

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

3(63) `2018

ЯКУТСКИЙ МЕДИЦИНСКИЙ ЖУРНАЛ



# 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)  
Mironova G.E., Doctor of Biology,  
Professor (Yakutsk)  
Mikhailova E.I., Doctor of Pedagogics,  
Professor (Yakutsk)  
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)  
Fedorova S.A., Doctor of Biology (Yakutsk)  
Husebek Anne, MD, Professor (Norway)  
Khusnutdinova E.K., Doctor of Biology,  
Professor (Ufa)

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

Computer design  
Nikolasjkina A.A.  
Chekurova S.M. (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's Column

#### Editorial

- 5 Egorova A.G., Klimova T.M., Romanova A.N.  
Territorial and gender differences  
in cardiovascular mortality in the RS (Ya)
- 9 Evseeva S.A., Savvina M.S., Burtseva T.E., Chasnyk V.G.  
Dynamics of the morbidity of children's population  
of the RS (Ya) for 1995-2015

#### Original researches

- 11 Gotovtsev N.N., Barashkov N.A., Borisova T.V., Pak M.V.,  
Alekseeva M.P., Innokentiev N.N., Loskutova K.S., Pshennikova V.G.,  
Rafailov A.M., Lekhanova S.N., Fedorova S.A.  
Analysis of the clinical outcomes of gastroduodenal diseases  
in Yakutia depending on the presence of the cytotoxin-associated  
gene A (*cagA*) in the *Helicobacter pylori*
- 15 Solovyev A.V., Barashkov N.A., Savvinova K.E., Gotovtsev N.N.,  
Teryutin F.M., Pshennikova V.G., Romanov G.P., Rafailov A.M.,  
Sazonov N.N., Dzhemileva L.U., Posukh O.L.,  
Khusnutdinova E. K., Fedorova S.A.  
The analysis of the resistance of heterozygous carriers  
of the c.-23+1G>A mutation in *GJB2* gene to diarrhea
- 18 Pavlova N.I., Solovyeva N.A., Dyakonova A.T., Filippova N.P.,  
Dodokhov V.V., Varlamova M.A., Kurtanov Kh.A.  
A study of the polymorphism RS9939609 of the FTO gene and  
RS738409 of the PNPLA3 gene as risk factors for the development  
of NAFLD in the Yakut population of type 2 diabetes mellitus
- 22 Tishkovets S.V., Razuvaeva Ya.G., Mondodoev A.G., Toropova A.A.  
Anti-inflammatory activity of the complex  
herbal remedy
- 25 Nikolaev V.M., Efremova S.D., Okhlopova E.D.,  
Alekseeva Z.N., Vinokurova F.V., Sofronova S.I.,  
Fedorova S.A., Chirikova N.K., Koryakina L.P.  
Influence of low temperatures on lipid peroxidation  
in tissue of experimental animals depending  
on exposure time

#### Methods of diagnosis and treatment

- 29 Kirillina M.P., Ivanova A.K., Popova I.D., Garmeva D.K.  
Analysis of frequency of occurrence of background  
and precancerous diseases of a cervix by results  
of a preventive and diagnostic cytological testing
- 32 Zakharova N.M., Gulyaeva N.A., Ammosova A.M., Markova S.V.,  
Khandy M.V., Artamonova S.Yu., Stepanova L.A., Egorova V.B.  
Analysis of oral microflora in children
- 35 Lytkina A.A., Chibyeva L.G.  
NSAID-gastropathy in patients with cardiac disease
- 37 Efremova S.D., Golderova A.S., Krivoshepkina Z.N.,  
Okhlopova E.D., Nikolaev V.M., Tsypanina E.V.,  
Ivanov P.M., Sazonov N.N.  
The water hardness and its relationships  
with the level of tumor markers among the inhabitants of Yakutia
- 40 Munchalova Ya.A., Egorova V.B., Alekseeva S.N.,  
Dmitrieva T.G., Ivanova O.N., Korkina A.P.  
Etiological, clinical features of secondary  
pyelonephritis in children



#### Healthy lifestyle. Prevention

- 43 Sidorova O.G., Kononova S.K., Barashkov N.N., Platonov F.A.,  
Fedorova S.A., Khusnutdinova E.K., Izhevskaya V.L.  
The analysis of social readiness of pregnant women from families  
burdened with hereditary spinocerebellar ataxia type 1 to undergo  
prenatal DNA test
- 45 Kardashevskaya N.E., Sosina T.A., Douglas N.I.,  
Burtseva T.E., Evseeva S.A., Struchkov S.T.  
The problem of skills forming for the protection  
of reproductive health of girls in the RS (Ya)
- 47 Konstantinova L.I., Mironova G.E., Krivoschapkina Z.N.,  
Efremova A.V., Okhlopko E.D., Olesova L.D.,  
Semenova E.I., Yakovleva A.I., Grigorieva A.A.  
Biochemical parameters of blood of sportsmen  
of Yakutia in different seasons of the year

#### Organization of Health, Medical Science and Education

- 50 Sleptsova S.S., Gogolev N.M., Petrova P.G., Borisova N.V.,  
Palshin G.A., Ammosov V.G., Burtseva T.E.  
The scientific activity of Medical Institute:  
prospection

#### Hygiene, Sanitation, Epidemiology and Medical Ecology

- 52 Krivoschapkin V.G., Timofeev L.F.  
Environmental health monitoring in the zone of activity  
of the mining industry in the Republic Sakha (Yakutia)
- 53 Egorova V.B., Fedorova M.A., Munkhalova Ya.A.,  
Dmitrieva T.G., Ivanova O.N., Alekseeva S.N.  
Clinico-laboratory features of meningitis in children
- 56 Borisova N.V., Koltovskaya G.A., Antipina U.D.  
Distribution of diselementosis and elemental pathology profile  
in women from different regions of the RS (Ya)
- 60 Dmitrieva T.G., Ostrelina A.O., Egorova V.B.,  
Munkhalova Ya.A., Ivanova O.N., Alekseeva S.N.  
Chronic hepatitis B in children and adolescents  
of representatives of the Mongoloid race
- 63 Argunova E.F., Kondratieva S.A., Kharabaeva E.M.,  
Yadreeva O.V., Nikolaeva S.A., Protopopova N.N.,  
Alekseeva S.N., Evseeva S.A., Burtseva T. E., Balanova V.S.  
Epidemiology of acute leukemia in children of the RS (Ya)

#### Actual topic

- 66 Burtseva T.E., Afanasyeva L.N., Argunova E.F.,  
Nikolaeva L.A., Kondratieva S.A., Kharabaeva L.M.,  
Nikolaeva S.A., Evseeva S.A., Chasnyk V.G.,  
Ivanov P.M., Fedorov F.F., Burnasheva K.I.  
The dynamics of the incidence rate of children and adolescents  
with oncological diseases in the RS (Y)
- 69 Mestnikova A.Z., Gogolev I.I., Diab Kh. M.,  
Machalov A.S., Fedotova E.E., Vasilyeva L.M.  
The results of cochlear implantation  
in the RS (Ya)
- 72 Suvirina M.B., Ushnitsky I.D., Yurkevich A.V.,  
Kobets A.R., Ivanova A.A., Ivanov A.V.  
Frequency and structure of pathological processes  
of periodontal tissues in the population  
of the Far Eastern region



**Arctic medicine**

- 75 **Lebedeva U.M.**  
Nutrition and iron deficiency states among women and children of Republic Sakha (Yakutia)
- 79 **Sofronova S.I., Romanova A.N.**  
Assessment of the total cardiovascular risk among indigenous population of Yakutia Arctic zone
- 81 **Sunkhalyrova T.K., Dodokhov V.V., Pavlova N.I., Kurtanov Kh.A.**  
Grave's disease. Modern representations and distribution in the territory of the Republic of Sakha (Yakutia)
- 84 **Komzin K.V., Petrova P.G., Strekalovskaya A.A., Samsonov S.N., Parshina S.S., Andreeva A.A.**  
Single nucleotide polymorphisms of *ADD1α*, *AGT*, *AGTR1* and *AGTR2* genes in different ethnic groups of Yakutia Arctic zone residents, suffering from arterial hypertension

**Nutrition in the North**

- 89 **Lebedeva U.M.**  
Epidemiology of nutrition and health of children and adolescents of the Republic of Sakha (Yakutia) based on the results of monitoring studies

**Scientific reviews and lectures**

- 92 **Solovyova N.A., Pavlova N.I., Kurtanov Kh.A., Varlamova M.A.**  
Cytokine mechanisms of formation of bronchial asthma and obesity
- 95 **Yakovleva A.E., Maksimova N.R.**  
Molecular-genetic causes of multiple exostosis chondrodysplasia

**Clinical case**

- 100 **Alekseeva S.N., Sukhomyasova A.L., Sofronova G.I., Androsova Z.P., Kondratyeva S.A., Gurinova E.E., Pavlova P.V.**  
Clinical case of propionic acidemia

**Experience exchange**

- 103 **Yavorsky A.A.**  
Medical and statistical aspects of studying the prevalence of abortions in the RS (Ya)
- 106 **Kutsyi M.B., Karasev M.S., Vladimirova N.Yu., Gorokhovskiy V.S., Stadnikova I.A., Grishina N.V., Serebrennikov A.G.**  
The experience of integration of the European guidelines on management of major bleeding during operative delivery among women with placenta percreta
- 108 **Ivanova O.N., Argunova E.F., Dmitrieva T.G., Munkhalova Ya.A., Egorova V.B., Alekseeva S.N.**  
The study of immunity in children with multiple papillomas
- 110 **Sazonova E.N., Yakovenko D.V., Lebedko O.A., Marochko A.Yu., Zharskiy S.L., Dobrykh VA, Rzyankina MF, Chepel' T.V.**  
Biosynthetic processes in cardiomyocytes of albino rats after administration of dihydroquercetin



## EDITOR'S COLUMN



*Dear colleagues!*

The editorial staff of the Yakut Medical Journal is glad to welcome you to the pages of the next issue of the publication.

Every year the number of clinical studies in the field of medicine is increasing, the doctors of different specialties enrich their knowledge

base, enabling to improve the quality of treatment and the prognosis of patients with various pathologies. Everyone who constantly works with patients has to realize personal responsibility for his professional competence. The purpose of our journal is to inform doctors about the current achievements of medical science and practice, having stated it in the most interesting and accessible form of presentation.

It's good to be aware that the geography of the authors of the Yakut Medical Journal expands with each issue. In the new issue of the journal, the authors from different regions of Moscow, St. Petersburg, Ufa, Saratov, Ulan-Ude, Novosibirsk, Khabarovsk, Syktyvkar and Yakutsk present their articles of various clinical focuses. In particular, comparative data of mortality from diseases of the circulatory system are presented depending on the territorial and gender characteristics of the population

of the Republic Sakha (Yakutia), clinical manifestations of various pathologies in children and adolescents, women's health, genetic aspects of gastroduodenal diseases, diabetes mellitus type 2 and etc. are covered. The total cardiovascular risk in the indigenous population of the Arctic zone of Yakutia is estimated. In our permanent section «Clinical case» a propionic academia case is described. Also, dear readers, you can get acquainted with the scientific directions of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov.

In the section «Our Anniversaries» we honor the respected and dear to us the jubilees of the Academician of the RAS Yuri Petrovich Nikitin and the Doctor of Medical Sciences, Professor Pyotr Mikhailovich Ivanov.

Dear colleagues, I wish you a pleasant and informative reading, have a success in scientific and practical activities!

*Director of the YSC CMP, MD A.N. Romanova*

## EDITORIAL

A.G. Egorova, T.M. Klimova, A.N. Romanova

## TERRITORIAL AND GENDER DIFFERENCES IN CARDIOVASCULAR MORTALITY IN THE SAKHA (YAKUTIA) REPUBLIC

DOI 10.25789/YMJ.2018.63.01

### ABSTRACT

**Aim of the study** was analysis of territorial and gender differences in cardiovascular mortality among the population of the Sakha (Yakutia) Republic.

**Materials and Methods.** We used the statistical data of the Yakut Republican Medical Information and Analytical Centre of the Ministry of Health and of the Federal State Statistics Service of the Republic of Sakha (Yakutia) for 2015 for the analysis. The standardised mortality rates were calculated on the basis of the "European Standard Population" (2013).

**Results.** In 2015 in Republic of Sakha (Yakutia) 3634 people aged 15 years and older died of cardiovascular diseases (ICD 10 codes - I10-I99). The standardised cardiovascular mortality rates of the population of 15 years and older were 1004.8 (95% CI 972-1038) per 100,000 population, coronary heart disease (CHD) – 255.4 (95% CI 239- 272), cerebrovascular diseases – 113.2 (95% CI 102- 124), other heart diseases – 544.1 (95% CI 520- 568) respectively. The proportion of deaths from hypertensive diseases (I10-I15) in the mortality pattern from cardiovascular diseases (CVD) was 0.7%; CHD (coronary heart disease, I20-I25) – 24.5%; cerebrovascular diseases (I60-I69) – 11.5%; other heart diseases (I30-I52) – 55.4%. We have established substantial differences in the mortality rates and age of death from CVD between the municipalities of the republic. The highest standardised mortality rates from CVD were in Zhigansk, Olenyoksky, and Nizhnekolymsky districts (1931-2178 per 100 000 population), the lowest in Verkhnevilyuysky, Even-Bytantaisky, and Abyisky districts (498-605 per 100 000 population). The lowest median age values were observed in the Even-Bytantaisky and Abyisky districts (55 and 56 years respectively), the largest in the Olenyokskiy and Churapchinsky districts (77 and 75 years respectively).

Men's mortality rate was 1.7 times higher than that of women (1339 and 789 per 100 000 people, respectively,  $p < 0.001$ ). Median age of death in men was 13 years less than in women (62 and 75 years, respectively,  $p < 0.001$ ).

**Conclusion.** The results of the study indicate that there are significant differences between municipalities in CVD-related mortality rates. The mortality rate among men according to 2015 is 1.7 times higher than among women. To manage the demographic situation in the region, it is necessary to search for the causes of existing differences in the death rates of the population.

**Keywords:** mortality, cardiovascular disease, standardization indices, age of death, gender differences, Sakha (Yakutia) Republic.



### Introduction

Cardiovascular diseases (CVD) remain the main cause of death in Republic of Sakha (Yakutia). The age-standardised mortality rates of the entire population of the republic from cardiovascular disease in 2015 amounted to 725,9 per 100 000 population (Russian Federation – 672.2 respectively). The proportion of CVD was 45,4% of all causes of death.

According to the administrative and territorial division, the territory of the Republic of Sakha (Yakutia) is divided into 34 districts (uluses) and 2 urban districts (Yakutsk and Zhatay). As of January 1st, 2015, the Republic's population was 956,896 persons. Settlement on Republic's vast territory causes differences in climatic, geographic, and environmental conditions of the habitat, socio-economic development, living standards, and in the age structure of the population.

**Aim of the study** is analysis of territorial and gender differences in cardiovascular mortality among the population of Republic of Sakha (Yakutia).

### Materials and Methods of Research

Database used in the study originates in the Yakut Republican Medical Information and Analytical Centre of the Ministry of Health and also includes statistical data of Federal Agency of Territorial State Statistics Service for the Republic of Sakha (Yakutia) for 2015 [1]. The analysis was carried out by the cause of death codes I10-I99 – Diseases of the Circulatory System according to ICD-10: I10-15 – hypertensive diseases; I20-25- coronary heart disease (CHD); I 60-69 - Cerebrovascular diseases; I30-52 Other Heart Diseases.

The indicators of the two urban districts (Yakutsk and Zhatay) were combined and presented under the name of Yakutsk (City of Republican Status). To eliminate heterogeneity in the age structure of the population of the municipalities of the Republic, we used a direct standardisation method. Standardised death rates were calculated on the basis of European Standard Population, revised by Eurostat in 2012 and published in 2013 [2].

We conducted statistical analysis of the data using IBM SPSS Statistics 22 software. The age of death is presented as median (Me) and interquartile (25 and 75%) distribution in Me (Q1; Q3) format. When comparing independent groups, we used a nonparametric Mann-Whitney test or 95% confidence interval. Critical value of the level of statistical significance of the differences (p) was set at 5%.

### Results and Discussion

In 2015, 3634 people aged 15 years

and over died in the Sakha (Yakutia) Republic from cardiovascular diseases (ICD 10 codes I10-I99). Of these, 2,085 were men and 1,549 were women. If we consider the structure of mortality from CVD, the proportion of deaths from hypertensive diseases (I10-15) was 0,7%; IHD (I20-25) – 24,5%; cerebrovascular diseases (I 60-69) – 11,5%; other heart diseases (I30-52) – 55,4%, other diseases – 7,6%.

Table 1 shows the mortality rates of the population of 15 years and older from cardiovascular diseases (ICD-10 codes I00-99) per 100,000 population. There are 5-fold differences in death rates between individual municipalities of the

Republic (224,6 and 1126 per 100,000 population, respectively). As you know, the general mortality rates depend on the characteristics of age (or any other) structure of the population. In this regard, there is a need to eliminate the influence of structural factors on its magnitude using an index method or methods for standardising coefficients.

We have identified significant discrepancies when analysing age structures of the population of municipal formations. For instance, the share of the population under the age of working age varied from 20 to 32,6%, and the proportion of people older than working age is from 9,7 to 21,5%.

**Table 1**

**Mortality rates of the population of 15 years and older from cardiovascular diseases in 2015**

Municipality	Population annual average number	Number of deaths	Per 100,000	Per 100,000*	Age of death, years**
Abyiskiy	3078	14	454,9	605,3	56 (41; 72)
Aldansky	32954	287	870,9	1420,6	67 (57; 78)
Tattinsky	11852	85	717,2	1463,3	73 (59; 82)
Allaaykhovskiy	2008	10	498,0	635,6	59 (40; 68)
Amginsky	11823	56	473,7	1024,9	70 (57; 78)
Anabarsky	2382	14	587,7	1390,7	61 (49; 78)
Bulunsky	6435	44	683,8	1388,1	60 (51; 70)
Verkhnevilyuysky	14691	33	224,6	498,0	61 (51; 75)
Verkhnekolymsky	3444	32	929,3	1306,0	63 (54; 74)
Verkhoyansky	8413	59	701,3	1138,2	61 (56; 69)
Viluysky	17820	138	774,4	1434,9	67 (56; 77)
Gornyy	8331	45	540,2	1211,3	69 (59; 84)
Zhigansky	3020	34	1126,0	2177,7	67 (60; 77)
Kobaiysky	9507	46	483,9	971,7	70 (57; 75)
Nyurbinsky	17323	99	571,5	1066,7	70 (58; 79)
Lensky	29711	193	649,6	1027,0	63 (53; 74)
Megino-Kangalassky	21842	128	586,0	1132,3	70 (58; 80)
Myrminsky	56329	217	385,2	978,4	62 (53; 75)
Momsky	2873	24	835,4	1414,7	68 (58; 76)
Namsky	17259	70	405,6	914,9	70 (59; 81)
Nizhnekolymskiy	3253	36	1106,8	1931,8	65 (57; 78)
Oymyakonsky	7365	65	882,6	1369,4	61 (51; 70)
Olekminsky	19703	131	664,9	1342,5	72 (61; 80)
Oleneksky	2769	22	794,7	1954,1	77 (67; 85)
Khangalassky	24890	104	417,8	763,2	67 (56; 78)
Srednekolymsky	5440	29	533,1	834,7	67 (51; 83)
Suntarsky	16895	87	515,0	846,9	68 (56; 77)
Tomponsky	10351	64	618,3	1247,8	68 (61; 77)
Ust-Aldansky	14986	60	400,4	766,4	67 (58; 79)
Ust-Maysky	5836	42	719,7	789,5	57 (51; 67)
Ust-Yanskiy	5512	45	816,5	1452,4	62 (52; 71)
Churapchinsky	14706	87	591,6	1483,2	75 (57; 82)
Even-Bytantaisky	2022	8	395,7	562,0	55 (48; 67)
Yakutsk	258988	927	357,9	814,9	70 (58; 81)
Neryungriysky	61958	299	482,6	961,2	63 (56; 75)
Republic of Sakha (Yakutia)	735760	3634	493,9	1004,8	67 (56; 78)

Note: \* – mortality rates, standardized by European Population Standard structure (2013); \*\* – data presented in Me (Q1; Q3).

Calculation of the standardized mortality indicators for the European population showed a change in the regional positions in mortality rating. In 21 of 35 municipalities, death rates exceeded the value of 1000 per 100,000 population. The highest standardised mortality rates from CVD were in Zhigansky, Oleneksky, Nizhnekolymsky districts (1931-2178 per 100,000 population), the lowest in Verkhnevilyuysky, Even-Bytantaisky and Abyisky districts (498-605 per 100,000 population).

Medians of the age of death from CVD in municipalities also statistically significantly differed ( $p < 0,001$ ). The lowest median age-of-death values were observed in the Even-Bytantaisky and Abyisky districts (55 and 56 years respectively), the largest in the Oleneksky and Churapchinsky districts (77 and 75 years, respectively).

The age-adjusted mortality rates of Republic's population of 15 years and older from CVD in 2015 were 1004,8 (95% CI 972- 1038) per 100,000 population; coronary heart disease (CHD) – 255,4 (95% CI 239- 272), cerebrovascular diseases – 113,2 (95% CI 102-124), other heart diseases – 544,1 (95% CI 520-568), respectively.

Due to the fact that the mortality of the male population, as a rule, exceeds the mortality in women, the mortality rates for each group were calculated separately (Table 2). Age structures of the male and female populations most significantly differed in the age groups 20-29, 60-69, 70 and older.

Comparison of men and women in terms of the age-standardised mortality rate per 100,000 population of the corresponding gender showed a statistically significant difference (Table 2). Thus, the mortality rate of men was 1,7 times higher than the death rate of women (1339 and 789 per 100,000 population, respectively,  $p < 0,001$ ). The median age of death in men was 13 years less than in women (62 and 75 years, respectively,  $p < 0,001$ ).

Analysis of age-specific mortality rates showed that the most significant differences in mortality between men and women were observed in the age groups of 30-59 years (Table 3).

At analyzing the age-standardized death rates from CHD and cerebrovascular diseases, we found that in all municipalities, except for the Verkhnevilyuysky district, the mortality rates of men were significantly higher than those of women (Table 4). At the same time, we identified areas with very high death rates from CHD and

Table 2

**Age-adjusted mortality rates in 2015 per 100,000 population of the corresponding gender**

ICD 10 code	Men (n=2085)	Women (n=1549)
I10-15 Hypertensive diseases	9,5 (95% CI 4-15)	6,0 (95% CI 2- 10)
I20-25 CHD	345,4(95% CI 316-375)	195,3 (95% CI 175-215)
I 60-69 Cerebrovascular diseases	145,9 (95% CI 127-164)	90,4 (95% CI 77-104)
I30-52 Other heart diseases	729,0 (95% CI 687-771)	426,6 (95% CI 398-455)
Other codes	109,1 (95% CI 91- 127)	70,2 (95% CI 58-82)
I10-I99 All codes	1338,8 (95% CI 1281-1396)	788,6 (95% CI 749- 828)
Age of death, years*	62 (Q153; Q373)	75 (Q163; Q182)

Note: 95% CI – 95% confidence interval; \* – the data is represented in the format Me (Q1; Q3).

Table 3

**Mortality rates per 100 000 population of the corresponding gender and age**

Age group, years	I10-15 Hypertensive diseases	I20-25 CHD	I30-52 Other heart diseases	I 60-69 Cerebro-vascular diseases	Other codes	I10-I99 All codes
Men						
15-19	0,0	0,0	9,9	0,0	0,0	9,9
20-29	0,0	3,7	22,2	4,9	2,5	33,3
30-39	0,0	24,0	101,4	10,7	6,7	142,8
40-49	0,0	73,0	232,2	34,8	14,9	354,9
50-59	8,1	267,9	483,9	92,6	39,0	891,4
60-69	9,6	491,9	852,8	290,7	146,9	1791,9
70 and older	41,5	1310,7	2853,7	497,7	472,9	5176,5
15 and older	3,7	154,2	326,0	68,6	40,7	593,1
Women						
15-19	0,0	0,0	0,0	0,0	0,0	0,0
20-29	0,0	1,3	7,9	1,3	1,3	11,8
30-39	0,0	4,1	27,1	6,8	6,8	44,7
40-49	0,0	12,6	64,5	12,6	1,6	91,2
50-59	2,8	38,0	180,0	28,1	16,9	265,8
60-69	2,3	155,8	381,6	76,8	56,5	673,0
70 and older	31,4	989,6	1975,3	432,0	349,5	3777,9
15 and older	2,9	93,7	225,6	46,3	34,6	403,1

cerebrovascular diseases were identified.

Mortality rate for ICD 10 code Other heart diseases (I30-52) in 2015 was 55,4% (2013 cases) of all CVD-related deaths. The most frequent causes of death were heart failure (code I50) – 1223 cases, cardiomyopathy (code I42) – 439, heart failure (I46) – 278, respectively. In-depth analysis of the causes of death from cardiomyopathy (code I42) revealed that 138 cases of 439 (31,4%) were diagnosed with alcoholic cardiomyopathy (I42.6) as the cause of death, 102 (23%) – other cardiomyopathies (I42.8), in 162 (36,9%) – unspecified cardiomyopathy (I42.9). The highest death rates from

alcoholic cardiomyopathy were observed in Allaikhovsky, Verkhoyansky, and Ust-Yansky districts (table 4).

Proportion of deaths from alcoholic cardiomyopathy in the structure of death from CVD in men was statistically significantly higher than that in women (4.8 and 2.4%, respectively,  $p < 0,001$ ). In both groups, the specific gravity of this cause of death was higher in employable age.

### Conclusions

Results of the study indicate that there are significant differences between municipalities in the mortality rates from CVD. According to the data of 2015,

Table 4

## Age-adjusted mortality rates in 2015 per 100,000 population of corresponding gender in context of municipalities

Municipality	CHD (I20-25)		Cerebrovascular diseases (I60-69)		Alcoholic cardiomyopathy (I42.6)		All codes (I10-I99)	
	men	women	men	women	men	women	men	women
Abyisky	0	0	0	46,7	0,0	0,0	809,4	502,3
Aldansky	982	637,6	307	173,8	126,8	16,9	1872,1	1110,5
Tattinsky	15,9	0	0	16,3	0,0	0,0	1745,1	1275,9
Allaahovsky	89	0	416,7	0	198,4	0,0	1511,7	97,1
Amginsky	64,2	42,5	24,8	26,6	0,0	0,0	1563	707,4
Anabarsky	0	0	0	0	93,1	0,0	1607,1	1277,1
Bulunsky	0	0	32,1	0	0,0	0,0	1582,3	1200,3
Verkhnevilyuysky	24	134,6	14,5	44,9	0,0	0,0	434,8	497,8
Verkhnekolymsky	287,4	0	345,7	196,7	0,0	0,0	1801,9	1062,1
Verkhoyansky	248,2	165,6	247,8	16,7	216,4	71,2	1534,5	842,8
Viluyusky	170,1	100,5	9,5	0	41,6	15,9	2023,1	1047,7
Gornyy	26,2	95,5	179,7	67,5	0,0	0,0	1601,4	951,4
Zhiganskiiy	0	147,5	0	0	0,0	0,0	3301,9	1648,5
Kobyaysky	0	97,2	126,6	48,6	38,2	0,0	1092,2	870,8
Nyurbinsky	0	0	0	0	0,0	10,3	1357	861
Lensky	478,5	169,3	359,6	167,3	109,4	41,6	1543,5	701,6
Megino-Kangalassky	961,3	386,8	148	107,3	34,1	0,0	1542,8	851,6
Myrnsky	849,3	541,4	155,7	117,2	51,0	8,2	1370,5	757,1
Momsky	0	231,5	72,2	115,7	0,0	0,0	1635,5	1214,6
Namsky	122,6	0	53,6	0	12,4	0,0	1347,2	634
Nizhnekolymskiy	0	0	48,6	0	0,0	0,0	2829,1	1386,9
Oymyakonsky	622,1	141,8	495,4	383,1	115,6	179,8	1629,6	946
Olekminsky	153,8	18,9	43,4	21	8,3	0,0	1940,4	1011,2
Oleneksky	0	0	0	0	0,0	0,0	2663,9	1548,2
Khangalassky	101,9	0	0	0	23,8	6,0	1009,4	588,5
Srednekolymsky	0	0	0	0	0,0	0,0	854,4	757,5
Suntarsky	623,2	279,2	203,8	62,4	21,8	0,0	1128,9	636,5
Tomponsky	0	39,8	0	0	0,0	0,0	1881,9	932,8
Ust-Aldansky	164,6	89,3	22	33	0,0	19,0	1199,8	474,3
Ust-Maysky	0	0	0	0	0,0	0,0	1316,7	431,1
Ust-Yanskiy	265,3	162,8	642,1	244,2	223,7	147,1	1689,6	1240,6
Churapchinsky	112,2	56	152,3	42	0,0	0,0	1518,6	1437,3
Even-Bytantskiy	0	0	0	0	0,0	0,0	1401	166,3
Yakutsk	265,5	156,3	153,6	92,4	20,6	6,1	1030,6	679,7
Neryungriysky	659,4	367,8	187,7	231,7	12,2	0,0	1238,8	781,3
Republic of Sakha (Yakutia)	345,4	195,3	145,9	90,4	33,2	10,1	1338,8	788,6

the mortality rate of men was 1,7 times higher than that of women. In order to manage the demographic situation in the region, it is necessary to search for the causes of differences in the death rate of the population.

*The work was carried out within the framework of research work "Contribution of Metabolic Syndrome to the Development of Coronary Artery Atherosclerosis in Yakutia's Population (M01; 05; 03)" (No. 0556-2014-0002).*

#### References:

1. Baza dannyykh pokazateley minicipalnykh

obrazovaniy. Territorialny organ federalnoy sluzhby gosudarstvennoy statistiki po Respublike Sakha (Yakutiya) [Database of Indicators for Municipalities. Territorial Body of the Federal Service of State Statistics for the Republic of Sakha (Yakutia)]. URL: <http://www.gks.ru/dbscripts/munst/munst98/DBInet.cgi> (cited June 28th, 2018).

2. Revision of the European Standard Population. Report of Eurostat's task force. Publications Office of the European Union. 2013. 121 pp. [Online]. 2013 (cited June 10th, 2018). URL: <http://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f>

44e8-b23d-5e8fa09b3f8f

#### The authors:

1. Egorova Aitalina Grigorievna, PhD, Chief Researcher Yakut Science Centre of Complex Medical Problems, Yakutsk, Russia, e-mail: [aitalina@mail.ru](mailto:aitalina@mail.ru);
2. Klimova Tatiana Mikhailovna - Associate Professor of the Department of Pharmacology and Pharmacy of the Medical Institute NEFU; senior researcher of the YSC CMP, Yakutsk, Russia;
3. Romanova Anna Nikolaevna - MD, Director of the Yakut Science Centre of Complex Medical Problems, Yakutsk, Russia, e-mail: [ranik@mail.ru](mailto:ranik@mail.ru).



S.A. Evseeva, M.S. Savvina, T.E. Burtseva, V.G. Chasnyk

**DYNAMICS OF MORBIDITY OF CHILDREN'S  
POPULATION REPUBLIC OF SAKHA  
(YAKUTIA) FOR 1995-2015**

DOI 10.25789/YMJ.2018.63.02

**ABSTRACT**

The article analyzes the morbidity of children in the Republic of Sakha (Yakutia) for 1995-2015. There is an increase in the morbidity rate of the child population, identified by referral to medical and preventive institutions, for many groups of diseases.

**Keywords:** children, morbidity, Republic of Sakha (Yakutia).

**Introduction**

The state of children's health is one of the most important indicators determining the future well-being of society. Increasing the birth rate, maintaining and strengthening the health of children are priority public tasks [1]. It is known that health indicators are the basis for planning the health care resources necessary to meet the existing needs of the population in various types of medical care [2].

**Purpose of the study** is to analyze the incidence population of children by class of diseases for 1995-2015 in the Republic Sakha (Yakutia).

**Materials and methods**

We carried out the analysis of indicators of the incidence of children by forms of diseases according to official medical statistics State institution «Yakut Republican Medical Information and Analytical Center of the Ministry of Health of the Republic of Sakha (Yakutia)» for 1995-2015.

**Results and discussion**

The increase in the indicator of the general morbidity of the children's population of the republic affected almost all classes of diseases. The indicator of the general morbidity of children's population since 1995 to 2015 increased from 1600.2 to 2718.7 per 1,000 children's population (Table 1).

The data of the retrospective analysis of statistical data allow us to state the following. A decrease in the incidence rate by class of infectious and parasitic diseases is noted. Perhaps this is due to the fact that the share of so-called «managed infections» has increased, vaccination against which is included in the national calendar of preventive vaccinations. Between the rates of incidence and vaccination there is direct correlation dependence. With active vaccination against mumps, measles and whooping cough, the incidence rate does not exceed acceptable standards.

On the class of neoplasms, there is an increase in the overall incidence (from

4.2 per 1000 of the child population to 15.0). For the child population, the high rates of growth of diseases of this class are not natural. Observed over the past year, the rate of increase in the incidence of this class indicates the need for deep fundamental research.

Diseases of blood and blood-forming organs are mainly connected with anemia. The incidence of anemia in the study period increased from 17.8 to 23.0 per 1,000 of population children.

With regard to the class of diseases of the endocrine system, eating disorders, metabolic disorders, there is a stabilization of the overall morbidity at the level of 35.4 - 35.5 per 1,000 children. This group of diseases is mainly represented by diabetes mellitus, thyroid diseases and growth retardation in children.

During the study period, there was a slight increase in the indicator of the

overall incidence of children's mental disorders and behavioral disorders. This indicator increased from 10.0 to 15.0 per 1,000 children. The increase in the incidence is due to mental disorders of a non-psychotic nature.

The group of diseases of the nervous system has consistently high rates. Diseases of the eye and adnexa have a tendency to increase, primarily due to myopia. With respect to the class of ear and mastoid disease, negative dynamics are also observed from 41.8 to 60.5 per 1000 children. At the same time, it should be noted a decrease in the incidence of chronic otitis media, which may be associated with effective therapy, since in recent years it seems possible to define a clear tactic of treatment and prevention of this disease.

Diseases of the circulatory system are a serious problem, which justifiably

**Table 1**

**The dynamics of the overall morbidity of childhood in the Republic of Sakha (Yakutia) in 1995 -2015 (per 1000 children's population)**

Name of classes and individual diseases	1995	2015	Dynamics
Total registered	1600,2	2718,7	1,7 times
Some infectious and parasitic diseases	117,9	64,7	1,8 times
Neoplasms	4,2	15,0	3,5times
Diseases of the blood and blood-forming organs	17,8	23,0	1,3times
	13,5	19,3	0,6 times
Diseases of the endocrine system, eating disorders including diabetes mellitus	35,4	35,5	0,9times
insulin-dependent	0,2	0,9	4,5 times
insulin-independent	0,05	0,03	-1,6 times
Mental and behavioral disorders	10,0	15,0	1,5times
Diseases of the nervous system including infantile cerebral palsy	160,4	164,0	1 times
Diseases of the eye and its adnexa	2,9	4,5	1,5 times
Of which: myopia	86,8(2001)	150,8	1,7 times
Diseases of the ear and mastoid process	27,7	40,6	1,5 times
of which: chronic otitis media	41,8(2001)	60,5	1,4 times
Diseases of the circulatory system	8,9	2,5	-3,5times
Diseases of the respiratory system	6,0	14,8	2,4times
Diseases of the digestive system	926,7	1536,8	1,6 times
Diseases of the skin of subcutaneous tissue	92,3	249,7	2,7 times
Diseases of the musculoskeletal and connective tissue	83,9	131,1	1,5times
Diseases of the genitourinary system	13,3	44,6	3,4times
Congenital malformations, malformations, deformations, chromosomal abnormalities	29,3	55,5	1,9times
Injury to poisoning and some consequences of external causes	14,0	31,1	2,2 times
	61,3	108,0	1,7times

Table 2

**The dynamics of the overall morbidity of the child population of the Russian Federation in 1991-2014 (per 100 thousand children's population)**

Name of classes and individual diseases	1991	2014	Dynamics
Total registered	140846,0	222926,2	In 1,58 times
Some infectious and parasitic diseases	9654,4	8714,8	- 1,1 times
Neoplasms	209,7	903,9	in 4,3 times
Diseases of the blood and blood-forming organs including anemia	873,1	2775,6	in 3,8 times
Diseases of the endocrine system, eating disorders including diabetes mellitus	692,7	2476,6	in 3,6 times
insulin-dependent	1379,5	3746,4	In 2,8 times
insulin-independent	40,2(1995)	96,0	in 2,4 times
Mental and behavioral disorders	5,1(1995)	1,3	-3,9times
Diseases of the nervous system including infantile cerebral palsy	2661,3	2938,5	in 1,1times
Diseases of the eye and its adnexa including myopia	....	8963,5	
Diseases of the ear and mastoid process of which: chronic otitis media	196,1	330,8	in 1,7times
Diseases of the circulatory system	...	11639,0	
Diseases of the respiratory system	2540,7	3279,3	in 1,3 times
Diseases of the digestive system	...	5838,6	
Diseases of the skin of subcutaneous tissue	379,1	144,5	- 2,6times
Diseases of the musculoskeletal and connective tissue	687,6	1955,4	in 2,84times
Diseases of the genitourinary system	86252,6	120756,3	in 1,4 times
Congenital malformations, malformations, deformations, chromosomal abnormalities	8413,0	13575,3	in 1,63times
Injury to poisoning and some consequences of external causes	5914,7	10046,0	in 1,77times
	1847,9	7556,7	in4,1 times
	2127,1	5410,2	in 2,55times
	1025,4	3359,8	in 3,28times
	7099,6	10302,7	in 1,45 times

removes their prevention and treatment to the level of one of the priority areas of health care. During this period, the incidence rate increased from 6.0 to 14.8 per 1,000 children.

The dynamics of indices of the class of diseases of the digestive organs is also another convincing evidence of the process of a steady increase in the burden of pathology from 92.3 to 249.7 per 1000 children. Perhaps, one of the reasons for the increase in the incidence of the pathology of the gastrointestinal tract in children was insufficient provision of school meals. Proper nutrition in educational institutions positively affects the health of children.

According to the class of skin and subcutaneous tissue diseases, the incidence rate is increasing from 83.9 to 131.1 per 1000 children during the period under review.

The most common are allergic dermatoses.

Similar to the previous class of pathology with a rapid increase in prevalence in children, the situation develops with regard to the class of diseases of the musculoskeletal system and connective tissue. The rate of increase is from 13.3 to 44.6 per 1,000 children. This class is mainly represented by functional disorders of posture and arch of the feet.

Analysis of the state and dynamics of the morbidity of the children's population by the pathology of the genitourinary system also revealed several problems requiring close attention. The increase in the overall incidence was from 29.3 to 55.5 per 1,000 children. The main causes of morbidity of the genitourinary system are such factors as hereditary predisposition, hypothermia, complications after the transferred viral infections.

Congenital anomalies and malformations, deformations and chromosomal violations also have outstripping rates of growth and consistent character of dynamics and pathology among children from 14.0 to 31.1 per 1000. The factor of pathological course of pregnancy combined with undeniable deterioration of environmental parameters and psychological stress in society play its negative role.

Injuries and poisonings in the children's population for the period under review also increased from 61.3 to 108.0 per 1,000 children. This requires interdepartmental work on the prevention of childhood injuries.

The dynamics of incidence rates

by class are similar to the Russian Federation indices where there is an increase in the incidence of all classes of diseases (Table 2).

#### Conclusions

Analysis of incidence rates of the child population clearly showed the evolution of individual classes of illnesses since 1995 on the appeal of the children's population to medical and preventive institutions. In general, there is an increase in the overall incidence of many classes of diseases. In fact, this indicator is a fairly real and effective tool for planning and optimizing the pediatric service in the region.

#### References:

1. Dranaeva G.G. Grigor'eva A.N., Burceva T.E. Sostoyanie zdorov'ya detej Respubliki Saha (Yakutiya) [State of health of children of the Republic of Sakha (Yakutia)] M-vo zdavoohraneniya Resp.Saha (Yakutiya), Yakut. nauch. centr KMP SO RAMN [Health Ministry of the Republic of Sakha (Yakutia), Yakut science centre CMP RAMS]. Yakutsk: Offset. 2009, P.176.
2. Tishuk E.A. Ocherk zabolevaemosti naseleniya Rossijskoj Federacii zachetvert' veka [A sketch of the incidence of the

Russian Federation's population in a quarter of a century] Medicinskaya statistika i orgmetodrabota v uchrezhdeniyah zdavoohraneniya [Medical statistics and the organization of work in health institutions]. 2017, №1, P. 3- 15.

3. Matalygina O.A. Formirovanie individual'nyh profilakticheskikh meropriyatij pri vyyavlenii minimal'nyh riskov zabolevaniya u detej v vozraste ot 3 do 18 let [Formation of individual preventive measures in detecting the minimum risks of the disease in children aged 3 to 18 years]. Saint Petersburg, 2012, P.76.

#### The authors:

1. Evseeva Sardana Anatolievna- Candidate of Medical Science, Senior Researcher of the YNC CMP, sarda79@mail.ru;
2. Savvina Maya Semenovna - Candidate of Medical Science, Senior Researcher of the YNC CMP, maya\_savvina@mail.ru;
3. Burtseva Tatyana Egorovna - Doctor of medical sciences, professor MI SVFU, head. lab. YNC CMP, bourtsevat@yandex.ru;
4. ChasnykVyacheslavGrigorievich - MD, Professor, SPb GPMA, chasnyk@gmail.com.

N.N. Gotovtsev, N.A. Barashkov, T.V. Borisova, M.V. Pak,  
M.P. Alekseeva, N.N. Innokentieva, K.S. Loskutova, V.G.  
Pshennikova, A.M. Rafailov, S.N. Lekhanova, S.A. Fedorova

## ANALYSIS OF THE CLINICAL OUTCOMES OF GASTRODUODENAL DISEASES IN YAKUTIA DEPENDING ON THE PRESENCE OF THE CYTOTOXIN-ASSOCIATED GENE A (CAGA) IN THE *HELICOBACTER PYLORI*

DOI 10.25789/YMJ.2018.63.03

### ABSTRACT

**Introduction.** The cytotoxin associated gene A (*cagA*) in the *Helicobacter pylori* genome is often associated with the formation of cytotoxins and induction of interleukin 8 (IL8) by gastric epithelial cells, which directly affects the immune response and entails inflammatory processes, affecting on clinical outcomes in patients with gastroduodenal diseases, caused by *Helicobacter pylori*. The clinical outcomes of gastroduodenal diseases, depending on the presence of *Helicobacter pylori cagA* gene, circulating in Yakutia, were not previously studied. The aim of this work is to study clinical outcomes in patients with gastroduodenal diseases in Yakutia, depending on the presence of the cytotoxin associated gene A in the *Helicobacter pylori*.

**Materials and methods.** Gastric biopsy specimens were obtained from 311 patients. According to the results of histological analysis, 172 patients had the presence of *H. pylori* and divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

**Results.** Chronic gastritis was established in 91 samples (52,9%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 81 samples (47,1%). Strains with *cagA*<sup>+</sup> status were identified in 118 samples (68,6%), and *cagA*<sup>-</sup> in 54 samples (31,4%). In the group from 18 to 70 years, a higher incidence of *cagA*<sup>+</sup> strains were found in comparison with the group of patients from 3 to 17 years which more often had *cagA*<sup>-</sup> strains ( $p < 0,001$ ). The cross-sectional analysis showed that statistically significant differences were found in the *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains between the clinical outcomes within a group of children ( $\chi^2 = 9,03$ ,  $p < 0,001$ ) (73,7%).

**Conclusion.** We showed relationship between *cagA*<sup>+</sup> strains of *Helicobacter pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known data that *cagA*<sup>+</sup> strains are more virulent and pathogenic than *cagA*<sup>-</sup> strains of *Helicobacter pylori*.

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

### Introduction

*Helicobacter pylori* (*H. pylori*) is one of the most common bacterial human pathogens, which is spread all over the world [20]. *H. pylori* infection is associated with the development of chronic gastritis, gastric or duodenal ulcers, gastric cancer and MALT-lymphoma [5, 12, 28]. In the absence of treatment, individuals who have been infected with *H. pylori* remain colonized during their lifetime due to increased viability and adaptability of the pathogen [4]. Previously, various virulence and pathogenicity genes of *H. pylori* infection have been described, such as *cagA*, *vacA*, *iceA* and *oipA* [6, 8, 10, 14]. The cytotoxin associated gene A (*cagA*) is often associated with the formation of cytotoxins and the induction of interleukin 8 (IL8) by gastric epithelial cells [19]. Most studies have shown that the presence *H. pylori* CagA protein, the relative risk of more severe gastroduodenal diseases is increased by 2-3 times [6, 15, 18]. Besides, some data indicate an increased risk of gastric cancer when patient infected by *cagA*<sup>+</sup> strains of *H. pylori* about 28,4 times [24]. It has been established that *cagA*<sup>+</sup> strains of *H. pylori* are also associated with more pronounced inflammation, cell proliferation and metaplasia of the gastric mucosa [25]. The first significant breakthrough in the study of CagA protein was the realization that its

gene is part of a large so-called island of pathogenicity (*cag* PAI), a region of horizontally acquired DNA that is embedded in the genome of more virulent *H. pylori* strains [7]. There is a hypothesis that *cag* PAI *H. pylori* serves as a transport system for other genes of virulence factors [13]. In addition to the direct effect of CagA proteins on epithelial synapses, the transmission of growth factor pulses and the cytoskeleton, CagA also has a pronounced pro-inflammatory effect [21]. Currently relevant is the study of the prevalence of *cagA* gene and its association with clinical outcomes of gastroduodenal diseases worldwide. For example, in some studies it has been shown that the presence of the *cagA* gene is associated with peptic ulcer diseases of the stomach and duodenum [2, 16, 26]. The clinical outcomes of gastroduodenal diseases, depending on the *H. pylori cagA* gene circulating in Yakutia, was not previously studied.

The aim of this work is to study the

analysis of the clinical outcomes of gastroduodenal diseases in Yakutia, depending on the presence of the cytotoxin associated gene A in the *Helicobacter pylori*.

### Materials and methods

Gastric biopsy specimens were obtained from April 2014 to January 2018 from 311 patients that admitted to the endoscopic department for fibrogastroduodenoscopy (FGDS) in endoscopic department of State autonomous institution of Republic Sakha (Yakutia) «Republican Hospital No. 1 – National Center of Medicine» (RH No.-1 NCM). To confirm the presence of *H. pylori* infection, gastric biopsy specimens were sent for histological examination to the pathoanatomical department of RH No.-1 NCM. According to the results of histological analysis, 172 patients (out of 311) were included in the study, who had the presence of *H. pylori*. The average age was 24,7 years (from 3 to 70). In accordance with macroscopic analysis of the mucosa and histological results, patients were divided into two

Table 1

Design of oligonucleotide primers for *H. pylori cagA* gene detection

Gene, fragment	Name of oligonucleotide primer	Sequence from 5' → 3'	The size of amplified fragment
<i>cagA</i>	<i>cagA</i>	F5'-GATAACAGGCAAGCTTTT-3' R5'-CTGCAAAAGATTGTTTGGCAG-3'	349 b.p.



groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Genomic DNA of *H. pylori* was isolated from frozen gastrobiopsies of the examined patients by using phenol-chloroform extraction [9]. Amplification of the required DNA fragments of *H. pylori* was performed using of the oligonucleotide primers described previously (Table 1), that flanking region, containing *cagA* gene [27]. Polymerase chain reaction (PCR) was performed on «Bio-Rad» thermocycler. Separation of amplification products was carried in the horizontal electrophoresis camera in a 2% agarose gel. Visualization of PCR products was performed by «Bio-Rad» gel video documentary device using Image Lab™ Software.

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

## Results

In the course of endoscopic and histological examination, in 172 (55,3%) out of 311 individuals had histologically confirmed the presence of *H. pylori* (fig. 1, a). The diagnosis of chronic gastritis was established in 91 cases (52,9%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 81 samples (47,1%) (fig. 1, b). Strains which have *cagA*<sup>+</sup> status were identified in 118 samples (68,6%), and *cagA*<sup>-</sup> status – in 54 samples (31,4%) (fig. 1, c).

There were no significant differences in clinical outcomes of gastroduodenal diseases in patients infected by *cagA*<sup>+</sup> or *cagA*<sup>-</sup> strains of *H. pylori* depending on the gender of the patients, as well as the place of birth and residence ( $p > 0,05$ ) (fig. 2, a, b). However, statistically significant differences between adult and child samples were shown, depending on the presence of *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains of *H. pylori*. Thus, in the group from 18 to 70 years, a higher incidence of *cagA*<sup>+</sup> strains

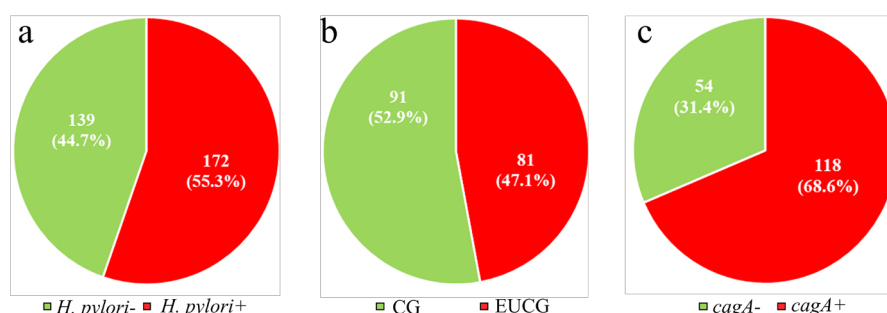


Fig. 1. Results of endoscopic, histological and molecular genetic research.

A. Number of patients, infected by *H. pylori*; B. The frequency of the sample of patients according to clinical diagnosis, depending on the presence or absence of erosions and ulcers; C. Sample of patients which have different *H. pylori* strains.

Note: CGEU – chronic gastritis with erosions and ulcers; CG – Chronic gastritis; *cagA*<sup>+</sup> – strains, which have *cagA* gene; *cagA*<sup>-</sup> – strains, which have not *cagA* gene.

were found in comparison with the group of patients from 3 to 17 years which more often had *cagA*-strains ( $p < 0,001$ ) (fig. 2, c).

