@s-vfu.ru. **TIMOFEEV Artem Leonidovich** – postgraduate student, Chair of Public Health and Health Care, General Hygiene and Bioethics. 677016 Yakutsk, ul. Oyunskogo, 27. E-mail: su-yuol@mail.ru.

Table 1

Provision of medical personnel in the city of Yakutsk and areas of the Central Economic Zone in 1990-2016 (per 10,000 us.)

Uluses	1990	1995	2000*	2005	2010	2011	2012	2013	2014	2015	2016
Provision of doctors											
Amginsky	33	26	29	31	35.8	32.6	32.7	32.3	33.6	31.2	31.7
Gorniy	34	29	28	37	40.2	41.8	39.7	40.6	39.0	41.2	40.1
Kobiai	30	29	25	28	38.2	33.0	32.2	31.8	33.4	31.4	31.9
M-Kangalassky	34	25	27	25	31.0	30.7	35.9	37.8	37.0	37.5	37.6
Namsky	33	31	31	30	28.4	27.1	29.1	30.7	31.8	32.3	31.1
Tattinsky	32	26	31	39	38.8	34.3	37.2	38.7	36.6	37.3	36.1
U-Aldan	30	24	25	26	31.5	28.0	30.7	30.9	32.8	34.8	34.8
Hangalass	29	32	32	27	31.8	30.6	32.4	32.1	31.5	33.1	34.4
Churapchinsky	34	29	24	31	30.1	29.9	29.1	28.2	31.0	34.3	34.3
City of Yakutsk	83	101	91	97	35.1	33.6	30.7	31.6	32.3	32.0	32.2
In the RS (Y)	42	44	46	50	52.6	48.3	47.7	47.9	48.5	48.1	48.4
Provision of nursing staff											
Amginsky	125	146	124	149	138.8	128.8	131.3	124.0	127.1	131.3	121.4
Gorniy	135	121	107	120	117.8	109.1	105.3	103.5	100.9	96.0	97.0
Kobiai	113	109	125	142	138.9	135.7	131.8	139.7	114.1	115.2	121.9
M-Kangalassky	121	114	99	99	98.2	96.3	97.8	100.8	101.9	105.5	104.0
Namsky	138	121	108	105	104.9	101.9	101.6	100.1	95.9	95.9	96.1
Tattinsky	151	145	146	135	141.0	128.3	135.9	132.0	127.5	128.5	127.9
U-Aldan	127	134	116	109	118.5	118.0	119.6	123.1	120.9	121.5	107.7
Hangalass	91	100	100	102	99.3	99.7	103.2	99.4	102.9	100.0	101.3
Churapchinsky	136	136	128	126	121.5	121.2	116.5	115.7	113.9	109.6	107.2
City of Yakutsk	152	201	189	180	51.7	50.4	45.8	49.4	49.6	49.9	49.3
In the RS (Y)	118	130	133	136	121.5	117.3	116.0	115.1	113.3	112.7	111.7

Note. Legend (In the Tables 1-3): 29.0 low security, 31.5 level below average, 43.2 level above average, 46.6 high security

cm.), This indicator on average in RS (Y) reached 267.0 in 2016 (Table 3). In Namsky and Churapchinsky Uluses, OCI security indicators turned out to be the worst (166.6 and 166.8 towns / cm,

respectively). It should be noted that years with insufficient OCI power were observed in these uluses for almost the entire period under consideration. In other uluses, average values prevailed.

II. The characteristic of the relationship of resource provision with some indicators of public health. This section provides an analysis of the possible relationship of a number of indicators characterizing public health with the resource supply of districts / uluses, according to correlation coefficients calculated for the period 2007-2016. The following population health indicators were analyzed:

1) medical and demographic - birth rate, mortality, natural population growth (NPG), infant mortality (InM);

2) incidence - general and primary (of the entire population, as well as adult and child);

3) primary disability (adult and child).

In this case, only those indicators were evaluated whose dynamics was distinct either upward or downward. Correlation coefficients with an average (0.30-0.69) and strong (0.70 and higher) degree of connection were taken into account.

Amginsky ulus. The period 2007-2016 characterized by a decrease in the provision of medical personnel and round-the-clock hospital beds, and this was combined with an increase in the overall incidence rate of the entire population ($r = -0.46-0.57$), and the general and primary incidence of the child population ($r = -0.56-0.75$).

Gorniy ulus. The provision of nurses decreased from 117.6 per 10,000 population in 2007 to 97.0 in 2016, and the provision of round-the-clock hospital beds from 114.1 to 73.6, respectively. During the same years, the primary incidence of the child population increases from 1686.4 ‰ to 2247.6 ‰ ($r = -0.42$ and $r = -0.63$, respectively). In addition, an inverse average correlation is traced between the deterioration in the availability of nurses and OCI with the dynamics of the general mortality rate.

Table 2

Provision of round-the-clock hospital beds in the city of Yakutsk and areas of the Central Economic Zone in 1990, 1995, 2000, 2005, 2010-2016. (per 10,000 population)

Uluses	1990	1995	2000	2005*	2010	2011	2012	2013	2014	2015	2016
Amginsky	173.0	161.8	134.7	146	101.7	91.5	93.3	94.0	94.1	85.8	83.7
Gorniy	164.0	137.6	130.4	130	102.6	98.0	99.3	97.5	91.6	82.5	73.6
Kobiai	142.0	126.4	142.0	179	121.3	107.1	111.9	112.6	112.6	98.0	86.8
M-Kangalassky	160.0	123.1	109.1	117	92.0	91.2	97.8	98.5	98.3	83.3	76.8
Namsky	151.0	159.0	140.6	117	72.6	71.4	71.2	70.7	69.5	59.5	53.2
Tattinsky	207.0	169.5	163.6	167	110.0	98.7	101.8	102.5	101.9	84.5	69.8
U-Aldan	184.0	156.4	142.9	123	109.4	103.5	95.0	95.6	95.6	80.5	68.1
Hangalass	146.0	153.1	132.9	126	95.2	94.1	94.6	94.8	94.9	80.8	67.5
Churapchinsky	175.0	158.2	136.6	134	86.4	84.4	83.5	83.6	83.3	70.5	57.9
City of Yakutsk	205.0	179.4	184.4	186	31.9	31.0	28.8	30.2	29.5	29.0	28.7
In the RS (Y)	156.0	150.4	142.0	153	109.8	107.5	106.8	106.9	106.4	98.1	92.0

Table 3

Provision of outpatient facilities in the city of Yakutsk and areas of the Central Economic Zone in 1990, 2000, 2005, 2010-2016.
(power in visits per shift)

Uluses	1990*	2000*	2005*	2010	2011	2012	2013	2014	2015	2016
Amginsky	188	278	277	289.5	268.9	272.8	275.0	276.3	276.4	276.1
Gorniy	267	286	285	291.8	280.2	281.3	282.2	279.7	276.3	274.4
Kobiai	179	237	253	264.1	253.1	262.4	266.9	268.6	270.0	273.4
M-Kangalassky	193	193	203	297.1	294.2	303.8	305.8	306.6	305.8	304.0
Namsky	183	193	182	177.0	175.3	174.0	173.0	171.0	168.5	166.6
Tattinsky	278	326	303	320.2	287.3	298.6	302.8	302.9	302.5	302.5
U-Aldan	276	289	297	310.6	293.5	304.4	308.2	309.2	309.5	309.5
Hangalass	208	248	250	253.4	252.6	260.5	264.0	265.7	266.1	266.1
Churapchinsky	137	178	171	170.4	170.0	167.9	167.6	167.4	166.8	166.8
City of Yakutsk	322	287	281	124.6	121.7	111.1	115.1	112.9	112.4	131.6
In the RS (Y)	214	272	274	258.6	255.8	258.2	259.7	260.2	260.6	267.0

Kobiai ulus. Reduced availability of medical personnel and round-the-clock hospital beds for the period 2007-2016 was accompanied by an increase in all considered types of general and primary morbidity, with the exception of the primary morbidity of the adult population. Strong feedback was observed between the availability of doctors and the overall incidence of the child population ($r = -0.75$). And here we can see the inverse average correlation between the deterioration in the availability of round-the-clock hospital beds and OCI with the dynamics of the general mortality rate ($r = -0.69$).

Megino-Kangalassky ulus. The deterioration in the availability of round-the-clock hospital beds is correlated with the growth of all types of general and primary morbidity under consideration (inverse mean relationship). But for other types of resource provision in this ulus, the dynamics are more than favorable. And here you can clearly see the positive dynamics of medical and demographic indicators - fertility, mortality and NPG. Moreover, we see a direct strong connection between the provision of doctors and OCI with fertility and NPG population ($r \geq 0.7$).

Namsky ulus. It was not possible to identify any patterns in the correlation coefficients, although there was a nega-

tive dynamics in the provision of nurses, round-the-clock hospital beds and OCI.

Tattinsky ulus. A decrease in the supply of nurses is correlated with an increase in the general and primary morbidity of both the whole and the children's population, and children have a strong relationship ($r = -0.79$ and -0.82). It is noteworthy that a significant decrease in the availability of round-the-clock hospital beds for the period under review (from 127.3 per 10,000 population to 69.8) is also combined with an increase in the general and primary morbidity of both the entire and the child population.

Ust-Aldan ulus. An increase in the availability of doctors from 29.4 per 10000 population in 2007 to 34.8 in 2016 is combined with a slight improvement in the disability indicators of both the adult and children's population. In turn, a decrease in the availability of round-the-clock hospital beds correlates with an increase in the overall incidence of both the whole and the adult population.

Hangalass ulus. The decrease in the availability of round-the-clock hospital beds is striking (101.4 per 10,000 population in 2007, 67.5 in 2016). At the same time, there is an increase in all types of general and primary morbidity considered by us, and in children, the relationship is strong ($r = -0.73-0.76$). And the

improvement in OCI security indicators is correlated with an increase in birth rates and NPG.

Churapchinsky ulus. The decrease in the resource provision of nurses, round-the-clock hospital beds and OCI correlates with the primary incidence of the child population ($r = -0.38-0.53$). In addition, a decrease in OCI coverage is combined with an increase in the primary incidence of the entire population.

The city of Yakutsk. For the period 2007-2016 There is a dynamic decline in the provision of nurses and around-the-clock hospital beds, and this is combined with an increase in childhood disability.

Conclusion. Thus, it becomes obvious that in a number of CEZ uluses, the situation with the provision of medical personnel, round-the-clock hospital beds and general medical facilities is generally unfavorable, with the exception of the provision of secondary medical personnel in 3 uluses (Amginsky, Kobayasky and Tattinsky).

In almost all uluses, there is a clear connection between a decrease in the level of resource provision with an increase in the general morbidity of the population. In some uluses there are correlation links with medical and demographic indicators. Another example: an increase in the supply of doctors from 29.4 per 10,000 population in 2007 to 34.8 in 2016 in the Ust-Aldan ulus is combined with a slight improvement in disability indicators, both for adults and children.

We conclude that the planned "optimization of health care" in the form of a reduction in the number of medical personnel, hospital beds and OCI without taking into account the dynamics of indicators characterizing the health of the population, can lead to a deterioration in public health.

The work was prepared based on the results of the project "Assessment, main trends in the natural and socio-economic status, human potential of the Central Economic Zone of the Republic of Sakha (Yakutia)" A comprehensive research program in the Republic of Sakha (Yakutia) aimed at developing its productive forces and social sphere in 2016-2020 years.

HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

V.V. Gribova, D.B. Okun, E.A. Shalfееva, B.O. Shcheglov,
M.Yu. Shchelkanov

CLOUD SERVICE FOR THE DIFFERENTIAL CLINICAL DIAGNOSTICS OF ACUTE RESPIRATORY VIRAL DISEASES (INCLUDING THOSE ASSOCIATED WITH HIGHLY CONTAGIOUS CORONAVIRUSES) WITH AN APPLICATION OF METHODS OF ARTIFICIAL INTELLIGENCE

DOI 10.25789/YMJ.2020.70.13

УДК 550.382.3:612.014.4

Valeria V. GRIBOVA – Doctor of Technical Sciences, Deputy Director for Research and a Head of the Laboratory of Intelligent Systems at the Institute of Automation and Control Processes of the Far Eastern Branch of the Russian Academy of Sciences (Vladivostok); Professor at the School of Natural Sciences of the Far Eastern Federal University (Vladivostok); e mail: gribova@iacp.dvo.ru; tel.: +79084498959; ORCID: 0000-0001-9393-351X. **Elena A. SHALFEEVA** – Ph.D., Senior Researcher at the Laboratory of Intelligent Systems at the Institute of Automation and Control Processes of the Far Eastern Branch of the Russian Academy of Sciences (Vladivostok); e mail: shalf@iacp.dvo.ru; tel.: +74232674170; ORCID: 0000-0001-5536-2875. **Dmitry B. OKUN** – Ph.D., Researcher at the Laboratory of Intelligent Systems at the Institute of Automation and Control Processes of the Far Eastern Branch of the Russian Academy of Sciences (Vladivostok); e mail: okdm@dvo.ru; tel.: +74232310424; ORCID: 0000-0002-6300-846X. **Bogdan O. SHCHEGLOV** – Student at the School of Biomedicine of the far Eastern Federal University (Vladivostok); e mail: b.shcheglov@mail.ru; tel.: +79147189825; ORCID: 0000-0002-2262-1831. **Mikhail Yu. SHCHELKANOV** – Doctor of Biology, Head of the International Scientific and Educational Center of Biological Safety, Far East Federal University (Vladivostok); Head of Laboratory of Virology, Federal Scientific Center of East Asia Terrestrial Biodiversity, Far Eastern Branch of the Russian Academy of Sciences (Vladivostok); Senior Researcher at the Laboratory of Marine Mammals, National Scientific Center of Marine Biology, Far Eastern Branch of the Russian Academy of Sciences, (Vladivostok); e mail: adorob@mail.ru; tel.: +79032689098; ORCID: 0000-0001-8610-7623.

Increasing population density and mobility contribute to the high incidence of the acute respiratory viral infections and the emergence of dangerous epidemic situations associated with them. The XXI century began with an epidemic (November 1, 2002 - July 31, 2003) caused by the coronavirus of Severe Acute Respiratory Syndrome (SARS-CoV) (*Coronaviridae, Betacoronavirus*); this was later followed by a pandemic was registered in 2009 (June 11, 2009–August 10, 2010) of the so-called Swine Influenza (H1N1) pdm09 (*Orthomyxoviridae, influenzavirus A*); in 2012, the Middle East Respiratory Syndrome coronavirus (MERS – CoV) (*Coronaviridae, Betacoronavirus*) showed its epidemic potential. December 2019 was the month of the beginning of epidemic of the modern COVID-19 (Coronavirus Disease 2019), etiologically related to SARS-CoV-2 (temporarily named 2019-nCoV – 2019 novel coronavirus). March 11, 2020 World health organization has announced the beginning of the COVID-19 pandemic. The modern paradigm of mass differential diagnosis of acute respiratory diseases is based on the indication of the pathogen using polymerase chain reaction (PCR), but this, firstly, does not exclude the establishment of a preliminary differential diagnosis based on clinical data, and secondly, differential clinical diagnosis comes to the fore during major epidemic outbreaks (especially in developing countries), the scale of which exceeds the practical possibilities of laboratory diagnostics. This is the reason why diagnostic decision-making support systems are one of the most promising areas of digitalization in the medical practice. This paper presents the results of the development of a medical diagnostic service that is based on a model of medical knowledge and an intelligent decision-maker. The model of medical knowledge, in turn, includes models of definitions, medical diagnosis, medical history, and justification of the decisions made. An intelligent decision-maker generates a structured report using common medical definitions about diseases that have either been confirmed or rejected by the system, and a detailed justification of the decisions made. The developed cloud service allows users to accumulate data on the clinical manifestations of acute respiratory viral infections and to use artificial intelligence methods to generate solutions that can significantly facilitate and speed up the establishment of the preliminary diagnosis.

Keywords: acute respiratory viral infections, highly contagious coronaviruses, differential clinical diagnostics, cloud services, artificial intelligence.

Introduction. Both increasing population density and intensification of the passenger mobility that brings together distant territories of Earth contribute to a high prevalence of acute respiratory viral infections and the emergence of dangerous epidemic situations associated with these infections [8, 9, 10].

The XXI century began with an epidemic (November 1, 2002 – July 31, 2003) caused by a coronavirus of Severe Acute Respiratory Syndrome (SARS-CoV) (*Coronaviridae, Betacoronavirus*), which had lethality of 9,6 % (774 / 8096). The epidemic process began in the South-Eastern provinces of China after the penetration of SARS-CoV from the bats, which function as its natural reservoir (*Chiroptera: Microchiroptera*) first in the population of intermediate hosts -

Himalayan civets (*Paguma larvata*) and later in the human population [10,13,18]. In 2009, a pandemic (June 11, 2009–August 10, 2010) of the so-called Swine Influenza A (H1N1) pdm09 began, which due to an application of modern vaccine technologies and the presence of etiotropic chemotherapeutic drugs became the least devastating of all the influenza pandemics known since the beginning of the XX century [6, 9, 12]. In 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (*Coronaviridae, Betacoronavirus*) has showed its epidemic potential. Its natural foci associated with bats (*Chiroptera*) are located on the Arabian Peninsula, and its intermediate hosts are one-humped camels (*Camelus dromedarius*). “Smoldering infection” of MERS-CoV according to the World Health Orga-

nization (WHO) at the beginning of 2020 had the lethality of 34,4 % (866 / 2519), including imported cases of infection in 27 countries around the globe. The largest epidemic outbreak resulting from the import of MERS-CoV occurred in the Republic of Korea (May 11 - July 10, 2015) where lethality has reached the level of 18,5 % (35 / 189) [11, 14].

The first patient with a new disease, named COVID-19 (Coronavirus Disease 2019), was officially registered in Wuhan, the administrative center of the Eastern Chinese province of Hubei on December 8, 2019. In early January 2020, it was established that the etiological agent of COVID-19 is a new Type 2 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2)¹ (*Coronaviridae, Betacoronavirus*), which together with the previously described SARS-CoV and the Chinese rufous horseshoe bat coronavirus (RsBtCoV – Rhinolphus sinicus coronavirus) form subgenus *Sarbecovirus*. The natural reservoir of SARS-CoV-2 is bats [16]. Intermediate hosts have not yet been reliably established but they appear to be pangolins (*Pholidota*) [17]. Currently, SARS-CoV-2, which has entered the human population, is spreading from person to person by airborne ways.

March 11, 2020 World health organization has announced the beginning of the COVID-19 pandemic: for this date in all parts of the world, including imported cases and related epidemic outbreaks in 113 countries, the lethality for COVID-19 has reached a figure of 3,6 % (4292 / 118319) [18].

The modern paradigm of mass differential diagnosis of acute respiratory diseases is based on the indication of the pathogen using a polymerase chain reaction [4, 7, 8, 9]. However, first, this does not preclude making a preliminary differential diagnosis based on clinical data. Second, differential clinical diagnosis comes to prominence during major epidemic outbreaks (especially in developing countries), which exceed the practical capabilities of laboratory diagnostics. This is the reason why diagnostic decision-making support systems are one of the most promising areas of digitalization in the medical practice.

The purpose of this work is to develop a cloud service with an application of artificial intelligence methods to search for hypotheses about a possible differential diagnosis of patients with acute respiratory disease with justification of the decisions made by the system, which is

¹The original temporary name of this virus was 2019-nCoV (novel coronavirus).

followed by prescribing of recommendations of the possible options for clarification of the diagnosis.

Materials and Methods. The medical diagnostics service is based on a software shell that includes models of medical knowledge and data and an intelligent solver (decision-maker). This models of medical information include a terminology model, a model of medical diagnosis, a model of medical history, and a model of explanation of hypotheses on decision [1, 2, 3, 5] (Fig. 1).

The terminology model is designed to describe all concepts used by doctors, called findings or observations or signs, which are necessary for making diagnosis. Such definitions include descriptions of possible symptoms (complaints), methods of the physical examination of the patients, definitive and structural descriptions of laboratory and instrumental studies. The model of medical diagnostics describes the structure and cause-and-effect relationships necessary to describe the clinical evidence of the diseases in dynamics of the pathological process, as well as taking into account the impact of treatment measures, and other possible events. The medical history model describes the structure used in medical institutions to describe information about a patient and includes a description of general data (sex and age of the patients, their complaints at admission, history of current disease, results of physical examination, etc.). The decision explanation model describes the structure where the intelligent solver generates a structured report using vocabulary of medical concepts. It not only contains information about the diseases either confirmed or rejected by the system, but also a detailed explanation of hypotheses on decision made specifying: what findings of the disease are / are not included in the clinical evidence of hypotheses about diseases, and if additional observations are needed for confirmation/rejection, the system tells the doctor what observations should be obtained additionally [1,2].

Results and Discussion. The cloud service, consisting of such a software shell and knowledge base,

is implemented on the IACPaaS platform in the certified Data Center of the Far Eastern Branch of the Russian Academy of Sciences. IACPaaS simultaneously supports three cloud service models: Platform as a Service (PaaS), Software as a Service (SaaS), and Desktop as a Service (DaaS).

The medical diagnostic model has the following features: description of the sets of symptoms of the diseases, including categories of users and reference ranges for laboratory and instrumental studies; formation of alternative sets of symptoms with different approaches to identify manifestations or diagnostic criteria of the disease that may differ across various medical institutions; description of the diagnosis taking into account etiology, pathogenesis, types of the course for the differential diagnosis of the diseases and selection of appropriate treatment methods; the ability to specify the measures of fuzziness of attributes such as modality, with the values “needed”, “typical”, “possible”, and a scale the probabilities of matching characteristics to a hypothesis about the diagnosis, which can be used if the experts have an agreement on what manifestations are appropriate to use when making decisions; consideration of values and characteristics of the signs, the effects of the events to account for external influences on the patient's body at different stages of the disease; consideration of different variations of dynamics of symptom values.

Formation of a knowledge base for the diagnosis of diseases is carried out by clinicians. For this purpose, the platform has a medical knowledge base editor with an intuitive interface (Fig. 2) developed on its basis. More specifically, the symptoms of viral infections were selected according to [8, 9, 10]. Data for the new COVID-19 disease are taken from [4, 15]. About 26 disease markers

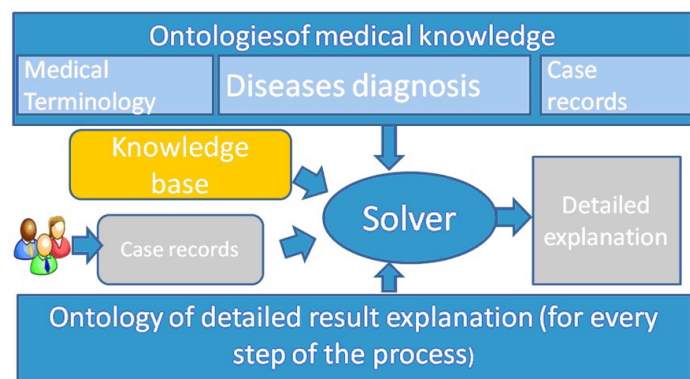


Fig. 1. Cloud service architecture for differential clinical diagnostics of acute respiratory viral diseases with an application of artificial intelligence methods.

were used to describe the manifestations of acute respiratory viral infections. The periods of manifestations of these stages and clarification of the features of each symptom are identified, which allows in particular to differentiate SARS, MERS, and COVID-19 from other infections of the respiratory tract of viral etiology. At the same time, for these particularly dangerous coronaviruses, it was possible to identify a set of markers of an early stage, the peak of the disease, a light (erased) course, a medium-severe form, and a severe complication in the form of primary viral pneumonia. To confirm the development of pneumonia, the following markers should be detected by X-rays: shadows in the lungs, unilateral and bilateral dense infiltrates, areas of necrotic changes, growth of connective tissue, fibrous scars, etc.

Using data that characterize several stages of disease development, the diagnostic service checks the facts from the patient's medical history, comparing them with all variations of the clinical manifestations. The results of the verification process may indicate confirmation of the hypothesis about the disease or indicate all the diseases that this patient might theoretically have.

Conclusion. The cloud service that was developed allows users to accumulate data on the clinical manifestations of acute respiratory viral infections (including those associated with particularly dangerous coronaviruses MERS-CoV, SARS-CoV, and SARS-CoV-2) and to use artificial intelligence methods to generate solutions that can significantly facilitate and speed up the establishment of preliminary diagnosis. In this case, the service can be used globally since both the information collection unit and the decision-making rules can be adjusted with consideration of specific national standards.

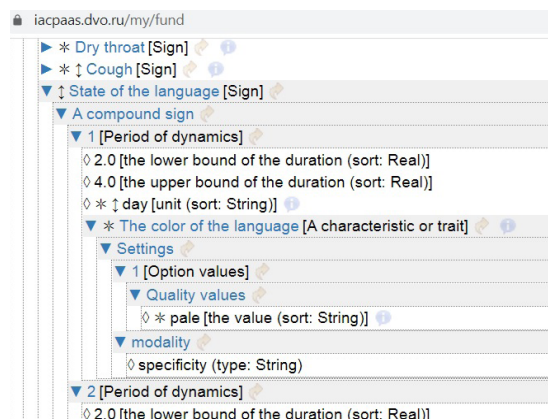


Fig. 2. Fragment of a symptom description in the medical knowledge database editor.

The research was carried out with partial financial support from the Russian Foundation for Basic Research (Projects 18-29-03131 and 19-29-01077), and The Program of the Priority Research Projects for the Comprehensive Development of the Far Eastern Branch of the Russian Academy of Sciences (Project 18-5-060).

References

- Грибова В.В., Окунь Д.Б., Краснов Д.А. Онтология базы знаний о лечении заболеваний. *Системный анализ в медицине (САМ 2017): мат-лы XI междунар. научн. конф.* Благовещенск: Амурская медицинская академия. 2017: 60-63. [Gribova VV, Okun DB, Krasnov DA. Knowledge base ontology for disease treatment. *System analysis in medicine (SAM 2017). Materials of the XI international scientific conference.* Blagoveshchensk: Amur Medical Academy. 2017: 60-63. (In Russ.).]
- Грибова В.В., Петряева М.В., Окунь Д.Б., Шалфеева Е.А. Онтология медицинской диагностики для интеллектуальных систем поддержки принятия решений. *Онтология проектирования.* 2018; 8(1): 58-73. [Gribova VV, Petryaeva MV, Okun DB, Shalfeeva EA. Medical Diagnosis Ontology For Intelligent Decision Support Systems. *Ontology of Designing.* 2018; 8(1): 58-73. (In Russ.).] DOI: 10.18287/2223-9537-2018-8-1-58-73.
- Грибова В.В., Клещев А.С., Москаленко Ф.М., Тимченко В.А., Шалфеева Е.А., Федорищев Л.А. Методы и средства разработки жизнеспособных облачных сервисов. *Вестник Дальневосточного отделения Российской академии наук.* 2016; 4: 133-141. [Gribova VV, Kleshev AS, Moskalenko PhM, Timchenko VA, Shalfeeva EA, Fedorishev LA. Methods and tools of viable intelligent services development. *Vestnik of Far Eastern Branch of Russian Academy of Sciences.* 2016; 4: 133-141. (In Russ.).]
- Министерство здравоохранения Российской Федерации. Профилактика, диагностика и лечение новой коронавирусной инфекции (2019-nCoV). Временные методические рекомендации (версия от 03.02.2020). М., 2020. [Ministry of Public Health of the Russian Federation. Prevention, diagnosis and treatment of novel coronavirus infection (2019-nCoV). Temporary guidelines (version from 03.02.2020). Moscow, 2020. (In Russ.).]
- Грибова В.В., Клещев А.С., Москаленко Ф.М., Тимченко В.А., Федорищев Л.А., Шалфеева Е.А. Облачная платформа IACPaaS для разработки оболочек интеллектуальных сервисов: состояние и перспективы развития. *Программные продукты и системы.* 2018; 3: 527-536. [Gribova VV, Kleshev AS, Moskalenko PhM, Timchenko VA, Fedorishev LA, Shalfeeva EA. IACPaaS cloud platform for the development of intelligent service shells: current state and future evolution. *Software & Systems.* 2018; 3: 527-536. (In Russ.).] DOI: 10.15827/0236-235X.031.3.527-536.
- Колобухина Л.В., Меркулова Л.Н., Щелканов М.Ю., [и др.] Пандемический грипп в России: отличительные особенности клинического течения и отсутствие ранней этиотропной терапии как

фактор риска развития тяжёлых форм заболевания. *Терапевтический архив.* 2011; 83(9): 48-53. [Kolobukhina LV, Merkulova LN, Schelkanov MYu, [et al.]. Pandemic influenza in Russia: specific features of clinical course and the absence of early etiotropic therapy as a risk factor of severe forms of the disease. *Ter. Arkh.* – 2011; 83(9): 48-53. (In Russ.).]

7. Львов Д.К., Альховский С.В., Щелканов М.Ю., [et al.]. Применение современных молекулярно-генетических технологий для обеспечения биологической безопасности. *Вестник Российской военно-медицинской академии.* 2014; 3: 115-127. [Lvov DK, Alkhovskiy SV, Schelkanov MYu, [et al.]. Application of modern molecular-biological techniques for provision of biological safety. *Vestnik Rossiiskoi voinno-meditsinskoi akademii.* 2014; 3: 115-127. (In Russ.).]

8. Пульмонология. Национальное руководство / Под ред. А.Г. Чучалина. М.: ГЭОТАР-Медиа, 2016. [Pulmonology. National guidance / Ed. A.G. Chuchalin. Moscow: GEOTAR-Media, 2016. (In Russ.).]

9. Руководство по вирусологии. Вирусы и вирусные инфекции человека и животных / Под ред. Д.К. Львова. М.: МИА, 2013. [Handbook of Virology. Viruses and viral infections of humans and animals / Ed. D.K. Lvov. Moscow: Med. Inf. Agency, 2013. (In Russ.).]

10. Чучалин А.Г. Тяжёлый острый респираторный синдром. *Терапевтический архив.* 2004; 76(3): 5-11. [Chuchalin AG. Severe acute respiratory syndrome. *Ter. Arkh.* 2004; 76(3): 5-11. (In Russ.).]

11. Щелканов М.Ю., Ананьев В.Ю., Кузнецов В.В., Шуматов В.Б. Ближневосточный респираторный синдром: когда вспыхнет тлеющий очаг? *Тихоокеанский медицинский журнал.* 2015; 2: 94-98. [Shchelkanov MYu, Ananiev VYu, Kuznetsov VV, Shumatov VB. Middle East respiratory syndrome: when will smouldering focus outbreak? *Pacific Medical Journal.* 2015; 2: 94-98. (In Russ.).]

12. Щелканов М.Ю., Колобухина Л.В., Львов Д.К. Грипп: история, клиника, патогенез. *Лечащий врач.* 2011; 10: 33-38. [Shchelkanov MYu, Kolobukhina LV, Lvov DK. Influenza: history, clinics, pathogenesis. *The Practitioner.* 2011; 10: 33-38. (In Russ.).] URL: <https://www.lvrach.ru/2011/10/15435275/>

13. Щелканов М.Ю., Колобухина Л.В., Львов Д.К. Коронавирусы человека (Nidovirales, Coronaviridae): возросший уровень эпидемической опасности. *Лечащий врач.* 2013; 10: 49-54. [Shchelkanov MYu, Kolobukhina LV, Lvov DK. Human coronaviruses (Nidovirales, Coronaviridae): increased level of epidemic threat. *The Practitioner.* 2013; 10: 49-54. (In Russ.).] URL: <http://www.lvrach.ru/2013/10/15435832/>

14. Щелканов М.Ю., Ананьев В.Ю., Кузнецов В.В., Шуматов В.Б. Эпидемическая вспышка Ближневосточного респираторного синдрома в Республике Корея (май-июль 2015 г.): причины, динамика, выводы. *Тихоокеанский медицинский журнал.* 2015; 3: 25-29. [Shchelkanov MYu, Ananiev VYu, Kuznetsov VV, Shumatov VB. Epidemic outbreak of Middle East respiratory syndrome in the Republic of Korea (May-July, 2015): reasons, dynamics, conclusions. *Pacific Medical Journal.* 2015; 3: 25-29. (In Russ.).]

15. Chinese National Committee on Public Health and Traditional Chinese Medicine. Program for the diagnosis and treatment of pneumonia associated with a new coronavirus infection. 4-th edition. Beijing, 2020. (In Chinese)

16. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, [et al.]. Genomic characterisation and

epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*. 2020; 395(10224): 565-574. DOI: 10.1016/S0140-6736(20)30251-8.

17. Liu P, Chen W, Chen JP. *Viral Metage-*

nomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (*Manis javanica*). *Viruses*. 2019; 11(11): E979. DOI: 10.3390/v11110979.

18. World Health Organization. Coronavi-

rus disease 2019 (COVID-19). Situation Report-40 (29 February 2020). URL: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf?sfvrsn=849d0665_2 (accessed 06.03.2020).

DOI 10.25789/YMJ.2020.70.14

УДК 616-022.7+616-093/-098

Ya.A. Akhremenko, A.E. Goncharov, V.V. Kolodzhieva,
E.Yu. Belonogova, D.V. Kolesnik, A.S. Mokhov, V.I. Ilarova,
L.A. Tarasova

MICROBIOLOGICAL CHARACTERISTICS OF STREPTOCOCCUS PNEUMONIAE STRAINS ISOLATED IN YAKUTSK

AKHREMENKO Yana Aleksandrovna

– Candidate of Medical Sciences, Docent, Associate Professor of the Department of Histology and Microbiology of Medical Institute, the North-Eastern Federal University named after M.K. Ammosov.

GONCHAROV Artemiy Evgenyevitch

– doctor of medical sciences, professor at the Department of Epidemiology, Parasitology and Disinfectology of North-Western State Medical University named after I.I. Mechnikov, Russian Federation, 191015, Saint-Petersburg, Kirochnaya St, 41, 8 (812) 303-50-00; head of Laboratory for Functional Genomic and Proteomic of Microorganisms of Department of Molecular Microbiology of Institute of Experimental Medicine, Russian Federation, 197376, Saint-Petersburg, Academica Pavlova St, 12, 8 (812) 234-68-68, e-mail: phage1@yandex.ru;

KOLODZHIEVA Viktoriya Vasilievna – candidate of medical Sciences, associate Professor of the Department of epidemiology, Parasitology and Disinfectology of North-Western State Medical University named after I.I. Mechnikov, Russian Federation, 191015, Saint-Petersburg, Kirochnaya St, 41, 8 (812) 303-50-00; e-mail: vika-el@yandex.ru;

BELONOGOVA Ekaterina Yurievna – PhD student at the Department of Molecular Microbiology of Institute of Experimental Medicine, Russian Federation, 197376, Saint-Petersburg, Academica Pavlova St, 12, 8 (812) 234-68-68, e-mail: katyushka1204@mail.ru;

KOLESNIK Dmitriy Sergeevitch – PhD student at the Department of Epidemiology, Parasitology and Disinfectology of North-Western State Medical University named after I.I. Mechnikov, Russian Federation, 191015, Saint-Petersburg, Kirochnaya St, 41, 8 (812) 303-50-00, e-mail: dmitry_kolesnik@mail.ru;

MOCHOV Aleksey Sergeevitch – PhD student at the Department of Epidemiology, Parasitology and Disinfectology of North-Western State Medical University named after I.I. Mechnikov, Russian Federation, 191015, Saint-Petersburg, Kirochnaya St, 41, 8 (812) 303-50-00, e-mail: docalexserg@gmail.com;

ILAROVA Vera Innokentievna – head of the Educational and scientific microbiological laboratory of the Clinic the North-Eastern Federal University named after M. K. Ammosov;

TARASOVA Lidia Andreevna – Candidate of Medical Sciences, Docent, Associate Professor of the Department of Histology and Microbiology of Medical Institute, the North-Eastern Federal University named after M.K. Ammosov.

Pneumococcus and pneumococcal infections are still among actively discussed problems, while there is a lack of information about the population structure in the North-East of Russia.

Objective: the identification of microbiological and molecular genetic characteristics of *S. pneumoniae* strains found during nasopharyngeal carriage in Yakutsk.

Materials and methods: we studied *S. pneumoniae* isolates, obtained from the discharges of nasopharynx in 69 patients from the age of 6 months to 85 years living in Yakutsk and undergoing a survey for acute and chronic diseases of the ENT organs (rhinitis, sinusitis, otitis), repeated acute respiratory viral infections and nasopharyngitis. Identification of the isolated cultures was performed using the time-of-flight mass spectrometry method on a Vitek MS analyzer. For uncertain results, we used test systems to detect *S. pneumoniae* DNA on PCR-RV. Identification of sensitivity to antimicrobial agents was determined by the disk diffusion method with an interpretation according to the EUCAST recommendations and the Clinical recommendations for determining the sensitivity of microorganisms to antimicrobial agents (version 2018-03). The microbiological analyzer Vitek II Compact was used to specify the phenotype of sensitivity / resistance.

Confirmation of species identification was carried out by amplification of the autolysin gene (*lytA*). Identification of serological types of the isolated *S. pneumoniae* strains was carried out using multiplex PCR. We were determining presence of genetic determinants of resistance to macrolide antibiotics *erm*, *mef* and *msr* as well as genes associated with the pathogenicity island PPI1 (*per*, *npIT*, *FtsW*).

Results: more than 80% of *S. pneumoniae* strains circulating among the population of Yakutsk are represented by serotypes 6A and 19F. In 50% of pneumococci 6A and 100% of serotype 19F pneumococci were detected all 3 genes associated with the pathogenicity island PPI1. Macrolide resistance was observed in all isolates of serotype 6A, while 80% of serotype 6A and 100% of serotype 19F showed the *ermB* resistance gene (MLSB phenotype) and 20% of serotype 6A pneumococci had the *mef* gene (M phenotype).

Conclusions: obtained data indicate the prevalence of virulent antibiotic resistant strains of *S. pneumoniae* among the population of Yakutsk and dictate the need for further epidemiological and microbiological studies of this problem.

Keywords: pneumococcus, nasopharyngeal carriage, virulence, resistance.

Introduction. Despite the insertion of mass vaccination, pneumococcus (*Streptococcus pneumoniae*) is one of the main causative agents of acute bacterial infections in children, especially under the age of 5 years [2-4].

The high incidence of pneumococcal infections is combined with a steady increase of the pneumococcus resistance to the antibacterial drugs that are most widely used in clinical practice. β -lactams and macrolides are the drugs of choice in the treatment of pneumococcal infections, therefore, the increase in *S. pneumoniae* resistance to these antibiotics becomes a significant clinical problem [4].

The resistance of *S. pneumoniae* to penicillin and other β -lactam antibiotics is due to a change in penicillin binding proteins (PBPs), enzymes that participate in

the final stages of cell wall synthesis [13].

The resistance to macrolides is mediated by two main mechanisms, which include changes in the binding target and antibiotic efflux from a bacterial cell. The first mechanism is due to the modification of the macrolide binding site with 23S-rRNA as a result of its methylation, which disrupts the interaction of the antibiotic with the target. The methylation is carried out by the methylase enzyme, which is encoded by the *erm* gene (*erythromycin ribosome methylation*) and causes a high level of resistance to macrolides. About 20 varieties of *erm* are described, however, the *ermB* variant plays the greatest role in the formation of resistance in pneumococcus. Most pneumococci with *ermB* demonstrate cross-resistance to all macrolides, as well as to lincosamides

and B streptogramin, as their targets are partially overlapped. This phenotype is called MLSB [1, 7].

The second mechanism of resistance to macrolides is concerned with their active excretion (efflux) from the bacterial cell with the help of a special pump built into the cell wall. The efflux pump is encoded by several variants of the *mef* gene (macrolide efflux). Mef-positive pneumococci have an M-phenotype, which is characterized by resistance to fourteen- and fifteen-membered macrolides, but maintaining sensitivity to sixteen-membered macrolides, lincosamides and B streptogramine [1, 3, 10].

Another urgent problem because of the vaccination that is carried out in the Russian Federation with conjugated pneumococcal vaccines is the possibility of genetic changes in the pathogen population under the influence of the applied vaccines. In this regard the importance belongs to the data that characterize the presence in the genomes of *S. pneumoniae* of mobile genetic elements associat-

tions and nasopharyngitis. Of these, 58 children (84%), 11 adults (16%), 25 inpatients (36.2%), 44 outpatients (63.8%).

The material was obtained from the nasopharynx using tampons that were placed in the transport Ames medium with coal. Chocolate agar cultures were incubated in airtight containers with gas generators to create microaerophilic conditions (bioMerieux) for 24 hours. Identification of the isolated cultures was performed using the time-of-flight mass spectrometry method on a Vitek MS analyzer. For uncertain results, we used test systems to detect *S. pneumoniae* DNA on PCR-RV. Identification of sensitivity to antimicrobial agents was determined by the disk diffusion method with an interpretation according to the EUCAST recommendations and the Clinical recommendations for determining the sensitivity of microorganisms to antimicrobial agents (version 2018-03). The microbiological analyzer Vitek II Compact was used to specify the phenotype of sensitivity / resistance.

coccal nasopharyngeal carriage in Yakutsk was 14.1% in 2010 and in 2017 was only 2.7% in the total structure of nasopharyngeal bacterial carriage. From the 69 obtained samples more than half of the confirmed *S. pneumoniae* isolates were represented by serotype 6A (53.8%), a third of the strains (30.8%) were assigned to serotype 19F, the rest 15.4% are presented by serotypes 7F and 23F.

In determining of the sensitivity to antimicrobial agents by the disk diffusion method, we paid attention to the presence of sensitivity / resistance to β -lactam antibiotics on a disk with 1 μ g of oxacillin (OX) and sensitivity / resistance to macrolides on a disk with 15 μ g of erythromycin (E). Thus, 42% of isolated pneumococci were resistant to β -lactams and 34.8% were resistant to macrolides, while 26.1% of the strains were resistant to both groups of drugs (Table 3).

Genetic study showed that the resistance to macrolides was noted in all isolates of serotype 6A, 80% of representa-

Table 1

Primers used in the study to identify the virulence genes

Gene	Primer sequence (5'→3')	Reference genome (GenBank Acc. №)	Localization in the reference genome		Source
<i>ftsW</i>	ATGGCTTCCCCGTGCTTTTA	AE005672.3	1001727	1001746	actual study
	AGATACGAGCGCCAGAATGG		1001901	1001882	
<i>pezT</i>	CGCGCAACTCCAAAAGAACA		989035	989054	
	CCCACCTGCAACATCTCCTT		989255	989236	
<i>npIT</i>	GGAGACCTTTCGGGAAGTGG		985812	985831	
	TGGTCCTCCAGTCAAGGCTA		986562	986543	

ed with invasive potential, which include the pathogenicity island PPI1 [5].

It should be noted that despite the availability of summarizing data from large multicenter studies [2], regional data is extremely important for understanding the trends in molecular epidemiology and resistance of pneumococci both in a specific territory and in the country as a whole, and there is a lack of information about the situation in the North-East of the Russia.

Research objective: the identification of microbiological and molecular genetic characteristics of *S. pneumoniae* strains found during nasopharyngeal carriage in Yakutsk.

Materials and methods. We studied *S. pneumoniae* isolates, obtained from the discharges of nasopharynx in 69 patients from the age of 6 months to 85 years living in Yakutsk and undergoing a survey for acute and chronic diseases of the ENT organs (rhinitis, sinusitis, otitis), repeated acute respiratory viral infec-

Primers used to detect the genetic determinants of antibiotic resistance of the macrolide

Праймеры	Sequence 5' → 3'	Gene	Product size (nucleotide couples)	Source link
<i>ermB-f</i>	ATTGGAACAGGTAAGGGC	<i>Erm B</i>	442	[8]
<i>ermB-r</i>	GAACATCTGTGGTATGGCG			
MEF 57-f	AGTATCATTAATCACTAGTGC	<i>MEF(A)</i>	346	[7]

Confirmation of species identification was carried out by amplification of the autolysin gene (*lytA*) [12]. Identification of serological types of the isolated *S. pneumoniae* strains was carried out using multiplex PCR [9]. The following primers were used to identify virulence genes and genetic determinants of resistance to macrolide antibiotics in the polymerase chain reaction (Table 1, 2).

Results and discussion: According to the data of the Educational and Scientific Microbiological Laboratory of the NEFU Clinic, the frequency of pneumo-

tives of this type had an *ermB* resistance gene and 50% of these pneumococci revealed all 3 genes associated to the pathogenicity island PPI1. The same genes, as well as all determinants of macrolide resistance were detected in *S. pneumoniae* of serotype 19F. 6 genotypes of pneumococci isolated during nasopharyngeal bacterial carriage in Yakutsk were characterized (Table 4).

Thus, more than 80% of the *S. pneumoniae* strains studied by us are represented by serotypes 6A and 19F. In 50% of pneumococci 6A and 100% of sero-

Table 3

Identified phenotypes of *S. pneumoniae* sensitivity / resistance to β -lactam and macrolides

Phenotype	Abs (%)	Abs (%)
OX-R E-S	11 (15.9)	Ox – R 29 (42)
OX – R E - R	18 (26.1)	
OX-S E-R	6 (8.7)	E – R 24 (34.8)
OX – S E - S	34 (49.3)	

type 19F pneumococci were detected all 3 genes associated with the pathogenicity island PPI1. Macrolide resistance was observed in all isolates of serotype 6A, while 80% of serotype 6A and 100% of serotype 19F showed the *ermB* resistance gene (MLSB phenotype) and 20% of serotype 6A pneumococci had the *mef* gene (M phenotype).

Conclusion. The obtained data indicate the prevalence of virulent antibiotic resistant strains of *S. pneumoniae* among the children of Yakutsk and dictate the need for further epidemiological and microbiological studies in this domain. Subsequent monitoring studies should be obviously aimed at assessing the impact of mass vaccination of the population on the genetic structure of the pneumococcal population, including assessing the appearance of new strains with high pathogenic and epidemic potential.

References

1. Козлов Р.С. Пневмококки: прошлое, настоящее и будущее. Смоленск: Смоленская государственная медицинская академия. 2005. 128 с. [Kozlov RS. Pneumococci: past, present and future. Smolensk: Smolenskaia gosudarstvennaia meditsinskaia akademiia. 2005. 128 p. (In Russ)]
2. Сидоренко С.В., Лобзин Ю.В., Харит

Variety of *S. pneumoniae* genotypes isolated in Yakutsk

Macrolide resistance genes			Genes associated to the pathogenicity island PPI1			Serotype	Erythromycin
<i>MSR</i>	<i>MEF</i>	<i>ermB</i>	<i>pezT</i>	<i>nplT</i>	<i>FtsW</i>		
-	-	+	+	+	+	6A	R
+	+	-	+	+	+	6A	R
-	-	+	-	+	+	6A	R
-	-	+	-	-	+	6A	R
-	-	+	-	+	+	6A	R
+	+	+	+	+	+	19F	I

С.М., Королева И.С., Таточенко В.К. Пневмококковая инфекция и современные возможности ее профилактики — эпидемиологический обзор ситуации в мире и в России. *Вопросы современной педиатрии*. 2010; 9 (1): 62–69. Библиогр.: с.69. [Sidorenko SV, Lobzin YuV, Harit SM, Koroleva IS, Tatochenko VK. Pneumococcal infection and modern possibilities of its prevention — an epidemiological review of the situation in the world and in Russia. *Voprosy sovremennoi pediatrii*. 2010; 9 (1): 62–69. (In Russ)]

3. Райнерт Р.Р., Тайши Б. Новые данные по эффективности 13-валентной пневмококковой конъюгированной вакцины в отношении инвазивных пневмококковых инфекций, пневмоний, острого среднего отита и назофарингеального носительства. *Педиатрическая фармакология* 2012; 3: 8–11. Библиогр.: с.11. [Rainert RR, Tajshi B. New data on the effectiveness of 13-valent pneumococcal conjugate vaccine against invasive pneumococcal infections, pneumonia, acute otitis media and nasopharyngeal carrier. *Pediatricheskaia farmakologiya* 2012; 9 (3): 8–11. (In Russ)]

4. Маянский Н.А., Алябьева Н.М., Лазарева А.В., Катосова Л.К. Серотиповое разнообразие и резистентность пневмококков. *Вестник РАМН*. 2014. 7–8: 38–45. Библиогр.: с.45. [Mayansky NA, Alyabyeva NM, Lazareva AV, Katosova LK. Serotype diversity and resistance of pneumococci. *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk*. 2014; 7–8: 38–45. (In Russ)]

5. Harvey RM, Stroehrer UH, Ogunniyi AD, Smith-Vaughan H C, Leach AJ, Paton JC. A variable region within the genome of *Streptococcus pneumoniae* contributes to strain-strain variation in virulence. *PLoS One*, 2011. 6(5). DOI: 10.1371/journal.pone.0019650

6. Cornick J.E., Bentley S.D. *Streptococcus pneumoniae*: the evolution of antimicrobial resistance to beta-lactams, fluoroquinolones and macrolides. *Microb. Infect.* 2012; 14: 573–583. DOI: 10.1016/j.jmicinf.2012.01.012.

7. Sutcliffe J, Grebe T, Tait-Kamradt A, Wondrack L. Detection of erythromycin-resistant determinants by PCR. *Antimicrob Agents Chemother* 1996;40:2562–6.

8. Amezaga MR., Carter PE., Cash P, McKenzie H. Molecular epidemiology of erythromycin resistance in *Streptococcus pneumoniae* isolates from blood and noninvasive sites. *J. Clin. Microbiol.* 2002. 40:3313–3318. DOI: 10.1128/JCM.40.9.3313–3318.2002

9. Pimenta FC., Gertz REJr, Roundtree A. Yu J, Nahm MH, McDonald RR, Carvalho Mda G., Beall BW. Rarely occurring 19A-like cps locus from a serotype 19F pneumococcal isolate indicates continued need of serology-based quality control for PCR-based serotype determinations. *J. Clin Microbiol.* 2009 Jul;47(7):2353–4. DOI: 10.1128/JCM.00704-09.