Also, significant differences were found in the comparison group for the clinical outcomes of gastroduodenal diseases, depending on the presence

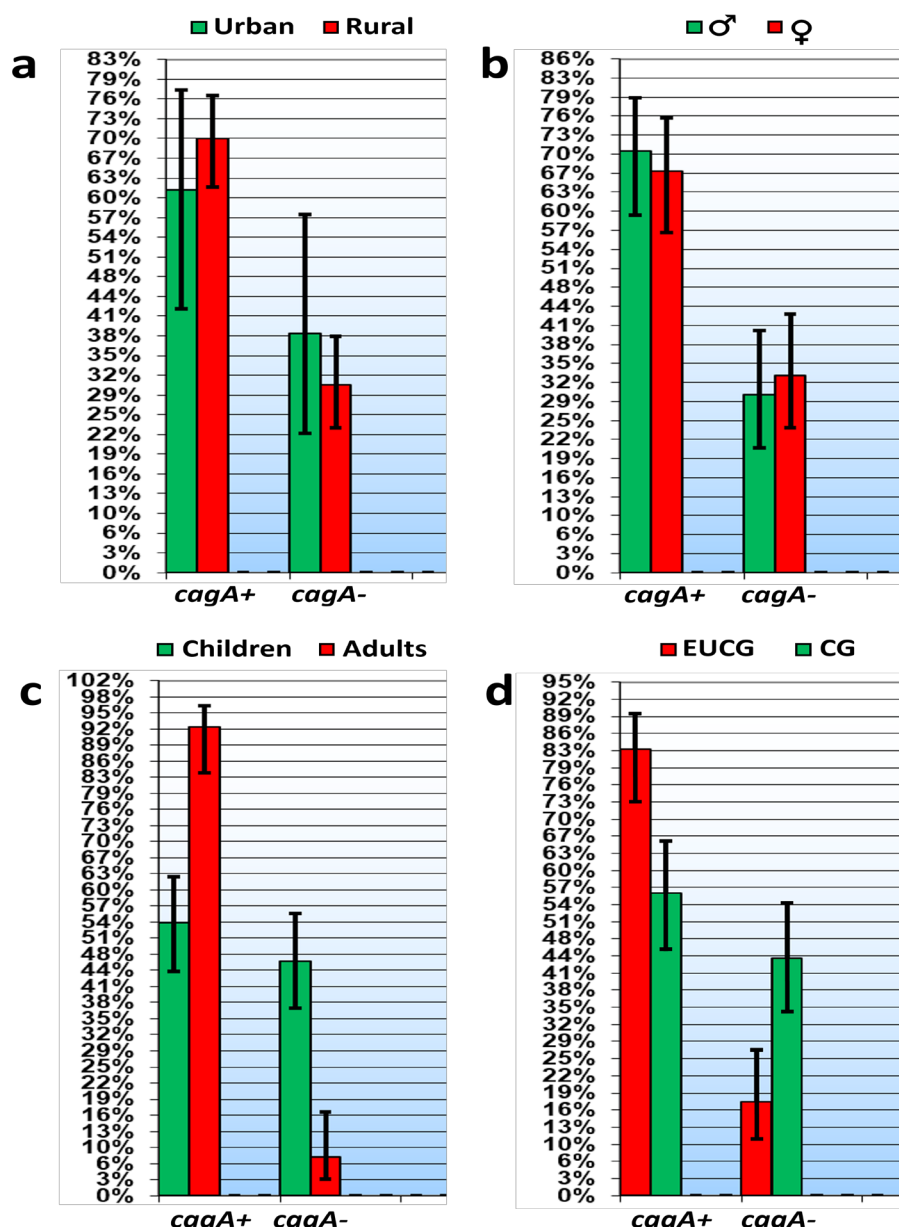


Fig. 2. Comparative analysis of the clinical outcomes of gastroduodenal diseases depending on the presence in patients of *cagA* gene.

a) depending by place of birth/residence; b) depending on the gender of patients; c) depending on the age (children/adults); d) depending by the established diagnosis.

Note: ♂ – male, ♀ – female.

of *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains of *H. pylori* ( $p<0,001$ ). Thus, it was found that *cagA*<sup>+</sup> strains were significantly more frequent in the sample of patients diagnosed with chronic gastritis with erosions and ulcers of the stomach and duodenum than in patients diagnosed with chronic gastritis which more often had *cagA*<sup>-</sup> strains ( $p<0,001$ ) (fig. 2, d).

A cross-sectional analysis of patients was performed for the presence of *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains, taking into account age and established diagnoses. Statistically significant differences were found in the cross-comparison of *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains between the clinical outcomes within a group of children (Table 2). Thus, in a sample of children diagnosed with chronic gastritis with erosions and ulcers, *cagA*<sup>+</sup> strains were significantly more frequent ( $\chi^2=9,03$ ,  $p<0,001$ ) (73,7%). In the sample of adults there were no significant differences by clinical outcomes ( $\chi^2=0,018$ ,  $p>0,05$ ).

#### Discussion

The prevalence of *cagA*<sup>+</sup> strains of *H. pylori* among patients with gastroduodenal diseases varies in different parts of the world [11]. In Yakutia the frequency of *cagA*<sup>+</sup> strains of *H. pylori* in patients with gastroduodenal diseases was 68.6%. Our result corresponds with the frequency of *cagA*<sup>+</sup> strains in Tunisia [22], Egypt [11], Palestine, Iran, Spain and Great Britain [references available on request]. However, obtained frequency of *cagA*<sup>+</sup> strains of *H. pylori* in Yakutia is lower than in some countries of South America, Africa, Europe, Asia, and higher than in some countries of North America,

**The cross-comparison of clinical outcomes within a group of children and adults by *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains**

Children (n=105)	Chronic gastritis (n=67)	<i>cagA</i> +	29 (43,3%)	$\chi^2=9,03$ p<0,001
		<i>cagA</i> -	38 (53,7%)	
	Chronic gastritis with erosive-ulcerative (n=38)	<i>cagA</i> +	28 (73,7%)	
		<i>cagA</i> -	10 (26,3%)	
Adults (n=67)	Chronic gastritis (n=24)	<i>cagA</i> +	22 (91,6%)	$\chi^2=0,018$ p>0,05
		<i>cagA</i> -	2 (8,4%)	
	Chronic gastritis with erosive-ulcerative (n=43)	<i>cagA</i> +	39 (90,7%)	
		<i>cagA</i> -	4 (9,3%)	
Total: 172				

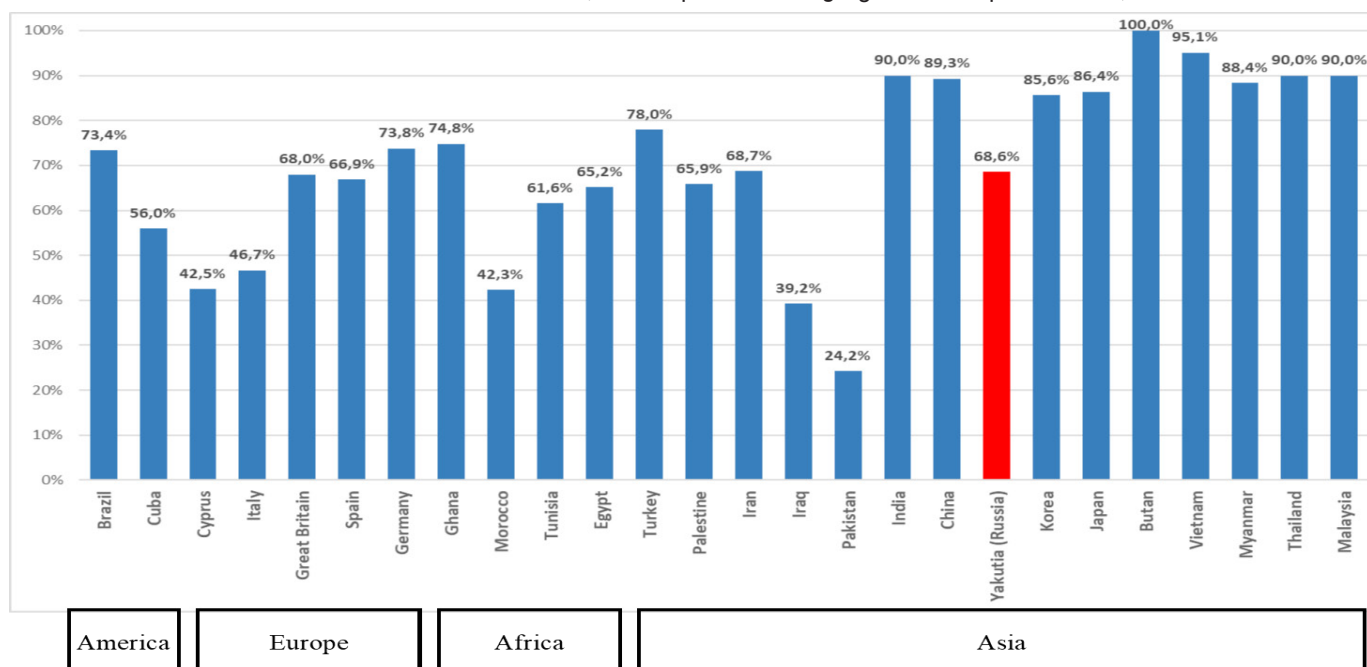
Africa, the Middle East and Europe (fig. 3).

When analyzing a sample of patients infected with *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains of *H. pylori*, statistically significant differences were found in the comparison group of patients, depending on the presence of erosive-ulcerous (fig. 2, d). Thus, in patients with erosions and ulcers, *cagA*<sup>+</sup> strains of *H. pylori* were significantly more frequent than in patients with chronic gastritis ( $p<0,001$ ). The result obtained by us is comparable with the results of similar studies of other authors [3, 17, 21, 23] and indicates about more pathogenic potential of *cagA*<sup>+</sup> strains of *H. pylori*.

Further analysis of patients age revealed a higher incidence of *cagA*<sup>+</sup> strains of *H. pylori* among adults (from 18-70) – 92,4% compared to children (from 3-17) – 53,7% ( $p<0,001$ ) (fig. 2, c). Our result agrees with the previously published work performed in Tunisia on a sample of patients with gastroduodenal diseases, where statistically significant difference was found between children and adults, with respect to the *cagA* gene

[22]. Thus, *cagA*<sup>+</sup> strains of *H. pylori* in adults were identified in 155 cases, and in children only in 18 cases [22]. It is known that the immune system of children has a number of features that make them more vulnerable to most infections [1]. Perhaps in the group of children *cagA*<sup>-</sup> strains can lead to chronic gastritis in the same way as *cagA*<sup>+</sup> strains, since in the group of children *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains were found with almost the same frequency (fig. 2, b). Perhaps obtained result indicates an imperfection of the immune system in children, which is more vulnerable to many infections, even having a small pathogenic potential [1].

Since the gender and place of birth/residence didn't show statistically significant differences ( $p>0,05$ ), we cross-compared *cagA*<sup>+</sup> and *cagA*<sup>-</sup> strains with clinical outcomes within the group of children and adults (Table 2). In the sample of children which were diagnosed with chronic gastritis with erosions and ulcers significantly more frequent *cagA*<sup>+</sup> strains (73,7%) than in children diagnosed with chronic gastritis (43,3%) ( $p<0,001$ ). In the sample of adults, this trend was not con-



**Fig. 3.** The frequency of *cagA*<sup>+</sup> strains of *H. pylori* in different parts of the world.



firmed, because *cagA*<sup>+</sup> strains prevailed over *cagA*<sup>-</sup> as in the group of patients diagnosed with chronic gastritis (91,6% and 8,4%) and in the group of patients diagnosed with chronic gastritis with erosions and ulcers (90,7% and 9,3%). Perhaps this can be explained by sampling effect.

### Conclusions

1) We have shown the relationship between *cagA*<sup>+</sup> strains of *H. pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known data that *cagA*<sup>+</sup> strains are more virulent and pathogenic than *cagA*<sup>-</sup> strains *H. pylori*.

2) It was shown that *cagA*<sup>-</sup> strains were more frequent among children (from 3 to 17) than in adults (from 18-70). Perhaps this can be explained by fact that in children the immune system is not as developed as in adults, which in turn explains the higher grade of susceptibility of children to many infections, not even so virulent and pathogenic.

*The study was supported by the Research of YSC CMP "The study of the genetic structure and the load of hereditary diseases of the Sakha Republic (Yakutia) populations", by the Project of the Ministry of Education and Science of the Russian Federation (#6.1766.2017), by the Project of the NEFU in Yakutsk "Genetic features of the population of Yakutia: gene pool structure, cold adaptation, psychogenetic characteristics, prevalence of certain genetic and infectious diseases", by the Federal Agency for Scientific Organizations program for support the bioresource collections by Institute «YSC CMP» collection «The Genome of Yakutia» (BRK 0556-2017-0003), RFBR (No. 18-54-16004\_NCNIL\_a, No. 18-05-60035\_Arctica) and by the Scientific and Educational Foundation for Young Scientists of Republic of Sakha (Yakutia) with the Project №17-2-009477 "Scientific and Educational Foundation as an instrument for young scientists to develop their professional competence and science popularization" 20171201015-2.*

### References

- Novikov D.K. Novikov P.D. Klinicheskaya immunologiya [Clinical immunology] uchebnoye posobiye [tutorial]. VG MU, 2006, pp. 1-392.
- Association of *cagA* and *vacA* Genotypes of *Helicobacter pylori* with gastric diseases in Estonia / H. Andreson, K. Lõivukene, T. Sillakivi [et al.] // J Clin Microbiol. – 2002. – 40. – P. 298-300.
- Association of *Helicobacter pylori cagA* Gene with Gastric Cancer and Peptic Ulcer in Saudi Patients / T. Saber, M.M. Ghonaim, A.R. Yousef [et al.] // J Microbiol Biotechnol. – 2015 Jul – 5(7) – P.146-53.
- Biofilm and *Helicobacter pylori*: From environment to human host / A. Garcia, M. J. Salas-Jara, C. Herrera [et al.] // World Journal of Gastroenterology. – 2014. – WJG. – 20(19). – P. 5632-5638.
- Blaser M.J. Ecology of *Helicobacter pylori* in the human stomach / Blaser M.J. // J Clin Invest. – 1997. – 100. – P. 759-762.
- Clinical relevance of *H. pylori cagA* and *vacA* gene polymorphisms / D. Basso, C.F. Zambon, D.P. Letley [et al.] // Gastroenterology. – 2008. – 135. – P. 91-99.
- Clinical Relevance of the *cagA*, *vacA*, and *iceA* Status of *H. pylori* / L.J. van Doorn, C. Figueiredo, R. Sanna [et al.] // Gastroenterology. – 1998. – 115(15). – P. 58-66.
- Clinical relevance of the *H. pylori* gene for blood-group antigen-binding adhesin / M. Gerhard, N. Lehn, N. Neumayer [et al.] // Proc Natl Acad Sci U S A. – 1999. – 96. – P. 12778-12783.
- Effective Methods of Nucleic Acids extraction for Analysis in Molecular Biology (review) / O.S. Antonova, N.A. Korneva, Yu. V. Belov [et al.] // Scientific Instrument Making. – 2010. – T. – 20. – № 1. – P. 3-9.
- Functional analysis of *iceA1*, a CATG-recognizing restriction endonuclease gene in *H. pylori* / Q. Xu, R. D. Morgan, R. J. Roberts [et al.] // Nucleic Acids Research. – 2002. – 30(17). – P. 3839-3847.
- Helicobacter pylori* genotypes among patients in a university hospital in Egypt: identifying the determinant of disease severity / F.A. Amer, R.H. El-Sokkary, M. Elahmady [et al.] // J. Microbiol. Infect. – 2013. – Dis. – 3. – P. 109-115.
- Helicobacter pylori* genotypes and expression of gastritis in erosive gastro-oesophageal reflux disease / A. Leodolter, K. Wolle, U. Peitz [et al.] // Scand J Gastroenterol. – 2003. – 38: 498-502.
- Helicobacter pylori* genotypes are associated with clinical outcome in Portuguese patients and show a high prevalence of infections with multiple strains / C. Figueiredo, L.J. van Doorn, C. Nogueira [et al.] // Scand J Gastroenterol. – 2001 Feb. – 36(2). – P. 128-135.
- Helicobacter pylori iceA*, clinical outcomes, and correlation with *cagA*: a meta-analysis / S. Shiota, M. Watada, M. Osamu [et al.] // PLoS ONE. – 2012. – 7(1):e30354.
- Helicobacter pylori* strain types and risk of gastric cancer: a case-control study / H. Enroth, W. Kraaz, L. Engstrand [et al.] // Cancer Epidemiol Biomarkers Prev. – 2000 Sep. – 9(9). – P. 981-985.
- Helicobacter pylori vacA*, *iceA* and *cagA* status and pattern of gastritis in patients with malignant and benign gastroduodenal disease / S. Miehlke, M. Schuppler, C. Frings [et al.] // Am J Gastroenterol. – 2001. – 96. – P. 1008-1013.
- Importance of *Helicobacter pylori oipA* in clinical presentation, gastric inflammation, and mucosal interleukin 8 production / Y. Yamaoka, S. Kikuchi, H.M. el-Zimaity [et al.] // Gastroenterology. – 2002 Aug. – 123(2). – P. 414-24.
- Infection with *Helicobacter pylori* strains possessing *cagA* is associated with an increased risk of developing adenocarcinoma of the stomach / M.J. Blaser, G.I. Perez-Perez, H. Kleanthous [et al.] // Cancer Res. – 1995. – May 15. – 55(10). – P. 2111-5.
- Jenks P.J. Clinical outcome after infection with *Helicobacter pylori* does not appear to be reliably predicted by the presence of any of the genes of the *cag* pathogenicity island / P.J. Jenks, F. Megraud, A. Labigne // Gut. – 1998. – 43. – P. 752-758.
- Kusters J.G. Pathogenesis of *Helicobacter pylori* Infection / J.G. Kusters, A.H.M. van Vliet, E.J. Kuipers // Clinical Microbiology Reviews. – 2006. – 19(3). – P. 449-490.
- Momenah A.M. *H. pylori cagA* and *iceA* genotypes status and risk of peptic ulcer in Saudi patients / A.M. Momenah, M.T. Tayeb // Saudi Med J. – 2007. – 28. – P. 382-385.
- Prevalence of *Helicobacter pylori vacA*, *cagA*, *iceA* and *oipA* genotypes in Tunisian patients / K.B. Mansour, C. Fendri, M. Zribi [et al.] // Ann. Clin. Microbiol. Antimicrob. – 2010. – 9. – P. 10-16.
- Risk for gastric cancer in people with *CagA* positive or *CagA* negative *Helicobacter pylori* infection / J. Parsonnet, G.D. Friedman, N. Orentreich [et al.] // Gut. – 1997. – 40(3). – P. 297-301.
- Rothenbacher D. *Helicobacter pylori* and gastric cancer / D. Rothenbacher, H. Brenner. // Gastroenterology. – 2004. – Volume 126. – Issue 7. – P. 1927.
- Suerbaum S. *H. pylori* infection / S. Suerbaum, P. Michetti. // N Engl. J. Med. – 2002. – 347. – P. 1175-1186.
- The EPIYA-ABCC motif pattern in *CagA* of *Helicobacter pylori* is associated with peptic ulcer and gastric cancer in Mexican population / F.O. Beltrán-Anaya, T.M. Poblete, A. Román-Román [et al.] // BMC Gastroenterology. – 2014. – 14:223.
- Tummuru M.K. Cloning and expression of a high-molecular-mass major antigen of *Helicobacter pylori*: evidence of linkage to cytotoxin production / M.K. Tummuru, T.L. Cover, M.J. Blaser // Infect Immun. – 1993 May. – 61(5). – P. 1799-809.
- Wroblewski L. E. *Helicobacter pylori* and Gastric Cancer: Factors That Modulate Disease Risk / L. E. Wroblewski, R. M. Peek, K. T Wilson // Clinical Microbiology Reviews. – 2010. – 23(4). – P. 713-739.

**The authors:**

1. GOTOVTSEV NYURGUN NAUMOVICH - Scientific researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakut Science Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 89141062015, e-mail: Donzcrew@mail.ru
2. BARASHKOV NIKOLAI ALEKSEEVICH - Candidate of biological sciences, Head of laboratory of Molecular genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81; E-mail: barashkov2004@mail.ru
3. BORISOVA TUYARA VALERIEVNA - student, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov", 677000, Yakutsk, Kulakovskiy st. 48. Phone: 89644290223, e-mail: borisovaty96@gmail.com
4. PAK MARIA VLADIMIROVNA - endoscopist of the endoscopic department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. e-mail: pakmv@mail.ru
5. ALEXEEVA MAVRA PAVLOVNA - endoscopist of the endoscopic department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4.
6. INNOKENTYEVA NATALYA NIKOLAEVNA - Post-graduate student, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov", 677010, Yakutsk, Oyunsky st. 27. Phone: 8-(4112) 36-30-46, e-mail: natalia\_inn@mail.ru
7. LOSKUTOVA KIUNNAI SAVVICHNA - Candidate of Medical Science, Head of the Pathoanatomical department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. e-mail: loskutovaks@mail.ru
8. PSHENNIKOVA VERA GENNADIEVNA - Scientific researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center for Complex Medical Problems", postgraduate student of NEFU. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81, e-mail: pshennikovavera@mail.ru
9. RAFAILOV ADUM MIKHAILOVICH - Candidate of Biological Sciences, Associate Professor, Department of Biology, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 48. Phone: 8-(4112) 49-68-42, e-mail: archinay@mail.ru
10. LEKHANOVA SARGYLANA NIKOLAEVNA - Candidate of Medical Science, Associate Professor, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov", 677010, Yakutsk, Oyunsky st. 27. Phone: 8-(4112) 36-30-46, e-mail: lehanovasn@mail.ru
11. FEDOROVA SARDANA ARKADIEVNA - Doctor of biological sciences, Head of the Research Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 46., e-mail: sardanaafedorova@mail.ru.

A.V. Solovyev, N.A. Barashkov, K.E. Savvinova, N.N. Gotovtsev, F.M. Teryutin, V.G. Pshennikova, G.P. Romanov, A.M. Rafailov, N.N. Sazonov, L.U. Dzhemileva, O.L. Posukh, E.K. Khusnutdinova, S.A. Fedorova

## THE ANALYSIS OF THE RESISTANCE OF HETEROZYGOUS CARRIERS OF THE C.-23+1G>A MUTATION IN *GJB2* GENE TO DIARRHEA

DOI 10.25789/YMJ.2018.63.04

**ABSTRACT**

The high carrier frequency of c.-23+1G>A mutation in the *GJB2* gene in Yakut population is might be explained not only by the factors of population dynamics (founder effect, genetic drift, small effective population size), but also can be due to the selective advantage of heterozygous mutations in the *GJB2* gene. Because the *GJB2* gene is expressed not only in the cochlea but also in other tissues, and in vitro studies conducted on cell cultures show that *GJB2*-mutant cells were more resistant to the infection of dysentery - *Shigella flexneri*. The **aim** of this study is the analysis of the resistance in heterozygous carriers of the c.-23+1G>A mutation in *GJB2* gene to diarrhea.

**Material and methods.** We examined 272 Yakut individuals, which was divided into two groups: the first group consisted from 238 individuals without c.-23+1G>A mutation, the second group consisted from 34 individuals with c.-23+1G>A mutation in heterozygous state. All respondents independently filled information about the number of cases of diarrhea in the last year, and indicated the most characteristic form of their stool.

**Results and Discussion.** In heterozygous carriers of the c.-23+1G>A mutation the cases of diarrhea in the last year were not registered in 22% of individuals, in individuals without mutation cases of diarrhea were not registered in 5% of individuals. According to the results of this study heterozygous carriers of the c.-23+1G>A mutation statistically significantly are less susceptible to diarrhea cases than individuals without this mutation. Thus, the obtained results can support the hypothesis about selective advantage of the *GJB2* gene mutant alleles carriers and partly explain the extremely high carrier frequency (10.3%) of the c.-23+1G>A mutation in the *GJB2* gene in Yakut population.

**Keywords:** *GJB2* gene, diarrhea, c.-23+1G>A mutation, heterozygous carriers.

**INTRODUCTION**

The results earlier studies in 6 population from Eastern Siberia (Yakuts, Dolgans, Evenks, Evens, Yukaghirs and Russians) show that carrier frequency

c.-23+1G>A mutation in the *GJB2* gene was one of the highest in the world (4.7%) and in the Yakut population was a local maximum of 11.7% [3]. Then on a larger sample of Yakuts populations

(n = 350), the extremely high incidence of heterozygous carriage was confirmed and amounted to 10.3%, which is comparable to the carrier frequency of the HbS allele (10%) associated with

sickle-cell anemia in Africa [6].

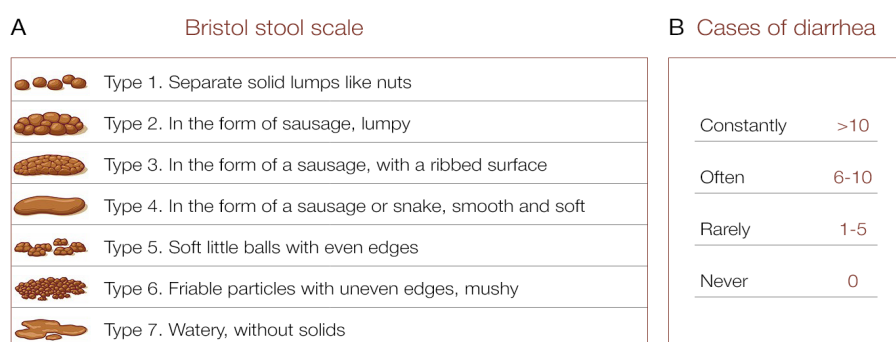
The high carrier frequency of the c.-23+1G>A mutation in Eastern Siberia may indicate a possible, but unknown, mechanism of the selective advantage of carriers of this mutation. Considering, that the *GJB2* gene is expressed not only in the tissues of the inner ear but also in the epidermal skin [7], and the formation storage center of the c.-23+1G>A mutation in Eastern Siberia probably explained by the increased survival rate of carriers of this mutation. Currently known that heterozygous carriers of p.Arg143Trp mutation in *GJB2* gene in some African country (Ghana), demonstrated a thicker layer of epidermis than in individuals without this mutation. The authors consider that epidermal thickening can protect against insect bites and limit cellular invasion of certain bacterial infections [8]. In 2009 was published the results studies of thicker layer of epidermis in heterozygous carriers of c.35delG mutation in Europe (Italy), where the same way confirmed data on a thicker layer of epidermis in individuals with c.35delG mutation in heterozygous state [5]. Moreover, *in vitro* studies conducted on cell cultures show that *GJB2*-mutant cells were more resistant to the infection of dysentery - *Shigella flexneri* [1], this data confirmed by the study of the frequency of cases of diarrhea in heterozygous carriers of c.35delG mutation in *GJB2* gene, where cases of diarrhea occurred significantly less than in individuals without this mutation [4].

The aim of this study is the analysis of the resistance in heterozygous carriers of the c.-23+1G>A mutation in *GJB2* gene to diarrhea.

#### Research materials and methods

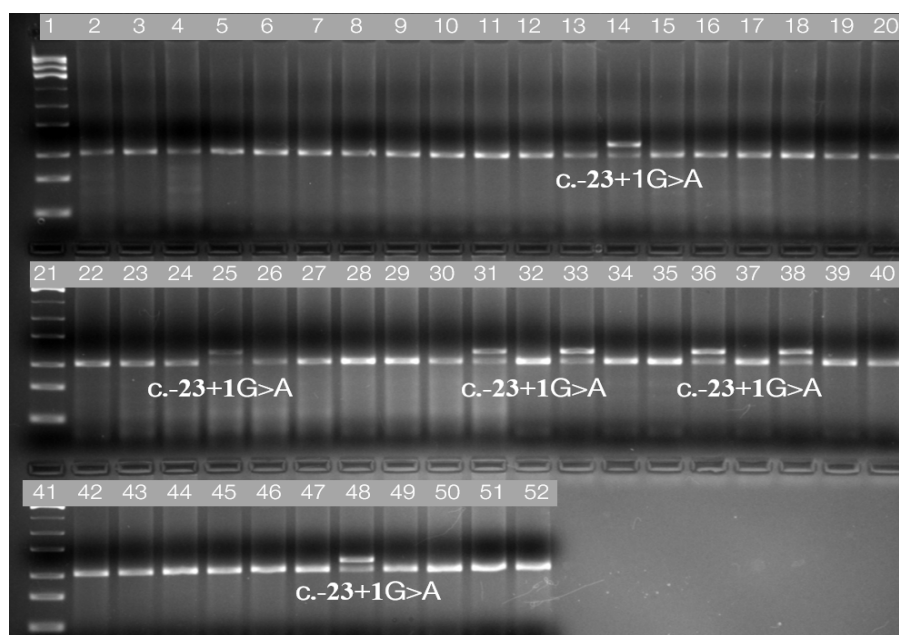
we examined 272 Yakut individuals, which was divided into two groups: the first group consisted from 238 individuals without c.-23+1G>A mutation, the second group consisted from 34 individuals with c.-23+1G>A mutation in heterozygous state. All respondents independently filled information about the number of cases of diarrhea in the last year (Fig. 1, B), and indicated the most characteristic form of their stool, according to the Bristol scale (Fig. 1, A). All respondents were healthy, there were no persons with Crohn's disease, cholecystitis and other diseases of the digestive tract. The mean age in respondents was  $20.3 \pm 2.04$  years, of them 62.4% of female and 37.5% of male.

The genomic DNA was extracted from lymphocytes of the peripheral blood. Amplification of the noncoding exon 1 and flanking intronic regions was performed using primers Ex1-F/Ex1-R



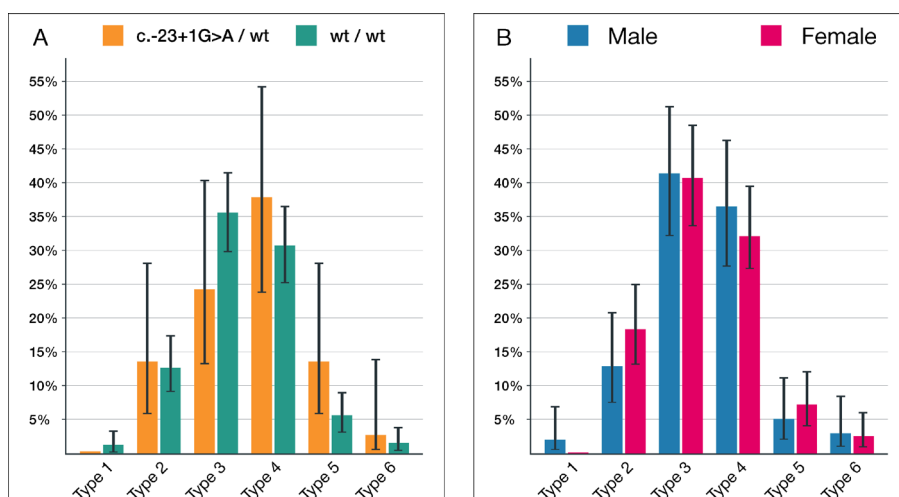
**Fig. 1.** The examples of the questionnaire in which the respondent independently chose one of the proposed options.

Note: A - Bristol stool scale. B - Number of diarrhea cases in the last year.



**Fig. 2.** Detection of *GJB2* mutation c.-23+1G>A in 4% agarose gel by PCR-restriction fragment length polymorphism analysis (*HphI*).

Note: Columns 1, 21, 41 - marker, columns 2-13, 15-24, 26-30, 32, 34, 35, 37, 39-47, 49-52 - individuals without mutation c.-23+1G>A, columns 14, 25, 31, 33, 36, 38, 48 - individuals with c.-23+1G>A mutation in heterozygous state.



**Fig. 3.** Distribution by stool type between *GJB2* genotypes and gender identity.

Note: A - The distribution stool type according *GJB2* genotypes, the yellow color is individuals with c.-23+1G>A mutation in heterozygous state, the green color is individuals without mutation. B - The distribution stool type according gender identity, the blue color is male, the pink color is female.



### The number of cases of diarrhea in the last year in heterozygous carriers and non-carriers of the mutation c.-23+1G>A in *GJB2* gene

The number of cases of diarrhea in the last year	All samples (n=272)				Female (n=170)				Male (n=102)			
	c.-23+1G>A/wt (n=34)	wt/wt (n=238)	$\chi^2$	p	c.-23+1G>A/wt (n=23)	wt/wt (n=147)	$\chi^2$	p	c.-23+1G>A/wt (n=11)	wt/wt (n=91)	$\chi^2$	p
<b>0 (never)</b>	<b>8 (23,5%)</b>	<b>12 (5,0%)</b>	<b>14,93</b>	<b>&lt;0,05</b>	<b>5 (21,7%)</b>	<b>7 (4,7%)</b>	<b>8,74</b>	<b>&lt;0,01</b>	<b>3 (27,2%)</b>	<b>5 (5,4%)</b>	<b>6,44</b>	<b>&lt;0,05</b>
1-5 (rarely)	14 (41,1%)	127 (53,3%)	1,77	>0,05	10 (43,4%)	83 (56,4%)	1,35	>0,05	4 (36,3%)	44 (48,3%)	0,57	>0,05
6-10 (often)	8 (23,5%)	56 (23,5%)	0,00	>0,05	5 (21,7%)	36 (24,4%)	0,08	>0,05	3 (27,2%)	20 (21,9%)	0,16	>0,05
>10 (constantly)	4 (11,7%)	43 (18,0%)	0,83	>0,05	3 (13,0%)	21 (14,2%)	0,03	>0,05	1 (9,0%)	22 (24,1%)	1,28	>0,05

Note: c.-23+1G>A/wt - individuals with c.-23+1G>A mutation in heterozygous state; wt/wt - individuals without c.-23+1G>A mutation; Differences were statistically significant when  $p < 0.05$ , is in bold font.

(5'-CCGGGAAGCTCTGAGGAC-3', 5'-GCAACCGCTCTGGGTCTC-3') with 10% Betaine (Sigma, USA) [9]. Detection of *GJB2* mutation c.-23+1G>A in 4% agarose gel by PCR-restriction fragment length polymorphism analysis with use of *HphI* endonucleases, according to manufacturer's specifications («New England Biolabs Inc», England).

Statistical analyzes were made on the MedStat, Biostat (McGraw-Hill, Inc. Version 3,03) software and Sampling (kindly provided by V. Macaulay and adapted by M. Metspalu). Differences between groups were tested with  $\chi^2$ -statistics. Differences were statistically significant when  $p < 0.05$ .

The local bioethics committee at the Yakut Science Centre of Complex Medical Problems (Yakutsk, Protocol 16, on April 16, 2009) approved this work and questionnaire.

#### Results and discussion

The results of respondents answers about most characteristic form of stool, show that more than 75% of the subjects surveyed had a normal stool form (type 3 – 39%, type 4 – 36%). A small number of respondents registered a tendency to constipation (type 1 – 1%, type 2 – 15%) or to diarrhea (type 5 – 7%, type 6 – 2%). After the distribution of the *GJB2* genotype, observed the same trend. A histogram of the distribution of stool types in individuals with c.-23+1G>A mutation in heterozygous state ( $n = 34$ ) and individuals without c.-23+1G>A mutation ( $n = 238$ ) is shown in Figure 3A. Distribution by gender and *GJB2*-genotype did not reveal statistically significant differences in stool types ( $p > 0.05$ ) (Fig. 3B).

In individuals with c.-23+1G>A mutation in heterozygous state ( $n = 34$ ), cases of diarrhea in the last year were not registered in 8 individuals out of 34, which was 23%. In individuals without c.-23+1G>A mutation, in the last year were not registered in 12 individuals out of 238, which was 5% (Table 1). We indicate significant differences when comparing these groups, were significantly less detected cases of diarrhea in individuals with c.-23+1G>A mutation in heterozygous state than in individuals without this mutation ( $p < 0.05$ ) in the last year. The distribution of the sample

by gender also revealed statistically significant differences among in the number of cases of diarrhea in male ( $p < 0.05$ ) and in female ( $p < 0.01$ ) (Table 1).

The results are consistent with previous studies in Italy, when to test hypothesis about that *GJB2* carriers might have an increased resistance to gastrointestinal infectious diseases, a cross-sectional study involving 203 subjects aged 19-65 years (63% women) was carried out. Subjects (170) were wildtype for the *GJB2* gene, whereas 33 carried one or more mutations variants. Significant effect for genotype was detected indicating lower diarrhea frequency for *GJB2* carriers. The present clinical results provide new insights on *GJB2* heterozygote advantage, further suggesting that it might consist in an increased resistance to gastrointestinal infections as already demonstrated by *in vitro* studies.

#### Conclusion

Thus, the results of this study support previous evidence that heterozygous carriers of *GJB2* gene mutations may have increased resistance to gastrointestinal diseases, in particular to diarrhea. The obtained results testify to the hypothesis of the selective advantage of heterozygous carriers of the mutant alleles of the *GJB2* gene, which can explain the extremely high frequency of heterozygous carriage (10.3%) c.-23+1G>A mutation in the Yakut population.

#### Acknowledgments

We thank all participants of this study.

The study was supported by the Ministry of Education and Science of the Russian Federation №6.1766.2017, Project NEFU M.K. Ammosov "Genetic features of the population of Yakutia: the structure of the gene pool, adaptation to cold, psychogenetic characteristics, the prevalence of certain hereditary and infectious diseases". Research of the YSC CMP "The study of the genetic structure and the load of hereditary diseases of the Sakha Republic (Yakutia) populations". Programs of Bioresource collections of the FASO Russia "Genome of Yakutia" (BRK: 0556-2017-0003) and Russian Foundation of Basic Research (#17-29-06016-ofi\_m, #18-54-16004\_NCNIL\_a, #18-015-00212\_A, #18-013-

00738\_A, #18-05-60035\_Arctica).

#### References

1. A deafness-associated mutant human connexin 26 improves the epithelial barrier in vitro / Y.K. Man, C. Trollove, D. Tattersall [et al.] // J. Membr. Biol. - 2007. - Vol. 218(1-3). - P. 29-37. DOI:10.1007/s00232-007-9025-0
2. Autosomal and uniparental portraits of the native populations of Sakha (Yakutia): implications for the peopling of Northeast Eurasia / S.A. Fedorova, M. Reidla, E. Metspalu [et al.] // BMC Evol. Biol. - 2013. - Vol. 13(127). DOI: 10.1186/1471-2148-13-127
3. Autosomal recessive deafness 1A (DFNB1A) in Yakut population isolate in Eastern Siberia: extensive accumulation of the splice site mutation IVS1+1G>A in *GJB2* gene as a result of founder effect / N.A. Barashkov, L.U. Dzhemileva, S.A. Fedorova [et al.] // Journal of Human Genetics. - 2011. - V. 56(8). - P.631-639.
4. Connexin 26 variant carriers have a better gastrointestinal health: is this the heterozygote advantage? / D. Vuckovic, B. Dalapiccola, A. Franze [et al.] // Eur. J. Hum. Genet. - 2015. - Vol. 23. - P. 563-564.
5. Does epidermal thickening explain *GJB2* high carrier frequency and heterozygote advantage? / P. D'Adamo, V.I. Guerci, A. Faretto [et al.] // Eur. J. Hum. Genet. - 2009. - Vol. 17(3). - P. 284-286. DOI:10.1038/ejhg.2008.225
6. Extremely High Carrier Frequency of the *GJB2* Splice Site IVS1+1G>A Mutation in Eastern Siberia is Comparable to the Carrier Frequency of the Sickle Cell Anemia in Africa / N.A. Barashkov, A.V. Solovyev, F.M. Teryutin [et al.] // J. Genet. Genome Res. 2014. 1:1.
7. Krawczak M. A role for overdominant selection in phenylketonuria? Evidence from molecular data / M. Krawczak, J. Zschocke // Hum. Mutat. - 2003. - Vol. 21(4). - P. 394-397. DOI:10.1002/humu.10205
8. Selection for deafness / C.G. Meyer, G.K. Amedofu, J.M. Brandner [et al.] // Nat. Med. - 2002. - Vol. 8(12). - P. 1332-1333. DOI:10.1038/nm1202-1332
9. Sirmaci A. The c. -23+1G>A mutation in the *GJB2* gene is prevalent and large deletions involving the *GJB6* gene are not present in the Turkish population / A. Sirmaci, D. Akcayoz-Duman, M. Tekin // J. Genet. - 2006. - Vol. 85(3). - P. 213-6.

### The authors

1. SOLOVYEV AISEN VASILIEVICH - Junior researcher, Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 46. Phone: 8-(914) 300-42-65, e-mail: nelloann@gmail.com
2. BARASHKOV NIKOLAI ALEKSEEVICH - Candidate of Biological Sciences, Head of laboratory of Molecular genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81; E-mail: barashkov2004@mail.ru
3. SAVVINOVA KIUNNIAI EGOROVNA - Student, Department of Biology, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 48. Phone: 8-(4112) 49-68-42, e-mail: nelloann@mail.ru
4. GOTOVTSEV NYURGUN NAUMOVICH - Scientific Researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakut Science Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(914)106-20-15, e-mail: donzcrew@mail.ru
5. TERUTIN FEDOR MIKHAILOVICH - Candidate of Medicine Sciences, Senior Researcher of Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 46., e-mail: rest26@mail.ru
6. PSHENNIKOVA VERA GENNADIEVNA - Scientific Researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center for Complex Medical Problems", postgraduate student of NEFU. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81, e-mail: pshennikovavera@mail.ru
7. ROMANOV GEORGII PROKOPIEVICH - Engineer, Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 46., e-mail: gpromanov@gmail.com
8. RAFAILOV ADUM MIKHAILOVICH - Candidate of Biological Sciences, Associate Professor of Department of Biology, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov ". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 48. Phone: 8-(4112) 49-68-42, e-mail: archinay@mail.ru
9. SAZONOV NIKOLAY NIKITICH - Doctor of Biological Sciences, Professor of Department of Biology, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov ". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 48. Phone: 8-(4112) 49-68-42, e-mail: saznikol@mail.ru
10. DZHEMILEVA LILYA USEINOVNA - Doctor of Medicine Sciences, Senior Researcher of Laboratory of Human Molecular Genetics, Federal State Budgetary Institute of Science Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences. Address: 450054, Yakutsk, Prospect of October 71. Phone: 8-(3472) 35-60-88, e-mail: dzhemilev@mail.ru
11. POSUKH OLGA LEONIDOVNA - Candidate of Biological Sciences, Senior Researcher of Laboratory of Human Molecular Genetics, The Federal Research Center Institute Of Cytology And Genetics The Siberian Branch Of The Russian Academy Of Sciences. Address: 630090, Novosibirsk, Lavrentiev avenue, 10. Phone: 8-(383)363-49-44, e-mail: posukh@bionet.nsc.ru
12. KHUSNUTDINOVA ELZA KAMILEVNA - Doctor of biological sciences, Professor, Director of the Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences. Address: 450054, Ufa, Prospect of October, 71. Phone: 8-(3472) 35-60-88, e-mail: elkh@anrb.ru
13. FEDOROVA SARDANA ARKADIEVNA - Doctor of biological sciences, Head of the Research Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovskiy st. 46., e-mail: sardanaafedorova@mail.ru

N.I. Pavlova, N.A. Solovyeva, A.T. Dyakonova, N.P. Filippova, V.V. Dodokhov, M.A. Varlamova, Kh.A. Kurtanov

## A STUDY OF THE POLYMORPHISM RS9939609 OF THE *FTO* GENE AND RS738409 OF THE *PNPLA3* GENE AS RISK FACTORS FOR THE DEVELOPMENT OF NAFLD IN THE YAKUT POPULATION OF TYPE 2 DIABETES MELLITUS

DOI 10.25789/YMJ.2018.63.05

### ABSTRACT

In order to study the frequency distribution of the polymorphism alleles rs9939609 of the *FTO* gene and polymorphism rs738409 of the *PNPLA3* gene among the Yakuts, 132 DNA samples of patients with type 2 diabetes and 70 DNA samples of healthy volunteers were tested.

The study of the frequency distribution of the polymorphism alleles rs9939609 of the *FTO* gene and polymorphism rs738409 of the *PNPLA3* gene in both groups showed no significant differences. Analysis of the frequency distribution of alleles and genotypes of the polymorphic variant of the *FTO* gene (rs9939609) in the group of patients with type 2 diabetes and healthy revealed a predominance of the T allele and a homozygous genotype of TT, except for a group of practically healthy men, which despite the prevalence of the T allele was characterized by the highest level of the heterozygous genotype AT. When analyzing the frequency distribution of the alleles and genotypes of the polymorphic version of the *PNPLA3* gene (rs738409), the allele G and the homozygous genotype GG prevailed in both groups. In the men and both groups studied, the G allele significantly prevailed over the C allele ( $p < 0.05$ ).

**Keywords:** *FTO* gene, adiponadine gene, type 2 diabetes mellitus, NAFLD, overweight, Yakuts.

### Introduction

Currently, obesity is an actual problem, which is associated with its progressive

spread and the severity of complications, which often cause the death of patients at a young age. To date, according to the

World Health Organization in the world - 39% of adults are overweight, and 13% are obese. In Russia, among the able-



bodied population, 25% are overweight and 30% obese [4].

Increased consumption of food, with the advantage of fats and carbohydrates, leads to the accumulation of excess weight and a violation of the natural physiological transformation of energy. Metabolic disorders in obese people with overeating lead to a relative insufficiency of insulin. As a result, type 2 diabetes is formed, which further exacerbates obesity. Genetic predisposition is one of the important factors in the pathogenesis of obesity [2]. It is estimated that 40-70% of the dispersion of the body mass index (BMI) can be attributed to direct or indirect genetic factors [8].

The full-genomic search for associations (GWAS) showed that the single nucleotide polymorphism (SNP) rs9939609, located in the first intron of the *FTO* gene (Fat Mass and Obesity Associated Gene), associated with a set of fat mass was significantly associated with obesity in various ethnic populations in both children and in adults [11]. The *FTO* gene encodes one of the lipolysis regulators, is involved in the control of adipocyte differentiation, energy homeostasis, leptin-independent appetite control. According to the results of previous studies, allele A of the *FTO* gene is associated with reduced lipolysis, a violation of appetite control, a lack of satiety after adequate food intake. The phenotypic manifestation of the *FTO* gene allele A is overweight, obesity due to overeating, which in turn is one of the common risk factors for the development of non-alcoholic fatty liver disease (NAFLD). Epidemiological data indicate a frequent combination of type 2 diabetes and NAZHBП characterized by the accumulation of lipids both in the hepatocytes themselves and in the intercellular space [1]. Patients with type 2 diabetes are characterized by insulin resistance, often obese, have dyslipidemia and increased activity of hepatic enzymes, they tend to accumulate fat in the liver regardless of BMI values, which causes a higher risk of developing severe liver pathology compared to patients not suffering from CD [7]. NAFLD is considered as an important medical and social problem because it includes a range of clinical and morphological concepts: liver steatosis, non-alcoholic steatohepatitis (NASH), which leads to the development of fibrosis and cirrhosis of the liver.

Recently, there have been studies that prove hereditary mechanisms for the development of NAFLD. Genetic risk factors for the development and progression of NAFLD have been found.

The involvement of the *PNPLA3* gene in the formation of cirrhosis and primary liver cancer has been proven. Polymorphism of this gene is a predictor of the progressing course of NAFLD and the main risk factor for the transformation of NAFLD into cirrhosis. Molecular genetic studies have shown that the *PNPLA3* gene located on the long arm of chromosome 22q13.31 is expressed in the membranes of hepatocytes and is responsible for intrahepatic lipid metabolism by coding the synthesis of adiponuclein, a protein regulating the activity of triacylglycerol lipase in adipocytes [10]. The most significant polymorphism in the *PNPLA3* gene is I148M (rs738409). Polymorphism I148M is the replacement of cytosine by guanine, which leads to a change in the amino acid isoleucine to methionine at position 148. This replacement causes a violation of the mechanism of lipid metabolism in the liver.

The purpose of our study was to study the frequency distribution of polymorphism alleles rs9939609 of the *FTO* gene and the polymorphism rs738409 of the *PNPLA3* gene among people suffering from type 2 diabetes of the Yakut population.

#### Materials and methods of research

The experimental part of the genotyping of polymorphism rs9939609 of the *FTO* gene and the polymorphism rs738409 of the *PNPLA3* gene was carried out in the laboratory of hereditary pathology of the department of molecular genetics of the Yakutsk Scientific Center of Complex Medical Problems. DNA samples from the YMC KMB biomaterial collection using the UМУ "Genome of Yakutia" (registration No. USU\_507512) were used for the study. Tested 132 DNA samples of patients diagnosed with type 2 diabetes, 91 of which belonged to women, 41 to men. The average age of participants in the study was  $58.8 \pm 0.43$  years. As a comparison group, a sample was collected with normal BMI and no diabetes mellitus ( $n = 70$ ) from 22 men and 48 women, whose mean age was  $27.2 \pm 0.47$  years. All participants in the study on ethnicity were Yakuts and lived on the territory of the RS (Y). The study

was conducted with the written consent of the participants.

The criteria for inclusion in the study were: the absence of liver damage by chronic viral hepatitis; all subjects were excluded: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hereditary hemochromatosis, Wilson-Konovalov's disease, and lack of alcohol abuse ( $> 30$  g / l).

For PCR and RFLP analysis, genomic DNA samples were isolated from the whole blood of patients by a standard phenol-chloroform method. Single nucleotide polymorphisms (SNP) were determined by polymerase chain reaction (PCR).

To carry out PCR, specific primers were used by Biotech-Industry Ltd., Moscow:

rs9939609 F: 5'-TGGGCCTGAAGTCCGAGGGT-3'  
rs9939609 R: 5'-CCGACACCACTGCCCTGCAG-3';  
rs738409 F: 5'-AACTGGCTCTTGAATGAAATAGGATTCAGA-3'  
rs738409 R: 5'-AGAGTAACAGAGACTATCCAAGTGCAGTAC-3'

After PCR, the amplification of rs9939609 of the *FTO* gene was subjected to restriction with the use of *ZmI* endonuclease (SibEnzyme LLC, Novosibirsk) for 3 hours at  $37^\circ\text{C}$ . The detection of RFLP products was carried out by horizontal electrophoresis in a 4% agarose gel plate with the addition of ethidium bromide-specific intercalating fluorescent DNA (RNA) dye-using a standard tris-acetate buffer at a field strength of  $\sim 20$  V / cm for 30 minutes (figure - 1).