10. Reinert R.R. The antimicrobial resistance profile of *Streptococcus pneumoniae*. *Clin. Microbiol. Infect.* 2009; 15 (Suppl. 3): 7–11. DOI: 10.1111/j.1469-0691.2009.02724.x.

11. Retsema J., Fu W. Macrolides: structures and microbial targets. *Int. J. of Antimicrob. Agents.* 2001; 3–10.

12. Wang X. et al. Clinical validation of multiplex real-time PCR assays for detection of bacterial meningitis pathogens. *J. Clin. Microbiol.* 50, 702–708 (2012)

13. Zapun C., Contreras-Martel T.V. Penicillin-binding proteins and beta-lactam resistance. *FEMS Microbiol. Rev.* 2008; 32: 361–385. DOI: 10.1111/j.1574-6976.2007.00095.x.

A.A. Nikitina, A.I. Pavlova, T.T. Gulyaev, V.F. Cherniavsky,
O.I. Nikiforov, I.A. Romanova, O.N. Sofronova

MODERN EPIZOOTIC AND EPIDEMIOLOGICAL CHARACTERISTICS OF LEPTOSPIROSIS IN THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.70.15

УДК 619-36.22:616.9 (571.56)

The article presents the results of the study of the forms of contamination of agricultural and wild animals, small mammals, as well as the infection of cohorts of the population with different types of leptospires. A wide variety of animal species, both domestic and wild, act as reservoirs of zoonotic diseases.

The etiological structure of leptospiroses and quantitative and serological indicators of immunological response in animals and humans have been studied. Modern epizootic and epidemiological evaluation of the intensity potential ("softening" of tension) and forecasting of the indicated problem (in the format of reduction, but not elimination of the nosological form) are given.

Occupation is a significant risk factor for humans. Direct contact with infected animals accounts for most infections in fur farmers, livestock technicians and hunters.

Keywords: etiological composition of leptospiroses, infection and immunostructure of agricultural and other animals, risks of human morbidity, monitoring.

Introduction. Leptospirosis in the Far North was first described by I.E. Trop and S.E. Getzold, who conducted a survey of population and animals in the Tyumen region in 1954-1960 [5, 19]. They also observed an outbreak in Khanty-Mansiysk (1959-1960), when the number of the diseased reached 132 people [5, 19].

A further basis for the study of leptospiroses was the disease of calves in one of the farms of the Nenets Autonomous District, when laboratory examination of 1093 domestic reindeers in 1.8% of them revealed antibodies to the leptospira of the serogroup *L. grippityphosa*. In some herds, animal infection was 6% [7]. Subsequently, a wide spread of leptospiroses in the Far North was detected from the Kola Peninsula to Chukotka [12, 13].

The possibility of rodent leptospirosis in the northern taiga of the Republic Sakha (Yakutia) was reported by E.V. Karaseva and E.I. Korenberg [5], who found in blood serum specific agglutinins to the leptospiroses of the serogroup *L. grippityphosa* in titer 1:800-1:1000.

However, studies indicating the presence of natural foci of leptospirosis in the high latitude zone were few and fragmentary.

In 1984 the first case [15] of human leptospirosis in Yakutia was registered in the Tatta region. During the next decade, zoonosis was registered in 11 regions of the republic, having a flare-up, group and sporadic character [9, 18], amounting to 0.2 to 2.0 cases per 100,000 population.

In the epizootic and epidemiological plan, the most dangerous [8, 11, 12, 13, 22] were animals infected with leptospirosis. Leptospirosis carriage both in the latent course of the infection process and in an infected animal against the background of its natural foci [14, 20] retained its limpopotential [6]. A special line was devoted to occupational risks [17].

The results of monitoring of epizootological and epidemiological observations in different zones of Yakutia were presented in a series of published works [2, 4, 9, 10, 15, 16, 18, 20, 21]. Zoning of the territory [22] and the practice of departmental (veterinary and sanitary) supervision [11, 12, 23] were supplemented by elements of the geoinformational approach (mapping). Scientific and methodological developments were introduced into veterinary and medical practice [1, 2, 3, 8, 22].

The **objective** of this paper is to provide modern epizootic, epidemiological and prognostic assessment of leptospiroses in Yakutia, including information and prevention proposals on the basis of monitoring data.

Materials and research methods. The study included retro- and prospec-

tive indicators of epizootic and epidemic processes in leptospirosis in Yakutia on the basis of annual departmental reports, information on antiepizootic measures in form 1-Vet A and infectious animal diseases in form 1-vet of the Department of Veterinary Medicine of the Republic Sakha (Yakutia) for 2003-2018, information on statistical observations and laboratory activity of the FBUZ "Center for Hygiene and Epidemiology" in form No. 2 for 1995-2018 and State reports for the period 1995-2019, stock data, literary publications and their assessment.

Statistical data processing was performed using descriptive statistics and comparative analysis methods in the "Office Microsoft Excel" program.

Results and discussion. Diagnosis of the etiological structure of leptospirosis was carried out on the basis of the Yakut Republican Veterinary Testing Laboratory, according to GOST 25386-91. The annual volume of laboratory tests was: cattle - up to 2100 animals, horses - up to 1600, up to 300 samples from pigs, small cattle and other domestic animals.

A comparative analysis of laboratory studies showed that cattle was the host of leptospira serogroups *L. grippityphosa* in 34.6% in 2004 and 43.6% of cases in 2018, *L. icterohaemorrhagiae* - 35.1 and 30.7%, *L. tarassovi* - 2.6 and 10.2%, *L. canicola* - 2.1 and 10.2% and *L. pomona* - 4.8 and 5.1%, respectively.

Horses were the hosts for the leptospira serogroup *L. icterohaemorrhagiae* in 22.5% of cases in 2004 and 35.2% in 2018, *L. grippityphosa* - 38 and 29.5%, *L. tarassovi* - 4.2 and 18.2%, *L. canicola* - 1.4 and 15.9%, respectively, *L. heb-*

NIKITINA Anastasia Afanasyevna – Head of Section of Veterinary Department of the Republic of Sakha (Yakutia), graduate student of the Arctic state Agrotechnology University, yakutiavet@mail.ru; **PAVLOVA Alexandra Innokentievna** – Doctor of Vet. Sciences, prof. Arctic state Agrotechnology University; Center for Hygiene and Epidemiology in the Republic of Sakha (Yakutia): **CHERNYAVSKY Viktor Fedorovich** – Ph.D., epidemiologist, epidotd@fbuz14.ru, **Nikiforov Oleg Innokentievich** - zoologist, **GULYAEV Timur Tuskulovich** - epidemiologist, **ROMANOVA Irina Aleksandrovna** – doctor -bacteriologist, **SOFRONOVA Oktyabrina Nikolaevna** – head. lab.

domadis in 2.8% in 2004, *L. pomona* in 1.1% of cases in 2018.

Leptospirosis among small cattle was represented by an unstable nosounit, manifested singly and periodically. In 2018, small cattle in 36.3% of cases turned out to be the host of the leptospira serogroup *L. sejroei*, in 27.2% of cases - *L. grippotyphosa*, in 18.2% - *L. tarassovi*, in 9.1% - *L. canicola* and *L. icterohaemorrhagiae*, and in dogs leptospirosis is represented in all cases by one type - *L. canicola*.

When analyzing studies in anthropogenic foci, it was found that the predominant hosts for the leptospira serogroup *L. grippotyphosa* were: cattle, horses and small cattle (43.6, 29.5 and 27.2%, respectively); for *L. icterohaemorrhagiae* - cattle in 30.7% of cases, horses - 35.2% and cattle - 9.1%, for *L. tarassovi* - horses and cattle in 18.2% of cases, cattle - 10.2%, for *L. canicola* - cattle in 10.2% of cases, horses - 15.9%, dogs - 100%, for *L. pomona* - cattle - 5.1%, horses - 1.1%. It was found that the attachment of certain leptospira to animal species was not absolute.

Using cattle as an example, we studied the facts of possible mixing — mixt infections of circulating leptospira species (Fig. 1).

In a comparative, selective, applied characteristic of the etiological structure of leptospira, it was revealed that if in 2006 the proportion of mixed serogroups was 68.2% of the studied ones (*L. pomona* - 1.1%, *L. tarassovi* - 2.9%, *L. grippotyphosa* - 0, *L. hebdomadis* - 0, *L. sejroei* - 1.1%, *L. canicola* - 2.9% and *L. icterohaemorrhagiae* - 20.0%), then in 2018 this figure was 4.6% of the studied (*L. pomona* - 6.8%, *L. tarassovi* - 6.3%, *L. grippotyphosa* - 22.8, *L. hebdomadis* - 0.8%, *L. sejroei* - 10.5%, *L. canicola* - 3.8%, *L. icterohaemorrhagiae* - 40.9%).

The number of foci of leptospirosis of animals during the analyzed period was constantly changing (Fig. 2).

The presented data indicate a fluctuating parameter of the monitored epizootological factor, with a decrease in its quantitative characteristics. The explanatory premise has a multifactorial (natural, economic, anthropogenic, climatic, administrative-economic, business-industrial, etc.) character.

The highest indicator for identifying dysfunctional points on leptospirosis was established in 2009 - 38, which is 15.4% of their total number for 2003-2018 (247 points), and the lowest indicator was established in 2004 - 1.6% (4 points). Their largest number falls on the period 2008-2011 - 128 points, subsequently the num-

ber ranged from 4 to 16. The largest proportion of dysfunctional points for this period were horses - 66.4%, cattle - 31.4%, pigs - 1.6%, bison - 0.8%. The share of research over 15 years on agricultural species of animals was: cattle - 47.6%, horses - 35.9, deer - 0.8, pigs - 6.9, small cattle - 8.0, fur animals - 0.8%.

From year to year there was an increase in targeted, applied, laboratory research, which had a planned state character. If in 2003 a total of 1509 animals were examined by the microagglutination reaction (of which 81.6% were studies of cattle, 4.6% of horses, 12.4% of pigs), then in 2018 6185 were conducted (of which 42% were studies of cattle, 38.1 - horses, 8.7 - pigs, 0.4 - deer, 7.9 - small cattle, 0.03 - fur animals and 3.46 - other animal species).

The percentage of studies on leptospirosis from the total population in 2018 was: cattle - 1.5%, horses - 1.4%, pigs - 2.87%, deer - 0.4%, fur animals - 0.03%, which in comparison with 2003 shows an increase by 3 times in cattle (0.4% in 2003), in horses by 28 times (0.05%), in pigs by 7 times (0.4%).

The analysis found that with a monthly cumulative distribution of animals seropositive for leptospirosis, the largest number of animals was detected from April to June and from November to December. It should be noted that the blood sampling was carried out as planned: in cattle and small cattle before pasture and at stabling, and in horses during mass preventive measures (from March to May and from October to November).

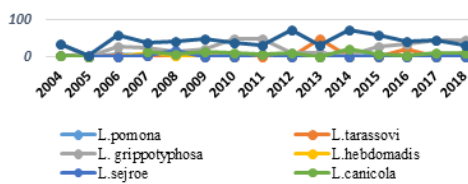


Fig. 1. The structure and dynamics of circulating leptospira species

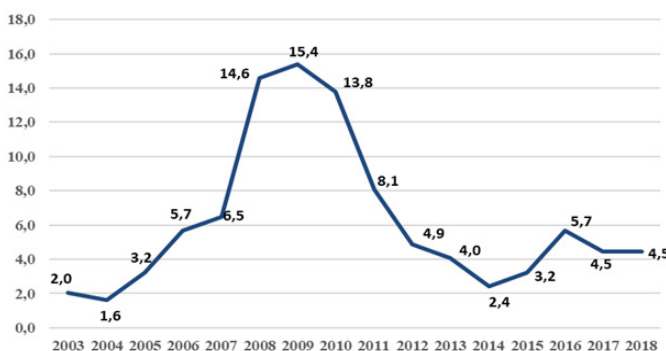


Fig. 2. The proportion of established dysfunctional points by years,%

On the basis of data on dysfunctional sites and the incidence of animals, we determined the territories of the spread of leptospirosis with 4 groups:

- to the 1st group, where the number of dysfunctional points ranges from 0 to 5, 20 districts are assigned, mainly in the Arctic zone (Anabarsky, Abyysky, Allaikhovskiy, Bulunsky, Verkhoyansky, Verkhnekolymsky, Gornyy, Zhigansky, Lensky, Mirnynskiy, Momy, Neryungrinsky, Nizhnekolymsky, Oleneksky, Oymyakonsky, Srednekolymsky, Tattinsky, Ust-Maysky, Ust-Yansky, Eveno-Bytantaysky). The proportion of dysfunctional points in this zone is 15.6% of their total number;

- 6 districts (Suntarsky, Nyurbinsky, Kobayasky, Ust-Aldansky, Aldansky) are assigned to the 2nd group, where from 6 to 10 dysfunctional points were registered during the analyzed period. The proportion of dysfunctional points in this zone is 20.5% of the total;

- 7 districts were included in the 3rd group (Olekminsky, Verkhnevilyuysky, Namsky, Tomponsky, Amginsky, Churapchinsky, Yakutsky), where the registered points range from 11 to 20 dysfunctional points. The proportion of dysfunctional points in this zone is 42% of their total number;

- The fourth group consisted of two districts (Vilyuysky and Megino-Kangalassky), where more than 21 dysfunctional points were established.

It should be noted that horse leptospirosis prevails in all groups. So, in the 1st group the number of dysfunctional points for horses is 65.7%, in the 2nd - 71.7, in the 3rd - 55.3, in the 4th - 53.1%. The proportion of dysfunctional points in the cattle in the 3rd group is 38.3%, in the 4th - 34.7%, in the 1st - 20%, in the 2nd - 19.6%. The largest number of dysfunctional points in the small cattle was noted in the 1st group - 14.3%, in the 3rd - 2.1, in the 4th - 2%. The largest number of dysfunctional points for pigs was noted

in the 3rd and 4th groups - 14.3%, in the 3rd - 2.1, in the 4th - 2%.

Thus, preliminary evaluations of epizootological zoning indicate that foci of concentration of a large number of horses and cattle are territories of risk for the occurrence and spread of leptospirosis.

The epizootic manifestations of leptospirosis in the Central zone of Yakutia are of particular note. They currently accounted for 80% of the total number in the republic; in the Arctic and North-Eastern zones - by 7.5%, in the Western and Southern zones - by 2.5%.

From a zoological and epidemiological position (for the period 2009-2018), 5911 specimens of mouse rodents were studied for natural foci, the contamination of which in some years was determined by ELISA: 2.03 - 2.7% of cases, and by PCR: among red voles - 0.38%, root voles - 1.9% and in narrow-crested voles - 5%.

Contamination of people occurred in natural and anthropogenic foci with leptospira serogroups *L. icterohaemorrhagiae*, *L. grippityphosa* and *L. pomona*. Serological examination of the population showed a wider spread of infection than previously thought. Leptospira serogroup *L. pomona* (25.0%) prevailed in the rural population, and *L. canicola* (27.9%) in the urban population.

A retrospective analysis of the morbidity (Fig. 3) on the territory of the Republic Sakha (Yakutia) demonstrates certain temporal-episodic and epidemiological features of leptospirosis and their determining factors.

The methods of graphic retroanalysis adopted in epidemiology have established that the incidence of leptospirosis was mainly sporadic in nature, with an intensive rate per 100 thousand people ranging from 0.2-2.0. Outbreaks and group cases were relatively rare, and there was a pronounced territorial unevenness. The most intensive epidemic process took place in rural areas, where the incidence of residents of villages and towns (3.7 per 100 thousand people) was several times higher than the incidence of the urban population (0.4 per 100 thousand people). Infection of people occurred in natural and anthropogenic foci in which the main sources of leptospira serological groups of *L. icterohaemorrhagiae*, *L. pomona*, *L. grippityphosa* were cage breeding foxes, gray rats, root voles (*Microtus oeconomus*) and red voles.

The current features of assessing the degree of tension of the epidemic situation include the facts of its "mitigation", when at the ascertaining of leptospira circulation among small mammals, there is no morbidity in the population, and no positive results were found in pool studies of materials from people (89 people). A similar situation was noted (2019) in other subjects of the Far Eastern Federal District: Kamchatka, Primorsky Territory,

Jewish Autonomous and Amur Regions [13, 14].

Assessing the past monthly dynamics of the incidence rate in the republic, it should be noted that, despite the relatively uniform intra-annual distribution of cases, the largest number of patients with leptospirosis was recorded in April-May. The reason for this was the outbreak of leptospirosis among the workers and maintenance staff of the fur farm and the Mastakh branch of the Mukuchinsky state farm of the Kobyai ulus, where the main etiological factor was the leptospira of the serogroup *L. pomona*, and arctic foxes of cage breeding were the source of infection.

Subsequently, during the examination of 287 persons admitted to the infectious and therapeutic departments of hospitals in Yakutsk, Neryungri, Verkhnevilyuysky, Kobuyaysky, Aldansky, Ust-Aldansky, Namsky, Khangalassky, Verkhoyansky, Ust-Maysky, Lensky, Megino-Kangalassky, Mirny and Oymyakonsky uluses with the diseases which are suspicious of leptospira, 96 individuals were revealed with serologically positive results in which titers of specific antibodies to leptospira of nine serological groups reached 1: 100-1: 3200. Taking into account the complex of clinical manifestations of the disease, the results of an epidemiological examination of foci and laboratory tests, the diagnosis of leptospirosis was established in 31 patients. In subsequent years, the designated group was not fixed.

In various age and occupational groups, the morbidity was not the same. To a large extent, it depended on the influence of the leading pathways and transmission factors, reflecting the forms and degree of contact of the population with sources of pathogens. Men at the age of 20-49 years were most at risk: fur farmers, livestock technicians and hunters. The etiological structure of patients represented by leptospira of 5 serological groups was dominated by *L. pomona* (41.9%), *L. grippityphosa* (25.8%) and *L. icterohaemorrhagiae* (19.3%).

Analysis of the epizootic situation shows that the average incidence rate, increasing from 2003 to 2008 (from 0.73 to 7.71), since 2009 has tendency to a

relative decrease (from 0.34 to 3.54). This may be due to an increase of 3 times in the annual vaccination coverage of farm animals against leptospirosis over 10 years and reached 384.407 goals in 2018.

Thus, due to the systematic, planned, correct organizational and health-improving work of veterinary specialists, the number of dysfunctional points decreased by 19 times, determining the relatively positive epizootiological and epidemiological situation in livestock farms and among the population.

Conclusion. Thus, thanks to the systematic, planned, properly set organizational and health-improving work of veterinary specialists, the number of dysfunctional points decreased by 19 times, determining the relatively positive epizootiological and epidemiological situation in livestock farms and among the population.

The materials presented indicate the need for further monitoring of the established facts and the identified clinical and laboratory, epizootological and epidemiological imbalances in the identified problem.

The choice of adequate and informative methods of laboratory-clinical research and expert assessments should be based on modern ideas about the epizootiological, epidemiological, clinical-laboratory and monitoring algorithm, which will make it possible to maximally objectify agricultural losses (damage) and the degree of percentage disability among the population with various forms of the disease.

References

1. Троп И.Е., Сергеев А.Ф., Тугутов Л.Д. [и др.]. Активное выявление, диагностика и профилактика лептоспироза в Якутии. Медицинская наука – практика (методические разработки, рекомендуемые для широкого внедрения в медицинскую практику. Новосибирск. 1990: 204-206. [Trop IE, Sergeev AF, Tugutov LD [et al.]. Active detection, diagnostics and prophylaxis of leptospirosis in Yakutia. Medical science, practice (methodological developments recommended for wide implementation in medical practice). Novosibirsk, 1990: 204-206. (In Russ.).]
2. Троп И.Е., Чернявский В.Ф., Сергеев А.Ф. [и др.]. Активное выявление, диагностика и профилактика лептоспироза в Якутии. Якутская республиканская СЭС и Хабаровский НИИ эпидемиологии и микробиологии. Якутск; Хабаровск, 1990: 9. [Trop IE, Chernyavsky VF, Sergeev AF [et al.]. Active detection, diagnostics and prophylaxis of leptospirosis in Yakutia. Yakut Republican SES and Khabarovsk Research Institute of Epidemiology and Microbiology. Yakutsk; Khabarovsk, 1990: 9. (Rotoprint) (In Russ.).]

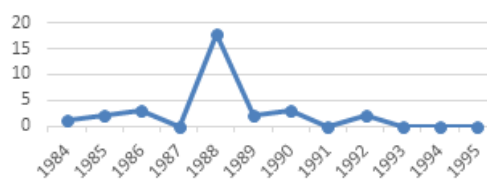


Fig. 3. Leptospirosis morbidity in the RS (Ya)

3. Троп И.Е., Чернявский В.Ф., Сергеев А.Ф. [и др.]. Активное выявление, диагностика и профилактика лептоспироза в Якутии. АМН СССР. СО АНМ СССР. Министерство здравоохранения РСФСР. Медицинская наука, практика (методические разработки рекомендуемые для широкого внедрения в медицинскую практику). Новосибирск, 1991: 49-58. [Trop IE, Chernyavsky VF, Sergeev AF [et al.]. Active detection, diagnostics and prophylaxis of leptospirosis in Yakutia. USSR Academy of Medical Sciences. SB ASM USSR. Ministry of public health of RSFSR. Medical Science, practice (methodical developments, recommended for wide implementation in medical practice). Novosibirsk, 1991:49-58. (In Russ..)]
4. Егоров И.Я., Федуллова Л.Г., Кочетова Т.И. Эпидемиологические особенности инфекционных и паразитарных заболеваний в Республике Саха (Якутия). Якутск, 1994: 34. [Egorov IYa, Fedulova LG, Kochetova TI. Epidemiological features of infectious and parasitic diseases in the Republic Sakha (Yakutia). Yakutsk, 1994: 34. (In Russ..)]
5. Карасева Е.В., Коренберг Э.И. Результаты серологических исследований сывороток крови от грызунов Центральной Якутии. Десятое совещание по паразитологическим проблемам и природно-очаговым болезням. Москва, 1959;1:123-124. [Karaseva EV, Korenberg EI. Results of serological research of blood sera from rodents of Central Yakutia. 10th meeting on parasitological problems and natural-focal diseases. Moscow, 1959; 1:123-124. (In Russ..)]
6. Коренберг Э.И. Сущность и значения понятия «Лоймопотенциал». *Медицинская паразитология и паразитарные болезни*. 2010; 4: 22-24. [Korenberg EI. Essence and Meanings of the Concept of "Loimopotential". *Medicinskaya parazitologiya i parazitarnye bolezni*. 2010; 4: 22-24. (In Russ..)]
7. Мефедьев В.В. Эпидемиологические наблюдения в очагах лептоспирозов Тюменской области и меры оздоровления антропогенного очага: Автореф. дис. ...канд.мед.наук. Ростов-на-Дону, 1966: 24. [Mefediev VV. Epidemiological observations in the leptospirosis foci of Tyumen region and measures of the anthropogenic focus recovery: PhD author's abstract. Ros-tov-on-Don, 1966:24. (In Russ..)]
8. Макарова Л.И., Никитина А.А. Об обеспечении стойкого эпизоотического ветеринарного благополучия в Республике Саха (Якутия). Междунар.научн.практ.конф. Современные проблемы и инновационные тенденции развития аграрной науки. г.Якутск, 10 ноября 2010:368. [Makarova LI, Nikitina AA. On ensuring a stable epizootic veterinary welfare in the Republic Sakha (Yakutia). International Scientific Conference on Modern Problems and Innovation Trends in Agricultural Science. Yakutsk, November 10, 2010:368. (In Russ..)]
9. Троп И.Е., Сергеев А.Ф., Чернявский В.Ф. [и др.]. Материалы комплексных исследований лептоспирозной инфекции в районах Якутской АССР. *Вопросы региональной гигиены, санитарии и эпидемиологии*. Якутск, 1990: 83-87. [Trop IE, Sergeev AF, Chernyavsky VF [et al.]. Materials of complex studies of leptospirosis infection in the regions of the Yakut ASSR. *Voprosy regional'noj gigieny, sanitarii i epidemiologii*. Yakutsk, 1990: 83-87. (In Russ..)]
10. Егоров И.Я., Марамович А.С., Чернявский В.Ф. [и др.]. Медицинские и социально-экологические проблемы в зоне строительства Амуро-Якутской железнодорожной магистрали (АЯМ). Параметры транспортных систем Республики Саха (Якутия). Якутск, 1995: 67-69. [Egorov IYa, Maramovich AS, Chernyavsky VF [et al.]. Medical and socio-ecological problems in the Amur-Yakutsk Railway (AYAM) Construction Zone. Parameters of Transport Systems of the Sakha Republic (Yakutia). Yakutsk, 1995: 67-69. (In Russ..)]
11. Нафеев А.А. Оценка эпидемиологического потенциала – основа мониторинга природно-очаговых инфекций. Сообщение 2. Лептоспирозы, иксодовые клещевые боррелиозы, туляремия. *ЗНИСС*, 2007; 6: 32-34. [Nafeev AA. Epidemiological potential assessment - basis for monitoring of natural-focal infections. Message 2. Leptospiroses, ixodic tick-borne borrelioses, tularaemia. *ZNISS*, 2007; 6: 32-34. (In Russ..)]
12. Нафеев А.А. Мониторинг – основа эпидемиологического надзора за природно-очаговыми инфекциями. *Сибирь-Восток*. 2003; 12:3-4. [Nafeev AA. Monitoring - the basis of epidemiological supervision over natural-focal infections. *Sibir'-Vostok*. 2003; 12: 3-4. (In Russ..)]
13. Нафеев А.А. Эпидемиолого-эпидемиологический надзор за природно-очаговыми инфекциями. *Здоровье людей и сфера обитания*. 2009; 2:16-19. [Nafeev AA. Epidemiological supervision over natural-focal infections. *Zdorov'e lyudej i sfera obitaniya*. 2009; 2:16-19. (In Russ..)]
14. О прогнозе изменения численности грызунов, насекомоядных и эпизоотического состояния по туляремии, ГЛПС, лептоспирозу и др. Роспотребнадзор РФ. Москва, 2019: 36. [On the forecast of changes in the number of rodents, insectivores and epizootic state for tularaemia, HFRS, leptospirosis etc. Rosпотребнадзор of Russia. Moscow, 2019: 36. (In Russ..)]
15. Сергеев А.Ф., Троп И.Е., Чернявский В.Ф. [и др.]. Лептоспирозы в Якутии. *Вопросы региональной гигиены, санитарии и эпидемиологии*. Якутск, 1987: 173-175. [Sergeev AF, Trop IE, Chernyavsky VF [et al.]. Leptospiroses in Yakutia. *Voprosy regional'noj gigieny, sanitarii i epidemiologii*. Yakutsk, 1987: 173-175. (In Russ..)]
16. Егоров И.Я., Макеев С.М., Марамович А.С. [и др.]. Сероэпидемиологическая разведка на лептоспирозы в центральной и южной Якутии. *Гомеостаз и инфекционный процесс*. Ч. 1. Саратов, 1996: 102-103. [Egorov IYa, Makeev SM, Maramovich AS [et al.]. Sero-epidemiological exploration on leptospiroses in central and southern Yakutia. *Gomeostaz i infekcionnyj process*. Ch. 1. Saratov, 1996: 102-103. (In Russ..)]
17. Чернявский В.Ф., Егоров И.Я., Теленков С.С. [и др.]. Система санитарно-эпидемиологической оценки профессионального риска природно-очаговых (зооантропонозных) инфекций. Актуальные проблемы охраны труда в Республике Саха (Якутия): Материалы межрегиональной научно-практической конференции. Якутск, 2006: 169-170. [Chernyavsky VF, Egorov IYa, Telenkov SS [et al.]. System of sanitary-epidemiological estimation of professional risk of natural-foci (zoanthroposis) infections. Actual problems of labour protection in Republic Sakha (Yakutia): Materials of inter-regional scientifically-practical conference. Yakutsk, 2006: 169-170. (In Russ..)]
18. Софронова О.Н., А.Ф. Тупицина, В.Ф. Чернявский Организация лабораторной диагностики лептоспирозов с использованием референс-штаммов. Титульное издание: издательство Якутского гос. университета. Якутск, 2000: 27. [Sofronova ON, Tupitsina AF, Chernyavsky VF. Organization of laboratory diagnostics of leptospiroses with use of reference-strains. Title edition: publishing house of Yakut state university. Yakutsk, 2000:27. (In Russ..)]
19. Токарев К.Н., Тимофеева С.С., Полова Е.М. Материалы о лептоспирозах в заполярье. Тр. Ленингр. ин-та эпидемиол. и микробиол. им Пастера. Ленинград, 1963; 25:270-276. [Tokarevich KN, Timofeeva SS, Popova EM. Materials about leptospiroses in polar region. Leningr. Institute of epidemiol. and microbiol. named after Paster. Leningrad, 1963; 25:70-276. (In Russ..)]
20. Тугутов Л.Д., Сергеев А.Ф., Чернявский В.Ф., Троп И.Е. Видовой состав и численность грызунов в очагах лептоспирозов в центральной Якутии. *Вопросы региональной гигиены, санитарии и эпидемиологии*. Якутск, 1987: 175-177. [Tugutov LD, Sergeev AF, Chernyavsky VF, Trop IE. Species composition and number of rodents in centers of leptospiroses in the central Yakutia. *Voprosy regional'noj gigieny, sanitarii i epidemiologii*. Yakutsk, 1987: 175-177. (In Russ..)]
21. Егоров И.Я., Марамович А.С., Макеев С.М. [и др.]. Эпидемиологическая и эпизоотологическая характеристика лептоспироза в Якутии. *Медицинская паразитология и паразитарные болезни*. 1996;1: 43-47. [Egorov IYa, Maramovich AS, Makeev SM [et al.]. Epidemiological and epizootological characteristics of leptospirosis in Yakutia. *J. Medicinskaya parazitologiya i parazitarnye bolezni*. 1996; 1:43-47. (In Russ..)]
22. Макеев С.М., Марамович А.С., Чернявский В.Ф. [и др.]. Эпидемиолого-эпизоотологическое районирование территории и профилактика лептоспирозов в Дальневосточном федеральном округе. *Проблема опасных инфекций*. Саратов, 2007; 94: 24-27. [Makeev SM, Maramovich AS, Chernyavsky VF [et al.]. Epidemiological and epizootic zoning of the territory and prophylaxis of leptospirosis in the Far Eastern Federal District. *Problema opasnyh infekcij*. Saratov, 2007; 94: 24-27. (In Russ..)]
23. Макеев С.М., Марамович А.С., Кондаков А.А. [и др.]. Эпидемиологическая характеристика и мониторинг лептоспироза в Сибири и на Дальнем Востоке. *Current issues on zoonotic diseases*. 2010: 36-42. [Makeev SM, Maramovich AS, Kondakov AA [et al.]. Epidemiological characterization and surveillance for leptospirosis in Siberia and at the Far East. *Current issues on zoonotic diseases*. 2010: 36-42. (In Russ..)]

T.M. Klimova, A.G. Egorova, A.G. Fedulova, A.A. Kuzmina,
I.Sh. Malogulova, M.S. Novikova, N.I. Gorshenin

BEHAVIOURAL DETERMINANTS OF DIPHYLLOBOTHRIASIS IN SAKHA REPUBLIC'S POPULATION

DOI 10.25789/YMJ.2020.70.16

УДК 616-002.951.21; 613.281

Diphyllobothriasis is an endemic disease for the Republic of Sakha (Yakutia), the prevalence of which remains at a high level (136.8 per 100,000 of the population in 2018). The study aims to analyse the behavioural factors contributing to the spread of diphyllobothriasis in Yakutia. The survey was carried out using social networks. The study involved 1021 people (815 women and 206 men) from Yakutsk and 32 municipal districts of the Republic of Sakha (Yakutia). The study showed among the population of the republic are preserved the traditions of eating raw fish and homemade salting fish. The part of the fish gets bypassing sanitary control. Technologies of homemade salting and cooking of fish are violated. The population is not well informed about the danger of infection with fish parasites and preventive measures.

We need the widespread introduction of wastewater disinfection technologies, improving the quality of treatment, monitoring fish products, conduct a qualitative helminthological examination of the population, verification of the effectiveness of deworming and inform the population about the methods for preventing parasitic infection.

Keywords: helminthiases, biohelminths, diphyllobothriasis, Yakutia, behavioural risk factors.

Diphyllobothriasis is a group of intestinal biohelminthoses, the causative agents of which are tape helminths of the class *Cestoidea*, *Diphyllobothrium* (*D.*) family. In the life cycle of helminth, copepods act as the first intermediate host, and fish as the second [8–10]. The final host is man, as well as some animals and birds that eat fish. About 14 out of more than 50 types of diphyllobothriids can be dangerous for humans [10]. Human infection occurs when eating fish with helminth larvae. Helminthiasis is found in many regions of the world, including North and South America, Europe, and Asia [10]. Parasites have epidemiological significance in Russia, Japan, and South America [1-3, 5-7]. According to experts, the number of people infected with tapeworms can reach 20 million in the world [10].

In Siberia and the Far East of Russia, according to Yastrebova V.K., the most common types of diphyllobothriids are *D. latum*, *D. dendriticum*, *D. klebanovs-*

kii (*D. luxi*), *D. ditremum* [5]. *D. latum* is currently considered the main causative agent of human diphyllobothriasis. For the Sakha Republic, Diphyllobothriasis is an endemic disease (1318 cases of the disease or 136.8 per 100,000 of the population in 2018), as evidenced by a comparison of incidence rates in the subjects of the North-East of the Russian Federation. Thus, according to the territorial bodies of the Federal Service for the Oversight of Consumer Protection and Welfare (Rosпотребнадзор), in 2018, 160 cases of diphyllobothriasis were recorded in the Irkutsk Region, 102 in the Republic of Buryatia, 22 in the Sakhalin Region, 15 in the Jewish Autonomous Region and 12 in the Amur Region, 5 in the Primorsky Territory, 2 in the Chukotka Autonomous Region, and 1 in the Kamchatka Region. In 2018, diphyllobothriasis (25%) takes 2nd place in helminthiases general incidence in Yakutia, after enterobiosis (70%) [2].

The main factors determining the spread of helminthiases, including diphyllobothriasis, are the levels of socio-economic development of territories and sanitary and hygienic training of the population. Thus, the spread of invasion is facilitated by the tradition of using raw or semi-raw fish, as well as an increase in the market of poor-quality fish products due to the absence or low quality of wastewater treatment (at the sewage treatment facilities of the republic).

Research Objective – studying the behavioural factors contributing to the spread of diphyllobothriasis in the Sakha Republic.

Materials and Research Methods. For the analysis, we used the data of the reports “On the State of the Environment and Environmental Protection of

the Sakha Republic in 2018 (<https://minpriroda.sakha.gov.ru>) and “On the State of Sanitary and Epidemiological Welfare of the Population in 2018” in the north-eastern regions of the Russian Federation (<http://rospotrebnadzor.ru>).

To assess the habits of the population contributing to the infection of diphyllobothriasis, a survey of available respondents was conducted using social networks. The study involved 1021 people (815 women and 206 men) from Yakutsk and 32 municipal districts of the Sakha Republic. The questionnaire included 16 questions devoted to various aspects of eating, cooking, and harvesting fish, as well as public awareness of measures to prevent infection with fish parasites.

Results. Analysis of the dynamics of morbidity of the population of the Sakha Republic by diphyllobothriasis over 15 years (2004-2018) showed a 2-fold decrease in rates from 264.9 to 136.8 per 100,000 population [2]. The true number of carriers of the parasite is probably significantly higher than official statistics. This is due to the lack of mandatory helminthological examinations, a pronounced clinical picture of infection, the over-the-counter selling of praziquantel (which is the drug of choice for diphyllobothriasis) and frequent self-medication among the population. Thus, the statistics reflect only cases of detection of diphyllobothriasis when visiting medical institutions and when examining maternity groups.

A survey to study consumer behaviour was conducted from May 25th, 2019 to June 9th, 2019. The main participants in the study were people of working age (Table). Of the respondents, 89% were born in Yakutia, 11% came from other regions of the Russian Federation. Of

Medical Institute, the M.K. Ammosov NEFU: **KLIMOVA Tatiana Mikhailovna** – Candidate of Medical Sciences, Associate Professor; Senior Scientist at Yakutsk Scientific Centre for Complex Medical Problems, biomedtykt@mail.ru. ORCID: 0000-0003-2746-0608. **FEDULOVA Aleksandra Georgievna** – Associate Professor, **KUZMINA Ariana Afanasyevna** – Candidate of Pharmaceutical Sciences, Head of Department, ORCID: 0000-0001-5220-0766, **MALOGULOVA Irina Shamilyevna** – Candidate of Biological Sciences, Associate Professor, ORCID: 0000-0003-0687-7949, **NOVIKOVA Margarita Semenovna** – senior student, **GORSHENIN Nikolay Igorevich** – senior student; **EGOROVA Aitalina Grigoryevna** – Candidate of Medical Sciences, Head of Laboratory at Yakutsk Scientific Centre for Complex Medical Problems.

these, 758 people (74.2%) lived in the city of Yakutsk, the rest were representatives of 32 municipal districts of Yakutia.

Eating Habits. The survey showed that 83% (852) of respondents consume raw frozen fish (in the form of a sliced planer and other dishes), while 67% (691) consume home-salted fish.

When asked, "Where do you get frozen or salted fish?", respondents indicated various sources (including a combination of different sources). Thus, 337 respondents purchase fish at local markets, 283 – at stores, 95 – at supermarkets, while 15 get it themselves (fishing). Also, in 618 cases, respondents mentioned that they were sent (treated) by friends or relatives. Thus, it should be assumed that a significant part of the fish consumed by the population does not pass sanitary control. Another question was, "When purchasing fish, do you ask for documents certifying the quality of the fish (veterinary certificate, the conclusion of a veterinary and sanitary examination)?" 88.1% (900) of respondents answered negatively. Only 12% (121) said they were interested in this.

Typical Fish Storing and Cooking. 62% (639 people) of respondents said they salted fish in their families at home. Of these, in 75% (478) cases, the fish is lightly salted, in 25% (161) the fish is highly salted. At the same time, 115 respondents indicated that they salted the fish for several minutes or hours, 331 – during the period from 1 to 2 days, 190 – from 2 to 4 days, and 3 – 5 or more days. These results indicate that local fish salting violates processing technologies that ensure product safety.

When cutting fish, 35% (356) of respondents have seen parasite larvae at least once. Of these, 28 noted that they discarded the infected part of the fish and continued to cook the remaining parts. Only 15.6% of buyers return the fish with contaminants to the seller (the presence of inclusions, larvae, etc.). The remaining percentage throw away the infected fish.

Public Awareness of Hygienic Preventive Measures. When asked, "Can frozen fish be a source of helminth infection?", 60% (607) of respondents answered in affirmatively, while 24% (174) denied this possibility; 17% (240) did not have a definite opinion (figure). Also, about 40% of respondents do not know that objects used in cutting contaminated fish can be dangerous. It is likely that 80% of respondents taste the fish in the cooking process (frying, boiling, or baking). Last year, 69.8% of respond-

Characteristics of Respondents

Group	n	%
Age, years	41	4.0
18-24	347	34.0
25-35	213	20.9
36-45	115	11.3
46-55	180	17.6
Over 55	125	12.2
Years spent in the Sakha Republic		
Under 5	37	3.6
5-9	22	2.2
10-14	6	0.6
15-20	26	2.5
Born in the Sakha Republic	904	88.5
Other	26	2.5

ents underwent microscopic examination for helminth eggs (faeces analysis) was carried out during the last year.

Thus, the survey results showed that among the population of the republic preserves its traditions of eating raw, home-salted fish. As a result, too often the fish ends up on the table bypassing sanitary control. When using at-home salting and cooking, our population violates fish processing technologies. The population is not well informed about the danger of infection with fish parasites and about the related preventive measures.

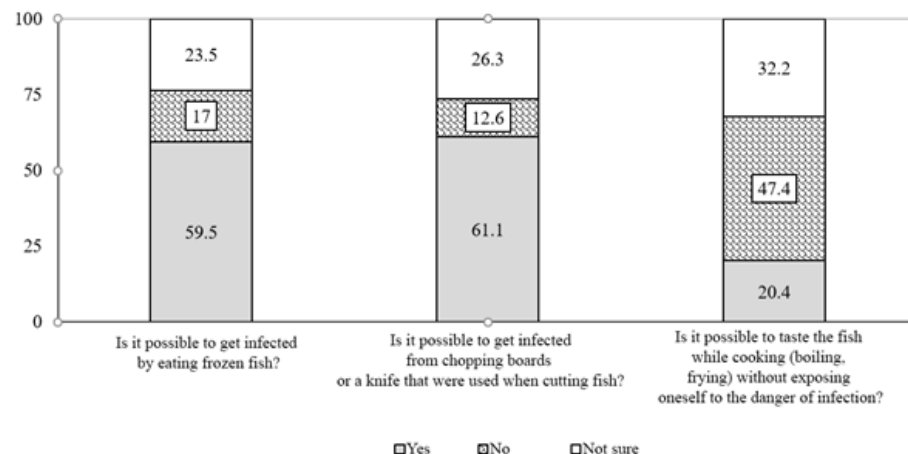
Discussion. Lack of treatment and disinfection of wastewater and frequent flooding of local settlements lead to the ingress of helminth eggs into water bodies. According to the Ministry of Ecology, Nature Management and Forestry of the Sakha Republic, in 2018, the republic had 28 treatment facilities (of which 20 were biological, 7 were mechanical, and 1 was physico-chemical). Some districts do not have wastewater treatment facilities, and in many areas, the technical condition of the facilities and outdated technologies do not provide regulatory

wastewater treatment. According to To-noeva N.C. et al. [4], treatment methods at the sewage facilities in Yakutsk (biological treatment) also do not ensure epidemiological safety of the water. When analysing samples of water and sediment from the n-filter after mechanical cleaning, we found ascaris and diphyllotriid eggs in 100% and 80% of cases, respectively. After repeated mechanical and biological treatment of water with activated sludge, the number of positive samples was 33% and 17%, after exposure to ultraviolet radiation – 18% and 9%, respectively.

The prevalence of diphyllotriasis among the population of Yakutia is caused by the characteristics of the traditional nutrition of the population, insufficient awareness of the risks of infection, and socio-economic factors. A low standard of living contributes to the search for other food sources, including independent fishing, the acquisition of fish from sellers without permits, and the use of home-made fish products. The tradition of eating raw fish, the ambiguous, non-specific symptoms during infection, low diagnostic efficiency, lack of control after deworming all lead to helminth prevalence. In addition, the widespread popularity of Southeast Asian cuisine using raw fish may become an additional risk factor for diphyllotriasis, which can change the spectrum of diphyllotriids circulating in Yakutia.

Conclusion. In the Sakha Republic, diphyllotriasis is an endemic helminthiosis, the spread and preservation of which is facilitated by socioeconomic and behavioural factors. These include a low standard of living, low sanitary and hygienic culture, violation of sanitary and hygienic standards, food traditions of the peoples of the North, and insufficient public awareness.

At the moment, to change the situ-



Awareness of the Sakha Republic's Population on Diphyllotriasis Preventive Measures

ation with the prevalence of diphyllorhosis in the Sakha Republic, we require the organisation of local water treatment devices in rural areas, the widespread introduction of modern technologies for wastewater disinfection (use of purification, ultraviolet radiation, and track-etched membranes), and the strengthening of fish product quality control measures. We also require qualitative helminthological examination of the population, monitoring the effectiveness of deworming and informing the population about methods of preventing infection with fish parasites. Conducting molecular genetic studies to confirm the fact that there are no errors in identifying *D. latum* as the sole or main causative agent of human diphyllorhosis in Yakutia holds scientific and practical importance. If other species of tapeworms of the Diphyllorhium family are found in the Yakutian population, we may require additional changes to the preventative programs.

References

1. Зеля О.П., Завойкин В.Д., Плющева Г.Л. Современная ситуация по дифиллоботриозу: эпидемиология и эпиднадзор. *Медицинская паразитология и паразитарные болезни*. 2017; 1: 52-59. [Zelja O.P., Zavoikin V.D., Pljushheva G.L. The Current Situation of Diphyllorhosis: Epidemiology and Epidemiological Surveillance. *Medicinskaja parazitologija i parazitarnye bolezni*. 2017; 1: 52-59. (In Russ.)]
2. Поляков В.Е., Иванова И.А., Полякова Н.П. Дифиллоботриоз. *Педиатрия*. 2007; 86(5): 104-8 [Poljakov V.E., Ivanova I.A., Poljakova N.P. *Pediatrija*. 2007; 86(5): 104-108. (In Russ.)]
3. Савченков М.Ф., Чумаченко И.Г., Турчинова Д.А. Дифиллоботриоз в Байкальском регионе (эпидемиологическое наблюдение). *Сибирский медицинский журнал*. 2008; 3: 88-90. [Savchenkov M.F., Chumachenko I.G., Turchinova D.A. Diphyllorhosis in Baikal'sky region (epidemiologic observation). *Sibirskij medicinskij zhurnal (Irkutsk)*. 2008; 3: 88-90. (In Russ.)]
4. Тоноева Н.Ч., Удальцов Е.А., Ефремова Е.А. Санитарно-паразитологическое состояние реки Лена в границах города Якутска. *Российский паразитологический журнал*. 2018; 12(2): 38-45. [Tonoeva N.Ch., Udal'cov E.A., Efremova E.A. Sanitary-Parasitological Status of Lena River within the city of Yakutsk. *Rossijskij parazitologicheskij zhurnal*. 2018; 12(2): 38-45. (In Russ.)]
5. Ястребов В. К. Эпидемиология дифиллоботриозов в Сибири и на Дальнем Востоке. *Эпидемиология и вакцинопрофилактика*. 2013; 72(5): 25-30. [Jastrebov V. K. Epidemiology of Diphyllorhosis in Siberia and the Far East. *Jepidemiologija i vakcinoprofilaktika*. 2013; 72(5): 25-30. (In Russ.)]
6. Lucas C., Fung L., Gagliardi S.M.B. [et al.] Diphyllorhosis, Brazil. *Emerg Infect Dis*. 2005; 11(10): 1598-1600. doi: 10.3201/eid1110.050377
7. Ikuno H., Akao S., Yamasaki H. Epidemiology of Diphyllorhosis *nihonkaiense* Diphyllorhosis, Japan, 2001-2016. *Emerg Infect Dis*. 2018; 24(8): 1428-1434. DOI: 10.3201/eid2408.171454
8. Muller R. Worms and Human Disease 2nd Edition. CABI Publishing; 2002; 300.
9. Kuchta R., Brabec J., Kubáčková P. [et al.] Tapeworm Diphyllorhosis *dendriticum* (Cestoda)-Neglected or Emerging Human Parasite? *PLoS Negl Trop Dis*. 2013; 7(12): e2535. DOI: 10.1371/journal.pntd.0002535
10. Scholz T., Garcia H.H., Kuchta R. [et al.] Update on the human broad tapeworm (genus diphyllorhosis), including clinical relevance. *Clin Microbiol Rev*. 2009; 22(1): 146-160. DOI: 10.1128/CMR.00033-08



M.H Syahidi, N.V. Savvina, L.F. Timofeev, O.G. Bessonova

MORTALITY AND LOST YEARS OF LIFE (YLL) DUE TO BREAST, CERVICAL, AND OVARIAN CANCER IN THE REPUBLIC SAKHA (YAKUTIA) IN 2006-2016

DOI 10.25789/YMJ.2020.70.17

УДК 616-006.611-69

Introduction: Breast, cervical, and ovary cancer are the most common caused-of death cancer in women population in the world, so does in Russia. This study aims to depict breast, cervical, and ovary cancer mortality and years of life lost (YLL) trends in the Republic of Sakha (Yakutia) in the period 2006-2016.

Methods: Data were obtained through the database of the Republic of Sakha (Yakutia) federal state statistics service (Rosstat) which included with ICD-10 code for cause of death.

Results: There were 11.1% deaths caused by breast cancer, 6.9% by cervical cancer, and 4.6% caused by ovary cancer from all death caused by cancer in women population in the research period. YLL from those cancers respectively were 9032, 7796, and 4545 life years. Average years of life lost (AYLL) of those cancers were 13.4; 20.1; and 16.2 life years.

Conclusion: Mortality, YLL, and AYLL due to breast and ovary cancer decreased when those variables increased in cervical cancer. Based on YLL, cervical cancer is now leading to a greater number of deaths among younger generations of women in the Republic of Sakha (Yakutia). Breast cancer remains the dominant cause of cancer death.

Keywords: breast cancer, cervical cancer, ovary cancer, cancer in women, YLL, AYLL, mortality from malignant neoplasms, Republic of Sakha (Yakutia).

Introduction. Breast cancer becomes the second death-leading cancer in the world with 2.088.849 new cases and 626.679 deaths in 2018 when cervical cancer and ovary cancer also in the top list of death-leading cancer. Breast, cervical, and ovary cancer are the most common female malignancy cancer types causing death even though they are preventable [6, 10].

Different from breast cancer which incidence and mortality rate are higher in high-income countries, cervical cancer has higher prevalence in poor countries when prevalence of ovary cancer has almost the same regardless of the income of the countries [5].

In 2012, 528 000 new cases with 266.000 death of cervical cancer in women were diagnosed worldwide. 85% of the cases were in low-income countries.

Breast cancer and ovary cancer are in the list of leading-to death cancer with 20 and 6.8 death per 100000 women respectively in America 2016 [8].

In Iran, years of life lost from breast and ovary cancer are 94.216 and 26.430 life-years respectively. Premature mortality costs from those cancers are 149.933.799 and 38.398.286 US dollars [13].

In Norway, Average years life lost of cervical cancer is the highest among other cancer most frequent cancer in women (25 life years) when AYLL of ovary cancer is slightly higher than AYLL of breast cancer (around 16 life years) [6].

Breast, cervical, and ovary cancer are also problems in Russia and Republic of Sakha (Yakutia) [1, 2, 3]. Breast cancer average annual age-standardized incidence (ASIRs) was 41,8 per 100000 women in 2004-2008 and the value increased to 45,6 per 100000 women in 2009-2013. Lower than breast cancer in

in Republic of Sakha (Yakutia) in period 2006-2016.

Data was taken from Russian federal state statistics service (Rosstat). The data was provided with ICD-10 diagnosis to categorize group of calculated disease. We then filtered the mortality caused by breast cancer (C50), , and cervical cancer (C53), and ovary cancer (C56).

The following formula was used to calculate individual YLL [10]:

YLL individual = End point – Age at death

Where: YLL = Years of Life Lost

End point = Life expectancy of the population

Age of death = Age of death of individual

Life expectancy of the population data was taken from federal state statistic service record of Republic of Sakha (Yakutia).

The average YLL (AYLL) was calculated by using formula:

$$AYLL = \frac{\text{Всего YLL}}{\text{Общее количество смертей от рака среди женщин в 2006 – 2016 гг}}$$

both of those periods, ASIRs of cervical cancer was 12,3 and increased to 13,8 per 100000 women [4].

This study aims to depict breast, cervical, and ovary cancer mortality and years of life lost (YLL) trends in the Republic of Sakha (Yakutia) in the period 2006-2016.

Materials and Methods. This study is about Years of Life Lost (YLL) of breast, ovary, and cervical cancer in women aged equal or more than 18 years old

Results and Discussion. In the period 2006-2016, there were 763 (11,1%) deaths caused by breast cancer, 387 (6,9%) deaths from cervical cancer, and 280 (4,6%) deaths from ovary cancer from all death caused by cancer in women population. From those numbers of deaths, Years of Life Lost (YLL) from breast cancer were 9032 (13,5%) life years, 7796 (11,6%) life years from cervical cancer, and 4545 (6,8%) life years from ovary cancer. Average Years of Life

SYAHIDI Muhammad Habibi — Master student of public health and health care, the general hygiene and bioethics. 677016 Yakutsk, Oyunsky St., 27. E-mail: syahidi.habibi@gmail.com. **SAVVINA Nadezhda Valeryevna** – Doctor Med. Sci., professor, Medical institute SVFU of M.K. Ammosov, the department of public health and health care, the general hygiene and bioethics. E-mail: nadvsavvina@mail.ru. **TIMOFEEV Leonid Fedorovich** – Doctor Med. Sci., Medical institute SVFU of M.K. Ammosov, professor of chair of public health and health care, the general hygiene and bioethics. 677016 Yakutsk, Oyunsky St., 27. E-mail: tfnauka@mail.ru. **BESSONOVA Oksana Germanovna** – Postgraduate of public health and health care, the general hygiene and bioethics. 677016 Yakutsk, Oyunsky St., 27. E-mail:

Lost (AYLL) of breast cancer was 13,4 life years, cervical cancer was 20,1 life years, and ovary cancer was 16,2 life years.

The death rate of breast cancer decreased from 14,1 to 9,3 per 100000 women in the period 2006-2016. The occurrence also happens in death rate due to ovary cancer from 5,3 to 4,6 per 100000 women. In contrast, death rate of cervical cancer increases almost twice from 4,9 to 8,5 per 100000 women.

The percentage number of death caused by cervical cancer reaches its peak in the age group 30-34 years old. Death caused by breast cancer is most common in the age group 35-35 and 45-49. 13,3% of death caused by ovary cancer in age 25-29 and 18,8% in age 40-44 years old (Fig. 1).

Compared to percentage number of death in 2006, breast and ovary cancer mortality percentage decreases from 12,5% to 8,3% and 4,3% to 4,1% in 2016. In contrast, number of death of cervical cancer increases from 7,9% in 2006 to 12,3% in 2016. The trends are also the same with their YLL in those periods (Table).

AYLL of breast cancer is hovering in number 12,0-14,5 through 2006 until 2016. In the same periods, AYLL of cervical and ovary cancer increases from 18,2 to 20,1 life years and 16,8 to 18,6 life years (Fig. 2).

From the results, we can see that the YLL of cervical cancer has exceeded the YLL of breast cancer despite it has lower number of death. It has no different pattern in all of Russian area [4]. The analysis of YLL underlined the fact that cervical cancer is now leading to a greater number of deaths among younger generations of Russian women. Breast cancer remains as the major death leading cancer in Republic of Sakha, despite its decreasing percentage mortality numbers.

Compared to death rate of breast and ovary cancer of United of states in 2016, Republic of Sakha has lower death rate when cervical cancer is not included as leading death cancer in United States [8]. Death rate of breast cancer in Ukraine is higher than in Republic of Sakha, when the death rate of cervical cancer is the same in both places [12].

Breast, cervical, and ovary cancer were contributors to female cancer mortality in republic of sakha (Yakutia). Even though YLL and AYLL due to breast and cervical cancer decreased, those two variables still increase due to ovary cancer.

AYLL value indicates the number of average shorting life in a person with the disease. AYLL of breast and cervical can-

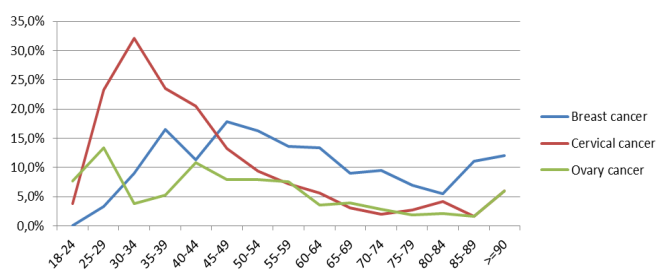


Fig. 1. The proportion of mortality from cancer of the breast, cervix and ovary from all cases of death from cancer in women in 2006-2016, in%

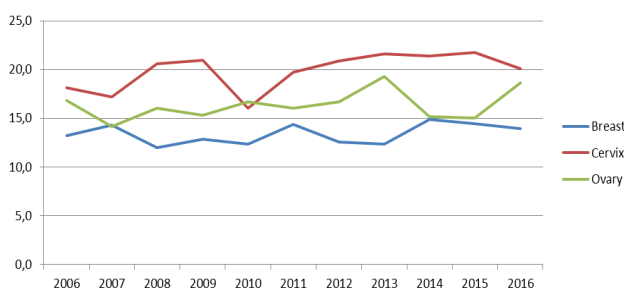


Fig. 2. Comparison of the average life years lost from cancer of the breast, cervix and ovary among oncological diseases in 2006-2016.

cer in Republic of Sakha is lower compared to their AYLL in Russia [4].

Some of the breast and cervical cancers factor risks are modifiable. alcohol use, excess body weight, and physical inactivity are included factor in causing breast cancer when smoking and unsafe sex contribute in occurrence of cervical cancer [9]. Healthy life-style behavior offers potential for reduction of their occurrence. In addition, primary prevention activity such as screening reduces chance of mortality case.

Conclusion. Trend of mortality, YLL, and AYLL due to breast and ovary cancer decreased in period 2006-2016 when those variables increased in cervical can-

References

1. Егорова А.Г., Климова Т.М., Романова А.Н. Региональные особенности заболеваемости и смертности от злокачественных новообразований в Республике Саха (Якутия). *Якутский медицинский журнал*. 2019; 2 (66): 86-88. [Egorova AG, Klimova TM, Romanova AN. Regional features of morbidity and mortality from malignant neoplasms in the Republic of Sakha (Yakutia). *Yakut Medical Journal*. 2019; 2 (66):86-88 (In Russ..)]
2. Афанасьева Л.Н., Гольдерова А.С., Бурнашева Л.С., Николаева Т.И., Мыреева С.А., Винокуров М.М., Макарова Н.Н., Иванов П.М. Злокачественные новообразования как важнейшая социально-экономическая проблема на Севере. *Якутский медицинский журнал*. 2019; (68):6-10. [Afanasyeva LN, Golderova AS, Burnasheva LS, Nikolayeva TI, Myreyeva

Comparative characteristics of mortality caused by specific cancer (breast cancer, cervical cancer and ovarian cancer), with YLL (YLL of each cancer / total YLL from death of all types of cancer)

Years	Death			YLL, %		
	Breast cancer	Cervical cancer	Ovary cancer	Breast cancer	Cervical cancer	Ovary cancer
2006	12.5	4.3	4.7	16.5	7.9	7.9
2007	11.1	5.5	4.5	16.6	10.0	6.6
2008	11.1	7.2	5.5	13.1	14.7	8.7
2009	12.0	5.6	4.5	15.1	11.4	6.8
2010	7.3	4.6	4.6	8.8	7.2	7.5
2011	12.0	5.8	4.3	14.4	9.6	5.7
2012	13.2	6.3	4.5	14.9	11.7	6.6
2013	10.9	8.3	3.6	12.0	16.1	6.3
2014	11.5	7.1	5.5	13.8	12.1	6.7
2015	12.1	7.7	5.0	14.1	13.5	6.1
2016	8.3	7.6	4.1	9.3	12.3	6.2

SA, Vinokurov MM, Makarova NN, Ivanov PM. Malignant neoplasms as the most important socio-economic problem in the North. *Yakut Medical Journal*. 2019; 4 (68): 6-10 (In Russ..)]

3. Каприн А.Д., Старинский В.В., Пертова. Злокачественные новообразования в России в 2017 году (заболеваемость и смертность). 2018: 131-133. [Kaprin AD, Starinskiy VV, Pertova. Malignant neoplasms in Russia in 2017 (morbidity and mortality). 2018: 131-133. (In Russ..)] Available at: http://www.oncology.ru/service/statistics/malignant_tumors/2017.pdf (Accessed: 4 January 2020).

4. Barchuk A [et al.] Breast and cervical cancer incidence and mortality trends in Russia 1980–2013. *Cancer Epidemiol*. 2018; 55: 73-80. DOI: 10.1016/j.canep.2018.05.008. URL: <https://www.ncbi.nlm.nih.gov/pubmed/29843073>

5. Broutet N., Eckert L.O., Bloem P. Comprehensive cervical cancer control. A guide to essential practice. Second edition. 2016: 137-142.

Brustugun O.T., Møller B., Helland A. Years of life lost as a measure of cancer burden on a national level. *Br. J. Cancer*. 2014; 5 (111):1014-1020. DOI: 10.1038/bjc.2014.364. URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4150272>

Danaei G [et al.] Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*. 2005; 9499 (366):17841793. DOI: 10.1016/S0140-6736(05)67725-2.

CDC. USCS Data Visualizations – CDC [Electronic resource]. URL: <https://gis.cdc.gov/Cancer/USCS/DataViz.html> (Accessed: 04.01.2020).

Federal State Statistics Service. Available at: <https://sakha.gks.ru>

Bray F [et al.] Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin*. 2018; 6 (68): 394-424. DOI: 10.3322/caac.21492.

WHO. WHO | Metrics: Disability-Adjusted Life Year (DALY). 2014. Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/ (Accessed: 5 January 2020).

World Health Organization. WHO Global Cancer Country Profiles: Ukraine // 2014. Available at: http://www.who.int/cancer/country-profiles/ukr_en.pdf?ua=1. (Accessed: 5 January 2020).

Khorasani S [et al.] Years of potential life lost and productivity costs due to premature cancer-related mortality in Iran. *Asian Pacific J. Cancer Prev*. 2015; 5 (16): 3. 1845-1850. DOI: 10.7314/APJCP.2015.16.5.1845.

L.P. Yakovleva, O.D. Kondratieva, M.N. Kondratieva

MAIN TRENDS IN THE INCIDENCE OF TUBERCULOSIS IN THE SAKHA REPUBLIC (YAKUTIA) OVER THE PERIOD FROM 2013 TO 2018

DOI 10.25789/YMJ.2020.70.18

УДК 616-002.5

The main trends in the tuberculosis (TB) incidence in the Sakha Republic (Yakutia), over the period from 2013 to 2018 were revealed.

The following rates were analyzed (based on reports from facilities subordinate to Ministry of Health of the Sakha Republic (Yakutia), and reports from all agencies irrespective of subordination): TB incidence rates among general population; TB incidence among adults; TB incidence among children and adolescents; TB incidence among urban and rural population; incidence of pulmonary TB; incidence of TB cases positive for M.tuberculosis (MTB); incidence of multidrug-resistant tuberculosis (MDR) in Sakha Republic (Yakutia) in the dynamics. Favorable epidemiologic situation for TB was observed. The obtained findings call for more improvements in conducting anti-TB activities among rural population, and comprehensive measures to decrease the incidence of MDR TB.

Keywords: tuberculosis, epidemiologic situation, incidence, incidence decrease rate.

Incidence rate of tuberculosis (TB) in general population is an important indicator used in analysis of epidemiologic situation of TB. Data on TB incidence serve an unbiased method for evaluating population health and changes in it, and also, one of measures used to assess the work of TB services and healthcare

facilities [4]. In view of this, monitoring of main trends in incidence rates over time is one of priority tasks, in terms of predicting the epidemiologic situation for TB and estimating quality of anti-TB care for population.

Aim: detect main trends in the TB incidence in the Sakha Republic (Yakutia), over the period from 2013 to 2018.

Methods: Based on reports from facilities subordinate to Ministry of Health of the Sakha Republic (Yakutia), and reports from all agencies irrespective of subordination, the following rates were analyzed: TB incidence rates among general population; TB incidence among adults; TB incidence among children and adolescents; TB incidence among urban and rural population; incidence of pulmonary TB; incidence of TB cases positive for M.tuberculosis (MTB); incidence of multidrug-resistant tuberculosis (MDR) in Sakha Republic (Yakutia) over the period from 2013 to 2018.

Data were extracted from national statistical reports and registries of persons with TB, collected and maintained within the scope of TB epidemiologic surveillance system of the

Phthisiatry Research-Practice Center.

Statistical data processing was performed using Excel 2010, and software packages Statistica-8 and Biostat. Time series analysis was performed, to calculate mean annual rates of increase/decrease. For trend construction, and detection of tendencies in TB incidence, we calculated 5-year rates of increase and mean increase rates, performed time series fitting using quadratic approximation function, and calculated R-squared (R²) coefficient.

Results: Incidence of TB in the Sakha Republic (Yakutia) (statistical form no. 8, including reports from all agencies irrespective of subordination) was 29% lower in 2018, compared to 2013 (54.2 per 100000 pop.). It was also 18.1% higher than the average rate in Russia (44.4), and 26.8% lower than the rate in Far-East Federal District (74.1). Over the 5-year study period, the largest decrease rate was observed in 2016 (-15.2%), the lowest – in 2015 (-1.1%); mean decrease rate was -7.1%. As is seen in Fig.1, there is a negative linear trend with R² value of 0.94, which suggests the existence of marked stable tendency to decrease in

YAKOVLEVA Ludmila Petrovna – Cand.Sci. (Medicine), Head of Republican Tuberculosis Treatment and Prevention Clinic, State-Funded Institution of the Sakha Republic (Yakutia), Phthisiatry Research-Practice Center, 677015, Sakha Republic (Yakutia), Yakutsk, ul. Petra Alekseeva 93, email: lpyak95@mail.ru Phone (office) +7(411) 44-80-33; **KONDRATIEVA O.D.** – Head of Tuberculosis monitoring office, State-Funded Institution of the Sakha Republic (Yakutia), Phthisiatry Research-Practice Center, 677015, Sakha Republic (Yakutia), Yakutsk, ul. Petra Alekseeva 93, email: rptd00@mail.ru Phone (office) +7(411) 44-80-37; **KONDRATIEVA M.** – medical statistician, Tuberculosis monitoring office, State-Funded Institution of the Sakha Republic (Yakutia), Phthisiatry Research-Practice Center, 677015, Sakha Republic (Yakutia), Yakutsk, ul. Petra Alekseeva 93, email: rptd00@mail.ru Phone (office) +7(411) 44-80-37

TB incidence in general population.

Based on reports from facilities subordinate to the Ministry of Health of the Sakha Republic (Yakutia) (form no. 33), TB incidence has declined by 29.4% over the study period (from 69.6 to 49.1 per 100000 pop.); it was 21.6% higher than the rate in Russia (38.5), but 24% lower than in the Far-East Federal District (64.6). Incidence decrease rate had been varying from -2.2% (2017) to -9.6% (2016); mean decrease rate was -6.4%. Overall, during the study period, there was a negative linear trend with high R2 value (0.98), i.e. a noticeable stable trend to decrease was observed.

TB incidence among adult population of Yakutia had decreased from 84.9 to 60.9 (per 100000), i.e. by 28.3%. Mean incidence decrease rate was -6.4%; the lowest and highest decrease rates were observed in 2017 (-2.4%) and 2016 (-9.5%), respectively. Over the study period, there was an observable negative linear trend with R2=0.96, signifying an apparent stable tendency to decreasing incidence of TB in adults.

Incidence of TB in children is one of key indicators of epidemiologic situation for TB [1]. In 2018, child incidence of TB in Yakutia was 33.6% lower, compared to 2013 (15.0 per 100000 pediatric population); it was 14.8% lower than in Far-East Federal District (17.6), but 44.7% higher than the same in Russia (8.3). Upsurges were observed in 2014 and 2016 (increase rates of 4.4 and 1.0%, respectively). Nevertheless, an observed negative polynomial trend with R2=0.96 along with the mean decrease rate of -7.5% speak for the presence of pronounced stable tendency to decrease in child TB incidence (Fig. 2).

Incidence of TB in adolescents declined by 20.7% (from 51.1 to 40.5, per 100000 adolescent population); mean decrease rate was -0.6%. This rate showed no tendency to decrease (R2=0.03), and the increase/decrease rate varied substantially, from 51.1% (2017) to 29.1% (2018).

Over the period from 2013 to 2018, incidence of TB in urban residents exceeded the incidence among rural population of Yakutia, although decrease rate was higher in urban population (Fig. 3). Urban incidence of TB was 41.2% lower in 2018 compared 2013 (52.2 per 100000 urban pop.). Rates of decrease were varying from -2.4% (2017) to -19.3% (2014); increase rate of 8.1% was observed in 2015 (from 71.6 to 77.4, per 100000 urban pop.); mean decrease rate was -9.5%. Over the 5-year period, negative polynomial trend with R2=0.86 was ob-

served, suggesting markedly stable tendency to decrease in urban TB incidence.

Incidence of TB in rural residents had decreased from 2013 to 2018 by 16.5% (from 60.6 to 50.6, per 100000 rural pop.), with the upsurges in 2014 (increase rate 13.0%) and in 2017 (minor increase rate 0.2%). Mean decrease rate was -2.7%, which, along with overall trends observed for the study period, such as polynomial trend with R2=0.63, speaks for moderate unstable tendency to decrease in rural TB incidence.

Pulmonary TB, invariably prevailing in the incidence structure, has a defining impact on the epidemiology of TB infection [3]. In Yakutia, over the last 5 years, 94.3 to 98.3% of all TB incidence was due to pulmonary TB.

Incidence of pulmonary TB in Yakutia, for the years 2013-2018, showed a negative linear trend with R2 of 0.98, suggesting strong stable tendency to decrease. Over the last 5 years, it decreased by 27.3%; mean decrease rate was -6.1%. The lowest decrease rate was observed in 2017 (-2.8%), the highest – in 2018 (-8.9%).

Incidence of MTB-positive pulmonary TB in Yakutia, over the study period, decreased by 12.3% (from 34.1 to 29.9), with an increase by 0.9% in 2014. Rates of decrease ranged

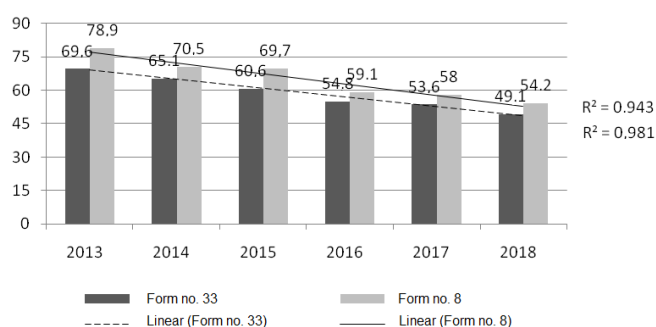


Fig. 1. Trends in incidence of tuberculosis among general population, Sakha Republic (Yakutia), 2013-2018 (statistical form no. 8 including all agencies, and form no. 33, per 100000 population).

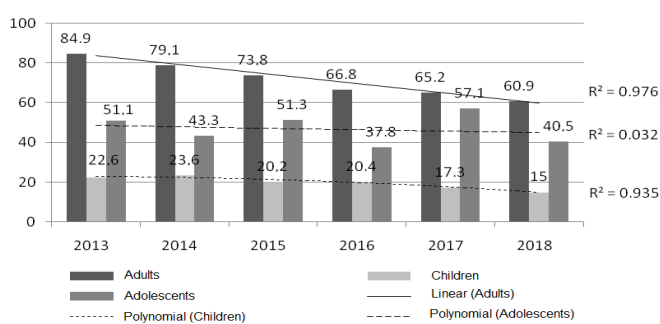


Fig. 2. Trends in tuberculosis incidence in adult, child and adolescent population, Sakha Republic (Yakutia), 2012-2017 (form no. 33, per 100000 pop.).

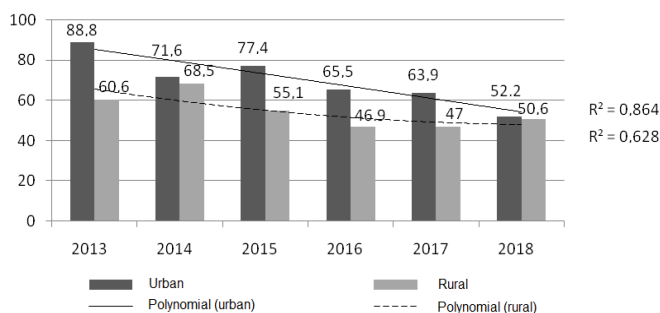


Fig. 3. Trends in incidence of tuberculosis among urban and rural population, Sakha Republic (Yakutia), 2013-2018 (form no. 33, per 100000 pop.).

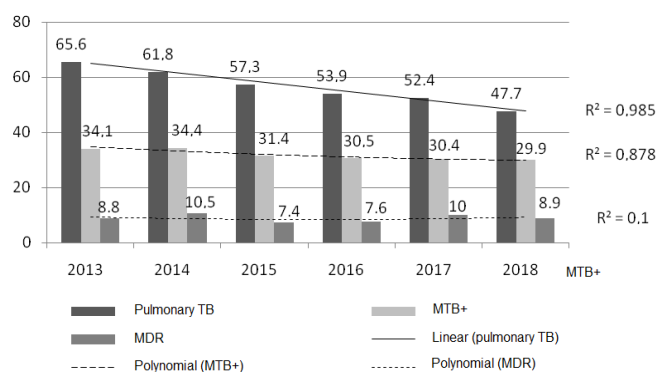


Fig. 4. Trends in incidence of pulmonary tuberculosis, MTB-positive tuberculosis, and multidrug-resistant tuberculosis, Sakha Republic (Yakutia), 2013-2018 (Form no. 33, per 100000 pop.).

from -0.3% (2017) to -8.7% (2015); mean decrease rate was -2.5%. A 5-year negative polynomial trend with $R^2=0.88$ suggests moderate stable tendency to decrease.

Incidence of primary MDR in new patients is an important measure of quality of TB diagnosis and treatment [2, 5]. Unlike the two above indicators, incidence of MDR TB in Yakutia, over the 5-year period, had no trend to decrease (Fig. 4). Compared to 2013, there was an increase by 1.1% (from 8.8 to 8.9, per 100000 pop.), while decreases were observed only in 2015 and in 2018 (by 29.5% and 11.0%, respectively). Mean increase rate in the incidence of MDR TB over the study period was 2.6%. This could be explained by better diagnosis, larger coverage of new patients with pulmonary TB with rapid tests for drug sensitivity, and timely notification of cases of MDR TB. As an example, in 2013, drug-sensitivity tests before therapy were performed in 89.6% of patients, while in 2017, the coverage was already 98.6%, and 97.2% in 2018.

Conclusions:

1. In Sakha Republic (Yakutia), over the period from 2013 to 2018, we estimated the epidemiologic situation for TB as favorable; this is supported by the apparent stable decrease trends in incidence rates in general population, incidence rates in child population (mean decrease rates -7.1 to 7.5%), and stable decrease trends in incidence of pulmonary TB, incidence of MTB-positive pulmonary TB (mean decrease rates -6.1 and -2.5%, respectively).

2. Over the period from 2013 to 2018, mean decrease rates of urban TB incidence (-9.5%) had been outpacing those in rural population (-2.7%). Urban incidence of TB had a pronounced stable tendency to decrease, whereas the trend to decrease in rural TB incidence was moderate and unstable. This calls for more improvements in conducting anti-TB activities among rural population, paying due respect to social and local context, socio-medical differences, disparities in materials and resources, differences in staffing with healthcare workers between administrative districts in Yakutia.

3. Incidence of MDR TB had no tendency to decrease. In 2018 vs. 2013, it increased by 1.1%; mean increase rate was 2.6%. This could be linked to more extensive coverage of new patients with rapid drug sensitivity tests, and to growing number of timely notified cases of MDR TB, over the study period. Nonetheless, this finding requires in-depth analysis, and comprehensive managerial actions to decrease the incidence of MDR TB.

References

1. Аксенова В.А. Инфицированность и заболеваемость туберкулезом детей как показатель общей эпидемиологической ситуации по туберкулезу в России. Проблемы туберкулеза. 2002;3:6-9. [Aksenova V.A. Tuberculosis infection and incidence as indicators of general epidemiologic situation for tuberculosis in Russia. Problemy tuberkuleza. 2002;3:6-9. (In Russ.)]
2. Винокурова М.К., Алексеева Г.И., Бурнашева А.У., Кондаков С.Н. Тенденции развития множественной лекарственной устойчивости у больных туберкулезом легких в РС(Я). В

книге: Актуальные проблемы и перспективы развития противотуберкулезной службы в РФ: Материалы 1-го Конгресса Ассоциации «Национальная ассоциация фтизиатров» (Санкт-Петербург, 18-20 октября, 2012 г.). Санкт-Петербург, 2012. С. 97-98. [Vinokurova M.K., Alekseeva G.I., Burnasheva A.U., Kondakov S.N. Trends in multidrug-resistant pulmonary tuberculosis in Sakha Republic (Yakutia). In: Priority problems and prospects for development of TB services in Russian Federation: Proceedings of the 1st Congress of the 'National Phthisiologists Association' Association (Saint-Petersburg, October 18-20, 2012). Saint-Petersburg, 2012. pp. 97-98. (In Russ.)]

3. Кондратенко Т.А., Дорофеева И.К., Черниговец Л.Ф., Максимова Е.А., Тютюнькова Н.Г. Особенности развития эпидемического процесса туберкулеза органов дыхания в городе Ростове-на-Дону за период с 1993 по 2007 год. В книге: Актуальные проблемы инфекционной патологии: Материалы Российской научно-практической конференции (Томск, ноябрь, 2009 г.). Томск, 2009. С. 79-81. [Kon-dratenko T.A., Dorofeeva I.K., Chernigovets L.F., Maksimova E.A., Tyutyun'kova N.G. Features of epidemiology of pulmonary tuberculosis in Rostov-on-Don over the period from 1993-2007. In: Priority problems of infectious pathology: Proceedings of Russian scientific-practical conference (Tomsk, November, 2009). Tomsk, 2009. pp. 79-81. (In Russ.)]

4. Цыбикова Н.М., Сон Е.Д. Динамика показателей заболеваемости и смертности от туберкулеза в России в 2005 году. Проблемы туберкулеза. 2007;7:8-11. [Tsybikova N.M., Son E.D. Trends in incidence and mortality of tuberculosis in Russia in 2005. Problemy tuberkuleza. 2007;7:8-11. (In Russ.)]

5. Яковлева Л.П., Бурнашева А.У., Кондратьева М.Н. Ситуация туберкулеза с множественной лекарственной устойчивостью возбудителя в Республике Саха (Якутия). Туберкулез и болезни легких. 2015;7:168-169. [Yakovleva L.P., Burnasheva A.U., Kondratieva M.N. Situation with multidrug-resistant tuberculosis in the Sakha Republic (Yakutia). Tuberkulez i Bolezni Legkikh. 2015; 7:168-169. (In Russ.)]



S.A.Galkin, A.G. Peshkovskaya, O.V. Roshchina, N.I. Kisel,
S.A. Ivanova, N.A. Bokhan

RELATIONSHIP OF COGNITIVE DISORDERS WITH CLINICAL FEATURES OF ALCOHOL DEPENDENCE

DOI 10.25789/YMJ.2020.70.19

УДК: 616.89-008

The aim of the study is to identify the relationship between indicators of cognitive functioning and clinical features of the formation and course of alcohol dependence.

Materials and methods: the study was conducted in a group of patients with alcohol dependence (n=94) after detoxification and a control group of mentally and somatically healthy individuals (n=30). As clinical data were age of first alcohol samples, age of onset of alcohol abuse, disease duration, numbers of hospitalizations, the scale of the Hamilton anxiety scale General clinical impressions scale assessment of alcohol withdrawal. Cognitive functioning was assessed using Go/No-go, Corsi, and Stroop computer tests.

Results: it was found that alcohol dependence causes a heterogeneous change in the level of cognitive functioning: violation of inhibitory control, decrease in the volume of spatial working memory, attention and cognitive flexibility. Statistically significant correlations were found between clinical data and the degree of cognitive impairment.

Conclusion: the earlier age of the first sample of alcohol significantly affects the reduction of brake control, which increases the risk of forming alcohol dependence at a young age. The age of alcohol dependence and the associated number of hospitalizations leads to impaired cognitive functioning in the form of reduced spatial working memory and cognitive flexibility. The severity of alcohol dependence primarily determines the degree of cognitive flexibility decline.

Keywords: alcohol dependence, cognitive functioning, clinic, memory, inhibitory control.

Introduction. Cognitive disorders observed in patients with alcohol dependence who do not show any other neurological complications are increasingly becoming the subject of attention of drug specialists because of their impact on treatment [8]. According to various studies, patients, suffering from alcohol dependence, from 50 to 80% have

cognitive disorders [8, 10]. A number of researchers associate the inability to abstain from alcohol consumption with a decrease in the ability to cognitive control (in particular, inhibition of automatic reaction), a systematic error of attention (attention bias), a violation of the processes of processing and storing new information, which in combination with some psychological characteristics of the individual corresponds to the ideas about the mechanisms of addictive behavior [4, 5, 13]. Early studies have shown that all patients with alcohol dependence have deviations in the results of neuropsychological tests from the accepted standards [2]. Qualitative analysis of cognitive disorders indicates the predominance of control function disorders and visual-spatial disorders in the neuropsychological status [2, 7].

However, despite the active development of research on cognitive functioning in mental and behavioral disorders abroad, domestic research remains scarce. Also, the question of the influence of clinical and dynamic features of alcohol dependence on higher mental functions is still open.

The **objective** of the study is to identify the relationship between indicators of cognitive functioning and clinical features of the formation and course of alcohol dependence.

Materials and methods. The study was conducted in a group of patients with alcohol dependence (age 44 [38; 50] years; n=94) after detoxification and a control group of mentally and somatically healthy individuals (age 39 [35; 46] years; n=30). Group formation and clinical verifi-

cation of the diagnosis is made on the basis of the Department of addictive States Institute of mental health Tomsk National Research Medical Center (NRMC) of the Russian Academy of Sciences. The study was conducted in accordance with the principles of the Helsinki Declaration of the world medical Association. All patients gave written informed consent to participate in the study and data processing, which was approved by the local ethics Committee at the research Institute of Mental health (Protocol No. 114). Inclusion criteria: verified diagnosis of alcohol dependence according to ICD-10 (F10. 2), informed consent to participate in the study, age 25-50 years. Exclusion criteria: the presence of severe organic brain disorders, traumatic brain injuries of any severity, mental retardation, refusal to participate in the study.

Data on the age of the first sample of alcohol, the age of the beginning of alcohol abuse, the duration of the disease and the number of hospitalizations were taken from patient histories. Additionally, the Hamilton Anxiety Rating Scale was used as psychometric tools. HARS), the scale of General clinical impression (the Clinical Global Impression - severity, CGI-s) and the alcohol withdrawal assessment scale (Clinical Institute Withdrawal Assessment - Alcohol revised, CIWA-Ar).

Cognitive functioning was assessed using Go/No-go, Corsi, and Stroop computer tests. The study of the level of attention and cognitive control was conducted using the Go/No-go test [6]. You need to press the button when presenting the Go stimulus and hold (sup-

Mental Health Research Institute, Tomsk National Research Medical Center (NRMC) of the Russian Academy of Sciences, 4, Aleutskaya Str., Tomsk, 634014, Russian Federation; Siberian State Medical University (SSMU), 2, Moscow Trakt, Tomsk, 634050, Russian Federation: **GALKIN Stanislav A.** – PhD Student, Mental Health Research Institute, Tomsk National Research Medical Center (NRMC) of the Russian Academy of Sciences, ORCID iD 0000-0002-7709-3917; **PESHKOVSKAYA Anastasia G.** – Researcher, Mental Health Research Institute, Tomsk NRMC. ORCID iD 0000-0002-3951-395X; **ROSHCHINA Olga V.** – Researcher, Mental Health Research Institute, Tomsk NRMC. ORCID iD 0000-0002-2246-7045; **KISEL Nataliya I.** – PhD, Mental Health Research Institute, Tomsk NRMC. ORCID iD 0000-0002-5607-7491; **IVANOVA Svetlana A.** – DM, Professor, Head of the Laboratory of Molecular Genetics and Biochemistry, Deputy Director for Science, Mental Health Research Institute, Tomsk NRMC, Tomsk, Russian Federation. ORCID iD 0000-0001-7078-323X; **BOKHAN Nikolay A.** – DM, Professor, Academician of the Russian Academy of Sciences academician, RAS, Director of the Mental Health Research Institute, head of the Department of psychiatry, psychotherapy, narcology with the course med. the psychology of the Siberian State Medical University of Russia, Tomsk, Russian Federation. ORCID iD 0000-0002-1052-855X.

press) this reaction when presenting the no-go stimulus. The time of presentation of the Go stimulus is 500 MS, the interval between stimuli is 800 MS. The level of spatially working memory was evaluated using the Corsi Block-Tapping test [9]. On the computer screen, 9 cubes appear, which in turn light up in yellow. The task of the study participant is to remember and reproduce this sequence. The test begins with a sequence of two cubes, and if the answer is correct, the length of the sequence increases. The test is terminated in the case of two consecutive erroneous reproductions of the sequence. A modified Stroop effect color test was used to assess cognitive flexibility [11]. The study participant chose the color that the words were written with, regardless of the meaning of these words. The number of words is 20. The time spent by each participant to complete the test was estimated.

Statistical data processing was performed using the Statistica 10 program. The data is presented in the form of Median [Q1; Q3]. Verification of compliance with the normal distribution law was performed using the Shapiro - Wilk test. The data obtained did not follow the normal distribution law. The nonparametric Mann-Whitney U-test was used to evaluate differences in cognitive functioning between two independent samples (control versus patients). The analysis of correlations of clinical and cognitive parameters in patients with alcohol dependence was carried out using the Spearman rank correlation coefficient. The differences were considered statistically significant at a significance level of $p < 0.05$.

Results. The clinical characteristics of patients with alcohol dependence are presented in Table 1.

According to the anxiety scale (HARS), patients had symptoms of anxiety, a moderate disorder was diagnosed on the CGI-s scale, and the average severity of alcohol abstinence on the CIWA-Ar scale.

When comparing the results of cognitive testing between the control group and patients with alcohol dependence, statistically significant differences were obtained (Table 2).

Patients with alcohol dependence made a statistically significantly higher number of errors in the Go/No-go task (for both signals), had less of the most correct reproduced sequence in the Corsi test, and patients needed more time to complete the Scab test compared to the healthy control group.

The analysis of the obtained data revealed statistically significant correlations between cognitive functioning and a

Table 1**Clinical features of patients with alcohol dependence**

Parameter	Me [Q1; Q3]
age of the first sample of alcohol	16 [15; 18]
age of onset of alcohol abuse	24 [20; 28]
disease duration	12 [5; 21]
number of hospitalizations	1 [1; 3]
HARS	18 [11; 24]
CGI-s	4 [4; 5]
CIWA-Ar	12 [7; 18]

number of clinical parameters of alcohol dependence (Table 3).

Discussion. In our work, we conducted a study of cognitive functioning in patients with alcohol dependence, and also identified statistically significant correlations between cognitive deficits and clinical features of the formation and course of alcohol dependence.

The results showed that alcohol dependence results in a heterogeneous change in the level of cognitive functioning: a violation of inhibitory control, a decrease in the volume of spatial working memory, attention, and cognitive flexibility. According to neuroimaging studies, cognitive dysfunction in patients with alcohol dependence occurs due to atrophy of the hippocampus and prefrontal cortex [12]. In addition, cognitive impairment is accompanied by electrophysiological changes in patients with alcohol dependence [1, 3, 14]. All this points to the multifactorial effect of chronic alcohol consumption, which significantly worsens the quality of life of a person.

As for the clinical features of the formation and course of alcohol dependence, statistically significant correlations were found with the level of cognitive functioning. An inverse correlation was found between the age of the first alcohol sample and errors in the "No-go" signal ($r = -0.4206$, $p = 0.006$). Thus, early initiation of alcohol use has a significant effect

Table 2**Results of cognitive testing of the study groups**

Tests	Control	Patients	p	
Go/No-go	Errors Go	1 [0; 5]	7 [3; 13]	0.00014
	Errors No-go	0 [0; 1]	1 [1; 2]	0.00057
Corsi	max. sequence	5 [5; 7]	4 [4; 6]	0.00135
t. Stroop	time (s)	62 [56; 76]	97 [84; 121]	0.00023

Note. Me [Q1; Q3]. p is the level of statistical significance when comparing groups using the Mann-Whitney U-test.

Table 3**Spearman correlation coefficients of clinical parameters and cognitive functioning in patients with alcohol dependence**

Parameter	Tests			
	Go/No-go		Corsi (max. sequence)	Stroop (time)
	errors Go	errors No-go		
Age of the first sample of alcohol	0.2948 $p = 0.058$	-0.4206* $p = 0.006$	-0.2022 $p = 0.205$	0.1205 $p = 0.061$
Age of onset of alcohol abuse	0.1413 $p = 0.079$	-0.1827 $p = 0.253$	0.1630 $p = 0.241$	0.0226 $p = 0.89$
Disease duration	0.2285* $p = 0.04$	-0.1825 $p = 0.103$	-0.2216* $p = 0.049$	0.0955 $p = 0.409$
Number of hospitalizations	0.1672 $p = 0.154$	-0.0311 $p = 0.793$	-0.2508* $p = 0.034$	0.2602* $p = 0.029$
HARS	-0.0697 $p = 0.529$	-0.0255 $p = 0.818$	-0.0022 $p = 0.984$	0.0358 $p = 0.751$
CGI-s	0.1321 $p = 0.229$	-0.0036 $p = 0.974$	0.0491 $p = 0.657$	0.2209* $p = 0.046$
CIWA-Ar	0.3572 $p = 0.057$	-0.1177 $p = 0.543$	-0.1311 $p = 0.498$	0.6131* $p = 0.0004$

Note. p - level of statistical significance of Spearman's rank correlation coefficient.

on inhibitory control (reducing it), which leads to the inability to abstain from alcohol consumption at a young age. A direct correlation with the number of errors on the activation signal "Go" ($r = 0.2285$, $p = 0.04$) and an inverse correlation with the level of spatial working memory ($r = -0.2216$, $p = 0.049$) was found between the duration of the disease (the experience of alcohol dependence). This detection is quite logical and is consistent with previously obtained data [4, 14]. In addition, patients with a high number of hospitalizations for alcohol dependence treatment were characterized by a lower amount of working memory ($r = -0.2508$, $p = 0.034$) and difficulty overcoming the Stroop effect (level of cognitive flexibility), as a result of which they spent much more time performing the test ($r = 0.2602$, $p = 0.029$). Similarly, according to the cgi-s and CIWA-Ar clinical scales, patients with a more severe course of alcohol dependence have significant violations of cognitive flexibility in the Stroop test ($r = 0.2209$, $p = 0.046$ on the cgi-s scale and $r = 0.6131$, $p = 0.0004$ on the CIWA-Ar scale, respectively).

Conclusion. Thus, we can draw a number of conclusions. First, the earlier age of the first sample of alcohol significantly affects the reduction of brake control, which increases the risk of forming alcohol dependence at a young age. Second, the age of alcohol dependence and the associated number of hospitalizations

leads to impaired cognitive functioning in the form of reduced spatial working memory and cognitive flexibility. Third, the severity of alcohol dependence primarily determines the degree of reduced cognitive flexibility.

The study was carried out with the financial support of the Tomsk region Administration and RFBR 19-413-703007.

References

1. Галкин С.А., Савочкина Д.Н., Невидимова Т.И. Нейрофизиологические корреляты алкогольной зависимости. *Наркология*. 2019; (4):44-48. [Galkin SA, Savochkina DN, Nevidimova TI. Neurophysiological correlates of alcohol dependence. *Narkologija*. 2019; (4):44-48. (In Russ.)]
2. Захаров В.В. Злоупотребление алкоголем: неврологические осложнения и современные подходы к терапии. *Эффективная фармакотерапия*. 2014; (8):36-43. [Zaharov VV. Alcohol abuse: neurological complications and modern approaches to therapy. *Jeftektivnaja farmakoterapija*. 2014; (8):36-43. (In Russ.)]
3. Максимова И.В. Когнитивные и электроэнцефалографические изменения у пациентов с алкогольной зависимостью, перенесших судорожный припадок. *Сибирский вестник психиатрии и наркологии*. 2018; (2):89-92. [Maksimova IV. Cognitive and electroencephalographic changes in patients with alcohol dependence who had a seizure. *Sibirskij vestnik psichiatrii i narkologii*. 2018; (2):89-92. (In Russ.)]
4. Пешковская А.Г., Галкин С.А. Когнитивный контроль при алкогольной зависимости и его нейрокорреляты. *Вопросы наркологии*. 2018; (12):65-80. [Peshkovskaja AG, Galkin SA Cognitive control in alcohol dependence and its neuro-correlates. *Voprosy narkologii*. 2018; (12):65-80. (In Russ.)]
5. Трусова А.В., Климанова С.Г. Когнитивный контроль при алкогольной зависимости: обзор современных исследований. *Клиническая и медицинская психология: исследования, обучение, практика*. 2015; (3):10. [Trusova AV, Klimanova SG. Cognitive control in alcohol dependence: a review of current research. *Klinicheskaja i medicinskaja psihologija: issledovanija, obuchenie, praktika*. 2015; (3):10. (In Russ.)]
6. Ahmadi A, Pearson G, Meda S. Influence of alcohol use on neuronal response to Go/No-Go task in college drinkers. *Neuropsychopharmacology*. 2013; (11):2197-2208. DOI: 10.1038/npp.2013.119
7. Bates ME, Buckman JF, Nguyen TT. A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychol Rev*. 2013; (1):27-47. DOI:10.1007/s11065-013-9228-3
8. Bernardin F, Maheut-Bosser A, Paille F. Cognitive Impairments in Alcohol-Dependent Subjects. *Front. Psychiatry*. 2014; (5):78. DOI:10.3389/fpsy.2014.00078
9. Brunetti R, Gatto C, Delogu F, eCorsi: implementation and testing of the corsi block-tapping task for digital tablets. *Front. Psychol*. 2014; (5):939.
10. Devere R. The Cognitive Consequences of Alcohol Use. *Practical Neurology*. 2016; (10):57-61.
11. Scarpina F, Tagini S. The Stroop color and word test. *Front. Psychol*. 2017; (8):557.
12. Staples MC, Mandyam CD. Thinking after Drinking: Impaired Hippocampal-Dependent Cognition in Human Alcoholics and Animal Models of Alcohol Dependence. *Front. Psychiatry*. 2016; (9). DOI: 10.3389/fpsy.2016.00162
13. Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addict. Biol*. 2013; (2):203-213. DOI: 10.1111/j.1369-1600.2011.00418.x.
14. Wilcox CE. Cognitive control in alcohol use disorder: deficits and clinical relevance. *Rev. Neurosci*. 2014; (1):1-24. DOI:10.1515/revneuro-2013-0054



S.I. Sofronova, A.N. Romanova, M.P. Kirillina

ASSOCIATION OF IL-6 GENE POLYMORPHISM WITH ARTERIAL HYPERTENSION AND ITS RISK FACTORS IN INDIGENOUS PEOPLES OF YAKUTIA

DOI 10.25789/YMJ.2020.70.20

УДК 616-008.9. 1-81(571.56)

A case-control study was conducted in Kolymaskoye and Andryushkino of Nizhnekolymsky district of Yakutia to determine the association of IL-6 gene polymorphism with arterial hypertension (AH) and risk factors. The relationship with AH and its risk factors for IL-6 gene polymorphism was obtained, namely, the influence of the G allele of the polymorphic locus C-174G and the C allele of the polymorphic locus C-572G on metabolic factors of atherogenesis. Hypertensive patients- carriers of the G allele of the C-174G polymorphic locus of the IL-6 gene, both in the homozygous and heterozygous versions, showed the highest average systolic blood pressure, a high incidence of abdominal obesity, lipid and carbohydrate metabolism disorders. The study of the polymorphic locus C-572G of the IL-6 gene in patients with hypertension showed the highest incidence of abdominal obesity, lipid and carbohydrate metabolism disorders in carriers of the C allele.

Keywords: gene IL-6, locus C-174G, C-572G, arterial hypertension, risk factors, indigenous people, Yakutia.

The mortality rate from diseases of the circulatory system in Russia in 2018 was 46.3%, of which 52.6% were from IHD [1]. One of the main risk factors for the development of cardiovascular complications is arterial hypertension (AH). AH in 2015 caused more than 10 million deaths and 200 million cases of disability [6]. The leading role in the development of AH is played by not only modifiable, but also non-modifiable and genetic features of the body [2]. The immune system also plays an important role. Thus, the *IL-6* gene encodes an anti-inflammatory cytokine, and therefore an increase in its concentration in the blood leads to an increased susceptibility to the development of atherosclerosis. The role of the immune mediator *IL-6* in the development of hypertension has been proven [8,11,13]. The literature describes that CG genotypes of G-174C polymorphism in the *IL-6* gene promoter increase gene transcription and are significantly associated with an increased content of TC, LDL and SBP [10,12], which determines the relationship of *IL-6* gene polymorphism with metabolic factors of atherogenesis. The results of studies with regard to the association of *IL-6* C-572G gene polymorphism and the risk of developing IHD, namely the effect of the C allele in the Chinese, are also described [3]. Other studies confirm the association

of -572GG and the G allele with the risk of developing ischemic stroke [15].

The study to determine the relationship of variants of the *IL-6* C-174G and *IL-6* C-572G genes with hypertension and its risk factors remains relevant, since it has not been previously conducted in indigenous peoples of the North.

Objective: to analyze the association of *IL-6* gene polymorphism with arterial hypertension and its risk factors in indigenous peoples of the Nizhnekolymsky district of Yakutia.

Materials and research methods.

The collection of material for the study was carried out under expeditionary conditions in the Arctic territory of Yakutia in places of compact residence of indigenous peoples in the Kolymaskoe and Andryushkino villages, Nizhnekolymsky district. A total of 212 people aged 20 to 70 years were examined. Random sampling was formed according to the lists of workers in the village administration. The response was 76%. It should be noted that Kolymaskoye village was dominated mainly by the Chukchi, and the Andryushkino village by the Yukagirs. Evens were found equally often in both settlements. The design of the study is presented in the form of "case-control", for which 150 representatives of indigenous peoples of the North were included in the study, which were divided into 2 groups: with AH (case) (n = 73) and without AH (control) (n = 77). The average age of respondents with AH was 53,52 ± 1,12, without AH 39,62 ± 1,26 years.

Inclusion criteria: representatives of indigenous people (Evens, Chukchi, Yukagirs).

Exclusion criteria: representatives of non-indigenous nationalities, Yakuts.

The research program included the following sections: a survey on the ques-

tionnaire to assess the objective state; informed consent of the respondent to conduct research; anthropometric examination with hip and waist measurement; blood sampling for biochemical studies from the cubital vein in the morning on an empty stomach with a 12-hour abstinence from food. Blood sampling from the cubital vein for molecular genetic studies was carried out in a tube with EDTA. Genomic DNA was isolated from peripheral blood leukocytes by the method of phenol-chloroform extraction. Polymorphism of the promoter region of the *IL-6* gene was studied at positions C-174G and C-572G. Allelic variants of the *IL-6* gene were tested using a polymerase chain reaction with real-time results (real-time PCR). Genotyping of the polymorphic AGT gene was performed with the usage of kits (Lytech R&D LLC, Moscow), on the «Real-time CFX96» amplifier (BioRad, USA) in accordance with the manufacturer's instructions. For quality control, 10% of randomly selected samples were subjected to repeated genotyping.

Laboratory methods of the research included blood lipids test total cholesterol (TC), triglycerides (TG), HDL Cholesterol, LDL Cholesterol, glucose test.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the V revision of Society of cardiology of Russian Federation (VNOK), 2012, into account the European recommendations, 2011. Hypercholesterolemia (HCS) is the level of total cholesterol (TC) ≥ 5,0 mmol/l, the high LDL Cholesterol level >3,0 mmol/l, the low HDL Cholesterol level <1,0 mmol/l on men; <1,2 mmol/l on women, the hypertriglyceridemia (HTG) is the TG level is ≥1,7 mmol/l; a hyperglycemia (HG) on an empty stom-

677000, The Republic of Sakha (Yakutia), Yakutsk, Sergelyakhskoe shosse, 4, Yakut science centre of complex medical problems: **SOFRONOVA Sargylana Ivanovna** – PHD, researcher, ORCID: 0000-0003-0010-9850, sara2208@mail.ru, 89841094825; **ROMANOVA Anna Nikolaevna** – MD, director, ORCID: 0000-0002-4817-5315, ranik@mail.ru, 8(4112)32-19-81; **KIRILLINA Marya Petrovna** – PHD, researcher, kirillinamp@mail.ru.

ach (a glucose in a blood plasma on an empty stomach $\geq 6,1$ mmol/l) or glucose intolerance (a glucose in a blood plasma in 2 hours after glucose loading within $\geq 7,8$ and $\leq 11,1$ mmol/l).