The amplification of rs738409 of the *PNPLA3* gene was subjected to restriction with the use of endonuclease *BstF5I* (SibEnzyme LLC, Novosibirsk) for 3 hours at  $65^\circ\text{C}$ . The detection of RFLP products was carried out by horizontal electrophoresis in a 4% agarose gel plate with the addition of ethidium bromide-specific intercalating fluorescent DNA (RNA) dye-using a standard tris-acetate buffer at a field strength of  $\sim 20$  V / cm for 30 minutes (figure - 2).

Interpretation of the results of

Table 1

PCR conditions			
Gene	Amplificate	Length of restriction fragments	PCR conditions
<i>FTO</i>	182 b.p.	AA – 154, 28 AT – 154, 28, 182 TT – 182	1. $95^\circ\text{C} - 4$ min 2. ( $94^\circ\text{C} - 30$ sec; $58^\circ\text{C} - 30$ sec; $72^\circ\text{C} - 1$ min)*35 3. $72^\circ\text{C} - 10$ min
<i>PNPLA3</i>	333 b.p.	CC: 200 и 133 b.p. GC: 333, 200 и 133 b.p. GG: 333 b.p	1. $95^\circ\text{C} - 5$ min 2. ( $94^\circ\text{C} - 30$ sec; $66^\circ\text{C} - 30$ sec; $72^\circ\text{C} - 40$ sec)*37 3. $72^\circ\text{C} - 5$ min

genotyping was performed on the basis of different patterns of bands: CC genotype 200 and 133 bp, CG genotype - 333, 200 and 133 bp, GG genotype -333 bp.

### Results and discussion:

Analysis of the frequency distribution of alleles and genotypes of the polymorphic version of the FTO gene (rs9939609) in the group of patients with type 2 diabetes and healthy did not reveal significant differences, in both groups allele T ( $p = 0.252$ ) and homozygous genotype TT ( $p = 0.820$ ) prevailed, practically healthy men, which despite the predominance of the T allele ( $p = 0.08$ ) was characterized by the highest level of heterozygous AT genotype ( $H_o = 0.546$ ).

The results of the analysis of the frequency distribution of alleles and genotypes of polymorphism rs9939609 of the FTO gene are presented in Table 2.

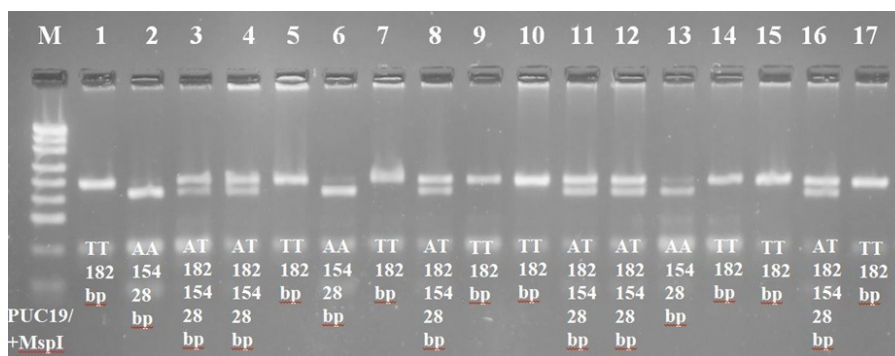
The analysis of BMI indices, characterizing the correspondence of the body weight of a person and its growth, showed that among patients with type 2 diabetes ( $n = 122$ ), overweight ( $n = 33$ ; 27%) and obesity prevailed ( $n = 81$ , 66.4 %). Compliance with normal BMI was noted in only 8 patients (6.6%).

The results of analysis of the frequency distribution of alleles and genotypes of polymorphism of the FTO gene (rs9939609) depending on the BMI parameters are presented in Table 3.

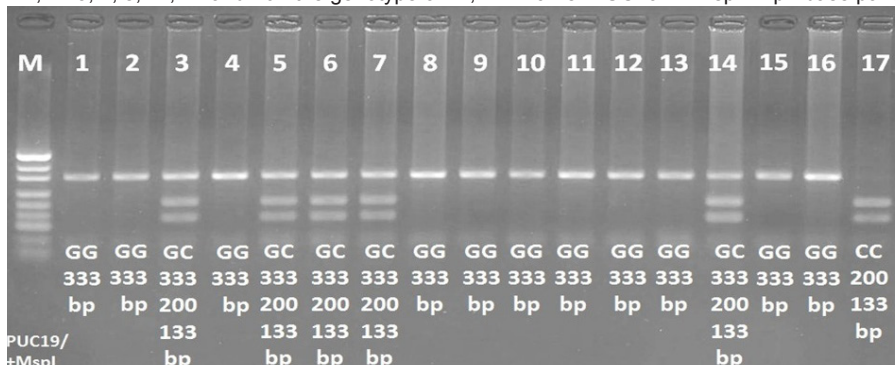
Table 3 shows that, regardless of gender, among patients with type 2 diabetes having an overweight and obesity, the allele T ( $p = 0.199$ ) prevailed. Analysis of the frequency distribution of genotypes showed the following, in the overweight group both in women and men, the heterozygous genotype of AT prevailed ( $p = 0.754$ ), whereas in obese patients the homozygous genotype of TT ( $p = 0.844$ ) was more prevalent. In studies Shilina NM. (2017), in contrast, notes in women 27 years and older the connection with obesity in carriers of genotypes of AT + AA in comparison with carriers of the genotype of TT [5].

Analysis of the allele and genotype distribution of the polymorphic variant of the PNPLA3 gene (rs738409) in the group of patients with type 2 diabetes and healthy did not reveal significant differences, in both groups allele G ( $p < 0.001$ ) and homozygous genotype GG prevailed (Table 4). In the men and both groups studied, the G allele significantly prevailed over the C allele ( $p < 0.05$ ).

According to the data of the “1000 genomes” project, the frequency of distribution of the allele G of the PNPLA3 gene (rs738409) is characterized by heterogeneity. When comparing



**Fig. 1** Electrophoregram of the amplification product of the *FTO* gene site in a 4% agarose gel. Note. Tracks No. 1, 5, 7, 9, 10, 14, 15 and 17 are the genotype of TT; № 2, 6 and 13 - genotype AA; № 3, 4, 8, 11, 12 and 16 - the genotype of AT; M - marker PUC19 / + Msp I. Bp - base pairs.



**Fig. 2** Electrophoregram of the amplification product of the *PNPLA3* gene site in a 4% agarose gel.

Note. Tracks № 17 - genotype CC, № 3, 5, 6, 7, 14 - genotype GC, № 1, 2, 4, 8, 9, 10, 11, 12, 13, 15, 16 - genotype of GG. M - marker PUC19 / + Msp I. bp - base pairs.

### Table 2

### Frequency distribution of alleles and genotypes of polymorphism rs9939609 of the *FTO* gene in the group of patients with type 2 diabetes and healthy individuals

	n		Genotype, %			Allele		$H_o$	$H_e$	$\chi^2$	p
			TT	AT	AA	T	A				
Patients with diabetes 2											
Wo-men	91	H	52,8	42,9	4,4	0,742	0,258	0,429	0,383	1,282	0,258
		O	55,1	38,3	6,7						
Men's	41	H	48,8	39,0	12,2	0,683	0,317	0,390	0,433	0,401	0,527
			46,6	43,3	10,1						
Healthy											
Wo-men	48	H	58,3	37,5	4,2	0,771	0,229	0,375	0,353	0,180	0,67
		O	59,4	35,3	5,3						
Men's	22	H	45,5	54,6	0,0	0,727	0,273	0,546	0,397	3,09	0,08
			52,9	39,7	7,4						

Note: n-quantity; O - observable; E is the expected; X2 is the chi-square; Ho -observed heterozygosity; He -expected heterozygosity.

### Table 3

### Frequency distribution of alleles and genotypes of the *FTO* gene (rs9939609) depending on BMI and sex in the group of patients with type 2 diabetes

ИМТ		Genotype, %			Allele		$H_o$	$H_e$	$\chi^2$	p
		TT	AT	AA	T	A				
Women (n=79)										
Overweight (BMI ≥ 25 кг/м2)	O	36,8	52,6	10,5	0,632	0,368	0,526	0,465	0,326	0,568
	E	39,9	46,5	13,6						
Obesity (BMI ≥ 30 кг/м2.)	O	51,7	45,0	3,3	0,742	0,258	0,450	0,383	1,824	0,177
	E	55,0	38,3	6,7						
Men's (n=35)										
Overweight (BMI ≥ 25 кг/м2)	O	28,6	64,3	7,1	0,607	0,393	0,643	0,477	1,691	0,193
	E	36,9	47,7	15,4						
Obesity (BMI ≥ 30 кг/м2 )	O	52,4	33,3	14,3	0,690	0,310	0,333	0,427	1,018	0,313
	E	47,7	42,7	9,6						

Table 4

Distribution of frequencies of alleles and genotypes of polymorphism rs738409 of *PNPLA3* gene in the group of patients with type 2 diabetes and healthy individuals

	n		Genotype, %			Allele		$H_o$	$H_e$	$X^2$	p
			CC	CG	GG	C	G				
Patients with diabetes 2											
Women	91	O	8,8	33	58,2	0,253	0,747	0,33	0,378	1,473	0,225
		E	6,4	37,8	55,8						
Men's	41	O	19,5	22	58,5	0,305	0,695	0,22	0,424	9,529	0,002
		E	9,3	42,4	48,3						
Healthy											
Women	49	O	4,1	38,8	57,1	0,235	0,765	0,388	0,359	0,309	0,578
		E	5,5	35,9	58,6						
Men's	24	O	25,0	16,7	58,3	0,333	0,667	0,167	0,444	9,375	0,002
		E	11,1	44,4	44,4						

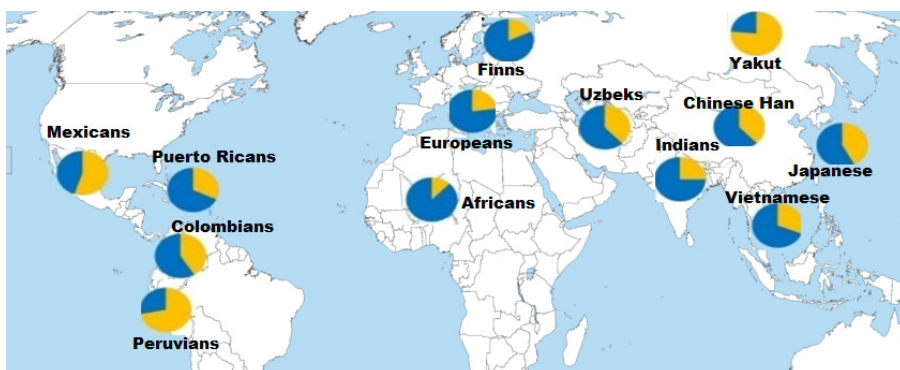


Fig. 3 Frequency of polymorphism rs738409 of the *PNPLA3* gene in different populations.

frequencies among healthy and patients with type 2 diabetes in different populations, the prevalence of G allele frequency in the Yakut population was established (Fig. 3).

In their studies of the Japanese population of patients with type 2 diabetes, M. Ueyama, N. Nishida (2015) and Kan H. et al. (2016), noted the high frequency of the G allele (48-48.8%) [12, 13]. In studies among the European population of patients with type 2 diabetes, Jean-Michel Petit et al. (2010), the allele frequency G was - 29.6% [11]. According to Cox A.J. (2011), the lowest frequency of occurrence of the G allele (13.7%) at the GG genotype frequency was 1.5%, had a population of African American patients with type 2 diabetes [6].

According to the researchers, the pathogenesis of NAFLD is played by the theory of two-stage lesion. At the first stage, against the background of visceral obesity and insulin resistance (IR) lipolysis increases, the concentration of free fatty acids (FFA) in the blood serum increases due to an increase in synthesis and inhibition of their oxidation in mitochondria with accumulation of triglycerides and a decrease in the excretion of fats by liver cells. So, there are conditions for the formation of fatty liver dystrophy - steatosis. At the same time, fatty hepatosis, regardless of the

cause, can contribute to high insulin levels due to reduced insulin clearance [3]. Despite the active study of the problem of NAFLD, absolute algorithms for the treatment of this disease have not been developed.

#### Conclusion

Today, the problem of NAFLD is very relevant and increasingly attracts the attention of researchers and practitioners.

The detection of the polymorphism markers of the *PNPLA3* (rs738409) and *FTO* (rs9939609) genes associated with the development of NAFLD will allow the formation of risk groups with the goal of carrying out preventive and therapeutic activities.

Analysis of the frequency distribution of alleles and genotypes of the polymorphic version of the *FTO* gene (rs9939609) in the group of patients with type 2 diabetes and healthy did not reveal significant differences, in both groups allele T ( $p = 0.252$ ) and homozygous genotype TT ( $p = 0.820$ ) prevailed, practically healthy men, which despite the predominance of the T allele ( $p = 0.08$ ) was characterized by the highest level of heterozygous AT genotype ( $H_o = 0.546$ ).

When analyzing the frequency distribution of alleles and genotypes of the polymorphic version of the *PNPLA3* gene (rs738409), there were no significant differences in the group of patients with type 2 diabetes and healthy,

in both groups allele G ( $p < 0.001$ ) and homozygous genotype GG prevailed. In the men and both groups studied, the G allele significantly prevailed over the C allele ( $p < 0.05$ ).

Timely detection of risk factors for NAFLD, maintenance of appropriate preventive work, adequate pharmacotherapy will reduce insulin resistance, obesity, including abdominal, incidence of diabetes, arterial hypertension and atherosclerosis leading to coronary heart disease, and reduce mortality from cirrhosis and increase life expectancy of the population.

#### References

1. Birjukova E.V. Rodionova Saharnyy diabet 2-go tipa i nealkogol'naja zhirovaya bolezni' pecheni – bolezni sovremennosti [Diabetes mellitus type 2 and non-alcoholic fatty liver disease – diseases of the present] Medicinskij al'manah [Medical almanac]. 2017, № 6 (51), P.130-135.
2. Dedov I.I. Shestakova M.V. Vikulova O.K. Epidemiologiya sakharnogo diabeta v Rossiyskoy Federatsii: kliniko-statisticheskiy otchet po dannym Federalnogo registra sakharnogo diabeta [Epidemiology of diabetes mellitus in the Russian Federation: clinical and statistical report on the Federal Register of Diabetes Mellitus] Sakhar-nyy diabet [Diabetes]. 2017, №1, Vol. 20, P.13-41. doi: 10.14341/DM8664
3. Pashenceva A.V. Verbovoj A.F. Sharonova L.A. Insulinorezistentnost' v terapeuticheskoy klinike [Insulin resistance in the therapeutic clinic] Ozhirenie i metabolism [Obesity and metabolism]. 2017, № 14(2), P. 9–17.
4. Razina A.O. Achkasov E.E. Runenko S.D. Ozhireniye: sovremennyy vzglyad na problem [Obesity: a modern view of the problem] Ozhireniye i metabolism [Obesity and metabolism]. 2016, № 13(1), P. 3-8. doi: 10.14341/OMET201613-8
5. Shilina N.M. [et al.] Fenotipicheskiye proyavleniya polimorfizma rs 9939609 gena FTO v diade mat-ditya. [Phenotypic manifestations of polymorphism rs 9939609 of the FTO gene in a mother-child dyad] Voprosy detskoy diyetologii [Questions of children's dietology]. 2017, № 15(4), P. 14–20. doi: 10.20953/1727-5784-2017-4-14-20
6. Association of *PNPLA3* SNP rs738409 with liver density in africanamericans with type 2 diabetes mellitus / A.J. Cox, MR. Wing, JJ. Carr, [et al.] // Diabetes & metabolism. – 2011. – Vol. 37, №5. – P.452-455. doi:10.1016/j.diabet.2011.05.001.
7. Costs and consequence associated with newer medications for glycemic control in type 2 diabetes / A. Sinha, M. Ragan, T. Hoerger [et al.] // Diabetes Care. – 2010. – Vol. 33. – P. 695–700.



8. The genetics of obesity: practical implications. / J. Hebebrand [et al.] // Int J Obes Relat Metab Disord – 2001. - № 25. - P. 10–17.
  9. Kan H. Influence of the rs738409 polymorphism in patatin-like phospholipase 3 on the treatment efficacy of non-alcoholic fatty liver disease with type 2 diabetes mellitus / H. Kan, H. Hyogo, H. Ochi, // Hepatol Res.– 2016 - Vol.46– E146–E153. doi: 10.1111/hepr.12552.
  10. PNPLA3 I148M polymorphism and progressive liver disease / P. Dongiovanni [et al.] // World Journal of Gastroenterology. – 2013. – Vol. 19. – №41. – P. 6969-6978.
  11. Association of FTO rs9939609 SNP with Obesity and Obesity- Associated Phenotypes in a North Indian Population / J. Prakash [et al.] // Oman Medical Journal – 2016. - Vol. 31, № 2. – P. 99-106
  12. Specifically PNPLA3-Mediated Accumulation of Liver Fat in Obese Patients with Type 2 Diabetes / J-M. Petit, B. Guieu, D. Masson, L. [et al.] // The Journal of Clinical Endocrinology & Metabolism. – 2010 - Vol. 95.– №12.– P.E430–E436 <https://doi.org/10.1210/jc.2010-0814>
  13. The impact of PNPLA3 and JAZF1 on hepatocellular carcinoma in non-viral hepatitis patients with type 2 diabetes mellitus/ M. Ueyama, N. Nishida, M. Korenaga [et al.] // J Gastroenterol. –2015.– Vol.51(4).– 370-9. doi: 10.1007/s00535-015-1116-6. Epub 2015 Sep 3.
- Information about authors:**
1. Pavlova Nadezhda Ivanovna – PhD (Biology), leading researcher, head of the laboratory of hereditary pathology; doctor laboratory assistant of the Scientific Clinical Diagnostic Laboratory of the FGBOU VO Yakutsk State Agricultural Academy, e-mail: [solnishko\\_84@inbox.ru](mailto:solnishko_84@inbox.ru);
  2. Soloveva Natalia Alekseevna – PhD, senior researcher, laboratory of population genetics; e-mail: [sonata608@yandex.ru](mailto:sonata608@yandex.ru);
  3. Dyakonova Alexandra Timofeevna - Jr. researcher, laboratory of hereditary pathology, e-mail: [dyakonovaa@bk.ru](mailto:dyakonovaa@bk.ru);
  4. Filippova Natalia Pavlovna - PhD (Biology), associate professor, scientific researcher, laboratory of population genetics, e-mail: [inniah1970@list.ru](mailto:inniah1970@list.ru);
  5. Dodokhov Vladimir Vladimirovich - PhD (Biology), senior researcher, laboratory of hereditary pathology; Senior Lecturer of the Department of TOS ATF FGBOU VO Yakutsk State Agricultural Academy; (phone: 89248760599; e-mail: [dodoxv@mail.ru](mailto:dodoxv@mail.ru));
  6. Varlamova Marina Alekseevna - researcher, laboratory of hereditary pathology e-mail: [varlamova.m@yandex.ru](mailto:varlamova.m@yandex.ru);
  7. Kurtanov Khariton Alekseevich - PhD, Chief Scientific Officer - Head of the Department of Molecular Genetics, e-mail: [khariton\\_kurtanov@mail.ru](mailto:khariton_kurtanov@mail.ru).

## S.V. Tishkovets, Ya.G. Razuvaeva, A.G. Mondodoev, A.A. Toropova

# ANTI-INFLAMMATORY ACTIVITY OF THE COMPLEX HERBAL REMEDY

DOI 10.25789/YMJ.2018.63.06

### ABSTRACT

During experiments on white rats of the Wistar line, anti-inflammatory activity of the extract of dry complex herbal remedy (*Juglans regia* L. Rich ex Kimth., *Corylus avellana* L., *Agrimonia eupatoria* L., *Bidens tripartita* L., *Xanthium strumarium* L., *Urtica dioica* L. *Lemna minor* L., *Cichorium intybus* L., *Onopordum acanthium* L.) was examined on models of acute exudative (carrageenan and formalin), chronic alternative and proliferative inflammation. It is found that phytoextract in doses of 100-300 mg/kg has antiexudative activity, reducing the exudation caused by phlogogenic agents. The tested extract has an anti-alterative effect, limiting the alteration of tissues with acetic acid and enhancing regenerative processes.

**Keywords:** complex remedy (*Juglans regia* L. Rich ex Kimth., *Corylus avellana* L., *Agrimonia eupatoria* L., *Bidens tripartita* L., *Xanthium strumarium* L., *Urtica dioica* L. *Lemna minor* L., *Cichorium intybus* L., *Onopordum acanthium* L.), anti-inflammatory activity.

### Introduction

Currently, hypothyroidism is one of the most common diseases of the endocrine system. According to epidemiological studies, the incidence of this disease in the population is about 2%; while in the group of women over 74 years old it reaches 21% [3]. Patients with hypothyroidism, against the decrease in the level of basal metabolism and anabolic processes in general, as well as the activation of free radical oxidation and the weakening of the body's antioxidant defense, show a slowdown in the regeneration of damaged tissues and recovery processes. Posttraumatic intoxication in turn aggravates disorders of thyroid regulation of intracellular metabolism [11].

To treat hypothyroidism, thyroid hormone preparations, drugs containing iodine, and preparations that affect the immune system (immunosuppressors and immunomodulators), as well as efferent therapy are used. Drug treatment methods for hypothyroidism, which are part of the scope of evidence-based

medicine, allow for achieving clinical results, while not always achieving the proper life quality for a particular patient, require compulsory medical supervision and often have side effects [5].

Of particular interest in the treatment of hypothyroidism are herbal remedies that, due to the synergism of biologically active substances, have systemic exposure on the body: normalize the level of hormones, manifest antioxidant, anti-inflammatory, psychotropic, cardioprotective and other actions, and thus contribute to delaying the administration of hormone replacement therapy or reducing the dose of hormones during its administration [4]. In the light of the development of personalized medicine, a complex herbal remedy consisting of: *Juglans regia* L. Rich ex Kimth., *Corylus avellana* L., *Agrimonia eupatoria* Ldb, *Bidens tripartita* L., *Xanthium strumarium* L., *Urtica dioica* L. *Lemna* L., *Onopordum acanthium* L is of interest. Earlier in animal experiments, it was found that this complex remedy exerts a pronounced pharmacotherapeutic

efficacy in experimental hypothyroidism, increasing the synthesis of thyroid hormones, peripheral conversion of fT4 to fT3, normalizing the cardiovascular parameters, increasing animal resistance to hypoxia [14].

The **study objective** was to evaluate the anti-inflammatory activity of the dry complex herbal remedy extract with thyroid-stimulating activity.

### Study materials and methods

the experiments were performed on Wistar rats of both sexes with an initial mass of 180-190 g. The animals were kept in standard vivarium conditions with the same care and nutrition, light and temperature conditions in accordance with Order No. 708H of the Ministry of Health of the Russian Federation of August 23, 2010 "On Approval of Laboratory Practice Regulations". Experimental studies were carried out in accordance with the "Work code for using experimental animals" (Appendix to the Order of the Ministry of Health of the USSR No. 755 of 12.08.77) and "Rules adopted in the European Convention for the Protection

of Vertebrates" (Strasbourg, 1986). Experimental studies are coordinated with the ethics committee of the Institute of General and Experimental Biology of the SB RAS (Protocol № 6 12.10.2016).

Animals were divided into 5 groups: one control and four experimental groups. Each group consisted of 8 animals. Animals of I - III experimental groups received an aqueous solution (10 ml / kg) of an extract of a dry complex herbal remedy, respectively (hereinafter phytoextract) in doses of 100, 200 and 300 mg / kg, animals of the IV group received referential preparation caleflon ("Vifitekh" Russia) in a dose of 100 mg / kg, the animals of the control group received water purified in an equivalent volume. The anti-inflammatory activity of the phytoextract was assessed in the setting of modeling the aseptic inflammation according to the Guidelines [9].

The antiexudative effect of the tested remedy was studied on two models: formalin and carrageenan edema [9]. In the first series of experiments, the tested phytoextract and referential preparation were administered 3 hours prior to subplantation into the hindlimb of the animal with a 3% formalin aqueous solution, and also at 5 and 18 hours after initiating the inflammation. In the second series of experiments, phytoextract and caleflon were administered to the animals of the test groups 1 hour before the administration of the phlogogenic agent (0.1 ml of a 1% aqueous solution of carrageenan). The severity of formalin and carrageenan edema was assessed 24 and 3 hours after initiating the inflammatory process by the oncometric method, according to the difference between the volume of the healthy and edematous legs. The antiexudative activity of the remedy tested was judged by the degree of suppression of the edema:

$\% \text{ edema suppression } s_{\text{degree}} = \Delta V_k - \Delta V_o / \Delta V_k$ ;

where:  $\Delta V_k$  is the difference in the volume of the legs with edema and without edema in the animals of the control group;  $\Delta V_o$  is the difference in mass of the legs with edema and without edema in the animals of the experimental group.

The alternative phase of the inflammatory reaction in white rats was reproduced by subcutaneous injection of 0.5 ml of a 9% solution of acetic acid into the back region [9]. The remedy tested and the reference preparation were administered 1 hour prior to the administration of the acetic acid solution and then daily once a day for 21 days. The antiallergic effect was assessed by the planimetric method according to the development degree of a necrosis and tissue regeneration on the 7th, 14th, 21st

and 28th days of the experiment.

To assess the proliferative activity of rats under ether anesthesia, a sterile cotton pad weighing 25 mg was implanted in the back region under aseptic conditions, after which the wound was closed layer-by-layer [9]. Phytoextract and caleflon were administered once a day for 7 days. The proliferative reaction was assessed by the difference between the weight of the dried granuloma and the initial mass of the cotton pad. The effect of the remedy tested on the proliferative component of chronic inflammation was expressed as a percentage of control.

The experimental material was processed using the methods of variation statistics with software like Microsoft Excel 2003 and Statistica 10. The study results are presented as the mean value (M) and the mean error (m). The reliability of the differences found between the mean values (M) of the groups was evaluated using the Student's t-test. Differences were considered statistically significant at  $p < 0.05$ .

### Results and discussion

The results of the study showed that phytoextract and caleflon at a dose of 100 mg / kg statistically significantly inhibited the leg edema of white rats by 24% compared to the control (Table 1). The most pronounced antiexudative effect of the test extract was in doses of 200 and 300 mg / kg: edema volume was 32% lower than in control group. In

the model of carrageenan edema, the tested phytoextract reduced the degree of edema by 24-31% compared to the control (Table 1). The most pronounced antiexudative effect of the phytoextract was in a dose of 200 mg / kg.

As the data presented in Table 2 show, the extract of a complex herbal remedy reduces the alteration of tissues and enhances regenerative processes in the inflammatory focus (Table 2). For example, on the 7th day of observation, administration of phytoextract to the animals at a dose of 100 mg / kg reduced the wound injury area by 27% compared to that of the control group animals, whereas the use of phytoextract in doses of 200 and 300 mg / kg reduced this index by only 21%. At this starting from 14 days the most pronounced anti-alterative effect, exceeding one of the reference preparation (caleflon), was shown by the phytoextract in doses of 200 and 300 mg / kg. Thus, in the animals of the first and third experimental groups, on the 14th day of observation, the area of the wound defect was lower by 13%, 26% and 25%, on the 21th day by 35%, 29% and 50%, and on 28 day by 30%, 36% and 51% respectively. Against the administration of caleflon to animals, the necrosis area was lower than that of control animals by 25%, 20%, 40% and 35% according to the observation time, which is comparable with the average indices of the experimental groups, but lower than

Table 1

Effect of the dry complex herbal remedy extract on the exudation degree with formalin and carrageenan edema in white rats

Group of animals	Formaline edema		Carrageenan edema	
	Leg volume difference, ml	Degree of edema suppression, %	Leg volume difference, ml	Degree of edema suppression, %
Control (H <sub>2</sub> O), n=8	0,41±0,032	-	0,48±0,026	-
Experimental I (phytoextract, 100 mg/kg), n=8	0,31±0,009*	24	0,35±0,024*	27
Experimental II (phytoextract, 200 mg/kg), n=8	0,28±0,034*	32	0,33±0,028*	31
Experimental III (phytoextract, 300 mg/kg), n=8	0,28±0,017*	32	0,34±0,034*	29
Experimental IV (caleflon, 100 mg/kg), n=8	0,31±0,018*	24	0,37±0,031*	23

Note. In the Tbl. 1-3 \* the differences are statistically significant between the control and experimental groups at  $P \leq 0.05$ ; n is the number of animals in the group.

Table 2

Effect of the dry complex herbal remedy extract on the alteration degree in white rats

Group of animals	Alteration ares, mm <sup>2</sup>			
	7th day	14 th day	21 th day	28 th day
Control (H <sub>2</sub> O), n=8	409,3±33,62	306,3±12,95	124,7±14,57	74,7±10,8
Experimental I (phytoextract, 100 mg/kg), n=8	297,3±23,85*	266,8±29,61	81,2±9,43*	52,7±7,47
Experimental II (phytoextract, 200 mg/kg), n=8	325,0±30,17	225,8±26,99*	88,3±11,89	47,5±4,95*
Experimental III (phytoextract, 300 mg/kg), n=8	324,3±21,13*	230,5±33,21*	61,8±5,51*	37,0±7,10*
Experimental IV (caleflon, 100 mg/kg), n=8	314,4±28,5*	240,2±23,2*	78,6±6,21*	50,3±3,20*



Table 3

Effect of the dry complex herbal remedy extract on the proliferation processes in white rats

Group of animals	Dry granuloma weight, mg	Granuloma formation degree, %
Control (H <sub>2</sub> O), n=8	62,8±4,53	
Experimental I (phytoextract, 100 mg/kg), n=8	68,0±5,21	8
Experimental II (phytoextract, 200 mg/kg), n=8	69,1±5,51	10
Experimental III (phytoextract, 300 mg/kg), n=8	66,3±5,33	6
Experimental IV (caleflon, 100 mg/kg), n=8	67,1±5,86	7

in the group of animals treated with the phytoextract in a dose of 300 mg / kg.

It was found that a moderate effect on the proliferative component of chronic inflammation is exerted by a phytoextract in a dose of 200 mg / kg (Table 3): the weight of the connective tissue capsule in the inflammatory focus increased by 10% compared to the control. The use of phytoextract in doses of 100 and 300 mg / kg exhibited a proliferative effect similar to the reference preparation (caleflon).

The ascertained pharmacological effect of the tested phytoextract results from the anti-inflammatory activity of its components. Thus, according to the literature, anti-inflammatory properties were detected in *C. avellana* L. [2, 15], *A. eupatoria* L. [8, 17], *X. strumarium* L. [1], *U. dioica* L. [7], *C. intybus* [10], *O. acanthium* [6], *L. minor* [13]. Some species of the genus *Juglans* L. are widely used as anti-inflammatory drugs in traditional medicine of many countries [19].

The anti-inflammatory activity of medicinal plants is implemented due to a wide range of biologically active substances: flavonoids (kaempferol, quercetin, luteolin, apigenin, etc.), hydroxycinnamic acids, phenol carboxylic acids, triterpenoids, vitamins (ascorbic acid, carotenoids, etc.) and others [12, 16, 18, 20, 21].

According to some authors [7], the anti-inflammatory effect of plants is also exerted due to the antioxidant effect of flavonoids, carotenoids, ascorbic acid and  $\alpha$ -tocopherol. Plant antioxidants directly neutralize the free radicals of neutrophils and macrophages and endoperoxides afforded in the cyclooxygenase reaction, and also potentiate anti-peroxide protection. Inhibition of peroxidation is accompanied by a decrease in the production of anti-inflammatory and algogenic factors - prostaglandins, kinins, IL-1, IL-6, IL-8, INF- $\gamma$ , TNF- $\alpha$ , complement and cell adhesion molecules, weakening the synthesis of collagen and glycosaminoglycans in fibroblasts.

### Conclusion

thus, the results obtained indicate that the extract of dry complex herbal remedy possesses antiexudative activity, reducing the exudation induced by phlogogenic agents. The test extract has an anti-alterative effect, limiting the alteration of

tissues with acetic acid and enhancing regenerative processes. Moderate proliferative activity was manifested by the phytoextract in a dose of 200 mg / kg. The pronounced anti-inflammatory activity of the complex agent is caused by a wide range of biologically active substances like flavonoids, terpenoids, carotenoids, essential oils, vitamins, organic acids and other compounds included in its formulation.

The study was carried out as a part of the state assignment No. AAAA-A17-117011810037-0.

### References

1. Bushueva G.R., Strelkova L.B., Kondakova N.V. Issledovanie biologicheskoy aktivnosti durnishnika obyknovennogo travy ehkstrakta suhogo i ot del'nyh frakcij s primeneniem specificheskikh fermentnyh biotest-sistem v usloviyah *in vitro* [Investigation of the biological activity of cockleburries of common herb extract of dry and separate fractions using specific enzyme biotest systems under *in vitro* conditions]. Voprosy biologicheskoy, medicinskoj i farmacevticheskoy himii [Problems of biological, medical and pharmaceutical chemistry]. 2016. 6. pp. 25-29.
2. Kalenichenko A. S., Maloshtan L.N. Skriningovoe issledovanie antikoagulyantnoj, membranostabiliziruyushchej i protivovospalitel'noj aktivnosti gustogo ehkstrakta iz list'ev leshchiny obyknovennoj [Screening study of anticoagulant, membrane stabilizing and anti-inflammatory activity of the thick extract from the leaves of *Corylus avellana*]. Farmakologiya ta likars'ka toksikologiya [Pharmacology and drug toxicology]. 2016. 2 (48). pp. 3-48.
3. Fadeyev V.V. [et al.]. Kachestvo kompensacii i samochuvstvie pacientov s pervichnym gipotireozom i ozhireniem [Quality of compensation and well-being of patients with primary hypothyroidism and obesity]. Klinicheskaya i ehksperimental'naya tireoidologiya [Clinical and experimental thyroidology]. 2016. 12 (2). pp. 28-32.
4. Korsun V.F., Korsun E.V. Fitoterapiya. Tradicii rossijskogo travnichestva [Phytotherapy. Traditions of Russian herbalism]. Moscow, 2010. 880 p.
5. Madiyarova M. Sch. [et al.]. Osobennosti

klinicheskoy kartiny, pokazatelej kachestva zhizni i kognitivnyh funkcij u pacientok s gipotireozom raznoj ehtiologii [Features of the clinical picture, quality of life and cognitive functions in female patients with hypothyroidism of different etiology]. Klinicheskaya i ehksperimental'naya tireoidologiya [Clinical and experimental thyroidology]. 2014. 10 (1). pp. 44-54.

6. Ivanova L.R. [et al.]. Protivovospalitel'naya aktivnost' ehkstrakta travy tatarnika kolyuchego [The anti-inflammatory activity of *Onopordion spinosum* extract]. Pharmacy [Pharmacy]. 2007. 4. pp. 39-40.
7. Burkova V.N. [et al.]. Protivovospalitel'noe i anal'geticheskoe dejstvie ehkstraktov iz *Urtica dioica* (Urticaceae) [Anti-inflammatory and analgesic effect of extracts from *Urtica dioica* (Urticaceae)]. Rastitel'nye resursy [Vegetable resources]. 2011. 47 (2). pp. 136-143.
8. Pozdnyakova S.P. [et al.]. Protivovospalitel'nye svoystva ehkstraktov *Agrimonia pilosa* Ledeb. i beresty *Betula pendula* Roth. [Antiinflammatory features of *Agrimonia pilosa* Ledeb. and *Betula pendula* Roth extracts]. Sibirskoe medicinskoe obozrenie [Siberian Medical Review]. 2011. 71 (5). pp.39-42.
9. Khabriev R.U. Rukovodstvo po ehksperimental'nomu (doklinicheskomu) izucheniyu novykh farmakologicheskikh veshchestv [Guide to experimental (preclinical) study of new pharmacological substances]. Moscow, 2012. 832 p.
10. Saibel O.L., Dargaeva T.D., Pupykin K.A. Izuchenie fenol'nyh soedinenij travy cikoriya obyknovennogo (*Cichorium intybus* L.) [Study of phenolic compounds of chicory grass (*Cichorium intybus* L.)]. Bashkirskij himicheskij zhurnal [Bashkirian chemical journal]. 2016. 23 (1). pp. 53-58.
11. Zolotukhin S.E. [et al.]. Svyaz' pokazatelej svobodno-radikal'nogo gomeostaza s tireoidnymi gormonami pri gipotireoze, pri tyazhelej mekhanicheskoy travme i pri ih sochetanii [Correlation between free radical homeostasis and thyroid hormones in hypothyroidism in severe mechanical trauma]. Aktual'ni problemi suchasnoy medicini: Visnik ukrains'koj medichnoy stomatologichnoy akademii [Actual problems of modern medicine: Bulletin of the Ukrainian Medical Stomatological Academy]. 2010. 10 (4). pp. 82-86.
12. Nikiforov L.A. [et al.]. Sravnitel'noe issledovanie veshchestv pervichnogo obmena ryaski maloj (*Lemna minor* L.), ryaski trojchatoj (*Lemna trisulca* L.) i mnogokorennika obyknovennogo (*Spirodella polyrrhiza* L. Schleid.) [A comparative study of the substances of the primary exchange *Lemna minor* L., *Lemna trisulca* L. and *Spirodella polyrrhiza* L. Schleid.]. Byulleten' sibirskoy mediciny [Bulletin of Siberian Medicine]. 2017. 16 (1). pp. 59-64.
13. Adekenov S.M. [et al.]. Fenol'nye

- soedineniya ehtanol'nyh izvlechenij *Lemna minor* L., *Lemna trisulca* L. i *Lemna polyrrhiza* L. Schleid. i ih immunomoduliruyushchaya aktivnost' [Phenolic compounds of ethanol extracts of *Lemna minor* L., *Lemna trisulca* L. and *Lemna polyrrhiza* L. Schleid and their immunomodulating activity]. Byulleten' sibirskoj mediciny [Bulletin of Siberian Medicine]. 2017. 16 (3). pp. 5-15.
14. Tishkovets S.V. [et al.]. Fitokorrekcija narushenij gormonal'nogo statusa i pokazatelej serdechno-sosudistoj sistemy u belyh kryz pri ehksperimental'nom gipotireoze [Phytocorrection of hormonal status disorders and cardiovascular system indicators at experimental hypothyroidism of white rats]. Kurortnaya baza i prirodnye lechebno-ozdorovitel'nye mestnosti Tuvy i sopredel'nyh regionov [Resort base and natural medical-health areas of Tuva and neighboring regions]. Kyzyl. 2017. pp. 101-104.
15. Yusifova D.Yu., Maloshtan L.N., Shatalova O.M. Farmakologicheskoe izuchenie ehkstrakta iz list'ev leshchiny obyknovennoj na modeli tromboflebita perifericheskikh sosudov uha krolika [The pharmacological study of leaves extract from the common hazel on the model of thrombophlebitis of peripheral vascular of rabbit's ear]. Ukraïns'kij biofarmacevtichnij zhurnal [Ukrainian biopharmaceutical magazine]. 2014. 6 (35). pp. 47-50.
16. Karamese M. [et al.]. Anti-oxidant and anti-inflammatory effects of apigenin in a rat model of sepsis: an immunological, biochemical, and histopathological study. Journal Immunopharmacology and Immunotoxicology. 2016. 3. pp. 228-237.
17. Santos T.N. [et al.]. Antioxidant, anti-inflammatory, and analgesic activities of *Agrimonia eupatoria* L. Infusion. Evidence-Based Complementary and Alternative Medicine. 2017. Article ID 8309894. pp. 1-13.
18. Ziyan L. [et al.]. Evaluation of the Anti-inflammatory Activity of Luteolin in Experimental Animal Models. Planta medica. 2007. 73. (3). pp. 221-226.
19. Ficker C.E. [et al.]. Inhibition of human pathogenic fungi by ethnobotanically selected plant extracts. Mycoses. 2003. 46. (1-2). pp. 29-37.
20. Paudel P. [et al.]. *Juglans regia* and *J. nigra*, two trees important in traditional medicine: A comparison of leaf essential oil compositions and biological activities. Nat. Prod. Commun. 2013. 8 (10). pp. 1481-1486.
21. Kashyap D., Tuli H.S., Sharma A.K. Ursolic acid (UA): a metabolite with promising therapeutic potential. Life Sciences. 2016. 146. pp. 201-213.
- The authors**
1. Tishkovets Svetlana Valeryevna - Post-graduate student scientist of the Laboratory of experimental pharmacology of the Institute of General and Experimental Biology SB RAS, Russia, 670047, Ulan-Ude, Sakhyanova str., 6, ph. +7 (3012) 433713, e-mail: [tcb-amur@yandex.ru](mailto:tcb-amur@yandex.ru)
  2. Razuvaeva Yanina Gennadyevna - doctor of biological sciences, Senior Research Scientist of the Laboratory of Biologically Active Substances Safety of the Institute of General and Experimental Biology SB RAS, Russia, 670047, Ulan-Ude, Sakhyanova str., 6, ph. +7 (3012) 433713, e-mail: [tatur75@mail.ru](mailto:tatur75@mail.ru)
  3. Mondodoev Alexander Gavrilovich - doctor of medical sciences, Head of the Department of Biologically Active Substances Safety of the Institute of General and Experimental Biology SB RAS, Russia, 670047, Ulan-Ude, Sakhyanova str., 6, ph. +7 (3012) 433713, e-mail: [amonbsc@mail.ru](mailto:amonbsc@mail.ru)
  4. Toropova Anyuta Alekseevna - candidate of biological sciences, Research Scientist of the Laboratory of Biologically Active Substances Safety of the Institute of General and Experimental Biology SB RAS, Russia, 670047, Ulan-Ude, Sakhyanova str., 6, ph. +7 (3012) 433713, e-mail: [anyuta-tor@mail.ru](mailto:anyuta-tor@mail.ru)

V.M. Nikolaev, S.D. Efremova, E.D. Okhlopko, Z.N. Alekseeva, F.V. Vinokurova, S.I. Sofronova, S.A. Fedorova, N.K. Chirikova, L.P. Koryakina

## INFLUENCE OF LOW TEMPERATURES ON LIPID PEROXIDATION IN TISSUE OF EXPERIMENTAL ANIMALS DEPENDING ON EXPOSURE TIME

DOI 10.25789/YMJ.2018.63.07

### ABSTRACT

The article reports the study on the influence of low temperatures on the intensity of free radical lipid oxidation and antioxidant protection in the tissues of internal organs (liver, kidneys, lungs, heart) in experimental animals, depending on the exposure time.

The few data available in the literature indicate that the effect of low temperatures on the organism of experimental animals is accompanied by the activation of free radical processes. We noted an increase in the concentration of low-molecular antioxidants in the organs of animals, whose exposure time in the cold lasted 1 hour. An increase in exposure time of rats in the cold to 3 hours is associated with an increase in catalase activity.

**The purpose of this study** was to study the effect of experimental animals on the processes of lipid peroxidation in tissues of internal organs (liver, kidneys, lungs, heart) during one-hour and three-hour exposure to low temperatures for 14 days.

The effect of cold on the processes of lipid peroxidation in the tissues of rats was investigated at a temperature ( $10 \pm 20^\circ\text{C}$  below zero). The processes of lipid peroxidation and antioxidant protection parameters were quantitatively studied by spectrophotometric method, using SPECORD 40 spectrophotometer, determining the content of dienic conjugates and malonic dialdehyde in the tissues of the internal organs (liver, kidneys, lungs and heart), the total content of low molecular weight antioxidants and catalase activity.

**Conclusion.** The ecological and biochemical reaction of the rat organism to the effect of cold is the activation of antioxidant protection, due to the increase in the rate of lipid peroxidation. In the first group of animals, whose exposure time in the cold lasted one hour, biochemical mechanisms of antioxidant protection are realized by increasing the concentration of low-molecular antioxidants in organs. An increase in the exposure time to three hours of rats in the cold is associated with an increase in the activity of the antioxidant enzyme catalase.

**Keywords:** low-temperature effect, lipid peroxidation, free radical lipid oxidation, lipoperoxidation, active oxygen species, malonic dialdehyde, diene conjugates, experimental animals, spectrophotometric methods, electrothermometer with needle sensor, adaptation.

### Introduction

One of the fundamental problems of biology at the present time is the study

of the state of the organism under the influence of various negative factors of the external environment, as well as ways

and means of increasing the resistance of the living organism to them. Such a factor in the extreme climatic and natural

conditions of the North is the effect of cold on tissues and the whole body.

Under the influence of low ambient temperatures there the biochemical, physiological shift of many functional systems of the organism occurs, which leads to the development of a new state, borderline between norm and pathology, called «adaptation».

At adaptation to the cold in the body of animals and humans, many metabolic processes are changing. At this time it is difficult to understand when the state of adaptation comes, accompanied by an increase in resistance of the organism. One of these indicators can be a state of biological membranes, which has an important role in the processes of cell life [1].

There is evidence in the literature testifying that the effect of low temperatures on the organism of experimental animals is accompanied by activation of peroxide processes [2, 9, 11, 12]. It is also known from literature data that a moderate intensification of peroxide processes in the body of animals and humans can contribute to an increase in the permeability of the cell membrane and facilitating the work of membrane proteins. However, excessive intensification of lipid peroxidation can lead to disruption of adaptation, which is manifested by denaturation and inactivation of proteins, delipidation of membranes, violation of cell division and growth, violation of the integrity of cell membranes [14, 17, 20]. Consequently, the functional state of cells, tissues, organs depends on the intensification of peroxide processes induced by exposure to low temperatures i.e. the ability of the body to adapt to the cold effects.

The purpose of our research was to study the effect of one- and three-hour exposure to low temperatures for 14 days on the processes of lipid peroxidation in the tissues of internal organs (liver, kidneys, lungs, heart) of experimental animals.

#### Material and methods of research

This study was approved by the local committee on biomedical ethics at the Yakut Scientific Center of Complex Medical Problems.

An experiment on the influence of low temperatures on lipid peroxidation in the tissues of the internal organs of rats was carried out on the Wistar line rats weighing 170-260 g. The effect of cold on the body of rats was investigated at a temperature of ( $10 \pm 20^\circ\text{C}$  below zero) for 14 days. Animals were divided into two groups: the first group animals were exhibited in the cold for 1 hour, of the second - for 3 hours. The temperature of the legs and tail in rats was determined

using an electrothermometer with a needle sensor. The control group consisted of intact animals.

The processes of lipid peroxidation and antioxidant protection parameters were quantitatively studied by spectrophotometric method, using SPECORD 40 spectrophotometer, determining the content of dienic conjugates and malonic dialdehyde in the tissues of the internal organs (liver, kidneys, lungs and heart), the total content of low molecular weight antioxidants and catalase activity.

At the end of the experiment removal of animals from the experience was carried out by decapitation in accordance with the requirements of humanity in accordance with Appendix No.4 to the Rules for carrying out work using experimental animals (The order of the USSR Ministry of Health No.755 dated 12.08.1977 «On the procedure for euthanasia (killing an animal)»).

100 mg of internal tissue (liver, kidney, heart and lung) were obtained from experimental animals that were washed with phosphate buffered saline (PBS) and homogenized in 1 ml of  $1 \times \text{PBS}$ .

Diene conjugates, formed in a result of double bond migration in polyunsaturated fatty acids, were determined by Danilova method [3]. After extraction in a mixture of heptane-isopropanol (2:1) and subsequent addition of a solution of HCl (pH 2.0) the diene conjugates were detected in the heptane phase at  $\lambda = 233 \text{ nm}$ , using a molar extinction coefficient of diene conjugates  $2.2 \times 10^5 \text{ M}^{-1} \times \text{cm}^{-1}$ . The amount of diene conjugates was expressed in  $\mu\text{mol/g}$  tissue.

The principle of the method for determining malonic dialdehyde is based on the formation at a high temperature of a colored trimethine complex with thiobarbituric acid [10]. The optical density of the colored complex at  $\lambda = 532 \text{ nm}$  was determined in comparison with the control sample. The molar extinction of malonic dialdehyde is  $1.56 \times 10^5 \text{ M}^{-1} \times \text{cm}^{-1}$ . The concentration of malonic dialdehyde was expressed in  $\text{nmol/g}$  tissue.

The method for determining the total content of low-molecular antioxidants is based on the ability to reduce  $\text{Fe(III)}$  to  $\text{Fe(II)}$  in the presence of antioxidants in an alcoholic solution of the sample [5]. The amount of formed  $\text{Fe(II)}$  was determined by the addition of orthophenanthroline, resulting in the formation of a colored complex, which was determined at a wave length  $\lambda = 510 \text{ nm}$ . Using a series of standard solutions of dihydrotraquetin in the concentration range 0.10-0.025  $\text{mg/ml}$ , the value of the molar extinction coefficient of the o-phenanthroline- $\text{Fe}$

(II) complex was obtained which was equal to  $5.28 \times 10^4 \text{ M}^{-1} \times \text{cm}^{-1}$ . The level of the total content of low-molecular antioxidants was expressed in  $\text{mg-eqQuercetin/g}$  of tissue.

The catalase activity was determined at a wave length  $\lambda = 410 \text{ nm}$  using a method based on the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate [6]. The millimolar extinction coefficient of hydrogen peroxide was  $22.2 \times 10^3 \text{ mM}^{-1} \times \text{cm}^{-1}$ . For the unit of catalase activity the amount of enzyme, involved in converting 1 mkat hydrogen peroxide in 1 sec. is taken under the given conditions.

Statistical processing of the data was carried out using the IBM SPSS Statistics 19 application statistical software package. The reliability of the differences between the averages was estimated using the Mann-Whitney U test. The data in the tables are presented in the form  $M \pm m$ , where M is the mean, m is the mean error. Probability of the validity of the null hypothesis was assumed for  $p < 0.05$ .

#### Results and discussion

The repeated, short-term effect of cold on the organism of experimental animals was chosen by us not accidentally, since it occurs quite often, both in everyday and in experimental situations.