Blood pressure (BP) was measured twice with an OMRON M2 Basic automatic tonometer (Japan) in a sitting position with calculation of average blood pressure with a margin of permissible measurement error of ± 3 mm Hg. (ESH 2002) according to the instructions for the correct measurement of blood pressure, outlined in the European clinical guidelines for the diagnosis and treatment of hypertension 2017. Hypertension is present at the 140/90 mmHg (2017 ACC/AHA Guideline).

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

The study was conducted according to Ethics Committee protocol YSC KMP on the respondent's informed consent to the processing of personal data and the study.

Statistical data processing was performed using standard methods of mathematical statistics using the SPSS software package (version 19.0). To define the characteristics, the arithmetic mean (M) and the characteristic's standard error of the mean (m) were calculated. Intergroup differences were evaluated using analysis of variance or non-parametric criteria. When comparing the frequencies of genotypes, the standard χ^2 criterion with the Yates correction was used. The relative risk (OR – odds ratio) of disease development at a certain genotype was calculated using the standard formula $OR = a/b \times d/c$, where a and b is the number of patients with and without the mutant genotype, respectively, and d, c is the number of people in the control group with and without the mutant genotype. OR is indicated with a 95% confidence interval. Differences were considered statistically significant at $p < 0.05$.

Results and discussion. This study is exploratory in nature due to the analysis of a small sample of the surveyed population. An attempt was made to analyze the association of *IL-6* gene polymorphism with AH and its risk factors. The effect of heterogeneity in comparisons is possible, which could affect the results.

The frequency of occurrence of genotypes and alleles of *IL-6 C-174G* and *IL-6 C-572G* among the examined groups was compared. All genotype frequencies do not correspond to the Hardy-Weinberg equilibrium, possibly due to a small sam-

ple of the studied groups, for *IL-6 C-174G* ($\chi^2=15.12$, $p=0.000$ for the case and $\chi^2=3.36$, $p=0.066$ for control), for *IL-6 C-572G* ($\chi^2=9.18$, $p=0.002$ and $\chi^2=7.76$, $p=0.005$, respectively). In all groups, a high frequency of homozygous GG genotype and G allele was noted; there were statistically significant differences in both the group of patients with AH and the frequency of GG genotype of *IL-6 C-572G* in the control.

We used 2 genetic models (dominant and recessive) to test the relationship between *IL-6 C-174G* and *IL-6 C-572G* with AH. We did not obtain significant differences in the frequencies of genotypes between hypertensives and normotensives, in all cases the dominant model for the minor G allele and the high frequency of the G allele prevailed (Table 1).

Depending on the genotype of the polymorphic locus C-174G of the *IL-6* gene, we analyzed the average level of systolic blood pressure (SBP) in hypertensive patients. Some effect of the G allele of *IL-6 C-174G* on the increase in the level of SBP was found. In individuals with hypertension, the average level of SBP in carriers of CC, CG, and GG genotypes was 146.67 ± 8.81 , 166.67 ± 10.22 , and 160.47 ± 2.28 mmHg, respectively, no significant differences were found ($p > 0.05$). Our data do not coincide with the studies of certain foreign scientists; in particular, the tendency for a more pronounced increase in SBP in carriers of the C allele has been described [10,12]. In normotensives, there were no special differences in the mean values of SBP. As for the polymorphic locus C-572G of the *IL-6* gene, in hypertensive patients with CC, CG and GG genotypes, the mean SBP was 155.71 ± 3.68 , 160.67 ± 4.41 and 160.98 ± 2.84 mmHg, respectively, no significant differences were noted. In a number of studies, the relationship of the polymorphic locus C-572G of the *IL-6* gene with the level of SBP was also not obtained [14].

AO plays an important role in the development of hypertension as a component of the metabolic syndrome. In individuals with AH, AO was significantly more often observed than in individuals without AH (78.1% and 29.9%, respectively, $p = 0.001$). We analyzed the distribution frequencies of the genotypes of the polymorphic loci C-174G and C-572G of the *IL-6* gene, depending on the presence of AO in the general population and separately in the "case" and "control". The frequency of AO in the general population of carriers of the CC genotype of the polymorphic locus C-174G was 50%, CG - 58.3%, GG - 53%, no

significant differences were noted. In the "case", depending on the relationship to these genotypes, it was 66.7%, 83.3% and 78.1%, respectively ($p > 0.05$), in the "control" - 22.3%, 33.3% and 30.0% ($p > 0.05$). We obtained a contradictory result in comparison with published data, which describes the relationship of the C allele at the -174 locus of the *IL-6* gene with visceral obesity in patients with hypertension [4], possibly associated with a small sample of subjects.

In the general population of carriers of the genotype CC of the C-572G locus, the AO frequency was 50%, CG - 52.8%, GG - 54.1%, the differences were insignificant. Hypertensive patients had a high rate of AO, 95.6%, 86.7% and 72.5%, respectively ($p > 0.05$). Thus, the highest frequency of AO was identified in individuals with AH - carriers of the C allele. In normotensive patients, the occurrence of AO was 22.4%, 28.6% and 34.0%, respectively, the differences are unreliable.

The assessment of the effect of genetic polymorphism on the biochemical blood parameters characteristic of hypertension is of particular interest. We analyzed the association of polymorphism of polymorphic C-174G and C-572G loci of *IL-6* gene with biochemical blood parameters in individuals with and without AH. Compared the average concentration of lipids and blood glucose in individuals with hypertension and without hypertension, depending on their belonging to a particular genotype (Table 2). In all respondents in the "case", the values of lipid metabolism, except for high density lipoprotein cholesterol (HDL cholesterol), were higher compared to the "control". Statistically significant differences were obtained in the average concentrations of low-density lipoprotein cholesterol (LDL cholesterol), TG and blood glucose in homozygous carriers of minor GG genotype *IL-6 C-174G*. In other cases, the indicators had no significant differences. When studying the relationship of *IL-6 C-572G* gene polymorphism with the same blood parameters, we obtained significant differences in hypertensive patients in the average LDL cholesterol values in carriers of a heterozygous genotype and blood glucose in individuals with a mutant homozygous genotype. For other indicators, there were no significant differences. Thus, we obtained the influence of the G allele on a significant increase in the concentration of atherogenic fractions of cholesterol and blood glucose in hypertensive patients.

We determined the frequency of lipid and carbohydrate disorders for indi-

Table 1

Frequency distribution of the *IL-6* C-174G and *IL-6* C-572G genotypes with and without hypertension according to the dominant and recessive models

Genotype	Genotype frequencies		χ^2	p	OR	95% CI	Allele	Allele frequencies		
	case	control						case	control	
<i>IL-6</i> C-174G										
Dominant model	CG+GG	0.959	0.987	1.14	>0.05	0.31	0.03-3.02	C	0.082	0.052
	CC	0.041	0.013							
Recessive model	CC+CG	0.123	0.091	0.41	>0.05	1.41	0.49-3.99	G	0.918	0.948
		0.877	0.909							
<i>IL-6</i> C-572G										
Dominant model	CG+GG	0.904	0.883	0.17	>0.05	1.25	0.44-3.55	C	0.199	0.253
	CC	0.096	0.117							
Recessive model	CC+CG	0.301	0.390	1.29	>0.05	0.68	0.34-1.33	G	0.801	0.747
		0.699	0.610							

viduals with and without hypertension, depending on the carriage of a particular *IL-6* C-174G genotype. In hypertensive patients, all values exceeded those of normotonic, except for carbohydrate metabolism. We compared the frequencies in relation to a particular genotype separately in individuals in the "case" and "control". In hypertensive patients, there were no differences in the ratio of a specific genotype to lipid and carbohydrate disorders ($p > 0.05$). In carriers of the CC genotype, the frequency of HCS was 33.3%, CG - 46.9% and GG - 55.6% ($p > 0.05$); HCS-LDL 33.3%, 50.0% and 59.4%, respectively, $p > 0.05$. Thus, carriers of the mutant GG genotype showed the highest frequency of lipid metabolism disorders, including the atherogenic fraction. In the literature, there are also confirmations from certain authors about the influence of the mutant homozygous genotype *IL-6* C-174G on atherogenesis [10]. We have not obtained any special influence of one or another allele on the frequency of lipid and carbohydrate disorders in normotonics.

As for the comparison of the frequencies of occurrence of HCS, HCS-LDL, HTG, Hypo- α -cholesterolemia (Hypo- α -CS), HG by *IL-6* C-572G genotypes, significant differences were not obtained in either the "case" or "control". In hypertensive patients, all indicators were also higher compared to the "control", but we found the highest occurrence of HCL in carriers of the C allele (CC - 57.1%, CG - 49.0% and GG - 40.0%, ($p > 0.05$); HCS-LDL - 71.4%, 66.7% and 52.9% ($p > 0.05$); Hypo- α -CS - 42.9%, 40.0% and 21.6% ($p > 0.05$); HG - 14.3%, 8.0% and 6.7%, respectively, $p > 0.05$. For other parameters in the "case" no difference was noted. In normotonics, the occurrence of all indicators is almost the same.

Conclusion. In the course of our ex-

ploratory study, certain results were obtained, the distribution of allelic variants of cytokine genes in patients with hypertension and relatively healthy individuals was revealed. The dominance of a homozygous mutant genotype was found in the polymorphic loci C-174G and C-572G of the *IL-6* gene in two groups.

Hypertensives - carriers of the G allele of the C-174G polymorphic locus of the *IL-6* gene, both in the homozygous and heterozygous versions, showed the highest average systolic blood pressure, a high incidence of abdominal obesity, lipid and carbohydrate metabolism disorders. The study of the polymorphic C-572G locus of the *IL-6* gene in individuals with hyper-

tension showed the highest incidence of AO, lipid and carbohydrate metabolism disorders in carriers of the C allele.

Thus, a relationship was obtained with AH and its risk factors for *IL-6* gene polymorphisms, namely, the influence of the G allele of the polymorphic locus C-174G and the C allele of the polymorphic locus C-572G on metabolic factors of atherogenesis.

All this serves as the basis for further more in-depth research of the indigenous population living compactly in the remote hard-to-reach communities in Russia's Arctic region, with a larger scope of research for targeted selection of therapeutic and preventive measures.

Table 2

The average levels of the lipid and carbohydrate spectrum in people with hypertension and those without hypertension, depending on the genotypes C-174G and C-572G of the *IL-6* gene ($M \pm m$)

Genotype frequency		TC	LDL Cholesterol	HDL Cholesterol	TG	Glucose
<i>IL-6</i> C-174G						
CC	Case	5.49±1.12	2.82±0.52	1.48±0.22	1.33±0.30	5.36±0.18
	p	0.817	0.628	0.393	0.441	0.432
	Control	4.88±0.31	2.23±0.09	1.98±0.21	0.75±0.19	5.60±0.35
CG	Case	5.59±0.35	3.64±0.21	1.70±0.15	0.93±0.11	4.50±0.15
	p	0.395	0.234	0.507	0.583	0.393
	Control	5.09±0.42	3.11±0.35	1.50±0.24	0.84±0.10	4.36±0.30
GG	Case	4.93±0.13	3.16±0.11	1.29±0.04	1.10±0.05	4.96±0.26
	p	0.106	0.039	0.182	0.025	0.007
	Control	4.66±0.10	2.87±0.08	1.37±0.04	0.91±0.05	4.21±0.09
<i>IL-6</i> C-572G						
CC	Case	5.02±0.15	3.16±0.33	1.16±0.11	1.07±0.10	5.02±0.60
	p	0.729	0.513	0.074	0.080	0.143
	Control	4.66±0.25	2.91±0.20	1.41±0.07	0.78±0.10	4.11±0.22
CG	Case	4.87±0.29	3.14±0.21	1.26±0.12	1.08±0.11	5.39±0.82
	p	0.326	0.049	0.215	0.236	0.153
	Control	4.56±0.16	2.70±0.12	1.45±0.08	0.88±0.10	4.33±0.16
GG	Case	4.82±0.38	3.14±0.12	1.38±0.04	1.09±0.06	4.73±0.21
	p	0.376	0.512	0.761	0.153	0.047
	Control	4.83±0.13	3.03±0.11	1.35±0.05	0.95±0.06	4.23±0.11

References

1. Российский статистический ежегодник. М., 2018; 694. [*Rossiiskij statisticheskij ezhegodnik. M.*, 2018; 694. (In Russ.)].
2. Ahn SY, Gupta C. Genetic programming of hypertension. *FrontPediatr.* 2018; 5:285. doi: 10.3389/fped.2017.00285
3. Hou H, Wang C, Sun F [et al.]. Association of interleukin-6 gene polymorphism with coronary artery disease: an updated systematic review and cumulative meta-analysis. *Inflamm Res.* 2015; 64(9):707-720.
4. Andrei Alkmim Teixeira, Beata Marie Redublo Quinto, Maria Aparecida Dalboni [et al.]. Association of IL-6 Polymorphism -174G/C and Metabolic Syndrome in Hypertensive Patients. *BioMed Research International.* 2015; 6. <https://doi.org/10.1155/2015/927589>
5. Herbert A., Liu C., Karamohamed S [et al.]. BMI modifies associations of IL-6 genotypes with insulin resistance: the Framingham study. *Obesity.* 2006; 8(14): 1454–1461. DOI: 10.1038/oby.2006.165
6. Forouzanfar M, Liu P, Roth G.[et al.] Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA.* 2017; 317(2):165-182. <https://doi.org/10.1001/jama.2016.19043>
7. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C. [et al.]. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology. American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018; 71(19):e127-e248. doi: 10.1016/j.jacc.2017.11.006.
8. Harrison DG. The immune system in hypertension. *AJP Advances in Physiology Education.* 2014; 38(1):20-4. DOI: 10.1152/advan.00063.2013
9. Anna Dobrucka-Głowacka, Beata Sarecka-Hujar, Dorota Raczkiwicz [et al.]. Interleukin-6 in cardiovascular disorders. *European Journal of Medical Technologies.* 2018; 3(20):23-30.
10. Riikola A. [et al.]. Interleukin-6 promoter polymorphism and cardiovascular risk factors: the Health 2000 Survey. *Atherosclerosis.* 2009; Vol.207 (2): 466-470.
11. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. *Circ Res.* 2015; 116(6):1022-33.
12. Hulkkonen J., Lehtimäki T., Mononen N. [et al.]. Polymorphism in the *IL6* promoter region is associated with the risk factors and markers of subclinical atherosclerosis in men: the Cardiovascular Risk in Young Finns Study. *Atherosclerosis.* 2009; 203(2): 454-458. DOI: 10.1016/j.atherosclerosis.2008.07.014
13. Singh MV, Chappleau MW, Harwani SC, Abboud FM. The immune system and hypertension. *Immunol Res.* 2014; 59(1-3):243-53.
14. Humphries SE, Luong LA, Ogg MS [et al.]. The interleukin-6 -174 G/C promoter polymorphism is associated with risk of coronary heart disease and systolic blood pressure in healthy men. *European Heart Journal.* 2001; 22(24): 2243-52. doi:10.1053/ehj.2001.2678
15. Yang X, Feng L, Li C, Li Y. Association of IL-6 -174G>C and -572C>G polymorphisms with risk of young ischemic stroke patients. *Gene.* 2014; 539: 258–262.



S.A. Evseeva, T.E. Burtseva, A.G. Egorova, A.M. Makarova,
M.S. Savvina, M.P. Slobodchikova

CAUSES AND MORTALITY INDICATORS OF CHILD POPULATION IN THE ARCTIC REGIONS OF THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.70.21

УДК 616-053.2(571.56)

The issue of medical aid improvement in the remote areas is a lot discussed at circumpolar Union meetings. It is clear that healthcare of the Arctic regions populations depends on the welfare of the country. However, we should notice that there are certain improvements in this field in the Republic Sakha (Yakutia). That is why it is actual to evaluate the mortality rate of the child population in the Arctic regions when huge government financed programs concerning maternity and childhood welfare are being held in the Republic Sakha (Yakutia). The article represents the official data of mortality rate in the child population of the five Arctic regions of the Republic Sakha (Yakutia) for the period of 2006-2018. For further detailed analysis of the child mortality a special database of the state institution "Yakut Republican medical information and analytical center of the Ministry of healthcare of the Republic Sakha (Yakutia)" was used. The database included all cases of mortality from 0 to 18 years of age for the period of 2006-2015, indicating the age, gender, nationality and causes of the death. The analysis of the mortality rate in the Arctic regions of the Republic Sakha (Yakutia) has revealed significant decrease of infant mortality from 29.8% to 4.2%, decrease of child mortality rate from 6.3% to 2.3%. On a whole, a decrease to the minimum level of the mortality rate in the child population of the Republic Sakha (Yakutia) can be constituted.

Key words: children, mortality, Arctic, external causes, injury, poisoning.

Introduction. The examination of the health status and factors of its formation in the Arctic regions has greatly increased in the recent years. It is associated with the realization of huge governmental projects concerning the development of industrial, transport and energy sectors in Russia. The main and high priority of scientific investigations in Yakutia is associated with the Arctic coast inhabiting people health. All circumpolar community studies phenomenal viability of the Arctic population [4]. It undoubtedly concerns the health of the coming generation, i.e. children

of the Arctic [2, 3, 5]. The Ministry of the healthcare in the Republic Sakha (Yakutia) has realized several federal and Republican programs to improve logistic and material support, medical personnel staffing in different medical institutions of the Arctic and Northern regions, undoubtedly it had an effect on the indicators of the health state of the population in the Arctic regions and the Far North [1, 2, 4]. The child mortality issues are being discussed a lot at the meetings of the circumpolar territories community [6, 7].

Objectives: The objectives are to analyze the child mortality in the Arctic regions of the Republic Sakha (Yakutia).

Materials and methods: We have analyzed the official medical data of child population in 5 Arctic coast regions of the Republic Sakha (Yakutia) for the period of 2006-2018. For further detailed analysis of the child mortality a special database of the state institution "Yakut Republican medical information and analytical center of the Ministry of healthcare of the Republic Sakha (Yakutia)" was used. The database included all the cases of mortality from 0 to 18 years of age for the period of 2006-2015, indicating the age, gender, nationality and causes of the death.

Results: According to the data from "Yakut Republican medical information and analytical center of the Ministry of healthcare of the Republic Sakha (Yakutia)", the mean indicator of the infant mortality has shown clear decrease from 17.0% in 2011 to 4.2% in 2018 (Table 1). In 2018 the infant mortality

rate has decreased to its historical minimum. For the following periods, there are several regions were no cases of infant mortality were registered (Allaikhovskiy (2012,2016, 2018), Anabarskiy (2016,2018), Bulunskiy (2014,2015,2017), Nizhne-Kolymskiy (2014, 2017,2018), Ust-Yanskiy (2015)). Infant mortality rate is one of the demographic factors that denote the level of healthcare development in the region. Such federal and Republican programs like "Public health and healthcare modernization" resulted in decrease of infant mortality in the Republic and the Arctic regions of the Republic Sakha (Yakutia) (see table 1).

As we can see in the table 2 the mortality rate from 0-18 in the Arctic regions tends to decrease, although the index is quite unstable for the period of 2006-2018. The index of mortality for the mentioned period tends to decrease up to 2.9% in 2016, and increase up to 8.1% in 2010.

A detailed analysis of the child mortality rate in the Arctic regions of the Republic Sakha (Yakutia) is based on the data of the Yakut Republican medical information and analytical center. This database is composed of all the cases of mortality from 2006 to 2015.

The child mortality rate dynamics is represented in the table 3. It is obviously seen that in standardization of indices the mortality rate, concerning the number of child population, in the Arctic regions is higher than the same in the Republic, except 2015.

As we can see in the table 4, the part of mortality rate in boys, aged from

EVSEEVA Sardana Anatolievna – Ph.D., senior staff scientist of the laboratory of pediatric health level monitoring, Yakut science centre of complex medical problems, sarda79@mail.ru; **BURTSEVA Tatiana Egorovna** – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, a head of the laboratory of Medical science center of complex medical problems, +7-914-294-32-44, bourtsevat@yandex.ru; **EGOROVA Aitalina Grigorievna** – Ph.D., senior staff scientist of the laboratory of pediatric health level monitoring, Yakut science centre of complex medical problems, aitalina@mail.ru; **MAKAROVA Avgustina Makarovna** – laboratory assistant, Medical science center of complex medical problems; **SAVVINA Maya Semyonovna** – Ph.D., senior staff scientist of the laboratory of pediatric health level monitoring, Yakut science centre of complex medical problems, maya_savvina@mail.ru; **SLOBODCHIKOVA Maya Pavlovna** – a senior lecturer of the department of foreign languages with the courses of Russian and Latin, Saint-Petersburg state pediatric medical university, limelight@mail.ru

Table 1

Dynamics of infant mortality in the Arctic regions of the Republic Sakha (Yakutia), (per 1000 of child population, %)

Regions	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Allaikhovskiy	40.8	18.5	...	20.0	15.4	18.9	...	25.0	...
Anabarskiy	36.6	13.0	54.7	...	18.2	14.7	15.6	12.7	12.7	13.3	...	13.0	...
Bulunskiy	16.8	15.0	...	16.4	16.0	20.0	14.0	7.0	16.0	...	10.5
Nizhnekolymskiy	54.9	11.0	26.0	36.2	41.5	12.8	13.3	12.2	...	12.7	14.7
Ust-Yanskiy	28.9	20.8	19.2	31.5	16.1	6.8	...	17.9	18.0	10.8
Total for the Arctic regions	29.8	7.8	16.1	16.3	19.3	17.0	14.9	16.3	7.3	8.9	9.7	11.2	4.2
Republic Sakha (Yakutia)	10.6	10.4	9.1	8.9	7.2	6.3	9.6	9.6	8.0	7.6	7.2	5.1	5.0
Russian Federation	10.2	9.4	8.5	8.1	7.5	7.4	8.6	8.2	7.4	6.5	6.0	5.6	5.1

Table 2

Mortality cases in children and adolescents in the Arctic regions of the Republic Sakha (Yakutia)

Regions	Абс. число												
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Allaikhovskiy	5	2	0	1	1	2	1	1	4	0	0	1	0
Anabarskiy	7	3	4	2	4	2	4	1	1	1	0	1	1
Bulunskiy	3	8	4	3	5	6	4	3	2	0	2	1	2
Nizhnekolymskiy	8	2	3	6	4	0	0	1	3	0	2	0	0
Ust-Yanskiy	3	3	2	4	5	4	6	8	4	2	2	3	1
Total for the Arctic regions	26	18	13	16	19	14	15	14	14	3	6	6	4
Arctic regions, %	6.3	4.7	3.6	5.7	8.1	6.8	6.8	6.3	6.4	1.5	2.9	3.7	2.3
Republic Sakha (Yakutia)	412	387	361	280	232	206	220	220	217	194	207	160	173

Table 3

Child mortality rate coefficient dynamics in the Arctic regions of the Republic Sakha (Yakutia)

Район	Mortality rate per 1000 of child population, ‰										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Allaikhovskiy	5.444	2.232	0.000	1.123	1.111	2.250	1.140	1.159	4.709	0.000	
Anabarskiy	4.754	2.123	3.034	1.567	3.120	1.591	3.252	0.816	0.824	0.833	
Bulunskiy	1.124	3.097	1.600	1.225	2.051	2.414	1.621	1.267	0.866	0.000	
Nizhnekolymskiy	5.722	1.455	2.199	4.478	3.059	0.000	0.000	0.766	2.275	0.000	
Ust-Yanskiy	1.316	1.408	0.931	1.879	2.339	1.885	2.850	3.839	1.928	0.958	
Total for the Arctic regions	2.976	2.143	1.584	1.979	2.356	1.737	1.879	1.785	1.803	0.388	
Republic Sakha (Yakutia)	1.535	1.472	1.399	1.101	0.918	0.814	0.867	0.863	0.845	0.747	

0 to 18 is 65% in 2006, and 33% in 2015. The mortality rate in girls composed 35% in 2006, and 67% in 2015. It is obvious that the rate is significantly higher in boys from 2006 to 2014, the death was caused by external factors like traumas, to which the boys seem more predisposed than the girls. In 2015 there were 3 cases in the whole structure of the mortality rate, 2 were caused by external factors and 1 was a case of a sudden death.

As we can see in the table 5, the main cause of mortality in child population aged from 0 to 18 is associated with external factors. The part of mortality caused by external factors composed

46% in 2006, 59% in 2007, 30% in 2008, 31% in 2009, 21% in 2010, 28% in 2011, 33% in 2012, 71% in 2013, 35% in 2014, 66% in 2015. The next factors of mortality are injuries, poisoning, and other perinatal conditions. On a whole, we can constitute that the external factor causing mortality in children prevails. An achieved decrease of the infant mortality is smoothed by increase of mortality in adolescents, caused by injuries.

Conclusion: The analysis of the child mortality in the Republic Sakha (Yakutia) revealed the following tendencies. A marked decrease of the infant mortality rate from 29.8% to 4.2%

is noticed in the period from 2006 to 2018. The level of the infant mortality rate in the Arctic regions is considerably higher than the rate in the other regions of the Republic Sakha (Yakutia) and the average numbers in Russia (5.0% in the Republic Sakha (Yakutia) and 5.1% in the Russian Federation in 2018). The results reveal the necessity of developing a new 3-level system of medical assistance for pregnant and parturient women and the system of their routing from the Arctic regions of the Republic Sakha (Yakutia).

On a whole the level of child mortality in the Arctic regions of the Republic Sakha (Yakutia) was 6.3% in 2006, and

Table 4

Gender based mortality cases dynamics in child population of the Arctic regions of the Republic Sakha (Yakutia)

Regions		Абс. число									
		2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Allaikhovskiy	M	5	1	0	1	1	1	1	0	2	0
	F	0	1	0	0	0	1	0	1	2	0
Anabarskiy	M	6	1	2	1	3	2	3	1	1	0
	F	1	2	2	1	1	0	1	0	0	1
Bulunskiy	M	1	7	4	1	3	3	1	3	1	0
	F	2	1	0	2	2	3	3	0	1	0
Nizhnekolymskiy	M	5	0	3	1	1	0	0	0	2	0
	F	3	2	0	5	3	0	0	1	1	0
Ust-Yanskiy	M	0	3	2	2	1	2	4	5	3	1
	F	3	0	0	2	4	2	2	3	1	1
Total for the Arctic regions of the Republic Sakha (Yakutia)	M	17	12	11	6	9	8	9	9	9	1
	%	65	66	84	37	47	57	60	64	64	33
	F	9	6	2	10	10	6	6	5	5	2
	%	35	34	16	63	53	43	40	36	36	67

Table 5

The dynamics of child mortality causes in the Arctic regions of the Republic Sakha (Yakutia), (absolute numbers)

Pathology structure	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total deaths	26	18	13	16	19	14	15	14	14	3
External causes of morbidity and mortality	12	9	4	5	4	4	5	10	5	2
Different perinatal conditions	10	8	8	2		2				
Injuries, poisoning and some other outcomes of external factors				4	3	4	2	3	2	
Diseases of the nervous system					4	2	2	1		
Some infectious diseases and parasite disorders					1					
Malformations									1	
Diseases of blood, hemopoietic organs, and other disorders involving immune mechanism						1				
Circulatory system disorders				1	1	1	2		2	
Disorders of the respiratory system	1	1		2	2				2	
Diseases of the digestive organs							2			
Diseases of the musculoskeletal system and connective tissue					1					
Inherited defects (birth defects), deformities and chromosome disorders	3								1	
Signs and symptoms of the defects, revealed during the clinical and laboratory tests, not included in the classification				2	2		2		1	1
Sudden death syndrome				2			2		1	1

2.3% in 2018. A considerable decrease up to the minimum of numbers of child mortality rate aged from 0 to 18 is noticed in the Arctic regions of the Republic Sakha (Yakutia).

From 2006 to 2015 the child mortality rate aged from 0 to 18 decreased from 2.976% to 0.388% in the Arctic regions of the Republic Sakha (Yakutia). Before 2014 the mortality rate in the Arctic regions was higher than the average numbers in the other regions of the Republic Sakha (Yakutia) (0.845% in 2014 in the Republic Sakha (Yakutia)). The mortality rate caused by the external factors tends to decrease in the Arctic regions of the Republic Sakha (Yakutia). Singular cases of child mortality were registered in 2015.

Extreme conditions of inhabiting in the Arctic regions demand differentiated approach in the development of regional mechanisms of the state policy in the field of healthcare and health service in the Far North of the Russian Federation. A possible development of medical subprogram should also be taken into account, as it can result in targeted modeling of the healthcare for the Arctic regions and decrease of child mortality rate. It should be noted that such Arctic model of healthcare should include not only practical support from practicing physicians but also scientific background.

Funding: It is a part of research of the Medical science centre of complex medical problems "Children health con-

dition monitoring in the Republic Sakha (Yakutia)" (state registration number: 0120-128-07-98); the project of the Ministry of science and higher education of the Russian Federation (2019-1472); and with a financial support from RFBR according to the research project #18-05-60035_Arctica.

References

1. Санников А.Л., Варакина Ж.Л., Сидоров А.В. Характеристика травматизма и инвалидности от внешних причин в Архангельской области и основные направления санаторно-курортной реабилитации последствий травм. *Современные проблемы науки и образования*. 2015; 4. [Sannikov A.L., Varakina Zh.L., Sidorov A.V. Characteristics of injuries and disability from external causes in the Arkhan-

gelsk region and the main directions of sanatorium-resort rehabilitation of the consequences of injuries. *Sovremenniyе problemy nauki i obrazovaniya*. 2015; 4. (In Russ.)] <http://science-education.ru/ru/article/view?id=20504> (date accessed: 02.03.2020).

2. Соколовская Т.А. Здоровье детей: основные тенденции и возможные пути его сохранения. *Современные проблемы науки и образования*. 2017; 4. [Sokolovskaya T. A. Children's health: main trends and possible ways to preserve it. *Sovremenniyе problem nauki i obrazovaniya*. 2017; 4. (In Russ.)] <http://science-education.ru/ru/article/view?id=26572> (date accessed: 02.03.2020).

3. Тырылгин М. А. Проблемы охраны здоровья населения Крайнего Севера (на примере региона Якутия). *Наука*. 2008; 303.

[Tyrlgin M. A. Problems of health protection of the population of the Far North (on the example of the region of Yakutia). *Nauka*. 2008; 303. (In Russ.)]

4. Чичахов Д.А., Вербицкая Л.И. Детская смертность в Республике Саха (Якутия). *Дальневосточный медицинский журнал*. 2010; 4: 42-43. [Chichagov D. A., Verbitskaya L. I. Child mortality in the Republic Sakha (Yakutia) Republic. *Dalnevostochniy medicinskiy zhurnal*. 2010; 4: 42-43. (In Russ.)] <http://www.fesmu.ru/elib/Article.aspx?id=232970>

5. Шигаев Н.Н., Кром И.Л., Еругина М.В., Дорогойкин Д.П. Междисциплинарный анализ социально детерминированных рисков здоровья детского населения. *Современные проблемы науки и образования*. 2016; 2. [Shigaev N. N., Krom I. L., Erugina M. V., Dorogoikin D.

L. Interdisciplinary analysis of socially determined risks of children's health. *Sovremenniyе problem nauki i obrazovaniya*. 2016; 2. (In Russ.)] <http://science-education.ru/ru/article/view?id=24246> (date accessed: 02.03.2020).

6. Collins S. A., Surmala P., Geraldine O., Greenberg Ch., Willison L. Causes and risk factors for infant mortality in Nunavut, Canada 1999–2011. *Pediatrics*. 2012; 12:190. <http://www.biomedcentral.com/1471-2431/12/190>

7. Skold P., Axelsson P., Karlsson L., Smith L. Infant mortality of Sami and settlers in Northern Sweden: the era of colonization 1750–1900. *Global Health Action*. 2011; 4: 8441. DOI: 10.3402/gha.v4i0.8441 https://www.researchgate.net/publication/51760521_Infant_mortality_of_Sami_and_settlers_in_Northern_Sweden_the_era_of_colonization_1750-1900

M.I. Mikhaylichenko, K.G. Shapovalov, V.A. Mudrov, O.S. Gruzdeva

THE ROLE OF MATRIX METALLOPROTEINASES AND THEIR INHIBITORS IN PATIENTS WITH LOCAL COLD INJURY

DOI 10.25789/YMJ.2020.70.22

УДК: 616-092.19

The urgency of the local cold injury (LCI) on the territory of the Russian Federation is conditioned by its geographical position, significant specific weight in the structure of the general traumatism, difficulties of etiopathogenetic therapy, disappointing treatment results, which leads to frequent loss of ability to work and permanent disability.

The aim of the study was to identify the dynamics of the level of collagenases of the second subfamily (MMR-2, MMR-9) and their inhibitors (TIMP-1 and TIMP-2) in the blood of those, who sustained local cold injury.

The study included 60 patients with frostbite of the distal segments of the lower extremities. The level of MMR-2, MMR-9, TIMP -1 and TIMP -2 was studied on the 5th and 30th days after the frostbite using a multiplex blood test with a set of biomedical reagents.

In patients with frostbite, the level of MMR-2 and MMR-9 in the blood serum increases relative to the control group in the early stages of cryodamage, as well as an increase in the index of the markers studied directly proportional to the volume of the affected tissues. A similar dynamics was observed in the study of parameters of matrix metalloproteinase inhibitors. Based on the obtained data and analysis of the linear regression equation, a predictive model was formed that allows us to suspect the level of tissue damage in the early stages of local cold injury with high accuracy.

Keywords: local cold injury, endothelial dysfunction, matrix metalloproteinases, inhibitors of matrix metalloproteinases.

The urgency of the local cold injury (LCI) on the territory of the Russian Fed-

Chita State Medical Academy 39a, Gorky street, Chita, 672000, Russian Federation; **MIKHAILICHENKO Maxim I.** – Assistant of department of faculty surgery with the course of urology. Chita state medical academy, Chita, Russian Federation. E-mail – angelo999@yandex.ru. ORCID № 0000-0001-8660-2982. Phone number: +79145222922.

SHAPOVALOV Konstantin G. – Head of the Department of anesthesiology, intensive care. DM, professor. Chita state medical academy, Chita, Russian Federation. E-mail – shkg26@mail.ru. ORCID № 0000-0002-3485-5176.

MUDROV Viktor A. – Associate professor of obstetrics and gynecology. Chita state medical academy, Chita, Russian Federation. E-mail – mudrov_viktor@mail.ru, ORCID № 0000-0002-5961-5400. **GRUSDEVA Olga S.** – Assistant of the Department of pathological anatomy. Chita state medical academy, Chita, Russian Federation. E-mail – lolgas18@gmail.com. ORCID № 0000-0002-1738-0850.

eration is conditioned by its geographical position, significant specific weight in the structure of the general traumatism, difficulties of etiopathogenetic therapy, disappointing treatment results [4,7,8]. The frequent loss of ability to work and high percentage of disability indicate the need for further studies of pathogenetic mechanisms of cryodamage. The study and identification of new markers of local cold injury contributes to an earlier diagnosis of the volume of tissue lesions, the creation of qualitatively new approaches to the complex treatment of frostbite of the extremities, as well as successful and fastest rehabilitation of patients [1, 8].

In recent years, scientific works clearly show the deepening of research by domestic and foreign authors on the features of the pathogenesis of cryodamage, early diagnosis of the volume of affected tissues, methods of surgical treatment of deep frostbite of the extrem-

ities and rehabilitation of patients [4, 8].

There is no doubt that endothelial dysfunction plays a fundamental role in the pathogenesis of frostbite [7-10]. Endothelial cells damaged by cold and secondary alterations, as well as cells attracted to the focus of inflammation, increase a large number of biologically active substances, including matrix metalloproteinases (MMR) and their inhibitors (TIMP).

Recent studies have shown that collagenases, as well as their inhibitors, play a significant role in the pathogenesis of connective tissue damage and its fibrosis in various pathologies [2]. Collagenases are Zn²⁺ and Ca²⁺ dependent induced endogenous peptidases involved in tissue rearrangement, by the destruction of its organic components, as well as the exchange of proteins of the interstitial matrix [2, 3]. MMR secretion is influenced by cytokines released by endothelial cells, fibroblasts, macrophages, platelets [3, 10].

Relatively recently, it has been established that MMR can be activated by low pH, hyperthermia and hypothermia, as well as by processes of lipid peroxidation [14]. MMR of the second subfamily play an important role. These include type IV endopeptidases-MMR-2 and MMR-9. This group of matrix metalloproteinases remodels native collagen, changing its conformation, which makes it difficult for cells to migrate to tissues for the implementation of inflammatory processes.

Tissue inhibitors of MMR are proteins that regulate the balance of connective tissue collagen, forming high-affinity complexes with collagenases, thereby leveling the pathological processes provoked by matrix metalloproteinases. The main sites of TIMP expression are the bone tissue and ovaries [8, 9, 16].

Collagenase inhibitors (TIMR-1 and TIMR-2) are little-known and unexplored biomarkers of alterations. Although in medical practice, these biomarkers are used quite successfully in stratifying the risks of undesirable cardiovascular events, arterial hypertension, diabetes mellitus, chronic renal failure and complicated obstetrics [4, 9, 10]. Evaluating the effectiveness of pathogenetically based therapy is extremely relevant and promising for patients with local cold trauma.

It should be noted that the optimal target values in the blood of MMR and TMR, which should be equalized in the course of research, are not yet regulated. At the same time, the scientific justification for determining the target values of markers of collagen balance, which plays an important role in proliferative processes closely related to the course of the wound process, can help control the quality of therapy and allow predicting the course of the wound process in cryodamage.

Purpose of research: to determine the dynamics of the level of collagenases of the second subfamily (MMR-2, MMR-

9) and their inhibitors (TIMP-1 and TIMP-2) in the blood of those, who sustained local cold injury.

Research materials and methods.

The study included 60 patients (40 men and 20 women), 20 of them with frostbite of the toes (group 1), in the second group of victims, the lesion spread to the pretarsal-molar joint (n=22), group 3 – patients with frostbite of the more proximal parts of the lower limb (n=18). Depending on the volume of the affected tissues, the study was performed on the 5th day after the injury. The average age of patients was 35±7 years. The level of MMR-2, MMR-9, TIMP -1 and TIMP - 2 was measured on the 5th and 30th days after frostbite in the same patients using a multiplex analysis of serum with a set of biomedical reagents. All patients were treated at the regional burn center on the basis of GUZ "City clinical hospital No. 1" in Chita with local cold injury of III-IV degree in the period from 2018 to 2019.

The control group consisted of relatively healthy people aged 30±10 years (n=28).

All patients and volunteers gave their written voluntary informed consent, in accordance with the requirements of the Helsinki Declaration of the world medical Association (ed. 2013)

The exception group included patients with severe somatic pathology: inflammatory processes of various localization, obliterating diseases of the arteries, nerve damage of the extremities, diabetes, hypertension, alimentary exhaustion and obesity, and individual dependence of various Genesis.

Statistical processing of the research results was carried out using the IBM SPSS Statistics Version 25.0 software package. The data obtained were systematized in the form of a median and a confidence interval. Considering the size of the control group of no more than 50

people, the normality of the distribution of features was assessed using the Shapiro-Wilk criterion. The statistical significance of the differences in indicators was assessed by comparing the critical and calculated values of the Kraskel-Wallis criterion with the subsequent determination of the significance level p. For a more precise description of the identified trends used the Mann-Whitney test, which allows to evaluate the performance differences between comparing groups in pairs with application of a Bonferroni correction when assessing the value of R. To assess the relationship between indicators we used the Spearman correlation coefficient (ρ). Based on the obtained values of ρ we revealed the closeness of the connection on a scale of Chedoke and its direction (direct or reverse). Subsequently, we calculated a segregated coefficient of determination, which shows the proportion of the explained dependence. The predictive model is built by linear regression.

The results and discussion. We note an increase in the level of MMR-2 and MMR-9 in serum in patients with frostbite relative to the control group in the early stages of frostbite. The level of MMR-2 decreased to the values of the control group, and the indicators of MMR-9 remained significantly higher than normal later in the period after the injury. This fact pathogenetically justifies a large number of complications in patients with frostbite.

In the late reactive period, the serum level of MMR-2 in patients with cryodamage is 3.4 times higher relative to control (p=0.011), on day 30-the values of MMR-2 do not differ in control indicators (p=0.103) (Table 1). The level of MMR-9 in patients with local cold injury on day 5 is 14.5 times higher than the control indicators (p=0.002), on day 30 – 12.5 times higher relative to the group of healthy volunteers (p<0.001) (Table 1).

Table 1

The content of matrix metalloproteinases and their inhibitors in the blood serum of victims with local cold trauma in different periods of cryodamage

Study group	MMP-2	MMP-9	TIMP-1	TIMP-2
Control group (n = 28)	2.3 (75% ДИ 2.16 – 2.45)	32.00 (75% ДИ 28.55 – 35.37)	734.4 (75% ДИ 733.51 – 770.20)	247.2 (75% ДИ 232.19 – 257.81)
First group (5 day) (n = 30)	7.97 (75% ДИ 7.59 – 8.20) p < 0.001	448.86 (75% ДИ 418.33 – 466.28) p < 0.001	1259.2 (75% ДИ 1230.83 – 1342.35) p < 0.001	555.2 (75% ДИ 528.46 – 578.94) p < 0.001
Second group (30 day) (n = 30)	4.53 (75% ДИ 4.27 – 4.92) p < 0.001 p ₁ <0.001	354.14 (75% ДИ 343.65 – 375.35) p < 0.001 p ₁ <0.001	1481.6 (75% ДИ 1462.76 – 1646.89) p < 0.001 p ₁ <0.001	478.4 (75% ДИ 472.65 – 555.55) p < 0.001 p ₁ =0.024

p – reliability of the difference in indicators relative to control; p₁-reliability of the difference in indicators relative to patients with frostbite in the late reactive period.

In patients with cryodamage of distal stop, the level of MMP-2 was 2.1 times higher relative to the control ($p < 0.001$), in patients with frostbite more proximal segments of the foot – the value of MMP-2 to 2.6 times higher than the benchmarks ($p < 0.001$). The level of MMP-2 in victims with the most severe frostbite is 3.5 times higher than the control values ($p < 0.001$) (Table 2). The level of MMP-9 in victims with frostbite of the toes is 4.9 times higher than the control indicators ($p < 0.001$), and in patients with more severe frostbite – 10 times higher relative to the control group ($p < 0.001$) (Table 2). In patients with group 3 frostbite, the level of MMP-9 increased by 14.5 times relative to the control values ($p < 0.001$) (Table 2).

In the late reactive period in patients with cryodamage, the TIMP-1 level is 1.7 times higher relative to the control ($p < 0.001$), on day 30 – the TIMP-1 value increased 2 times relative to the control ($p < 0.001$) (Table 1). The TIMP-2 Level in patients on day 5 from the moment of cryodamage is 2.3 times higher than the control indicators ($p < 0.001$), on day 30 – 2.2 times higher relative to the control group ($p < 0.001$) (Table 1).

In patients with cryodamage of distal stop, the level of TIMP-1 in the blood 2 times higher relative to the control ($p < 0.001$), in patients with frostbite more proximal segments of the foot – value TIMP-1 is 1.8 times higher than the benchmarks ($p < 0.001$). The level of TIMP-1 in the patients with the most severe frostbite is 1.6 times higher than the control values ($p < 0.001$) (Table 2). The level of TIMP-2 in patients with local cold injury of the toes is 2.1 times higher

than the control indicators ($p < 0.001$), in patients with more severe frostbite – 2.2 times higher relative to the control group ($p < 0.001$) (Table 2). In patients with group 3 frostbite, the level of TIMP-2 is 2.3 times higher than the control value ($p < 0.001$) (Table 2).

The data obtained during the study indicate an increase in the content of matrix metalloproteinases and their inhibitors in the blood serum of those, who sustained cold trauma. At the same time, significant dynamics of the studied markers does not occur in the long-term period of cryodamage. Probably, during frostbite, a significant failure in the remodeling of the cytoskeleton, tissue repair, angiogenesis occurs, and there are prerequisites for an atypical, prolonged course of reparative processes.

Previously conducted research in patients with deforming arthrosis, in complicated obstetrics, in patients with CHD, aimed at detecting matrix metalloproteinases and their inhibitors, also revealed a persistent increase in the level of the studied predictors in the serum of patients [2, 5, 10, 11]. Scientists have concluded that metalloproteinases are one of the pathogenetic causes of chronization of any pathology [5, 6]. It is possible that collagenases are the predictor of the adverse course of local cold injury. This is also proved by the large number of adverse consequences of injury. According to a number of authors, complications are present in the majority of patients with local cold trauma [3, 4, 9].

The increased content of matrix metalloproteinase inhibitors probably indicates an attempt on the part of the body to sta-

bilize the emerging catastrophe in the center of alterations. We found a sharp increase in TIMP-1 and TIMP-2 in all periods of cryodamage. Attention is drawn to the fact that there is no correlation of TIMP in patients with the most extensive lesions and the mildest injury limited to the toes. It is also necessary to indicate that the level of TIMP does not decrease for 30 days from the moment of cryodamage. This phenomenon is probably associated with the death of bone tissue, since inhibitors of matrix metalloproteinases are deposited mainly in osteocytes [2, 6, 11, 18].

Thus, there is a high degree of parallelism between the value of matrix metalloproteinases and their inhibitors in blood serum and the level of damage to the distal segments of the lower extremities (Table 3).

According to modern scientific data, with fibrotic tissue disorganization, the MMP index decreases, and the level of their inhibitors on the contrary increases. When collagen is degraded, on the contrary, the content of collagenases increases, and inhibitors decrease [2, 12]. In patients with frostbite, we see an increase in all the studied biomarkers of the matrix metalloproteinase system and their inhibitors, even in the case of a relatively mild cold injury.

Relatively recently, V. A. Tumansky and T. A. Khristenko [6] have shown that MMP and TIMP levels are significantly increased in patients with pancreatic cancer. Given that the complex of MMP and TIMP is formed by the "key-lock" type [5, 6], the authors suggested that the increase in the level of such biologi-

Table 2

The content of matrix metalloproteinases and their inhibitors in the blood serum of victims with local cold trauma depending on the volume of affected tissues

Study group	MMP-2 (ng/ml)	MMP-9 (ng/ml)	TIMP-1 (ng/ml)	TIMP-2 (ng/ml)
Control group (n = 28)	2.3 (75% ДИ 2.16 – 2.45)	32.00 (75% ДИ 28.55 – 35.37)	734.4 (75% ДИ 733.51 – 770.20)	247.2 (75% ДИ 232.19 – 257.81)
First group (n = 20)	4.65 (75% ДИ 4.43 – 4.77) $p < 0.001$	126.50 (75% ДИ 126.99 – 147.95) $p < 0.001$	1488.0 (75% ДИ 1420.76 – 1540.74) $p < 0.001$	513.6 (75% ДИ 486.84 – 529.16) $p < 0.001$
Second group (n = 22)	6.78 (75% ДИ 6.75 – 7.14) $p < 0.001$ $p_1 < 0.001$	314.50 (75% ДИ 315.29 – 326.41) $p < 0.001$ $p_1 < 0.001$	1292.8 (75% ДИ 1252.00 – 1352.05) $p < 0.001$ $p_1 = 0.159$	536.8 (75% ДИ 495.50 – 576.50) $p < 0.001$ $p_1 = 0.778$
Third group (n = 18)	7.97 (75% ДИ 7.59 – 8.20) $p < 0.001$ $p_1 < 0.001$ $p_2 < 0.001$	448.86 (75% ДИ 418.33 – 466.28) $p < 0.001$ $p_1 < 0.001$ $p_2 < 0.001$	1259.2 (75% ДИ 1230.83 – 1342.35) $p < 0.001$ $p_1 < 0.001$ $p_2 = 0.007$	555.2 (75% ДИ 528.46 – 578.94) $p < 0.001$ $p_1 = 0.013$ $p_2 = 0.021$

p – reliability of the difference in indicators relative to control; p1-reliability of the difference in indicators relative to 1 group of patients; p2-reliability of the difference in indicators relative to 2 groups of patients.

cal "locks" is a reflection of the antitumor reaction and cells with an attempt to limit the focus of alterations. It is possible that a similar biological phenomenon of cell microenvironment formation is realized in patients with frostbite, aimed at delineating the focus of damaged tissues by rough remodeling of the extracellular matrix and changing the conformation of the cell membrane.

MMR 2 in combination with other collagenases is known to inhibit angiogenesis. This phenomenon is associated with their ability to form antiangiogenic peptides by converting plasminogen into angiostatin, which inhibits proliferation and exacerbates endothelial cell apoptosis [6, 13]. This is another confirmation of the probable biological feasibility of increased MMR expression in patients with frostbite. Inhibition of microcirculation was confirmed by our earlier studies in patients with local cold trauma [3, 8, 9]. Collagenases have been found to have an inhibitory effect on inflammation by processing a significant amount of chemokines, including pro-inflammatory interleukins. Probably, the inhibitory effect of MMR-2 is associated with worsening endothelial dysfunction and the formation of a large number of adverse sequential reactions, forming a kind of protective reaction of the body to increasing perifocal inflammation [3].

It was found that the level of IL-1, IL-8, IL-12 and TNF α in the blood was increased during all periods of cryodamage [9, 10]. However, in the later periods of frostbite, the level of Pro-inflammatory interleukins decreases, but still remains above normal values. However, the level of MMR-9 remains high in patients and in remote periods of local cold injury. Synthesis of these metalloproteinases occurs mainly in macrophages, as well as platelets, which realize their functions in the interstitial [6, 14]. One of the features of MMR-9 is the chemotaxis of fibroblasts into the interstitial space for the implementation of repair processes [12, 16, 17]. On the other hand, MMR-9 contributes to collagen desmoplasia [11, 15]. Remodeling of collagen in the lesion site provokes discoordination of proliferation and, as a result, a prolonged and unfavorable course of the wound process.