Measurement of temperature using an electrothermometer with a needle sensor showed that the effect of cold primarily manifested itself in lowering the temperature of the paws and tail of experimental animals. At the exposure for 1 hour, the temperature of the paws decreased to  $20.5 \pm 0.50^\circ\text{C}$ , the temperature of the tail decreased to  $21.4 \pm 0.70^\circ\text{C}$ , at the exposure for 3 hours, the temperature of the paws was  $22.2 \pm 0.60^\circ\text{C}$ , tail -  $23.8 \pm 0.30^\circ\text{C}$ . In the intact group of rats, the temperature of the paws was  $27.3 \pm 0.80^\circ\text{C}$ , the temperature of the tail corresponded to  $25.1 \pm 0.60^\circ\text{C}$ . Lowering of the temperature indicates a violation of microcirculation in the limbs of experimental animals. Microcirculation disorder leads to the hypoxia, which potentiates the generation of active oxygen species (initiators of lipid peroxidation) in mitochondria [14, 20].

The results of the evaluation of lipid peroxidation indicators in the tissues (liver, kidney, lung, heart) of rats obtained in the course of the experiment are presented in Table 1.

According to the data of the experimental animals of the first group in comparison with intact animals in the liver tissues the concentration of malonic dialdehyde was 1.6 times lower, but the content of diene conjugates was 1.7 times higher. In the tissues of kidneys the



Table 1

**The concentration of diene conjugates ( $\mu\text{mol/g}$ ) and malonic dialdehyde ( $\text{nmol/g}$ ) in the tissues of the internal organs of experimental animals**

Organ	Diene conjugates			Malonic dialdehyde		
	Control	1st group	2nd group	Control	1st group	2nd group
Liver	3,79 $\pm$ 0,18	6,52 $\pm$ 0,39*	2,56 $\pm$ 0,13*	10,73 $\pm$ 0,52	6,64 $\pm$ 0,33*	6,16 $\pm$ 0,36*
Kidneys	1,00 $\pm$ 0,01	5,55 $\pm$ 0,27*	3,66 $\pm$ 0,18*	16,30 $\pm$ 0,81	9,74 $\pm$ 0,47*	18,86 $\pm$ 0,84
Lungs	5,13 $\pm$ 0,20	7,10 $\pm$ 0,35*	2,77 $\pm$ 0,12*	15,25 $\pm$ 0,76	5,02 $\pm$ 0,25*	9,17 $\pm$ 0,43*
Heart	2,66 $\pm$ 0,13	4,51 $\pm$ 0,21*	3,31 $\pm$ 0,16*	6,34 $\pm$ 0,31	5,83 $\pm$ 0,24	9,26 $\pm$ 0,34*

\*  $p < 0.05$  in comparison with control group.

content of malonic dialdehyde was 1.7 times lower, and diene conjugates were higher by 5.5 times. In the lung tissues we observed a decrease in malonic dialdehyde by 3 times and an increase in diene conjugates by 1.4 times. In heart tissue, the level of malonic dialdehyde was 1.1 times lower, and the content of diene conjugates was 1.7 times higher.

In the liver tissue of rats of the second group, we observed a decrease in the level of diene conjugates by 1.5 times and malonic dialdehyde - 1.7. We found an increase in the concentration of diene conjugates and malonic dialdehyde in the kidney tissue by 3.6 and 1.2 times, respectively. In lung tissues, the content of diene conjugates was 1.8 times lower, and the level of malonic dialdehyde was 1.6 times less than the control value. In heart tissue, the concentration of diene conjugates was 1.2 times higher than the control value, and malonic dialdehyde - 1.4 times.

The indicators of catalase activity and the concentration of the total content of low-molecular antioxidants in tissues (liver, kidney, lung, heart) of rats are presented in Table 2.

In the liver tissues of experimental animals of the first group, we observed an increase in the concentration of low-molecular antioxidants by 1.8 times. The activity of catalase was 1.4 times lower than in intact animals. In the kidneys, the content of low-molecular antioxidants was 2.0 times higher, and catalase activity was 1.7 times lower. In the tissue of the myocardium, we noted a tendency to increase the low-molecular antioxidants by 1.02 times and a significant decrease in catalase activity by 1.5. In lung tissues,

the level of low-molecular antioxidants was 22.0 times higher, and catalase activity was 1.7 times lower.

With an increase in the exposure time of rats in the cold in the tissues of the liver, kidneys, lungs, the level of low-molecular antioxidants was higher in comparison with the control by 4.2 times; 1.3 and 48.3 times, respectively. In heart tissue, the concentration of low-molecular antioxidants was less than control by 2 times. The catalase activity in liver and kidney tissues was 1.4 times higher than control and 1.3 times, respectively, and no significant differences were found in lung and heart tissues.

Our data have demonstrated that the state of lipid peroxidation in the body of experimental animals depends on the exposure time in the cold. In animals of the first group, peroxide processes in all organs proceeded more actively at the initial stages, as evidenced by the accumulation of primary products of peroxidation - diene conjugates. The level of malonic dialdehyde (the final product of lipid peroxidation) was below the control values in all organs.

With an increase in the exposure time of experimental animals in the cold, the intensity of free radical reactions in the tissues of internal organs changes, as evidenced by a change in the concentrations of diene conjugates and malonic dialdehyde. So, we noted a decrease in the concentration of diene conjugates and malonic dialdehyde in the tissues of the liver and lung and their increase in the tissues of the kidneys and heart.

In the first group of animals exposed to cold, an increase in the concentration of

low-molecular antioxidants in all tissues of the organs (liver, kidney, lungs, heart) may be related to their mobilization in response to stressful exposure to low temperatures. The increase in the concentration of low-molecular antioxidants in the tissues of the kidneys is probably due to the fact that in response to the effects of cold, catecholamines and glucocorticoids are released which are necessary for thermoregulatory heat production [1, 4, 7].

In the second group of animals, with increasing of exposure time, a high content of low molecular weight antioxidants (LMWA) in the lung tissues is noted. Our results coincide with the literature data. There is information in the literature that the main component of mucus is mucin, secreted by epithelial cells and possessing antioxidant properties. It is shown that type 2 pneumocytes secrete  $\alpha$ -tocopherol, in mucus we also reveal an increase in the concentration of reduced glutathione [15, 18], ascorbic acid [13]. Uric acid, flavonoids and bilirubin also enter the non-enzyme system of the lungs, as they have antioxidant functions [16, 19]. An increase in the concentration of low-molecular antioxidants in the liver tissues is due to the fact that most endogenous antioxidants are synthesized in it, both low-molecular and high-molecular. In addition, hepatocytes are able to accumulate fat-soluble antioxidants -  $\alpha$ -tocopherol, retinol.

Reducing the concentration of low-molecular antioxidants in the tissues of the kidneys and heart is associated with the depletion of their reserve due to the acceleration of the processes of lipid peroxidation. Earlier we showed that an increase in the concentration of products of lipid peroxidation - malonic dialdehyde and diene conjugates is a consequence of increased generation of reactive oxygen species and, first of all, superoxidation-radical, which turns into hydrogen peroxide under the action of superoxide dismutase [7]. Therefore the activity of catalase in the tissues of the organs of both groups is increased as a result of an increase in the concentration of its substrate-hydrogen peroxide.

The decrease in the activity of catalase in all tissues of the experimental animals of the first group confirms the fact that in the mechanism of adaptation of the organism of rats to a multiple, one-hour exposure to cold low-molecular antioxidants have a leading role. With an increase in the exposure time of experimental animals to 3 hours, the enzymatic activity of catalase in the tissues of the liver and kidneys increases by 1.4 and 1.3 times, respectively. It is

Table 2

**The total content of low-molecular antioxidants ( $\text{mg-eqQuercetin/g}$ ) and catalase activity ( $\mu\text{cat/g}$ ) in the tissues of internal organs of experimental animals**

Organ	Total content of low-molecular antioxidants			Catalase		
	Control	1st group	2nd group	Control	1st group	2nd group
Liver	16,54 $\pm$ 2,14	29,78 $\pm$ 1,45*	69,57 $\pm$ 2,54*	21,15 $\pm$ 1,78	15,14 $\pm$ 2,52*	29,38 $\pm$ 1,74*
Kidneys	38,12 $\pm$ 2,47	76,57 $\pm$ 3,62*	49,45 $\pm$ 2,87*	17,48 $\pm$ 1,65	10,45 $\pm$ 4,62*	22,45 $\pm$ 1,51*
Lungs	2,14 $\pm$ 0,18	44,18 $\pm$ 2,35*	103,32 $\pm$ 3,78*	17,12 $\pm$ 0,12	9,89 $\pm$ 4,45*	16,41 $\pm$ 0,79
Heart	32,47 $\pm$ 0,17	33,21 $\pm$ 1,47	16,39 $\pm$ 1,18*	13,24 $\pm$ 1,35	8,56 $\pm$ 1,21*	14,50 $\pm$ 4,08

likely that in these tissues the content of low-molecular antioxidants is insufficient to inhibit free-radical reactions.

### Conclusion

Thus, the ecologic-biochemical reaction of the rat organism to the effect of cold is the activation of antioxidant protection due to an increase in the rate of lipid peroxidation. In the first group of animals, whose exposure time in the cold lasted 1 hour, biochemical mechanisms of antioxidant protection are realized on account of increasing the concentration of low-molecular antioxidants in organs. An increase in the exposure time (to 3 hours) of rats in the cold is associated with an increase in the activity of the antioxidant enzyme - catalase.

*The work was carried out with the financial support of the state project of the Ministry of Education and Science of the Russian Federation No.6.1766.2017. PCH, the project of NEFU named after M.K. Ammosov: «Genetic features of the population of Yakutia: the structure of the gene pool, adaptation to cold, psychogenetic characteristics, the prevalence of some hereditary and infectious diseases» and the program of bioresource collections of the Russian FANO «The Genome of Yakutia» YSC CMP (BRK: 0556-2017-0003).*

### References

- Shapovalenko N.S. [et al.] Vliyanie holodovogo stressa na intensivnost' perekisnogo okisleniya lipidov i antioksidantnyuyu sistemu tkanej eksperimental'nyh zhivotnyh [Effect of cold stress on the intensity of lipid peroxidation and the antioxidant system of tissues of experimental animals]. Byulleten' fiziologii i patologii dyhaniya [Bulletin of the physiology and pathology of respiration]. Blagoveshensk, 2011, № 39, P. 22 - 25.
- Gorodetskaya I.V. Evdokimova O.V. Vliyanie izmeneniya tireoidnogo statusa na fermentativnyy i nefermentativnyy komponenty antioksidantnoj sistemy organizma pri dejstvii stressorov razlichnoj prirody [Influence of the thyroid status change on the enzymatic and non-enzymatic components of the body's antioxidant system under the action of stressors of different nature] Zhurnal Grodnenskogo gosudarstvennogo medicinskogo universiteta [Journal of Grodno State Medical University]. Grodno, 2013, №3, P. 80 - 83.
- Danilova L.A. Spravochnik po laboratornym metodam issledovaniya [Handbook on laboratory methods of research]. SPb.: Piter, 2003, P. 398. - 399.
- Arbykin Yu.A. [et al.] Dinamika ul'trastrukturnykh izmenenij pochek pri obshchem pereohlozhdении organizma [Dynamics of ultrastructural changes in the kidneys at general over-cooling of the organism] Sibirskij medicinskij zhurnal. Siberian Medical Journal, Tomsk, 2015, Vol. 30, №3, P. 65 - 68.
- Ermakov A.I. Metody biohimicheskogo issledovaniya rastenij [Methods of biochemical research of plants]. Leningrad: Agropromizdat, 1987, 430 p.
- Korolyuk M.A. Ivanova L.N. Maierov I.G. Metod opredeleniya aktivnosti katalazy [Method for determination of catalase activity] Laboratornoe delo [Laboratory work], 1988, №1, P. 16-19.
- Nikolaev V.M. Golderova A.S. Osobennosti adaptacionnoj reakcii u eksperimental'nyh zhivotnyh pri vozdeystvii nizkikh temperatur [Features of the adaptation reaction in experimental animals under the influence of low temperatures]. Yakutskij medicinskij zhurnal [Yakut medical journal]. Yakutsk, 2006, №4, P. 21-23.
- Panin L.E. Osobennosti ehnergeticheskogo obmena [Features of energy metabolism] Mekhanizmy adaptacii cheloveka v usloviyakh vysokikh shirot [Mechanisms of human adaptation in conditions of high latitudes]. Leningrad, Medicina, 1980, P. 87 - 97.
- Pozdnyakova O.N. [et al.] Rannie izmeneniya urovnya produktov perekisnogo okisleniya lipidov v krvi i tkanyah u krys, adaptirovannyh k holodovomu vozdeystviyu [Early changes in the level of products of lipid peroxidation in blood and tissues in rats adapted to the cold effect]. Vestnik pomorskogo universiteta [Bulletin of the Pomor. University]. Seriya: «Estestvennye i tochnye nauki» [Series: «Natural and exact sciences»], Vypusk [Issue 3], 2006, P.42 - 44.
- Pavlikhina L.V. [et al.] Sovremennye metody v biohimii [Modern methods in biochemistry]. Moscow: Medicine, 1977, P. 147 - 151.
- Tikhonov V.I. Vliyanie holinotropnykh sredstv na izmenenie soderzhaniya tripletnoj formy kisloroda tkani pecheni i sposobnosti gomogenata pecheni producirivat' aktivnye formy kisloroda pri ohlazhdenii u krys [Influence of cholinotropic agents on the change in the content of the triplet oxygen form of liver tissue and the ability of liver homogenate to produce active forms of oxygen at cooling in rats] Obzory po klinicheskoy farmakologii i lekarstvennoj terapii [Reviews of clinical pharmacology and drug therapy]. Saint-Petersburg, 2016, Vol. 14 (4), P. 3 - 8.
- Yurtaeva E.Yu. Dorovskikh V.A. Simonova N.V. Ehffektivnost' prirodnykh antioksidantov pri adaptacii organizma k holodu [The effectiveness of natural antioxidants in the adaptation of the organism to cold] Byulleten' fiziologii i patologii dyhaniya [Bulletin of the physiology and pathology of respiration]. Blagoveshensk, 2017, Vypusk [Issue 63], P. 70 - 74.
- Anderson R. Ascorbic acid neutralizes reactive oxidants released by hyperactive phagocytes from cigarette smokers / R. Anderson, A.J. Theron, G.L. Ras // Lung.-1988. -Vol.166.-№3.P.149 - 159.
- Bhattacharya S. Reactive oxygen species and cellular defense system / S. Bhattacharya // Free radicals in human health and disease. - 2015. - P. 17 - 29.
- Cantin A.M. Extracellular glutathione suppresses human lung fibroblast proliferation / A.M. Cantin, P. Larivel, R.O. Begin // Amer. J. Respir. Cell. Mol. Biol. - 1990. - N3. -P. 79 - 85.
- Cross C.E. Oxidants, antioxidants and respiratory tract lining fluids / C.E. Cross, A. Van der Vliet, C.A. O'Neill // Environ. Health Perspect. - 1994. - Vol.102. - Suppl.10. - P. 185 - 191.
- Lipid peroxidation: mechanisms, inhibition, and biological effects / E. Niki [et. al] // Biochemical and biophysical research communications. - 2005. - 338. - P. 668 - 676.
- Normal alveolar epithelial lining fluid contains high levels of glutathione / A. Cantin [et. al] // J.Appl.Physiol. - 1987. - V.63. - P. 152 - 157.
- Type 2 pneumocytes secrete vitamin E together with surfactant lipids / B. Rustow [et al] // Amer. J. Physiol. -1993. -Vol.265. - P. 133 - 139.
- Yin H. Free radical lipid peroxidation: mechanisms and analysis / H. Yin, L. Xu, N.A. Porter // Chemical Reviews. - 2011. -111: P. 5944-5972.

### The authors

Yakut Scientific Center of Complex Medical Problems:

- Nikolaev Vyacheslav Mikhailovich - PhD, head of the department of studying adaptation mechanisms, YSC CMP, 677010, Yakutsk, ul. Sereglyakhskoye shosse 4, tel.: (4112) 32-19-81; Associate Professor of the Department of Agronomy and Chemistry, Yakut State Agricultural Academy, 677007, Sakha (Yakutia) Republic, Yakutsk, Shergaleiskoye 3 km., 3, tel.: 8 (4112) 507-971, fax: 8 (4112) 358-162, e-mail: Nikolaev1126@mail.ru,
- Efremova Svetlana Dmitrievna - junior researcher of the department of studying adaptation mechanisms, YSC CMP, 677010, Yakutsk, ul. Sergelyakhskoye shosse 4, tel.: (4112) 32-19-81, e-mail: esd64@mail.ru,
- Okhlopko Elena Dmitrievna - Chief Scientific Officer, Head of Immunology Laboratory, Department for Studying Adaptation Mechanisms, YSC CMP, 677010, Yakutsk, ul. Sergelyakhskoye highway 4, tel.: (4112) 32-19-81, e-mail: elena\_ohlopko@mail.ru,
- Alekseeva Zinaida Nikolaevna - junior researcher of the department of studying

- adaptation mechanisms, YSC CMP, 677010, Yakutsk, ul. Sergelyakhskoye highway 4, phone: (4112) 32-19-81, e-mail: gzinaida@mail.ru,
5. Vinokurova Fekla Vasilievna - Researcher, Department for the Study of Adaptation Mechanisms, YSC CMP, 677010, Yakutsk, ul. Sergelyakhskoye highway 4, phone: (4112) 32-19-81, e-mail: vfekla@gmail.com,
6. Sofronova Sargilana Ivanovna - PhD, Chief Scientific Officer Head of the Scientific and Organizational and Information Publishing Division, YSC CMP, 677010, Yakutsk, ul.

- Sergelyakhskoye highway 4, tel.: (4112) 32-19-81, e-mail: sara2208@mail.ru;
7. Fedorova Sardana Arkadevna - Doctor of Biological Sciences, Head of the Research Laboratory of Molecular Biology, North-Eastern Federal University named after M.K. Ammosov, 677000, Yakutsk, ul. Kulakovskiy, 46, k.504, phone: (4112) 49-68-42, e-mail: sa.fedorova@s-vfu.ru;
8. Chirikova Nadezhda Konstantinovna - Candidate of Physical and Mathematical Sciences, Leading Researcher of the Biological Department, Institute of Natural Sciences, Biology, North-Eastern Federal

University named after M.K. Ammosov, 677000, Yakutsk, ul. Kulakovskiy, 46, k.504, phone: (4112) 49-68-42, e-mail: hofnung@mail.ru;

9. Koryakina Lena Prokopievna - Candidate of Science, Associate Professor of the Department of Physiology of Agricultural Animals and Ecology, Yakutsk State Agricultural Academy, 677007, Sakha (Yakutia) Republic, Yakutsk, 3 km Sergelyakhskoye Str., 3, tel.: 8 (4112) 507-971, fax: 8 (4112) 358-162, e-mail: koryrinalp\_2017@mail.ru.

## METHODS OF DIAGNOSIS AND TREATMENT

M.P. Kirillina, A.K. Ivanova, I.D. Popova, D.K. Garmaeva

# ANALYSIS OF FREQUENCY OF OCCURRENCE OF BACKGROUND AND PRECANCEROUS DISEASES OF A CERVIX BY RESULTS OF A PREVENTIVE AND DIAGNOSTIC CYTOLOGICAL TESTING

DOI 10.25789/YMJ.2018.63.08

### ABSTRACT

The analysis of results of a cytological research in women aged from 18 up to 88 years as a method of early diagnosis of background and precancerous diseases of a cervix is carried out. The received results confirm the high predictive value of this method. Early detection and treatment of background and precancerous diseases of a cervix will promote real decrease in incidence and cervical cancer mortality.

**Keywords:** screening, oncocytology, diagnostics, dysplasia, cervical cancer.

### Relevance

The cervical cancer (CC) is one of the most widespread oncological diseases of reproductive system of women: its specific weight fluctuates from 12 to 20% of all malignant tumours of a female genital [5]. Remaining in top three in structure of incidence of female reproductive organs after a breast cancer and endometrium and without yielding the position in structure of mortality where it takes the second place among oncological diseases at women, cervical cancer continues to cause irreplaceable damage in the most active layers of female population [13].

Annually in the world 528 thousand new patients with cervical cancer and 266 thousand deaths from this disease (7.9% of the total number of the women malignant tumours) are registered. Wide circulation of cervical cancer is noted in developing countries of which 78% of cases are the share, and his share reaches 15% of number of all malignant tumours at women (in the developed countries of 4.4%) [2].

Many authors note a certain staging and staging of pathological processes of a cervix in the course of carcinogenesis. Development of cervical cancer isn't

lightning process: according to WHO data, on average 3-8 years, 10-15 more years undergo transition of a dysplasia to in situ cancer before development of microinvasive cancer and as much – before transition to a spread form [9].

Cervical cancer arises against the background of the benign processes which have received the name of background diseases which in itself aren't precancerous states more often, but on their background focal proliferative changes of an epithelium can develop. These processes differ in a big variety of pathological changes, each of them has morphological criteria. They can have the dyshormonal, inflammatory and post-traumatic cause [3, 10]. Precancerous processes consist of a dysplasia of various degrees.

Most often cervical cancer is revealed in the senior age group (60–70 years and more), however recently appears many publications describing cases of developing of this disease at women of reproductive age [3]. So, growth of incidence of cervical cancer among young women is noted: at the age of 15–24 years — by 4 times; 25–34 years — by 2,5 times [11,12]. Unfortunately, it should be noted that find in a considerable part

of patients of cervical cancer already at late stages of a disease (III-IV) when the efficiency of modern methods of treatment sharply decreases [13].

In this regard early diagnosis and treatment of background and precancer diseases and also initial forms of cervical cancer, certainly, can be the important actions directed to decrease in cancer cases and reduction of number of the started forms [8].

**Research objective:** to study occurrence of background and precancerous diseases of a cervix and also their combination by results of a cytological research.

### Materials and methods of a research

The analysis of cytological material of a cervix of 7600 women aged from 18 up to 88 years with the preventive and diagnostic purpose, during 2017 is carried out to laboratory of a pathomorphology, histology and cytology of Clinic of Medical institute of NEFU.

Material of a cytological research were smear from a mucous layer of cervix and the cervical channel. Age classification of Y.Y. Eliseev (2006) according to which persons of 18-29 years treat young age, 30-44 years to mature, 45-59 years – an average, 60-74 – by advanced age



[4] has been applied to identification of tendencies of epidemic process in various age groups.

Diagnostics was carried out by coloring of glasses by method of Romanovsky - Gimza. The cytological diagnosis was established according to clinicomorphological classification of Y.V. Bokhman (1976).

### Results and discussion

The studied cytological material from 7600 women on age structure was distributed as follows: of 18 - 29 years - 2645 women (34,8%), of 30-44 years - 2315 women (30,4%), of 45-59 years - 1840 women (24,2%) and are also more senior 60 years - 800 women (10,5%).

It should be noted that very important factor of efficiency of screening of cervical cancer is the sensitivity of a cytological research. According to various authors it makes from 66% to 83%. The bad intake of material, in 10-30% - wrong interpretation of cytological data is the reason of false-negative answers in 70-90% of cases [10]. The most often not informative material is received at capture of dabs from the cervical channel; the absence in smear of cells of an endocervical epithelium is noted in 8-18% of cases. Thereof glandular and ferruterosus and squamous cell cervical cancer are most often passed in screening [14]. In our research «material isn't informative» have made 143 cases (1,9%) and «the glandular epithelium isn't taken» - 1472 cases (19,4%) of total number of the studied women. What indicates prevalence of a human factor, such as bad intake of material, lack of the special tools guaranteeing capture of material from all zones, reception of the patient during periods and also dependence on climatic conditions.

The cytological conclusion of «Cytogramm without features» in case of receiving full-fledged material can be considered as the instruction on lack of pathological changes of cervix. According to us the «Cytogramm without features» group (estrogenic and atrophic type of smear) is in the lead and makes 34,7% (2640 women) of the total number of researches (Fig. 1).

Inflammatory processes are diagnosed for 2814 (37%) women. Which main share is the share of age of 18-29 years - 956 (34%) a case and 45-59 years - 728 (28,1%) a case. Various factors can be the reasons of inflammatory process of cervix (cervicitis): a bacterial imbalance, thinning of a multilayered flat epithelium in a postmenopause with accession of inflammatory process (an atrophic colpitis), various physical and chemical impacts, infections, etc. [8].

According to literary data [7] quite often meets at women of reproductive age dysbiosis vagina florum (not inflammatory infectious syndrome connected with dysbacteriosis of vaginal flora) and comes to light in 40-50% of cases. This tendency is traced also in our research. So, the maximum frequency of occurrence of a dysbiosis of flora (a bacterial vaginosis) is diagnosed for women at the age of 18-29 years - 740 women (40,7%) and 30-44 years - 693 women (38,2%). Today it is established that the bacterial vaginosis is also risk factor, and sometimes and one of the causes of heavy pathology of female genitals and complications of pregnancy and childbirth [1].

Now the greatest interest among infections, sexually transmitted, is represented by chlamydia and papillomavirus. It is connected partly with high frequency detection of these infections at gynecologic patients. Among patients with pathology of a cervix of a chlamydia are found in 40-49% of cases [6]. According to our data, in 47 cases (1,7%) indirect symptoms of chlamydiosis have been diagnosed. The largest frequency has been registered aged 30-44lt (38,3%). Data of a cytological research at detection of a chlamydial infection are approximate and have to be complemented with other methods of a research (the immunofluorescent analysis etc.).

In the last decades as a problem of virus carcinogenesis of cervical cancer the virus of papilloma of the person (HPV) has moved to the forefront [10]. Now more than 100 HPV various types from which 30 infect a genital path of the person [8] are identified. According to us, indirect symptoms of a viral infection are diagnosed for 689 patients

and makes 24,5% of all background diseases with infectious agents. The maximum number is noted in age group of 18-29 years and 30-44 years - 269 (39%). It is recommended to these women to pass the HPV test. The method of the polymerase chain reaction (PCR) has the highest sensitivity, but we unfortunately don't possess data on control after treatment, in particular data of PCR. Full elimination of a virus meets at carriers with the good immune status. Disappearance effect of virus defeat at a repeated fence of dab at bearers of HPV is explained by it.

From modern positions pathological changes on a neck of the uterus can be divided into background, precancer (pretumoral) and tumoral processes. In clinical practice carry true erosion, pseudo-erosion to background diseases, a leukoplakia, an eritroplakia, polypses, etc., to precancer - CIN II and CIN III.

Influence of a number of endogenous and exogenous hormones is the main reason for prevalence of background diseases at women of reproductive age. It is confirmed by numerous researches of other authors [8, 11]. Frequency of occurrence of pathologies of a cervix at the persons of various age groups is specified in Tab.

From Table it is visible that the highest rate of background diseases is the share of women in the age period of 30-44 years - 212 (37,6%) and 18-29 years - 187 (33,2%) women. By results of a cytological research by us it has been

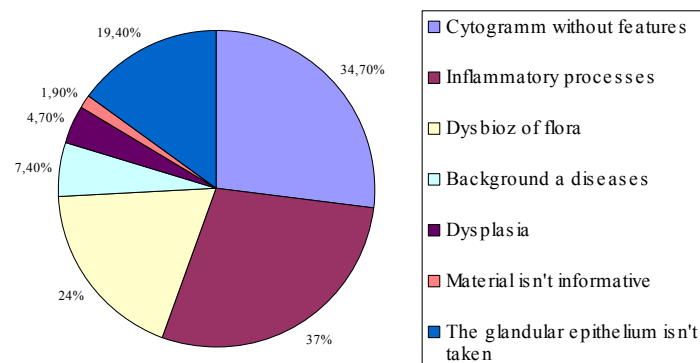


Fig. 1. Results of a cytological research.

### Frequency of occurrence of background diseases of the cervix in different age groups, n (%)

	Age, years				TOTAL
	18-29	30-44	45-59	60 and over	
Hyperkeratosis of the flat epithelium	12 (30)	16 (40)	10 (25)	2 (5)	40 (7,1)
Squamous cell metaplasia, alternate cell hyperplasia	127 (30,4)	149 (35,7)	102 (24,5)	39 (9,3)	417 (74)
Proliferation of glandular epithelium	35 (51,5)	30 (44,1)	2 (2,9)	1 (1,5)	68 (12)
Hyperplasia of the type of dysplasia	13 (34,2)	17 (44,7)	7 (18,4)	1 (2,6)	38 (6,7)
	187 (33,2)	212 (37,6)	121 (21,5)	43 (7,6)	563 (7,4)

established that the most often diagnosed pathology of a neck of the uterus was the squamous cell metaplasia (a reserve and cellular hyperplasia) which makes 74%. The maximum frequency of occurrence is noted in age category of 30-44 years (35,7%) and 18-29 years (30,4%) that it is connected with intensive influence of sex hormones (estrogen) at women of active reproductive age. At 68 (12%) women there was a registered proliferation of a ferruterosus epithelium was diagnosed much less often hyperkeratosis which has been found in 7,1% of cases of the total number of background diseases. At the same time, the maximum frequency of occurrence was noted by this pathology at the age of 30-44 years (40%).

Dysplasia of the cervix of varying severity have been revealed in 359 cases that has made 4,7% of total number of the studied women. Among them at 220 women (61,3%) the dysplasia of the CIN I, 84 women (24,5%) is revealed – (CIN II) and CIN III degree of a dysplasia 38 women had a dysplasia of the II degree registered that has made 10,6% of all dysplasia of a cervix in the examined group. At the same time the maximum number of dysplasia was noted in age group of 18-29 years (32%) and 30-44 years (33%). While, 87 (24,2%) cases it is revealed at women at the age of 45-59 years and 39 (11%) cases at the age of 60 years and is more senior. It should be noted that the high frequency of occurrence of a dysplasia of the I degree says that she can come to light also at inflammation of a cervix when at a cytological research reparative atypical cages – dysplasia equivalents are found. These phenomena often disappear after anti-inflammatory treatment [9].

According to our data, the analysis of frequency of occurrence of dysplasia depending on age (Fig. 2) has shown that in identical set met at women of fertile age (18-29 years and 30-44 years) a CIN I (19,7% and 19,2%) and CIN II (7,2% and 7,5%). At women at the age of 30-

44 years the big frequency of detection of a CIN III (3,9%) was noted. CIN III with transition to cancer is diagnosed in 4 cases and has made 1,1%. At the same time, 2 (0,5%) a case it has been revealed at the age of 30-44 years and on 1 (0,3%) to a case at the age of 45-59 years and 60 years and is more senior. Cervical cancer cytological has been revealed in 2 cases and has made 0,5% of total number of the revealed dysplasia. Thus, the results received by us testify to the high frequency of occurrence of dysplasia at women of reproductive age.

It is known that contamination of a HPV infection increases risk of development of a dysplasia by 10 times. In the examined group of women, the frequency of identification of a combination of dysplasia and indirect symptoms of a viral infection was 207 (57,6%) cases from all dysplasia in the examined group. Considering that in the conditions of Clinic of MI only primary cytological research is conducted, definite answer about interrelation of a dysplasia and carriage of a virus by results of our research can't be given. At identification of suspicion of pathology of cervix the patient has to pass the second stage of inspection (profound diagnostics).

For search of predictive signs of cellular proliferation with the adverse forecast for stages of early cellular changes the new technology of preparation of cytomedicines – liquid cytology gains ground now. Today the given method is the most informative in diagnostics of intraepithelial neoplasia, convenient as for the patient (a single intake of material) and for the doctor (a possibility of use of one material in various researches).

### Conclusion

Thus, the results of a cytological research received by us quite will be coordinated with data of literature. At the present stage of development of clinical medicine identification not only initial stages of cancer, but also background and precancerous diseases as they most

often meet at socially active group of women of reproductive age is important. Being one of the few nosological forms of malignant tumours, cervical cancer has the recognizable preclinical phase, the long period of development, in communication with what there are real opportunities for prevention of this disease of way of introduction to practical health care of reliable and highly effective screening programs.

*The article is carried out in the framework of the research «Epidemiological aspects of malignant tumors in the Far North, development of modern methods of early diagnosis, prevention using highly informative fundamental research methods.» (No. 0556-2014-0006).*

### References

1. Akopyan T.Eh. Bakterial'nyj vaginoz i vaginal'nyj kandidoz u beremennyh (diagnostika i lechenie) [A bacterial vaginosis and vaginal candidiasis at pregnant women (diagnostics and treatment)] Diss...kand.med.nauk. [PhD diss...]. Moscow, 1996.
2. Aksel' E.M. Zabolovaemost' i smertnost' zlokachestvennyh novoobrazovaniy organov zhenskoy reproduktivnoy sistemy v Rossii [Incidence and mortality of malignant new growths of bodies of female reproductive system in Russia] Onkoginekologiya [Oncogynecology]. Moscow, №1, 2015, p.6-15.
3. Bazhutova G.A. Vozmozhnosti citologicheskogo metoda issledovaniya pri profilakticheskom osmotre materiala shejki matki [Possibilities of a cytological method of a research at routine inspection of material of a neck of the uterus] Klinicheskaya laboratornaya diagnostika [Clinical laboratory diagnostics]. Moscow, 2004, №10, p.38-40.
4. Vozrastnye bolezni: poln. sprav. [Age diseases] Pod.red. YU. YU. Eliseev [edition Y.Y. Yeliseyev]. Moscow, Ehksmo, 2007, 736p.
5. Davydov M. I., Aksel' E. M. Statistika zlokachestvennyh novoobrazovaniy v Rossii i v stranah SNG v 2008 g. [Statistics of malignant tumours in Russia and in the CIS countries in 2008] Vestn. RNC im. H. H. Blohina RAMN [Vestn. N.N. Blochin RNC RAMS]. Moscow, 2010, V.21, №2, Pril.1, 160p.
6. Kutlin A.V. Immunohimicheskie i biologicheskie svoystva monoklonal'nyh antitel k Chlamydia trachomatis [Immunochemical and biological properties of monoclonal antibodies to Chlamydia trachomatis] Zhurnal mikrobiologii, ehpidemiologii i immunobiologii [Magazine of microbiology, epidemiology and

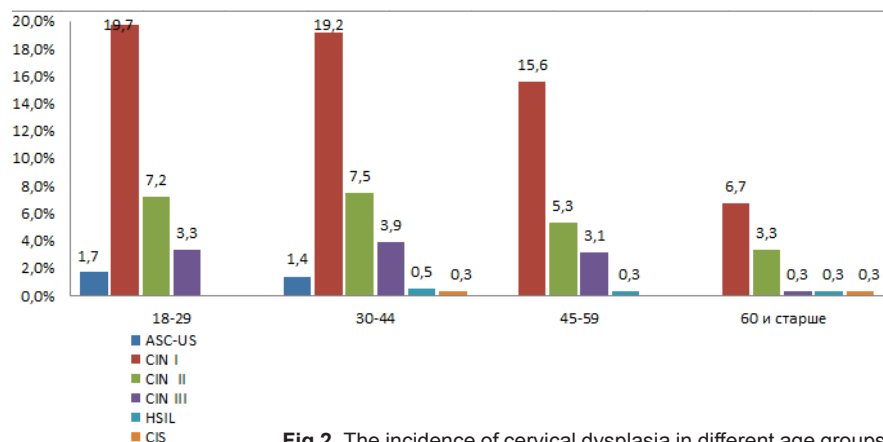


Fig.2. The incidence of cervical dysplasia in different age groups.

- immunobiology]. Moscow, 1996, №1, p.3-6.
7. Makarov I.O. Bakterial'nyj vaginoz: sostoyanie izuchennosti problem [Bacterial vaginosis: state of problem study] Akusherstvo, ginekologiya i reproduksiya [Obstetrics, gynecology and reproduction]. Moscow, 2013, V.7, №4, 20p.
  8. Novik V.I. Ehpideologiya raka shejki matki, faktory riska, skringing [Epidemiology of cervical cancer, risk factors, screening] Prakticheskaya onkologiya [Practical oncology]. Moscow, 2002, V.3. №3, p.156-165.
  9. Polyakova V.A. Onkoginekologiya [Oncogynecology]. Moscow: izd-vo «Medicinskaya kniga» [Publ. house "Medical book", 2001, 192p.
  10. Rogovskaya S.I. Vozmozhnosti kol'poskopii [Possibilities of a colposcopy] Zabolevaniya shejki matki, vlagalishcha i vul'vy [Diseases of cervix, vagina and vulva] Pod red. V.N. Prilepskoj [under the editorship of V.N. Prilepskaya]. Moscow, 2000, 250p.
  11. Rusakevich P.S. Zabolevaniya shejki matki: simptomatika, diagnostika, lechenie, profilaktika [Diseases of cervix: symptomatology, diagnostics, treatment, prevention]. Moscow, 2000, 368p.
  12. Chissov V.I. Metodologiya i organizatsiya skringinga raka shejki matki [Methodology and the organization of screening of cervical cancer] Posobie dlya vrachej [Manual for doctors]. Moscow, 2004, 32p.
  13. Antonsson A. General acquisition of human papillomavirus infections of skin occurs in early infancy / A.Antonsson, S. Karanfilovska, P.G. Lindqvist, B.G. Hansson // J. Clin. Microbiol. - 2003. - Vol. 41, No6. - P.2509–2514
  14. Coob C.J. Suggested approaches to reporting benign cervical smears that lack endocervical columnar cells / C.J. Coob // Acta Cytol. – 1986. – Vol.30. – P.317-318.

#### The authors

1. Kirillina Maria Petrovna - Ph.D. (biology), Leading researcher, Yakut science Center of complex medical problems, Head of laboratory Clinic of Medical institute, M.K.Ammosov Nord-Eastern Federal University, Yakutsk, kirillinamp@mail.ru;
2. Ivanova Anna Konstantinovna- cytologist, Clinic of Medical institute, M.K.Ammosov Nord-Eastern Federal University in Yakutsk, ivanova.ak11@gmail.com;
3. Popova Irina Dmitrievna - medical assistant Clinic of Medical institute, M.K.Ammosov Nord-Eastern Federal University, Yakutsk;
4. Garmaeva Darima Kyshekhtovna - Ph.D. M.D (Medicine) professor, Medical institute, M.K.Ammosov Nord-Eastern Federal University, Yakutsk dari66@mail.ru.

N.M. Zakharova, N.A. Gulyaeva, A.M. Ammosova, S.V. Markova, M.V. Khandy, S.Yu. Artamonova, L.A. Stepanova, V.B. Egorova

## ANALYSIS OF ORAL MICROFLORA IN CHILDREN

DOI 10.25789/YMJ.2018.63.09

### ABSTRACT

To study the microflora of the oral cavity, 485 children and adolescents living in Yakutsk were examined. We've taken smears from the mucous throat and tonsils for microbiological analysis of the oral microflora, also used the method of rapid diagnosis - Streptatest, for the presence of b-hemolytic streptococcus of group A (BHSA). When studying the qualitative and quantitative composition of the oral microflora of frequently ill children, it was revealed that 16.3% are carriers of the pathogenic and conditionally pathogenic flora - a trigger factor in the development of chronic tonsillitis. In the examined children yeast fungi of the genus *Candida* were found - in 8,7%, bacteria of the genus *Staphylococcus* - in 1,3%, in the genus *Streptococcus* - in 7,5%, in the genus *Klebsiella* - in 1,3%. In 80% of the children in the crops, monoculture growth was detected. With abundant growth, 6.6% of microorganisms were detected, with moderate growth - 46.7% and with scant - 46.7%. As a result of the treatment, the children notice a shift in the anaerobic index to the normal range, which contributes to the provision of conditions for improving the life of the obligate microflora. In Children's Infectious Diseases Hospital (CIDH), children with acute tonsillopharyngitis, acute pharyngitis, and angina were examined. All patients underwent a rapid Streptatest test for the streptococcal etiology of the infection. According to the rapid test, 37% of patients were positive. Timely establishment of BHSA allowed conducting eradication antibacterial therapy, which led to recovery without complications. Streptatest can be widely used in the rapid diagnosis of streptococcal infection for the detection of BHSA in patients with angina and acute tonsillopharyngitis without age restrictions.

**Keywords:** children, microflora of the oral cavity, diagnostics, streptococcal infection.

### Introduction

Normally, the microbial composition of the oral cavity is formed by various kinds of microorganisms: bacteria, viruses, protozoa. In a healthy organism, the constant microflora serves as a biological barrier, preventing the proliferation of pathogenic microorganisms coming from the external environment; participates in the self-cleaning of the oral cavity, is a constant stimulant of local immunity [1]. Persistent changes in the composition and properties of microflora due to a decrease in the reactivity of the organism, resistance of the mucous membrane of the oral cavity, as well as certain therapeutic measures, can lead to the appearance of various diseases of the oral

cavity, the causative agents of which are pathogenic microorganisms from outside as well as conditionally pathogenic representatives of the constant microflora of the oral cavity [4].

To conditionally-pathogenic representatives of the constant microflora of the oral cavity the bacteria of anaerobic type of respiration, streptococci, constitute 30-60% of the whole microflora of the oropharynx. Streptococci caused streptococcal infection – a polymorphic in its clinical manifestations of bacterial infection. B-hemolytic streptococcus group A (BHSA) causes a wide range of diseases in childhood: streptococcal respiratory tract infections, tonsillitis, pharyngitis, their complications - cervical lymphaden-

itis, peritonsillar and zaglone abscesses, sinusitis, mastoiditis, otitis media, pneumonia, etc. [7, 10]. This is due to the anatomical location of the tonsils in the area of the airway cross and upper digestive tract, their constant traumatization and infection, as well as the age-related features of the child's immune system [5]. The peak incidence falls on the average and senior school age.

In recent decades, there has been a steady trend towards an increase in the incidence of chronic tonsillitis and its "rejuvenation" [6]. The starting factor of development are pathogenic or conditionally pathogenic microorganisms persisting in the lymphoid tissue of the tonsils due to a weakened antigen-spe-



cific immune response of the organism. With prolonged contact of microflora with tonsil tissues, conditions are created for permanent alteration and exudation on the background of active proliferation processes [8, 10]. In turn, chronic foci of inflammation in the pharynx change the immunobiological balance and cause the development of immunopathological conditions, of which the leading are allergic reactions of a delayed type and the formation of immune complexes [8, 12].

Often the etiological factors of the development of chronic tonsillitis are b-hemolytic streptococcus of group A (BHSA), staphylococci, *Haemophilus influenzae*, pneumococci, moraxella, mycoplasmas, fungi and viruses (adenoviruses, cytomegaloviruses, herpes viruses.) In recent years, the importance of polymicrobial infection is emphasized. chronic tonsillitis is 12-16% according to the data of various authors and is one of the most frequent diseases in the structure of chronic diseases of childhood.

The reliable statistics of classical streptococcal infection according to the data of the 20th century showed temporary (cyclic) fluctuations both in terms of the incidence of the disease and in the severity of the disease associated with the increased virulence of streptococcus. V.D. Belyakov (1996), after studying the dynamics of the incidence of streptococcal infection, revealed 3 of its peak, accompanied by high mortality, and warned: "We are entering the XXI century, in the first half of which, according to the laws of streptococcal infection, it must show its power, as it was in the early twentieth century" [2].

Currently, streptococcal infection caused by BHSA, the most common bacterial infection, the disease is mainly manifested in childhood - estimated prevalence is 3 000 - 100 000 children per year. At the same time, only 20-30% of ill children are treated with classical clinical symptoms of pharyngitis or tonsillitis, and since clinical differentiation from viral and bacterial infections is difficult even for an experienced physician, clinically streptococcal infections are often not diagnosed [6]. Due to the wide variety of clinical manifestations, the final diagnosis is established only after additional laboratory confirmation (allocation of streptococcus from the material of lesions, increase in the titer of O-antistreptolysin). For rapid verification of streptococcal infection, around 200 test systems have been developed in the world, however many of them have low diagnostic value and are not able to adequately replace bacteriological research.

In order to quickly determine BHSA in the oral cavity, Streptatest was registered in Russia in June 2010. This method has been used in European medicine for 8 years, during which time it has become a method of routine diagnosis for physicians of various specialties [12]. Streptatest is used without age restrictions, by doctors in polyclinics and hospitals; considering the compactness of the system, it is used during home calls; the test is effectively used in closed collectives, kindergartens and schools. The expediency and necessity of using Streptatest for express diagnostics of streptococcal tonsillopharyngitis in children is explained by the rationalization of the use of antibiotics for streptococcal infection.

Antibacterial therapy at the moment takes a leading place in the conservative therapy of chronic tonsillitis. The most serious problem of such treatment is the constant growth of resistance of pathogenic microorganisms to antibacterial drugs [3, 8, 9]. At the same time antibiotics are not effective enough to suppress the growth of encapsulated microbes that have a polysaccharide membrane – *Haemophilus influenzae*, *Streptococcus pneumoniae*, some anaerobes [11].

Thus, the study of the microflora of the oral cavity is an actual direction of modern science to develop new approaches to maintaining and correcting the normal microflora of the oral cavity with the goal of preventing and treating inflammatory diseases.

**The purpose of the study:** to study the microflora of the oral cavity in children who are often ill and sick with acute tonsillopharyngitis.

#### Materials and methods of research

485 children and adolescents living in Yakutsk were included in the study. Of these, 80 children often (from 5-6 to 8-9 times a year) had respiratory diseases; the age of children - from 5 to 7 years, attended children's educational institutions. The children were taken smears from the mucous throat and tonsils for microbiological analysis of the microflora of the oral cavity.

In the Children's Infectious Diseases Hospital (CIDH) 405 children from early to old age who were on inpatient treatment with acute tonsillitis, acute tonsillitis, tonsillitis were examined. When entering the hospital, all patients underwent general clinical studies: a general blood test, a general urine test, for the etiologic diagnosis, the rapid diagnostic method - Streptatest, for the presence of BHSA was used. The test is a diagnostic for the detection of a specific antigen of group A streptococcus in the material obtained

with a smear from the mucous membrane of the posterior pharyngeal wall and palatine tonsils. The kit includes 2 reagents that allow the extraction of the antioxidant BHCA from the material, a test strip working on an immunochromatographic principle. On the membrane of the test strip in the test zone, an immobilized antibody was applied to the specific antigen of BHSA, and in the control zone, an extraction reagent. The appearance of the purple band indicates a positive result, while its absence denotes a negative result.

The results were processed using parametric and nonparametric methods. The average arithmetic "M" was calculated; the mean error of the mean "m". The reliability of the differences in the "p" results of the study was assessed by the Student's test. Differences were assessed as significant at  $p < 0.05$ .

#### Results and discussion

*Candida* yeast fungi in 7 (8.7%), bacteria of the genus *Staphylococcus* - in 1 (1.3%), and in the genus *Streptococcus* - in 6 (in the study of the microflora of the oral cavity were observed in microbiological analysis of the oral cavity) 7.5%), the genus *Klebsiella* - in 1 (1.3%). In 80% of the children in the crops, monoculture growth was detected. In 1 (7.7%) girls, bacteria of several genera were simultaneously found: *Streptococcus*, *Klebsiella* and *Candida* fungi. From the anamnesis of this girl it is known that she was born on the 26th week of pregnancy, she was on artificial ventilation for a long time, until she was 2 years old she was repeatedly treated in the pulmonology department of the Pediatric Center of Republican Hospital №1 – NCM with the diagnosis: bronchopulmonary dysplasia. The kindergarten visits from the age of 4, for the last three years it has been ill on average 8 times per year, with the following diagnoses: pharyngitis, acute respiratory disease, bronchitis, catarrhal sinus, stomatitis.

It is noteworthy that the parents of children, in the analysis of which yeast fungi of the genus *Candida* were found, noted uncontrolled self-treatment with antibiotics of a wide spectrum of action, which could lead to an increased growth of yeast-like fungi resistant to most antibiotics.

Seven-year-old boy, in the analysis of which was found staphylococcus, within the last year 4 times had a follicular sore throat.

In 7 (53.8%) children with microbiological examination of feces revealed a dysbacteriosis of III-IV degrees.

In addition to the qualitative composition of microorganisms in the study of

smears, their degree of growth was determined (abundant, moderate and lean). With abundant growth, 1 (6.6%) of microorganisms were detected, with a moderate one - 7 (46.7%) and with scant - 7 (46.7%).

After a seven-day antibacterial therapy with augmentin, the number of children who had pathogenic bacteria detected in the crops of the contents of the lacunae decreased to 50%, while the persistence of bacteria persisted in 37.5% of the children, but the degree of colonization decreased. In 12.5% of children after administration of antibacterial therapy, changes in the microbial landscape of the oral cavity were not observed (Table).

With further monitoring of children within one year, the incidence of respiratory diseases decreased to 3-4 times on average. Thus, treatment with augmentin provides a reduction in the frequency of carriage of pathogenic flora and the degree of contamination of the tonsils, positively influences the microbial landscape of the oral cavity.

With the use of seven-day antifungal therapy with fluconazole, a negative result was observed in all children in the control study.

During treatment with children, allergic reactions and side effects of the use of augmentin and fluconazole were not noted.

In CIDH children received acute tonsillopharyngitis, acute pharyngitis, tonsillitis, noted an acute onset of the disease: an increase in body temperature above 38 ° C, severe pain in the throat, especially when swallowed, patients often complained of headache, pain in muscles and joints, a decrease appetite, weakness. According to the physical examination in children with angina, there was a bright hyperemia, hypertrophy of the tonsils, suppurative supplements on the tonsils, lymphadenopathy. In the peripheral blood marked leukocytosis.

Given the clinical picture of the disease, all patients underwent a rapid Streptatest test for the streptococcal etiology of the infection. According to the rapid test, 37% of patients (149 people) had a positive result. In children with streptococcal infection of the upper respiratory tract, rhinorrhea, cough, subfebrile body temperature, hyperemia, edema of the posterior pharyngeal wall, mild lymphadenopathy were noted.

Deciphering the etiology of the disease is fundamentally important, since streptococcal infection requires adequate eradication therapy. Eradication of BHSA contributes not only to eliminating the symptoms of infection, but also pre-

**Intensity of bacterial colonization of pharyngeal tonsils before and after treatment (n = 13)**

Causative agent	Degree of dissemination of pharyngeal tonsils, n							
	Abundant growth		Moderate growth		Lean growth		No growth	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
<i>Streptococcus</i>	-	-	3	-	3	3	-	3*
<i>Staphylococcus</i>	-	-	1	-	-	-	-	1
<i>Klebsiella</i>	1	-	-	1	-	-	-	-
Fungi genus <i>Candida</i>	-	-	3	-	4	-	-	7

\* p<0,05.

vents early and late complications, and also prevents the spread of infection, the formation of immunopathological options (acute rheumatic fever, glomerulonephritis). The use of antibiotics not only prevents the spread of streptococcal infection, but also reduces the number of carriers of the pathogen [6].

The drug of choice for the treatment of angina, tonsillopharyngitis in a hospital was cephalosporins of the 3rd generation, because until now,  $\beta$ -hemolytic streptococci are highly sensitive to penicillin and cephalosporins. In 10% (15 patients) due to intolerance or an allergic reaction, macrolides (klatsid) were administered orally. Antibiotic therapy was 10 days. With the use of antibacterial therapy, body temperature quickly normalized, pains in the throat ceased, and general symptoms came to a stop.

All children in addition to antibiotic therapy are prescribed non-steroidal anti-inflammatory drugs (nurofen, naise) [12], symptomatic treatment. Against the background of the therapy, all children had a positive dynamics; the children were discharged with improvement for further monitoring of the local pediatrician at the place of residence.

#### Conclusion

In the study of the qualitative and quantitative composition of the oral microflora of frequently ill children, it was revealed that 16.3% are carriers of the pathogenic and conditionally pathogenic flora - the triggering factor of the development of chronic tonsillitis. As a result of the treatment, the children notice a shift in the anaerobic index to the normal range, which contributes to the provision of conditions for improving the life of the obligate microflora.

Using the method of rapid diagnosis of Streptatest in patients with angina, acute tonsillopharyngitis of children, BHSA was detected in 37% of patients. Timely establishment of BHSA allowed conducting eradication antibacterial therapy, which

led to recovery without complications. Streptatest can be widely used in the rapid diagnosis of streptococcal infection for the detection of BHSA in patients with angina and acute tonsillopharyngitis without age restrictions.

#### References

1. Baranov A.A. Gorelov A.V. Kaganov B.S. Ostrye respiratornye zabolevaniya u detej. Lechenie i profilaktika [Acute respiratory diseases in children. Treatment and prevention]. Moscow, 2004, 84 p.
2. Belyakov V.D. Surprisy streptococovoj infekcii [Surprises of streptococcal infection]. Bulletin of the RAMS, 1996, No. 11, p.24-28.
3. Garashchenko T.I. Zabolevaniya glotki u detej i ih antibakterialnaya terapiya [Diseases of the pharynx in children and their antibacterial therapy]. Materia Medica, 2004, No. 3-4, 45 p.
4. Zakharov A.A. Ilyina N.A. Analys microflory rotovoj polosti obsledovannyh lydej s razlichnymi zabolevaniyami [Analysis of the microflora of the oral cavity of the examined people with various diseases]. Progress in Modern Natural Science, 2007, No. 12, p.141-143.
5. Krasnova E.I. Kreten S.O. Optimizatsiya terapii streptococovoj infekcii rotoglotki s primeneniem bakterialnyh lizatov [Optimization of therapy of streptococcal infection of the oropharynx with the use of bacterial lysates]. Children's infections, 2011, V. 10, No. 1, p. 52-56.
6. Krasnova E.I. Kreten S.O. Streptococovaya infectia u detej: sovremennye podhody k protivovospalitelnoj terapii [Streptococcal infection in children: modern approaches to anti-inflammatory therapy]. The Russian Herald of Perinatology and Pediatrics, 2010, V. 55, No. 4, p.76-80.
7. Kryukov A.I. Luchsheva Y.V. Balandin A.V. et al. Rationalnaya antibiotikoterapiya pri angine i chronicheskom tonsillite [Rational antibiotic therapy for angina and chronic tonsillitis]. Consilium Medicum, 2005, V. 7, No. 4, p.297-300.

8. Pokrovsky V.I. Briko N.I. Ryapis L.A. Streptococci i streptococcosy [Streptococcus and streptococcosis]. Moscow, Geotar-Media, 2008, 540 p.
  9. Strachunsky L.S. Kozlov S.N. Sovremennaya antimicrobnaya chimioterapiya [Modern antimicrobial chemotherapy]. Moscow, 2002, p.342-344.
  10. Tsvetkov E.A. Adenotonsillity i ih oslozheniya u detej [Adenotonsillitis and its complications in children]. Sankt-Peterburg, 2003, p.83-87.
  11. Dlugosz C.K. Chater R.W. Engle J.P. Appropriate Use of Nonprescription Analgesics in Pediatric Patients]. J Pediatr Health Care, 2006, V. 5, No. 20, p.316-325.
  12. Gieseke K.E. Evaluating the American Academy Pediatrics diagnostic standard for Streptococcus pyogenes pharyngitis: Backup culture versus repeat rapid antigen testing]. Pediatrics, 2003, No. 111, p.66-70.
- The authors**
1. Nadezhda Mihailovna Zakharova, MD, associate professor of the Department of Propaedeutics of Children's Diseases of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  2. Nadezhda Andreevna Gulyaeva, MD, associate professor of the Department of Infectious Diseases of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  3. Aelita Mihailovna Ammosova, MD, associate professor of the propaedeutics department of children's illnesses of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  4. Sardana Valerievna Markova, Candidate of Medical Science, associate professor of the propaedeutics department of children's illnesses of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  5. Maria Vasilievna Khandy, MD, Professor of the Department of Propaedeutics of Children's Diseases of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  6. Sargylana Yurievna Artamonova, MD, associate professor of the propaedeutics department of children's illnesses of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  7. Lena Anatolievna Stepanova, MD, associate professor of the propaedeutics department of children's illnesses of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: nadezdamix15@mail.ru;
  8. Vera Borisovna Egorova, MD, associate professor, pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov Northeastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: veraborisovna@yandex.ru.

## L.A. Lytkina, L.G. Chibyeva NCAIDS- GASTROPATHY IN PATIENTS WITH CARDIAC DISEASE

DOI 10.25789/YMJ.2018.63.10

### ABSTRACT

The character of clinical endoscopic features of gastropathies, induced by the intake of non-steroidal anti-inflammatory drugs, was evaluated in patients with cardiac pathology.

The clinical picture of NSAIDs-gastropathies in patients with IHD was characterized by a mismatch of symptoms and endoscopic changes. This manifested itself in the fact that in the presence of a bright endoscopic picture (erosion, ulcer), NSAIDs-gastropathies were often asymptomatic. In contrast, in most patients who have noticed pain or other dyspeptic disorders, endoscopic examination revealed minimal changes in the mucosa of the gastroduodenal zone. Therefore, carrying out endoscopic control, preferably in the early stages of treatment, is the most necessary and mandatory method of preventing serious complications.

**Keywords:** nonsteroidal anti-inflammatory drugs, gastroduodenal lesions, gastric ulcer, ischemic heart disease.

### Introduction

Today one of leading places in medical practice is occupied by nonsteroid antiinflammatory medicines (NCAIDs). Medicines of this class have a wide range of clinical effects and are used at diseases of osteomuscular and cardiovascular system and also at a number of other states and diseases [4]. It is no secret that NCAIDs can cause a number of undesirable reactions owing to which the therapeutic value of this class of medicines can be significantly limited [1, 6]. Traditionally on the first place among these reactions put the NCAIDs -gastropathy. The term a NCAIDs-gastropathy designate the erosive cankers of a gastroduodenal zone which are arising against the background of intake of these medicines and having the reference klinik and endoscopic picture.

This pathology is bound to systemic action of NCAIDs and develops irrespective of a way of introduction with formation of erosion and ulcers in the mucosa of the top departments of digestive tract, and in certain cases with complications life-endangering - bleedings and perforations [5, 7].

The ischemic heart disease occupies one of the leading positions in structure of incidence of the population. The pathogenesis of an ischemic disease is characterized by the developing and progressing violations of system of a hemostasis that dictates need of use of continuous antiagregantny therapy. The "gold" standard for this purpose are the medicines created on the basis of Acidum acetylsalicylicum (AAS) [2].

The long-lived reception by ischemic heart disease patients of Acidum

acetylsalicylicum increases risk of emergence of the dyspepsia phenomena and also development of erosion and stomach ulcers and the duodenum. In this regard there are relevant questions of early diagnostics and adequate therapy of the NCAIDs -gastropathy with ischemic heart disease patients [3].

**Research objective** – to estimate the nature of clinical and endoscopic features of the gastropathies induced by intake of nonsteroid antiinflammatory medicines at patients with heart pathology.

### Material and research techniques

The research included 87 patients, with the ischemic heart disease patients various forms which were on treatment in "YGB №3" and cardiological office of the Yakut city hospital. The gastropathy induced by reception of NCAIDs took place in 32 cases that made 36,8% of



total number of observations. All patients included in a research the progressive time took various AAS drugs. Therefore, all presented cases of defeat of a gastroduodenal zone at ischemic heart disease patients, allow us to believe presence of the NCAIDs -gastropathy at them. Average age of the surveyed  $63.7 \pm 3.5$  years.

For the solution of objectives there were conducted: clinical (studying of complaints, collecting anamnesis of a disease, data of objective physical inspection) and laboratory and instrumental research methods.

By all patient included in a research besides all-clinical inspection it was carried out esophagogastroduodenoscopy which is the main instrumental method of confirmation of presence at the patient of the NCAIDs -gastropathy

**Results and discussion.** In the analysis of the IHD various forms it became clear that the most often erosive defeats of a gastroduodenal zone meet at patients with the progressing stenocardia (59,4%) and a sharp myocardial infarction (21,8%). And only 6, 2% fell to the share for the first time of the arisen stenocardia.

As a result of the conducted clinical examination from 32 ischemic heart disease patients with the diagnosed NCAIDs -gastropathy clinical manifestations were observed at 21 (65,6%). By results of studying of complaints of the most often sick slight pains and feeling of a discomfort in epigastric area 14 (66,6%) disturbed. Dyspepsia symptoms in the form of nausea, vomiting and heartburn were noted in 23, 8%, 4,7% and 14,3% of cases.

The carried-out analysis of risk factors showed that at patients of an ischemic heart disease with the - NCAIDs gastropathy such factors as an age generally prevail 65 years (71,9%) and duration of administration of drugs of this group (68,7%) are more senior.

It should be noted that the clinical picture was characterized by discrepancy between a symptomatology and endoscopic changes. It was shown by the fact that in the presence of a

bright endoscopic picture (an erosion, an ulcer) NCAIDs -gastropathies often proceeded asymptotically. On the contrary, at most of the patients, noting pains or other dyspepsia frustration, at an endoscopic research minimum changes of a gastroduodenal zone mucosa came to light.

At assessment of an endoscopic picture at patients from the ischemic heart diseases accepting NCAIDs the polymorphism of changes of a mucosa of a gastroduodenal zone was noted. The simple and multiple erosion of a mucosa of a stomach localized in antral department - 63,2% and also hyperemia and hypostasis mucous a stomach of 24,5% of patients met most often. 8,6% with the most frequent localization in a bulb fell to the share of erosion of a mucosa of a duodenum. Stomach ulcer and a duodenum were found in 3,7% of cases, of them the majority was made by duodenum bulb mucosa ulcers.

#### Conclusion

Thus, clinical manifestations of the NCAIDs -gastropathy and changes revealed at an endoscopic research in a mucosa of a gastroduodenal zone of ischemic heart disease patients in most cases do not correspond therefore endoscopic monitoring, especially in early terms of treatment, is an obligatory method of prophylaxis of heavy complications (bleedings, perforations).

#### References

1. Alekseenko S.A. Sivak M.A. Sovremennyye podhody k profilaktike NPVP-gastropatii [Current approaches to the prevention of NSAID gastropathy] *Dal'nevostochnyy medicinskij zhurnal* [Far east medical journal]. Khabarovsk, 2015, No. 2, p.123-128.
2. Vyortkin A.L. . Aristarhova O.Y. Adonina E.V. , et al. Bezopasnost' i farmakoekonomicheskaya ehffektivnost' primeneniya razlichnykh preparatov acetilsalicylovoj kisloty u pacientov s ishemicheskoy bolezn'yu serdca [Safety and pharmacoeconomic effectiveness of use of various medicines of acidum acetylsalicylicum for patients with an ischemic heart disease] *Russkij medicinskij zhurnal* [Russian Medical Journal]. Moscow, 2009, V. 17. No. 8 , p.15-19.

3. Zvenigorodskaya L.A. Bondarenko E.Y. Novye vozmozhnosti gastroprotekcii u pacientov s IBS na fone priema antiagregantnoj terapii malymi dozami aspirina [New options of gastroprotection for patients with IHD receiving anti-aggregant therapy with low-dose aspirin] *Serdce* [Heart]. Moscow, 2008. V. 7. No. 2 , p.118-120.
4. Morozova T.E. Rykova S. M. CHukina M. A. NPVP-gastropatii u bol'nyh s sochetannoj patologiej serdechno- sosudistoj sistemy i zabolevaniyami sustavov i pozvonochnika [ NSAID gastropathy in patients with comorbid diseases] *Eksperimental'naya i klinicheskaya gastroenterologiya* [Experimental & clinical gastroenterology ] . Moscow, 2015, V. 118. No. 6 , p.64-70.
5. Karateev A.E. Moroz E.V. Problema NPVP – gastropatii: sovremennyye predstavleniya [Problem of NSAIDs-gastropathy: modern views] *Meditsinskij alfavit* [Medical alphabet]. Moscow, 2017, V4. No. 40, p.13-20 .
6. Shavlovskaya O.A. Preimushchestva NPVP, selektivnykh inhibitorov COG-2 v terapii bolevoogo sindroma [Advantages of NSAIDs, from chronic cyclooxygenase-2 inhibitors in the treatment of pain syndrome] *Spravochnik poliklinicheskogo vracha* [Reference book of a polyclinic doctor]. Moscow, 2014. No. 3 , p.46-49.
7. Hariforoosh S. Adverse Effects of Nonsteroidal Antiinflammatory Drugs: An Update of Gastrointestinal, Cardiovascular and Renal Complications / S. Hariforoosh, W. Asghar, F. Jamali // *J Pharm Pharm Sci.* – 2013. – No. 16 (5). – P. 821–847.

#### The authors:

Medical Institute of the M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia:

8. Chibyeva Lyudmila Grigoryevna - Doctor of Medical Sciences, professor of the department of propaedeutics and faculty therapy with endocrinology and exercise therapy. E-mail: chibyeva\_l@mail.ru;
9. Lytkina Alina Albertovna - post-graduate student of the department of propaedeutic and faculty therapy with endocrinology and exercise therapy, E-mail: gidro1777@mail.ru.



S.D. Efremova, A.S. Golderova, Z.N. Krivoschapkina,  
E.D. Okhlopko, V.M. Nikolaev, E.V. Tsybandina,  
P.M. Ivanov, N.N. Sazonov

## THE WATER HARDNESS AND ITS RELATIONSHIPS WITH THE LEVEL OF TUMOR MARKERS AMONG THE INHABITANTS OF YAKUTIA

DOI 10.25789/YMJ.2018.63.11

### ABSTRACT

A total of 675 residents aged 18 to 79 years living in 6 different regions of the Republic of Sakha (Yakutia), 461 men and 214 women were examined. The purpose of the study was to assess the extent of the relationship between the level of tumor markers, depending on the rigidity of used water. The concentration of tumor markers in blood serum was determined by the method of enzyme immunoassay. 54.1% of all surveyed people use unpurified water for drinking purposes. Of the six surveyed areas in only three (Namsky District, Verkhnekolymsky District, Aldansky District), the water hardness level corresponded to the norm. The correlation analysis found significant direct correlation between the level of tumor markers and water hardness: AFP ( $r = 0.134$ ,  $p = 0.000$ ), CEA ( $r = 0.211$ ,  $p = 0.000$ ), PSA ( $r = 0.360$ ,  $p = 0.000$ ) and CA-125 ( $r = 0.290$ ,  $p = 0.000$ ).

**Keywords:** water hardness, tumor markers, Yakutia.

### Introduction

Yakutia has huge reserves of water resources, on its territory there are more than 700 thousand large and small rivers, which is about 30% of all rivers in Russia. On the territory there are about 825 thousand lakes with an area of more than 1 ha, which is more than 40% of Russia's lakes. [1]. The surface waters of Yakutia belong to moderately polluted waters, although a large number of toxic elements are emitted in sewage. Large-scale polluters of surface waters are cities, large settlements located along the river basins. High levels of pollution are facilitated by: - the presence of permafrost, which does not allow seepage to surface water, which leads to contaminated water spilling over the surface; - Due to prolonged winter, short summer, biological treatment of polluted water is slow. If in the European territory of Russia contaminated water is cleared through 200-300 km, then in the rivers of Yakutia it is not cleared up to 1500 km [3]. Yakutia, according to the incidence rate of some nosological forms of malignant tumors, belongs to the regions that are among the leaders of not only Russia but also in the world. In terms of the incidence of malignant tumors of the esophagus, liver and lung, both in men and women, the republic is among the territories with the highest rates among the remaining regions of the Russian Federation [2].

Water objects on the territory of the Republic of Sakha (Yakutia) are used for drinking and household water supply of the population, electricity generation in gold mining, diamonds, non-metallic building materials, wastewater discharge and other purposes. The main consumers of water are industry (diamond and gold

mining, mining of precious metals, electric power and housing and communal services) [6].

In the conditions of ecological trouble, the immune, endocrine and central nervous systems react before other systems, causing a wide range of functional disorders. Among oncological diseases, diseases of lung tissue, skin and digestive organs are characterized by special eco-dependency, since there is direct contact with environmental factors - air and water [4].

According to WHO, 85% of all diseases in the world are associated with water pollution, because in such water contains more than 13000 toxic elements, including chlorine and its organic compounds, salts of heavy metals, nitrates, pesticides, which leads to the development of serious human diseases, including diseases of the cardiovascular system, malignant diseases. In this regard, the study of the relationship between the quality of water used and the health status of the population, in particular the level of specific markers that assess the risk of cancer, is of interest. The purpose of the study was to assess the degree of relationship between the level of tumor markers and the contamination of water used.

### Methods and materials of the study

A total of 675 residents aged 18 to 79 years living in 6 different regions of the Republic of Sakha (Yakutia), 461 men and 214 women were examined. The national composition of the surveyed persons was represented by 246 Yakuts, 194 indigenous small-numbered peoples of the North (Evenki, Evens and Dolgans), 236 people (Russians, Tatars, etc.). The

environmental impact is significantly influenced by anthropogenic pressures on the territory, including the population and different types of technogenic pollution. The regions we surveyed were ranked according to the stress factor index (SFI) (E.I. Burtseva, 2006), which reflected a comprehensive assessment of the state of the environment surrounding environmental impacts (including mountain mass extracted from the earth's interior, pollutant emissions in atmosphere, discharge of polluting wastewater), Gorny District refers to areas with low load (I); Anabarsky District - with reduced load (II); Namsky District - with medium load (III), Verkhnekolymsky District - with increased load (IV); Aldansky and Lensky Districts - with a high load (VI, V) (Table 1).

The surveyed areas of Yakutia belong to various zones of Yakutia, according to climatic and anthropogenic pressures. The Gorny and Namsky Districts belong to the Central zone of Yakutia, Anabarsky and Verkhnekolymsky Districts - to the Arctic zone, Lensky and Aldansky Districts - to the Southern industrial zone.

Blood for laboratory tests was taken from the ulnar vein in the morning on an empty stomach. To identify the risk groups for oncopathological conditions, we were determined of concentration of tumor markers by the enzyme immunoassay method: alfa-fetoprotein (AFP), cancer embryonic antigen (CEA), for men prostate-specific antigen (PSA), for women CA-125 in serum using test kits of the firm « Vector-Best » (Novosibirsk, Russia). Data of the chemical composition of water, taken from ponds used by residents for drinking purposes (Matta River - Magarass

Table 1

Characteristics of the surveyed population by age and sex

Locality, District of the Republic of Sakha (Yakutia)	SFI (Burtseva E.I., 2006)	Total surveyed	Men / women	Average age
v. Magarass, Gorny District	low load	54	10 / 44	42,00 ± 10,45
v. Modut, Namsky District	medium load	119	41 / 78	45,82 ± 11,65
v. Saskylakh, Anabarsky District	reduced load	135	37 / 98	48,26 ± 13,33
v. Nelemnoe, Verkhnekolymsky District	increased load	138	50 / 88	44,45 ± 13,6
v. Vitim, Lensky District	high load	65	11 / 54	46,52 ± 14,67
v. Tommot, Aldansky District	high load	164	65 / 99	44,23 ± 11,40

village, Gorny District; in the area of water intake of the Lena River - Modut village, Namsky District; SPNT «The Yasachnaya basin» - Nelemnoe village, Verkhnekolymsky District; Peleduy River - Vitim village, Lensky District; Aldan River - Tommot village, Aldansky District) have been provided by the Office of the Hydrometeorological Service of the RS (Y).

The study was approved by the decision of the Local Ethical Committee of the FSBSI «YSC of the CMP» and was carried out with the informed consent of the test subjects in accordance with the ethical norms of the Helsinki Declaration (2000). Statistical processing of data was carried out using the SPSS Statistics 19 software package. The normality of the distribution of quantitative indicators was verified using the Kolmogorov-Smirnov test. Standard methods of variational statistics were used: calculation of average values, standard deviation. The data in the table are presented in the form  $M \pm \sigma$ , where  $M$  - is the mean,  $\sigma$  - is the standard deviation. To study the relationships between the variables, a pair correlation procedure was used using the Spearman's test (for variables measured in the rank scale), where  $r$  - is the correlation coefficient, and  $p$  - is the significance of the result. When comparing the quantitative indices of the groups, the significance of the differences was assessed using the Student's t-test for the normal distribution and the Mann-Whitney test for the abnormal distribution. The results were considered to be statistically significant with the values of the achieved significance level  $p < 0.05$ .

### Results and discussion

The survey data (response - 94.2%) were analyzed, in which the respondent asked the question: «Which water do you drink most often for drinking purposes?» Chose 4 options for response (1 - water from harvested ice, 2 - packaged, 3 - filtered, 4 - unpurified). The analysis of the survey data showed a different nature of the answers that have common trends depending on the place of residence.

Thus, 54.1% of all surveyed people drink unpurified water for drinking purposes; 23.6% - melt water, 20.1% - filtered water and only 2.3% - packaged water.

Residents of the Arctic zone (Verkhnekolymsky and Anabarsky Districts) consume mostly unpurified water (91.2% and 59.5%, respectively). The Central regions (Namsky and Gorny Districts), where there is no centralized water supply, drink melt water from the lakes and rivers (58% and 92.6%, respectively). In industrial regions of Yakutia (Aldansky and Lensky Districts), the proportion of people who use packaged or filtered water is much higher than in other regions, which indirectly indicates a low quality of water. However, in the Aldansky District, the proportion of people using unpurified water is predominant (61.5%).

The water hardness of these settlements indicates significant differences: very soft water is noted in Gorny (0.8 mmol / L) and Anabarsky Districts (0.9 mmol / L). In Lensky District the water hardness value is the highest (7.86 mmol / L), almost unfit water for consumption for drinking purposes (up to 7 mmol / L). Of the six surveyed districts, only three (Namsky, Verkhnekolymsky, Aldansky) had a water hardness level of 1.5 mmol / L to 7 mmol / L (Figure 2).

Undoubtedly, a high index of water hardness in the Peleduy River is caused by a high concentration of chlorides (1.58

\* TLV), sulfates (2.8 \* TLV), sodium (2.4 \* TLV), copper (1.6 \* TLV) and manganese (2.5 \* TLV) and strontium belonging to the 3rd danger class exceeds the TLV by 3.9 times. It should be noted that the concentration of calcium and magnesium in the Peleduy River was the highest in comparison with other regions, although the upper limits of the TLV were not exceeded.

The conducted correlation analysis of the chemical substances, depending on the water hardness, established strong positive correlation links on the concentration of chlorides ( $r = 0.969$ ,  $p = 0.000$ ), calcium ( $r = 0.889$ ,  $p = 0.000$ ), sulfates ( $r = 0.848$ ,  $p = 0.000$ ) and magnesium ( $r = 0.860$ ,  $p = 0.000$ ), negative correlations from the iron concentration ( $r = -0.774$ ;  $p = 0.000$ ) of lead ( $r = -0.562$ ;  $p = 0.000$ ).

To determine the significant relationships between water hardness and blood parameters, ranking was carried out: 1 group included residents of areas with soft water (Gorny District,  $n = 189$ ), 2 - with normal hardness of water (Namsky, Anabarsky, Verkhnekolymsky and Aldansky,  $n = 421$ ), 3 - with hard water (Lensky district,  $n = 65$ ). The conducted correlation analysis established significant direct correlation links of the tumor marker level with increasing water hardness: AFP ( $r = 0.134$ ;  $p = 0.000$ ); CEA ( $r = 0.211$ ;  $p = 0.000$ ), PSA ( $r = 0.360$ ,  $p = 0.000$ ) and

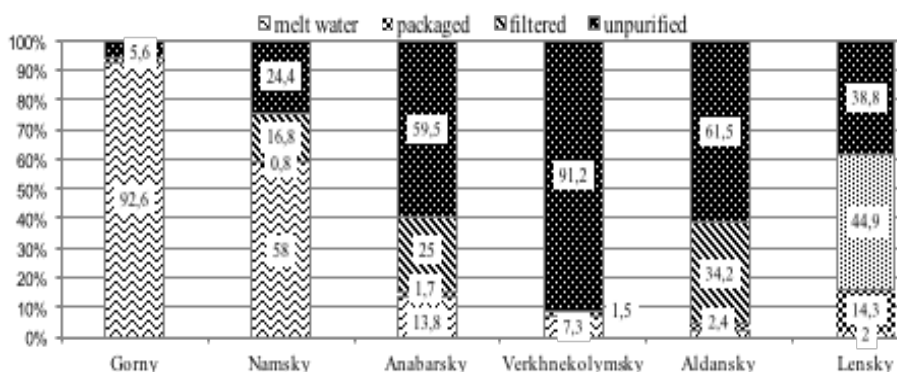


Fig. 1. The distribution of the surveyed persons, depending on the type of water consumed for drinking purposes.



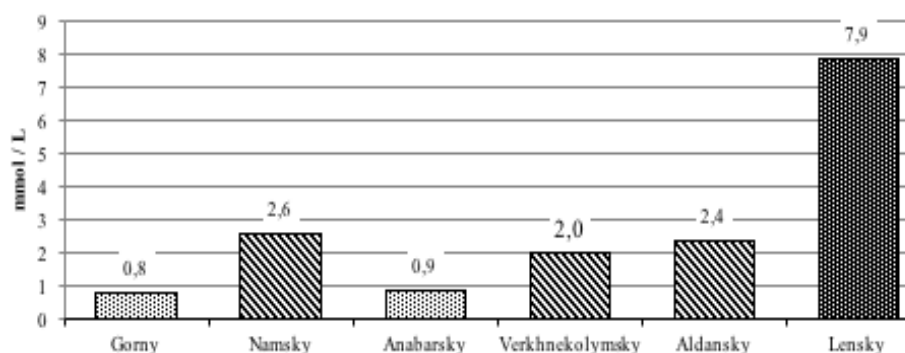


Fig. 2. Indicators of water hardness in the surveyed districts.

Table 2

The level of tumor markers in residents, depending on the hardness of water

Tumor markers	1 group (soft water)	2 group (normal water)	3 group (hard water)	p
Alpha-fetoprotein (AFP);	6,65±0,34	7,41±0,16	7,63±0,35	0,045 <sup>1,2</sup> 0,047 <sup>1,3</sup>
0-10 pg/ml	2,26±0,10	3,12±0,08	3,77±0,12	0,000 <sup>1,2</sup> 0,000 <sup>1,3</sup> 0,003 <sup>2,3</sup>
Cancer embryonic antigen (CEA); 0-5 pg/ml	1,07±0,09	2,25±0,11	2,27±0,50	0,000 <sup>1,2</sup> 0,039 <sup>1,3</sup>
Prostate-specific antigen (PSA); 0,3-4,0 pg/ml	14,14±1,66	25,2±0,73	15,71±0,95	0,000 <sup>1,2</sup> 0,000 <sup>2,3</sup>
CA-125; 0-35 pg/ml				

CA-125 ( $r = 0.290$ ,  $p = 0.000$ ) (Table 2).

Tumor markers expressed by low-differentiated cells are not only associated with a tumor, but also with the presence of chemical, toxic environmental factors. CEA serves as a sign of malignant growth of any nature and localization and is completely nonspecific. CEA is a nonspecific marker for any type of tumor and reflects the general carcinogenic background of the organism. With regular use of hard water, the risk of various diseases of the internal organs increases, in the first place, of the liver and kidneys [5].

Thus, the results obtained by us indicate that the residents who drink water contaminated with chemicals for drinking purposes are at increased risk of cancer.

### Conclusions

1. 54.1% of all the surveyed people drink unpurified water for drinking purposes; 23.6% - melt water, 20.1% - filtered water and only 2.3% - packaged water.

2. The water hardness of these districts indicates significant differences: very soft water is noted in the Gorny and Anabarsky Districts. In Lensky Districts, the value of water hardness is the highest,

almost unfit for consumption for drinking purposes. Of the six surveyed districts in only three (Namsky, Verkhnekolymsky, Aldansky), the level of water hardness corresponded to the norm.

3. The correlation analysis found significant direct correlation of the level of tumor markers with increasing water hardness: AFP ( $r = 0.134$ ,  $p = 0.000$ ), CEA ( $r = 0.211$ ,  $p = 0.000$ ), PSA ( $r = 0.360$ ,  $p = 0.000$ ) and CA-125 ( $r = 0.290$ ,  $p = 0.000$ ).

### References

1. Burtseva Ye.I. Geoekologicheskiye aspekty razvitiya Yakutii [Geoecological aspects of the development of Yakutia]. Novosibirsk: Nauka, 2006, 269p.
2. Ivanov P.M., Tomskiy M.I., Kipriyanova N.S. Zlokachestvennyye novoobrazovaniya v Yakutii v nachale tret'yego tysyacheletiya [Malignant neoplasms in Yakutia at the beginning of the third millennium]. Yakutsk: «Smik-Master. Poligrafiya», 2012, 168 p.
3. Lapteva N.I. Ekologicheskoye sostoyaniye poverkhnostnykh vod: ucheb, posobiye [Ecological state of surface waters: textbooks, manual]. Moscow: Akademiya, 2001, p.20-25.
4. Mikheyeva G.Kh., Gataullin I.G., Biktemirova R.G. Zagryazneniye

okruzhayushchey sredy faktor riska formirovaniya zabolevayemosti onkologicheskoy patologiyey v Ul'yanskoyskoy oblasti [Pollution of the environment is a risk factor for the formation of the incidence of oncological pathology in the Ulyanovsk region]. Tyumenskiy meditsinskiy zhurnal [Tyumen medical journal], 2012, No.4, p. 20-22.

5. Turovskiy B.V., Inyukina T.A. Opasnyye i vrednyye primesi prirodnkh i pit'yevykh vod. [Dangerous and harmful impurities of natural and drinking waters] Politematicheskii setevoy elektronnyy nauchnyy zhurnal Kubanskogo gosudarstvennogo agrarnogo universitet [The Political Network Electronic Scientific Journal of the Kuban State Agrarian University], 2014, No 102, p. 432-445.
6. Ammosova M.N. et.al. Ekologicheskaya situatsiya v zolotodobyvayushchey promyshlennosti Respubliki Sakha (Yakutiya) [Ecological situation in the gold mining industry of the Republic of Sakha (Yakutia)] Fundamental'nyye i prikladnyye issledovaniya: problemy i rezul'taty [Fundamental and applied research: problems and results]. 2014, No.15, p.21-25.

### The authors

Federal State Budget Scientific Institution «Yakut Scientific Center of Complex Medical Problems» 677000 st. Sergelyakhskoye shosse, 4.

North-Eastern Federal University M.K. Ammosov 677000 st. Belinskogo

1. Efremova Svetlana Dmitrievna - Junior Researcher of the Laboratory of Immunology, FSBSI «YSC CMP», esd64@mail.ru;
2. Golderova Aitalina Semenovna - Doctor of Medical Sciences, PTI « M.K. Ammosov NEFU », hoto68@mail.ru;
3. Okhlopova Elena Dmitrievna - Candidate of Biology Science, Leading Researcher - Chief of the Immunology Laboratory of the FSBSI «YSC CMP», elena\_ohlopova@mail.ru;
4. Nikolaev Vyacheslav Mikhailovich - Candidate of Biology Science, Chief Researcher- Chief of DSAM of the FSBSI «YSC CMP», Nikolaev1126@mail.ru;
5. Tsyndina Evgenia Viktorovna - Junior Researcher of the Laboratory of Immunology, FSBSI «YSC CMP», tsyndina93@mail.ru;
6. Ivanov Pyotr Mikhailovich - Doctor of Medical Science, senior researcher FSBSI «YSC CMP»;
7. Sazonov Nikolai Nikitich - Doctor of Biology Science, BGF « M.K. Ammosov NEFU».

Ya.A. Munkhalova, V.B. Egorova, S.N. Alekseeva, T.G. Dmitrieva,  
O.N. Ivanova, A.P. Korkina

## ETIOLOGICAL, CLINICAL FEATURES OF SECONDARY PYELONEPHRITIS IN CHILDREN

DOI 10.25789/YMJ.2018.63.12

### ABSTRACT

The high frequency of pyelonephritis, as well as its tendency to be chronic and progressive, gives the problem of timely diagnosis and treatment of pyelonephritis a particular urgency. Among the factors predisposing to secondary pyelonephritis, the abnormalities of the development of the urinary system that cause disturbances in urodynamics have always been given importance.

The article presents the results of the study of the etiological, clinical features of secondary pyelonephritis in children, depending on the type of abnormality of the development of the kidneys and urinary tract. 150 children with microbial-inflammatory diseases of the urinary system were examined. As a result of the study, it was revealed that pyelonephritis dominates the structure of microbial-inflammatory diseases of the urinary system. Among the abnormalities of kidney and urinary tract development in this group of patients, the following were identified: vesicoureteral reflux, neurogenic dysfunction of the bladder, kidney doubling, kidney dystopia, nephroptosis, kidney hypoplasia, renal agenesis, renal dysplasia. According to our data, the secondary pyelonephritis in the structure of secondary chronic pyelonephritis is secondary to vesicoureteral reflux (25.5%) and neurogenic bladder dysfunction (52.2%). In the study of the complications of vesicoureteral reflux with chronic pyelonephritis secondary revealed that the major complication is nephropathy reflux with the development of chronic renal insufficiency, which was observed in 12.5% of cases. Despite the fact that vesicoureteral reflux is more common in girls, the more severe course of the disease was noted in boys and, consequently, reflux-nephropathy often developed in boys. Reflux-nephropathy does not have a typical clinical picture, is characterized by a steadily progressing course with the development of nephrosclerosis.

It has been revealed that pyelonephritis more and more clearly appears as a secondary process. According to our data, in the structure of secondary chronic pyelonephritis, the greatest percentage is secondary pyelonephritis against the background of neurogenic dysfunction of the bladder and against a background of vesicoureteral reflux. In this case, children more often recorded neurogenic dysfunction of the bladder in a hyporeflexive type. And among children with vesicoureteral reflux, the prevalence of vesicoureteral reflux on the left was more often noted. Recently, the concept of obstruction of the urinary tract has undergone significant changes and has become more capacious.

**Keywords:** children, infection of the urinary system, secondary pyelonephritis, malformations.

### Introduction

In recent decades, there has been an unfavorable upward trend in the child population of recurrent pyelonephritis, which is formed against the background of congenital malformations of the urinary system [7]. The average annual rate of increase in the incidence of urinary tract infection is 6.1% [1, 5]. The severity of the problem is due to a high incidence of pathogenetic factors of infection of the urinary system (reflux-uropathy, congenital malformations of the urinary system with violation of urodynamics, a combination of vesicoureteral reflux and neurogenic bladder dysfunction, urolithiasis, hemolytic-uremic syndrome, intestinal microbiocenosis, etc.), and also a feature of uropathogenic properties of pathogens, their ability to persistence, high antibiotic resistance [1]. The high frequency of pyelonephritis, as well as its tendency to be chronic and progressive, gives the problem of timely diagnosis and treatment of pyelonephritis a particular urgency. Among the factors predisposing to secondary pyelonephritis, the abnormalities of the development of the urinary system that cause disturbances in urodynamics have always been given importance. In the structure of all congenital malformations, the anomalies of the genitourinary system occupy the third

place. There are more than 50 diseases of the urinary system as hereditary and congenital, as well as acquired, both primary and secondary, which result in the development of chronic renal failure. But the most common cause of chronic renal failure in children is congenital and hereditary diseases of the kidneys and urinary tract. Among the risk factors for the development of microbial-inflammatory kidney diseases in children, obstruction of the urinary tract is one of the leading places [2]. Normal urodynamics is one of the factors that prevent the spread of microorganisms and their adhesion on the surface of uroepithelium.

The consequences of kidney damage in childhood are so significant that timely detection of them is a problem not only medical but also social [7]. The social significance of the problem is reinforced by the fact that the treatment of these patients at all stages of the development of the pathological process often becomes expensive, including through the need for repeated outpatient visits to the doctor and hospitalizations, and they often experience a significant deterioration in the quality of life [8].

The number of children with recurrent course of various variants of infections of the urinary system is constantly increasing, making it necessary to search

for more effective ways of treating renal microbial-inflammatory infection on the basis of modern principles of preventive, clinical and rehabilitation nephrology [1]. The study of the infectious and inflammatory pathology of the organs of the urinary system is inextricably linked with the definition of its etiology [5, 6]. For many years, the main causative agent of pyelonephritis in children is *E.coli* (inoculation from urine ranges from 60 to 87.3% [1], which has a large number of virulence factors [1, 2, 3, 8]. However, over the past decade, a change the structure of the causative agents of urinary system infections in children due to an increase in the frequency of other representatives of the *Enterobacteriaceae* family (*Klebsiella*, *Proteus*, *Enterobacter*), as well as Gram-positive coccal flora and aerobic Gram-negative rods [3, 6], which indicates the need for a regular microbiologic monitoring of uropneoprase in children with urinary system infections in the regions of the Russian Federation [4].

**The aim** of our study was to study the etiological, clinical features of secondary pyelonephritis in children, depending on the type of abnormality of the development of the kidneys and urinary tract.

### Materials and methods of research

150 children with microbial-inflammatory diseases of the urinary system, hos-

pitalized in the nephrologic and urological departments of the Pediatric Center of the National Center of Medicine from 2010 to 2017, 85 girls, 65 boys were examined. The diagnosis of pyelonephritis was verified in accordance with the classification proposed by M. Studenikin (1982). All patients were assessed the degree of activity of the pathological process (severity of intoxication, pain, dysuric syndromes), the functional state of the kidneys, bacteriological examination of urine, instrumental methods of studying the kidneys and urinary tract (ultrasound, intravenous urography, cystography).

#### Results and discussion

In the structure of microbial-inflammatory diseases of the urinary system acute pyelonephritis was verified in 83 (55.3%) patients, in 60 (40.0%) children pyelonephritis was secondary, and in 7 (4.7%) children with chronic pyelonephritis of structural and functional disorders of the urinary system at the time of the examination not found.

Among the abnormalities of kidney and urinary tract development in the studied patients, the following were identified: vesicoureteral reflux, neurogenic dysfunction of the bladder, kidney doubling, kidney dystopia, nephroptosis, kidney hypoplasia, renal agenesis, renal dysplasia. According to our data, the secondary pyelonephritis often occurred on the background of vesicoureteral reflux (25.5%) and neurogenic bladder dysfunction (52.2%). These data coincide with the literature data, which confirm the emergence of secondary pyelonephritis by infection of the urinary system against a background of urodynamics disturbance caused most often by vesicoureteral reflux and neurogenic dysfunction of the bladder.

We have identified the clinical features of secondary pyelonephritis in the background of various abnormalities of kidney and urinary tract development.

Neurogenic bladder dysfunction (NBD) is a violation of reservoir and evacuation functions of the bladder, which develop due to damage to the mechanisms of regulation of urination of various geneses and at different levels. NBD refers to functional abnormalities of kidney development. In this group of patients there were 31 children (52.2%), and 20 (64.5%) children with NBD in a hyporeflexive type and 11 (35.5%) - in a hyperreflex type. The combination of hyperreflex NBD with vesicoureteral reflux was 11.8%.

Bladder ureter reflux (BUR) is one of the most common diseases of the lower urinary tract in children. BUR met in 15

children (25%), at the age of 1 year, the disease showed up in 6.3% of cases. Right BUR was detected in 5 children (33.3%), on the left - in 10 children (66.7%). Analysis of the age structure of patients showed that the proportion of children under 5 years is 33.3%, from 6-9 years - 40.7%, from 10-13 years - 26.0%. At analyzing the distribution of children by sex, taking into account age groups, it was found that the BUR occurs with the same frequency (33%) in boys and girls from 2 to 5 years; in children 6-9 years: girls - 47%, boys - 33%; from 10-13 years: girls - 20%, boys - 33%.

Development of BUR in 62.5% of children was preceded by an unfavorable course of the prenatal period. In 40.6% of cases in their mothers there were complications of pregnancy in the form of anemia, gestosis, threat of interruption, etc., in 12.5% of cases, pregnancy was accompanied by extragenital pathology, in 9.4% of cases there was a combination of complications of pregnancy and extragenital pathology. In addition, in 8% of cases, BUR was registered in mothers, and only in 37.5% there was a smooth course of pregnancy.

The main clinical manifestations in children under 1 year were severe symptoms of intoxication with high hyperthermia, increased excitability, and lack of body weight. The clinical picture in older children was characterized by periodic temperature rises, accompanied by pallor of the skin, lethargy, headache. Pain in the abdomen was aching, usually in the lumbar, subcostal area or along the ureter.

At laboratory-instrumental diagnostics of vesicoureteral reflux in children the following was revealed. As a rule, a symptomatic complex of urinary infection was detected, characterized by leucocyturia, bacteriuria, hypostenuria, nocturia, increased ESR. In the case of the formation of focal nephrosclerosis, a tendency to hypo- and isostenuria, polyuria was added, persistent proteinuria appeared. Ultrasound diagnosis tentatively determined the degree of dilatation of the cavity system, the size of the kidneys, the thickness of the parenchyma, variants of its deformation. Intravenous urography, not being a diagnostic test for reflux, nevertheless allowed to suspect the presence of pathological processes in the lower parts of the urinary tract. So, for the presence of BUR, hypotension of the ureters can indicate, especially if it is of a one-sided nature, dilatation of the cavity system and the distal ureter. Mictorial cystography is the main method of reflux diagnostics, which makes it possible to

reveal not only its presence, but also the degree of expression.

At examining children with BUR, the following abnormalities of the development of the organs of the urinary system were revealed: dysplasia, hypoplasia, kidneys doubling in 36% of children; neurogenic dysfunction of the bladder - in 24%, of them hyporeflexive type - in 14%, in the hyperreflexive type - in 10% of children. Double-sided BUR was noted in 56.2% of cases, unilateral - in 43.8%. Second-degree BUR occurred in 18.8% of cases, grade III - in 71.9%, IV degree - in 9.4% of cases.

In accordance with the tasks set, we analyzed the effectiveness of treatment in children with BUR against chronic secondary pyelonephritis. Of all hospitalized children, 56.2% of patients received conservative treatment. Great attention was paid to conservative treatment of antibiotic therapy, physiotherapy. In assessing the efficacy of conservative therapy, it was noted that in boys with first-degree BUR a good result was achieved in 72% of cases, with II degree of BUR in 57%; in girls with first degree PMR - in 67%, with II degree of BUR - in 64%. Surgical treatment was performed in 43.8% of the children.

At studying the complications of BUR against the background of chronic secondary pyelonephritis, it was found that the main complication is reflux-nephropathy with the development of chronic renal failure, which was noted in 12.5% of cases. Despite the fact that BUR is more common in girls, the more severe course of the disease was observed in boys and, consequently, reflux-nephropathy more often developed in boys. Reflux-nephropathy does not have a typical clinical picture, is characterized by a steadily progressing course both in the presence of BUR and after its regression. Factors contributing to the formation and increase in the degree of nephrosclerosis include long-persistent BUR, the recurring course of infection of the urinary system, neurogenic dysfunction of the bladder, dysplasia of the canvas tissue.

Doubling of the kidneys is one of the most common malformations, which is transmitted by an autosomal recessive type of inheritance. Among the investigated patients, kidneys were doubled in 6 children (10%). Doubling of the left kidney was determined in 3 children (50%), the right kidney in 2 children (33.3%), incomplete doubling of both kidneys in 1 child (16.7%). In 2 children (33.3%), the doubled kidney was complicated by hydro-nephrosis, in 1 child (16.7%) - BUR. The main clinical symptoms were abdominal



pain - in 66.6% of cases, microhematuria - in 47.3% of cases, arterial hypertension - in 3.3% of cases.

Among the anomalies of the situation dystopia of the kidneys is the most common pathology. Dystopic kidneys are retained in their position due to abnormally developed vessels that provide blood circulation in the early stages of embryonic development or insufficient growth of the ureter in length. With kidney dystopia there were 4 children (6.7%). The leading symptom in kidney dystopia in children was pain when the position of the body changed. The most pronounced pain syndrome was detected in a child with pelvic dystopia of the kidneys.

Nephroptosis, excessive mobility of the kidneys, was determined in 6 children (10%). Among them, nephroptosis of the left kidney was detected in 1 child (16.7%), nephroptosis of the right kidney - in 5 children (83.3%). All children clinically detected abdominal pain and in 60% of cases - dyspepsia.

In 2 (3.3%) children, normonephronic hypoplasia of the kidneys was detected. There were no special clinical manifestations in this pathology in children.

In our group of patients there were 8 children (13.3%) with kidney agenesis unilateral (KAU). The cause of KAU is most often the failure of the inductive interaction of the ureteral outgrowth and the nephrogenic strand, which causes degeneration and resorption of the structure of the latter. Left kidney anogenesis was detected in 2 children (25%), right - in 6 (75%). One child had hypertension.

Kidney dysplasia was detected in 3 children (5%), all children had severe urinary syndrome, which was characterized by massive leukocyturia, mild proteinuria and 2 children with hematuria. One child had a recurrent abdominal syndrome.

In a bacteriological study of urine conducted against the background of antibacterial therapy, microflora was isolated in 28% of cases. In the development of the microbial-inflammatory process of the urinary system in 90.3% of cases there was a monoinfection, in 9.7% of cases the association of uropathogens - *E. coli* + *Str. faecium*, *Proteus mirabilis* + *Str. epidermidis*, *Citrobacter freundii* + *Klebsiella oxytoca*. The microbial inflammatory process was mainly caused by *E. coli* (42%) and *Klebsiella pneumoniae* (16.1%). Antibiotic therapy was carried out taking into account the sensitivity of antibiotics and uroseptics.

### The conclusion

Thus, pyelonephritis appears more and more clearly as a secondary process. According to our data, in the structure of secondary chronic pyelonephritis, the greatest percentage is secondary pyelonephritis against the background of neurogenic dysfunction of the bladder and vesicoureteral reflux. In this case, children more often recorded neurogenic dysfunction of the bladder in a hyporeflexive type. And among children with vesicoureteral reflux, the prevalence of BUR on the left was more often noted. Recently, the concept of obstruction of the urinary tract has undergone significant changes and has become more capacious. It unites now not only representations of mechanical obstacles to the flow of urine, but also dynamic, or, as they are called, "functional" disorders of the urinary tract, their hyper- or hypokinesia, dystonia, which also violate the normal passage of urine. Disorders of bladder emptying with neurogenic dysfunctions are accompanied by urodynamic disorders in both lower and upper urinary tract, which explains the rather high occurrence of pyelonephritis in children with neurogenic bladder dysfunction.

### References

1. Vyalkova A. A. Aktualnyye problemy tubulointerstitsialnogo porazheniya pochek u detey [Actual problems of tubulointerstitial kidney lesions in children] *Pediatriya* [Pediatrics]. 2008. V. 87, No. 3, p. 122–127.
2. Ignatova M.S. (red.). *Detskaya nefrologiya: Rukovodstvo dlya vrachey* [Pediatric Nephrology: A Guide for Physicians]. Moscow, MIA, 2011, 696 p.
3. Ignatova M. S. Problemy progressirovaniya bolezney pochek u detey i sovremennyye vozmozhnosti renoproteksii [Problems of kidney disease progression in children and modern possibilities of renoprotection] *Nefrologiya i dializ* [Nephrology and Dialysis]. 2005. V. 4, No. 7, p. 428–434.
4. Papayan A.V., Savenkova N.D. (red.) *Klinicheskaya nefrologiya detskogo vozrasta. Rukovodstvo dlya vrachey* [Clinical Nephrology of Childhood. A guide for doctors] St. Petersburg, Levsha, 2008, 600 p.
5. Lukyanov A.V. *Infektsii mochevoy sistemy u detey (etiologiya, mekhanizmy razvitiya, dispanserizatsiya)* [Infections of the urinary system in children (etiology, development mechanisms, clinical examination)] Avtoref. diss... dokt. med. nauk. [Thesis abstract... Doctor of Medical Sciences] Omsk, 2005,

45 p.

6. Natochin Yu.V., Mukhin N.A. *Vvedeniye v nefrologiyu* [Introduction to nephrology]. Moscow, GEOTAR, 2007, 152 p.
7. Pekareva H. A., Panteleyeva Ye. YU., Loskutova S. A., Chuprova A. B. Osobennosti techeniya i diagnostiki puzyrno-mochetochnikovogo refluksa u detey [Peculiarities of the course and diagnosis of vesicoureteral reflux in children] *Pediatriya* [Pediatrics], 2008, No 3, p. 31–36.
8. Lopatkin N. A. (red.) *Urologiya: Nats. rukovodstvo* [Urology: The national. guide]. Moscow, GEOTAR-Media, 2009.