Based on the analysis of the linear regression equation, which included the initial indicators (values of matrix metalloproteinases and their inhibitors), the significance of indicators in the structure of the predictive model was determined (Table 4).

Considering the insufficient significance, the TIMP-1 indicator was re-

Table 3

The actual degree of parallelism between the value of matrix metalloproteinases and their inhibitors and the level of damage to the lower extremities

Parameter	Spearman correlation coefficient	Statistical significance	Relationship strength on a scale of Chedoke
MMP-2	0.797	< 0.001	High straight
MMP-9	0.907	< 0.001	High straight
TIMP-1	- 0.186	0.002	Weak reverse
TIMP-2	0.381	< 0.001	Moderate straight

Table 4

Significance of indicators in the structure of the predictive model

Model	Non-standardized coefficients		Standardized coefficients		Significance in the model structure
	B	Standard error	Beta	r	
Constant	- 0.466	0.181		- 2.575	0.011
MMP-2	0.165	0.017	0.378	9.578	0.0001
MMP-9	0.003	0.0001	0.511	12.970	0.0001
TIMP-1	- 6.809	0.0001	- 0.019	- 0.643	0.520
TIMP-2	0.001	0.0001	0.136	4.170	0.0001

Table 5

Summary for the resulting predictive model

Model	R	R ²	adjusted R ²	The standard error of estimate
$K = 0.165 \times \text{MMP-2} + 0.003 \times \text{MMP-9} + 0.01 \times \text{TIMP-2} - 2.5$	0.873	0.763	0.760	0.451

moved from the structure of the original model. As a result, a pattern was determined by repeated linear regression, which is expressed by the formula: $K = 0.165 \times \text{MMP-2} + 0.003 \times \text{MMP-9} + 0.01 \times \text{TIMP-2} - 2.5$, the name of the units of measurement of indicators is ng/ml. At values Of K from 1.0 to 4.4, frostbite of the toes is diagnosed, at K from 4.4 to 5.4, the lesion boundary extended to the pre-tarsal-metatarsal joint, more than 5.4 - to the level of the lower third of the lower leg (Table 5).

Taking into account the value of the adjusted coefficient of determination (0.760), we can consider the relationship between the coefficient of K and the level of damage to the distal segments of the lower extremities in local cold trauma to be quite strong.

Consequently, the analysis of the obtained data allows to establish that increased expression of collagenase and their inhibitors reflects the severity and course of the cold injury due to endothelial dysfunction and formation of fibrosis in the lesions and the perifocal. It is possible that an imbalance of the collagenase

system can cause structural and functional changes in the extracellular matrix and cellular structures, contributing to their pathological remodeling and fibrosis [3, 7, 9, 10].

Conclusions:

1. It was found that the level of matrix metalloproteinases increases in the blood of patients with local cold injury. The increase in the collagenase index in the blood serum of patients is directly proportional to the severity of the injury.

2. It is revealed that the performance of inhibitors collagenase increased significantly in all periods of cryodamage. Increasing levels of inhibitors collagenase is not directly dependent on the severity of cold injury.

3. The pattern formed on the basis of the studied markers can serve as a predictive criterion for early determination of the severity of cryodamage.

References

1. Васина Л.В., Власов Т.Д., Петрищев Н.Н. Функциональная гетерогенность эндотелия (обзор). *Артериальная гипертензия*. 2017;

(2): 88-102. [Vasina LV, Vlasov TD, Petrishchev NN. Functional heterogeneity of the endothelium (review). *Hypertension*. 2017; (2): 88-102. (In Russ).]

2. Егорова Е.Н., Мазур В.В., Калинин М.Н., Мазур Е.С. Взаимосвязь эндотоксемии, факторов системного воспаления и компонентов системы матриксных металлопротеиназ – тканевых ингибиторов металлопротеиназ при ХСН. *Сердечная недостаточность*. 2012; 72(4): 233-236. [Egorova E. N., Mazur VV, Kalinkin MN, Mazur ES. Relationship of endotoxemia, factors of systemic inflammation and components of the matrix metalloproteinase system-tissue inhibitors of metalloproteinases in CHF. *Heart failure*. 2012; 72(4): 233 — 236. (In Russ).]

3. Коннов Д.Ю., Малайчиков А.В., Шаповалов К.Г., Коннов В.А. Закономерности изменений параметров микроциркуляции и электрофизиологических показателей сердечного ритма при критической гипотермии. *Забайкальский медицинский вестник*. 2017;4: 17-24. [Konnov DYu, Malyarchikov AV, Shapovalov KG, Konnov VA. Regularities of changes in microcirculation parameters and electrophysiological parameters of heart rate in critical hypothermia. *Zabaikalsky medical journal*. 2017; 4: 17-24. (In Russ).]

4. Николаев В.М., Алексеев Р.З., Федорова С.А. Интенсивность свободнорадикального окисления липидов в организме больных холодовой травмой. *Якутский медицинский журнал*. 2018; 2: 34-38. [Nikolaev VM, Alekseev RZ, Fedorova SA. Intensity of free radical oxidation of lipids in the body of patients with cold trauma. *Yakut medical journal*. 2018; 2: 34-38. (In Russ).]

5. Соломакина Н.И., Беленков Ю.Н. Прогностическое значение тканевого ингибитора матриксных металлопротеиназ - 1 (TIMP-1) у больных ХСН. *Сердечная недостаточность*. 2010; 61(5): 281-284. [Solomakhina NI., Belenkov YuN. Prognostic value of a tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) in patients

with CHF. *Heart failure*. 2010; 61(5): 281-284. (In Russ).]

6. Туманский В. А., Христенко Т. А. Иммуногистохимическое исследование MMP-2, TIMP-1 при гиперпластических полипах и аденокарциноме желудка кишечного типа. *Морфология*. 2017; 11(3): 21-28. [Tumanskiy VA, Khrystenko TA. Immunohistochemical study of MMP-2, TIMP-1 in hyperplastic polyps and intestinal-type gastric adenocarcinoma. *Morphologia*. 2017;11(3): 21-28. (In Russ).]

7. Целуйко С.С., Заболотских Т.В., Дудариков С.А., Красавина Н.П., Корнеева Л.С. Действие холода на организм. Криопротекторы и средства противоишемической защиты тканей. *Якутский медицинский журнал*. 2018; 2(62): 48-55. [Tseluyko SS, Zabolotskikh TV, Dudnikov SA, Krasavina NP, Korneeva LS. The Effect of cold on the body. Cryoprotectants and means of anti-ischemic protection of fabrics. *Yakut medical journal*. 2018; 2(62): 48-55. (In Russ).]

8. Шаповалов К.Г. Отморожения в практике врача анестезиолога-реаниматолога. *Вестник анестезиологии и реаниматологии*. 2019; 16(1): 63-68. <https://doi.org/10.21292/2078-5658-2019-16-1-63-68>. [Shapovalov K.G. Frostbites in the practice of an anesthesiologist and emergency physician. *Messenger of anesthesiology and resuscitation*. 2019;16(1): 63-68. <https://doi.org/10.21292/2078-5658-2019-16-1-63-68>. (In Russ).]

9. Шаповалов К.Г., Томина Е.А., Михайличенко М.И., Иванов В.А., Витковский Ю.А. Содержание цитокинов в крови больных при местной холодовой травме. *Медицинская иммунология*. 2008; 10(1): 89-92. [Shapovalov KG, Tomina EA, Mikhailichenko MI, Ivanov VA, Vitkovsky YA. The content of cytokines in the blood of patients with local cold injury. *Medical immunology*. 2008;10(1): 89-92. (In Russ).]

10. Юлдашева Д.Ю. Роль матриксных металлопротеиназ и их ингибиторов при развитии гиперплазии эндометрия. *Фундаментальные исследования*. 2015; 1(4): 845-847. [Yuldasheva DY. The Role of matrix metallopro-

teinases and their inhibitors in the development of endometrial hyperplasia. *Fundamental study*. 2015; 1(4): 845-847. (In Russ.) URL: <http://fundamental-research.ru/ru/article/view?id=37434> (дата обращения: 17.01.2020)].

11. Blankenberg S., Rupprecht HJ, Poirier O. Plasma concentrations and genetic variation of matrix metalloproteinase-9 and prognosis of patients with cardiovascular disease. *Circulation*. 2003; 107(12): 1579-1585.

12. Gilbert Estelle's J. Expression of angiogenic factors in endometriosis: relationship to fibrinolytic and metalloproteinase systems. *Human Reproduction*. 2007; 22(8): 2120-2127.

13. Kingma CF, Hofman II, Daanen HM. Relation between finger cold-induced vasodilation and rewarming speed after cold exposure. *European Physiology*. 2019; 119(1): 171-180. DOI: 10.1007.

14. Lopez-Rivera E. Matrix metalloproteinase 13 mediates nitric oxide activation of endothelial cell migration. *PNAS*. 2005; 102(10): 3685-3690. DOI: 10.1093/humrep/dem149.

15. Miao MS, Xiang LL, Bai M, Cao LH. Frostbite animal model preparation specification (draft). *Zhongguo Zhong Yao Za Zhi*. 2018; 43(2): 410-414. DOI: 10.19540.

16. Pino M. Association between MMP1 and MMP9 activities and ICAM1 cleavage induced by tumor necrosis factor in stromal cell cultures from eutopic endometria of women with endometriosis. *Reproduction*. 2009; 138 (5): 837-847.

17. Pan Y, Thapa D, Baldissera LJ, Argunhan F, Aubdool AA, Brain SD. Elevance of TRPA1 and TRPM8 channels as vascular sensors of cold in the cutaneous microvasculature. *Pflugers Arch*. 2018; 470(5): 779-786. DOI: 10.1007.

18. Zhang H. Role of Matrix Metalloproteinases and Therapeutic Benefits of Their Inhibition in Spinal Cord Injury. *Neurotherapeutics*. 2011; 8: 206 – 220. DOI: 10.1007/s13311-011-0038-0.

19. Cauchy E, Davis CB, Pasquier M, Meyer EF, Hackett PH. A New Proposal for Management of Severe Frostbite in the Austere Environment. *Wilderness Environ Med*. 2016; 27(1): 92-99. DOI: 10.1016.



I.N. Molodovskaya, E.V. Tipisova, V.A. Popkova, A.E. Elfimova,
D.S. Potutkin

PHOTOPERIODIC VARIATION OF THYROID HORMONES AND AUTOANTIBODIES IN MALES OF THE EUROPEAN NORTH

DOI 10.25789/YMJ.2020.70.23

УДК [612.44-055.1:577.175.44]
(470.1/.2)(045)

Aim: to study the circannual dynamics of the concentrations of TSH, thyroglobulin, total and free fractions of iodothyronines, and thyroid autoantibodies in 20 healthy men (average age 33.8 ± 1.1 years), who are permanently resident in Arkhangelsk ($64^{\circ}32'N$), and examine the relationship between these measurements and the climatic factors, such as daylight hours, ambient temperature, pressure, and humidity.

Materials and methods. An analytical, prospective, uncontrolled study was conducted with voluntary informed consent. Blood samplings for the assay of the above hormones were collected quarterly during one calendar year. The serum concentration of hormones and antibodies was determined using enzyme-linked immunoassay.

Results. Significant intra-annual rhythms of total iodothyronine concentration were found with lower values in the autumn-winter period. The annual variation in serum thyroid peroxidase antibodies showed a slight, but statistically significant increase in antibody levels in the autumn-winter period compared to the spring one. The levels of thyroglobulin, a marker of thyroid activity, were statistically significantly higher in the spring compared to the autumn period. There were no significant seasonal rhythms in TSH, free iodothyronines and thyroglobulin antibodies.

Conclusion. A study of the circannual rhythms in the level of thyroid hormones in the adult male population of the European North showed year-round variation in total iodothyronines. Only the differences in thyroxine level can be explained by the climatic factors such as air pressure and daylight hours. At the same time, the seasonal variation of total iodothyronine, thyroglobulin and thyroid peroxidase antibody was characterized by small amplitude of the year-round rhythm.

Keywords: thyroglobulin antibodies, thyroid peroxidase antibodies, thyroid stimulating hormone, thyroglobulin, thyroxine, triiodothyronine, photoperiodicity.

Introduction. Seasonal changes in TSH and iodothyronine levels are known both in euthyroid individuals living in extreme Arctic and subarctic environmental and in individuals with a long stay in the Antarctic [8, 9, 16]. Most studies showed an increase in TSH in the winter or through prolonged exposure to cold temperatures [8, 16], in several studies

an increase in T3 was observed [8], however, a decrease in iodothyronine levels was also observed [6, 16]. Previous research of seasonal and photoperiodic changes in thyroid hormones in adult residents of the European North showed an increase in the T4 content during the minimum daylight hours, while the T3 content was significantly higher during the maximum daylight hours [5]. Yakut men and women both displayed significant declines of free fractions of iodothyronines, and significant increase in TSH from summer to winter, which indicates a strict relationship between the hormones involved in the axis of the hypothalamus-pituitary-thyroid gland [13]. The results of a study of the circannual variations of thyroid hormones levels in the adult population of Western Siberia revealed the maximum TSH in February-March in men and in January-February in women, with minimal TSH in September-October and August-September in men and women, respectively. Moreover, the maximum T3 levels accrue to April-May in both men and women, and T4 – September-October [1]. On the other hand, only a few studies revealed seasonal variations in the levels of free fractions of iodothyronines [13]. Since thyroglobulin values were affected by small changes in the thyroid gland volume, some authors consider thyroglobulin as a sensitive indicator of thyroid activity [10]. At the same time, the seasonal variability of thyroglobulin has been poorly studied [8].

Thyroid antibodies can be detected not only in patients with autoimmune diseases, but also in people without severe thyroid dysfunction [2]. Intra-annual dynamics of autoantibody levels can be mediated by seasonal changes in thyroid function associated with daylight hours and temperature. At the same time, seasonal variation of thyroid autoantibodies in the available literature is represented by singular works. So, in the study by Lutfaliev G.T. it was shown an increased level of thyroglobulin antibodies (Anti-Tg) in the winter [3].

Most of the studies lacked reliability as they were conducted before the development of new and efficient assays methods of statistical analysis [5], or it was a retrospective study [7], based on extensive databases which were got from different people in different year seasons. So it remains poorly known the question of seasonal and photoperiodic dynamics of hormones in the same representatives of the population.

The aim of the study was to study the circannual dynamics of the concentrations of TSH, thyroglobulin, total and free fractions of iodothyronines, and thyroid autoantibodies in healthy men and examine the relationship between these measurements and the climatic factors, such as daylight hours, ambient temperature, pressure, and humidity.

Material and methods. 20 euthyroid men (mean age 33.8 ± 1.1 years) residing in Arkhangelsk ($64^{\circ}32'N$) took part in a prospective, analytical, uncontrolled

MOLODOVSKAYA Irina Nikolaevna – candidate of biological sciences, scientific researcher, N. Laverov Federal Center for Integrated Arctic Research, 163000, Arkhangelsk, Lomonosova av. 249, pushistiy-86@mail.ru, +79115550701; <http://orcid.org/0000-0003-3097-9427>; **TIPISOVA Elena Vasilievna** – doctor of biological sciences, chief researcher, N. Laverov Federal Center for Integrated Arctic Research, 163000, Arkhangelsk, Lomonosova av. 249, tipisova@rambler.ru, +79095555095, <http://orcid.org/0000-0003-2097-3806>; **POPKOVA Victoria Anatolievna** – candidate of biological sciences, senior researcher, N. Laverov Federal Center for Integrated Arctic Research, 163000, Arkhangelsk, Lomonosova av. 249, victoria-popkova@yandex.ru, +79216754501, <http://orcid.org/0000-0002-0818-7274>; **ELFIMOVA Alexandra Eduardovna** – candidate of biological sciences, senior researcher, N. Laverov Federal Center for Integrated Arctic Research, 163000, Arkhangelsk, Lomonosova av. 249, a.elfimova86@mail.ru, +79217209022, <http://orcid.org/0000-0003-2519-1600>; **POTUTKIN Dmitry Sergeevich** – junior researcher, N. Laverov Federal Center for Integrated Arctic Research, 163000, Arkhangelsk, Lomonosova av. 249, d.potutkin@narfu.ru, +79021981974, <http://orcid.org/0000-0002-9738-7517>.

study on the basis of Voluntary Informed Consent. The study was conducted in accordance with the ethical principles stated in Declaration of Helsinki of 1964 (revised in Seoul in 2008). Criteria for inclusion in the study were: age from 25 to 44 years, passing regular (at least once a year) preventive or medical examination, absence of cardiovascular complaints, systemic diseases and endocrine pathology. Blood for the study was obtained on an empty stomach in the morning. The survey of the same men was carried out quarterly in the period from March to December. With the help of fully automated ELISA analyzer Elisys Uno (Germany) the serum levels of thyroid-stimulating hormone - TSH, total triiodothyronine - T3, total thyroxine - T4, free triiodothyronine - fT3, free thyroxine - fT4, thyroglobulin, thyroid peroxidase antibody – Anti-TPO, thyroglobulin antibodies – Anti-Tg (using test kits from Alkor-Bio, Russia) were determined by enzyme immunoassay. Statistical analysis was performed using the statistical software STATISTICA 10. The normality of distribution of continuous variables was tested by Shapiro-Wilk's W test. In accordance with the obtained results, a nonparametric repeated measures analysis of variance for dependent factorial measures (Friedman test) was used, followed by pairwise comparison using the Wilcoxon test to assess the significance of differences between the two related samples. Spearman's rank correlation coefficient was calculated to measure the strength and direction of the relationship between two variables. A probability value of $p < 0.05$ was considered statistically significant.

Results. In the present study, the annual dynamics of the total iodothyronines (T3 and T4) was noted, at the same time, there were no significant seasonal rhythms of the free iodothyronines, which was also shown in the studies by D. Santi et al. [15] (Table). Minimum T3 levels were observed in autumn and winter, and maximum - in the spring and summer, while the examined group of men was characterized by moving of T3 values to the lower limit of normal in spring and summer, and in autumn and winter the median of T3 was below the lower limit of normal. The proportion of individuals with decreased serum T3 was statistically significantly lower in the fall and winter than in the summer, which was 65% versus 35% ($p = 0.03$). The level of T4 was statistically significantly reduced in winter compared to other periods of the year.

Serum TSH levels were highest in winter and lowest in autumn, however, there were no statistically significant differences

between the four periods of the year. At the moment many authors identify the value of $2.5 \mu\text{MU} / \text{L}$ as the upper control limit of TSH level due to the fact that its higher values may be associated with impaired thyroid function in the future. So in the present study the prevalence of its increased values were defined [12]. Thus, the proportion of individuals with TSH levels of more than $2.5 \mu\text{MU}/\text{L}$ was statistically significantly higher in the winter than in the autumn and corresponds to 60% versus 25% ($p = 0.01$). In addition, it was found that the annual maximum of serum TSH level (winter) corresponds to the annual minimum of T4, which indicates that the annual spread of T4 partially determines the level of TSH.

The study of the annual variation of thyroid autoantibody levels revealed statistically significantly lower Anti-TPO levels in spring compared to the autumn-winter period with a maximum in December, while there was no seasonal dynamics of Anti-Tg levels. In the study group of men, there were no individuals with positive antibodies whose concentrations exceed the physiological limits, and the median values of autoantibody levels were so low that they did not exceed one unit of measurement, and their spread within one season of the year was also insignificant, which may indicate a low autosensitization in the examined group of healthy men and their ability to maintain body balance and health in the North.

An analysis of the correlation relationships, carried out on the entire database without separation by photoperiods, showed that only the serum T4 level sig-

nificantly correlated with climatic factors, that is, with daylight hours expressed in minutes ($r = 0.31$; $p = 0.005$), and with atmospheric pressure ($r = -0.32$; $p = 0.004$).

Discussion. The study of Variability in Hormone Concentrations in men of the European North suggests that periods of increasing daylight hours and maximum daylight hours (spring and summer) are characterized by increased levels of hormones that activate metabolic processes (T3 and T4). The absence of seasonal dynamics of the free iodothyronines may indicate the preservation of a sufficient serum level of biologically active thyroid hormone fractions throughout the year, which are necessary for adaptation to changing environmental conditions, while the functional activity of the thyroid gland decreases during the minimum duration of daylight hours, as indicated by significantly lower levels of T4 in the winter. A higher TSH level in winter compared to other periods corresponds to a similar prospective study of healthy men in Finland [16]. Elevated TSH levels in winter may be associated with a decrease in iodothyronine levels in the pituitary gland or with a decrease in the release of somatostatin or dopamine from the hypothalamus. The data presented in this study on a decrease in total iodothyronines levels in the winter period as well as data from studies of subjects wintering on Antarctic bases, which showed a decrease in serum T3 and T4 and an increase in TSH levels, confirm this conclusion [14].

The seasonal dynamics of thyroid hormones can be caused not by a change in the clearance of hormones by thyroid cells, but by a change in the intrinsic

Quantitative data of blood parameters in men of the city of Arkhangelsk depending on the photoperiod of the year (the results are presented as a median and 10/90 percentiles)

Variable	March	June	September	December	p-value
TSH 0,23-3,4 $\mu\text{IU}/\text{l}$	2.43 (1.12; 3.81)	2.17 (1.22; 4.24)	1.81 (0.95; 4.69)	2.64 (1.14; 4.16)	$p > 0.05$
T3 1,0-2,8 nmol/l	1.04 (0.86; 1.37)	1.09 (0.82; 1.38)	0.92 (0.73; 1.21)	0.94 (0.75; 2.26)	$p_{1-3} = 0.004$ $p_{2-3} = 0.004$ $p_{2-4} = 0.003$
T4 53-158 nmol/l	111.91 (95.96; 134.31)	113.45 (101.41; 126.49)	111.07 (87.22; 128.79)	99.03 (90.59; 117.13)	$p_{1-4} = 0.002$ $p_{2-4} = 0.0002$ $p_{3-4} = 0.014$
св. T3 2,5-7,5 pmol/l	5.09 (4.16; 5.59)	5.21 (4.69; 6.68)	5.35 (4.39; 5.85)	5.23 (4.30; 6.07)	$p > 0.05$
св. T4 10,0-23,2 pmol/l	12.55 (11.20; 14.90)	13.05 (11.70; 14.90)	12.90 (10.30; 15.20)	12.90 (11.70; 15.10)	$p > 0.05$
Thyroglobulin 2-50 ng/ml	28.5 (10.58; 54.2)	22.75 (8.55; 52.2)	20.64 (7.91; 49.45)	21.16 (9.69; 62.2)	$p_{1-3} = 0.036$
Anti-Tg <65 U/ml	0.0 (0.0; 0.58)	0.0 (0.0; 0.29)	0.0 (0.0; 0.87)	0.0 (0.0; 0.58)	$p > 0.05$
Anti-TPO <30 $\text{Ед}/\text{мл}$	0.08 (0.0; 2.59)	0.24 (0.0; 5.99)	0.49 (0.08; 8.25)	0.65 (0.0; 6.39)	$p_{1-3} = 0.0005$ $p_{1-4} = 0.008$

thyroidal synthetic activity, independent marker of which can be thyroglobulin secretion [8]. So, in our study, the minimum values of thyroglobulin in the autumn-winter period correspond to minimum values of T3 and T4, and the maximum levels of thyroglobulin in the spring period correspond to those for TSH. Thus, we could assume that our study demonstrated a decrease in the thyroidal synthetic activity in the autumn-winter period, followed by a TSH-mediated compensatory increase in the levels of total iodothyronines in the spring.

According to Lutfaliev G.T. and Churkina T.S. the annual dynamics of autoantibodies was associated with changes in natural and climatic factors [3], and therefore, the point of interest was studying the intra-annual fluctuation of autoantibody levels in the same people living in the same climatic conditions. Although there were no representatives with positive antibodies in the studied sampling of healthy men, the dynamics of the absolute values of Anti-TPO showed significant intra-annual changes. The seasonal fluctuations of Anti-TPO with the maximum values in December correspond to the ideas of Nelson R.J. and Demas G.E. that many types of immune reactions are usually enhanced during the minimum duration of daylight hours [11].

The duration of daylight hours and air pressure turned out to be the determining factors affecting the annual dynamics of thyroxine, according to the data of the correlation analysis. At the same time, the correlation relationships of the studied hormones and antibodies with air temperature and humidity were not shown. Since the seasonal variation in levels of total iodothyronines, thyroglobulin and thyroid peroxidase antibodies was characterized by a small amplitude of the year-round rhythm, it can be assumed that healthy young men aged 25 to 44 years old, living permanently in the European North environmental, are successfully adapted and experience slight impact of environmental factors. In this connection, the question of seasonal dynamics of indicators of the hypothalamic-pituitary-thyroid system in men older than 45 years and in the representatives

of the female population of the European North remains open.

Conclusion. The main results of this study are that the serum concentrations of T3 and T4 in healthy young men affected by seasonal fluctuations, with higher levels in the spring and summer compared to the fall and winter, while the levels of free iodothyronines and TSH are independent of year season. The study showed a significant decrease in thyroglobulin levels from spring to autumn. Seasonal dynamics are also noted in relation to Anti-TPO levels.

The results of the correlation analysis showed that only differences in T4 levels can be explained by climatic indicators, such as air pressure, and daylight hours.

The reported study was funded by the FCIArctic according to the research project: "Elucidation of the modulating effect of the catecholamine levels on the hormonal profile in humans and aquatic organisms of the European North" (AAAA-A19-119120990060-0).

References

1. Барабаш Л.В., Левицкий Е.Ф., Кремено С.В. К вопросу совершенствования диагностических критериев с учетом цирканнуальных ритмов адаптивных систем организма в условиях Западной Сибири. *Бюллетень сибирской медицины*. 2015;14(3)10-7. [Barabash L.V., Levitsky Ye.F., Kremeno S.V. To the question of diagnostic criteria perfection in view of circannual variation of organism functioning adaptive systems in conditions of Western Siberia. *Bulletin of Siberian Medicine*. 2015; 14(3)10-7 (In Russ.).]
2. Горенко И.Н. Уровни антител к тканям щитовидной железы у эутиреоидных мужчин и женщин, жителей Арктической Зоны Российской Федерации. *Клиническая лабораторная диагностика*. 2019; 64 (9):541-5. [Gorenko I.N. Thyroid antibodies levels in euthyroid men and women - residents of the Arctic Zone of the Russian Federation. *Klinicheskaya Laboratornaya Diagnostika*. 2019; 64 (9):541-5. (In Russ.).] DOI: 10.18821/0869-2084-2019-64-9-541-545.
3. Лютфалиева Г.Т., Чуркина Т.С. Роль аутоантител в адаптивных механизмах регуляции функциональной Активности тиреоидных гормонов и тиреотропного гормона гипофиза у жителей севера. *Экология человека*. 2010;10:33-6. [Lutfaliev G.T., Churkina T.S. Autoantibodies' role in adaptive mechanisms of regulation of functional activity of thyroid hormone and thyrotropin hormone of hypophysis in northern inhabitants. *Human Ecology*. 2010;10:33-6. (In Russ.).]
4. Прохорова Э.М. Биологические ритмы и здоровье. *Сервис Плюс*. 2010;3:20-6. [Prokhorova E.M. Biological rhythms and health. *Service PLUS*. 2010;3:20-6. (In Russ.).]

ova E.M. Biological rhythms and health. *Service PLUS*. 2010;3:20-6. (In Russ.).]

5. Раменская Е.Б. Влияние сезонности и фотопериодизма на гормональный профиль жителей Севера. *Адаптация и резистентность организма на Севере (физиолого-биохимические механизмы)*. Сыктывкар; 1990. [Ramenskaya E.B. The influence of seasonality and photoperiodism on the hormonal profile of the inhabitants of the North. *Adaptation and body resistance in the North (physiological and biochemical mechanisms)* Syktyvkar; 1990. (In Russ.).]

6. Palinkas L.A., Reed H.L., Reedy K.R. [et al.] Circannual pattern of hypothalamic-pituitary-thyroid (HPT) function and mood during extended antarctic residence. *Psychoneuroendocrinology*. 2001;26(4):421-31. DOI: 10.1016/S0306-4530(00)00064-0.

7. Kim T.H., Kim K.W., Ahn H.Y. [et al.] Effect of seasonal changes on the transition between subclinical hypothyroid and euthyroid status. *J Clin Endocrinol Metab*. 2013;98(8):3420-9. DOI: 10.1210/jc.2013-1607.

8. Do N.V., Mino L., Merriam G.R. [et al.] Elevation in serum thyroglobulin during prolonged Antarctic residence: effect of thyroxine supplement in the polar 3, 5, 3-triiodothyronine syndrome. *J Clin Endocrinol Metab*. 2004;89(4):1529-33. DOI: 10.1210/jc.2003-031747.

9. Palinkas L.A., Reedy K.R., Shepanek M. [et al.] Environmental influences on hypothalamic-pituitary-thyroid function and behavior in Antarctica. *Physiol Behav*. 2007;92(5):790-9. DOI: 10.1016/j.physbeh.2007.06.008.

10. Robbins R.J., Chon J.T., Fleisher M. [et al.] Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? *J Clin Endocrinol Metab*. 2002; 87:3242-7. DOI: 10.1210/jcem.87.7.8702.

11. Nelson R.J., Demas G.E. Seasonal changes in immune function. *Q Rev Biol*. 1996; 71(4):511-48. DOI: 10.1086/419555.

12. Kratzsch J., Fiedler G.M., Leichterle A. [et al.] New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. *Clin Chem*. 2005;51(8):1480-6. DOI: 10.1373/clinchem.2004.047399.

13. Levy S.B., Leonard W.R., Tarskaia L.A. [et al.] Seasonal and socioeconomic influences on thyroid function among the Yakut (Sakha) of Eastern Siberia. *Am J Hum Biol*. 2013; 25:814-20. DOI: 10.1002/ajhb.22457.

14. Vining R., McGinley R., Holliday L. [et al.] Seasonal variation in hormonal concentrations in Australian Antarctic personnel. *Endocrine Society of Australia Proceedings*. 1983; 26:79.

15. Santi D., Spaggiari G., Brigante G. [et al.] Semi-annual seasonal pattern of serum thyrotropin in adults. *Sci Rep*. 2019;9(1):10786. DOI: 10.1038/s41598-019-47349-4.

16. Hassi J., Sikkilä K., Ruokonen A. [et al.] The pituitary-thyroid axis in healthy men living under subarctic climatological conditions. *J Endocrinol*. 2001; 169(1):195-203. DOI: 10.1677/joe.0.1690195.



SCIENTIFIC REVIEWS AND LECTURES

N.A. Danilov, T.E. Burtseva, Y.A. Munkhalova,
M.P. Slobodchikova

METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

DOI 10.25789/YMJ.2020.70.24

УДК 612.015.38 ББК 54.15

The article represents review of metabolic syndrome in children and adolescents. Obesity pandemic, which is common all over the world, outlines significant social issues, resulting in cardio-vascular disorders, the leading cause of mortality and disability. The concern of increasing tendency of cardio-vascular disorders among children and adolescents for the last decades is growing [5]. According to the National Medical Research Center for Endocrinology (2017) from 13-15% of children suffer from obesity in Russia, among them 5-8% school children.

This number of obese children is twice higher than in France, 1.5% higher than in England and is reaching the number of obese children in the USA (17%) [9]. Increase of obesity in children is doubling each 30 years resulting in a threat to national security [6].

Keywords: metabolic syndrome, obesity, children, adolescents.

Yakutia is referred to the regions with extreme conditions for living, resulting in high-energy consume taken in with food and nutrients and their high expenditure for normal activity of the organism. The traditional diet rich in protein and lipid is being substituted by the diet rich in carbohydrate and protein for the last decades [2, 7], moreover the motor activity of teenagers tends to decrease. The combined action of both factors leads to increase of obesity rate consequently resulting in cardio-vascular disorders.

Of greatest concern is the dangerous tendency to increase CVD mortality among children and young people, noted in recent decades [4]. According to the endocrinology research center of the Ministry of Health (2017), 13-15% of children in Russia are obese, 5-8% are students. This number exceeds 2 times the number of children with obesity in France, 1.5 times more than in England and approaches the number of children with obesity in the United States (17%) [9]. The rate at which the incidence is

increasing, the number of sick children doubles every 30 years, and this suggests a threat to national security [5].

The prevalence of metabolic syndrome (MetS) in overweight children and adolescents is 30-50% worldwide [1]. The first description of metabolic syndrome is known to be introduced by a Swiss physician E. Kylin in 1923, named as 'a syndrome involving hypertension, hyperglycaemia and hyperuricaemia' [5]. The concept of metabolic syndrome was first suggested by Gerald Reaven in 1988 [11], the syndrome was defined as a complex of such metabolic and clinical disorders as abdominal obesity, arterial hypertension, dyslipidemia, insulin-resistance, glucose intolerance or diabetes mellitus type 2 [12]. Clear diagnostic criteria of metabolic syndrome in adolescents above 16 were constituted by the International diabetes federation in 2007, they were based on analogous adults' criteria [1]:

- Tryglycerides level ≥ 1.7 mmol/L;
- High-density lipoprotein level < 1.03 mmol/L;
- An increase in arterial pressure $\geq 130/85$ mm Hg;
- An increase value of venous plasma glucose on an empty stomach ≥ 5.6 mmol/L or diagnosed diabetes mellitus type 2 and/or other disorders of carbohydrate metabolism.

However, the representatives of different medical organisations disagreed the clinical and diagnostic significance of each component included in the diagnostic criteria. In 2009 the following international research associations: International diabetes federation (IDF), International heart, lung and blood institute (NHLBI), American heart association (AHA), World heart federation (WHF), International atherosclerosis society (IAS), and International association for the study of obesity (IASO) together represented unified criteria for diagnosis of metabolic syndrome

in children and adolescents (Table), nowadays these criteria are used all over the world [4].

Obesity is not just esthetic problem, it is severe disease which affects physical, social and psychological well-being of children [8], and moreover, it results in such diseases as ischemic disease, diabetes mellitus, arterial hypertension, malignant neoplasms.

Despite high prevalence of metabolic syndrome there is still no unified classification of it. The following classification, based on the classifications of M.I. Balabolkin et al, G.A. Melnichenko et al, V.A. Peterkova et al, seems most relevant in pediatric practice [1]:

- Initial obesity:
 - Exogenous constitutional or alimentary constitutional;
 - monogenous forms (mutation of leptin gene mutation, the leptin gene receptor mutation, POMC deficiency, convertase 1 gene mutation, PPAR- γ 2 gene;
 - Secondary obesity:
 - genetic (resulting from Prader-Willi syndrome, Laurence-Moon-Biedl-Bardeet syndrome, Cogan syndrome, Albright syndrom etc.)
 - cerebral (tumours and traumas of CNS, infectious diseases, mental disorders etc.)
 - endocrine (hypothyroidism, polycystic ovary syndrome, adrenal gland disorders etc.)
 - iatrogenic (associated with medication intake)
- By the character of fat accumulation:
- Abdominal (android) type when the fat is accumulated in the waistline or upper part of the waistline / the upper part of the trunk)
 - Gynoid obesity when the fat is accumulated in thighs, hips, butt etc.
 - Middle pattern when fat is distributed more or less evenly.

The abdominal (visceral) type of obesity leads to the development of metabol-

DANILOV Nikolai Andreyevich – a post-graduate student of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, +7-981-793-1727, danilov.na.94@mail.ru; **BURTSEVA Tatiana Yegorovna** – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, a head of the laboratory of the Yakutsk science center of complex medical problems, +7-914-294-3244, bourtsevat@yandex.ru; **MUNKHALOVA Yana Afanasievna** – PhD, associate professor, a head of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, +7-914-270-7107, tokmacheva@mail.ru; **SLOBODCHIKOVA Maya Pavlovna** – a senior lecturer of the department of foreign languages with the courses of Russian and Latin languages, St. Petersburg state pediatric medical university, limelight@mail.ru, +7-911-908-7772

ic syndrome. It is established that visceral fat tissue is characterized by endocrine and paracrine activity [1].

Metabolic syndrome associated with insulin resistance results in overstimulation thus leading to further exhaustion of pancreatic islets. This can result in impaired glucose tolerance and diabetes mellitus type 2 [1]. Persistent hyperglycemia or glucose toxicity may lead to beta-cell dysfunction and decreased sensitivity of beta-cells. It triggers the early stage of stimulated insulin secretion and impairs its impulse secretion. In developed insulin resistance the first stage, when vesicles empty the collected insulin, the insulin secretion is absent. In the second stage the basal secretion is monotonous. Thus, despite excessive insulin secretion the glucose level is not normalized, causing a viscous circle: hyperglycemia – hyperinsulinemia – insulin resistance – hyperglycemia – hyperinsulinemia. It results in glucose tolerance disorder thus causing diabetes mellitus type 2.

Arterial hypertension in metabolic syndrome is directly associated with the main pathogenic trigger, i.e. compensatory hyperinsulinemia, which develops on the preexisting insulin resistance background [10]. The investigations have shown that children with metabolic syndrome have high mean night-time systolic BP and diastolic BP, time index of hypertension at night, more decreased level of night-time systolic BP and diastolic BP [6]. Moreover, the mechanisms of arterial hypertension in metabolic syndrome associated with hyperleptinemia are being discussed last time; persistent dyslipid-

emias result in atherosclerotic changes of renal vessels causing renovascular hypertension [16].

It is necessary to underline that pathologic process in metabolic syndrome affects not only the heart but also the vessels of all kinds and levels, i.e. the cardiovascular pathology. Thus, cardiovascular syndrome including arterial hypertension is represented by the vegetative dysfunction (including heart beat rate variability), endothelial dysfunction and systolic and diastolic myocardial dysfunction. The level of expression of cardiovascular disorders in children and adolescents with metabolic syndrome mentioned above varies individually and depends on the degree of insulin resistance expression.

Dyslipidemia is considered as the decrease in the level of high density lipoproteins (HDL) below minimum normal numbers and hyperglyceridemia more than >1.7 mmol/L. Dyslipidemia is one of the most important criterion in metabolic syndrome diagnosing. The development of dyslipidemia is directly associated with non-alcoholic fatty liver disease (NAFLD) and insulin resistance. Moreover, there is positive correlation between dyslipidemia, non-alcoholic fatty liver disease and development of atherosclerosis [16].

It is proved that insulin resistance promotes further development of hypertriglyceridemia. Hyperglycemia and hyperinsulinemia break the lipoprotein synthesis: liver starts producing excessive amount of tryglicerides from glucose. Moreover, the Bogalusa heart study revealed that insulin resistance is closely associated with increased sensitivity of LDL receptors to cholesterol. Protein gly-

cation in hyperglycemia greatly contributes to the development of atherosclerosis. Glycated VLDL and LDL circulate in blood for a longer period of time, as receptors do not recognize them and have longer period of half-life. Glycated HDL are better metabolized, glycated collagen better bonds together with VLDL-cholesterol and LDL-cholesterol [1, 3].

The main hypothesis for non-alcoholic fatty liver disease (NAFLD) pathology is 'two-hit hypothesis', represented in 2002 [3]. According to the 'two-hit hypothesis' the liver damage is associated with two components. Firstly, the so-called 'first hit', is associated with obesity caused by fatty diet and insulin-resistance, that might be responsible for depositing of tryglicerides in hepatocytes. The 'second-hit' results in oxidative stress. The inflammatory cytokines, adipokines, mitochondrial dysfunction and endoplasmic reticulum stress trigger the condition to the non-alcoholic steatohepatitis.

For the last years it was modified into 'multiple parallel-hit hypothesis'. According to which NAFLD was determined as epiphenomenon of several metabolic mechanisms, including genetic and environmental factors, interactions between liver, fatty tissue, pancreatic gland and intestine [13].

Accumulation of lipids in the form of tryglicerides and free fatty acids is responsible for NAFLD development. Dyslipidemia is considered as the main component for metabolic syndrome according to IDF (International diabetes federation) criteria, constituted in 2007. It was considered as the main triggering factor for NAFLD development.

Diagnostic criteria for metabolic syndrome (2009)

Age	Obesity	Triglycerides (TG)	HDL	BP	Glucose (mmol / L)
6 to <10 years-old	≥90 percentile	MetS cannot be diagnosed, but the following investigations should be carried out if there is MetS in a family history; diabetes mellitus type 2, dyslipidemia, cardiovascular disorders, arterial hypertension			
Metabolic syndrome					
10-16 years-old	≥90 percentile	≥1.7 mmol/L (≥150 mg/dl)	<1.03 mmol/L (≤40 mg/dl)	Systolic BP≥130 mm Hg or diastolic BP≥85 mm Hg	≥5.6 mmol/L (≥100 mg/dl) or diagnosed diabetes mellitus type 2; If the concentration is ≥5.6 mmol/L peroral glucose tolerance test is recommended
Metabolic syndrome (Adults IDF criteria are used)					
>16 years-old	Central obesity: waist circumference ≥94 cm in Caucasian males and ≥80 cm in Caucasian females (racial/ethnic prevalence for other groups)	≥1.7 mmol/L (≥150 mg/dl)	For males <1.03 mmol/L (≤40 mg/dl) For females <1.29 mmol/L (≤50mg/dl) or specific therapy of such disorders in anamnesis	Systolic BP≥130 mm Hg or diastolic BP≥85 mm Hg or previously diagnosed arterial hypertension treatment	≥5.6 mmol/L (≥100 mg/dl) or diagnosed diabetes mellitus type 2; If the concentration is ≥5.6 mmol/L peroral glucose tolerance test is recommended

The diagnosis of metabolic syndrome is composed of several stages:

1 stage – the initial attendance of the doctor, including the collection of anamnesis of the current illness, family history (for genetic predisposition to obesity), diabetes mellitus type 2, the diseases of cardiovascular and hepatobiliary systems, social anamnesis checking the dietary habits, social and economic welfare of the family, physical activity; physical examination, including antropometry (height, weight, BMI, waist circumference, thigh circumference), arterial BP [1].

2 stage – laboratory and instrumental diagnosis – biochemical analysis of blood, detection of glucose, alanine transaminase and aspartate transaminase levels in blood, lipidogram; hormone tests – thyroid hormones, hypothalamo-pituitary-adrenal and gonadal axis (Adrenocorticotropic (ACTH) and somatotropic hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, aldosterone, renin, testosterone etc.; instrumental investigations like ECG, holter monitoring ECG, 24-hour monitor test, ultrasound investigation of the organs of abdominal cavity, echocardiography; if necessary – endoscopic investigations of the organs of gastrointestinal tract, CT-scan/MRI for the brain and abdominal cavity imaging; consultation of the related specialists [1].

The treatment of metabolic syndrome should have an integrated approach and consist of several procedures correcting complex of medical treatment and psychotherapy.

First of all, the lifestyle should be changed starting with the diet and increased physical activity. American academy of pediatrics recommends at least 60 minutes of daily moderate physical activity for children older than 5 [14]. Physical activity increases metabolism of hepatic mitochondrial substrate, and decreases substrate availability for lipogenesis and insulin resistance causing mitochondrial biogenesis in the liver and muscles. It is evidently shown that physical exercises stimulate decrease of insulin level on an empty stomach and insulin-resistance in children and adolescents. It is necessary for lipid profile improvement increasing the concentration of HDL and decreasing the concentration of LDL, and tryglicerides [14]. Moreover, physical activity improves the endothelium function with the following decrease of systolic and diastolic BP without any association with the kind of physical activity (aerobic or muscle-strengthening exercises).

Secondly, one of the most important

components for metabolic syndrome treatment is the change of diet or dietary intervention. The main goal of dietary intervention is a decrease of calorie, the second goal is to achieve macronutrient balance decreasing the amount of carbohydrate intake, and achieving the balance of protein and fat intake to physiological norm according to the ratio 1:1:4 (in correlation of protein : fat : carbohydrate). Moreover, it is important to follow fractional nutrition to normalize metabolic process. The whole family of the patient should undoubtedly undergo dietary intervention, it is recommended to achieve psychological comfort of the patient that he/she is not discriminated because of his/her illness but improve dietary habits of all the family. If the child is subjected by overeating mental illness then it is necessary to have psychological therapy together with the specialist.

The medical treatment of obese children is restricted as there is high negative impact of anorectic drugs which is not recommended in most of the countries. The only recommended drug for pediatric use in the territory of the Russian Federation is orlistat, which is limited to the age of the patient and is recommended only for children above 12. It can be used only in such a case when one year of previous treatment including the change of a lifestyle was with no effect.

The effectiveness of surgical treatment is disputable. On the one hand, surgical operation can considerably reduce the weight at once, but on the other hand, there are strict requirements for surgical intervention [15], high price [11], absence of cogent data on the safety of bariatric appliances in a long-term perspective and high risk of complications [16] which limit such choice of treatment.

Treatment of arterial hypertension in children with metabolic syndrome is aimed at achievement maintenance of the arterial pressure equaling to $\leq 130/80$ mm Hg in adolescents older 13 [14]. The approach is aimed at a lifestyle modifying, which are mentioned above. If the modification did not result in decrease of the arterial blood pressure, then the medical treatment is recommended. The medication starts with enalapril, inhibitor of angiotensin-converting-enzyme (ACE), which is administered in its minimum dosage. In 4-6 weeks after administration of hypotensive medication the patient should visit a doctor for therapy controlling and changing the dosage if necessary. If mono-therapy is inefficient, the combined hypotensive therapy is recommended, the lifestyle should undoubtedly be changed.

The treatment of diabetes mellitus type 2 caused by metabolic syndrome or glucose tolerance disorder should be treated according to the treatment protocol for such conditions.

Conclusion. Metabolic syndrome is complex and complicated issue for the healthcare. It is associated with many components and factors resulting in complex and high cost of diagnosis for the disease requiring multidisciplinary approach to the treatment and prevention of the condition. This thesis is confirmed by the information discussed in the article as the prevalence of metabolic syndrome is directly associated with obesity especially occurred in the last decades. Further research works are necessary, especially cooperated researches with medical specialists of the various fields to reveal the early symptoms or predictors of the condition prevent such severe conditions like primary hypertension or diabetes mellitus in adults, which can result in disability in its long-term perspective.

Ethno-geographic data for metabolic syndrome in each region are not less important, they can reveal genetic features for inhabiting population, traditional dietary habits and its quality, climate, physical activity and character of labour. All these factors should be taken into account in the further research of complex symptoms.

References

1. Бокова Т.А. Метаболический синдром у детей: учебное пособие. *Форте-принт*, 2013; 23. [Bokova T.A. Metabolic syndrome in children: tutorial. *Forte-print*, 2013; 23. (In Russ..)]
2. Борисова И.З., Лебедева У.М., Степанов К.М. Актуальные вопросы культуры питания населения Якутии: современное состояние, проблемы и перспективы развития. *Вестник Северо-Восточного университета имени М.К. Аммосова*, 2017.4:55-58. [Borisova I.Z., Lebedeva U.M., Stepanov K.M. Food culture in Yakutia: current state, problems and prospects of development. *Vestnik Severo-Vostochnogo universiteta imeni M. Ammosova*, 2017.4:55-58. (In Russ..)]
3. Захарова И.Н., Звенигородская Л.А., Яблочкова С.В. Метаболический синдром и неалкогольная жировая болезнь печени у детей. *Экспериментальная и клиническая гастроэнтерология*, 2011.11:44-48. [Zakharova I.N., Zvenigorodskaya L.A., Yablochkova S.V. Metabolic syndrome and non-alcoholic fatty liver disease in children. *Ekspperimentalnaya i klinicheskaya gastroenterologia*, 2011.11:44-48. (In Russ..)]
4. Захарова И.Н., Мальявская С.И., Творогова Т.М. Метаболический синдром у детей и подростков. Определение. Критерии диагностики. *Медицинский совет*, 2016.16:103-109. [Zakharova I.N., Malyavskaya S.I., Tvorogova T.M. Metabolic syndrome in children and adolescents. Definition. Diagnostic criteria. *Medicinskii sovet*, 2016.16:103-109. (In Russ..)] DOI:10.21518/2079-701X-2016-16-103-109

5. Кедринская А.Г., Образцова Г.И., Нагорная И.И. Поражения сердечно-сосудистой системы у детей с ожирением. *Артериальная гипертензия*, 2015.21(1):6-15. [Kedrinskaya A.G., Obraztsova G.I., Nagornaya I.I. Cardiovascular lesions in children with obesity. *Arterialnaia hipertensia*, 2015.21(1):6-15. (In Russ.)]
6. Лебедькова С.Е., Рощупкин А.Н. Артериальная гипертензия у детей с метаболическим синдромом. *Оренбургский медицинский вестник*. 2013.1:64-67. [Lebedkova S.E., Roshupkin A.N. Arterial hypertension in children with metabolic syndrome. *Orenburgskii medicinskii vestnik*.2013.1:64-67. (In Russ.)]
7. Евсеева С.А., Егорова А.Г., Саввина М.С., Бурцева Т.Е., Слободчикова М.П. Особенности питания детей школьного возраста в сельской местности Республики Саха (Якутия). *Якутский медицинский журнал*, 2019.4:78-80. [Evseyeva S.A., Egorova A.G., Savvina M.S., Burtseva T.E., Slobodchikova M.P. Dietary habits of school children in rural areas of the Republic of Sakha (Yakutia). *Yakut medical journal*, 2019. 4:76-78. (In Russ.)] DOI:10.25789/YMJ.2019.68.22
8. Отто Н.Ю., Сагитова Г.Р., Никулина Н.Ю. Частота метаболического синдрома и других осложнений ожирения в практике детского эндокринолога. *Вестник Волгоградского государственного медицинского университета*. 2018.3:93-98. [Otto N.Yu. Sagitova G.R., Nikulina N.Yu. Frequency of metabolic syndrome and other complications of obesity in practice of a child endocrinologist. *Vestnik Volgogradskogo gosudarstvennogo medicinskogo universiteta*. 2018.3:93-98. (In Russ.)] DOI:10.19163/1994-9480-2018-3(67)-93-98
9. Посохова Н.В., Болотова Н.В. Ожирение как фактор формирования артериальной гипертензии у детей и подростков. *Педиатрия*. 2015.5:127-131. [Posokhova N.V., Bolotova N.V. Obesity as a forming factor of arterial hypertension in children and adolescents. *Pediatria*. 2015.5:127-131. (In Russ.)]
10. Armstrong S., Bolling C., Michalsky M. Pediatric metabolic and bariatric surgery: evidence, barriers, and best practices. *AAP section on obesity, section on surgery. Pediatrics*. 2019.6. DOI: 10.1542/peds.2019-3223
11. Bussler S., Penke M., Flemming G. Novel insights in the metabolic syndrome in childhood and adolescence. *Hormone research in paediatrics*. 2017.88:181-193. DOI: 10.1159/000479510
12. D'Adamo E., Castorani V., Nobili V. Liver in children with metabolic syndrome. *Frontiers in Endocrinology*. 2019.10. DOI: 10.3389/fendo.2019.00514
13. Fornari E., Maffei C. Treatment of metabolic syndrome in children. 2019.10. DOI:10.3389/fendo.2019.00702
14. Higgins V., Adeli K. Pediatric metabolic syndrome: pathophysiology and laboratory assessment. *EJIFCC*. 2017.1:25-42.
15. Pratt J., Browne A., Browne N.T. ASMBS pediatric metabolic and bariatric surgery guidelines. *Surgery for obesity and related diseases: official journal of the American society for bariatric surgery*. 2018.18: 882-901. DOI: 10.1016/j.soard.2018.03.019
16. The RISE consortium. Obesity and insulin sensitivity effects on cardiovascular risk factors: comparisons of obese dysglycemic youth and adults. *Pediatric diabetes*. 2019.7:849-860. DOI: 10.1111/peidi.12883



POINT OF VIEW

L.E. Tabikhanova, L.P. Osipova, S.S. Kovalev, U.N. Kavai-ool,
A.N. Sariglar, T.V. Churkina, M.R. Khantemirova

FEATURES OF THE GENE POOL OF THE TUVINIAN ETHNOS BASED ON THE STUDY OF BLOOD GROUP ANTIGENS IN COMPARATIVE PERSPECTIVE

DOI 10.25789/YMJ.2020.70.25

УДК 612.118.221.2(517.1)

The indigenous population of the Tuva Republic is characterized by a complex multi-component ethnogenesis, which involved ancient Euro-poid, northern Samoyedic and Keto-speaking tribes, as well as Turkic and Mongolian-speaking natives of Central Asia. The aim of the study was description of the Tuvinians gene pool in comparison with the modern Siberian populations.

Materials and methods. The alleles and haplotypes frequencies of blood groups AB0, MN, Rhesus and Kell in the Kyzyl indigenous population sample (N=502) were determined using the traditional direct hemagglutination method.

Results. The high frequency (0.033) of the A2 allele of the AB0 system characterizing the population of Europoid origin was shown. The ratio of the alleles M (0.621) and N (0.379) of the MN system corresponded to the populations of Yakuts, Kazakhs and Mongols. Rhesus Tuvinians showed both Mongoloid features - high frequency cDe (0.318) and rhesus-negative haplotype cde and Cde, which characteristic Europoid populations (total frequency 0.074) on frequencies haplotype systems. The marker of "Europoid" allele K of system Kell was revealed with frequency 0,019. The Tuvinians was clustered with Turkic populations of South Altaians and Yakuts on the map of genetic distances, while the Samoyedic group of Nganasans, Forest and Tundra Nenets formed a separate cluster. The clusters of northern Khanty, Komi-Zyryans and Russians Siberia, including the Old Believers, are also located in a separate cluster. It is shown that alleles and haplotypes of systems MN, Rhesus and Kell, A2 and B on system AB0 made the greatest contribution to differentiation of populations.

Conclusion. The present study shown that the Tuvinians of Kyzyl are genetically close to the Yakuts and South Altaians, and the combination of Europoid and Mongoloid genetic markers reflects their complex ethnic history.

Keywords: Tuvinians, population frequency of genetic markers of blood groups, AB0, MN, Rhesus, Kell.

Introduction. Tuvinians are the indigenous population of the Republic of Tuva, belonging to the Central Asian anthropological type of Mongoloid race. They speak the language of the Uigur group of Turkic languages [2]. Anthropological and serological research indicates heterogeneity of Tuvinians and their unique

position among other groups of Siberia, Central Asia and Kazakhstan. The researches of historians, archeologists, anthropologists have shown that the ancient Europoids, northern Samoyedic and Keto-speaking tribes, and also Turkic and Mongolian-speaking natives from Central Asia took part in the formation of the Tuvinian gene pool [1, 2]. Genetic studies of mitochondrial DNA and Y-chromosomes confirmed these assumptions [22, 24, 27]. A number of anthropometric signs and frequency of genetic markers shows that Tuvinians have more similarity with the South Siberian groups which have been formed with participation of the Europoid component - Altaians and Khakassians, and also with Samoyeds, than with Central Asian peoples - Mongols, Buryats, Kalmyks and Yakuts [2, 22, 27].

Molecular and biological methods of research have been developing rapidly in recent decades. However, serological studies connected to determination of blood group frequencies have not lost their relevance for studying human populations [7, 8, 12, 16]. This is due to the low cost, good reproducibility, independent of subjective evaluation criteria, availability of studies in the field and the possibility of comparison with populations previously studied on a given panel of blood group systems [6, 11, 13, 18, 21, 23, 27].

The aim of the research is to study the allele and haplotype frequencies of blood groups AB0, MN, Rhesus and Kell in a

sample of Tuvinians in the town of Kyzyl and compare them with some Siberian populations belonging to other linguistic groups.

Material and research methods. The material was collected during expedition works in September 2019 on the basis of the Republican Center of Medical Prevention of the Kyzyl (Team Leader - M.S. Tabikhanova L.E.) The research was conducted within the framework of agreements between Tuva Research Center, Novosibirsk State University and the Federal Research Center Institute of Cytology and Genetics of The Siberian Branch of the Russian Academy of Sciences (ICG SB RAS). This study was approved by the Bioethical Committee of the ICG SB RAS. It was carried out in accordance with the requirements of the documents "Ethical principles of scientific medical research with human participation" and "Rules of clinical practice in the Russian Federation".

Blood was taken with disposable needles from the elbow vein from individuals who expressed their willingness to participate in the research and voluntary signed an informed consent. Preliminarily, each of the subjects filled in a specially designed questionnaire that indicated the nationality of their ancestors up to 2-3 generations. In the course of the study, a sample of ethnic Tuvinians (N=502) was formed from natives, mainly from the western and central regions of Tuva, who did not indicate ancestors of other

The Federal Research Center Institute of Cytology and Genetics, The Siberian Branch of the Russian Academy of Sciences, Russian Federation, 630090, Novosibirsk, Prospekt Lavrentyeva, 10 and Novosibirsk State University, Russian Federation, 630090, Novosibirsk, Pirogova st.2: **TABIKHANOVA Ludmila Edmundovna** - Junior Researcher, ORCID ID 0000-0002-5547-8189, Scopus Author ID 24437440800, tabikhan@bionet.nsc.ru, 8-913-753-9785; **OSIPOVA Ludmila Pavlovna** - candidate of biological sciences, leading researcher, ORCID ID 0000-0001-7602-1156, Scopus AuthorID 57203881313, ludos77@yandex.ru; **KOVALEV Sergey Sergeevich** - Junior Researcher, kovalev1994@bionet.nsc.ru; **CHURKINA Tatyana Valerievna** - Junior Researcher, tanchurkina@yandex.ru; **KHANTEMIROVA Mira Rashitovna** - Junior Researcher, hantemiramira@mail.ru, Tuva Research Center, 667000, Internationalnaya St., 117 A, Kyzyl, Republic of Tyva, Russia: **KAVAI-OOL Urana Nikolaevna** - Doctor of Biological Sciences, leading researcher, 8 (39422) 6-62-23, absunur@mail.ru, Republican Center of Medical Prevention, 6670058, Druzhby St., 44, Kyzyl, Republic of Tyva, Russia: **SARYGLAR Aidyn Nikolaevich** - chief medical doctor, (39422) 5-80-14, rcmp-09@mail.ru

nationalities in their lineage. 18% of the sample consists of adolescents aged 16-18 years, persons aged 19-39 years - 37%, 40-59 years -33%, 12% are 60-70 years old. The female part of the sample is 73 per cent, while the male part is 27 per cent.

"Hematologist" Ltd. (EritroTestM-Colyclons anti -A, -A1, -B, -M, -N, -C, -Cw, -c, -D, -E, -e and anti-Kell) determined blood group affiliation in the field laboratory by direct hemagglutination method using sets of diagnostic reagents for typing human blood groups. Frequencies of alleles and haplotypes of systems AB0, Rhesus and Kell were calculated by a method of the maximum plausibility with use of the computer program developed by the employee of ICG SB RAS Kirichenko A.V. Allele frequencies *M* and *N* were defined on the basis of observed frequencies of phenotypes of system MN. For construction of maps of genetic distances between populations, and also for revealing the contribution of alleles and haplotypes in differentiation processes was used A.V. Kirichenko's program, that developed on the basis of Harpending and Jenkins's method [25].

Results and discussion. The quantities and frequencies (%) of blood group phenotypes in the Tuvianian sample are shown in Table 1, and the allele and haplotype frequencies of blood groups are shown in Table 2.

The frequency distribution of alleles of the AB0 system in the Tuvianian samples is characterized by a high occurrence of allele *O* (0.670), which is typical for indigenous Siberian populations [4, 6, 10, 13, 15, 18, 20, 27]. The frequency of allele *B* in the studied samples corresponds to the frequency interval described in the literature for Tuvianian populations (0.103-0.210) [2, 3, 10]. According to the literature, zones with the opposite ratio of AB0 system genes frequencies are distinguished in the Tuva territory [2]. The group of Tuvianians of Kyzyl, which, according to the survey data, consists of 90% of natives of the western and central regions, demonstrates increase in the frequency *A*, characteristic for this geographical localization, compared with *B*. In the southern and eastern regions the opposite trend is observed, indicating increase in the Mongoloid component [2, 3]. The frequency of the marker "Europoid" allele *A2* (0.033) is significant, and falls into the range corresponding to the Russian samples 0.024-0.070 [21].

The maximum frequency of the allele *N* of the MN system from Siberian populations was found in the Nganasan (0.713) [20], followed by a decrease in the allele

N of the MN system, up to 0.206-0.233 in the northern Altaians [4]. Yakuts also demonstrate a low frequency of this allele (0.234-0.255) [13], which is associated with their southern origin. Russian populations are characterized by an average frequency *N* in the range of 0.449-0.469 [21]. A low allele frequency *N* (0.379) was observed in Tuvianians of Kyzyl city; it is statistically significantly lower than that in the Shinaan population of eastern Tuva

(0.491) [3]. The low frequency allele *N* is typical for Kazakhs (0.357) [9], Mongols (0.413) [5] and Tuvianians of the Tojin group in the north-east of Tuva (0.363-0.417) [3, 10].

Tuvianians in Kyzyl demonstrate the highest possible frequency of haplotype *CDe* of Rhesus system (0,569). At the majority of the South Siberian (South and North Altaians) [4, 18], Central Asian populations (Mongols and Yakuts) [5, 13], and also Tundra Nenets [27], this indicator is raised (0,522-0,549) in comparison with Russians [21] and inhabitants of the North of Siberia - Komi, Khanty, Nganasans (0,253-0,432) [6, 20]. The Rhesus *cDE* haplotype is considered a marker for northern Mongoloids. Its maximal value is found at Nganasans of the Taimyr Peninsula (0,622) [20], and minimal - at Russians of Siberia (0,162) [21]. The intermediate value of frequency haplotype *cDE* at Tuvianians (0,318) makes them similar to Mongols, a population of Yakuts of Nurbinsky ulus and South Altaians [5, 13, 18]. Two individuals with rhesus-negative phenotype were found, which was not registered in the previous works on Tuvianians [3, 10]. Total frequency haplotype *cde* and *Cde*, causing "Europoid" rhesus-negative phenotype at Tuvianians is equal 0,074. Such value of frequency rhesus-negative haplotype characterizes also Forest (0,069) and Tundra (0,096) Nenets and North Altaians Kumans (0,094) [4, 15, 27]. No marker allele C^w for Europoid populations was found in the studied sample of Tuvianians. It is fixed with considerable frequency 0,038 presence "ancient" haplotype *cDe*.

Among Tuvianians we found carriers of allele *K* (0.019) of the **Kell** system, which is absent in many Siberian populations (Nganasans, Yakuts, Forest Nenets and South Altaians) [13, 15, 18, 20], and is registered with statistically significantly lower frequency in North Khanty (0.001) and Tundra Nenets (0.003) [6, 27]. Among the North Altaians this marker Europoid allele was found with a frequency of 0.012-0.040, while in the Russians (0.031-0.074) and Komi (0.076) this index is statistically significantly higher [4, 6, 21].

Figure 1 presents a map of genetic distances between 16 populations of indigenous peoples of Northern Eurasia, built on 15 alleles and haplotypes (*O*, *A1*, *A2*, *B*, *K*, *M*, *N*, *CDe*, *cDE*, *cDe*, *cde*, *CDE*, C^wDe) 4 genetic blood systems (AB0, MN, Rhesus and Kell) by the Harpending and Jenkins method. It shows the mutual location of the populations of Russians, Komi, Khanty, Samoyedic (Nganasans, Forest and Tundra

Table 1

Quantities of blood group phenotypes in the studied sample of Tuvianians of Kyzyl (N=502).

Blood group system	Phenotype	quantity (n)	Frequency (%)
AB0	0(I)	229	45.6
	A1(II)	102	20.3
	A2(II)	20	4.0
	B(III)	119	23.7
	A1B(IV)	24	4.8
	A2B(IV)	8	1.6
MN	MM	201	40.0
	NN	80	15.9
	MN	221	44.1
Rhesus	CCDee	179	35.6
	CcDEe	174	34.7
	CcDee	53	10.6
	ccDEE	54	10.7
	ccDEe	38	7.6
	ccDee	2	0.4
	ccdee	1	0.2
	CCDEe	1	0.2
	Ccdee	1	0.2
Kell	K	19	3.8
	kk	483	96.2

Table 2

Frequencies of alleles and haplotypes blood groups in the studied sample of Tuvianians.

Blood group system	Allele, haplotype	Frequency
AB0	<i>O</i>	0.670
	<i>A1</i>	0.134
	<i>A2</i>	0.033
	<i>B</i>	0.163
MN	<i>M</i>	0.621
	<i>N</i>	0.379
Rhesus	<i>CDe</i>	0.569
	<i>cDE</i>	0.318
	<i>cDe</i>	0.038
	<i>cde</i>	0.060
	<i>Cde</i>	0.014
	<i>CDE</i>	0.001
Kell	<i>K</i>	0.019
	<i>k</i>	0.981

Nenets) and Turkic-speaking groups (South Altaians, Yakuts, and Tuvinians), which differ in linguistic identity, in the space of two main components deriving 74% of the total variability. We can see that Tuvinians are clustered with other Turkic-speaking populations of South Altaians and Yakuts. Genetic closeness of Yakuts to Tuvinians and Altai was shown earlier at the analysis of mtDNA lines [17, 19, 26], and also by the results of full genomic analysis [19]. Separately located is the Samoyedic group of Nganasans, Forest and Tundra Nenets, as well as clusters of North Khanty, Komi-Zyryans and Russians of Siberia, including the Old Believers. The maximum distance separates the sample of the indigenous population of Kyzyl from the Komi, Nganasans, and also from the North Khanty, whose gene pool obviously contains other ethnic components.

Figure 2 shows the graphical location of genetic markers used to build a map of genetic distances (Fig. 1). It can be noted that the greatest contribution to differentiation of populations is made by the alleles and haplotypes most removed from a point of intersection of axes of coordinates: "Europoid" markers (*cde*, *K* and *C^w*), alleles *M* and *N* of system MN, haplotypes *cDE* and *CDe* of system Rhesus. The ABO system is informative for the *A2* and *B* alleles.

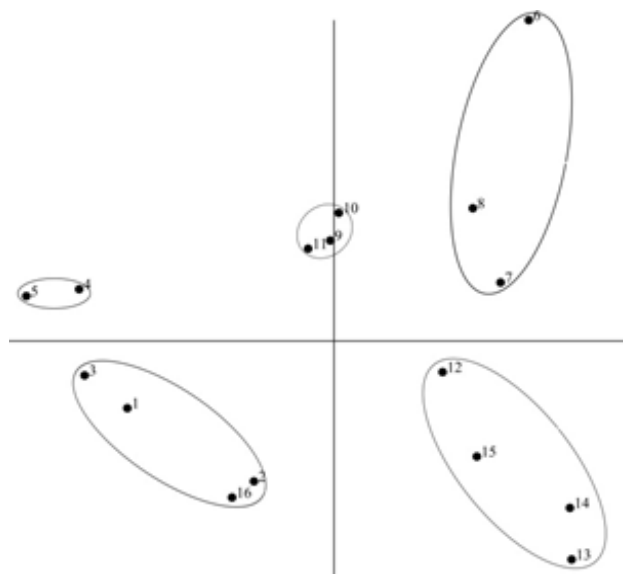


Fig. 1. Map of genetic distances between 16 Siberian populations, constructed on 15 alleles and haplotypes of 4 genetic systems of blood by Harpending and Jenkins method. Note: 1 - Russians Old Believers of Isetsk area, 2 – Russian Old Believers of settlement Burnyi, 3 - Russians of the Tyumenskaya oblast [21], 4 – Komi-Zyryans of settlement Gorki and Pitlyar, 5 – Komi-Zyryans of s. Vosyakhovo, Ovgort, p. Muzhi and Shuryshkary [6], 6 - Nganasans, 7 - Forest Nenets [9], 8 - Tundra Nenets [27], 9 - Khanty of s. Lopkhari, 10 - Khanty of s. Ovgort [6], 11 - Khanty of s. Lopkhari, 12 - South Altaians [18], 13 - Yakuts of Nyurbinsk ulus, 14 - Yakuts of Ust-Aldan ulus [13], 15 - Tuvinians of Kyzyl, 16 - Russians of Kyzyl (N=23) [own data].

Conclusion.

Thus, the present study shows that among the studied 16 Siberian populations Tuvinian Kyzyl are genetically closest to the Yakuts and South Altaians in terms of allele and haplotype frequencies of blood groups ABO, MN, Resus and Kell. It was found out that Tuvinians are characterized by a combination of Europoid and Mongoloid features, which reflects their complex ethnogenesis.

The results of the research presented

in the article were obtained within the framework of the state task of the IGC SB RAS (№0324-2019-0041-C-01). The expedition work in Kyzyl was carried out at the expense of the Russian Science Foundation (project № 19-15-00-219). The authors express their deep gratitude to the residents of Kyzyl, who took part in this study, to all the staff of the Tuva "Republican Center of Medical Prevention", including nurses Khertek A.A., Sevek S.A., Deputy Chief Doctor Agapova N.V., Kuular A.V. and Head Nurse Grishina N.K. Technical assistance in the study was provided by Moletotova N.A., Galieva E.R. and Orlov Y.L.

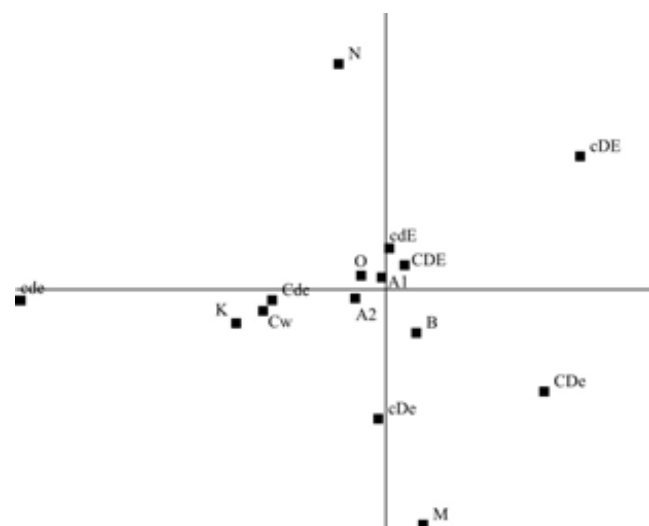


Fig. 2. The arrangement of 15 alleles and haplotype 4 genetic systems of blood in space of two main components concerning 16 populations of Siberia, presented on fig. 1.

References

1. Алексеева Т.И. Антропологические особенности современных тувинцев. Кефалометрия и кефалоскопия. *Антропо-экологические исследования в Туве*. М.: Наука. 1984;75–114. [Alekseeva TI. Anthropological features of modern Tuvans. Kefalometry and kefaloscopy. *Anthropological and ecological studies in Tuva*. М.: Nauka. 1984; 75–114. (In Russ.)]
2. Богданова В.И. Антропологический состав и вопросы происхождения тувинцев. *Проблемы антропологии древнего и современного населения Советской Азии*. Новосибирск: Наука. 1986;108-161 [Bogdanova VI. Anthropological composition and questions of Tuvans origin. *Problems of anthropology of ancient and modern population of Soviet Asia*. Novosibirsk: Nauka. 1986;108-161. (in Russ.)]
3. Пузырев В.П., Эрдыниева Л.С., Кучер А.Н. и др. Генетико-эпидемиологическое исследование населения Тувы – Томск: СТТ. 1999;256. [Puzyrev VP, Erdynieva LS, Kucher AN et al. Genetic-Epidemiological study of the Tuva population. Tomsk: СТТ. 1999;256. (In Russ.)]
4. Сукерник Р.И., Карафет Т.М., Абанина Т.А. и др. Генетическая структура двух обособленных популяций коренных жителей Сибири (северных алтайцев) по результатам изучения групп крови и изоферментов. *Генетика*. 1977; 13(5):911-917. [Sukernik RI, Karafet TM, Abanina TA et al. Genetic structure of the two isolated populations of aboriginal inhabitants of Siberia (of the northern Altai Mountains): according to the results of the investigation of blood groups and isoenzymes. *Генетика*. 1977; 13(5):911-917. (In Russ.)]
5. Батсуурь Ж., Самбуугийн Н., Шнейдер Ю.В. и др. Генетическая структура монголов по локусам ABO, MN, Rh, EsD, GLO1, PGM1, AcP, 6-PGD, Hp, Gc, Tf, C'3 и ChE2. *Генетика*. 1991; 27(2):316-325. [Batsuur J, Sambuugiin N, Schneider YuV et al. Genetic structure of Mongolian loci ABO, MN, Rh, EsD, GLO1, PGM1, AcP, 6-PGD, Hp, Gc, Tf, C'3 and ChE2. *Генетика*. 1991; 27(2):316-325. (In Russ.)]
6. Осипова Л.П., Карафет Т.М., Табиханова Л.Э. и др. Генетический полиморфизм популяций коренного населения Шурышкарского района ЯНАО по классическим маркерам групп крови и Y-хромосомы. *Коренное население Шурышкарского района Ямало-Ненецкого автономного округа: демографические, генетические и медицинские аспекты*. Новосибирск: ИПП "Арт-Авеню". 2005;200. [Osipova LP, Karafet TM, Tabikhanova LE et al. Genetic polymorphism of the indigenous population of Shuryshkarskiy district of YaNAO by classical markers of blood groups and Y-chromosomes. *Indigenous population of Shuryshkarskiy district of Yamal-Nenets autonomous*

district: demographic, genetic and medical aspects. Novosibirsk: IPP "Art-Avenue". 2005; 200 (In Russ..)]

7. Гусаченко Л.А., Литовченко О.Г. Распределение антигенов групп крови у мокша и эрзя Республики Мордовия. *Ульяновский медико-биологический журнал*. 2017; (3):159-164 [Gusachenko LA, Litovchenko OG. Distribution of blood-group antigens in Moksha and Erzya (Republic of Mordovia). *Ul'yanovskiy mediko-biologicheskiy zhurnal*. 2017; (3):159-164 (In Russ..)] DOI 10.23648/UMBJ.2017.27.7087

8. Давыдова Л.Е. Распределение групп крови в Республике Саха (Якутия). Связь с гепатитами В и С. *Здравоохранение Дальнего Востока*. 2017; (1):38-41 [Davydova LE Blood groups distribution in the Sakha Republic (Yakutiya), connection with B and C hepatitis. *Zdravookhraneniye Dal'nego Vostoka*. 2017; (1):38-41(In Russ..)]

9. Иванов В.П., Тостановская А.И., Шмидт С.И. Фенотипические частоты эритроцитарных антигенов систем АВО, Резус, MN, их генофонд и сравнительное изучение среди жителей Центрального Казахстана. *Генетика*. 1977; 13(8):1462-1466. [Ivanov VP, Tostanovskaya AI, Schmidt SI. Phenotypical structure of erythrocytes antigens of ABO, Rh, MN systems, their gene pool and comparative study in the population of the Central Kazakhstan. *Genetika*. 1977; 13(8):1462-1466. (In Russ..)]

10. Рычков Ю.Г., Перевозчиков И.В., Шереметьева В.А. и др. К популяционной генетике коренного населения Сибири. Восточные Саяны. *Вопросы Антропологии*. 1969;(31):3-32. [Rychkov YuG; Perevozchikov IV; Sheremetyeva VA et al. To population genetics of the indigenous population of Siberia. Eastern Sayans. *Voprosy Antropologii*. 1969; (31):3-32. (In Russ..)]

11. Карафет Т.М., Посух О.Л., Осипова Л.П. Популяционно-генетические исследования коренных жителей сибирского севера. *Сибирский экологический журнал*. 1994; 1(2):113-127. [Karafet TM, Posukh OL, Osipova LP. Population and genetic studies of the indigenous people of the Siberian North. *Sibirskiy ekologicheskiy zhurnal*. 1994; 1(2):113-127. (In Russ..)]

12. Магомедова М.А. Полиморфизм систем групп крови АВО и резус-фактор в отдельных районах Дагестана. *Известия Дагестанского государственного педагогического университета. Естественные и точные науки*. 2015;

4(33):57-60 [Magomedova MA Polymorphism of blood group systems of AVO and rhesus factor in some regions of Dagestan. *Izvestiya Dagestanskogo gosudarstvennogo pedagogicheskogo universiteta. Yestestvennyye i tochnyye nauki*. 2015; 4(33):57-60 (In Russ..)]

13. Кириллина В.И., Прокопьева Ю.Н., Осипова Л.П. и др. Описание структуры генофонда Нюрбинской и Усть-Алданской популяций народа саха. *Популяционно-генетическое изучение народа саха. Популяционно-генетическое изучение народа саха. Якутск*: 2001; 55-88. [Kirillina VI, Prokopyeva YuN, Osipova LP et al. Description of gene pool structure of Nyurbina and Ust-Aldan populations of the Sakha people. *Popular genetic study of the Sakha people*. Yakutsk: 2001; 55-88. (In Russ..)]

14. Дамба Л.Д., Балановская Е.В., Жабагин М.К. и др. Оценка вклада монгольской экспансии в генофонд тувинцев. *Вавиловский журнал генетики и селекции*. 2018; 22(5):611-619. [Damba LD, Balanovskaya EV, Zhabagin MK et al. Estimating the impact of Mongol expansion on gene pool of Tuvans. *Vavilovskiy zhurnal genetiki i selektsii*. 2018; 22(5):611-619. (In Russ..)] DOI: 10.18699/VJ18.402

15. Сукерник Р.И., Карафет Т.М., Абанина Т.А. и др. Популяционная структура лесных ненцев. Сообщение I. Распределение групп крови в шести субпопуляциях. *Генетика*. 1979; 15(2):327-332. [Sukernik RI, Abanina TA, Karafet TM et al. Population structure of the Forest Nentsy. I. Distribution of blood groups in six subisolates. *Genetika*. – 1979; 15(2):327-332. (In Russ..)]

16. Белопухов В.М., Тураев Р.Г., Бельская Е.Е. и др. Распределение групп крови среди доноров Республики Татарстан. *Казанский медицинский журнал*. 2015; 96(3):437-440. [Belopukhov VM, Turaev RG, Belskaya EE et al. Distribution of the blood groups among the donors of Tatarstan Republic. *Kazanskiy meditsinskiy zhurnal*. 2015; 96(3):437-440. (in Russ)] DOI: 10.17750/KMJ2015-437

17. Федорова С.А. Генетические портреты народов Республики Саха (Якутия): анализ линий митохондриальной ДНК и Y-хромосомы. Якутск: Издательство ЯНЦ СО РАН. 2008; 235. [Fedorova SA. Genetic portraits of peoples of the Sakha Republic (Yakutia): analysis of mitochondrial DNA and Y-chromosome lines. Yakutsk: Izdatel'stvo YANTS SO RAN. 2008; 235. (In Russ..)]

18. Posukh OL, Osipova LP, Kashinskaya YuO et al. A Genetic Study of the South Altaian Population of the Mendur-Sokkon Village, Altai Republic. *Russian Journal of Genetics*. 1998; 34(1): 92-98.

19. Fedorova SA, Tomsky MI, Reidla M et al. Autosomal and uniparental portraits of the native populations of Sakha (Yakutia): implications for the peopling of Northeast Eurasia. *BMC Evolutionary biology*. 2013;13(1):127.

20. Karaphet TM, Sukernik RI, Osipova LP et al. Blood groups, serum proteins, and red cell enzymes in the Nganasans (Tavghi)-reindeer hunters from Taimir Peninsula. *Am.J.Phys.Antropol.* 1981; 56(2):139-145. DOI: 0002-948318115602-0139502.50

21. Posukh OL, Osipova LP, Kashinskaya YuO et al. Characteristic Features of the Gene Pool of Russian Old Believers from Siberia, Assessed by Studying the Polymorphism of Blood Groups, Isozymes, and Serum Proteins. *Russian Journal of Genetics*. 1998; 34(40):431-438.

22. Golubenko MV, Salukov VB, Kucher AN et al. Distribution of Mongoloid Haplogroups of Mitochondrial DNA among Indigenous Population of the Tuva Republic. *Russian Journal of Genetics*. 2001; 37(6):831-839.

23. Tarskaia LA, Bychkovskaia LS, Pai GV et al. Distribution of the ABO blood groups and the HP, RF, GC, PI and C3 serum proteins in Yakuts. *Russian Journal of Genetics*. 2002; 38(5):548-552.

24. Kharkov VN, Khamina KV, Medvedeva OF et al. Gene-pool structure of Tuvinians inferred from Y-chromosome marker data *Russian Journal of Genetics*. 2013; 49(12):1236-1244. DOI: 10.1134/S102279541312003X

25. Harpending HC, Jenkins T. Genetic distances among Southern African populations. *Methods and theories of anthropological genetics*. Albuquerque: Univ. New Mexico Press.1973; 177-199.

26. Pakendorf B, Stoneking M, Novgorodov IN et al. Investigating the effects of prehistoric migrations in Siberia: genetic variation and the origins of Yakuts. *Human Genetics*. 2006; 120(3):334-353.

27. Osipova LP, Posukh OL, Ivakin EA et al. The Gene Pool of Native Inhabitants of the Samburg Tundra. *Russian Journal of Genetics*. 1996; 32(6):722-728.



T.V.Polivanova, V.A.Vshivkov

RELATIONSHIP OF FAMILY PREDISPOSITION FOR GASTRIC PATHOLOGY WITH GERD AND EROSIVE- ULCERATIVE LESIONS OF THE GASTRODUODENAL ZONE IN SCHOOLCHILDREN IN SIBERIA

DOI 10.25789/YMJ.2020.70.26

УДК 616.33/34 - 053.2 (571.)

To study the prevalence of gastroesophageal reflux disease (GERD), erosive and ulcerative diseases of gastroduodenal zone and their association in schoolchildren from different regions of Siberia with hereditary predisposition to stomach pathology, schoolchildren from the Republic of Tyva, Buryatia and Evenkia were examined. The prevalence of GERD among schoolchildren in Tyva was higher than in Buryatia and Evenkia. The destructive process of stomach mucosa and duodenum was also higher in Tyva. In children with erosive ulcerative lesions of the gastroduodenal zone, comorbidity of the esophagus was also more frequently determined.

The significant influence of family predisposition to stomach pathology on the prevalence of GERD, erosive-ulcer diseases of gastroduodenal zone, as well as their association in Siberian schoolchildren was established. At the same time, territorial features influence the severity of these processes.

Keywords: children, gastritis with erosions, ulcer disease, GERD, hereditary predisposition.

Chronic diseases of the upper gastrointestinal tract are mostly classified as multifactorial [4, 5, 9]. Among risk factors, family predisposition plays a major role in their formation [11, 13]. Its realization is carried out under the influence of unfavorable factors of external environment that reflects the level of organism's resistance to their influence. Nutrition, stresses, bad habits, etc. are considered among environmental factors with negative impact on the organism. At the same time by the level of negative influence they can have different significance for the organism, up to failure of its adaptation reserves and disease development [2, 8]. This may be one factor with a pronounced negative

impact on the functional systems of the organism, leading to the formation of pathology, or, more often, a complex of adverse factors [12, 17]. At the same time, different regions of the world have their own set of environmental factors with various negative impacts on the human body, which, to a large extent, determine the level of regional risk of disease development [6]. Thus, ecologically unfavorable environment for human habitation and increased risk of gastrointestinal diseases development is considered to be the Far North. Moreover, in Siberia, the structure of diseases of the stomach and esophagus has regional, ethnic, and age-related features [1, 14, 16]. Speaking about these features, it is necessary to note especially presence in the region of territories with extremely high incidence of adult population of stomach and esophagus cancer. In particular, these are the territories of the Tyva Republic and Buryatia [1, 3]. In this connection, the data on the role of specific factors in the development of children's stomach and esophagus diseases, i.e., in the age period of pathology occurrence in the majority of adults, are of interest [1, 3]. In particular, the data on the role of family predisposition in their occurrence, this can be used in preventive measures of formation and progression of pathology.

The **objective** of the research is to study the prevalence of gastroesophageal reflux disease, erosive and ulcerative diseases of the gastroduodenal zone and their association with hereditary predisposition to stomach pathology in schoolchildren from different regions of Siberia.

Materials and methods. The cross-sectional method was used to collect data on gastroenterological complaints in children and anamnestic data on the presence of digestive pathology in children's relatives using standardized questionnaires in various regions of Siberia: in the Republic of Tyva (1535 schoolchildren), Buryatia (790) and Evenkia (1369). A total of 3,694 school children aged from 7 to 17 years were examined. The research in the regions was carried out by the expedition method in localities that are identical in their socio-economic level.

All children over 15 years of age and parents of young children involved in the study gave a written form of informed consent to participate in the experiment, according to the Helsinki Declaration of the World Medical Association, which regulates the conduct of scientific research. The form of informed consent and the research Protocol were reviewed and approved by the ethics Committee of Federal Research Centre «Krasnoyarsk Scientific Centre» Siberian Division of Russian Academy of Sciences, Krasnoyarsk.

Groups of school children were randomly selected from the number of children with gastroenterological complaints in each region and underwent esophago-gastroduodenoscopy (FGS). An instrumental study of the upper gastrointestinal tract in Tyva was conducted for 283 children, in Buryatia - 110 and in Evenkia - 205. The gender-age composition of the surveyed schoolchildren in the regions was identical.

Mrs. POLIVANOVA Tamara Vladimirovna – Full Professor (Medicine), Chief Scientific Worker of Clinical Division of the Pathology of Digestion System in Adults and Children of Scientific Research Institute for Medical Problems of the North of Federal Research Centre «Krasnoyarsk Scientific Centre» of Siberian Division of Russian Academy of Sciences; Partizana Zheleznyaka Str., 3G, Krasnoyarsk, 660022, Russian Federation; tel.: +7 950 990 57 09; E-mail: tamara-polivanova@yandex.ru; **Mr. VSHIVKOV Vitaliy Alekseevich** – PhD (Medicine), Senior Scientific Worker of Clinical Division of the Pathology of Digestion System in Adults and Children of Scientific Research Institute for Medical Problems of the North of Federal Research Centre «Krasnoyarsk Scientific Centre» of Siberian Division of Russian Academy of Sciences; Partizana Zheleznyaka Str., 3G, Krasnoyarsk, 660022, Russian Federation; tel.: +7 923 280 06 98; E-mail: vitali1983@mail.ru.

Criteria for including children in a study using FGS: 1. Age from 7 to 17 years; 2. Absence of acute inflammatory diseases in children; 3. Absence of chronic diseases of other body systems in the acute stage; 4. Absence of functional insufficiency of organs and body systems; 5. Presence of internal complaints.

The GERD in children was diagnosed in accordance with the children's consensus on pathology [10]. During screening, the presence of weekly heartburn was taken as a criterion for diagnosing GERD. Heartburn was understood as a burning sensation in the retrosternal region. Based on the results of an instrumental study of the upper gastrointestinal tract, two clinical variants of GERD were identified: 1. non-erosive (NERD), based on the presence of weekly heartburn in the child in the absence of erosive and ulcerative changes in the esophageal mucosa and 2. erosive form, diagnosed in the presence of erosive esophagitis.

Statistical analysis of the results was performed using the Statistica 6.1 software package (StatSoft, USA). The analysis of the statistical significance of differences in qualitative characteristics was carried out using the Yates-corrected χ^2 criterion and the Fischer two-way exact criterion. The statistical significance of differences in features was estimated at $p < 0.05$ [7].

Results and discussions. Based on the clinical manifestations of heartburn, GERD was diagnosed among the examined contingent of schoolchildren in 6.4%. Significant territorial differences in the prevalence of pathology in children were noted. In Tuva, 9.5% of schoolchildren had GERD manifestations. These are significantly higher in comparison with the prevalence of the disease among schoolchildren in Buryatia (4.1%; $p = 0.0001$) and Evenkia (4.2%; $p = 0.0001$). The prevalence of GERD in Evenkia and Buryatia was identical ($p = 0.8988$).

The prevalence of GERD in children with a burdened family history of gastric pathology was assessed. It was found that in schoolchildren with a burdened family history, the frequency of GERD increased (in 9.8% compared with 4.6% of the prevalence of the disease among children without a burdened family history; $p = 0.0001$). We consider this result as a consequence of the increased effect of the acid factor, which is inherent in patients with diseases of the stomach and GERD. A connection with a family predisposition for gastric pathology indicates genetic mechanisms for the implementation of the negative impact of this factor in the occurrence of the disease. At

the same time, Siberia is a huge territory, which includes various climatogeographic zones, significantly differing in the geochemical composition of soil and water. Extreme environmental factors can enhance the negative role of a family predisposition to the disease in the formation of the pathological process; in particular, which is the basis for the onset of clinical manifestations of GERD. Territorial features of the prevalence of diseases are formed. This is clearly demonstrated by the results of our study. Thus, the association of GERD with a family predisposition to the pathology of the digestive organs in schoolchildren was determined independently of the region and the particular climatic conditions of residence (Table 1). This highlights the special, dominant role of family predisposition in the formation of the disease.

At the same time, differences in the severity of this association in children of different regions draw attention to themselves, which reflects the negative impact of environmental factors. GERD prevalence rates among schoolchildren with a family history of gastric pathology in Tuva were significantly higher (11.8%) than among schoolchildren in Buryatia (6.7%; $p = 0.0001$) and Evenkia (8.4%; $p = 0.0001$). The result, in our opinion, indicates the presence on the territory of Tyva of environmental factors with a more pronounced negative effect on the body. Such factors in Tuva can be pronounced iodine deficiency [15], which is accompanied by hypothyroidism and characteristic motor disorders of the gastrointestinal

tract. The alpine climate, which distinguishes Tuva from other territories, can have a negative effect on the function of the gastrointestinal tract. Maybe this is a factor in the specifics of nutrition. It is important that the indigenous people are the titular nations in Buryatia and Tuva. Moreover, the uniqueness of the indigenous population of Siberia lies in their genetic diversity. In this connection, it is impossible to exclude a certain influence, again, of genetic factors characterizing the belonging of a population to a specific ethnic group. All this needs further study.

The relationship of family predisposition and GERD in children, the severity of which has certain differences under the influence of environmental factors, forms regional features of not only the prevalence, but also the severity of damage to the esophagus. To a certain extent, this fact is confirmed by the results of instrumental studies of the upper sections of the gastrointestinal tract (Table 2). GERD with erosive esophagitis was mainly diagnosed in schoolchildren with a family history of gastric pathology (in 3 (1.2%) cases versus 1 (0.3%) in schoolchildren without a family history). Significant differences were not obtained, due to the fact that pathology is not widespread in childhood and adolescence compared with adults.

In the course of the study, it was noted that there was no obvious increase in erosive and ulcerative diseases in schoolchildren with a family predisposition to stomach pathology, there was only a tendency in children of Buryatia and Even-

Table 1

Screening for GERD in children with gastrointestinal complaints in Tyva, Buryatia, and Evenkia

Region	Burdened family history of gastric pathology	n	GERD	
			n	%
Tyva	1. Yes	626	74	11,8
	2. No	909	72	7,9
Buryatia	3. Yes	254	17	6,7
	4. No	536	15	2,8
Evenkia	5. Yes	379	32	8,4
	6. No	990	25	2,5
All regions	7. Yes	1259	123	9,8
	8. No	2435	112	4,6
p-level (significance of feature differences)			$p^{1-2}=0,0105$ $p^{1-3}=0,0235$ $p^{1-5}=0,0911$ $p^{3-4}=0,0095$ $p^{5-6}=0,0001$ $p^{2-4}=0,0001$ $p^{2-6}=0,0001$ $p^{7-8}=0,0001$	

Note: GERD - gastroesophageal reflux disease.

kia (Table 3). A similar trend was not observed in Tyva, which is regarded as the result of a pronounced negative influence of external factors, and the significance of the influence of such a factor as family predisposition goes by the wayside. An argument in favor of this may be an extremely pronounced problem with cancer incidence in adult residents of Tyva [1], which is evidence of the existence of factors in the region with an extremely negative effect on health parameters. Another argument may be the highest rates of erosive-ulcerative pathology of the gastroduodenal zone in Tyva and in children without a family predisposition to stomach pathology (17.4%). Moreover, its growth was formed by an increase in almost all nosological units in the structure of erosive-ulcerative pathology.

Analyzing the relationship of GERD

and diseases with erosive and ulcerative changes in the mucosa of the gastroduodenal zone, it was noted that the association of these pathological processes increases sharply in schoolchildren with a burdened family history of gastric pathology (Table 4).

Thus, the highest rates of GERD were determined in schoolchildren with a family predisposition in the presence of erosive and ulcerative changes in the gastric mucosa and duodenum. The prevalence of GERD in schoolchildren with erosive-ulcerative lesions of the gastroduodenal zone increased in individuals with a family history of gastric pathology (30.3% versus 18.9% in individuals without a destructive process in the stomach and duodenum; $p = 0.1299$) and in schoolchildren without a family predisposition to gastric pathology (25.8% versus 7.4% in individ-

uals without a destructive process in the stomach and duodenum; $p = 0.0006$). This insignificant trend was observed in the populations of schoolchildren examined in all three territories. A closer associative relationship between the diseases was observed in Buryatia and Evenkia. In schoolchildren of these regions, even in the absence of erosive and ulcerative lesions, in the presence of a family predisposition to gastric pathology, clinical manifestations of GERD were more often present. This, in our opinion, indicates the importance of genetic mechanisms in the implementation of pathological processes. Excellent territorial data were established in Tyva, where the influence of family predisposition to gastric pathology on the association between diseases (GERD and erosive ulcers) was not determined. In fact, this strengthens the arguments in favor of the position of the dominant influence of the regional environmental conditions of this territory in the formation of the considered diseases.

Conclusion

Thus, a family predisposition to gastric pathology is a significant factor influencing the risk of developing GERD and erosive and ulcerative diseases of the gastroduodenal zone and their association in schoolchildren. This affects the prevalence of pathological processes. In addition to the family predisposition, the external environment has a pronounced effect on the prevalence of these pathological processes in schoolchildren, which forms some regional features of the prevalence of these diseases, as well as their relationship. Moreover, under certain conditions, a family predisposition acts as a factor with a dominant influence on the formation of pathological processes, while in others, the role of unfavor-

Table 2

Frequency and forms of GERD in endoscopically examined schoolchildren in Tyva, Buryatia, and Evenkia with intestinal complaints

Region	Burdened family history of gastric pathology	n	Erosive GERD		Non-erosive GERD	
			n	%	n	%
Tyva	1. Yes	162	3	1,9	36	22,2
	2. No	121	0	0	23	19,0
Buryatia	3. Yes	53	0	0	8	15,1
	4. No	57	0	0	1	1,8
Evenkia	5. Yes	40	0	0	5	12,5
	6. No	165	1	0,6	6	3,6
All regions	7. Yes	255	3	1,2	49	19,2
	8. No	343	1	0,3	30	8,7
p-level (significance of feature differences)					$p^{3-4}=0,0108$ $p^{5-6}=0,0256$ $p^{7-8}=0,0002$ $p^{2-4}=0,0017$ $p^{2-6}=0,0001$	

Table 3

Frequency and structure of erosive-ulcerative pathology in children of Tyva, Buryatia, Evenkia with intestinal complaints

Region	Burdened family history of gastric pathology	n	Erosive-ulcerative pathology		Erosive gastritis		Erosive duodenitis		Gastric ulcer		Duodenal ulcer	
			abc.	%	abc.	%	abc.	%	abc.	%	abc.	%
Tyva	1. Yes	162	23	14.2	12	7.4	9	5.6	2	1.2	5	3.1
	2. No	121	21	17.4	13	10.7	8	6.6	2	1.7	3	2.5
Buryatia	3. Yes	53	6	11.3	4	7.5	1	1.9	0		2	3.8
	4. No	57	2	3.5	2	3.5	0	0	0	0	0	0
Evenkia	5. Yes	40	4	10.0	3	7.5	2	5.0	0	0	0	0
	6. No	165	8	4.8	5	3.0	4	2.4	0	0	2	1.2
All regions	7. Yes	255	33	12.9	19	7.5	12	4.7	2	0.8	7	2.7
	8. No	343	31	9.0	20	5.8	12	3.5	2	0.6	5	1.5
p-level (significance of feature differences)			$p^{2-4}=0.0102$ $p^{2-6}=0.0005$		$p^{2-6}=0.0079$		$p^{2-4}=0.0469$ $p^{2-6}=0.0809$					

Note: GERD - gastroesophageal reflux disease.

Table 4

Association of erosive and ulcerative lesions of the gastroduodenal mucosa and GERD in schoolchildren in Siberia

Region	Burdened family history of gastric pathology	Presence of erosive and ulcerative defects of the stomach and duodenum	n	GERD	
				n	%
Tyva	Yes	1. Yes	23	8	34.8
		2. No	139	31	22.3
	No	3. Yes	21	8	38.1
		4. No	100	15	15.0
Buryatia	Yes	5. Yes	6	1	16.7
		6. No	47	7	14.9
	No	7. Yes	2	0	0
		8. No	55	1	1.8
Evenkia	Yes	9. Yes	4	1	25.0
		10. No	36	4	11.1
	No	11. Yes	8	0	0
		12. No	157	7	4.5
All regions	Yes	13. Yes	33	10	30.3
		14. No	222	42	18.9
	No	15. Yes	31	8	25.8
		16. No	312	23	7.4
p-level (significance of feature differences)				$p^{3-4}=0.0142$	
				$p^{6-8}=0.0144$	
				$p^{14-16}=0.0001$	
				$p^{15-16}=0.0006$	
				$p^{3-11}=0.0402$	
				$p^{4-8}=0.0098$	
			$p^{4-12}=0.0032$		

able environmental factors in their occurrence sharply increases. Obviously, an increase in the association of erosive and ulcerative diseases of the gastroduodenal zone and GERD against the background of an increase in their prevalence can be expected in the face of an increase in the complex effect of these factors.

References

1. Аксель Е.М. Статистика злокачественных новообразований желудочнокишечного тракта. *Сибирский онкологический журнал*. 2017;16(3):5-11. [Axel EM. Gastrointestinal cancer statistics. *Sibirskiy onkologicheskij zhurnal*. 2017; 16(3):5-11. (In Russ.)]. DOI: 10.21294/1814-4861-2017-3-5-11.

2. Туманян С.В., Моисеенко Т.И., Орос О.В. [и др.]. Влияние мультимодальной анестезии и анальгезии на механизмы адаптации кровообращения онкогинекологических больных в послеоперационном периоде. *Медицинский вестник Юга России*. 2018; 9(1):80-85. [Tumanyan SV, Moiseyenko TI, Oros OV. [et al.]. Influence of multimodal anesthesia and analgesia on mechanisms of blood circulation adaptation of oncogynecologic patients in the postoperative pe-

riod. *Medical Herald of the South of Russia*. 2018; 9(1):80-85. (In Russ.)]. DOI: 10.21886/2219-8075-2018-9-1-80-85.

3. Дулганов П.К., Данчинова А.М. К изучению этнического фактора в эпидемиологии злокачественных опухолей пищевода в Республике Бурятия. *Бюл. Вост.-Сиб. науч. центра СО РАМН*. 2007;53(1):170-171. [Dulganov PK, Danchinova AM. To the study of the ethnic factor in the epidemiology of malignant tumors of the esophagus in the Republic of Buryatia. *Byulleten' Vostochno-Sibirskogo nauchnogo tsentra Sibirskogo otdeleniya Rossiyskoy akademii meditsinskih nauk*. 2007;53(1):170-171. (In Russ.)].

4. Поливанова Т.В., Вшивков В.А. Ассоциация показателей циркулирующего лептина с клинико-морфологическими проявлениями гастрита в зависимости от индекса массы тела у школьников без ожирения. *Якутский медицинский журнал*. 2019;65(1):10-14. [Polivanova TV, Vshivkov VA. Association of the indices of circulating leptin with gastritis clinical morphological signs depending on body mass index in schoolchildren without obesity. *Jakutskij medicinskij zhurnal*. 2019; 65(1):10-14 (In Russ.)]. DOI: 10.25789/YMJ.2019.65.03.