### The authors

1. Munkhalova Yana Afanasievna - Candidate of Medical Sciences, Head of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: tokmacheva@mail.ru
2. Egorova Vera Borisovna - Candidate of Medical Sciences, Associate Professor, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: veraborisovna@yandex.ru
3. Alekseeva Sargylana Nikolaevna - Candidate of Medical Sciences, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: sargylanao@mail.ru
4. Dmitrieva Tatyana Gennadievna - doctor of medical sciences, professor of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. Contact phone: 8 (914) 2310839. E-mail: dtg63@mail.ru
5. Ivanova Olga Nikolaevna - doctor of medical sciences, professor of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: olgadoctor@list.ru
6. Korkina Anna Petrovna - student of the pediatric department of the Medical Institute of the M.K. Ammosov North-Eastern Federal University.
7. Address: 677018, Yakutsk, ul. Oyunsky, 27.
8. E-mail: korkinaaaa@mail.ru

O. G. Sidorova, S.K. Kononova, N.A. Barashkov, F.A. Platonov,  
S.A. Fedorova, E.K. Husnutdinova, V.L. Izhevskaya

## THE ANALYSIS OF SOCIAL READINESS OF PREGNANT WOMEN FROM FAMILIES BURDENED WITH HEREDITARY SPINOCEREBELLAR ATAXIA TYPE 1 TO UNDERGO PRENATAL DNA TEST

DOI 10.25789/YMJ.2018.63.13

### ABSTRACT

The analysis of social readiness of pregnant women from burdened families to undergo the prenatal DNA diagnostics program of spinocerebellar ataxia type 1 (SCA1) neurodegenerative monogenic disease is provided in the article. The research opens some social problems of pregnant women with risk of SCA1 for generation that will allow defining further competent tactics of the medicogenetic and social help to the families burdened with SCA1.

**Keywords:** prenatal diagnostics of hereditary diseases, spinocerebellar ataxia type 1, social readiness, tainted families.

### Introduction

Spinocerebellar Ataxia Type 1 (SCA1) – an incurable, hereditary, autosomal dominant monogenic disease of the motor system, which is mainly late-onset and the general symptom is dystaxia resulting from cerebellum lesions, its communications and the corresponding sensory systems [1,3].

Frequency of SCA1 in Yakutia is 46 cases on 100 thousand people of rural population in comparison with 1-2:100 thousand people of the world population. In connection with SCA1 high prevalence in the Yakut population and with the lack of effective treatment, great attention is paid to primary prenatal wellness [5, 7].

Since the beginning of the 21<sup>st</sup> century, in practical health care of Yakutia there was a possibility of prenatal DNA testing of neuromuscular, hereditary degenerative diseases that gives the chance to future parents to make important decisions, concerning pregnancy prolongation. With the implementation of modern medical technologies and the programs of hereditary diseases prenatal screening in applied medicine of the Republic of Sakha (Yakutia), there are ethical and social issues [2, 4, 7].

The **purpose** of the research is the analysis of social readiness of pregnant women of the families tainted with SCA1 to take part in prenatal DNA diagnostics of one of the most widespread neurodegenerative diseases in Yakutia – SCA1, so that will allow to define further competent tactics of medicogenetic and social help.

Materials and methods of the research

According to the register of hereditary and congenital diseases of the medicogenetic center №1 of the National Center of Medicine of the Republic of

Sakha (Yakutia), 1197 patients, from whom 252 people with Spinocerebellar Ataxia Type 1, were under regular medical check-up in the group of hereditary diseases with the autosomal dominant mode of inheritance [8].

The analysis of personal information of 77 pregnant women who addressed on prenatal medicogenetic consultation from the burdened families with SCA1 is carried out.

Sociological (documentary, biographical) analysis methods and Sturges' statistical methods were used in the research. Data of the social relations of pregnant women were collected by direct interviews. Registration card poll specially developed for this purpose and data logging obtained from respondents were held, according to the parameters and demands to reliability while using this method.

### Results and discussion

In the research there were investigated 77 pregnant women from the burdened families with SCA1 living in the territory of the Republic of Sakha (Yakutia) aged from 19 up to 42 years. Average age of the interviewed women was 27,1±6,06 years, and 5,2% of women were 35 plus.

Along ethnic lines, 89,6% women are Sakha, 6,5% - Evenks, 3,9% - admixed nationality (half-breed). In connection with high probability of mixture of half-breed, this indicator was not taken into account in the final analysis of data.

It should be said, that the respondent women have rather high education level: 53,2% with higher education, 11,7% - non-complete higher education, 35,1% - advanced education. Among women with the higher education experts of social orientation – doctors and teachers prevail.

Based on the information about marital status, it is possible to speak about a positive situation of the respondents: it is a first marriage of 4/5 women and this indicator positively affects the general vital activity of a person.

Surveying a **financial position of the respondents** it should be noted, that the respondents assess their financial position as an average (72%). Average monthly earnings of the examined families varies from 40 to 50 thousand rubles. The main sources of income are the salary from the main work, casual earnings, self-employment, child allowance, and other types of grants.

From among 77 pregnant women, there are 51 (66,2%) of them agreed to undergo a prenatal test (**Group A**), 26 (33,8%) pregnant women refused conducting prenatal testing (**Group B**).

From the total number of the participants in the research, 50 (64, 9%) women are from the families tainted with SCA1 (**Group 1**), and 27 pregnant women (35,1%) are spouses of the men from the tainted families (**Group 2**).

Following the results of pre-symptomatic DNA testing, five men (18, 5%) of **Group 2** are healthy and weren't carriers of a mutant gene, so that they didn't participate in further researches.

### Analysis of pregnant women who underwent prenatal DNA testing.

Among 46 pregnant women who underwent prenatal DNA testing – 31 women (67, 4%) are presymptomatic bearers of a mutant gene (**Group A1**), and 15 (32,6%) of them have husbands from the tainted families (**Group A2**).

22 pregnant women have negative result of prenatal DNA testing (47, 8%); in all cases there was prolongation of pregnancy. There are 14 women with

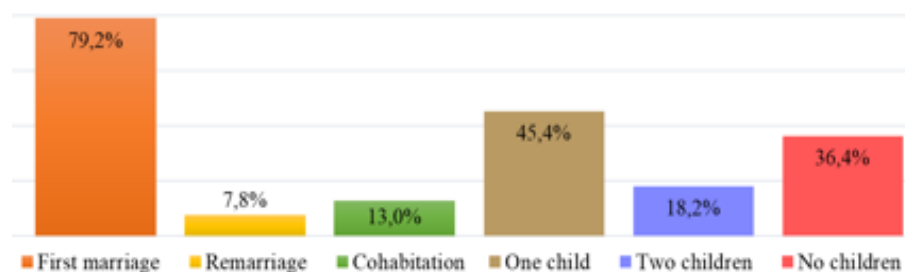


Fig.1. Marital status and parental status.

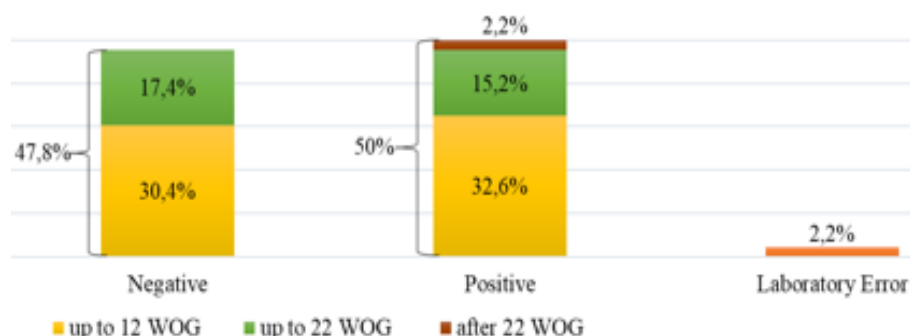


Fig. 2. DNA test results in relation with gestational age.

gestational age up to 12 weeks (63, 6%), up to 22 weeks of pregnancy – 8 women (36, 4%) (Fig. 2)

23 pregnant women have positive result of prenatal DNA testing (50%), from whom five families (21, 7%) made the decision on pregnancy prolongation, and in 18 cases (78, 3%) the decision on abortion was made. Durations of gestation: 15 women were at 12 weeks of pregnancy (32, 6%), 7 women – at 22 weeks (15, 2), and one pregnant woman – over 22 weeks (2,2%).

In one case (2, 2%) the analysis prenatal DNA didn't carry out because of a laboratory error (Fig. 2).

Figure 2. DNA test results in relation with gestational age

26 pregnant women refused from conducting invasive testing, from whom 19 (73, 1%) are presymptomatic carriers of a gene of SCA (**Group B1**), and 7(26,9%) women's husbands are a carrier (**Group B2**).

In our opinion, getting of presymptomatic test by a woman during the current pregnancy 12 (46, 2%) (**Group B1**) was a cause of refusals in most cases. 9.9 women (34, 6%) (**Group B1, B2**) had a strong reluctance to know the result of prenatal testing; absence on the procedure without reason explanation – in 5 cases (19,2%) (**Group B1, B2**).

### Conclusions

The conducted researches taped that most of the respondents (51 person; 66,2%) are ready to undergo prenatal DNA test.

It is found that the education level

practically does not influence making decision on getting prenatal DNA test. The respondents with the higher education in Group A were 58, 7%, and in Group B – 77%.

In **Group A** there are registered marriages in 36 families (78, 3%), and cohabitation or repeated marriages (unstable marriages) – in 10 families (21, 7%). In **Group B** there are registered marriages in 20 families (76, 9%), and repeated or unstable marriages, cohabitation – in 6 families (23, 1%).

By the results of the research, social readiness to participate in prenatal DNA testing in the families where women are carriers of a gene (**Group 1**) prevails over prenatal appealability in families, where husbands are representatives of families with SCA1 (**Group 2**).

The major factor of social readiness defining prenatal behavior in families with SCA1 is the traditional and historically developed relation to a disease in the tainted families. Women from **Group A1** are more motivated for prenatal DNA testing. In **group B2** refusal factors are uninformedness, family's lack of knowledge about the hereditary nature of the disease, terrify of social stigma.

The informedness events of the tainted families for the female line (**Group A1**), which were held earlier, have a positive impact on the activity of women and social readiness to undergo prenatal DNA testing.

In this regard, there is a need of development of the program for informing and rising of appealability of men (**Group**

2) who are representatives from the families tainted with SCA1 to prenatal medicogenetic consultation.

*This work is performed within a research "Studying of genetic structure and the hereditary pathology burden of populations of the Republic of Sakha (Yakutia)", 0120-128-07-97.*

### References

1. Zubri G.L. Goldfarb L.G. Savvin A.P. Korotov M.N. Nasledstvennaya mozzhechkovaya ataksiya v Yakutii [Hereditary cerebellar ataxia in Yakutia] Pervaya Vsesoyuzn. Konf. po meditsineskoi genetike: tezisy [First nationwide conference of medical genetics: abstracts. ]. Moscow: AMN SSSR, 1975, P. 60-62.
2. Izhevskaya V.L. Eticheskie problem prenatalnoi diagnostiki [Ethical problems of prenatal diagnostics] Jurnal akusherstva i jenskih bolezney [Journal of obstetrics and female diseases]. Saint Petersburg, 2011, V. LX, issue 3, P. 203-211.
3. Illarionovskiy S.N. Rudenskaya G.E. Ivanova-Smolenskaya I.A. Markova E.D. Klyushnikov S.A. Nasledstvennie ataksii i paraplegii [Hereditary ataxia and paraplegias]. Moscow: MEDpress-inform, 2006, p. 153.
4. Kononova S.K. Fedorova S.A. Stepanova S.K. [et al.] Organizatsionnye, metodicheskie i eticheskie problem DNK-diagnostiki monogenicheskikh zabolevaniy v praktike mediko-geneticheskoi konsultatsii Yakutii [Organizational, methodical and ethical problems of DNA diagnostics of monogenic diseases in practice of medicogenetic consultation of Yakutia] Medicinskaya genetika [Medical genetics]. Moscow, 2006, application 1, p. 14-17.
5. Platonov F.A. Nasledstvennaya mozzhechkovaya ataksia v Yakutii: dis. D-ra med. nauk [Hereditary cerebellar ataxia in Yakutia: diss. of MD]. Moscow, 2003, P. 178.
6. Sukhomyasova A. L. Maksimova N.R. Nogovitsyna A.N. Raznoobrazie nasledstvennoi patologii v Respublike Sakha (Yakutia) po dannim respublikanskogo geneticheskogo registra nasledstvennoi i vrozhdennoi patologii [Diversity of hereditary pathology in the Republic of Sakha (Yakutia) according to the national genetic register of hereditary and congenital pathology] Geneticheskoe issledovanie naseleniya Yakutii [Genetic study of the population of Yakutia] pod. red. Puzireva V. P., Tomskego M. I. [ed. Puzirev V.P., Tomsky M.I.]. Yakutsk, P.78-84.
7. Sidorova O.G. Kononova S.K. Stepanova S.K. et al. Sostiyanie prenatalnoi DNK-diagnostiki nasledstvennih



- nervno-mishechnih zabolevaniy v Yakutii [A condition of prenatal DNA diagnostics of hereditary neuromuscular diseases in Yakutia] Problemi vilyuskogo encefalomyelita i drugih neurodegenerativnih zabolevaniy v Yakutii: Tez.dokl. III mezhdunarodnoi nauch-prakt. konf. Yakutsk [Abstr. of the III international research and training conference "Problems of the Vilyusk encephalomyelitis and other neurodegenerative diseases in Yakutia"]. Yakutsk, 2006, P. 54-55.
8. Platonov F.A. Illarioshkin S.N. Kononova S.K. et al. Spinocerebelyarnaya ataksia pervogo tipa v Yakutii: rasprostranennost' i kliniko-geneticheskie sopostavleniya

[Spinocerebellar ataxia type 1 in Yakutia: prevalence and clinicogenetic comparisons] Medicinskaya genetika [Medical genetics]. Moscow, 2004, V.5, No. 8, p. 242-248.

#### The authors

YSC CMP, Yakutsk, Russia:

1. Sidorova Oksana Gavriylevna - researcher, [okssi66@mail.ru](mailto:okssi66@mail.ru);
2. Kononova Sardana Kononovna - Candidate of Biological Sciences, Senior Researcher, [konsard@rambler.ru](mailto:konsard@rambler.ru);
3. Barashkov Nikolai Alekseevich - Ph.D., leading researcher, head of lab., [barashkov2004@mail.ru](mailto:barashkov2004@mail.ru);
4. Platonov Fedor Alekseevich - Doctor of

Medicine, [platonovy@mail.ru](mailto:platonovy@mail.ru);

5. Fedorova Sardana Arkadevna - Doctor of Biological Sciences, Senior Research Scientist, Head of Biology lab., IEN M.K. Ammosov NEFU, [sardaanafedorova@mail.ru](mailto:sardaanafedorova@mail.ru);
6. Khusnutdinova Elza Kamilevna - Doctor of Biological Sciences, Professor, Acting Director of the Institute of BiG URC RAS, (Ufa), [elzakh@rambler.ru](mailto:elzakh@rambler.ru);
7. Izhevskaya Vera Leonidovna - MD, prof., Deputy Director of the Medical Genetic Scientific Center (Moscow), [izhevskaya@med-gen.ru](mailto:izhevskaya@med-gen.ru).

N. E. Kardashevskaya, T. A. Sosina, N. I. Douglas,  
T. E. Burtseva, S. A. Evseeva, S.T. Struchkov

## THE PROBLEM OF SKILLS FORMING ON REPRODUCTIVE HEALTH OF GIRLS IN THE SAKHA REPUBLIC (YAKUTIA)

DOI 10.25789/YMJ.2018.63.14

### ABSTRACT

The authors report a survey of respondents on reproductive health of girls. Retrospective study includes 176 respondents. According to the results of the study, it was revealed that young people had insufficient knowledge of contraception, as well as psychological readiness for the artificial termination of pregnancy. The study identified the main factors in reducing the reproductive potential of girls of fertile age.

**Keywords:** reproductive health, girls, contraception, abortion, sex education, the Arctic, Yakutia.

### Introduction

The Republican authorities set the goal to reach one million people by the centenary of the Yakut ASSR formation (resolution of the government of the Sakha Republic (Yakutia) of December 25, 2013 No. 461). According to the Federal service of state statistics, the number of permanent population of the Sakha Republic (Yakutia) for 2017 amounted to 962.8 thousand people - these data show us that Yakutia has not retained its million status [1]. According to statistics for previous years - the population reached the number of 955.9 thousand people in 2012. Despite the active introduction and implementation of measures and programs to improve the birth rate in the country and particular in the Sakha Republic (Yakutia), there is no expected population growth. The children born in the 1990s during the demographic crisis have entered reproductive age, which also aggravates the demographic situation in the Sakha Republic at the moment. Nevertheless, a million Yakutians by 2022 is considered a very real goal. One of the ways to achieve this goal we see in the implementation of the preserving principle of the reproductive health of young people, especially young girls, starting from adolescence [2].

### Materials and methods of research.

We conducted a survey of the somatic and reproductive health of girls. A total of 176 girls aged 17 to 22 of different ethnic backgrounds were interviewed (table 1). The survey was conducted on the basis of higher educational institutions in Yakutsk. The questionnaire contained: social and anamnestic data. When collecting anamnesis, attention was paid to: the nature of menstrual function, the characteristics of sexual life, contraception, transferred gynecological diseases, previous surgical interventions, reproductive function. Statistical analysis of the study results was carried out using the programs: "Office Microsoft Excel 2010".

### Results of the study

According to the state of somatic and reproductive health of the examined girls: the leading positions in the structure of somatic diseases are diseases of the respiratory and gastrointestinal tract - every third or fourth. The Evenk girls often suffered from cardiovascular diseases compared to Yakutian and Russian girls.

Assessment of menstrual function showed that the age of menarche ranged from 12 to 14.5 years. The duration of menstruation varied from 3 to 6 days, averaging 4.1±1.5 days. In the structure

of menstrual dysfunction in girls of all groups, dysmenorrhea predominated. Each eleventh girl has signs of polymenorrhea. Oligomenorrhea among Russian girls - every fourth, Yakutian girls - every fifth, which is significantly less when compared with Evenk girls.

Evaluation of the gynecological diseases structure has shown that the leading position is occupied by benign diseases of the cervix and inflammatory diseases of the uterus and appendages.

In the questionnaire data it is indicated that every second mother smokes in the girls' families (51.2%), 15.1% of respondents admitted in tobacco smoking, in the Yakut and Evenk group (31.7%) there is a tendency to increase the number of smokers compared to Russian (24%) and Evenks (27%). Among the reasons that prompted to start smoking: 80% of respondents indicated

Table 1

Respondents			
Nationality	Amount	Part, %	Average
the Russians	21	11,9	19±1,3
the Yakuts	128	72,7	20±1,4
the Evenks	19	10,8	20±1,0
others	8	4,5	19±2,2

Table 2

## Information sources on contraceptive behavior

Information source	%
Girlfriends	43%
Literary sources	30%
School	18%
Mother	9%

that they smoke "for the company", 12.5% "because it's fashionable" and 7.5% "in order not to differ from the rest". They were able to have alcohol in the company - 46.1%. Most of them drink beer and alcoholic cocktails (85%).

Among the examined girls, 153 respondents (86.94%) were sexually active. There is a tendency to increase the number of sexually active girls among the rural residents in comparison with urban (67.5% and 53.5%, respectively). The beginning of sexual life at the age of 14 was in 2.27% (4) of girls, at the age of 15 years - 4.54% (8), up to 18 years - in 38.63% (56).

As for the number of sexual partners: only about 46% of sexually active girls are focused on monogamous sexual relations, the remaining 54% of the respondents had two or more sexual partners.

With regard to sex education: every third (32%) of the surveyed girls believes that they do not have sufficient knowledge about sex life and methods of contraception, and 6% - believe that they do not have any knowledge about the methods of safe sex life.

The contraceptive behavior of the studied girls is characterized by a commitment to low-effective methods of contraception. The most frequently used condom (67,32%), interrupted sexual intercourse (13,73%), COC (Combined oral contraceptives) (7,19%). Reliable methods (COC+condom contraception) adhere to 5.23%. 6.54% of respondents do not use contraception.

The analysis of information sources on contraception and sexual safety showed that only 9% of the respondents discussed this topic with their mothers, almost every second girl received the information from girlfriend, every third student resorted to literary sources, almost every fifth girl received information during school (table 2).

The number of girls surveyed is characterized by pre-marriage sexual

relations and a low level of psychosocial readiness for responsible sexual and marital partnership (only 19.5% do not accept premarital sexual relations).

## Conclusion

Medical and social behavior of girls of reproductive age in the Sakha Republic (Yakutia) is characterized by adherence to low-effective methods of contraception (condom: 67.32%, interrupted sexual intercourse: 13.73%, COC-7.19%, reliable methods of COC + contraceptive condom - 5, 23% . 6.54% do not use contraception). Lack of knowledge of young people in contraception, psychological readiness for the artificial termination of pregnancy are the main factors in reducing the reproductive potential of child-bearing age girls. [2,4,5,6].

The presented research is intended to draw the attention of specialists to the need to protect the reproductive health of girls in the Sakha Republic (Yakutia).

It is necessary to develop a number of programs at the state level, which should include:

- compulsory sex education program in schools in parallel with public education;
- creation of information centers with the involvement of gynecologists, contraceptive specialists, dermatovenerologists, teachers;
- quality pre-abortion psychological counseling;
- programs of an annual comprehensive survey of young girls, taking into account the characteristics of reproductive behavior with the aim of early detection and prevention of reproductive health disorders;
- carrying out pre-school preparations and popularizing the mother's school.
- programs to strengthen the family and support young families.'

## References

1. Zernyuk A.D. Problemy formirovaniya reproduktivnogo povedeniya starsheklassnikov [Problems of formation of reproductive behavior of senior pupils] Reproduktivnoye zdorov'ye detey i podrostkov [Reproductive health of children and adolescents]. Saint Petersburg, 2006, No.1, pp.79-85.
2. Manukhin I.B. Ryzhakov V.V. Fedosova G.N. Profilaktika reproduktivnykh poter' [Prevention of reproductive losses]. Stavropol, 1999, p.239.
3. Nikolayeva M.G. Grigoriev E.E. Mediko-sotsial'naya problema abortov v molodezhnoy srede i puti yeyo resheniya [Med-

ical and social problem of abortion in the youth environment and ways to solve it] Vestnik Rossiyskogo universiteta družby narodov. Seriya Meditsina. Akusherstvo i ginekologiya [Herald of the Russian University of Peoples' Friendship. Series Medicine. Obstetrics and gynecology]. Moscow, 2008, No. 5, pp.171-176.

4. Douglas N.I. Pavlova T.Yu. Burtseva T.E. Reproduktivnoye zdorov'ye zhenskogo naseleniya Respubliki Sakha (Yakutiya): reguliruyushchiye faktory i rezervy optimizatsii [Reproductive health of the female population of the Republic of Sakha (Yakutia): regulatory factors and reserves of optimization]. Yakutsk: Publishing House of NEFU, 2013, pp. 38-96.
5. Uvarova Ye.V. Reproduktivnoye zdorov'ye devochek podrostkovogo vozrasta/Rossiskii vestnik perinatologii i pediatrii [Reproductive health of adolescent girls [Russian herald of perinatology and pediatrics]. Moscow, 2003, vol. 48, No. 5, pp.8-9.
6. Uvarova Ye.V. Reproduktivnoye zdorov'ye devochek Rossii v nachale XXI veka/ Akusherstvo i ginekologiya [Reproductive health of Russian girls at the beginning of the XXI century [Obstetrics and a gynecology]. Moscow, 2006, Appendix, pp.27-30.

## The authors

1. Kardashevskaya Nadezhda Egorovna, clinical resident of the Obstetrics and Gynecology Department, Faculty of postgraduate education of doctors of medical institute M.K. Ammosov NEFU, 89243694511, E-mail: nadechek9437@gmail.com
2. Sosina Tuyara Anatolievna, clinical resident of the Obstetrics and Gynecology Department, FPED MI, M.K. Ammosov NEFU, 89241741644, E-mail: Integraka22@gmail.com
3. Douglas Natalia Ivanovna, obstetrician-gynecologist, doctor of medical sciences, head of Obstetrics and Gynecology Department, FPED MI, M.K. Ammosov NEFU, 89246626722, E-mail: nduglas@yandex.ru
4. Burtseva Tatiana Egorovna - doctor of medical sciences, professor of MI NEFU, head. lab. Yakutsk Scientific Center of Complex Medical Problems, 8 (914) 294-32-44, bourtsevat@yandex.ru
5. Evseeva Sardana Anatolievna - junior researcher of Yakutsk Scientific Center of Complex Medical Problems, sarda79@mail.ru, contact. phone: 89679111195
6. Struchkov Sergey Timofeevich- student M.K. Ammosov NEFU, [sergey17011990@gmail.com](mailto:sergey17011990@gmail.com), конт. телефон: 89841005807.

L.I. Konstantinova, G.E. Mironova, Z.N. Krivoschapkina,  
A.V. Efremova, E.D. Okhlopko, L.D. Olesova,  
E.I. Semenova, A.I. Yakovleva, A.A. Grigoryeva

## BIOCHEMICAL PARAMETERS OF BLOOD OF SPORTSMEN OF YAKUTIA IN DIFFERENT SEASONS OF THE YEAR

DOI 10.25789/YMJ.2018.63.15

### ABSTRACT

A biochemical study was conducted among athletes - freestyle wrestlers of Yakutia in different seasons of the year. The clinical and biochemical indices obtained by us, reflecting the state of the body of the wrestlers, show that there were no abnormalities in the athletes surveyed by us. At the same time, at the part of the sportsmen surveyed by us, the activity of enzymes (except ALP) was moderately increased in all seasons of the year, especially in the autumn-winter period. Thus, increased values of ALT activity in the autumn period were noted in 36% of wrestlers, and in winter - in 41%. ACT activity in autumn exceeded normal values in 36% of the wrestlers surveyed by us, and in winter - in 29%. Increase in activity of LDH enzymes (up to 535,5 E / L in all seasons of the year), KFK (up to 622,8 E / L in winter), transaminase (in autumn and winter periods) and creatinine (up to 113,5  $\mu\text{mol} / \text{l}$  in all seasons of the year) is a consequence of the influence of intense physical loads associated with the activation of energy substrates.

**Keywords:** biochemical research, athletes, freestyle wrestlers.

Biochemical blood monitoring is one of the leading places in the overall complex of examinations and monitoring of the state of the body and the level of training of athletes. Biochemical parameters allow to diagnose signs of fatigue under the influence of physical activity at an early stage and to make adjustments in the training process taking into account these indicators [3].

It was found that ATP reserves in the muscles are exhausted in a few seconds when performing intensive physical work. For the resynthesis of ATP in skeletal muscle of the person there are three types of anaerobic (creatinekinase, or lactate; glycolytic, or lactic; micinsky) and aerobic mitochondrial mechanisms. With the depletion of the creatine kinase system, the bioenergy of muscle contraction is provided depending on the type of muscle glycolysis and/or oxidative phosphorylation. The described mechanisms of energy supply to the muscles are the basis for the selection of biochemical markers characterizing their condition [5]. These markers include creatine kinase, or creatine phosphokinase (KFK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST). In addition to markers of muscle activity are also important indicators showing the state of metabolism.

The aim of the study was to study the changes in biochemical parameters characteristic of freestyle wrestlers, depending on the seasons of the year.

Materials and methods of research. The object of our study were 102 men of yakut nationality, aged 18 to 29 years,

athletes – freestyle wrestlers of School of the highest sports skill of Yakutsk and students of the Institute of physical culture and sports NEFU in the name of M.K. Ammosova having high sports qualification: candidates for masters of sports, masters of sports, masters of sports of international class, honored masters of sports. The study was conducted in different seasons: summer (June), autumn (October), winter (December), spring (March).

The material for biochemical analysis was serum taken from the ulnar vein in the morning on an empty stomach in a state of relative muscle rest.

Laboratory studies were conducted in the laboratory of biochemical mechanisms of adaptation of the Federal state budgetary scientific institution «Yakut Science Centre of complex medical problems».

Determination of the activity of aspartate- (AST) and alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinekinase (KFK), gammaglutonylpeptidase (GGT), creatinine, urea, total protein, glucose, total cholesterol, very low (VLDL), low (LDL) and high density lipoprotein cholesterol (HDL), triglycerides (TG), serum albumin were carried out by enzymatic method on the biochemical analyzer «Labio 200» using the reagents «BIOCON» (Germany).

The obtained data were statistically processed using the package of applied statistical programs SPSS 17.0. Arithmetic mean values (M) and errors of mean values (m) were calculated for all indicators in each group. The

level of significance was considered significant at  $p \leq 0,05$ . The significance of the differences was determined using nonparametric Mann-Whitney tests. To identify the conjugacy of indicators, the Spearman linear correlation coefficient was calculated.

### The results and discussion

Biochemical parameters of blood serum of the athletes studied by us are presented in table 1. According to our data, the level of total protein, total cholesterol, glucose, alkaline phosphatase, creatinine, urea, uric acid and the activity of gammaglutamyltransferase in the blood of the examined athletes corresponded to normal values. At the same time, the activity of transaminases in the blood serum of wrestlers increased in autumn and winter.

Increased activity of transaminases during exercise is also associated with transamination of amino acids, which are oxidized to alpha-ketoacids and «burn» in the Krebs cycle. Increased activity of AST is not only a marker of heart damage, and in 99% of cases indicates the degree of catabolism of amino acids in healthy people, as well as the intensity of thermogenesis. And increased ALT activity in 99% of cases indicates the rate of anabolism in the body of practically healthy people associated with the synthesis of glucose from pyruvate formed as a result of transamination of alanine [6]. The increased ALT and AST values obtained by us are consistent with the literature data. Thus, in N.M. Gorokhova and L.V. Timoshenko (2007) noted that «The athletes of such sports as Taekwondo, lightweight, and



**Dynamics of biochemical parameters of blood serum of freestyle wrestlers, depending on the season of the year**

Summer (n=18)	Autumn (n=11)	Winter (n=17)	Spring (n=33)	p
LDH (225-450 u/l)				
-	436,0 (406,0; 532,0)	496,0 (369,0; 535,5)	499,0 (420,0; 535,0)	0,717
KFK (<190 u/l)				
-	345,0 (195,0; 412,0)	454,5 (151,0; 622,8)	274,0 (191,0; 487,8)	
KFK-MB(<25 u/l)				
27,2 (6,9; 32,0)	-	-	-	
ALP (до 258 u/l)				
218,0 (187,8; 258,5)	236,0 (187,0; 252,0)	218,0 (179,0; 261,5)	221,0 (191,5; 266,0)	0,960
TRIG (0,5-1,7 mmol/l)				
0,7 (0,6; 0,9)	0,9 (0,6; 1,2)	0,7 (0,4; 1,0)	0,7 (0,6; 0,9)	0,187
CHOL (3,6-6,5 mmol/l)				
4,3 (3,6; 5,1)	5,5 (4,2; 5,9)	4,8 (4,1; 5,4)	4,7 (4,2; 5,0)	0,055
Uric acid (268-488 μmol/l)				
287,0 (252,34 330,8)	307,5 (260,3; 368,0)	336,0 (225,0; 355,0)	316,0 (263,0; 366,0)	0,739
GGT (11-50 u/l)				
18,5 (13,8; 21,8)	17,0 (13,0; 21,0)	16,0 (12,0; 24,5)	23,0 (20,0; 29,0)	0,392
ALT (up to 30 IU)				
25,0 (21,8; 28,3)	27,0 (18,5; 43,5)	27,0 (21,0; 36,0)	22,0 (18,5; 27,5)	0,117
AST (up to 40 IU)				
27,5 (23,8; 37,0)	41,0 (27,0; 70,0)	35,0 (26,5; 43,5)	31,0 (25,5; 36,0)	0,047
GLU (3,3-5,5 mmol/l)				
4,4 (4,1; 4,6)	4,8 (4,8; 5,4)	4,7 (4,5; 5,1)	4,8 (4,6; 5,4)	0,047
UREA (1,7-8,3 5 mmol/l)				
5,5 (4,4; 6,5)	5,8 (5,0; 6,2)	5,4 (4,9; 5,8)	5,8 (5,3; 6,8)	0,682
CREA (53-97 μmol/l)				
91,0 (85,8; 107,3)	93,0 (83,0; 102,0)	92,0 (90,0; 100,5)	103,0 (96,5; 113,5)	0,196
BELOK (65-85 g/l)				
77,0 (74,6; 79,3)	78,7 (77,2; 81,4)	77,0 (74,5; 78,3)	78,3 (75,9; 81,9)	0,552
Albumin (34-48 g/l)				
48,6 (47,4; 50,2)	47,9 (46,0; 49,6)	46,4 (44,0; 49,9)	49,6 (47,8; 51,3)	0,392
HDL (0,78-2,2 mmol/l)				
1,2 (1,1; 1,3)	1,2 (1,1; 1,3)	1,3 (1,0; 1,6)	1,6 (1,3; 1,7)	
LDL (1,68-4,53 mmol/l)				
2,4 (2,0; 3,3)	4,1 (3,4; 4,4)	2,9 (1,7; 3,2)	2,6 (2,3; 3,1)	
VLDL (0,8-1,5 mmol/l)				
0,3 (0,3; 0,4)	0,3 (0,3; 0,5)	0,2 (0,2; 0,3)	0,3 (0,3; 0,4)	
CATR (<3)				
2,4 (1,8; 3,3)	3,9 (2,2; 4,2)	2,0 (1,4; 2,4)	1,9 (1,6; 2,7)	

Note-the data are presented in the form of median and interquartile distribution in Me format (Q1; Q3); p-achieved level of statistical significance of differences in comparison of groups (Friedman criterion).

weightlifting, with short-term physical stress is an increase in the activity of ALT and AST. The increase in the activity of AST is associated with the intensification of cellular respiration due to the more intense formation of oxaloacetate entering the tricarboxylic acid cycle and the synthesis of ATP necessary for muscle contraction» [2].

The simultaneous increase in ALT and

LDH activity is the result of accelerated glucose oxidation. It is known that the increase in the threshold of anaerobic oxidation of glucose is associated with an increase in the fitness of athletes. LDH level in blood plasma of the wrestlers surveyed by us was increased in all seasons of year, but is most expressed – in the winter-spring periods of year. In winter, the elevated values of LDH was

observed in 53% of the athletes (the activity of the enzyme ranged from of 369,0 u/l to 535,5 u/l). In the spring the high activity of this enzyme were detected in 36% of the wrestlers. The increase in LDH activity to 535,5 E / l can be due to the high rate of oxygen utilization and developing hypoxia in working muscles, because the high demand of muscles for energy substrates in conditions of oxygen deficiency is satisfied by anaerobic oxidation of glucose.

It is impossible to exclude influence of climatic factors of the North. Therefore, the increase in LDH activity in more than half of the wrestlers we examined in winter is associated not only with an increase in anaerobic oxidation of glucose, but also with the influence of extreme climatic conditions in which athletes train in Yakutia. Back in the 80s of the last century, it was shown that «a Characteristic feature of the processes of adaptation to the extreme conditions of the North is the development of a kind of syndrome that resembles chronic hypoxia and is called «circumpolar hypoxic syndrome». The main physiological manifestation of this syndrome is hidden or apparent respiratory failure» [1,4].

The content of creatine kinase in the blood of the athletes studied during the year exceeds the normal values by 2-2,5 times and the increase in lactate dehydrogenase in the autumn, winter and spring periods of the year, probably indicate an overstrain of muscle tissue when performing high-intensity physical activity. We should not forget that such an increase in the activity of KFK may indicate damage to cardiomyocytes [7]. On the other hand, a statistically significant increase in KFK in freestyle wrestlers compared to the control group (236,65±40,17 E/l) (p<0,05) is a consequence of the adaptation of the body to intense physical activity, requiring a significant reserve of creatine phosphate – a source of ATP. It should be noted that the surveyed students who made up the control group engaged in the General program of Universities, LDH activity was equal to 361,05±12,06 E/l.

By measuring the plasma activity of sarcoplasmic enzymes (KFK, LDH), the diagnosis of micro-injuries of muscle tissue is carried out. The increase in their activity in the blood plasma reflects a significant change in the permeability of the membrane structures of the myocyte, up to its complete destruction. This fact reflects the adaptation of the athlete's body to high intense physical activity. In the diagnosis of injuries from time to time use a combination of

biological and clinical parameters, for example, the activity of LDH and KFK in plasma concentrations of myoglobin and malondialdehyde, white blood cells, and physiological muscle parameters. In the biochemistry of sports, a significant increase in tissue enzymes in the blood is an indicator of the inadequacy of physical activity, the development of fatigue. The rate of disappearance of tissue enzymes indicates the rate of recovery of the body. If their activity in the blood is maintained during the rest, it indicates a low level of training of the athlete, and possibly the pre-pathological condition of the body. The above points to the need for biochemical control in high performance sports.

There was a slight increase in serum albumin in the spring, probably due to weight loss.

The analysis of lipid metabolism in athletes revealed a relatively high coefficient of atherogenicity ( $3,94 \pm 0,77$ ) ( $p < 0,01$ ) in the autumn, due to a decrease in HDL cholesterol ( $1,17 \pm 0,27$ ) ( $p < 0,05$ ), an increase in LDL cholesterol ( $3,83 \pm 0,41$ ) ( $p < 0,01$ ) and VLDL cholesterol ( $0,39 \pm 0,06$ ), probably this is due not only to nutritional factors, but also with increased utilization of cholesterol. The level of HDL cholesterol and LDL cholesterol in all seasons were within the normal range.

Reduction of VLDL cholesterol to  $0,39$  mmol/l may be due to the high rate of cholesterol utilization as a precursor of steroid hormones (activation of the adrenal cortical layer under intense physical activity).

Thus, the data obtained by us the results of clinical and biochemical parameters, reflecting the basic metabolism, indicate that the pathological deviations in the examined athletes were not. The increase in the activity of enzymes (LDH, KFK, transaminases) is a consequence of the influence of intense physical activity associated with the activation of energy substrates and with the intensification of cellular respiration and ATP synthesis necessary for muscle

contraction. The increase in the autumn season of the atherogenicity coefficient due to the reduction of HDL cholesterol, increase in LDL cholesterol and VLDL cholesterol is probably due not only to nutritional factors, but also to increased utilization of cholesterol.

### References

1. Avtsyn A.P. Zhavoronkov A.A. Patologiya cheloveka na Severe [The pathology of man in the North]. Moscow, Medicine, 1985, 416 p.
2. Gorokhov N.M. Tymoshenko L.V. Izmenenie aktivnosti otdel'nykh fermentov syvorotki krovi u sportsmenov raznykh spetsializatsiy pri vypolnenii kratkovremennoy fizicheskoy nagruzki [Change in the activity of individual serum enzymes in athletes of different specializations when performing short-term physical exertion] Teoriya i praktika fizicheskoy kul'tury [Theory and practice of physical culture], 2007, No. 7, pp. 26-28.
3. Dubrovsky V.I. Sportivnaya meditsina. 2-e izdanie [Sports medicine. 2nd edition] M.: «Vlados», 2002, 450 p.
4. Elfimov A.I. Fiziologicheskie osobennosti adaptivnykh reaktsiy kardiopul'monnoy sistemy cheloveka v razlichnykh usloviyakh sredy obitaniya [Physiological features of adaptive reactions of the cardiorespiratory system of the person in various conditions of an inhabitancy] Avtoreferat dissertatsii doktora meditsinskikh nauk [The author's abstract of the dissertation of the Doctor of Medical Sciences] M., 1996.
5. Nikulin B.A. Rodionov I.I. Biokhimicheskij kontrol' v sporte [Biochemical control in sports] Nauchno-metodicheskoe posobie [Scientific and methodical allowance] Moscow, Soviet sport, 2011, 232 p.
6. Rosly I.M. Vodolazhskaya M.G. Pravila chteniya biokhimicheskogo analiza: Rukovodstvo dlya vracha [Rules for reading biochemical analysis: A guide for a doctor] 2-ed., rev. and additional. M, Medical Information Agency LLC, 2014, 100 p.
7. Fomin N.A. Gorokhov N.M. Tymoshenko L.V. Osobennosti aktivnosti fermentov syvorotki krovi u sportsmenov i netrenirovannykh lits [Features of the activity of serum enzymes in athletes

and untrained persons] Teoriya i praktika fizicheskoy kul'tury [Theory and practice of physical culture] 2006, No. 1, pp. 9-11.

### The authors

1. Konstantinova Lena Ivanovna, researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, konstanta.l@mail.ru.
2. Mironova Galina Egorovna, Professor of the Department of Biology of the Institute of Natural Sciences of the North-Eastern Federal university in the name of M.K. Ammosov, Doctor of Biological Sciences, Professor, mirogalin@mail.ru.
3. Krivoschapkina Zoya Nikolaevna, Senior Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, zoyakriv@mail.ru.
4. Efremova Agraena Vladimirovna, Senior Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, a.efremova01@mail.ru.
5. Okhlopova 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.
6. 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.
7. Semyanova Evgenya Ivanovna, Senior Researcher, PhD of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, kunsuntar@mail.ru.
8. Yakovleva Alexandra Ivanovna, researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, sashyak@mail.ru.
9. Grigoryeva Anastasia Anatolyevna, researcher of the Department of adaptation mechanisms study of the Yakut Science Centre of complex medical problems, nastiagrigoryeva@gmail.com.



## ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

S. S. Sleptsova, N. M. Gogolev, P. G. Petrova, N. V. Borisova,  
G. A. Palshin, V. G. Ammosov, T. E. Burtseva

## THE SCIENTIFIC ACTIVITY OF MEDICAL INSTITUTE: PROSPECTION

DOI 10.25789/YMJ.2018.63.16

The research work is the priority of the Medical Institute of North-Eastern Federal University. In present the 22 departments and employs 150 staff, including 35 doctors and 90 candidates of Sciences, the average age of the faculty for 47 years. The growth and impact of research is of course linked to scientific staff, thus in the period since 2008 employees of the Medical Institute defended 10 theses for the degree of Doctor of Medical Sciences and 60 - for the degree of Candidate of Medical Sciences. To date, the share of the settled is 83.3%. In medical school work Petrova P. G. - academician of the Academy of Sciences of Sakha (Yakutia), honored worker of higher school of Russia, honored scientist of Sakha (Yakutia), Krivoshepin V. G. - academician of the Academy of Sciences of Sakha (Yakutia), honored worker of science of the Russian Federation, Tobokhov A.V. - academician of the Academy of Sciences of Sakha (Yakutia), honored scientist of Sakha (Yakutia) Alekseev R. Z., Basharin K. G., Palshin G. A., M. V. Khandy.

Successfully work teams of scientific schools, recognized in Russia and abroad: school under the leadership of P. G. Petrova «Physiological and medical aspects of health of various groups of the population in the Republic of Sakha (Yakutia)» and school of Professor M. V. Khandy «Regional features of physiology and pathology of childhood in the North.» Conducting fundamental, applied and clinical studies in 7 laboratories of the clinic for the study of etiology, pathogenesis and peculiarities of diseases in the North allows for clinical and research work at a high level. On the basis of laboratory carried out fundamental, search and applied scientific researches directed on the decision of actual problems of medical, biological, pharmaceutical science and health care, creating innovative strategies and infrastructure research activities. Since 2011, when the Arctic innovation center of NEFU was established and registered small innovative enterprises (SIE): «Gifts of Yakutia» (Director E. E. Borisov), «Genodiagnostic» (Director N. R. Maximova) and «BIO-Spectrum» (Director Y. A. Akhremenko). Since 2011 them was 6 know-how, obtained 6 patents of the Russian Federation, won

more than 10 grants on the development of innovation infrastructure, totaling more than 5 million.

The main scientific direction of the medical Institute for many years was the theme of «Physiological and medical aspects of health of different population groups in the Republic of Sakha (Yakutia)», which included directions for the development and implementation of health and medical technologies in order to enhance the quality of life of the population in the North, medico-ecological monitoring of the health status of the population in the area of industrial development of the North; the study of the dynamics and development of long-term forecasts of demographic development and preservation of health of the population of Sakha (Yakutia).

We have great advances in genomic medicine, our genetics are known worldwide due to the discovery of new diseases from the group of hereditary metabolic diseases and the identification of new gene mutations. On the basis of educational and scientific laboratory «Genomic medicine» fundamental and applied research in the field of medical genetics, the search for new mutations in ethnically isolated populations of the Sakha (Yakutia), implemented a test system and molecular techniques for the diagnosis of hereditary and genetically-predisposed diseases. In 2017, the laboratory staff has developed a biochip for DNA diagnostic of being a carrier of five hereditary diseases: 3-M syndrome, SOPH syndrome, tyrosinemia type 1, hereditary methemoglobinemia type I, hereditary non-syndromic deafness 1A type, and also developed a fluorescent test systems based on graphene oxide for DNA diagnostics carrier 3-M syndrome in the population of Sakha (Yakutia). These test systems are more effective analogues (in qualitative and economic terms) than modern methods of routine DNA diagnostics (PCR-RDRP, PCR in real time). The laboratory staff received two patents for the invention in 2017: «Method of diagnosing point mutations in native DNA using graphene oxide» (patent of the Russian Federation No. 2614111) and «Method of simultaneous diagnosis of hereditary diseases» (Patent of the Russian Federation No. 2627115). In the future, the laboratory plans to introduce

test systems and molecular technologies based on biological microchips and PCR in the «real-time» mode for the diagnosis of hereditary and hereditary predisposed diseases, to participate in molecular screening for frequent monogenic diseases in conjunction with the Medical genetic center of the National Center of Medicine of Sakha (Yakutia), to carry out genetic support in transplantation, oncology, reproduction using next-generation sequencing methods (NGS), genetic certification of the population (carrier of frequent monogenic diseases, «sports passport», «passport of women's health», etc.).

In the field of regenerative medicine, the material and technical base of the laboratory for the development of cellular biomedical products in the clinic is equipped, conservation and transplantation of skin fibroblasts are carried out. Today, dermal cells are used to treat patients with thermal lesions in the Thermal Trauma Department of RBN2. One of the bold and promising directions is the creation of a composite tissue-engineered transplant of functional liver tissue. The project involves the search for and development of new innovative methods of radical treatment of irreversible liver lesions, ensuring the extension of life of patients and maximum functionality, the demand is determined by the increasing frequency of severe liver diseases in the country. This technology will replace organ transplantation, which has a number of side effects, potential risks and long queues for their implementation. At the first stage there is a search for new materials for the manufacture of tissue-engineered matrix for the transplantation of cultured cells together with the Department of Chemistry of NEFU and Technopark of Yakutia.

For many years, leading professors of the medical Institute have been working on clinical testing and implementation of modern diagnostic, therapeutic and reconstructive methods for thermal injury. Now there is a development of the Protocol of «Controlled tissue regeneration» on the basis of a reasonable choice of modern wound coatings depending on the stage and course of the wound process, the volume of tissue defect and local blood supply monitoring data, monitoring of



antibiotic resistance and improving the effectiveness of antibiotic therapy of the wound process in patients with thermal trauma and improving reconstructive plastic surgery of scar tissue changes, applied in cosmetology practice in patients with consequences as a result of thermal injury.

Every year the number of publications, including journals, refereed by the RF HAC and foreign publications cited in the databases of Scopus and Web of Science, is growing. Leading professors of the medical Institute for publication activity (h-index): Maksimova N. R. - 13, Krivoschapkin V. G. - 12, Petrova P. G. - 8, Savvina N. B. - 7. Since 2009 teachers of the Medical Institute published 1058 scientific articles in peer-reviewed journals of the RF HAC, 1681 publications were registered in the database of RSCI, 149 articles in Scopus and 112 publications in the Web of Science. The total number of scientific citations in the RSCI was 268. For 10 years, 82 monographs, 228 educational and methodical manuals were published, 38 of them with the stamp of UMO of the Ministry of health of the Russian Federation, guidelines and recommendations, more than 95 collections of scientific papers, numerous articles and abstracts were published at various national, national and international conferences, symposia and congresses. With 2015 comes the e-series of the journal «Vestnik NEFU: Medical Sciences» (chief editor Petrova P. G.), from 2016 edition included in the database of RSCI.

For 10 years more than 45 scientific works on grants and target programs of various levels, international clinical studies, topics on analytical departmental target programs of the Ministry of education and science of the Russian Federation, on state Order of the Ministry of education and health, on FTP, through the Bortnik Fund, on grants of the head of the Republic Sakha (Yakutia), etc. the total amount of funding amounted to 95 908 666 rubles. Annually teachers of the Medical Institute apply for grants of international, Federal and national levels, joint research projects with colleagues from Russian universities and research institutes, from 2009 to 2017 received 33 patents.

Also, the Institute staff organizes scientific and practical conferences, schools, symposia, round tables on the most topical issues of medical science, one of the most important scientific events, bringing the main achievements of the year, is the traditional national Congress «Ecology and human health in the North» (<http://ehhn.s-vfu.ru/>).

According to the results of recent years, the Congress was attended by an average of more than a thousand participants from among scientists, teachers and health professionals.

The teachers of the Institute successfully works in many scientific areas, the results of research are being implemented in practice. The main of them are, first, fundamental and applied scientific research to monitor the health and quality of life of the population of the region, and secondly, the study of the load of hereditary and congenital diseases among the population of the region by the development of methods of diagnosis and treatment of congenital diseases, hereditary and multifactorial diseases of the population, as well as the development and implementation of science-based predictive models of health indicators.

In accordance with the priorities of the project «Strategy of socio-economic development of the Republic of Sakha (Yakutia) up to 2030 with the determination of the key directions to 2050» approved by the resolution of the government of the RS (Ya) from 26.12.2016 No. 455, the Government of the Republic implemented the program of comprehensive scientific research. In the framework of the integrated programme of scientific research, the medical Institute NEFU implemented the state contract on the theme: «A multi-factor study of the health status of the indigenous and alien population of the RS (Ya) in order to optimize regional programs to improve the quality of life of the inhabitants of the Republic, taking into account territorial and ethnic characteristics in the conditions of modern socio-economic development.» As part of this work, a comprehensive survey of the population in 4 districts of Yakutia was conducted, where a multifactorial study of the health status of the population was conducted, including a medical examination of the population, a laboratory analysis of blood on 68 parameters, blood sampling for molecular genetic studies.

Since 2017 implementation of the project «System medical and environmental monitoring of the health status of the population living in close proximity to the areas of falling of the separated parts of the launch vehicles in the regions of the Republic of Sakha (Yakutia)», within which a survey of the population in Aldan, Kobyai, Vilyuisk and Verkhnevilyuisk districts was conducted.

The capacity of the medical Institute of NEFU to organize and conduct research works from year to year is expanding. In 2017 on the initiative of the rector

of North-Eastern Federal University Mikhailova E. I., formed a medical cluster on the basis Medical Institute, hospitals and the simulation training centre of the University for the solution of strategic tasks in the sphere of protection of public health. The activity of the cluster is a system of sustainable interaction of the main components: education, science, innovation and practice. The cluster members are the Academy of Sciences of the RS (Ya), the Ministry of Health of the RS (Ya), the Ministry of Nature Protection of the RS (Ya), the Ministry of Education of the RS (Ya), «Technopark of Yakutia», medical organizations of the Republic, as well as the Chukotka Autonomous district, Kamchatka region, Magadan region. In addition to the teaching staff and research staff, young scientists are also involved in the scientific activities of the Medical Institute, they are students and graduate students in the student scientific communities in various areas of medical science.