5. Запруднов А.М., Григорьев К.И., Харитонов Л.А. [и др.]. Проблемы и перспективы современной детской гастроэнтерологии. *Педиатрия. Журнал им. Г.Н. Сперанского*. 2016;6:10-18. [Zaprudnov AM, Grigoriev KI, Hari-

tonova LA. [et al.]. Problems and perspectives of modern pediatric gastroenterology. *Pediatrics. Journal them. G.N. Speransky*. 2016;6:10-18 (In Russ.)].

6. Прусаков В.М., Прусакова А.В. Динамика риска заболеваемости и адаптационного процесса как показатели воздействия локальных факторов окружающей среды на население. *Гигиена и санитария*. 2018; 97(2):124-131. [Prusakov VM, Prusakova AV. The dynamics of the risk of the morbidity and the adaptation process as indices of the impact of local environmental factors on the population. *Hygiene and sanitation*. 2018; 97(2):124-131. (In Russ.)]. DOI: 10.18821/0016-9900-2018-97-2-124-131.

7. Реброва О.Ю. Описание статистического анализа данных в оригинальных статьях. Типичные ошибки. *Медицинские технологии. Оценка и выбор*. 2011;4:36-40 [Rebrova OYu. Description of Statistical Analysis of Data in Original Articles. Typical Errors. *Medical technology. Evaluation and selection*. 2011; 4: 36-40 (In Russ.)].

8. Сетко Н.П., Булычева Е.В. Оценка адаптационных резервных возможностей детского организма как основа диагностики донозологических состояний. *Вопросы школьной и университетской медицины и здоровья*. 2015;4:53-54 [Setko NP, Bulycheva EV. Evaluation of adaptation reserve opportunities of the child's body as the basis in diagnosis of prenosological states. *Voprosy shkol'noy i universitetskoy meditsiny i zdorov'ya*. 2015;4:53-54 (In Russ.)].

9. Турдыева Ш.Т. Выявление групп риска хронической гастродуоденальной патологии среди детей и подростков. *Вопросы детской диетологии*. 2015;13(6):18-22. [Turdyeva ShT. Identification of risk groups for chronic gastroduodenal pathology among children and adolescents. *Voprosy detskoy dietologii*. 2015; 13(6):18-22. (In Russ.)].

10. Sherman PM, Hassall E, Fagundes-Neto U. [et al.]. A Global, Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Pediatric Population. *Am J Gastroenterol*. 2009;104(5):1278-95. DOI: 10.1038/ajg.2009.129.

11. Cam S. Risk of gastric cancer in children with Helicobacter pylori infection. *Asian Pac J Cancer Prev*. 2014;15(22):9905-8. DOI: 10.7314/apjcp.2014.15.22.9905.

12. Guibas GV, Megremis S, West P. [et al.]. Contributing factors to the development of childhood asthma: working toward risk minimization. *Expert Rev Clin Immunol*. 2015;11(6):721-35. DOI: 10.1586/1744666X.2015.1035649.

13. Castillo-Montoya V, Ruiz-Bustos E, Valencia-Juillerat ME. [et al.]. Detection of Helicobacter pylori in children and adolescents using the monoclonal coproantigen immunoassay and its association with gastrointestinal diseases. *Cir Cir*. 2017; 85(1):27-33. DOI: 10.1016/j.circir.2016.05.008.

14. Kurilovich SA, Reshetnikov OV. Epidemiological studies in gastroenterology: long-term siberian experience of Helicobacter pylori and related diseases. *Eksp Klin Gastroenterol*. 2015;(3):4-10.

15. Osokina IV. Iodine deficiency cretinism in Tuva Republic, Siberia. *Acta Scientific Nutritional Health*. 2019; 3(12):72-74.

16. Belkovets AV, Kurilovich SA, Reshetnikov OV. [et al.]. Prevalence and peculiarity of corpus atrophic gastritis in population with high level of Helicobacter pylori infection. *Eksp Klin Gastroenterol*. 2016 ; (9):8-13.

17. Tian J, An X, Fu M. Pediatric cardiovascular risk factors. *Minerva Pediatr*. 2017; 69(3):225-229. DOI: 10.23736/S0026-4946.16.04713-7

Yu.R. Akhmedinova, L.S. Evert, T.V. Potupchik

BRAIN NEUROTROPHIC BDNF LEVEL AT TEENAGERS WITH SYNCOPAL CONDITIONS

DOI 10.25789/YMJ.2020.70.27

УДК 616.8-009.832-053.6

The aim of the study was to assess the level of cerebral neurotrophic factor BDNF in the blood plasma of adolescents with syncopal conditions.

Materials and methods: 225 people (boys and girls) aged 12-17 years were examined, of which 63 adolescents with a history of neurogenic syncope (main group) and 162 without syncope (control group). The plasma BDNF content (in pg / ml) was determined on a Multiscan FC apparatus (Finland) using the Quantikine® ELISA ELISA using the R&D systems® reagent kit (USA). The obtained data were processed in the program "Statistica 12".

Results: lower levels of BDNF in the blood plasma of adolescents with neurogenic syncopal conditions were detected. A large number of individuals with slightly and significantly reduced BDNF levels among adolescents with syncope episodes were found.

Discussion: taking into account the significant role of BDNF in modulating neuroplastic processes, the decrease in its level detected by us can probably be regarded as a metabolic marker of the risk of the occurrence and presence of neurodegenerative processes in the brain tissue of adolescents with recurrent syncope. This assumption can be confirmed by further studies.

Conclusions: syncope in adolescents is associated with lower levels of cerebral neurotrophic factor BDNF. Among adolescents with syncope, there are more individuals with slightly- and significantly reduced BDNF levels compared to the group without syncope.

Keywords: adolescents, syncope, cerebral neurotrophic factor BDNF.

Introduction. Syncope (fainting) is an episode of sudden short-term loss of consciousness associated with a sharp weakening of postural muscle tone and characterized by a spontaneous restoration of cerebral functions. The main signs of a syncope are sudden development, short duration and reversibility. The problem of neurogenic syncope states related to psychosomatic disorders is currently an urgent medical problem [2]. An equally important task is the timely diagnosis and effective correction of these disorders, taking into account the peculiarities of metabolic processes in the brain tissue and affecting the functioning of the central nervous system [6,7,10,13].

According to the results of large population studies, the frequency of syncope in children is 126 per 100,000 children and adolescents [16,18,19]. According to epidemiological data, 15-20% of adolescents experience at least a single episode of syncope before reaching the age of 18 years [3]. The frequency of occurrence of episodes of syncopal conditions in schoolchildren of the city of Krasnoyarsk according to a questionnaire survey is 7.6%, with a predominance in girls, compared with boys, and in older students, compared with children of primary school age [5]. The most frequent and significant types of syncope in children and adolescents include: vasovagal syncope (up to 90% of all cases of syncope); orthostatic syncope (8-10%); respiratory affective seizures (only in children from 6 months to 2 years old); toxic / medicinal syncope (poisoning, side effects of drugs, are rare); cardiogenic syncope (about 5% of all cases of syncope).

There are many reasons that can provoke attacks of loss of consciousness. In most cases, syncopal conditions are primarily neurogenic in nature and are mediated by conditioned or unconditionally reflex mechanisms of regulation of the cardiovascular system, causing the body to respond to external influences. However, they can occur during decompensation of severe somatic diseases and cerebral pathological processes that threaten the life of the child (brain tumor, cerebral aneurysm, etc.).

The immediate cause of syncope is a sharp and sudden decrease in blood supply to the brain below the level necessary to maintain adequate brain tissue metabolism. The consequence of repeat-

ed episodes of cerebral hypovolemia in children with syncopal conditions and neuron hypoxia arising from it may lead to the development of degenerative processes in the substance of the brain.

A special role in the modulation of neuroplastic processes is played by neurotrophic germ factors (NTF). To date, the most studied is the brain neurotrophic factor - brain-derived-neurotrophic-factor (BDNF). It refers to physiologically active polypeptides that regulate the growth and differentiation of neurons during phylogenesis, contribute to the formation of new synaptic connections in the postnatal period. BDNF plays a crucial role in the pathogenesis of neurodegenerative diseases, in the restoration of functions in traumatic and vascular lesions of the nervous system. BDNF is a protein with a molecular weight of 27 kDa and is expressed in fibroblasts, astrocytes, neurons, platelets, as well as in lemmocytes [17]. During the development of the nervous system, BDNF is involved in the differentiation of neurons, in synaptogenesis, and plays a role in long-term potentiation and synaptic plasticity. It is believed that it can play a role in the formation of memory.

Since embryonic development of platelets and neurons comes from the same precursor in the scallop, the concentration of BDNF in the blood may reflect the level of synthesis of BDNF in the central nervous system. To date, 2 types of BDNF receptors are known: the first are low-affinity NGF receptors with a molecular weight of 75 kDaltons (LNGFR), the second are high-affinity receptors for tropomyosine kinase-B with a molecular weight of 145 kDaltons (TrkB) [15]. These

AKHMEL'DINOVA Yuliya Rinatovna - 6th year student of the pediatric faculty of KrasGMU; Russia, 660022, Krasnoyarsk, ul. Partizan Zheleznyak, 1, e-mail: axmeldinova@mail.ru; **EVERT LIDIYA Semenovna** - Doctor of Medical Sciences, Chief Researcher at the Clinical Department of Somatic and Mental Health of Children, Research Institute of the Ministry of Railways, FIC KSC SB RAS; Russia, 660022, Krasnoyarsk, ul. Partizan Zheleznyak, d. 3G; Professor of the Department of General Professional Disciplines FSBEI of HE "KSU named after N.F. Katanova"; Russia, 665000, Abakan, ul. Khakasskaya, 68; <https://orcid.org/0000-0003-0665-7428>; e-mail: lidiya_evert@mail.ru; **POTUPCHIK Tat'yana Vital'evna** - candidate of medical sciences, associate professor of the Department of Pharmacology and Pharmaceutical Consulting with a course at FSBEI HE "KrasGMU named after prof. V.F. Voyno-Yasenetsky" Ministry of Health of the Russian Federation; Russia, 660022, Krasnoyarsk, st. Partizan Zheleznyak, d.1; <https://orcid.org/0000-0003-1133-4447>; e-mail: potupchik_tatyana@mail.ru

receptors determine the specificity of the action of BDNF. The functional activity of neurotrophic factors (including BDNF) is quite high. During the development of the nervous system, they participate in the differentiation, maturation of neurons and the formation of synapses. In the adult body, they play a neuroprotective role, protect brain neurons from hypoxia and ischemia [14]. BDNF and the serotonergic system, interacting with each other in the central nervous system and modulating brain processes together, are involved in the pathogenesis of anxiety, depression and impaired cognitive processes in humans.

Antidepressant therapy increases the production of BDNF, which leads to the restoration of processes of neurogenesis and neuronal plasticity. In recent years, the possibility of using a serum BDNF concentration indicator and / or BDNF gene polymorphisms to predict or evaluate the effectiveness of a response to therapy has been widely studied. The identification of the significant role of NTF and, in particular, BDNF in stimulating neuroplasticity is promising in the treatment of vascular, traumatic and neurodegenerative diseases of the nervous system.

The aim of our study was to assess the level of cerebral neurotrophic factor BDNF in adolescents with neurogenic syncopal conditions.

Materials and research methods.

The object of the study was adolescents 12-17 years old (boys and girls) in the amount of 225 people, the subject of the study was the neurotrophic factor BDNF. The main group consisted of 63 adolescents with neurogenic syncope, and 162 adolescents without a history of syncope were included in the control group. Information about the presence of syncope was obtained by questioning.

The level of neurotrophic factor BDNF in the blood plasma was determined on a Multiscan FC apparatus (Finland, 2009) using the Quantikine® ELISA ELISA using the R&D systems® reagent kit (USA). The BDNF content in the analyzed plasma samples was expressed in PG / ml.

The survey was carried out after obtaining written informed consent to participate in the study of parents of adolescents under 15 years old or the adolescents themselves over the age of 15 years. The study was approved by the Ethics Committee of the Federal State Budgetary Institution of Science and Technology of the Federal Research Center of the Kola Scientific Center of the SB RAS (Minutes No. 1 dated March 16, 2020).

Statistical processing of the obtained data was carried out by non-parametric statistics methods in the program "Statistika 12" [8]. The results of the analysis of quantitative traits are presented as the median (Me) and interquartile range (Q25 – Q75). Binary features are presented as % share and boundaries of the confidence interval estimated by the Wilson method. The achieved level of significance of differences (p) for quantitative indicators was determined by the Mann – Whitney U-test, for binary characters, by the Pearson χ^2 criterion. Differences between groups were considered statistically significant at a achieved level of $p \leq 0.05$.

Results and discussion. To assess the level of BDNF in the blood plasma of the examined adolescents at the first stage, we developed internal standards for this indicator: the percentile values of the cerebral neurotrophic factor in adolescents in the control group were determined. The 5 % values in adolescents in the control group were 256 pg / ml, 10 % - 321 pg / ml, 15 % - 394 pg / ml, 25 % - 527 pg / ml, 50 % - 823 pg / ml, 75 % - 1122 pg / ml, 85 % - 1420 pg / ml, 90 % - 1660 pg / ml and 95 % - 1990 pg / ml. Criteria for assessing BDNF levels are presented in tables 1 and 2.

As a result of the study, it was found that among the examined with syncopal conditions there was a greater number of adolescents with a slightly reduced level of BDNF (14.3%, CI = 7.9-24.3%) compared with the control group (6.6%, CI = 3.9-10.9%, $\chi^2 = 3.93$, $p = 0.0475$). The proportion of adolescents with a significantly reduced level of the analyzed factor was also significantly larger in the group with a history of syncope (10.0%, CI = 4.9-19.2%) than in the group without syncope (1.5%, CI = 0.5-4.4%, $\chi^2 = 10.36$, $p = 0.0013$). Relative to other gradations of blood plasma BDNF level, there were no statistically significant differences in the compared groups, but there was a clear tendency for a greater number of individuals with BDNF levels below the normative values among adolescents with syncopal conditions. At the same time, the results of our comparative analysis revealed a tendency toward a higher incidence of adolescents with normal and elevated levels of BDNF in the group without a history of syncope.

A comparative analysis of the quantitative values of the level of BDNF in the blood plasma of adolescents with syncope and without syncope in the history is illustrated in table 3.

As can be seen from the table above, adolescents with syncopal conditions had

a statistically significantly lower content of cerebral neurotrophic factor BDNF in plasma compared to the level of a similar indicator in adolescents without syncope in history.

Numerous studies in recent years have shown that BDNF plays a significant role in the pathophysiology of a large number of diseases and pathological conditions. A decrease in the content of this neurotrophic factor has been established in a number of diseases and syndromes, with impaired memory and cognitive functions. Thus, a decrease in the level of BDNF was detected in adult patients with chronic tension headache [11] and those with memory impairment and cognitive dysfunction [1].

It has been established that there are fewer individuals with normal plasma concentrations of BDNF and a greater proportion of individuals with a low content of this indicator in adolescents with connective tissue dysplasia syndrome, dorsopathy, autonomic dysfunction syndrome, arterial hypertension, recurrent cephalgia and asthenic syndrome. Adolescents with a violation of psychoemotional status are characterized by a lower content of BDNF in plasma, a tendency to a decrease in the concentration of BDNF was revealed as the severity of distress, depression, anxiety, somatization and asthenia increased [12].

A relationship was found between the level of serum concentration of cerebral neurotrophic factor in children with hypoxic-ischemic brain lesions in which the serum concentration of BDNF was 1.3-1.6 times lower [4]. T.V. Samsonova (2013) found a decrease in the adaptive capabilities of the apparatus of autoregulation of cerebral circulation and autonomic regulation in adolescent children who underwent perinatal hypoxic brain lesions of moderate severity, associated with a decrease in the production of neuropeptide P substance 10-14 years old and brain neurotrophic factor BDNF - at the age of 15-17 [9].

Our data confirm the identified T.V. Samsonova (2013) direction of changes in the level of BDNF in adolescents with a history of PPCNS and the subsequent development of autonomic dysfunction. In our study, syncopal conditions in the examined adolescents had a neurogenic etiology due to the presence of autonomic dysfunction syndrome predominantly of the vagotonic type, and in patients with hypertension, the sympathicotonic type. In the history of most of the examined there were indications of a perinatal lesion of the central nervous system.

To date, the important role of BDNF

Table 1

Criteria for assessing normal and elevated plasma BDNF levels

Percentile range		BDNF percentile range		Plasma BDNF
≥ 25	≤ 75	≥ 527	≤ 1122	normal
> 75	≤ 85	> 1122	≤ 1420	slightly increased
> 85	≤ 90	> 1420	≤ 1660	moderately elevated
> 90	≤ 95	> 1660	≤ 1990	significantly upgraded
> 95		> 1990		high

Table 2

Criteria for evaluating a reduced level of BDNF in plasma

Percentile range		BDNF percentile range		Plasma BDNF
< 25	≥ 15	< 527	≥ 394	slightly reduced
< 15	≥ 10	< 394	≥ 321	moderately reduced
< 10	≥ 5	< 321	≥ 256	significantly reduced
< 5		< 256		lower

in modulating neuroplastic processes, in the regeneration of brain neurons and the restoration of their functions, is well known. In our opinion, a decrease in plasma levels of BDNF can be regarded as a metabolic marker for the presence and risk of neurodegenerative processes in the brain of adolescents with repeated episodes of neurogenic syncope.

Conclusions:

1. The presence of syncope in adolescents is associated with a lower level of cerebral neurotrophic factor BDNF in blood plasma.

2. Among adolescents with syncope, there are more individuals with a slightly and significantly reduced level of BDNF compared to the group without a history of syncope.

3. The assessment of the significance of a reduced level of BDNF in blood plasma as a metabolic marker for the presence and risk of neurodegenerative processes in the brain tissue of adolescents with syncopal conditions is relevant and requires further study.

References

1. Гомазков О.А. Сигнальные молекулы мозга и эпигенетические факторы при нейродегенеративных и психических расстройствах. *Журнал неврологии и психиатрии*.

2015;10:102-110. [Gomazkov OA. Signal molecules of the brain and epigenetic factors in neurodegenerative and mental disorders. *Zhurnal nevrologii i psikiatrii*. 2015;10:102-110. (In Russ.).] DOI: 10.17116/jnevro2015115101102-110

2. Макаров И.В. Клиническая психиатрия детского и подросткового возраста. СПб.: Наука и Техника; 2013. [Makarov IV. Clinical psychiatry of child and adolescent growth. SPb.: Nauka i Tehnika; 2013. (In Russ.).]

3. Мутафьян О.А. Аритмии сердца у детей и подростков (клиника, диагностика и лечение). СПб.: Невский диалект; 2003. [Mutafyan OA. Cardiac arrhythmias in children and adolescents (clinic, diagnosis and treatment). SPb.: Nevskii dialekt; 2003. (In Russ.).]

4. Новикова Д.А., Арсеньева Е.Н. Влияние комплексной терапии на содержание нейротрофических факторов у новорожденных детей с церебральной ишемией. *Российский педиатрический журнал*. 2012;5:9-13. [Novikova DA, Arsen'eva EN. The effect of complex therapy on the content of neurotrophic factors in newborns with cerebral ischemia. *Rossiyskiy pediatricheskiy zhurnal*. 2012;5:9-13. (In Russ.).]

5. Нягашкина Е.И. Клинико-функциональная характеристика детей, страдающих синкопальными состояниями и аффективно-респираторными приступами: автореф. дис. ... канд. мед. наук. Красноярск; 2008:24. [Nyagashkina EI. Clinical and functional characteristics of children suffering from syncopal conditions and affective respiratory attacks: abstract. dis. ... cand. med. sciences. Krasnoyarsk; 2008:24. (In Russ.).]

6. Эверт Л.С., Покидышева Л.И., Егоров А.А. [и др.]. Оценка психоэмоционального статуса, латерального фенотипа и высших мозговых функций у детей и подростков: программа для ЭВМ; ФГБНУ «Научно-исследовательский

институт медицинских проблем Севера». Красноярск, 2016. Гос. рег. программы для ЭВМ № 2016614566. [Evert LS, Pokidysheva LI, Egorov AA. [i dr.]. Assessment of the psychoemotional status, lateral phenotype, and higher brain functions in children and adolescents: a computer program; Federal State Budgetary Scientific Institution Scientific Research Institute of Medical Problems of the North. Krasnoyarsk, 2016. State. reg. computer programs No. 2016614566. (In Russ.).]

7. Потупчик Т.В., Веселова О.Ф., Эверт Л.С. Ноотропные препараты при нарушениях когнитивных функций у детей. *Врач*. 2016;4:75-78. [Potupchik TV, Veselova OF, Evert LS. Nootropic drugs in children with cognitive impairment. *Vrach*. 2016; 4:75-78. (In Russ.).]

8. Реброва О.Ю. Статистический анализ медицинских данных. Применение пакета прикладных программ «STATISTICA». М.: Медиа Сфера; 2002. [Rebrova OYu. Statistical analysis of medical data. Application of the STATISTICA application software package. M.: Media Sphere; 2002. (In Russ.).]

9. Самсонова Т.В. Применение семакса в восстановительном лечении детей первого года жизни с перинатальным гипоксическим поражением головного мозга. *Российский вестник перинатологии и педиатрии*. 2013;5:109-114. [Samsonova TV. The use of Semax in the rehabilitation treatment of children of the first year of life with perinatal hypoxic-ischemic brain damage. *Rossiyskiy vestnik perinatologii i pediatrii*. 2013; 5:109-114. (In Russ.).]

10. Эверт Л.С., Терещенко С.Ю., Реушева С.В. [и др.]. Способ оценки нарушений психосоматического статуса у детей и подростков. *Современные проблемы науки и образования*. 2016;4. URL: <http://www.science-education.ru/article/view?id=24897> [Evert LS, Tereshchenko SYu, Reusheva SV [i dr.]. A method for assessing violations of psychosomatic status in children and adolescents. *Sovremennye problemi nauki i obrazovaniya*. 2016;4. URL: <http://www.science-education.ru/article/view?id=24897> (In Russ.).]

11. Тянь К.В., Калинин П.П., Ракитова А.В. Уровень нейротрофического фактора головного мозга у пациентов с головной болью напряжения. *Российский журнал боли*. 2018;2(56):76. [Tyan KV, Kalinskiy PP, Rakitova AV. Level of brain neurotrophic factor in patients with tension headache. *Rossiyskiy zhurnal boli*. 2018; 2(56):76. (In Russ.).]

12. Эверт Л.С., Потупчик Т.В., Реушева С.В. [и др.]. Уровень мозгового нейротрофического фактора BDNF у подростков с дисплазией соединительной ткани и различными психосоматическими синдромами. *Современные проблемы науки и образования*. 2018; 5. URL: <http://science-education.ru/article/view?id=28072> [Evert LS, Potupchik TV, Reusheva SV [i dr.]. The level of cerebral neurotrophic factor BDNF in adolescents with connective tissue dysplasia and various psychosomatic syndromes. *Sovremennye problemy nauki i obrazovaniya*. 2018;5. URL: <http://science-education.ru/article/view?id=28072> (In Russ.).]

13. Эверт Л.С., Реушева С.В., Паничева Е.С. [и др.]. Эмоционально-поведенческие расстройства у школьников южных регионов Сибири с синкопальными состояниями. *Международный журнал прикладных и фундаментальных исследований*. 2014;9(2):140-144. [Evert LS, Reusheva SV, Panicheva ES [i dr.]. Emotional-behavioral disorders in schoolchildren of the southern regions of Siberia with syncopal conditions. *Mezhdunarodniy jurnal prikladnih i fundamentalnih*

Table 3

The content of BDNF in the blood plasma of adolescents with syncope and without syncope (in pg / ml)

Groups	M	N	Me	25%	75%	Std. Dev.	P ₁₋₂
1 gr. - without syncope	999.53	162	892.00	590.00	1190.00	643.31	0.0135
2 gr. - with syncopal conditions	814.12	63	705.00	471.00	1009.00	453.10	

issledovanii. 2014; 9 (2):140-144. (In Russ.)]

14. Kuipers S.D., Bramham C.R. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: new insights and implications for therapy. *Curr Opin Drug Discov Devel.* 2006; 9:580-586.

15. Leininger Gina M., Vincent Andrea M. The role of growth factors in diabetic peripheral

neuropathy. *Journal of the Peripheral Nervous System.* 2004; 9(1):26.

16. Maron B.J. Sudden death in young athletes. *N Engl J Med.* 2003; 349(11):1064-1075.

17. Martinowich K., Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci.* 2007; 10:1089-1093. DOI:10.1038/nn1971

18. Mcleod K.A. Syncope in childhood. *Arch Dis Child.* 2003; 88(4):350-353. DOI:10.1136/adc.88.4.350

19. Verhaaren H.A., Vanakker O., Coster V. [et al.]. Use of an event recorder in the decision for pacemaker implantation in a child with syncope. *Eur J Pediatr.* 2002; 161(5):267-269. DOI: 10.1007/s00431-002-0928-6

E.V. Ferubko

INVESTIGATION OF THE ROLE OF PHENOLIC COMPOUNDS IN THE MECHANISM OF ACTION OF THE NEW AGENT FOR PREVENTION AND TREATMENT OF DIGESTIVE DISEASES

DOI 10.25789/YMJ.2020.70.28

УДК: 615;615.243;616.33;616.34

The article presents a study on pharmacological activity of phenolic compound complex isolated from the polycomponent extract "Hexaphyte", which has choleric activity.

The aim of the study was to determine the role of the phenolic compound complex in the mechanism of action of hexaphyte.

The results of successive series of experiments to determine the role of phenolic compounds in the mechanism of action of "Hexaphyte" extract, including in the manifestation of choleric activity, concluded that the phenolic compound complex isolated from hexaphyte had a positive effect on the manifestation of choleric, antioxidant and membrane-stabilizing activity of extract "Hexaphyte".

Keywords: polycomponent plant extract, phenolic compound complex, choleric action.

Introduction. Digestive diseases occupy a leading place in the general structure of human diseases, and they have a recurrent course, a functional nature of the disorders, and the organic nature of the pathology [14, 9].

The use of plant-derived choleric agents is indicated for chronic diseases of the liver, gall bladder, and biliary tract [11]. The range of herbal medicines with choleric activity is small and is represented by plant composition (species), as well as purified extracts in the form of tablets (flamin, caleflon and hofitol), a solution for oral administration (hofitol), tablets of alcohol, etc. [4].

In this regard, the expansion of the range of drugs with choleric activity is promising. Given this circumstance, the creation of new and effective drugs based on a rational herbal composition is appropriate [5, 12, 13].

Based on information-analytical analysis of the literature and preliminary phytochemical study of raw plant materials, the authors developed the dry extract under the code name "Hexaphyte" that has

choleric activity due to the presence of biologically active substances, mainly of phenolic nature [8].

In this regard, the aim of our study was clarifying the role of the phenolic compound complex isolated from hexaphyte for interpretation its action mechanism, in particular, its choleric activity.

Materials and methods. The object of the research is the phenolic compound complex isolated from extract "Hexaphyte".

The dry extract under the code name "Hexaphyte" was obtained from the following species of medicine plant raw materials: flowers of dwarf everlast (*Helichrysum arenarium* L.) – 300g, flowers of tansy (*Tanacetum vulgare* L.) – 100g, rose hips (*Rosa* sp.) – 100g, leaves of common nettle (*Urtica dioica* L.) – 100g, leaves of peppermint (*Mentha piperita* L.) – 50g, roots of liquorice (*Glycyrrhiza glabra* L.) – 50g.

The hexaphyte was obtained during simultaneously component extraction with hot water (75-85o C). It contains polysaccharides, flavonoids, carotenoids, organic acids, vitamins, macro- and micronutrients, essential oils and other natural compounds. Extract "Hexaphyte" was standardized according to a complex of flavonoids in terms of luteolin standard and isosalipurposide standard, while the content of flavonoids is regulated at least 4% in the first case and at least 15% in the second case [8].

The phenolic compound complex of hexaphyte was obtained by eluting with an alcohol-water mixture in increasing concentration on a polyamide sorbent produced by the WOEL company.

This work was carried out in accordance with the Federal Law "On Medicinal Products" and the "Guidelines for Conducting Preclinical Studies of Medicines". The experiments were performed on 120 outbred male rats with an initial weight of 180-200 g. The animals were obtained from the Federal State Budgetary Scientific Institution Biomedical Technology Research Center of the Federal Medical and Biological Agency of Russia; they lived in the vivarium having free access to food and water. Pharmacological studies were carried out according to the Order of the Ministry of Health of the Russian Federation No. 199n dated 04/01/2016 "On the approval of the rules of good laboratory practice", according to the norms of good laboratory practice (GLP). The research was approved by the Institute's Bioethical Commission (protocol No. 7 of October 1, 2018).

We studied the effect of phenolic compound complex isolated from hexaphyte on the liver choleric function in intact rats with a single dose of 100 mg/kg or 500 mg/kg.

Bile of rats anesthetized with sodium thiopental, 45 mg/kg, was obtained according to the standard procedure [7] using a polyethylene cannula inserted

FERUBKO Ekaterina Vladimirovna – PhD (candidate of medical sciences), head of the department of experimental and clinical pharmacology; Federal State Budgetary Scientific Institution "All-Russian Scientific Research Institute of Medicinal and Aromatic Plants" Address: Greene St., 7. Moscow, 117216, Russian Federation, e-mail eferubko@yandex.ru.

into the common bile duct. The degree of choleric activity of the phenolic compound complex isolated from hexaphyte was estimated by the secretion rate and by the total amount of bile secreted, which was collected every hour for 4 hours, as well as by the content of bile acids in bile.

The antioxidant activity of the complex of phenolic compounds isolated from hexaphyte was determined by its intragastric course application in the indicated doses one time per day for 10 days. The medicine was applied to rats suffering from tetrachloromethane (CCl₄) hepatitis, starting from 2 days after the first injection of the damaging agent. Liver damage was induced by intragastric administration to rats of a 50% oil solution of carbon tetrachloride in a volume of 0.4 ml/100g of an animal weight, one time per day for 4 days [2]. The control group rats received water purified in an appropriate volume according to a similar scheme. The analysis were carried out after 7, 14 and 21 days from the start of the experiment. To assess the free radical lipid oxidation, the method of lipid chemiluminescent analysis was used. Spontaneous chemiluminescence of liver lipids, as well as induced luminescence of homogenate from this organ was recorded on a special quantum-meter installation designed to measure weak light fluxes [3]. Lipids were extracted from liver tissue according to the method of Folch J. et al. [10] with a chloroform-methanol mixture freshly prepared in a 2:1 ratio by volume.

The results of the studies were processed statistically using Microsoft Office Excel 2007, Statistica 6.0. Arithmetic mean (M), arithmetic mean error (m) were calculated. The normality of the distribution of variables was determined based on distribution histograms, asymmetry values and excesses. The Student's parametric t-criterion was used to evaluate the validity of the differences in samples close to the normal distribution. Differences between the compared values considered significant at the level of the probability of 95% and more ($p < 0.05$) [1].

Results and discussion. In order to clarify the mechanism of hexaphyte action, special experiments were carried out with the introduction of a complex of phenolic compounds isolated from it to rats.

Primary, the rats were arranged into following groups: the control (8 rats), experimental 1 (8 rats), and experimental 2 (8 rats) ones. The complex of hexaphyte phenolic compounds was administered to intact rats of the experimental groups once per os in doses of 100 mg/kg or 500

mg/kg. The rats of the control group were injected in equivolume amounts of purified water according to a similar regimen.

The effect of the phenolic compound complex isolated from hexaphyte on the bile secretion in intact rats has been studied (Table 1).

cholate-forming and cholate-releasing effects of the amount of phenolic compound complex studied were determined.

Subsequently, in accordance with the objectives of the study, special experiments were conducted to evaluate the antioxidant effect of the hexaphyte phe-

Table 1

The effect of the hexaphyte phenolic compound complex on bile secretion in intact rats

Group of animals	Dose, mg/kg	Bile secretion rate, mg/min per 100.0g				
		1 hour	2 hour	3 hour	4 hour	5 hour
Control	-	4.1±0.3	4.3±0.4	3.9±0.4	3.2±0.1	2.8±0.2
Experimental 1	100	3.6±0.2	4.9±0.4	5.6±0.5*	4.7±0.4*	3.4±0.2
Experimental 2	500	4.2±0.2	5.9±0.5*	6.4±0.5*	6.4±0.5*	5.2±0.3*

Note. In the Tables 1-3 * - p-values <0.05 represented significant differences.

The results presented in the Table 1 show that the administration of above indicated phenolic compound complex to intact rats was accompanied by an acceleration in bile secretion. This specific pharmacological effect of the phenolic compound complex applied at a dose of 500 mg/kg was more pronounced than at a dose of 100 mg/kg. The choleric reaction under these conditions was longtime; it took 4-5 hours. Thus, the choleric action of the phenolic compound complex isolated from hexaphyte is established.

The effect of the phenolic compound complex isolated from hexaphyte on bile acid content in bile in intact rats was studied (Table 2).

nolic compound complex. In a model of toxic hepatitis caused by the introduction of carbon tetrachloride to rats, the changes in free radical oxidation rate of liver lipids under the influence of the plant phenolic complex has been studied.

Primary, the rats were arranged into following groups: intact (24 rats); control (24 rats), experimental 1 (24 rats); experimental 2 (24 rats) ones. Animals of the first experimental group were administered with hexaphyte phenolic compound complex into the stomach through a tube in a dose of 100 mg/kg, one time per day for 10 days, starting from 2 days after the first injection of the damaging agent. Animals of the second experimen-

Table 2

The effect of the hexaphyte phenolic compound complex on the bile acid content in the bile of intact rats

Group of animals	Dose, mg/kg	Bile acid content per 1 hour, mg/100.0g				Total cholate per 4 hours, mg/100.0g
		2 hour	3 hour	4 hour	5 hour	
Control	-	1.50±0.4	1.35±0.3	0.80±0.4	0.61±0.1	4.26±0.3
Experimental 1	100	1.80±0.4	2.80±0.6*	2.19±0.5*	1.25±0.4*	8.04±0.5*
Experimental 2	500	2.46±0.4	2.56±0.5*	2.77±0.5*	2.08±0.2*	9.87±0.5*

The administration of above indicated phenolic compound complex to intact rats was accompanied by increase in bile acids biosynthesis, due to this, their content in the secreted bile increased by almost 2 times compared with the data in the control. The established pharmacological effect of the phenolic compound complex at 500 mg/kg was also more pronounced than when used at 100 mg/kg. As a result of the experiments carried out, the

tal group were administered with hexaphyte phenolic compound complex in a dose of 500 mg/kg according to a similar regimen.

The animals of the control group were injected with purified water in equivolume amounts according to a similar regimen. Intact animals were used as an additional control group.

The parameters of liver lipid chemiluminescence under the influence of

a complex of extracted phenolic compounds in experimental (CCI4) hepatitis in rats were changed in time; it was evaluated on days 7, 14 and 21 (Table 3).

er. As a result, functional and structural changes occur, which are manifested by an increase in biligenic process and bile excretion, by decrease in severe meta-

Table 3

Changes in liver lipid chemiluminescence (imp./s) under the influence of the extracted phenolic compound complex in experimental (CCI4) hepatitis in rats

Liver lipid chemiluminescence indices				
Research term	Liver lipid chemiluminescence indices in intact rats	in rats suffering from experimental hepatitis (control)	Liver lipid chemiluminescence indices in rats suffering from experimental hepatitis treated with hexaphyte phenolic compound complex at a dose of:	
			100 mg/kg	500 mg/kg
7-e	51.5±3.8	153.6±15.4	113.3±10.3*	101.0±9.5*
14-e	49.2±5.9	168.2±6.2	112.2±7.2*	96.7±12.1*
21-e	47.5±3.2	75.0±9.0	62.4±7.4	63.2±3.1

The results of the study showed that the introduction of the hexaphyte phenolic compound complex can be recognized by pronounced glow inhibition of liver lipids. Against the background of the introduction of the total complex of phenols at a dose of 100 mg/kg, the rate of radical reactions decreases by 15.2% - 33.3% depending on the timing of the study and the development of the pathological process in the liver.

A more pronounced inhibitory effect on the processes of free radical lipid oxidation in the damaged organ was found when the phenolic complex was applied at a dose of 500 mg/kg. At the hepatitis development time on days 7, 14 and 21, a decrease in the level of weak luminescence of liver lipids was 25.5%, 42.6% and 15.8%, respectively.

Thus, the intensity of free radical lipid oxidation under the influence phenolic compound complex isolated from extract "Hexaphyte" is significantly reduced. This ability of plant phenols is due to their membrane-stabilizing effect [6].

Having a membrane-stabilizing effect, phenolic compound complex isolated from hexaphyte can increase the functional activity of hepatocytes, and mobilize the reserve capabilities of the liv-

er. As a result, functional and structural changes occur, which are manifested by an increase in biligenic process and bile excretion, by decrease in severe meta-

bolis disorders and prevention of gross disorders in the structure of the hepatobiliary system organs.

Conclusion. The results of successive series of experiments to determine the role of phenolic compounds in the mechanism of action of "Hexaphyte" extract, including in the manifestation of choleric activity, concluded that the phenolic compound complex isolated from hexaphyte had a positive effect on the manifestation of choleric, antioxidant and membrane-stabilizing activity of extract "Hexaphyte".

References

1. Боровиков В.П. Популярное введение в современный анализ данных в системе STATISTICA. М.: Горячая линия. Телеком, 2014:288. [Borovikov VP. A popular introduction to modern data analysis in the STATISTICA system. M.: Goryachaya liniya, Telekom, 2014:288 (In Russ.)]
2. Буеверов А.О. Лекарственные поражения печени. *Российский медицинский журнал*. 2012; 3: 107-110 [Bueverov AO. Liver damage with drugs. *Rossiiskij medicinskij zhurnal*. 2012; 3: 107-110 (In Russ.)]
3. Владимиров Ю.А. Свободные радикалы и антиоксиданты. *Вестник РАМН*. 1988; 7: 43-50. [Vladimirov YuA. Free radicals and antioxidants. *Vestnik RAMN*. 1988; 7: 43-50 (In Russ.)]

4. Государственный реестр лекарственных средств – URL <https://grls.rosminzdrav.ru/> (дата обращения: 07.01.2020). [State Register of Medicines (In Russ.) – URL <https://grls.rosminzdrav.ru/> (accessed on 07.01.2020)]

5. Лубсандоржиева П.-Н.Б. Разработка и стандартизация фитосредств для лечения и профилактики заболеваний органов пищеварения. Улан-Удэ: Изд-во БНЦ СО РАН, 2016:280. [Lubsandorzhieva P.-NB. Development and standardization of herbal medicines for the treatment and prevention of digestive diseases. Ulan-Udeh: Izd-vo BNC SO RAN, 2016:280 (In Russ.)]

6. Николаев С.М. Фитофармакотерапия и фитотерапия заболеваний. Улан-Удэ: Изд-во БГУ, 2012:286. [Nikolaev SM. Phytopharmacotherapy and disease phytopharmacoprophylaxis. Ulan-Udeh: Izd-vo BGU, 2012:286 (In Russ.)]

7. Руководство по проведению доклинических исследований лекарственных средств. Ч.1. М.: Гриф и К, 2012:944. [Guidelines for preclinical studies of drugs. Part 1. M.: Grif i K, 2012:944 (In Russ.)]

8. Ферубко Е.В., Николаев С.М., Даргаева Т.Д. Средство, обладающее желчегонной активностью, и способ его получения. Патент №2700681 Российской Федерации МПК А61К 36/185, А61К 36/28, А61К 36/738 А61К 36/534, А61К 36/484, А61П 1/16. Оpubл. 19.09.2019, Бюллетень № 26. [Ferubko EV, Nikolaev SM, Dargaeva TD. Agent with choleric activity, and method for its preparation. Patent No. 2700681 of the Russian Federation, IPC Codes A61K 36/185, A61K 36/28, A61K 36/738 A61K 36/534, A61K 36/484, A61P 1/16. Published 19.09.2019, Bulletin №26 (In Russ.)]

9. Циммерман Я.С. Нерешенные и спорные проблемы современной гастроэнтерологии. М.: МЕДпресс-информ, 2013:224. [Cimmerman YaS. Unresolved and controversial issues of modern gastroenterology. M.: MEDpress-inform, 2013:224 (In Russ.)]

10. Folch J [et al.] A simple method for the isolation and purification of total lipids from animal tissues. *J Biol Chem*. 1957; 226: 497–509.

11. Hirschfield GM [et al.]. Pathogenesis of cholestatic liver disease and therapeutic approaches. *Gastroenterology*. 2010; 139: 1481-1496. DOI: 10.1053/j.gastro.2010.09.004.

12. Samani MA [et al.]. Medicinal plants with hepatoprotective activity in Iranian folk medicine. *Asian Pac J Trop Med*. 2015; 5(2): 146-157. DOI: [https://doi.org/10.1016/S2221-1691\(15\)30159-3](https://doi.org/10.1016/S2221-1691(15)30159-3)

13. Valero A [et al.]. Natural products: Perspectives in the pharmacological treatment in gastrointestinal anisakiasis. *Asian Pac J Trop Med*. 2015; 8(8): 612-617. DOI: 10.1016/j.apjtm.2015.07.017

14. Zhang A [et al.] Recent advances in natural products from plants for treatment of liver diseases. *Eur J Med Chem*. 2013; 63:570-577. DOI: <https://doi.org/10.1016/j.ejmech.2012.12.062>

A.A. Barilo, S.V. Smirnova, I.V. Borisova

FEATURES OF THE SPECTRUM OF SENSITIZATION DERMATORESPIRATORY MANIFESTATIONS OF ALLERGY IN CHILDREN OF KHAKASSIA

DOI 10.25789/YMJ.2020.70.29

УДК 616.248-053.2

The study examined the characteristics of the spectrum of sensitization to food and inhalant allergens in children of Khakassia with atopic dermatitis in combination with respiratory manifestations of allergies based on allergological history, objective examination data, and skin testing results (prick-test). It is defined, that risk factors for the development of dermatorespiratory syndrome in children with upper respiratory tract damage or multiple organ respiratory tract damage may include: long course of the atopic dermatitis, manifestation of atopic dermatitis in the 1st year of life, aggravated heredity, pruritus, seasonality of the disease, high concentration of total IgE in blood serum, the presence of sensitization to food and pollen allergens, multivalent sensitization to milk, egg, cereals. Our study showed that the children of Khakassia have features of the sensitization spectrum depending on the expansion of the "shock" organs of atopy from atopic dermatitis to dermatorespiratory syndrome.

Keywords: dermatorespiratory syndrome, atopic dermatitis, allergens, sensitization.

Introduction. Atopic dermatitis (AD) is a key factor in the start of the "atopic march", which is characterized by the staged development of sensitization and the transformation of pathology from skin manifestations to damage to the respiratory tract. The combined clinical manifestations of allergic skin and respiratory tract damage are referred to in the literature as dermatorespiratory syndrome (DRS) [1, 7]. DRS is characterized by the expansion of the spectrum of sensitization to causally significant allergens with the development of polyvalent allergies, often to food and inhalant allergens [2, 4]. Moreover, the spectrum of sensitization to

certain allergens has regional characteristics, which is associated with environmental and ethno-household characteristics of the region where patients live [3]. The steady increase in morbidity, the severe clinical course of pathology with the defeat of several "shock" organs and systems necessitates the study of clinical and immunological features of the systemic manifestations of allergies, with the aim of developing effective measures to prevent the progression of atopy.

Purpose of the research was to study the characteristics of the spectrum of sensitization to food and inhalant allergens in children of Khakassia with atopic dermatitis in combination with respiratory manifestations of allergies.

Materials and methods. A retrospective examination of children of Khakassia, patients with atopic dermatitis, who were under the supervision of an allergist-immunologist, was performed. We analyzed 63 case histories of 34 children aged 1.5 to 18 years. The following nosological groups were distinguished: group 1 — atopic dermatitis (n=20, average age - 5,0 ± 1,6 years), group 2 — atopic dermatitis in combination with allergic rhinitis (n=22, average age - 6,5 ± 1,1 years), group 3 - atopic dermatitis in combination with bronchial asthma (n=21, average age - 5,0 ± 0,9 years), in its pure form - in 28,6% (n=6), or in combination with allergic rhinitis - a single respiratory tract disease (one way, one disease) - in 71,4% (n=15).

All examined underwent determination of the concentration of total IgE in blood serum by enzyme-linked immunosorbent assay.

The study of the spectrum of sensitization to food and inhalant allergens was carried out on the basis of an allergological history, objective examination data, and skin test results (prick test) taking into

account the size of the blistering reaction and the magnitude of hyperemia. For statistical analysis, the Statistica 6.0 application package was used with the non-parametric Mann-Whitney test; calculation of generalizing coefficients: median (Me) and mean error (m). Data on the concentration of total IgE in blood serum are presented as medians, 25 and 75 quartiles [Me, Q 25 - Q 75]. Comparison of qualitative characteristics in groups was carried out by the method of variational analysis using the exact Fisher test. Differences were considered statistically significant at $p < 0.05$.

Results and discussion. In all groups of patients, children's (manifestations of the disease from 2 to 12 years old) and teenage (over 12 years old) forms of atopic dermatitis dominated. The highest incidence of childhood atopic dermatitis was noted in group 3 - in 85,7% (n=18), and adolescent in the second group - in 36,4% (n=8). Infant form of atopic dermatitis (from birth to 2 years) was observed only in children of the 1st group - in 10% (n=2) cases. Consequently, the presence of childhood and adolescent forms of AD is a risk factor for the development of systemic manifestations of allergies with damage to both the upper and lower respiratory tract, which is consistent with the literature [8].

The manifestation of AD in most patients occurred in the first year of life: in the 1st group of patients in 68,4% (n=13/19), in the 2nd group - in 90% (n=18/20), in the 3rd group - in 100% (n=20/20) cases, $p_{1,3}=0.006$. Moreover, the debut of AD up to 6 months of age in group 1 was noted in 42% (n=9/19), group 2 - in 90% (n=18/20), group 3 - in 85% (n=17/20) cases, $p_{1,2}=0.004$, $p_{1,3}=0.01$.

Analysis of anamnestic data on the duration of breastfeeding showed that in the 2 group of patients breastfed up to

Scientific Research Institute of Medical Problems of the North – a separate division of the Federal Research Center «Krasnoyarsk Science Center» of the Siberian Branch of the Russian Academy of Sciences, Krasnoyarsk: Corresponding author: **Anna A. BARILO** - candidate of medical sciences, senior researcher at the Laboratory of Clinical Pathophysiology of the Research Institute of Medical Problems of the North - a separate unit of the Federal Research Center of the Siberian Branch of the Russian Academy of Sciences; Address: Russian Federation, 660022, Krasnoyarsk, 660022, Partizan Zheleznyak Str, d.3g; tel.: 89135584020, e-mail: anntomsk@yandex.ru; **Svetlana V. SMIRNOVA** - MD, professor, head of the scientific direction of the Research Institute of Medical Problems of the North - a separate subdivision of the Federal Research Center of the Kola Science Center SB RAS; Address: Russian Federation, 660022, Krasnoyarsk, 660022, Partizan Zheleznyak Str, d.3g; tel.: +7 (391) 228-06-81, +7 (391) 228-06-83, e-mail: svetvita@mail.ru; **Irina V. BORISOVA** - candidate of medical sciences, doctor allergist-immunologist; Address: Russian Federation, 660022, Krasnoyarsk, 660022, 78-Volunteer Brigade Str-21; tel. +79835745520, e-mail: krasdoc-tor@yandex.ru.

1 month of age there were 28,5% (n=4) children, which is more compared with the indicators of other groups: 5,6% (n=1) in group 1 and 5,8% (n=1) in group 3. In addition, breastfeeding up to 1 year was less frequently observed in group 2 patients compared with groups 1 and 3: 14,2% (n=2) versus 27,8% (n=5) and 41,2% (n=7). Children who were breast-fed from birth in groups 1, 2, and 3 comprised 5,6% (n=1), 7,1% (n=1), and 5,8% (n=1), respectively.

The duration of the course of AD was statistically significantly longer in the groups of patients with dermatorespiratory manifestations (group 2 and 3) compared with the group of patients with AD with isolated skin lesions (group 1): 6,5±1,0 years and 5,0±1,0 years relative to 3,5±0,8 years, $p_{1,2}=0.003$, $p_{1,3}=0.1$, $p_{2,3}=0.06$. Burdened heredity was most often observed in patients of groups 2 and 3, mainly along the maternal side, in comparison with group 1: 82,3% (n=14/17) and 80% (n=12/15) relative to 52,6% (n=10/19). Complaints of skin itching: in group 1 in 63,1% (n=12/19), in the second group in 89,5% (n=17/19), in group 3 in 75% (n=15/20) cases, $p_{1,2}=0.05$. Therefore, the prolonged course of the AD contributes to the progression of the disease with the development of respiratory forms of atopy. There is evidence in the literature about the association of AD and the risk of developing respiratory allergies. Moreover, in 60% of children with severe course of AD, bronchial asthma develops [8].

The concentration of total IgE in serum was: in the 1st group - 48,5 IU / ml [27,5; 121,5], in the 2nd group - 53,0 IU/ml [41,0; 59,0], in the 3rd group - 189,0 IU/ml [37,0; 371,0], $p_{1,3}=0.01$, $p_{2,3}=0,2$. It should be emphasized that with the expansion of the shock territories of AD to DRS, the concentration of IgE in the blood serum increases, which is consistent with the literature [8].