In the future, the scientific activity of the Institute is preparing to resume the work of the dissertation Council on medical Sciences, work to increase the amount of funding for research, expand the ties of mutually beneficial cooperation of the University with interested Russian universities, scientific institutions, which will undoubtedly increase the quality and quantity of research work, increase the number of publications in high-rated scientific journals and increase the rating of the Department among medical universities of the country.

Today, thanks to our University, we have an excellent base, trained, qualified personnel, there is a practical reserve and experience that will allow us to realize our most daring plans in life.

### The authors

677016, Oyunsky str., 27, Yakutsk, Russia:

1. Sleptsova Snezhana Spiridonovna - doctor of medical Sciences, associate Professor, head of Department of infectious diseases, Phthisiology and dermatovenerology, Medical Institute of M. K. Ammosov North-Eastern Federal University, [sssleptsova@yandex.ru](mailto:sssleptsova@yandex.ru);
2. Petrova Palmira Georgievna - doctor of medical Sciences, Professor, head of the Department of normal and pathological physiology of the Medical Institute M. K. Ammosov North-Eastern Federal University, E-mail: [mira44@mail.ru](mailto:mira44@mail.ru);
3. Borisova Natalya Vladimirovna - doctor of medicine, Professor, Department of normal and pathological physiology of the medical Institute, M. K. Ammosov North-Eastern Federal University, E-mail: [Borinat@](mailto:Borinat@)

- yandex.ru;
4. Gogolev Nikolai Mikhailovich, candidate of medical Sciences, associate Professor, Director of the Medical Institute of M. K. Ammosov North-Eastern Federal University, gogrcemp@rambler.ru;
  5. Palshin Gennady Anatolyevich, doctor of medicine, Professor, Department of traumatology, orthopedics and disaster medicine of the Medical Institute of M. K. Ammosov North-Eastern Federal University, E-mail: palgasv@mail.ru;
  6. Ammosov Vladimir Gavrilovich, candidate of medical Sciences, associate Professor, Clinic Director M. K. Ammosov North-Eastern Federal University, E-mail: klinika-mi@mail.ru;
  7. Burtseva Tatyana Egorovna, doctor of medicine, Professor, Department of Pediatrics and pediatric surgery, Medical Institute M. K. Ammosov North-Eastern Federal University, E-mail: bourtsevat@yandex.ru.

## HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

V.G. Krivoschapkin, L.F. Timofeev

### ENVIRONMENTAL HEALTH MONITORING IN THE ZONE OF ACTIVITY OF THE MINING INDUSTRY IN THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2018.63.17

#### Introduction

The activities of mining industry are fraught with pollution of the environment, primarily water sources which are a priority for the field being developed by heavy and rare-earth metals. Their subsequent entry into river ecosystems and migration along the ecological chain: phyto-zoobenthos - fish population - floodplain vegetation - milk, meat of domestic animals - man, further threatens the development of severe somatic and neurological diseases, included in the literature under the common name "microelementoses".

#### The content of the work and discussion

The mining industry is one of the main components of the industrial development of Yakutia in the 20th century, including gold mining in the Aldan region, diamonds in Mirny, tin in Ust-Yansky, and so on. With all its huge contribution to the economy and state budget of the republic, one should not forget the negative aspects of the activities of various enterprises of the industry.

Fresh in memory a sad precedent with the Vilyui group of uluses, when as a result of careless negligence of the enterprises of ALROSA in the 80-90s of the last century, the incidence of abnormalities in the development of children and malignant tumors increased sharply among the population, which was explained in our studies joint with Tomsk geneticists as a manifestation of chemical mutagenesis. In addition, the incidence of endocrine pathology, the pathology of the blood system, cardiovascular, digestive, urinary and other body systems has increased significantly. There were signs of negative trends in the demographic indicators of the population. This precedent was studied by the participants of the research expedition of the SB RAS, the results of

the studies were formalized in the form of a Scientific Report, the materials of the expedition were published in numerous publications in the form of scientific articles and monographs. The medical part of the expedition was headed by prof. V.G. Krivoschapkin.

With the aim of "restoring the health of the population and the ecology of the region", ALROSA has so far paid 8 regions of the diamond province to the budget, and in recent years, one-percent deductions from its profits. Recently, the activity of mining enterprises in the Arctic zone of the Republic of Sakha (Yakutia) has significantly increased - the Tomtor deposit of rare-earth metals (niobium), the Anabar diamond deposit are being developed, and the development of the Mangazeya silver-mercury deposit will start next year, etc. In doing so, consider the following:

The Arctic ecosystem is characterized by a very limited ecological capacity, therefore, it is less resistant to anthropogenic and technogenic pollution, and much more time is required to inactivate and detoxify pollution compared to other regions. Under these conditions, even the minimum concentrations of contamination in a relatively short period of time can increase to toxic and life-threatening concentrations. This is a shortening of the food (trophic) chain in the Arctic.

The Arctic is the territory of compact residence of indigenous small-numbered peoples of the North (indigenous peoples). According to the population census of 2002 and 2010, in 8 years out of 45 ethnoses from the number of indigenous peoples in 25 there was a decrease in the population, 7 of which reduced the population by 3-7 times, 2 ethnic groups disappeared altogether [1]. Consequently, environmental pollution and the inclusion of heavy and rare earth metals in the food / food chain

under northern / arctic ecosystems can be detrimental to the fate of the ethnic groups that inhabit them.

Nowadays, according to our studies of 2015, the content of microelements in the blood of residents of village of Zhilinda of the Olenek Evenk national ulus are within the limits of reference values (Table 1). In addition, there are data from the administration of the Olenek Evenk national ulus on the content of microelements in the water environment of the Tomtor rare-earth metal deposit (Table 2). Another matter, their dynamics in the conditions of industrial production on the territory of this region is of interest.

To exclude the negative impact of environmental pollution on the health of the population in the mining zone, we developed a methodology for medical and environmental monitoring (annex). At the same time, it should be noted that in practice there is an Environmental Monitoring carried out by the Center for Environmental Monitoring of the Ministry of Nature Protection of the Republic of Sakha (Yakutia). And Medico-ecological monitoring is purely our Yakut know-how.

Medico-ecological monitoring is a dynamic study of environmental pollution (annex) with a periodicity of 3 or 5 years.

An important part of monitoring is the study of the level of morbidity in the body's basic systems, such as cardiovascular, respiratory, digestive, urinary, endocrine, musculoskeletal, etc. The peculiarity of medical-ecological monitoring is the search in the clinical manifestation of the pathology of these body systems of the features characteristic for this and that type of microelementosis. The obtained indicators are analyzed each time in comparison with the initial state of the environment, the health of the population, incl. demographic indicators, quality of life before the development of this field.

#### Conclusion

Thus, a series of medical and

Table 1

The content of microelements in the blood ( $\mu\text{g} / \text{l}$ )

Microelements	n	Me (Q25-Q75)	Reference values
Nickel (Ni)	100	< 13	1-28
Cadmium (Cd)	79	0,8 (0,6-1,1)	0,01-2
	21	< 0,5	
Cobalt (Co)	100	< 6	0,05-0,1
Chromium (Cr)	20	1,0 (0,7-1,2)	0,05-0,5
	80	< 6	
Zinc (Zn)	47	975 (754-1289)	543-1130
	53	< 625	
Copper (Cu)	100	959 (664-1295)	750-1300
Arsenic (As)	100	< 13	2-62
Ferrum (Fe)	100	2515 (2020-3347)	600-1800

environmental studies in the monitoring mode with a certain periodicity in the zone of activity of mining enterprises will allow to identify environmental pollution and the development of human medical pathology caused by it in the form of microelementoses in their early stages, which will be a significant contribution of Yakut scientists to environmental medicine. Such a methodical approach will help to save the population of the North / Arctic, including the indigenous small population of the North, from the negative impact of the inevitable further development of the Arctic's natural resources.

#### Reference

Data of the All-Russia Population Census of 2002 and 2010 [www.gks.ru](http://www.gks.ru).

#### Parameters of Medical and Environmental Monitoring

- Radiation situation;
- The content of priority for this field of heavy and rare earth metals in the environment;
- The content of the same metals in human blood;
- Basic medical and demographic indicators
- birth rate, mortality, natural population growth, life expectancy, etc.;
- Morbidity of the population with diseases of the circulatory system, respiratory and digestive organs, urogenital, musculoskeletal and endocrine systems, blood and hematopoietic tissue, and other pathologies;
- Disability;
- Indicators of the main types of metabolism
- lipid, protein, carbohydrate, mineral, vitamin;
- The main indices of immunological

Table 2

Micronutrients content in the water environment of the Tomtor rare-earth metal deposit (in MPC, 2015) \*

Microelements	Water environment	Excess of MPC
Fe (ions)	brook Pomanistochka R. Anabar	in 9-10 times 2,5 times
Cu (copper)	R. Malaya Kuonapka	in 3,5-4,4 times
Mn (manganese)	R. Malaya Kuonapka	in 1,5 times

\* The content of aluminum, lead, arsenic, mercury, antimony, bismuth, beryllium, uranium, thorium, etc. is lower than the established standards.

Application homeostasis - AFP, REO, gamma-IFN, IL-16, IL-6, SRB;  
- Quality of life of the population on the questionnaire of WHO KZh-100.

#### The authors

1. KRIVOSHAPKIN Vadim Grigorievich - Doctor of Medical Sciences, Professor, Academician of the Academy of Sciences of the Republic of Sakha (Yakutia), Adviser of the Academy of Sciences of the RS (Ya). Cont. Tel. 8-914-305-46-35. E-mail: kukai1937@gmail.com;
2. TIMOFEEV Leonid Fedorovich - MD, professor of the Department of Public Health and Public Health, General Hygiene and Bioethics of the Medical Institute M.K. Ammosov NEFU. Address: 677000 Yakutsk, ul. Oyunsky, 27. Cont. Tel. 8-914-225-88-45. E-mail: tfnauka@mail.ru.

V.B. Egorova, M.A. Fedorova, Ya.A. Munchalova,  
T.G. Dmitrieva, S.N. Alekseeva

## CLINICO-LABORATORY FEATURES OF MENINGITIS IN CHILDREN

DOI 10.25789/YMJ.2018.63.18

#### ABSTRACT

Meningitis continues to be the most common form of central nervous system damage in children. In the structure of neuroinfections, the frequency of meningitis in children is about 30%, remain an important medical and social problem due to the weighting of their current course. Acute meningitis has a high frequency of severe forms, high lethality, expansion of the spectrum of etiopathogenesis and their resistance to the most common antibiotics, difficulties in differential diagnosis.

The article analyzes the clinical and laboratory features of meningitis in children and their outcomes according to the data of the State Institution of Children's Departments of the Republic of Sakha (Yakutia) «Children's Infectious Clinical Hospital». The clinical manifestations, the etiological landscape of meningitis in children, and the demonstrators of laboratory analyzes were studied. A retrospective analysis of 40 medical charts of inpatient patients according to the GBU RS (Y) «Children Infectious Clinical Hospital» for 2016 was conducted.

In the etiologic structure, serous meningitis of enterovirus etiology (90%) predominated among meningitis with refined etiology, which was confirmed by laboratory tests. The causative agents of enteroviral meningitis in children in Russia, European countries, the United States and Japan in the last 10-20 years were most often ECHO30, ECHO11 [1, 4].

In children with meningitis, in most cases, moderate forms of the disease with a hypertensive syndrome leading in the clinic, polymorphism of clinical manifestations, febrile fever, rigidity of the occipital muscles, catarrhal phenomena were observed. Most of the children were hospitalized 24 hours after the onset of the disease, while there were certain difficulties in the clinical diagnosis at the prehospital stage. Thus, meningitis was suspected only in 70% of cases, in others, food toxicoinfection, acute gastroenteritis, acute respiratory viral infection, acute nasopharyngitis, enterovirus infection, acute enterocolitis, acute enteritis were suspected.

At the hospital stage, the most informative for the diagnosis of a neuroinfectious disease are changes in the cerebrospinal fluid, which closely contacts the structures of the nervous tissue.

**Keywords:** neuroinfections, meningitis, children, etiology.

#### Introduction

Meningitis is an inflammation of the membranes of the brain and subarachnoid space, which often lead to adverse

effects. In the structure of neuroinfections, the frequency of meningitis in children is about 30%, remain an important medical and social problem due to the

weighting of their current course. Acute meningitis has a high frequency of severe forms, high lethality, an expansion of the etiological spectrum and difficulties



in differential diagnosis [1, 3].

Despite the sporadic incidence in the Russian Federation as a whole among children, the incidence is 2.48 per 100,000 children under 17 [5]. It should be noted that viral meningitis prevails (up to 75%) compared with bacterial one (up to 25%). However, bacterial meningitis remains relevant, as late diagnosis and lack of treatment in 100% of cases lead to death, and severe disabling effects are possible even with adequate therapy.

The analysis of clinical and laboratory diagnostics, the results of treatment of meningitis of various etiologies shows that the most urgent problems of practical medicine at the present stage are: early clinical diagnosis at the prehospital stage, transportation of patients to specialized departments, diagnosis and laboratory confirmation of the diagnosis in the hospital, correct assessment of the severity of the condition patient with subsequent adequate therapy [2, 4].

**The purpose** of our work was to study the clinical and laboratory features of meningitis and their outcomes in children of different ages.

#### Materials and methods of the study

The work was carried out on the basis of the GBU RS (Y) "Children's Infectious Clinical Hospital". A retrospective analysis of the case histories (f.003 / y) of children treated with a diagnosis of viral meningitis, bacterial meningitis, viral-bacterial meningitis and serous meningitis, of unspecified etiology, was conducted.

In 2016, 40 children were treated at the Children's Infectious Clinical Hospital for the treatment of meningitis of various etiologies, of which 65% (26 people) were boys, 35% (14 people) were girls. By age composition: from 2 months. up to 3 years - 2 people (5%), from 3 to 6 years - 8 people (21%), from 7 to 16 years - 22 people (70%). Among the patients, rural residents - 10 children (25%), urban - 30 (75%).

#### Results and discussion

In most cases (18 children - 45%) there was a development of enterovirus meningitis. In 10 children (25%) bacte-

rial meningitis was diagnosed, in 9 children (22.5%), meningitis had a mixed viral-bacterial etiology, in 3 children (7.5%) - serous meningitis, of unspecified etiology.

Hospitalization in the hospital in most cases (34 children - 85%) occurred within the first three days after the disease, 6 children (15%) were admitted in later periods.

In case of enteroviral meningitis, children (18 prs) were hospitalized on the 1st day of the disease - 4 (22%), on the second day - 7 (39), on the third day - 4 (22), in later terms - 3 (17%).

In case of bacterial meningitis (10 children), 2 children (20%) were admitted on the first day, 5 (50) on the second - 1 (10), 2 (20%) were hospitalized in later periods.

In case of virus-bacterial meningitis (90 children), 3 (33.3%) were hospitalized on the first day after the onset of the disease, on the second - 4 (44.4), on the third - 1 (11.1), later - 1 (11.1%).

Patients with a diagnosis of serous meningitis of unspecified etiology (3 children): 1 child received a transfer from another department (after the bronchopneumonia), on the second - 1 child, on the third - 1 child.

The analysis showed that patients were mainly in the direction of "first aid" (57%), by self-reversal (5%), in the direction of the district pediatrician (27%), in the direction of the central district hospital (7%), transfer from another ward (5% %).

Patients were referred to the hospital with various preliminary diagnoses: acute meningitis - 70% of cases, "food toxicosis" - 11%, "acute gastroenteritis" - 5%, "acute respiratory viral infection, acute nasopharyngitis" - 5%, "enterovirus infection" - 3%, "acute enterocolitis" - 3%, "acute enteritis" - 3%.

A study of the seasonality of meningitis made it possible to identify a large incidence of meningitis in the summer months, as well as in the autumn period. Peak hospitalization of patients fell in August - 40% (Fig. 1).

An analysis of the etiological structure

of acute meningitis among our patients indicates a large proportion of meningitis of the unspecified etiology of 50% (20 cases).

Among meningitis with specified etiology (20 cases), enterovirus infection was confirmed in 18 children (90%), herpes simplex virus was detected in 1 child (5%), hemophilic infection in 1 child (5%). This may be due to the early onset of antibiotic therapy, to the collection of biological material, as well as to the limited capabilities of the diagnostic laboratory (Fig. 2).

The onset of the disease was 100% acute regardless of the etiology of meningitis. The most common clinical symptoms in children with meningitis were nonspecific manifestations - increased body temperature, lethargy, inhibition, decreased appetite, which were observed in all cases. Catarrhal phenomena in the initial stage were observed in 29% of patients (of which tonsillitis was detected in 64%, pharyngitis - 27%, follicular angina - 18%).

In addition, often with objective examination, stiff neck muscles were observed in 66% of patients, photophobia in 16%. Less frequently, the positive Kernig symptom was 13%, and the symptoms of Brudzinski in 5% of cases. Vomiting as a cerebral symptom, caused by cerebrospinal fluid hypertension, not associated with eating and not bringing relief, was observed in 71%, of which single vomiting occurred in 32%, multiple vomiting 39%.

In blood tests on admission, leukocytosis in viral meningitis ranged from  $10-15.3 \times 10^9 / L$  in 44%, an increase in ESR to 25 mm / h in 82%.

In bacterial meningitis, leukocytosis within  $10-18 \times 10^9 / L$  in 55%, an increase in ESR of 35-54 mm / h in 80%.

With viral-bacterial meningitis, leukocytosis ranges from  $10-14 \times 10^9 / L$  in 50%. With serous meningitis of unknown etiology, leukocytosis was noted within  $10-22 \times 10^9 / L$ , ESR 32-35 mm / h.

Analysis of cerebrospinal fluid in bacterial meningitis revealed a neutrophilic

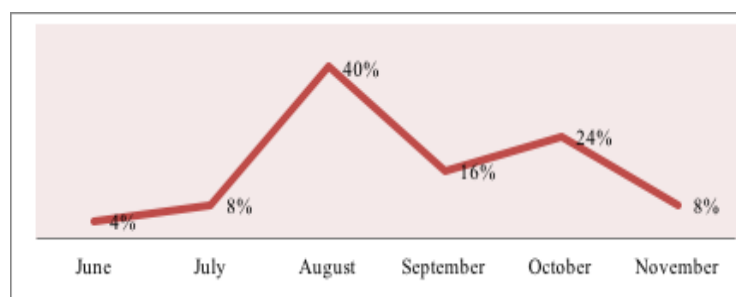


Fig. 1. Distribution of the incidence of meningitis, depending on the season.

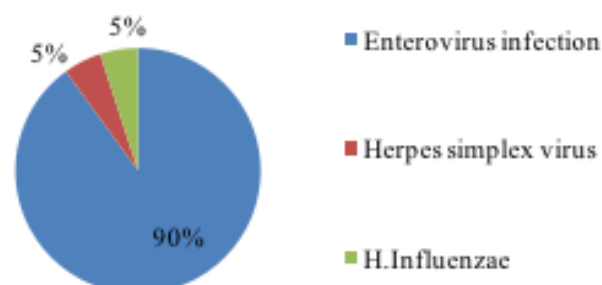


Fig. 2. Etiological structure of meningitis with specified etiology.

cytosis within 15.3-395 cells in 1 µl, in one child 1600 in 1 µl. The increase in protein level was observed only in 22% of cases, the decrease in glucose level in 62%. Reduction of chlorides in 35%.

In children diagnosed with enteroviral meningitis, the cytosis was within 150-501 cells in 1 µl, which was lymphocytic in nature. An increase in protein levels occurred in 31%, a decrease in chloride levels was observed in 38%, an increase in glucose level in 41%.

In viral-bacterial meningitis, cytosis within 7-173 cells in 1 µl was of a mixed nature. Decrease in chloride levels in 100%, increase in protein level in 13%. The glucose level remained within normal limits.

In serous meningitis, pleocytosis was lymphocytic, cytosis 160-314.6 in 1 µl.

The duration of inpatient treatment averaged 14 days: for enterovirus meningitis, an average of 14 days, for bacterial meningitis - 20 days, for virus-bacterial meningitis - 16 days, for serous meningitis, unspecified - 14 days. Analysis of the outcomes of the disease showed that the bulk of children were discharged in a satisfactory state 84% of children and with an improvement of 16%. With improvement, children were discharged, who, with a background of ongoing treatment, showed a persistent positive dynamics.

#### The conclusion

Thus, meningitis more often hurt boys than girls. Age characteristics distinguish the predominance of school-age children. Patients with meningitis had moderate-severe forms of the disease, with a predominance in the clinical picture of hypertensive syndrome, nonspecific symptoms, and moderately expressed meningeal symptoms. Difficulties in clinical diagnosis at the prehospital stage are associated with the nonspecificity of the initial manifestations. Most of the children were hospitalized 24 hours after the onset of the disease, while there were certain difficulties in the clinical diagnosis at the prehospital stage. Thus, meningitis was suspected only in 70% of cases, in others, food toxicoinfection, acute gastroenteritis, acute respiratory viral infection, acute nasopharyngitis, enterovirus

infection, acute enterocolitis, acute enteritis were suspected.

In the etiological structure of meningitis in children aged 2 months up to 17 years, the following pathogens prevailed: enterovirus - 90%, hemophilus influenzae - 5%, herpes simplex virus - 5%. There remains a large proportion of cases with an unspecified etiology - 50%, which requires improvement of approaches to diagnosis.

Etiologic and clinical polymorphism of infectious diseases of the nervous system determines the problematic issues of their diagnosis and treatment, the main ways of solving which are continuous clinical and laboratory and epidemiological monitoring with analysis of the pathogen characteristics and current features of the infection process, determining the priority link of pathogenesis, targeted improvement of therapeutic tactics with rational use of medicines and technologies. At present, the issue of vaccine prevention of neuroinfections remains urgent.

#### References

1. Demina A.V., Netesov S.V. Enterovirusnaya infekciya: mnogoobrazie klinicheskikh proyavlenij [Enterovirus infection: a variety of clinical manifestations] Byulleten' SO RAMN [Bulletin of the SB RAMS]. Novosibirsk, 2009, №6, pp.116-123.
2. Sejbil' V.B., Frolochkina T.I. Seroznyj meningit [Serous meningitis] Mikrobiologiya [Microbiology], 2006, №1, pp. 87-92.
3. Simachenko O.V., Germanenko I.G., Lisickaya T.I. Izuchenie kliniko-ehpidemiologicheskikh i diagnosticheskikh markerov meningita u detej na sovremennom eh tape [Study of clinical and epidemiological and diagnostic markers of meningitis in children at the present stage] Medicinskaya panorama [Medical panorama], 2010, pp. 10-13
4. Skripchenko N.V., Alekseeva L.A., Ishchenko I.A., Krivosheenko E.M. Cerebrospinal'naya zhidkost' i perspektivy ee izucheniya [Cerebrospinal fluid and prospects for its study] Rossijskij vestnik perinatologii i pediatrii [Russian Bulletin of Perinatology and Pediatrics], 2011, №6, pp.88-96.
5. Skripchenko N.V., Ivanova M.V., Vil'nic A.A., Skripchenko E.YU. Nejroinfekcii u

detej: tendencii i perspektivy [Neuroinfections in children: trends and perspectives] Rossijskij vestnik perinatologii i pediatrii [Russian Bulletin of Perinatology and Pediatrics], 2016, №4, pp. 9-22.

#### The authors:

1. Egorova Vera Borisovna - Candidate of Medical Sciences, Associate Professor, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [ve-raborisovna@yandex.ru](mailto:ve-raborisovna@yandex.ru)
2. Fedorova Michiliye Alekseevna - the resident of group O-P-16 of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [michiliyef@mail.ru](mailto:michiliyef@mail.ru),
3. Munkhalova Yana Afanasievna - Candidate of Medical Sciences, Head of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [tok-macheva@mail.ru](mailto:tok-macheva@mail.ru).
4. Dmitrieva Tatyana Gennadiyevna - doctor of medical sciences, professor of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [dtg63@mail.ru](mailto:dtg63@mail.ru).
5. Ivanova Olga Nikolaevna - doctor of medical sciences, professor of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [olgadoctor@list.ru](mailto:olgadoctor@list.ru);
6. Alekseeva Sargylana Nikolaevna - Candidate of Medical Sciences, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: [sargylanao@mail.ru](mailto:sargylanao@mail.ru).



N.V. Borisova, G.A. Koltovskaya, U.D. Antipina

## DISTRIBUTION OF DISELEMENTOSIS AND ELEMENTAL PATHOLOGY PROFILE IN WOMEN FROM VARIOUS REGIONS OF THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2018.63.19

### ABSTRACT

Stability of the chemical composition of the body is one of the most important and mandatory conditions for its normal functioning. Accordingly, deviations in the content of chemical elements caused by environmental, climatic-geographical factors or diseases will lead to a wide range of disorders in the state of health. Therefore, the identification and evaluation of deviations in the exchange of macro- and microelements, as well as their correction, are a promising direction of modern medicine.

The **objective** of the work is to reveal the regularity of distribution of diselementoses and the elemental profile of pathology the content of chemical elements in the hair of women from various regions of the Republic of Sakha (Yakutia).

**Keywords:** microelements, ecology, Yakutia, health, North.

Stability of the chemical composition of the body is one of the most important and mandatory conditions for its normal functioning. Accordingly, deviations in the content of chemical elements caused by environmental, climatic-geographical factors or diseases will lead to a wide range of disorders in the state of health. Therefore, the identification and evaluation of deviations in the exchange of macro- and microelements, as well as their correction, are a promising direction of modern medicine.

According to observations of Russian scientists, the complex of biomedical and ecological factors, strictly specific for components of both northern ecosystems and northern human populations, participates in the formation of human health in the North [1, 2, 6, 10]. These features in many components of northern ecosystems came to an optimal balance and stabilized, and in the human physiological systems, in particular in the immunogenetic apparatus, were remembered and determined. The destabilizing factor of the natural environment is technogenic and anthropogenic pollution of the biosphere [5, 7, 8].

Due to the limited northern ecosystems, the parameter of ecological capacity, as well as the slowed down rate of biological degradation of toxicants, even their minimal contents have the ability to accumulate to concentrations that are toxic to the living organism. At present, pollution of the environment with heavy metals creates serious problems for the safe agricultural use of soils near industrial cities, metallurgical enterprises and highways. Heavy metals are supplied to soils of agrocenoses with gas-dust streams, fertilizers, pesticides during irrigation, and also when sewage sludge is

used as fertilizer [4, 9, 12].

The Republic of Sakha (Yakutia) is by its biogeochemical characteristics a unique region of the Russian Federation. Seasonal thawing of soils varies from a dozen centimeters in the north to 2-3 m in the south. Soils of Yakutia are characterized by a lack of calcium, phosphorus, potassium, cobalt, copper, iodine, molybdenum, boron, zinc, a sufficient amount of manganese and a relative excess of strontium, especially along river floodplains [4, 12]. Soils and bottom sediments of the Lena-Vilyui watershed are deficient in the content of copper, boron and molybdenum and are enriched in manganese, iron and cobalt [7]. Bottom deposits due to their high sorption properties can be considered as an integral indicator of anthropogenic load on the hydrosphere and their study should be given an important place in the general system of observations of the state of the aquatic environment. The composition of lake and river water in general is characterized by low mineralization and low content of fluorine, copper and molybdenum, a decrease in the intensity of water migration of zinc, manganese and copper, an increase in the migration activity of tin, vanadium and potassium. Accordingly, under such conditions, the content of calcium, phosphorus, chlorine and magnesium in the forage grasses of native plants is significantly reduced [8, 12].

The **objective** of the work is to reveal the regularity of distribution of diselementoses and the elemental profile of pathology in women from various regions of the Republic of Sakha (Yakutia).

### Materials and methods of the research

Using the multielement analysis system by AES-ISP and MS-ISP methods,

the content of chemical elements (Al, As, Ca, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, P, Pb, Se, Si, Sn, Ti, V, Zn,  $\mu\text{g} / \text{g}$ ) in the hair of 555 women from various regions of the Republic of Sakha (Yakutia) was investigated.

The choice of hair as an object of analysis was due to numerous publications confirming the suitability of hair analysis to assess the elemental status of the population [3, 11].

As a reference, a hair sample from the Shanghai Institute of Nuclear Physics of the Academy of Sciences of the People's Republic of China (GBW09101) was used. For the removal of surface contamination and degreasing of hair, the method of preparation of hair samples recommended by the IAEA is applied. To do this, the hair is treated with acetone for 10-15 minutes, and then washed three times with distilled water. Hair drying is performed at room temperature for 10-15 minutes.

Standard working solutions are prepared by diluting the reference standard multielement solutions. Preparation of working standards consists in bringing an aliquot of the support solution to the required volume with dilute nitric acid or deionized water for aqueous solutions. The obtained concentrations are calculated and entered for calibration in the WinLab32 software package. The internal standard is added to the finished working standard - a solution of indium nitrate,  $\text{C}_{\text{In}} \approx [1000 \text{ mg} / \text{l}]$ , calculated at 100  $\mu\text{l}$  for every 10 ml of the standard solution. Working standards are expended in 1-5 days.

A solution of SOS (a standard sample of the hair composition) is prepared from standard hair of known concentration (imported) or selected from the discharge of waste samples. Used to monitor the



correct measurement of concentrations during serial measurements, for example, every 10 measurements. A «verification standard» can also be used as a control, which is prepared on the basis of 10% (by volume) of nitric acid by adding GSO elements of known concentration.

The analysis of the samples is carried out using the ISP-AES method using the Optima 2000 DV (PerkinElmer) instrument (determination of Ca, Mg, P, Zn, K, Na), as well as the ICP-MS method using the Elan 9000 (PerkinElmer) (Al, As, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, Se, Si, Sn, Ti, V).

Statistical processing of the data was carried out using Microsoft Excel XP and Statistica 6.0. In assessing the reliability of the differences, the value  $p < 0.05$  was used. Statistical processing of the obtained experimental material was carried out on IBM-PC using the Excel software package. The arithmetic mean ( $M$ ) and its error ( $m$ ), the standard deviation ( $\sigma$ ), the coefficient of pair correlation ( $r$ ) were calculated. Assessment of the reliability of the differences between the data obtained in the study groups was carried out according to Student's  $t$ -criterion.

### Results

As shown by the analysis of the obtained data, for women living in different regions of the Republic of Sakha (Yakutia), there are significant differences in the content of chemical elements in the hair. The observed differences are mainly due to the original "elemental portrait" of residents of the polar and, to a greater extent, southern regions of the Republic, while the "elemental portraits" of residents of the western and central regions and Yakutsk are reliable there are practically no differences and they can be considered "average" for the surveyed region (Table 1).

The elemental status of women residing in the southern regions can be considered the most "peculiar": they have relatively higher content in the hair of Ca compared to other groups of areas, against the background of a relatively reduced concentration of such chemical elements as Al, Be, Cd, Cr, Li, Pb, and also Mg, K, Na and I. Thus, it can be concluded that the least common among the surveyed areas is the load of the most common toxic elements Al, Be, Cd and Pb, while the reduced content in the hair Cr and K may be considered Xia as an unfavorable factor indicates the relative lack of these elements in the body of women.

Unlike the southern regions, the female population of the Arctic regions is characterized by the maximum content in

the hair of toxic chemical elements Cd, Hg, Pb, Mn. Attention is also drawn to the highest concentration in the hair of Fe (although no significant differences were established).

Residents of the central regions are characterized by a relatively high content of Ca, Mg and Li hair, and western groups of uluses - high content of Al.

The relatively high content of Ca and Mg women in hair is probably of purely physiological character. According to modern data [15], the average content of these elements in women's hair is significantly higher than that of men.

### The discussion of the results

The obtained results at comparing the hair composition of the female population of the central regions of the Republic Sakha (Yakutia) and Yakutsk seem to be the result of a high degree of urbanization, which significantly changes the natural elemental balance of population groups, including women (the population of the arctic, western and southern areas in the vast majority rural).

In order to reveal the most characteristic features of the "elemental portrait"

of the female population of the Republic of Sakha (Yakutia), we estimated the frequency of the deviation of the content of chemical elements in the hair from the norm boundaries [13, 14, 16]. The data presented that, there is a significant difference between the frequencies of imbalances of chemical elements in the hair of women from different regions of the Republic of Sakha (Yakutia) (Table 2 - 3)

A number of imbalances (deficiencies or excesses) in the content of chemical elements in hair have been established, characteristic for all the surveyed groups of areas. Thus, for women, regardless of their place of residence, there is a relatively lower content of Ca, Co, Mg (excluding central regions), P, Se and Zn and a relatively high content of Mn and Na (in all groups of regions, the frequency of deficit / excess of these elements in the hair exceeded 30%).

The individual features of elemental portraits of groups of regions as a whole correspond to those established in the analysis of the absolute content of chemical elements in women's hair. Thus, for residents of the Arctic regions, the fre-

Table 1

Average content of chemical elements in the hair of women living in different regions of the Republic of Sakha (Yakutia),  $\mu\text{g/g}$

Element	Regions of the Republic of Sakha (Yakutia)					Reliable differences between districts **
	arctic n = 61	western n = 120	southern n = 151	central n = 121	Yakutsk * n = 102	
Al	8,51±0,57	14,2±2,05	4,74±0,59	4,71±0,32	9,64±1,04c,d	4, 5
As	0,05±0,005	0,1±0,056	0,05±0,009	0,03±0,004	0,07±0,017	
B	1,79±0,36	0,98±0,17	1,21±0,51	1,14±0,19	0,8±0,14a	
Be	0,01±0,001	0,01±0,001	0,003±0,001	0,01±0,001	0,01±0,001c	2, 4
Ca	559±49	853±108	1525±130	2162±526	1700±186a,b	2, 3, 4, 5
Cd	0,14±0,02	0,06±0,01	0,03±0,001	0,04±0,01	0,08±0,01a,c	1, 2, 3, 4
Co	0,04±0,01	0,04±0,01	0,03±0,01	0,03±0,01	0,05±0,01c	
Cr	0,61±0,04	0,53±0,04	0,36±0,03	0,46±0,06	0,52±0,05c	2, 4
Cu	11,83±0,29	10,94±0,25	12,07±0,51	9,94±0,44	13,37±0,91b	
Fe	46,85±9,64	21±2,37	35,44±16,89	15,7±1,46	25,06±1,53a,d	
Hg	2,72±0,42	0,74±0,08	0,68±0,04	0,66±0,13	1,2±0,2a,b,c	1, 2, 3
I	5,98±4,97	1,3±0,18	0,78±0,12	0,85±0,19	2,11±0,56c	2
K	830±190	543±102	217±121	255±70	295±52a,b	2
Li	0,05±0,005	0,05±0,01	0,02±0,003	0,16±0,053	0,09±0,026c	3, 5, 6
Mg	82±8	155±23	99±12	586±105	191±23a,c,d	3, 5, 6
Mn	4,17±0,44	1,8±0,27	2,19±0,23	1,81±0,26	2,62±0,27a,b	1, 2, 3
Na	1332±292	847±150	444±181	1027±209	527±126a	2
Ni	0,49±0,06	0,38±0,05	0,52±0,07	0,41±0,07	0,57±0,05b	
P	140±4	168±6	165±16	147±5	217±61	
Pb	3,82±0,64	1,45±0,22	0,43±0,06	1,52±0,57	2,2±0,54c	1, 2, 3, 4
Se	0,39±0,05	0,49±0,09	0,54±0,05	0,23±0,05	0,39±0,04c	
Si	19±2,04	48±7,31	50,9±8,37	45,81±9,03	49±6,64a	
Sn	0,32±0,06	0,25±0,05	0,30±0,05	0,38±0,07	0,63±0,11a,b,c	
V	0,05±0,01	0,07±0,01	0,06±0,01	0,04±0,01	0,06±0,01	
Zn	195±10	167±5	177±4	177±10	195±8b,c	1

Note. In the Tables 1-3 \* reliable differences in comparison with Yakutsk: a - arctic regions, b - western regions, c - southern regions, d - central regions

\*\* 1 - arctic / western; 2 - arctic / southern; 3 - arctic / central  
4 - western / southern; 5 - west / central; 6 - south / central.

Table 2

**Frequency of the increased content of chemical elements in the hair of women in the Republic of Sakha (Yakutia), depending on the place of residence, %**

Element	Regions of the Republic of Sakha (Yakutia)					Reliable differences between districts **
	arctic n = 61	western n = 120	southern n = 151	central n = 121	Yakutsk * n = 102	
Al	3,28	5,83	2,00	0,00	5,88	
As	0,00	0,85	0,00	0,00	0,98	
B	4,76	0,00	1,54	0,00	2,04	
Be	0,00	0,00	0,00	0,00	0,00	
Ca	0,00	10,00	18,00	23,81	23,53a,b	3
Cd	21,31	1,67	4,67	28,57	9,90b,c	1, 2
Co	0,00	0,83	1,33	0,00	1,96	
Cr	21,31	15,83	4,00	4,76	10,78a	2, 4
Cu	3,28	4,17	7,33	0,00	7,84	
Fe	40,98	21,67	6,67	0,00	22,55a,c,d	1, 2, 3, 4
Hg	37,29	2,80	2,14	4,76	16,48a,b,c	1, 2, 3
I	9,09	10,53	2,17	0,00	15,28d	
K	75,41	47,50	21,33	47,62	37,25a,c	1, 2, 3, 4, 6
Li	0,00	3,45	1,33	42,86	6,86	3, 5, 6
Mg	6,56	25,00	13,33	76,19	31,37a,c,d	1, 3, 5, 6
Mn	72,13	35,83	38,00	47,62	58,82a,b,c	1, 2
Na	78,69	45,00	28,00	90,48	43,14a,c,d	1, 2, 5, 6
Ni	4,92	2,59	7,33	4,76	9,80	
P	8,20	29,17	14,67	19,05	21,57a	1, 4
Pb	32,79	7,50	3,33	28,57	12,75a,c,d	1, 2, 5, 6
Se	1,64	2,59	2,00	0,00	0,00	
Si	6,56	32,48	27,33	19,05	26,47a	1, 2
Sn	3,28	1,74	4,00	4,76	12,87a,b,c	
V	4,92	5,04	11,33	9,52	2,97c	
Zn	34,43	8,33	7,33	9,52	18,63a,b,c	1, 2, 3

Table 3

**Frequency of reduced content of chemical elements in the hair of women in the Republic of Sakha (Yakutia), depending on the place of residence, %**

Element	Regions of the Republic of Sakha (Yakutia)					Reliable differences between districts **
	arctic n = 61	western n = 120	southern n = 151	central n = 121	Yakutsk * n = 102	
Al	1,64	6,67	1,33	0,00	12,75a,c,d	
As	0,00	0,00	0,00	0,00	0,00	
B	0,00	0,00	0,00	0,00	0,00	
Be	0,00	0,00	0,00	0,00	0,00	
Ca	68,85	55,00	36,00	23,81	27,45a,b,c	2, 3, 4, 5
Cd	0,00	0,00	0,00	0,00	0,00	
Co	63,93	70,83	48,67	19,05	40,20a,b,c,d	2, 3, 4, 5, 6
Cr	3,28	34,17	31,33	4,76	12,75a,b,c,d	1, 2, 5, 6
Cu	18,03	35,83	48,00	76,19	21,57b,c,d	1, 2, 3, 5, 6
Fe	1,64	27,50	27,33	33,33	11,76a,b,c,d	1, 2, 3
Hg	0,00	0,00	0,00	0,00	0,00	
I	72,73	38,60	78,99	61,90	68,06b,c	1, 4, 5, 6
K	1,64	19,17	32,67	0,00	30,39a,b,d	1, 2, 4, 5, 6
Li	14,75	6,03	51,33	0,00	9,80c,d	2, 4, 6
Mg	47,54	36,67	55,33	4,76	20,59a,b,c,d	3, 4, 5, 6
Mn	3,28	25,83	3,33	0,00	4,90b	1, 4, 5
Na	4,92	15,83	13,33	0,00	4,90b,c	1, 5, 6
Ni	0,00	0,00	0,00	0,00	0,00	
P	42,62	20,00	46,00	42,86	33,33a,b,c,d	1, 4, 5
Pb	0,00	0,00	0,00	0,00	0,00	
Se	29,51	38,79	32,67	66,67	48,04a,b,c,d	1, 3, 5, 6
Si	39,34	25,64	26,00	9,52	22,55a	1, 2, 3, 5, 6
Sn	0,00	0,00	0,00	0,00	0,00	
V	0,00	0,00	0,00	0,00	0,00	
Zn	40,98	45,83	55,33	71,43	42,16c,d	2, 3, 5, 6

quency of excessive accumulation in the hair of both essential (Cr, Fe, K, Mn, Na, Zn) and toxic (Cd, Hg, Pb) chemical elements is characteristic of the inhabitants of the Arctic regions as compared with other regions. As a result, the reduced content of Cu, Cr, Fe, K is relatively less common here, and relatively more often, the reduced content of Ca, Mg and Si.

The southern zone can be considered the most "element-deficient" group of regions, which also corresponds well with the results obtained on the basis of the analysis of absolute values. In the southern regions, the most extensive group of chemical elements is established, whose content in the hair of the examined women is below the norm limits. Among these can be classified as Ca, Co, Cr, Cu, Fe, I, K, Li, Mg, P, Se, Si and Zn. At the same time, the increased content of chemical elements in hair, with the exception of the excess of Mn and Na already described, is not characteristic of the "elemental portrait" of local women.

The regions of the Republic of Sakha (Yakutia), which are part of the western zone, differ and fully correspond to the general indices given at the beginning of the section, except for the increased content in hair Si, Fe and P, and also lower - Co and Mn, which here is more common (32, 21, 29, and 71 and 25%, respectively). The deficit in the hair I is relatively less pronounced in the local female population (38% vs. an average of 70-80% in other regions).

Women from the central regions of Yakutia are characterized by relatively high frequencies of excess accumulation in hair Ca, Mg, Cd, Na, Li, Pb and decreased - Cr. It is interesting to note that the reduced content of electrolyte elements K, Na, and Li in hair is not found at all here, but deficiencies in hair of Fe, Cu and Zn are widespread. As can be seen from the above data, the central regions of the Republic of Sakha (Yakutia) have a number of features characteristic of both polar (the prevalence of excess accumulation of Cd, Pb toxicants) and other areas (widespread prevalence of essential chemical element deficiencies), that is, the greatest imbalance in elemental metabolism.

The urban population (Yakutsk) differs from the other surveyed groups of areas with a relatively higher frequency of reduced Se, but deficiencies in the hair of Ca, Mg and P are less common here. On the contrary, there are abundant Ca and Mg excesses with a sufficiently high frequency, the accumulation of Mn and Sn is more typical for the population.

Thus, the observed regularity (the

increase in the intake of chemical elements in the organism of the women of the Republic of Sakha (Yakutia) towards the south-south), established in the analysis of the absolute content of chemical elements in the hair of the adult population, is generally confirmed, as in the analysis of the frequency of imbalances, established using the boundaries of the normal content of chemical elements in human hair. However, in the latter case, the peculiarities of the elemental balance of the population of the central regions of the Republic of Sakha (Yakutia) are becoming noticeable, breaking out their reduced scheme. The high frequency of excessive accumulation here of a number of chemical elements makes these regions related to the Arctic.

By analogy with the above data on the difference in the elemental composition of the hair of women (expressed in absolute figures), we also performed an analysis of the differences in the frequency of imbalances in the content of chemical elements in the hair of the examined.

For women living in the central regions of Yakutia, the risk of hyperelementosis of such essential elements of Ca, Mg and Na is more typical. At the same time, women are characterized by a relatively high frequency of reduced content in hair of essential chemical elements. Thus, residents of the Arctic regions of Yakutia are more often found to have deficiencies of Ca and Mg; southern regions - Cr, P and Zn, the western group of areas - Cr, the central regions - P, Se, Zn, Yakutsk - P, Se and Zn.

### The conclusion

The obtained results show that the risk of hyperelementosis in the female population of the Republic of Sakha (Yakutia) is significantly increasing in the direction of south-south; in the direction of north-south the risk of development of hypo-elemental diseases increases significantly. At the same time, the central regions of the republic are an exception to the general scheme: the prevalence of excessive accumulation in the hair as toxic and essential chemical elements is also great here, as in the arctic regions of the republic.

The imbalance of elements, regardless of its causes, can be an independent pathogenetic factor, since the most important role of macro- and microelements in the processes of vital activity of the organism is known. Therefore, the current stage of development of the pathogenesis of various diseases and intoxications requires the study of pathological processes at cell levels, subcellular structures, membrane and enzyme systems.

### References

1. Agadzhanyan N.A. Vel-danova M.V. Skalny A.V. *Jekologicheskij portret cheloveka i rol' microelementov* [Ecological portrait of a person and the role of microelements]. Moscow: Izd-vo KMK [Publishing house KMK], 2001, 236 p.
2. Agadzhanyan N.A. *Etnicheskie problemy adaptacionnoy fiziologii* [Ethnic problems of adaptive physiology]. Moscow: Izd-vo RUDN [Publishing House of the Peoples' Friendship University of Russia], 2007, 57 p.
3. Borisova N.V. *Mediko-fiziologicheskoe obosnovanie adaptivnyh reakcij organizma studentov v jekstremal'nyh usloviyah Jakutii: avtoreferat dis. ... doktora medicinskih nauk: 14.03.03, 03.03.01* [Medico-physiological substantiation of adaptive reactions of an organism of students in extreme conditions of Yakutia: the author's abstract of the dissertation. ... doctor of medical sciences: 14.03.03, 03.03.01]. Mesto zashchity: Yakutsk, GOU VPO «Jakutskij gosudarstvennyj universitet» [Place of defense: Yakut State University], 2011, 218 p.
4. Gudkov A.B. Popova O.N. Lukmanova N.B. *Jekologo-fiziologicheskaja harakteristika klimaticeskikh faktorov Severa: obzor literatury* [Ecological and physiological characteristics of climatic factors of the North: review of literature]. *Jekologija cheloveka* [Ecology of man], 2012, №01, pp.12-17.
5. Kaznacheev V.P. *Problema adaptacii cheloveka* [The problem of human adaptation]. Novosibirsk: *Nekotorye itogi i perspektivy issledovanij* [Some results and prospects of research], 1978, 56 p.
6. Avtsyn A.P. Zhavoronkov A.A. Rish M.A. [et al.] *Mikroelementozy cheloveka: etiologiya, klassificaciya, organopatologiya* [Microelementoses of man: etiology, classification, organopathology]. Moscow: *Medicina* [Medicine], 1991, 496 p.
7. Borisova N.V. Antipina U.D. Markova S.V. [et al.] *Rol' elementnogo disbalansa v razvitiy otdelnyh patologij u detej Vilyiskogo regiona* [The role of elemental imbalance in the development of individual pathologies in children in the Vilyui region]. *Jakutskij medicinskij jurnal* [Yakut Medical Journal], 2016, № 3 (55), pp.46-49.
8. Savvinov D.D. Sazonov N.N. *Microelementy v severnyh ekosistemah* [Microelements in northern ecosystems]. Novosibirsk: Nauka, 2006, 208 p.
9. Skalnaya M.G. *Gigienicheskaya ocenka vliyaniya mineralnyh componentov racionalnogo pitaniya i sredy obitaniya na zdorovie naseleniya megapolisa: avtoref. dis. ... doktora med.nauk* [Hygienic assessment of the effect of the mineral components of the diet and the habitat on the health of the population of the megapolis: author's abstract. dis. ... doctor med. sciences]. Moscow: 2005, 42 p.
10. Skalny A.V. *Himicheskie elementy v fiziologii i jekologii cheloveka* [Chemical elements in human physiology and ecology]. Moscow: Izdatelskij dom «Onix 21 vek»: Mir [The publishing house „Onyx 21 century“: Mir], 2004, 216 p.
11. Skalny A.V. *Ustanovlenie granits dopustimogo soderzhanija chimicheskikh elementov v volosah detej s primeneniem tsentilnyh chkal* [Establishment of the limits of the permissible content of chemical elements in children's hair using centile scales]. *Vestnik S-Peterburgskoy GMA im. I.I. Meshnikova* [Herald of the I. I. Mechnikov St. Petersburg State Medical Academy], 2002.-№1-2 (3), pp.62-65.
12. Skalny A.V. *Jekologo-fiziologicheskoe obosnovanie effektivnosti ispolzovaniya macro- i microelementov pri naruchenyah gomeostaza u obsleduemyh iz razlichnyh klimatogeographicheskikh regionov: diss.... dokt.med.nauk* [Ecologic-physiological substantiation of efficiency of use of macro- and microelements at disturbances of a homeostasis at surveyed from various climatogeographical regions: diss. ... doctor med. sciences]. Moscow: 2000, 352 p.
13. Skalny A.V. Bykov A.T. *Jekologo-fiziologicheskie aspekty primeneniya macro- i microelementov v vosstanovitelnoy medicine* [Ecological and physiological aspects of the application of macro- and microelements in restorative medicine]. Orenburg: RIK GOU OGU [REC of GOU OSU], 2003, 198 p.
14. Skalny A.V. Rudakov I.A. *Bioelementy v medicine* [Bioelements in medicine]. Moscow: Izdatelskij dom «Onix 21 vek»: Mir [The publishing house „Onyx 21 century“: Mir], 2004, 272 p.
15. Borisova N. V. Petrova P.G. Markova S.V. *Imbalance of Macro- and Micronutrients in the Environment and Biosubstrates of Residents Living in the Diamond Mining region of Yakutia*. *International Journal of Biomedicine*, 4 (3), 2014, New York, pp.179-181.
16. Meissner D. *Evaluation of trace elements status using biochemical indicators*, 1993, pp.1074–1078.

### The authors

Medical Institute NEFU, Yakutsk, Russia:

1. Borisova Natalia Vladimirovna - doctor of medical sciences, professor of the Department Normal and pathological physiology, email: [borinat@yandex.ru](mailto:borinat@yandex.ru);
2. Koltovskaya Galina Aleksandrovna - Postgraduate Student, Normal and Pathological Physiology, e-mail: [koltov79\\_galya@mail.ru](mailto:koltov79_galya@mail.ru);
3. Antipina Ulyana Dmitrievna - Candidate of Medical Sciences, Associate Professor of the Normal and Pathological Physiology Department.