Data on the characteristics of food allergies in children with dermatorespiratory syndrome are extremely few in the literature [1, 2]. When analyzing the spectrum of sensitization to food allergens, it was noted that in group 3, the sensitization to fish (cod, hake) was statistically significantly more often compared with groups 1 and 2: 75,0% (n=12/16) versus 22,2% (n=4/18) and 33,3% (n=7/21), respectively, $p_{1,3}=0.002$, $p_{2,3}=0.01$ (Table 1). It is noted that the presence of food allergies to fish in patients with AD over 14 years of age increases the risk of developing bronchial asthma [5], which is consistent with our data. Sensitization to cow's milk is more often defined in groups 1 and 2 in comparison with group 3: 70,0%

(n=14/20) and 77,3% (n=17/22) relative to 47,6% (n=10/21), respectively, $p_{2,3}=0.04$.

There were no statistically significant differences in sensitization to other food allergens of animal origin between the examined groups. However, it was noted that in the group of patients with AD with multiple organ damage to the respiratory tract (group 3), sensitization to chicken meat was more often defined in comparison with 1 and 2 groups: 57,1% (n=12/21) versus 30,3% (n=6/20) and 40,9% (n=9/22).

An analysis of the spectrum of sensitization to allergens of plant origin showed that in group 3, a sensitization to rice was statistically significantly more often compared with group 1: 52,4% (n=11) versus 15% (n=3), respectively, $p_{1,3}=0.01$. In group 3, the sensitization to beets and pears was statistically significantly more often compared with group 1: 55,6% (n=10/18) versus 15,4% (n=2/13), $p_{1,3}=0.02$ and 35,7% (n=5/14) relative to 0% (n=0/11), $p_{1,3}=0.03$, respectively.

There were no statistically significant differences in sensitization to other food-borne allergens of plant origin between the examined groups. However, it was

noted that sensitization to cereals was more often determined in groups of patients with DRS in comparison with AD with isolated skin lesions, however, the data were not statistically significant. Buckwheat sensitization was determined in all groups, but most often in patients with DRS: in group 3 - in 38,1% (n=8) and in group 2 - 31,8% (n=7) cases, while in 1 group in 25% (n=5).

Bivalent sensitization to the main food allergens was statistically significantly more often observed in group 1 - 55,0% (n=11/20), compared with groups 2 and 3 - 40,9% (n=9/22) and 20,0% (n=4/20), respectively, $p_{1,3}=0.02$. Polyvalent sensitization to the main food allergens in group 1 was noted in 30,0% (n=6/20) cases, in group 2 - 45,5% (n=10/22), group 3 - 45,0% (n=9/20).

According to the literature, the incidence of sensitization to inhaled allergens in patients with AD is up to 89% [7]. According to the allergological history, seasonal exacerbations of the underlying disease (DRS or AD) were statistically significantly more often detected in groups 2 and 3 compared with group 1: 45,5% (n=10) and 42,9% (n=9) versus 5% (n=1),

Table 1

Features of the spectrum of sensitization to food allergens in patients of the selected groups, n (%)

Allergen	Group			
	1	2	3	p
Animal origin				
Cow's milk	14 (70)/20	17 (77.3)/22	10 (47.6)/21	2.3=0.04
Beef meat	8 (40)/20	9 (40.9)/22	8 (38.1)/21	–
Egg yolk	9 (47.4)/19	10 (47.6)/21	9 (45)/20	–
Chicken Egg Protein	9 (47.4)/19	6 (27.3)/22	6 (31.6)/19	–
Whole Chicken Egg	13 (65)/20	12 (54.5)/22	12 (57.1)/21	–
Chicken's meat	6 (30)/20	9 (40.9)/22	12 (57.1)/21	–
Fish	4(22.2)/18	7(33.3)/21	12(75.0)/16	1.3=0.002 2.3=0.01
Plant origin				
Cereals	11 (55)/20	17 (77.3)/22	13 (61.9)/21	–
Wheat Flour Protein	9 (45)/20	9 (40.9)/22	9 (45)/20	–
Rye flour protein	3 (17.6)/17	5 (23.8)/21	4 (20)/20	–
Barley grits	5 (27.8)/18	11 (50)/22	8 (40)/20	–
Oat groats	3 (17.6)/17	10 (54.5)/22	8 (40)/20	–
Rice	3 (15)/19	6 (27.3)/22	11 (52.4)/20	1.3=0.01
Buckwheat	5 (25)/19	7 (31.8)/22	8 (38.1)/20	–
Citrus	5 (31.2)/16	8 (50.0)/16	8 (57.1)/14	–
Beet	2 (15.4)/13	9 (45)/20	10 (55.6)/18	1.3=0.02
Carrot	6 (42.9)/14	8 (38)/21	11 (61.1)/18	–
Cucumber	4 (30.8)/13	10 (52.6)/19	9 (50.0)/18	–
Tomato	5 (45.5)/11	10 (62.5)/16	6 (46.2)/13	–
Cabbage	4 (36.4)/11	6 (54.5)/11	8 (61.5)/13	–
Apple	2 (18.2)/11	5 (26.3)/19	4 (22.2)/18	–
Pear	0 (0)/11	3 (18.8)/16	5 (35.7)/14	1.3=0.03
Grape	2 (20)/10	9 (56.2)/16	6 (46.2)/13	–
Banana	4 (33.3)/12	4 (22.2)/18	7 (46.7)/15	–

Note: p-values are indicated only for $p < 0.05$.

Table 2

Features of the spectrum of sensitization to inhalant allergens in patients of the selected groups, n (%)

Allergen	Group			p
	1	2	3	
Pollen				
Meadow grass	10 (50)/20	17 (77.2)/22	16 (76.2)/21	–
Trees	11 (55)/20	12 (54.5)/22	15 (71.4)/21	–
Weed grass	10 (50)/20	15(68.2)/22	17 (80.1)/21	1.3=0.04
Household				
Dermatophagoides pteronyssinus	3(25)/12	10(58.8)/17	7(43.8)/16	–
Dermatophagoides farinae	2(18.2)/11	9(60)/15	6 (50.0)/12	1.2=0.03
House dust	9(64.3)/14	12(66.7)/18	13(65.0)/20	–

respectively, $p_{1,2} = 0.002$, $p_{1,3} = 0.004$.

The analysis of the spectrum of sensitization to inhalant allergens in the selected groups showed that sensitization to pollen allergens was detected in 51,6% in group 1 (n=31/60), in 66,7% in group 2 (n=44/66), in group 3 - in 76,2% (n=48/63), $p_{1,3} = 0.005$ (table 2).

Sensitization to weed pollen was statistically significantly more often defined in group 3 compared with group 1: 80.1% (n=17/21) versus 50% (n=10/20), respectively, $p_{1,3} = 0.04$, which may indicate the role of these allergens in the development of allergic rhinitis and bronchial asthma in patients with DRS. There were no statistically significant differences in sensitization to other pollen allergens between the examined groups. However, sensitization to pollen of meadow grasses was more often observed in the group of patients with atopic dermatitis in combination with allergic rhinitis (group 2), which also suggests that these allergens play a role in upper respiratory tract damage in DRS.

Polyvalent sensitization to pollen of a mixture of meadow, weed grass and trees is defined in group 3. The high frequency of sensitization to plant pollen in DRS is probably a risk factor for multiple organ damage to the respiratory tract, as a barrier to the penetration of pollen allergens. The lowest frequency of sensitization to pollen allergens was observed in patients with AD (group 1). However, taking into account the fact that the clinical manifestations of seasonal AD in this category of patients are noted in only 5% (n=1/20) of cases, the frequency of sensitization to pollen allergens in group 1 is quite high - 51,6% (n=31/60) Sensitization to pollen allergens of patients with AD can be associated with cross-sensitivity to food prod-

ucts of plant origin based on the binding of specific IgE to homologous structures of the allergen [8].

In the study of sensitization to household allergens, the highest frequency of sensitization to house dust was observed in group 2 in comparison with group 1: 62,0% (n=31/50) versus 37,8% (n=14/37), $p_{1,2} = 0.02$. Dermatophagoides farinae house dust mite sensitization was statistically significantly more often determined in the group of patients with DRS (group 2) compared with the group of patients with AD (group 1): 60% (n=9/15) and 18,2% (n=2/11), respectively, $p_{1,2} = 0.03$. Dermatophagoides pteronyssinus house dust mite sensitization was also more common in group 2 compared with other groups, but did not reach statistical significance. In the group of patients with AD compared with the groups of patients with DRS, sensitization to house dust mites Dermatophagoides farinae and Dermatophagoides pteronyssinus was relatively low, while sensitization to house dust was detected in 64,3% (n=9/14) of cases, which, according to the literature, can be associated with damage to the epidermal barrier and percutaneous sensitization to aeroallergens in patients with AD [1, 7, 8].

Conclusion. As a result of the studies, it was found that dermatorespiratory syndrome is more often noted in childhood and adolescent AD. The childhood form of AD is a risk factor for the development of DRS with multiple organ damage to the respiratory tract (allergic rhinitis and bronchial asthma), and adolescent form of atopic dermatitis with allergic rhinitis.

Risk factors for the development of DRS in children with upper respiratory tract infections or multiple organ respi-

ratory tract infections may include: prolonged course of AD, manifestation of AD in the 1st year of life, aggravated heredity, pruritus, seasonality of the disease, high concentration of total IgE in blood serum, presence sensitization to food and pollen allergens, multivalent sensitization to milk, egg, cereals.

Thus, our study allows us to determine the characteristics of sensitization with the indication of causally significant allergens, to find out their influence on the formation of the sensitization spectrum depending on the expansion of the "shock" organs of atopy from atopic dermatitis to dermatorespiratory syndrome in children of Khakassia.

References

1. Барило А.А., Борисова И.В., Смирнова С.В. Дерматореспираторный синдром как проявление пищевой аллергии у детей. *Российский аллергологический журнал*. 2019;16(1-2):32-34. [Barilo AA, Borisova IV, Smirnova SV. The dermatorespiratory syndrome as a manifestation of food allergy in children. *Rossiiskij allergologicheskij zhurnal*. 2019; 16 (1-2): 32-34. (In Russ..)]
2. Барило А.А., Борисова И.В., Смирнова С.В. Особенности спектра пищевой сенсibilизации при атопической бронхиальной астме у детей. *Российский иммунологический журнал*. 2019; 13 (22), 2: 147-149. [Barilo AA, Borisova IV, Smirnova SV. Features of the spectrum of food sensitization with atopic bronchial asthma in children. *Rossiiskij immunologicheskij zhurnal*. 2019; 13 (22), 2: 147-149. (In Russ..)]
3. Иванова О.Н., Гольдерова А.С. Поллиноз у детей Республики (Якутия). *Якутский медицинский журнал*. 2017;1 (57): 34-36. [Ivanova ON, Golderova AS. Pollinosis in children of the Republic Sakha (Yakutia). *Jakutskij medicinskij zhurnal*. 2017; 1 (57): 34-36. (In Russ..)]
4. Barni S, Liccioli G, Sarti L et al. Immunoglobulin E (IgE)-Mediated Food Allergy in Children: Epidemiology, Pathogenesis, Diagnosis, Prevention, and Management. *Medicina (Kaunas)*. 2020; 56 (3): E111. DOI: 10.3390/medicina56030111.
5. Čelakovská J, Josef B, Vaneckova J et al. Food Hypersensitivity Reactions to Seafish in Atopic Dermatitis Patients Older than 14 Year of Age - The Evaluation of Association with Other Allergic Diseases and Parameters. *Indian J Dermatol*. 2020; 65 (2): 97-104. DOI: 10.4103/ij.d.403_18.
6. Dey D, Mondal P, Laha A et al. Sensitization to Common Aeroallergens in the Atopic Population of West Bengal, India: An Investigation by Skin Prick Test. *Int Arch Allergy Immunol*. 2019;178 (1): 60-65. DOI: 10.1159/000492584.
7. Gray CL, Levin ME, Du Toit G. Respiratory comorbidity in South African children with atopic dermatitis. *S Afr Med J*. 2017; 107 (10): 904-909. DOI: 10.7196/SAMJ.2017.v107i10.12418.
8. Hill DA, Spergel JM. The atopic march: Critical evidence and clinical relevance. *Ann Allergy Asthma Immunol*. 2018; 120(2): 131-137. DOI: 10.1016/j.anai.2017.10.037.

CLINICAL CASE

R.D. Filippova, T.Yu. Pavlova, S.I. Danilova, M.V. Maslova

PREGNANCY AND CHILDBIRTH IN A PATIENT WITH SWYER SYNDROME (CASE REPORT)

DOI 10.25789/YMJ.2020.70.30

УДК 618.3-036.88

The article describes a clinical case of pregnancy and childbirth resulting from assisted reproductive technologies using donor oocytes in a patient with Swyer syndrome. Patient V., 35 years old, was admitted to the Perinatal Center of GAU RB No. 1-NCM in Yakutsk in February 2019 with a diagnosis: Pregnancy, 31-32 weeks. Cephalic presentation. IVF-induced pregnancy (donor egg). Feto-placental insufficiency, impaired uteroplacental blood flow of 1 A degree. Concomitant diseases: Swyer syndrome (impaired sexual differentiation), the patient's karyotype as of June 30, 2015 was XY (male). Rhesus negative blood affiliation without isosensitization; gestational diabetes mellitus, diffuse goiter 0-1 degree.

She was examined at the Novosibirsk Regional Clinical Diagnostic Center in Novosibirsk State Medical University (2015), and found to have karyotype 46 XY, passport gender does not match the karyological one, diagnosis: Swyer syndrome. Since 2016, the patient has been taking Femoston® 2/10, which has caused the menstrual cycle to begin. Menses 3 days, moderate, painless, cycle 28 days.

This 2nd pregnancy in 2019 occurred after the 4th IVF attempt (egg donation, cryotransfer of 2 embryos). In a planned manner, according to a combination of relative indications: gonadal dysgenesis (removal of rudimentary gonads in 2001), pregnancy after IVF using donor oocytes, primipara 35 years of age, 38 weeks pregnant, was delivered by cesarean section under conditions of spinal anesthesia. A girl was born weighing 2850 g and 49 cm long, with an Apgar score of 8 out of 8 points. Postpartum lactation was sufficient. Sutures from the anterior abdominal wall were removed on the 8th day, and the mother and her newborn were discharged home on the 12th day in satisfactory condition.

Thus, absolute infertility due to gonad dysgenesis can be successfully overcome with the help of donor oocytes as part of the assisted reproductive technology program.

Keywords: Swyer syndrome, pregnancy, assisted reproductive technologies, in vitro fertilization.

Advances in reproductive technologies have made it possible, with the help of donor programs, to overcome absolute infertility caused by the absence or functional unsuitability of gametes.

Of particular scientific and practical interest is the group of patients with gonadal dysgenesis, for whom the mandatory signs are a sharp anatomical and functional underdevelopment of the gonads, the female type of differentiation of the genital ducts and externalia. The gonads in this form of the disease are most often represented by biologically inert connective tissue rudiments. The presence of morphologically inert rudiments of gonads, regardless of the genotype of the embryo, determines the differentiation of the reproductive ducts according to the female (main) type [4].

Attempts at the genotypic classification

of this syndrome have not been successful due to the fact that a completely similar clinical presentation can be observed with different karyotypes, while the same karyotype can be observed in different clinical presentations [1]. Nevertheless, for practical convenience, it is customary to subdivide gonadal dysgenesis into two clinical forms: typical and "pure", which are characterized by the following general symptoms: primary amenorrhea, lack of female secondary sexual characteristics, infertility. However, the typical form of gonadal dysgenesis is also characterized by the presence of somatic abnormalities (body height below 145 cm, excess fat deposition on the anterior abdominal wall, short neck with pterygoid folds, skeleton abnormalities – sternum impression, narrow pelvis, syndactyly, etc., malformations of internal organs – narrow aortic isthmus, non-closed interventricular septum, Botallo's duct, etc.).

With the "pure form" of gonadal dysgenesis (Swyer syndrome also belongs to this group), somatic abnormalities are absent, the disease is manifested by primary amenorrhea, infertility, genitalia infantilism and the absence of female secondary sexual characteristics in patients. Patients have a correct physique, normal height, underdeveloped mammary glands, no signs of pubic hair. The external genitalia are developed according to the female type with hypoplasia. The vagina is capacious, the uterus is undersized. The tubes are thin, long, crimped. In the place of the ovaries, the rudiments of gonads are localized. Histologically, the gonads are a stroma consisting of

fibroblast cells whose nuclei do not contain sex chromatin. In the stroma, sterile seminiferous tubules are found, lined with an immature type of Sertoli epithelium, and clusters of typical Leydig cells. Hormonal examinations show a significantly increased level of gonadotropins in the blood and a low level of estradiol. In order to produce phenotypic-correcting effect in patients with gonad dysgenesis, prolonged hormone replacement therapy is used. It is strongly recommended to remove the rudiments in patients with the presence of the Y chromosome in the karyotype, since the prolonged intake of estrogens significantly increases the frequency of tumor development from the remnants of testicular tissue. Before the advent of in vitro fertilization, such patients were doomed to be childless.

The first report of a twin pregnancy in a patient with XY gonad dysgenesis as a result of embryo donation and its successful delivery appeared in 1989 [6]. The first experience in implementing the program "oocyte donation" in Russia was gained at the Moscow center for the treatment of infertility "EKO" [1]. However, this program used so-called "extra" oocytes obtained in the IVF program for the treatment of infertility in other women or the ova of the patient's relatives.

In 1983, Alan Trounson et al. from Australia reported a successful pregnancy in a woman with bilateral ovarian removal, as well as in a patient with primary ovarian failure using donor embryos [5, 8]. In 1984, P. Luitjen et al. for the first time published information about pregnancy resulting from IVF-OD in a woman with

PHILIPPOVA Rosa Dmitrievna - MD, Head of Department of Obstetrics and Gynecology, M.K. Ammosov North-Eastern Federal University, www.s-vfu.ru, Yakutsk, E-mail: rosa-filipp@mail.ru, mob. Tel: 8-914-105-52-83; **PAVLOVA Tatyana Yuryevna** - PhD, Director of the Perinatal Center of Republican Hospital No.1, National Center of Medicine, Yakutsk, E-mail: tatyanaupavl@mail.ru, mob. tel: 8-924-872-71-64; **DANILOVA Sargylana Ivanovna** - Deputy Director of the Perinatal Center of Republican Hospital No.1, National Center of Medicine, Yakutsk, E-mail: dsargylana66@mail.ru, mob. tel: 8-914-224-96-98; **MASLOVA Maria Vladimirovna** - Senior Lecturer, Department of Obstetrics and Gynecology, Medical Institute, M.K. Ammosov North-Eastern Federal University, Yakutsk, E-mail: marivlad1888@mail.ru mob. tel: 8-914-293-03-82.

primary ovarian failure [7]. There are absolute indications for the use of donor oocytes: premature ovarian failure, natural menopause, amenorrhea due to bilateral ovariectomy, radiation or chemotherapy, gonad dysgenesis [6].

Clinical case: patient V., 35 years old, was admitted to the Perinatal Center of GAU RB No. 1-NCM in Yakutsk in February 2019 with a diagnosis: Pregnancy, 31-32 weeks. Cephalic presentation. IVF-induced pregnancy (donor egg). Feto-placental insufficiency, impaired uteroplacental blood flow of 1 A degree. Concomitant diseases: Swyer syndrome (impaired sexual differentiation), the patient's karyotype as of June 30, 2015 was XY (male). Rhesus negative blood affiliation without isosensitization; gestational diabetes mellitus, diffuse goiter 0-1 degree.

Upon admission to the hospital, the patient agreed to the processing of personal data, as well as gave her informed consent to the publication of the medical data presented in the article (in anonymous form).

Anamnesis: due to primary amenorrhea and tumor formation in the small pelvis in 2001, at the age of 17 years, an elective surgery was performed, the gonads removed, the omentum resected. Histological conclusion: dysgerminoma. In 2015, she was examined at the Novosibirsk Regional Clinical Diagnostic Center, Novosibirsk State Medical University, and found to have karyotype 46 XY, passport gender does not match the karyological one, diagnosis: Swyer syndrome. Since 2016, the patient has been taking Femoston® 2/10, which has caused the menstrual cycle to begin. Menses 3 days, moderate, painless, cycle 28 days.

To address the possibility of pregnancy planning using assisted reproductive technologies (ART), she turned to the Mother and Child Center, Novosibirsk.

1st pregnancy in 2017 – IVF by a donor egg, non-developing pregnancy at 5-6 weeks, vacuum aspiration was carried out, without complications.

2nd pregnancy in 2019 – this pregnancy occurred after the 4th IVF attempt (egg donation, cryotransfer of 2 embryos). Last menstruation July 10, 2018, the first half of pregnancy proceeded with moderate toxicosis (vomiting 3-4 times a day, weight loss 8 kg.). Symptomatic and hormonal treatment: Proginova® up to 16 weeks, Utrogestan® 200 mg 3 times a day (to date). Combined screening of the 1st trimester passed, an increase in hCG. The second half of pregnancy went smoothly. Examined in the antenatal clinic of the Perinatal Center with a period

of 27-28 weeks of pregnancy. The conclusion of the medical consultation as of January 16, 2019 – there is a high risk of premature birth, it is recommended to continue monitoring, planned cardiocytography, hospitalization according to indications. Examined in the medical-genetic center: 26 weeks pregnant. Aggravated gynecological history (IVF-induced pregnancy, donor egg). Increased hCG in the blood. The patient's karyotype is 46 XY (male gender), on hormone therapy. The chromosomal pathology risk for the fetus is increased to 5%. Cardiotocography of the fetus is within normal limits. Prevention of Rhesus immunization with immunoglobulin Rhes (D) anti-Rhesus carried out. Objectively: condition satisfactory, height – 157 cm, weight – 64.5 kg. Proper physique, satisfactory nutrition, mammary glands Tanner stage 2, hair growth on the border type. The skin is clean, normal color. Peripheral lymph nodes not enlarged. Heart sounds clear, rhythmic. Vesicular breathing, no wheezing. Blood pressure – 110/70 mm Hg, pulse – 76 beats/min. Respiratory rate – 16 breaths per minute. The abdomen is soft, painless. The uterus is normotonic, painless. Longitudinal lie. Head above the entrance to the small pelvis. Regular fetal movement. The fetal heartbeats clear, rhythmic up to 140 beats/min. Urination painless, sufficient. No swelling. Discharge white, sparse. Taking Duphalac®, stool regular.

When performing ultrasound and biochemical screening in the first trimester, ultrasound screening in the second trimester, no irregularities in the development of the fetus were found. Dopplerometric indicators of uterine and fetal-placental blood flow were within the reference values up to 37/38 weeks of pregnancy. The examination was performed 1-2 times a week after 32–34 weeks of pregnancy. At the gestational age of 37/38 weeks, a II degree hemodynamic disorder was detected (increased vascular resistance in the uteroplacental blood flow).

In a planned manner, according to a combination of relative indications: gonadal dysgenesis (removal of rudimentary gonads in 2001), pregnancy after IVF using donor oocytes, primipara 35 years of age, 38 weeks pregnant, was delivered by cesarean section under conditions of spinal anesthesia. A girl was born weighing 2850 g and 49 cm long, with an Apgar score of 8 out of 8 points. Postpartum lactation was sufficient. Sutures from the anterior abdominal wall were removed on the 8th day, and the mother and her newborn were discharged home

on the 12th day in satisfactory condition.

Thus, absolute infertility due to gonad dysgenesis can be successfully overcome with the help of donor oocytes as part of the assisted reproductive technology program [1.2]. The absence or anatomical and functional underdevelopment of gonads causes a high risk of miscarriage and, accordingly, the need for long-term hormonal therapy during pregnancy in this group of patients.

The authors declare no apparent or potential conflicts of interest related to the publication of this article.

References

- Исакова Э.В., Аржанова О.Н., Шляхтенко Т.Н., Корсак В.С. Беременность и роды при дисгенезии гонад (случай из практики). *Проблемы репродукции*. 2000; 2: 29-31. [Isakova EV, Arzhanova ON, Shlyakhtenko TN, Korsak VS. Pregnancy and delivery at gonads dysgenesis (case from practice). *Problemy reprodukcii*. 2000; 2:29-31. (In Russ..)]
- Мишарина Е.В., Боровик Н.В., Ярмолинская М.И. [и др.] Беременность у пациентки с синдромом Свайера и сахарным диабетом 1-го типа, наступившая в результате применения ЭКО (описание клинического случая) *Журнал акушерства и женских болезней*. 2018; 5(67):85–90. doi: 10.17816/JOWD67585-90 [Misharina EV, Borovik NV, Yarmolinskaya MI [et al.]. Pregnancy in a patient with Swyer syndrome and type 1 diabetes mellitus, which occurred as a result of IVF application (description of a clinical case). *Zhurnal akusherstva i zhenskikh boleznej*. 2018; 5 (67): 85–90. doi: 10.17816/JOWD67585-90. (In Russ..)]
- Здановский В.М., Заева В.В., Аншина М.Б. Беременности и роды у женщин без яичников и с нефункционирующими яичниками (первый опыт применения программы овум donation в России) *Проблемы репродукции*. 1995; 1:83-86. [Zdanovskiy VM, Zaeva VV, Anshina MB. Pregnancy and childbirth in women without ovaries and with non-functioning ovaries (first experience of the ovum donation program application in Russia). *Problemy reprodukcii*. 1995; 1:83-86. (In Russ..)]
- Савицкий Г.А. Хирургическое лечение врожденных аномалий полового развития в гинекологической практике. Москва: Медицина; 1975. [Savitsky GA. Surgical treatment of congenital anomalies of sexual development in gynecological practice. Moscow: Medicine; 1975. (In Russ..)]
- Trounson A, Leeton J, Besanko M [et al.]. Pregnancy established in an infertile patient after transfer of a donated embryo fertilised in vitro. *Br Med J (Clin Res Ed)*. 1983; 286 (6368): 835-838. doi: 10.1136/bmj.286.6368.835.
- Sauer MV, Lobo RA, Paulson RJ. Successful twin pregnancy after embryo donation to a patient with XY gonadal dysgenesis. *Am J Obstet Gynecol*. 1989; 2:380-381.
- Lutjen P, Trounson A, Leeton J. [et al.] The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature*. 1984; 307(5947):174-175. doi: 10.1038/307174a0.
- Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. *Nature*. 1983; 305(5936):707-709. doi: 10.1038/305707a0.

O.N. Ivanova, T.E. Burtseva, N.N. Protopopova,
S.A. Kondratieva, M.P. Slobodchikova, D.M. Furman

A CLINICAL CASE OF WISKOTT-ALDRICH SYNDROME

DOI 10.25789/YMJ.2020.70.31

УДК616.8-008.6

Wiskott-Aldrich syndrome is a disease, characterized by combined insufficiency of both humoral and cellular immunity, it is inherited by X-chromosome recessive linkage and is expressed by the following triad of signs: recurring chronic microbial inflammations, hemorrhagic syndrome, and eczema [3]. The syndrome was first described by A. Wiskott in 1937, he described a case of three boys from the same family suffering from thrombocytopenia combined with severe eczema and secondary infections, while their four sisters did not show any of these symptoms. The prevalence of Wiskott-Aldrich syndrome is 4 : 1 000 000. It mostly affects boys. Molecular defect results in absence of WASP protein (Wiskott-Aldrich syndrome protein), coded by WASP gene, it is localized in the short arm of X-chromosome [1, 4]. The objective of the article is to describe clinical and laboratory characteristics of Wiskott-Aldrich syndrome in a 2-month-infant. We represent a clinical case of the Russian infant having triad of signs characteristic to Wiskott-Aldrich syndrome. It is the first case in the department of oncohaematology of the Pediatric center, Republican hospital №1, National health center for medical examination.

Keywords: immunodeficiency, inheritance, survey, immunology, genetics.

Wiskott-Aldrich syndrome is a disease, characterized by combined insufficiency of both humoral and cellular immunity, it is inherited by X-chromosome recessive linkage and is expressed by the following triad of signs: recurring chronic microbial inflammations, hemorrhagic syndrome, and eczema [3]. The syndrome was first described by A. Wiskott in 1937, he described a case of three boys from the same family suffering from thrombocytopenia combined with severe eczema and secondary infections, while their four sisters did not show any of these symptoms. The prevalence of Wiskott-Aldrich syndrome is 4 : 1 000 000. It mostly affects boys. Molecular defect results in absence of WASP protein (Wiskott-Aldrich syndrome protein), coded by WASP gene, it is localized in the short arm of X-chromosome [1, 4].

The **objective** is to describe the clinical and laboratory characteristics of Wiskott-Aldrich syndrome in a 2-month infant.

We describe a clinical case of Wiskott-Aldrich syndrome in a 2-month Russian infant experiencing a triad of signs characteristic to such inherited disease as Wiskott-Aldrich syndrome. The boy had been hospitalized to the department of oncohaematology from September to November of 2019.

On the 30th of November 2019 a two-month male infant was hospitalized to the department of oncohaematology of the Pediatric center, Republican hospital #1, National health center for medical examination. He was referred from the regional hospital with the complaints of periodical scarlet streak of blood in stool, conjunctival hemorrhage, decreased level of platelets in common blood count. The entrance diagnosis was vertically transmitted infection of the viral or bacterial origin, vertically transmitted secondary thrombocytopenia, unconfirmed immunodeficiency, and anal abscess.

The anamnesis showed that the child was born from the first pregnancy, the pregnancy ran smoothly. The mother gave a natural childbirth at the 39th week of pregnancy. At the moment of hospitalization the infant was breastfed. After the childbirth hemorrhagic discharge from the anus and subconjunctival hemorrhage of the left eye were noticed. The complete blood count showed decreased level of platelets.

On admission the infant was examined by a haematologist and a pediatrician. The condition of the infant was assessed as grave and poor. The skin surface was swarthy and moderately moist. The mucous membranes of the oral cavity were pink and moist. The pharynx was not hyperemic. The tonsils were not enlarged, no coating was noticed. Peripheral lymph nodes were not enlarged. The nasal breathing was not complicated. No cough and breathlessness were present. The

auscultation showed vesicular breathing with no rales. The heart sounds were rhythmic and loud. On palpation the abdomen was soft and painless. The stool was regular and solid. The liver was enlarged (1 cm below the costal margin). The spleen was not enlarged. No dysuria, the urine did not change. No meningeal and focal signs were noticed. The stool was with scarlet streak of blood.

The blood test for clotting time detection and complete blood count were administered. The blood test showed that the clotting time was within the normal rate: the Duke method of clotting time: 1 minute; blood coagulation time according to Sukharev: 3,20 min.

The complete blood count of the blood corpuscles revealed reticulocytosis and thrombocytopenia. The reticulocytes were 35.0. Thrombocytes were 36.0% (normally it is 100-420). Thrombocrit value was 0.04% (normally it is 0.15% - 0.4%). The results showed expressed anemia and activation of hemopoiesis.

The biochemical analysis of the blood test revealed high level of the total bilirubin and direct bilirubin.

The PCR test for infection did not reveal mycoplasma, ureaplasma and cytomegalovirus infections.

The immunoglobulin results were IgM – 0.01 gr/l; IgG – 6.9 gr/l, IgA – 0.00 gr/l; IgE total – 0.00 gr/l. Total absence of M immunoglobulin, A and E immunoglobulins, and low level of G immunoglobulin were reported. These results indicated a possible initial immunodeficiency case.

Immunogram shows CD+46%; CD4+43%; CD8+3%; CD19+31%; CD-HLA-DR+2%; CD 25+8%; CIC (circulating immune complexes) 14%. The immunogram revealed low level of T-suppressors, and B-cells.

Fecal occult blood test was positive.
No HIV for 11.01.2019.

IVANOVA Olga Nikolaevna – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, olgadoctor@list.ru; **BURTSEVA Tatiana Egorovna** – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, a head of the laboratory of the Yakut science centre of complex medical problems, bourtsevat@yandex.ru; **PROTOPOPOVA Nadezhda Nikoaeвна** – a hematologist of the highest medical category, department of oncohematology, Republican hospital №1, National health center; **SLOBODCHIKOVA Maya Pavlovna** – a senior lecturer of the department of foreign languages with the courses of Russian and Latin languages, St. Petersburg state pediatric medical university, limelight@mail.ru. Furman Daria Mikhailovna – 6th year student of MI NEFU.

The child underwent several instrumental procedures.

The colour Doppler ultrasound imaging revealed oval window (0.26cm), enlarged right atrium cavity (1.83cm), right ventricle (1.0cm), tricuspid valve regurgitation, ectopic attachment of mitral valve chords, and additional left ventricular trabeculae.

The colonoscopy revealed total hemorrhagic colitis. Distally the dorsal part was not accessible because of the mucous membranes hemorrhage when they came into contact with the apparatus. The walls of large intestines were elastic and air could stretch the walls. The lumen of sigmoid, ascending, transverse and descending colons seemed normal, the folds were of the normal height, there was greenish substance in the curves of the colon. The mucous membrane of the transverse and descending colons was unevenly hyperemic with the signs of hemorrhagic erosions. A great number of erosions with size from 0.25 to 0.5 cm was scattered, the vesicular pattern was clear. Mucous membrane of the sigmoid colon was hyperemic with hemorrhagic erosions, the vesicular pattern was unclear. The rectal lumen was normal, the mucosa was unclear with scattered hemorrhagic erosions (0.2cm). Perianal examination revealed a scar of paraproctitis.

Esophagogastroscope revealed no abnormalities.

According to the results of the investigation further consultation with gastroenterologist and allergist-immunologist was recommended.

The consultations of the specialists revealed a case of early childhood death in the maternal anamnesis. The mother told that her own brother had died at early age. For the following 20 years only girls were born in this family. The immunogram determined absence of M immunoglobulin, A and E immunoglobulins, low level of G immunoglobulin, low level of T-suppressors, and B-cells. There was marked decrease of platelet count in a peripheral blood and platelets count by Fonio method, thus revealing protein molecule destruction. These molecules participate in the process of platelet formation. The results showed the decrease of the quantity of platelets and quality of the cells, which is characteristic to the initial immunodeficiency, i.e. Wiskott-Aldrich syndrome.

The clinical diagnosis, based on the results of the investigations, examination and family history taking, was: initial immunodeficiency, Wiskott-Aldrich syndrome, infantile atopic dermatitis in the restricted form.

Gastroenteric visual and instrumental examinations revealed hemorrhagic intestinal erosion. The consultation of the specialists could help specify the diagnosis and it was decided to refer the biological material of the whole blood with further molecular genetic test (WaSP) to the National medical research center of childhood hematology, oncology and immunology. The PCR-diagnosis of the genetic locus was positive [1].

The final diagnosis was Wiskott-Aldrich syndrome, initial immunodeficiency, immune thrombocytopenia, infantile atopic dermatitis, in the restricted form with mild severity.

Concomitant diseases were non-infectious gastroenteritis, unconfirmed colitis, erosive hemorrhagic colitis, postsurgical condition after operated abscess in perianal area, normochromal anemia of mixed genesis.

During the period of hospitalization at the department of oncohematology of the Pediatric center of the National health center the patient was administered: the ward nursing by the mother, special diet #15, breastfeeding, pankreatin ¼ tablets 3 times a day, fenistil 2 drops 2 times a day lasting for 5 days, and elidel cream externally.

The patient was referred to the immunological department of the National medical research center of childhood hematology, oncology and immunology for further examination, a substitutive therapy was administered [2, 4, 5]. At the moment the patient is treated with immunovenin 0.1-0.4 gr/kg each month.

The following scheme of inpatient examination was recommended:

1. Regular check-up at the following specialists: a pediatrician, an immunologist, and a hematologist.

2. Laboratory investigations: complete blood count (with obligatory leucocyte count) once every 2-3 months. Biochemical blood test with hepatic enzymes activity detection, protein C-reactivity – every 6 months, urine analysis every 6 months, and in cases of intercurrent diseases.

3. Instrumental investigations: electrocardiogram – once a year, ultrasonic

imaging of the abdominal cavity – once a year, X-Ray examination of the chest – once a year.

4. Consultations: immunologist every 3 months during the first year of examination, then every 6 months; surgeon – once a year, oculist – every 6 months; dentist – once a year, and otolaryngologist – once a year.

5. Vaccinations are contraindicated.

Conclusion. We have described a clinical case of Wiskott-Aldrich syndrome in a 2-month infant. Microbial inflammation in the form of paraproctitis, hemorrhagic syndrome in the form of erosive hemorrhagic colitis and eczema, which was later diagnosed as atopic dermatitis, was revealed clinically [3]. Thus we have described a classic triad of Wiskott-Aldrich syndrome. A detailed family history taking became a key moment in the diagnosis of the congenital disease. The anamnesis revealed high mortality rate of the male infants at early childhood, which possibly could be connected with microbial inflammation associated with initial immune deficiency. The diagnosis of the congenital disease is undoubtedly due to molecular-genetic investigations [1]. A due time diagnosis, substitutive therapy and competent clinical examination can predict and prolong the life for Wiskott-Aldrich syndrome patients [2, 4, 5].

References

1. Кузьменко Н.Б., Варламова Т.В., Мерсианова И.В. Молекулярно-генетическая диагностика первичных иммунодефицитных состояний. *Вопросы гематологии онкологии и иммунопатологии в педиатрии*. 2016; 15(1):10-16. [Kuzmenko N. B., Varlamova T.V., Mersiyanova I.V. Molecular genetic diagnostics of primary immunodeficiency states. *Voprosy gematologii i immunologii d pediatrii*. 2016; 15(1):10-16. (In Russ.)]
2. Buchbinder D., Nugent D.J., Fillipovich A.N. Wiskott-Aldrich syndrome: diagnosis, current management, and emerging treatments. *Applied clinical genetics*. 2014; 7:55-66.
3. Chen N., Zhang Z.Y., Liu D.W. The clinical features of autoimmunity in 53 patients with Wiskott-Aldrich syndrome in China: a single-center study. *European journal of pediatrics*. 2015; 174(10):1311-1318.
4. Hacein-Bey A.S., Gaspar H.B., Blondeau J. et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. *JAMA*. 2015; 313(15): 1550-1563.
5. Worth A.J., Thrasher A.J. Current and emerging treatment options for Wiskott-Aldrich syndrome. *Expert review of clinical immunology*. 2015; 11(9): 1015-1032.

K.E. Popova, T.E. Popova

PSORIATIC ARTHRITIS: CLINICAL OBSERVATION

DOI 10.25789/YMJ.2020.70.32

УДК 616.72-002.77.-08-02

Psoriatic arthritis is a chronic inflammatory disease of the joints, spine, and spondylitis arthritis that is commonly seen in patients with psoriasis. The prevalence of this severe pathology in patients with psoriasis, according to different authors, ranges from 13.5 to 47% (an average of 36%), and the prevalence of psoriasis in the population is 0.06 - 1.4%. Important factors in the development of psoriatic arthritis include a genetic predisposition, immune disorders associated with collagen disorganization, type II, as well as the presence of foci of bacterial, chlamydial and other types of infections. Clinically, psoriatic arthritis has similarities with rheumatoid arthritis, which requires careful differential diagnosis. In this regard, specialists will be interested in the clinical observation of a family case of psoriasis with the addition of a complication such as psoriatic arthritis.

Keywords: psoriasis, psoriatic arthritis, dermatosis.

Introduction. Psoriatic disease is a systemic inflammatory disease that affects the skin, joints and joints [9]. Psoriatic diseases of the skin, enthesion and joints have a common pathophysiology based on activation of the innate immune system, as well as on the generation of pathogenic T cells that cause inflammation. Immunopathology in psoriasis and psoriatic arthritis (PA, PsA) is controlled by a combination of genetic factors and external factors, such as mechanical stress, which accelerate inflammation [2]. Inflammation in the context of psoriatic disease is considered systemic, and not least because both conditions are associated with increased cardiovascular risk, osteoporosis, and metabolic disorders [9]. The prevalence of PA in patients with psoriasis, according to different authors, ranges from 13.5 to 47% (an average of 36%), and the prevalence of psoriasis in the population is 0.06 - 1.4%. The causes of joint damage have not yet been elucidated. Important risk factors for PA include a genetic predisposition, immune disorders associated with collagen disorder, type II, as well as the presence of foci of bacterial, chlamydial and other types of infections [1-4]. In 2006, diagnostic criteria for CASPAR PA were proposed, which are presented in Table [6].

Psoriatic arthritis (PsA) is an immuno-mediated, clinically heterogeneous disease characterized by arthritis, enthesitis, dactylitis, spondylitis and psoriasis of the skin and nails. Persistent joint inflammation in patients with PA can lead to structural damage, which can lead to a

decrease in physical function and quality of life. Structural damage can occur quickly, and permanent damage to the joint can occur if patients do not receive timely and appropriate treatment [5].

Difficulties in the diagnosis of PA are associated with similarities to rheumatoid arthritis, gout due to the absence of specific clinical markers [7]. The diagnosis of rheumatoid arthritis (RA) is mainly based on the clinical symptoms and serological positivity of rheumatoid factor (RF) and / or antibodies to anti-citrulline peptides (anti-CCPs), while only clinical and imaging features help diagnose the disease [7].

We present a clinical observation of a family case of psoriasis complicated by psoriatic arthritis.

Purpose of the study is a demonstration of a family case of psoriatic arthritis and differential diagnosis with rheumatoid arthritis, gout.

Materials and research methods. The data of the clinical observation of a patient with a diagnosis of Psoriatic arthritis, polyarthritic variant, severe course, activity of the II stage, functional insufficiency of the II – III stage are presented. Background: Common vulgar psoriasis, exudative, off-season, stationary stage.

From the anamnesis, it is known that the patient has been ill for about 11 years, when for the first time pinkish-red papules appeared on the scalp and extensor surface of the elbow and knee joints, covered with loose silver-white scales clearly distinguished from healthy skin. Later, pain in all joints of the 3rd and 4th toes of both feet joined. Within two years, the pain spread to the knee joints. The patient was diagnosed with Rheumatoid arthritis. Psoriasis. The patient refused the proposed therapy.

In the last two years, severe exacerbations with increased arthralgic syndrome involving new joints and subfebrile temperature about two times a year. A "radish-like" deformation of the toes and a "sausage-like" deformation of the fingers

appeared. Patient is constantly taking Nise 2 tablets 2 times a day.

Development was according to age. Contacts with infectious patients denied. Blood transfusion denied. Hereditary history: a mother aged 52 was diagnosed with Psoriasis, psoriatic arthritis.

The patient suffers from arterial hypertension for 6 years: an increase in blood pressure up to 150/90 mm Hg, she constantly takes antihypertensive therapy with the drug Prestanz once a day in the morning.

An allergic history is not burdened.

Objectively: Height 175 cm, body weight 95 kg. BMI of 31.02 kg / m², which corresponds to obesity of 1 degree. The presence of psoriatic plaques on the scalp, on the extensor surfaces of the right shoulder, elbow joints, as well as both knee joints. There is a psoriatic triad: stearin stain, terminal film and the phenomenon of "blood dew" Polotebnov. "Radish-like" deformation of the toes and "sausage-like" deformity, edema and hyperemia of the 2nd, 3rd and 4th fingers of the right hand and 2nd and 3rd fingers of the left hand. All joints of the feet and hands are enlarged. Pathological mobility in the distal interphalangeal joints of the fingers.

General blood test: Red blood cells - $4.5 \cdot 10^{12} / l$; hemoglobin - 145 g / l; white blood cells - $6.5 \cdot 10^9 / l$ (segmented - 68%, lymphocytes - 31%, monocytes - 1%); platelets - $353 \cdot 10^9 / l$; ESR - 42 mm / h.

Urinalysis - without features.

Rheumatic tests: CRP - 2 mg/L, RF - OTR, Antistreptolysin-0 - 152 U ml, uric acid - 0.3 mmol/L, A-CCP - 20 U/L.

Bacterial inoculation of synovial fluid - without features.

ECG: Sinus rhythm. Left ventricular hypertrophy. EOS is rejected to the left. Heart rate 68 in 1 minute.

X-ray of the hands: The articular fissures of the proximal interphalangeal joints of the 2nd, 3rd, 4th fingers are narrowed. The heads of the 2nd, 3rd and 4th

POPOVA Kristina Evgenyevna – physician-therapist, St. Petersburg State Budgetary Health Institution "City Polyclinic No. 100 of the Nevsky District of St. Petersburg"; **POPOVA Tatiana Egorovna** – MD, Deputy Director for Science, Federal State Budgetary Scientific Institution "Yakut Science Centre of Complex Medical Problems (YSC CMP)", Prof. M.K. Ammosov MI NEFU, tata2504@yandex.ru, Yakutsk, Russia.

Diagnostic criteria for psoriatic arthritis, CASPAR

Psoriatic joint inflammation can be diagnosed in a patient with peripheral arthritis, spondylitis and sacroiliitis or enthesitis and ≥ 3 points from the following:	
1. Symptoms of psoriasis (psoriatic skin changes detected by a rheumatologist or dermatologist): - psoriasis in a personal or family history (in a relative of I or II degree) - psoriatic changes are present at the moment	1 point 2 point
2. Typical psoriatic changes in the nails (separation of the nail, depressions in the nail plate and hyperkeratosis), established during an objective examination	1 point
3. A negative result of determining the rheumatoid factor by any method (with the exception of the latex test), it is best ELISA or nephelometric method	1 point
4. Dactylitis , defined as swelling of the entire finger (the so-called sausage finger) at the moment or in the history recorded by a rheumatologist	1 point
5. Radiological signs of periarticular bone proliferation in the form of fuzzy limited ossification at the edges of the joint (with the exception of osteophytes) on radiographs of the wrist or foot	1 point

metacarpal bones are corroded, reduced in size, with the presence of marginal patterns and cystic enlightenments. There are no heads of the 1st metacarpal bone on the right and heads of the proximal phalanx of five fingers (osteolysis).

X-ray of the feet: Erosion in combination with proliferation of bone tissue in the interphalangeal joint of the big toe, the first tarsal-metatarsal joint and dislocation in the II-V metatarsophalangeal joints. In several fingers erosion of the tuberosity of the distal phalanges.

X-ray of the knee joints in 2 projections: uneven narrowing of the joint gap, marginal bone growths, subchondral osteosclerosis are determined.

Dermatologist consultation: Common vulgar psoriasis, exudative. Off-season option. Stationary stage.

Differential diagnosis with rheumatoid arthritis, gout and other systemic lesions was carried out. According to the CASPAR scale, the patient has 6 points: psoriasis in a personal family history (for mother) - 1 point, psoriatic changes are present at the moment - 2 points, a negative result for determining rheumatoid factor - 1 point, dactylitis - 1 point, radiological signs of periarticular bone proliferation in the form of a fuzzily limited ossification at the edges of the joint - 1 point [9]. Thus, on the basis of

complaints, medical history, clinical and paraclinical data, the diagnosis was established: Psoriatic arthritis, polyarthritic variant, severe course, activity of the II stage, functional insufficiency of the II – III stage. Background: Common vulgar psoriasis, exudative. Off-season option. Stationary stage. Concomitant: Hypertension 2, AH-2, risk -3. Obesity I Art.

The therapy was carried out with non-steroidal anti-inflammatory drugs (NSAIDs), cytostatic therapy with methotrexate with an initial dose of 10 mg followed by an increase to 20 mg, hepatoprotectors, sodium thiosulfate to relieve exacerbation of psoriatic elements, salicylic acid externally. During treatment, psoriatic elements on the skin decreased, infiltration around the rashes became less noticeable, Voronov's pseudo-atrophic rims formed, itching completely disappeared, inflammation of the affected joints became less, and arthralgic syndrome regressed.

Conclusions. This case makes doctors wary of psoriatic arthritis, the difficulty of differential diagnosis with such specific diseases as rheumatoid arthritis, gout. The active identification of patients with psoriatic arthritis requires, first of all, the correct interpretation of anamnestic, clinical, laboratory, radiological data. The presented clinical observation indicates

a significant contribution of the genetic predisposition to the development of the disease. The presented clinical observation indicates a significant contribution of the genetic predisposition to the development of the disease. An important point is that patients with psoriatic arthritis have an increased risk of cardiovascular disorders [8]. A correctly diagnosed diagnosis is the appointment of the only correct treatment and the prevention of complications that can lead to disability of the patient.

References

1. Butov Yu.S., Potekaev N.N. Dermatovenereology: a guide for doctors. 2017; 206-220.
2. Vasilieva L.V., Evstratova E.F., Nikitin A.V. A comparative analysis of the effectiveness of basic methotrexate therapy in combination with chromolaser therapy and methotrexate monotherapy in patients with psoriatic arthritis. 2016.- S.19-24.
3. Bakulev A. L., Fitileva T. V., Novoderezhkina E. A., Gilloty I., Tian H., Hove T., Petri G. Psoriasis: clinical and epidemiological features and treatment issues. *Bulletin of Dermatology and Venereology*. 2018; 94 (3): 67-76.
4. Korotaeva TV, Korsakova YL, Loginova EH and others. Psoriatic arthritis. Clinical recommendations for diagnosis and treatment. *Modern rheumatology*. 2018; 12 (2): 22–35.
5. Van der Heijde D, Gladman DD, Kavanaugh A, Mease PJ. Assessing structural damage progression in psoriatic arthritis and its role as an outcome in research. *Arthritis Res Ther*. 2020 Feb 3;22(1):18. doi: 10.1186/s13075-020-2103-8.
6. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006; 54(8):2665–2673.
7. Margarida Souto-Carneiro, Lilla Tóth, Rouven Behnisch, Konstantin Urbach, Karel D Klika, Rui A Carvalho, Hanns-Martin Lorenz. Differences in the serum metabolome and lipidome identify potential biomarkers for seronegative rheumatoid arthritis versus psoriatic arthritis. *Ann Rheum Dis*. 2020; 0:1–8. Doi: 10.1136/annrheumdis-2019-216374.
8. Ma J, Liang N, Chen J, Bai Y. The association between biologic agents and the risk of cardiovascular events in patients with psoriasis and psoriatic arthritis: A protocol for a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019 Nov;98(47):e18063. doi: 10.1097/MD.00000000000018063.
9. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med*. 2017; 376(10):2095–2096. doi: 10.1056/NEJMra1505557