Dmitrieva T.G., Ostrelina A.O., Egorova V.B.,  
Munkhalova Ya.A., Ivanova O.N., Alekseeva S.N.

## CHRONIC HEPATITIS B IN CHILDREN AND ADOLESCENTS REPRESENTATIVES OF THE MONGOLOID RACE

DOI 10.25789/YMJ.2018.63.20

The article is devoted to problem of infectology and pediatrics. Ethnic features of the course of chronic hepatitis were studied in Russia and other countries. In previous studies in Yakutia, a high incidence of chronic viral hepatitis was established. The share of the indigenous population (Yakut and the small indigenous peoples of the north) in the RS (Y) does not exceed half, but among children with chronic hepatitis B it is two thirds of cases. Among the indigenous population representatives of the indigenous population of Yakutia (the Yakuts and small indigenous peoples of the north) belong to the Mongoloid race. This article presents the result of a study of epidemiological, clinical and laboratory data of children and adolescents diagnosed with chronic viral hepatitis B. A comparative analysis of the data of patients of the Mongoloid and Caucasoid race was carried out. Due to the fact that the chronic hepatitis B clinic is meager, most patients learn about their disease only after the examination. After a detailed poll, complaints were found about the deterioration of health, malaise, fatigue noted. On the second place in frequency there were nasal bleedings. Also, pain syndrome and dyspeptic complaints were noted. It is established that in children and adolescents of the Mongoloid race there is a tendency to a more severe course of the disease. In these patients, weight loss and low growth were more common. They are more often identified with complaints related to impaired liver function; marked cytolytic syndrome, signs of violations of protein-synthetic liver function; more pronounced changes in the liver parenchyma according to ultrasound. The leading role of family contact in the structure of transmission routes indicates the importance of social factors in the onset of the disease. The prevalence of representatives of indigenous nationalities among patients with chronic hepatitis shows that in addition to the social factors affecting the epidemic process, there are probably genetic factors determining the frequency and extent of liver damage in patients with chronic hepatitis B.

**Keywords:** children, adolescents, chronic hepatitis B, the Mongoloid race.

### Introduction

The general incidence of children and adolescents under 17 with chronic viral hepatitis, in recent years, in the RF has a tendency to decrease. Reduction is due to a decrease in the number of newly detected chronic hepatitis B. Conducting mass immunization of the population against hepatitis B in the Russian Federation allowed to reduce the incidence of acute hepatitis B. However, in some regions of the country HBV still occupies a leading place among children, the highest incidence rates of children and adolescents with chronic viral hepatitis were noted in the Far Eastern Federal District [2]. The Republic of Sakha (Yakutia) belongs to regions with high endemicity [1, 5]. In recent years, several papers have appeared devoted to the study of the prevalence of HG in different ethnic groups. In Canada and Australia, the study of the epidemiological and clinical data of chronic hepatitis B in aboriginal and alien populations was conducted. In recent years, several papers have appeared devoted to the study of the prevalence of chronic hepatitis in different ethnic groups. In Canada and Australia, the study of the epidemiological and clinical data of chronic hepatitis B in aboriginal and alien populations was conducted. In the territory of the Russian Federation, such studies were conducted in Tyva. Such works were conducted in China, Mongolia, Japan and other Asian countries. Our data are consistent with

the data of a number of authors who studied chronic hepatitis in adults in the RS (Y) and in other regions, these studies indicate a higher incidence of chronic hepatitis in representatives of the Mongoloid race and a more severe course of the disease [3,4] Genetic factors affecting outcomes of CG [7,6].

The **purpose** of our study was to study the features of the epidemiological process and the clinical picture in patients of indigenous and non-indigenous nationality in the Republic of Sakha (Yakutia).

### Materials and methods of research

153 patients were examined under the supervision of chronic hepatitis B at the age from 1 year to 16 years. According to ethnicity, the patients were distributed as follows: children of the Yakut nationality accounted for 70.5% (108 patients), Russian patients - 20.9% (32 patients), representatives of small indigenous peoples of the North (5.8%) (7 patients), other nationalities - 3.9% (6 patients).

The study was conducted on the basis of the Pediatrics Clinic of the National Center of Medicine of the RS(Y) and Children's City Clinical Hospital №2. When establishing the diagnosis, epidemiological, clinical, biochemical data, serological and molecular-biological markers of viral hepatitis were taken into account.

The selection criteria for the study group were the presence of hepatitis B verification by the method of enzyme immunoassay and polymerase chain

reaction. The monitoring of patients, in addition to the clinical examination, included an evaluation of the results of routine biochemical and instrumental methods of investigation. The clinical and laboratory data were processed using the statistical package IBM SPSS STATISTICS 19. The normal distribution of the quantitative variables was checked using the Kolmogorov-Smirnov test with the Lilliefors correction and the Shapiro-Wilk test. Depending on the nature of the distribution, the Student's t-criterion, the nonparametric criteria of Mann-Whitney and Kruskal-Wallis, were used for comparison of independent groups by quantitative characteristics. When comparing dependent groups, the Wilcoxon test.

### Results and its discussion

Chronic hepatitis B is much more common in children and adolescents of indigenous nationality: the Yakuts accounted for 70.5% (108 patients), (ICS) - 5.7% (7 patients), Russians 20.9% (32 patients), other nationalities - 3.9% (6 patients). Wherein, it should be borne in mind that according to official statistics in the Republic of Sakha (Yakutia) Yakut make up 45.54%, Russian - 41.15%, small indigenous peoples of the North - 1.23%. The share of the indigenous population (Yakut and the small indigenous peoples of the north) in the RS (Y) does not exceed 47%, but among children with chronic hepatitis B it is 75.2%. Such distribution of sick children on a national basis allows to assume

presence of ethnic features of a course of a virus defeat of a liver.

When analyzing the data of the epidemiological anamnesis, the following data were obtained. A high frequency of family contact in children and adolescents of patients with chronic hepatitis B has been revealed. 26 patients had an indication of parenteral manipulation in the anamnesis (17.4%). Transfusion of blood products in the history was revealed in 15 patients (10.2%). 102 children (67.1%) were treated at the dentist. There were no statistically significant differences in patients of different nationalities.

As a rule, complaints were not actively presented, but after a detailed interview in 33.3% of cases (51 children) the following complaints were revealed: worsening of health, malaise, increased fatigue were noted in 34 patients (22.1%). On the second place in frequency there were nasal bleedings - in 32 patients (21.3%). Pain syndrome was noted in 29 patients (19.8%). Complaints of a dyspeptic nature were noted in 26 patients (16.9%).

Thus, the most frequent complaints were related to a violation of liver function. Violation of detoxification function manifested itself in the reduction of health and headaches, synthetic - in nosebleeds. Pain and dyspeptic syndromes, apparently, are associated with chronic diseases of the gastrointestinal tract. In patients with chronic hepatitis B, gastrointestinal disorders were found in 82.1% of cases, and pathology of the biliary tract in 30.3% of cases. There were no statistically significant differences in the incidence of complaints between patients of different nationalities, but there was a trend towards greater manifestation of liver function abnormalities in children and adolescents of indigenous nationality (Table 1).

Children and adolescents of indigenous nationality complained 1.8 times more often (Table 2). Complaints of intoxication (deterioration of well-being) were more frequent in 1.5 times more often, nasal bleedings - 1.8 times more frequent, headaches were noted only in patients of indigenous nationality.

The physical development of patients with chronic hepatitis B was assessed by centile tables developed for RS (Ya) and taking into account ethnic differences. In patients with chronic hepatitis, in most cases, a disharmonious development has been observed in terms of body weight deficiency. Low body mass indexes in more than half of the children diagnosed with CHB show evidence of chronic intoxication. And pathologically low growth was met 2.2 times less often than patho-

logically low body weight. When analyzing the data of physical development in patients of different nationalities, it was noted that children of non-indigenous nationality had, in general, a large body weight and a higher growth (Table 2).

The syndrome of jaundice in chronic hepatitis B is not characteristic. Visually, jaundice was detected only in 12 patients, which amounted to 7.8% of all cases. Part of the patients were diagnosed with "extrahepatic signs", which include palmar erythema, telangiectasia, and widening of the venous pattern on the skin of the chest and abdomen. These signs were rare. Statistically significant differences were revealed in the frequency of extrahepatic signs between chronic hepatitis patients of indigenous and non-indigenous nationality: 12.2% (14 children) and 5.2% (2 children), respectively ( $p < 0.05$ ).

The severity of cytolytic syndrome was assessed by the levels of ALT and AST in the serum of the patient. The incidence of ALT elevation in CHB was 4.6% (7 patients). In all patients, the ALT level did not exceed the laboratory norm by 2 times (2 N). The level of ALT in patients

with chronic hepatitis B ranged from 4.0 to 67 U / l and averaged  $23.1 \pm 12.3$  U / l. The frequency of increase in AST in chronic hepatitis B was 29.4% (45 patients). In all patients, the index did not exceed 1.5 N. The level of AST in patients with chronic hepatitis B ranged from 8.0 to 60.2 U / l and averaged  $32.0 \pm 12.1$  U / l. In absolute values, the change in AST levels was greater than ALT, although no statistically significant differences were revealed.

In patients with CHB, cytolytic syndrome was found in almost a third, statistically significant differences were noted between the frequency of hyperfermentemia in ALT and AST ( $p < 0.02$ ). Significantly larger, the frequency of increase in AST levels indicates more severe changes in hepatocytes.

The increase in the level of total bilirubin was noted in 18.3% of cases (28 patients). The level of total bilirubin among patients with hyperbilirubinemia averaged  $23.3 \pm 15.8$   $\mu\text{mol} / \text{l}$  in patients with chronic hepatitis B, and in all cases the direct fraction prevailed. Thus, in all patients, the increase in total bilirubin did not reach high values, and exceeded the

Table 1

Complaints of patients with chronic hepatitis B of the Mongoloid and Caucasoid race

Complaints	Patients with chronic hepatitis (n=153)				p
	Mongoloid race (n=115)		Caucasoid race (n=38)		
	n	%	n	%	
Complaints	43	37,3	8	21,1	>0,05
Complaints of malaise	28	24,3	6	15,8	>0,05
Dyspeptic complaints	20	17,4	6	15,8	>0,05
Abdominal pain without clear localization	11	9,6	4	10,5	>0,05
Pain in the right hypochondrium	4	3,5	1	2,6	>0,05
Pain in epigastrium	7	6,1	2	5,2	>0,05
Nasal bleeding	27	23,5	5	13,2	>0,05
Headache	4	3,4	0	0	>0,05
Dryness of the skin	5	4,3	3	7,8	>0,05
Itchy skin	3	2,6	1	2,6	>0,05
Stool disorder	7	6,1	2	5,2	>0,05

Table 2

Physical development of patients with chronic hepatitis B of the Mongoloid and Caucasoid race

Centile	Patients with chronic hepatitis (n=153)							
	Mongoloid race (n=115)				Caucasoid race (n=38)			
	Body mass		Growth		Body mass		Growth	
	n	%	n	%	n	%	n	%
< 3	6	5,2	3	2,6	1	2,6	0	0
3-10	22	19,1	4	3,5	5	13,2	1	2,6
10-25	35	30,4	21	18,3	9	36,8	4	10,5
25-75	45	39,1	61	53,1	18	47,4	21	55,3
75-90	3	2,6*	16	13,9	3	7,9*	6	15,8
90-97	2	1,7	10	8,7	1	2,6	5	13,2
> 97	2	1,7	0	0	1	2,6	1	2,6

\* Differences are statistically significant  $p < 0,05$ .

norm by 2.25 times, and on average by no more than 18% of the norm.

The change in the level of total protein was noted in 19.6% of patients with chronic hepatitis B (30 children). This index in patients with hypoproteinemia averaged  $58.9 \pm 3.5$  g / l in patients with CHB. More often, hypoalbuminemia was noted in 22.9% (35 patients). In these patients, the level of albumin in the blood serum averaged  $34.2 \pm 2.2$  g / l in patients with chronic hepatitis B. The change in fat metabolism is most often manifested by an increase in the level of cholesterol. The frequency of hypercholesterolemia in patients with chronic hepatitis B (HBsAg +) was 18 children (11.7%), the cholesterol ranged from 2.8 to 8.7 mmol/l and averaged  $5.2 \pm 0.9$  mmol/l.

Statistically significant differences between patients of different nationalities were found only in the frequency of hyperbilirubinemia ( $p < 0.05$ ). With respect to some other indicators, a trend towards greater severity among children and adolescents of indigenous nationality has been noted. The increase in ALT levels of more than 1.5 N in indigenous children is twice as common, and the excess of this indicator in 2 N in non-indigenous people was not noted at all. While the frequency of hypoproteinemia is comparable, the decrease in albumin in indigenous patients is 2 times more common (Table 3).

The decrease in the synthetic function of the liver is also indicated by the change in PTI. In patients of indigenous nationality, the decrease in PTI was registered in 6.9% of cases (8 children), in non-indigenous patients - in 5.3% of cases (2 children). Changes in parenchymal organs according to ultrasound were observed in no more than a third of patients with chronic hepatitis B. As a rule, hepatomegaly and splenomegaly were not expressed, the increase in liver size did not exceed 15-20% of the age norm, an increase in the spleen - 10% (Table 4).

Statistically significant differences between patients of different nationalities have been identified by the frequency of hepatosplenomegaly and increased echinostensity of the liver parenchyma. Also, in children of indigenous nationality, the wall of the gallbladder was 2.4 times more common.

#### The conclusion

Thus, based on the presented data, the following conclusions can be drawn. The features of the epidemiological process of chronic hepatitis in children and adolescents in the RS (Ya) include the ethnicity of patients. The prevalence of representatives of indigenous nationalities among patients with chronic hepatitis and the leading role of family

					Table 3
Biochemical blood test data of patients with chronic hepatitis B of the Mongoloid and Caucasoid race					
Index	Patients with chronic hepatitis (n=153)				p
	Mongoloid race (n=115)		Caucasoid race (n=38)		
	n	%	n	%	
AJIT 1,5 N	6	5,2	1	2,6	>0,05
AJIT >2N	1	0,9	0	0	>0,05
ACT 1,5 N	37	32,2	8	21,1	>0,05
ACT >2N	1	0,9	0	0	>0,05
Hyperbilirubinemia	25	21,7	3	7,9	<0,05
GGT >N	1	0,9	0	0	>0,05
Alkaline phosphatase >N	1	0,9	0	0	>0,05
Total protein <N	22	19,1	8	21,1	>0,05
Albumen < N	30	26,1	5	13,2	>0,05
Cholesterol > N	14	12,2	4	10,5	>0,05
$\beta$ - lipoproteins	5	4,3	0	0	>0,05
Triglycerides	1	0,9	0	0	>0,05

					Table 4
Ultrasound of patients with chronic hepatitis B of the Mongoloid and Caucasoid race					
Index	Patients with chronic hepatitis (n=153)				p
	Mongoloid race (n=115)		Caucasoid race (n=38)		
	n	%	n	%	
Hepatomegaly	28	24,3	9	23,7	>0,05
Hepatosplenomegaly	9	7,8	1	2,6	<0,05
Inhomogeneous ehostruktura	12	10,4	3	7,9	>0,05
Increase echoplotnosti	15	13	1	2,6	<0,05
Galling of the wall of the gallbladder	11	9,6	3	3,9	>0,05
Strengthening the vascular pattern	12	10,4	5	13,2	>0,05

contact in the structure of transmission routes indicate the importance of ethnic and social factors in the onset of the disease. Undoubtedly, there is a tendency to more severe impairment of liver function in children and adolescents of indigenous nationalities. This is expressed in a greater frequency of complaints related to impaired liver function, more significant changes in the biochemical blood test and large changes in the liver parenchyma according to ultrasound. In addition to social factors that influence the epidemic process, there are probably genetic factors that determine the frequency and extent of liver damage in patients with chronic hepatitis B. The identification of these factors requires further research.

#### References

1. Dmitrieva T.G. Osobennosti ehpidemiologii i techeniya hronicheskikh gepatitov u detej v respublike Saha (Yakutiya) [Features of epidemiology and chronic hepatitis in children in the Republic of Sakha (Yakutia)]
2. Baranov A.A. Namazova-Baranova L.S. Volynets et al. Zabolevaemost' hronicheskimi virusnymi gepatitami detskogo naseleniya v Rossijskoj Federacii za period 2003-2012 gg. [Incidence of chronic viral hepatitis in children in the Russian Federation for the period 2003-2012]. Moscow: «Ul'tra Print», 2012, 46 p.
3. Kozhanov T.V. Il'chenko L.Yu. Klushkina V.V. et al. Inficirovannost' virusami gepatitov «uslovno» zdorovogo naseleniya respubliki Tyva [Infection with hepatitis viruses of a «conditionally» healthy population of the Republic Tuva] Ros. zhurn. gastroenterologii, gepatologii, koloproktologii [Rus. Journal of gastroenterology, hepatology, coloproctology]. Moscow, 2014, Prilozhenie [App.] № 43, p.24.
4. Malov S.I. Badrah D. Malov I.V. Rasovyje osobennosti hronicheskogo virusnogo gepatita S u mongoloidov [Racial features of chronic viral hepatitis C in Mongoloids] Ros. zhurn. gastroenterologii,

Rossijskij pediatricheskij zhurnal [Russian pediatric journal]. 2015, V.18, №2, p. 5-13.



- gepatologii, koloproktologii [Rus. Journal of gastroenterology, hepatology, coloproctology]. Moscow, 2014, Prilozhenie [App.] № 43, p.27.
5. Slepova S.S. Tihonova N.N. Samsonova V.K. Osobennosti techeniya hronicheskikh virusnyh gepatitov v Yakutii [Features of the course of chronic viral hepatitis in Yakutia] Infektsionnye bolezni [Infectious diseases]. 2011, №9, p.343.
  6. Plancoulaine S. Dissection of familial correlations in hepatitis C virus (HCV) seroprevalence suggests intrafamilial viral transmission and genetic predisposition to infection / S. Plancoulaine, M.K. Mohamed, N. Arafa [et al.] // J.Med. Virol.- 2008. - V.57, №9. - P. 1268-1274.
  7. Yang Y. Hepatitis B virus infection in families

with unfavorable prognoses in northwest China / Y. Yang, L. Jin, Y.L. He [et al.] // J.Med. Virol. - 2013. - V.85, №11. - P. 1893-1899.

#### The authors

1. Dmitrieva Tatyana Gennadiyevna - doctor of medical sciences, professor of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677000, Yakutsk, str. Oyunsky, 27. E-mail: dtg63@mail.ru
2. Ostrelina Anzhelika Olegovna - postgraduate student of the pediatrics and pediatric surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677000, Yakutsk,

str. Oyunsky, 27. E-mail: angela198948@gmail.com

3. Egorova Vera Borisovna - Candidate of Medical Sciences, Associate Professor, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: veraborisovna@yandex.ru
4. Munkhalova Yana Afanasievna - Candidate of Medical Sciences, Head of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of the M.K. Ammosov North-Eastern Federal University. Address: 677018, Yakutsk, ul. Oyunsky, 27. E-mail: tokmacheva@mail.ru.

E.F. Argunova, S.A. Kondratiev, E.M. Karavaeva,  
O.V. Andreeva, S.A. Nikolaev, N.N. Protopopov, S.N. Alekseev,  
S.A., Evseeva, T.E. Burtseva, V.S. Balanova

## THE ACUTE LEUKEMIA EPIDEMIOLOGY IN CHILDREN OF THE SAKHA REPUBLIC (YAKUTIA)

DOI 10.25789/YMJ.2018.63.21

#### ABSTRACT

The article presents the analysis of frequency indicators: primary morbidity, mortality in acute leukemia in children of the Sakha Republic (Yakutia) for the period from 2000 to 2016. The incidence of acute leukemia, acute lymphoblastic leukemia, acute non-lymphoblastic leukemia in children's population of the SR are average and comparable with those of other regions of the Russian Federation. In dynamics there is a decrease in mortality from leukemia due to the therapy improvement and the quality of accompanying therapy.

**Keywords:** leukemia, epidemiology, children, Yakutia.

#### Introduction

The oncological diseases belong to the category of socially significant diseases in children. Mortality from these diseases in the group of children older than one year in Russia and other developed countries is on the second place, after injuries and accidents [4, 8].

Acute leukemia (AL) is the most frequent oncological disease of childhood, accounting for 31.3% in the structure of malignant tumors in children [8].

During the last 30 years there is an improvement of the AL treatment results and the disease from a fatal became curable for more than 70 % of patients [7]. This was made possible by the introduction of modern methods of diagnosis, high-intensity programs of polychemotherapy, improvement of accompanying therapy. Modern treatment of patients with acute leukemia belongs to the category of high-tech and expensive. The financial costs of treatment depend directly on the morbidity and mortality rate, which requires constant epidemiological monitoring [5].

The Oncology Department of the

Pediatric center Republican hospital №1-National Medicine center is the only specialized Department in the Sakha Republic (Yakutia). Since 2003 it participates in the multicenter controlled clinical study of treatment protocols of ALL "Moscow-Berlin". Since 2000, the incidence of AL in the RS (Ya) has been continuously monitored [1].

**The purpose of the study:** the study of the frequency indicators: disease incidence, mortality in acute leukemias in children of the Sakha Republic (Yakutia) over the period 2000 to 2016.

#### Material and methods of research

A retrospective epidemiological study of AL in children aged 0 to 15 years living in the territory of Yakutia for the 17-year period (from 01.01.2000 to 31.12.2016) was conducted.

The Sakha Republic (Yakutia) is the largest region of the Russian Federation, its territory is 3103.2 thousand km<sup>2</sup>. The population of Yakutia is 964 330 people. The average annual number of children aged 0 to 15 years during the observation period was 233427,5 ± 3170,8. The data for the child population of Sakha Republic (Yakutia) for the years were given in the

Federal service of state statistics for Sakha (Yakutia). All nosological forms of acute leukemia (AL) corresponding to the codes of the International statistical disease classification and health-related problems were noted, 10th revision – ICD-10: acute lymphoblastic leukemia – ALL (C91.0), acute myeloid leukemia-AML (c92.0, C92.4, C92.5, C92.7, C92.9, C93.0, C93.3, S94.2).

Medical records were analyzed to obtain information about cases of diseases. A "rough" morbidity/mortality rate was calculated. The calculation of the morbidity rate was carried out according to the formula:  $Y = n \times 105/N$ , where Y is the morbidity rate (per 100 thousand population of the corresponding age) for the year; n is the number of first – time cases of the disease for the year; N is the average annual population of the studied age group [9].

The calculation of the mortality rate was carried out by the formula:  $Z = n \times 105/N$ , where Z is the mortality rate (per 100 thousand population of the corresponding age) for the year; n is the number of deaths per year; N is the average annual population of the studied

age group [9]. Statistical processing was carried out with the help of SPSS-16, MC Excel-07 application software package.

### Research results and discussion

During this period, there were 144 cases of AL in children from 5 days to 14 years, including 113 (78.5%) children with ALL and 31 (21.5%) – with AML. On average,  $8.5 \pm 0.69$  patients with AL,  $6.6 \pm 0.62$  children with ALL and  $1.8 \pm 0.28$  – with AML were detected annually. The information about the year on the AL identification is presented in table 1. Children with AL aged 0 to 4 years were 60 (41.6%), of the age to 1 year were 8 infants (5.5%), from 5 to 9 years – 51 (35.4%), from 10 to 14 years – 33 (23%). Among the cases of AL were 64 (44.5%) girls and 80 (55.5%) boys, the ratio of sex 1:1.25. Distribution of patients by ethnicity: Sakha-76 (52.8%), Russian – 51 (35.4%), others – 17 (11.8%). Children of the urban population were 76 (52.8%), rural – 68 (47.2%).

The average annual rate of primary morbidity in children was  $3.8 \pm 0.33$  cases per 100 thousand children from 0 to 15 years (fluctuations from 1.86 to 6.63) (Fig. 1). This indicator is the average and close to those given for a number of regions of Russia [2, 3, 5, 7, 10 - 12], but lower than in Russia [8] and much lower than in Germany and Australia [13, 14]. The linear trend, constructed by regression analysis, is almost horizontal, indicating a stable level of morbidity during the observation period.

The average annual rate of morbidity in children of OL aged 0 to 4 years was  $4.85 \pm 0.59$ , 5 to 9 years –  $4.26 \pm 0.64$ , 10 to 14 years –  $2.53 \pm 0.48$ . The incidence was higher between 0 and 4 years and 5 to 9 years, lower between 10 and 14 years.

Out of 144 children with AL in remission are 98 (68.0%), of them in the second remission – 2 children (children with ALL). Died a total of 40 patients (27.8 percent), information about the 6 children are absent mainly due to the departure of their families outside the country. Mortality under AL amounted to 1.07 per 100 thousand children's population, which is slightly lower than the same indicator in Russia-1.22 [8]. Over 17 years of observation in the dynamics of mortality in AL significantly decreased, as seen by the linear trend (Fig. 2).

Out of 113 patients with ALL aged 0 to 4 years were 53 (46.9%), of them up to 1 year were 6 (5.3%), from 5 to 9 years – 40 (35.4%), from 10 to 14 years – 20 (17.6%) children. The largest number of children with ALL was between 2 and 5 years – 50 (44.2%), the so-called "infant peak", which corresponds to the literary data. Among ALL cases were 51 (45.2%)

girls and 62 (54.8 %) boys, sex ratio 1 : 1.21.

The average annual rate of primary morbidity in children with ALL in the SR was  $3.0 \pm 0.27$  cases per 100 thousand children (fluctuations from 1.86 to 5.68) (table 2). This indicator is comparable with similar indicators of other regions of Russia: the Republic of Buryatia –  $2.22 \pm 0.16$  [3], Astrakhan –  $3.1 \pm 0.21$  [12], Bryansk –  $2.92 \pm 0.26$  [7], Omsk region –  $2.6 \pm 0.25$  [6], the Republic of Komi –  $2.85 \pm 0.26$  [11], but lower than in economically developed countries [13, 14]. The linear trend is almost horizontal, which indicates a stable level of ALL morbidity during the observation period (Fig. 3).

The incidence of ALL children aged 0 to 4 years was  $4.28 \pm 0.49$ , 5 to 9 years –  $4.34 \pm 0.64$ , 10 to 14 years –  $1.53 \pm 0.48$ . The incidence is higher at ages 0 to 4 years and 5 to 9 years, and almost 3 times lower at ages 10 to 14 years.

Out of the 113 children with ALL, 86 children are in remission, which is 71.6%. 22 (19.3%) of the child died, there is no information about 5 children. The mortality rate for ALL was 0.59 per 100,000 children. This indicator at ALL during the time of observation is steadily decreasing (Fig. 4)

Among children with AML there are 13 (42.0%) girls, 18 (58.0%) boys, the sex ratio 1,0:1,3, as well as in ALL indicates the prevalence of boys. Age distribution: 0 to 4 years-7 (22.5%), 5 to 9 years – 11 (35.5%), 10 to 14 years – 13 (42.0%) children. In AML, unlike ALL, older children prevailed, with a positive correlation with the age of 10 years ( $r=,180$ ,  $p<0.05$ ) and 14 years ( $r=,240$ ,  $p<0.01$ ). The primary incidence of AML was  $0.83 \pm 0.1$  per 100 thousand children, which is also comparable with data from other regions of the Russian Federation. The linear trend in the incidence of AML is also almost horizontal. The average annual AML incidence in children aged 0 to 4 years was  $0.56 \pm 0.17$ , 5 to 9 years –  $0.92 \pm 0.19$ , 10 to 14 years –  $1.0 \pm 0.23$ . This figure is higher at the age of 5 to 14 years, in the age aspect of 0 to 4 years, the incidence is almost 2 times lower.

Out of 31 children

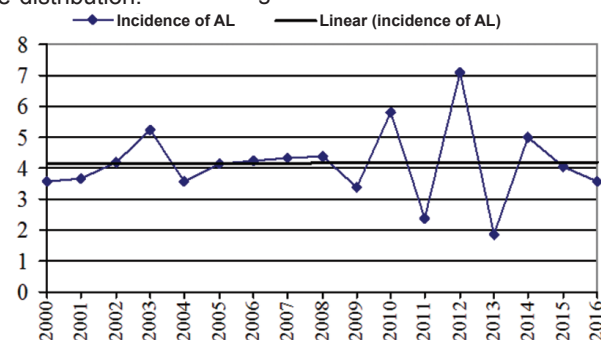
**The number of children with AL in the period from 2000 to 2015**

Year	Number of identified cases		
	AL	ALL	AML
2000	9	8	1
2001	9	8	1
2002	10	7	3
2003	12	8	4
2004	8	6	2
2005	6	5	1
2006	8	5	3
2007	8	8	0
2008	9	7	2
2009	7	7	0
2010	12	8	4
2011	5	5	0
2012	14	12	2
2013	4	4	0
2014	11	8	3
2015	7	4	3
2016	5	3	2
Total	144	113	31

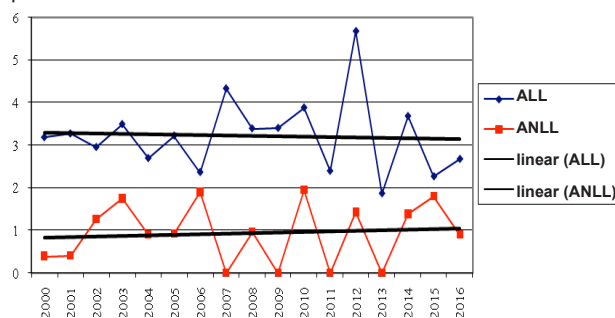
with AML in remission are 12 (38.7%), 18 died (58.1%), there is no information about 1 child. The death rate was 0.48 per 100 thousand children's population. During the observation, this indicator also decreases, but remains at a high level (Fig. 5).

### Conclusion

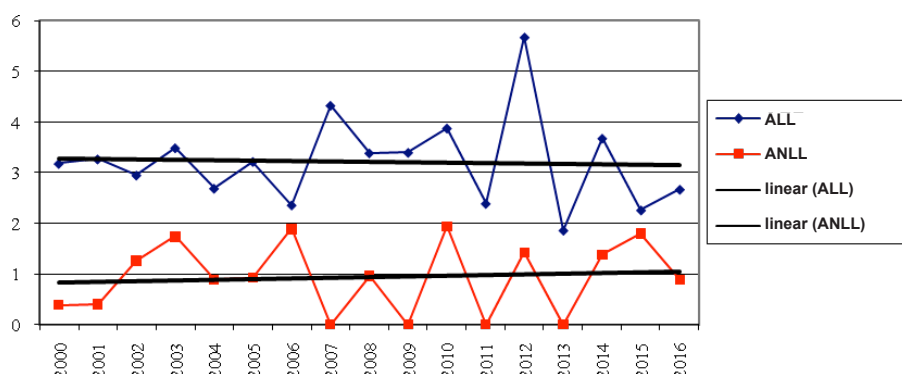
The primary morbidity rates of AL, ALL, AML in the children's population of the Sakha Republic are average and comparable with similar indicators of other regions of the Russian Federation,



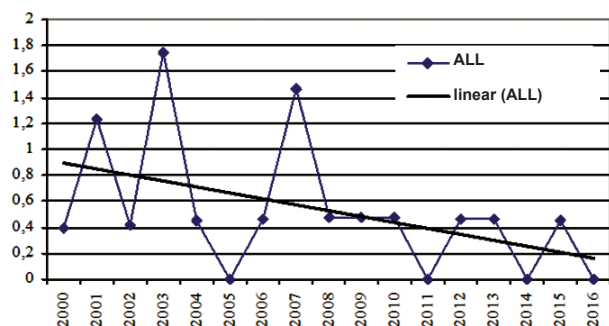
**Fig. 1.** The dynamics of the primary incidence rate of acute leukemia of the child population of the Sakha Republic for the period 2000-2016 and linear trend.



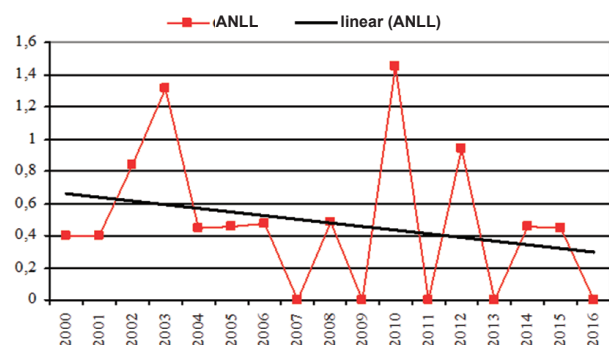
**Fig. 2.** The dynamics of the death rate in the case of AL for 100 thousand children from 0 to 14 years in the Sakha Republic for the period from 2000-2016 and linear trend.



**Fig. 3.** The dynamics of the primary incidence rate of ALL and ANLL in the children's population of the Sakha Republic for the period from 2000-2016 and linear trend.



**Fig. 4.** The dynamics of the mortality rate in case of ALL in 100 thousand children's population from 0 to 15 years in the Sakha Republic for the period from 2000-2016 and linear trend.



**Fig. 5.** The dynamics of the death rate in case of AML per 100 thousand children's population from 0 to 15 years in the Sakha Republic (Yakutia) for the period from 2000-2016 and linear trend.

but lower than in economically developed countries. The incidence rates of AL, ALL, AML remain stable during the follow-up period. The ALL more common in patients aged 2 to 5 years, with AML are older than 10 years. Mortality in AL remains at a fairly high level, mainly due to high mortality in AML. Over the period of observation, there is a decrease in this indicator, both, in General, and with ALL and AML. The significant reduction in mortality was observed in ALL. Participation in multicenter studies of treatment protocols of ALL "Moscow-Berlin" and quality improvement of accompanying therapy contributed to the reduction of this indicator.

## References

1. Argunova E. F., Kondrat'eva S. A., Slepcev O. V. *Struktura, ehpidemiologiya i lechenie zlokachestvennyh novoobrazovaniy u detej respubliky Saha (Yakutiya)* [Structure, epidemiology and treatment of malignant neoplasms in children of the Sakha Republic (Yakutia)] *Mezhregional'naya nauch.-prakt. konf. «Aktual'nye voprosy klinicheskoy mediciny na Severe»* [Interregional scientific.-prakt. Conf. "Actual issues of clinical medicine in the North"]. Yakutsk, 2013, p. 24-30.
2. Balasheva I. I., Luchinina L. F., Desyatova L. F. *50 let kliniko-ehpidemiologicheskikh issledovaniy ostryh lejkozov u detej Tomskoj oblasti* [50 years of clinical and epidemiological studies of acute leukemia in children of Tomsk region] *Sibirskij onkologicheskij zhurnal* [Siberian journal of Oncology]. Tomsk, 2010, No 1 (37), p. 23-28.
3. Budaeva D. D., Chernov V. M., Romyancev A. G. *Lejkozy u detej v Respublike Buryatii* [Leukemia's in children in the Republic of Buryatia] *Gematologiya i transfuziologiya* [Hematology and Transfusiology]. Moscow, 2000, V. 45, No 6, p. 16-21.
4. Davydov M. I., Durnov L. A., Polyakov V. G. *Sovremennye aspekty organizatsii detskoj onkologicheskoy pomoshchi v Rossijskoj Federatsii* [Modern aspects of the organization of children's cancer care in the Russian Federation] *Consilium medicum. Detskaya onkologiya*. Prilozhenie [Consilium medicum. Pediatric Oncology. Application]. Moscow, 2002, p. 6-8.
5. Zhukovskaya E. V., Spichak I. I., Basharova E. V. *Zabolevaemost' ostryimi lejkozami i ih rasprostranennost' v detskoj populyatsii CHelyabinskoy oblasti za period 1974-2003 gg.* [Incidence of acute leukemia And their prevalence in the children's population of the Chelyabinsk region for the period 1974-2003] *Voprosy gematologii/onkologii i immunopatologii v pediatrii* [Hematology/Oncology and immunopathology in Pediatrics]. Moscow, 2005, V. 4, No 1, p. 24-20.
6. Kockaya N. N. *EHpidemiologicheskie karakteristiki ostrogo limfoblastnogo lejkoza u detej Omskoj oblasti za period 1993-2010 gg.* [Epidemiological characteristics of acute lymphoblastic leukemia in children of Omsk region for the period 1993-2010] *Voprosy gematologii/onkologii i immunopatologii v pediatrii* [Hematology/Oncology and immunopathology in Pediatrics]. Moscow, 2012, V. 11, No 1, p. 9-13.
7. Krylova V. V., Rakov M. A., Rogacheva E. R. *Zabolevaemost' ostryimi lejkozami v detskoj populyatsii razlichnyh territorij Bryanskoy oblasti za period 1994-2007 gg.* [Incidence of acute leukemia in the children's population of various territories of the Bryansk region for the period 1994-2007] *Voprosy gematologii/onkologii i immunopatologii v pediatrii* [Hematology/Oncology and immunopathology in Pediatrics]. Moscow, 2010, V. 9, No 4, p. 15-18.
8. Men' T. H., Polyakov V. G., Aliev M. D. *EHpidemiologiya zlokachestvennyh novoobrazovaniy u detej Rossii* [The Epidemiology of malignant tumors in children of Russia]. *Onkopediatriya* [Onkopediatriya]. Moscow, 2014, No 1, p. 7-12.
9. Savilov E. D. [et al.] *Primenenie statisticheskikh metodov v ehpidemiologicheskom analize* [The application of statistical methods in epidemiological analysis]. Moscow: MEDpress-inform, 2004, 112 p.
10. Teplyakova U. D., Savis'ko A. A., Aslanyan K. S. *Zabolevaemost' ostryimi lejkozami u detej Rostovskoy oblasti za period 1991-2010 gg.* [Incidence of acute leukemia in children of Rostov region for the period 1991-2010] *Fundamental'nye issledovaniya* [Basic research]. Moscow, 2012, No 2, p. 363-367.
11. Shestakova V. V., Turabov I. A., Karmanov A. L. *Zabolevaemost' ostryimi lejkozami detej v Respublike Komi* [Incidence of acute leukemia in children in the Republic of Komi] *Onkopediatriya* [Onkopediatriya]. Moscow, 2015, V 2, No 1. - p. 48-53.
12. Halturina I. L. *Ostrye lejkozy u detej Astrahanskoy oblasti: chastotnye karakteristiki, kachestvo diagnostiki i rezul'taty lecheniya*: avtoref. dis. ... kand. med. nauk : 14.00.09, 14.00.29 [Acute leukemia's in children of the Astrakhan region: the frequency characteristics,



the quality of diagnosis and results of treatment: author. dis. ... kand. honey. sciences : 14.00.09, 14.00.29]. Moscow, 2007, 26 p.

13. Childhood Cancer Incidence in Australia, 1983-2006. URL: <http://www.cancerqld.org.au/>
14. German Childhood Cancer Registry. Annual Report. 2015/ URL: <http://www.kinderkrebsregister.de/dkk-rg/latest-publications>

#### The authors

Yakutsk, Russia:

1. Argunova Elena Filippovna, Candidate of Medical Science, MI SVFU, [eargunova@mail.ru](mailto:eargunova@mail.ru)
2. Kondratieva Sargylana Afanasyevna - head

of oncology department of the Pediatric Center RH # 1-NMC, [gematologia@mail.ru](mailto:gematologia@mail.ru)

3. Kharabaeva Elena Mikhailovna - children's oncologist of the oncology department of the Pediatric Center RH # 1-NMC, [gematologia@mail.ru](mailto:gematologia@mail.ru)
4. Yadreeva Olga Valerievna, hematologist of the oncology department of the Pediatric Center RH # 1-NMC, [gematologia@mail.ru](mailto:gematologia@mail.ru)
5. Nikolaeva Sargylana Afanasyevna - children's oncologist of the oncology department of the Pediatric Center RH # 1-NMC, [gematologia@mail.ru](mailto:gematologia@mail.ru)
6. Protopopova Nadezhda Nicolaevna, hematologist of the oncology department of the Pediatric Center RH # 1-NMC, [gematologia@mail.ru](mailto:gematologia@mail.ru)
7. Alexeeva Sargilana Nikolaevna - Candidate

of Medical Science, MI SVFU, [eargunova@mail.ru](mailto:eargunova@mail.ru)

8. Evseeva Sardana Anatolievna - candidate of medical sciences of Yakut Science Center of Complex Medical Problems, [sarda79@mail.ru](mailto:sarda79@mail.ru), contact. phone: 89679111195
9. Burtseva Tatyana Egorovna - doctor of medical sciences, professor of MI NEFU, head. lab. Yakut Science Center of Complex Medical Problems, 8 (914) 294-32-44, [bourtsevat@yandex.ru](mailto:bourtsevat@yandex.ru)
10. Balanova Varvara Sergeyevna, 6th year student of the Pediatric Department of the Medical Institute of M.K. Ammosov NEFU, [ayabalana@mail.ru](mailto:ayabalana@mail.ru)

## ACTUAL TOPIC

T.E. Burtseva, L.N. Afanasyeva, E.F. Argunova, L.A. Nikolaeva, S.A. Kondratieva, L.M. Kharabaeva, S.A. Nikolaeva, S.A. Evseeva, V.G. Chasnyk, P.M. Ivanov, F.F. Fedorov, K.I. Burnasheva

## DYNAMICS OF ONCOLOGICAL DISEASES MORBIDITY INDICATOR OF CHILDREN AND ADOLESCENTS IN THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2018.63.22

### ABSTRACT

We have analyzed the morbidity rates of oncological diseases of children and adolescents of the Sakha Republic for 2000 - 2015 according to hospitalization data in the Pediatric Center RH № 1-NCM.

The data of official medical statistics on the population's appeal to the medical and prophylactic institutions of the Sakha Republic are very contradictory and determine some morbidity dynamics. The data of hospitalized morbidity tend to increase and are mainly associated with the repeated income of children and adolescents contingent with a diagnostic and therapeutic purpose. The most real picture of the oncological morbidity extent in children and adolescents is given by the number of newly diagnosed neoplasms according to the data of the department in the Sakha Republic for children with oncological pathology. Annually about 30 cases of newly diagnosed tumors are noted. In the dynamics of the number of children and adolescents with oncopathology has a tendency to increase.

In our opinion, the real picture of oncological morbidity extent in the Sakha Republic (Yakutia) can be given by a single register of cancer patients created by using information technologies, which will take into account the personal data of patients with a mandatory indication of residence place, ethnicity, age, sex and other characteristics of the child.

**Keywords:** children, morbidity, oncology, Yakutia.

### Introduction

The study of the cancer epidemiology in children and adolescents has special significance every year. Annually, the morbidity of malignant neoplasms in the Russian Federation is 15.0 per 100,000 people, about 3,500 children and adolescents with newly diagnosed neoplasms [5]. The oncogenesis processes of children are very interesting, because they have a rare probability of malignant neoplasm, selectivity of damage to certain organs and systems. One of the main points in conducting oncoepidemiological studies in children and adolescents is to elucidate the factors leading to oncological pathology. It can be environmental, genetic and other endogenous factors.

Meanwhile, the literature has few

works devoted to the study of morbidity, mortality of children and adolescents from malignant neoplasms by regions of the Russian Federation. The reasons for this are not only a small number of cancer registers that control oncological morbidity and mortality in the field for a long time, but also the methodological level in the use of information bases in epidemiological studies in the Russian Federation [4]. Meanwhile, children and adolescents with oncological pathology in the Sakha Republic are observed in the only oncological unit of the Republican Hospital Pediatric Center №1-National Medicine centre. And this gives preconditions for the study of oncoepidemiology in children and adolescents.

We have analyzed the morbidity rates

of oncological diseases of children and adolescents of the Sakha Republic for 2000 - 2015 according to hospitalization data in the Pediatric Center RH № 1-NCM.

### Results

The general morbidity indicator of children under 14 in the Sakha Republic for the period 2000-2015 has increased by 70.8% (Table 1). Today, changes in the sickness structure of children are evident. Reduction in the overall children morbidity has occurred in such classes: «some infectious and parasitic diseases», «endocrine system diseases, eating disorders, metabolic and immunity disorders.» A significant increase in the overall morbidity in the following classes of diseases: «neoplasms», «diseases of the nervous system», «eye and

adnexa diseases», «ear and mastoid disease», «digestive diseases» and «diseases of the musculoskeletal system and connective tissue», «congenital anomalies». In the structure of the overall incidence of the «neoplasms» diseases group has increased from 4.4 per 1,000 children to 15.6 per 1,000 in 2015.

The overall morbidity rate of adolescents 15-17 years in the Sakha Republic is presented in Table. 1. The investigated indicator for the interesting period of time has increased in such disease classes as «neoplasms», «diseases of the musculoskeletal system» which has a three-fold increase in morbidity, «respiratory diseases», «ear and mastoid disease», «injuring and poisoning» have increased by 2 times. In the structure of the overall adolescents morbidity, the «neoplasm» disease group has increased from 2.4 per 1,000 to 11.8 in 2015.

Thus, there is an increase in the overall child and adolescents morbidity in the «neoplasm» disease group. Since the indicator of the overall morbidity depends on the population's circulation, it is clear that with the development of new approaches and principles of therapy for children and adolescents with oncological pathology, this indicator has the right to a tendency to increase, as there is a repeated appeal of this category of patients for diagnostic and therapeutic purposes.

The gender characteristics analysis of the child and adolescent malignant neoplasms morbidity revealed the following features. As shown in Table 2, the tendency towards an increase in the malignant neoplasms morbidity in boys is noted at the age of 15-19 years (10.6 in 2001, 19.8 per 100 thousand population in 2015). The dynamics shows a tendency to increase the morbidity of this contingent in the health system, so in 2001 it was 47.5; 2005. - 49.0; 2010. - 88.8; 2015- 50.9 per 100 thousand of the population.

The Table 3 presents the most frequent localizations of the malignant neoplasms in male children and adolescents. In the form of the most frequent localizations of the malignant neoplasms in male children and adolescents has following results in 2015 the I place - lymphomas (12.9); II - leukemia (11.0), III - malignant neoplasms of CNS (8.7), IV - malignant neoplasms of bone and cartilage (6.3 per 100 thousand population). Although, 2010 shows completely different structure: the 1st place - CNS; II - leukemia, III - lymphoma, IV - malignant neoplasms of bone and cartilage.

The detection of malignant neoplasms bone and cartilage in this contingent is relatively stable (2001-8.1, 2005-4.1,

2010-5.5, 2015-6.3 per 100 thousand Population). The most frequently recorded pathology is registered at the age of 15-19 years (2001-4.2, 2005-4.1, 2010-2.6, 2015-3.3 per 100 thousand population).

The detection of malignant neoplasms of CNS in this contingent is not stable, there are periods with the high incidence rate (2001-13.1, 2005-9.5, 2010-27.6, 2015-8.7 per 100 thousand population). In 2010 this pathology is most often detected in the group of children from birth to 9 years, so 0-4 years incidence rate is 10.8; 5-9 years - 11.7 per 100 thousand of the population. Most often, this pathology is recorded at the age of 15-19 years (2001-6.3, 2005-4.1, 2010-5.1, 2015-3.3 per 100 thousand population).

The leukemia morbidity in boys tends to decrease between 2010-2015 in the childhood and adolescence. In general, leukemia occupy the second place in the morbidity structure after lymphomas in 2015, and it should be noted that leukemia is detected in all age periods.

There is an increase in the children and adolescents morbidity in male lymphomas in dynamics since 2001, so in 2001, - 5.1; 2015 -12.9 per 100 thousand of the population. It increased almost two times. In general, lymphoma is detected in children 15-19 years.

As shown in Table 4, the most common malignant neoplasms detected at the age of 0-4 years, 15-19 years. In the dynamics there is a tendency to increase the malignant neoplasms morbidity among this contingent, so in 2001 it was 46.7; 2005. - 44.2; 2010. - 45.9; 2015 - 68.8 per 100 thousand of the population.

Table 5 presents the most frequent localizations of malignant neoplasms in children and adolescent females. In the structure of the most frequent localizations of malignant neoplasms in children and adolescents females by the end of 2015 the I place is leukemia (17.5), II - malignant neoplasms of CNS (14.2), III - malignant neoplasms of bone

Table 1

**The indicator dynamics of the general child and adolescents morbidity for 2000-2015 in the Sakha Republic for the main diseases classes (per 1000)**

Name of disease classes	2000	2005	2010	2015
General child morbidity from 0 to 14 years				
All diseases	1623,6	2195,2	2769,3	2773,3
C00-D48	4,4	11,6	14,2	15,6
Neoplasms				
General adolescents morbidity 15-17 years				
All diseases	111,1	735,4	2001,6	2390,8
C00-D48	2,4	7,7	7,1	11,8
Neoplasm				

Table 2

**The morbidity rates of male children and adolescents with malignant tumors in 2001, 2005, 2010 and 2015. (per 100 thousand population) [1-3]**

Age	2001	2005	2010	2015
0-4	17,7	14,3	32,3	14,3
5-9	7,4	8,8	23,4	7,9
10-14	11,8	7,4	17,7	8,9
15-19	10,6	18,5	15,4	19,8
Total	47,5	49,0	88,8	50,9

Table 3

**The most frequent localizations of malignant neoplasms in male children and adolescent in 2001, 2005, 2010 and 2015 (per 100 thousand population) [1-3]**

Age	2001	2005	2010	2015
Bone and cartilage				
0-4	...	...	...	...
5-9	...	...	2,9	...
10-14	3,9	...	...	3,0
15-19	4,2	4,1	2,6	3,3
Total	8,1	4,1	5,5	6,3
CNS				
0-4	2,9	2,9	10,8	2,4
5-9	...	...	11,7	...
10-14	3,9	2,5	...	3,0
15-19	6,3	4,1	5,1	3,3
Total	13,1	9,5	27,6	8,7
Leukemia				
0-4	10,4	8,6	5,4	2,4
5-9	2,0	...	8,8	5,3
10-14	6,2	2,5	8,9	...
15-19	...	4,1	2,6	3,3
Total	18,6	15,2	25,7	11,0
Lymphoma				
0-4	2,6	2,9	2,7	...
5-9	...	8,8	...	...
10-14	...	2,5	3,0	3,0
15-19	2,5	4,1	5,1	9,9
Total	5,1	18,3	10,8	12,9

and cartilage (8.7 per 100 thousand population).

The detection of malignant neoplasms bone and cartilage in this contingent tends to increase (2001-6.3, 2005-9.8, 2010-5.5, 2015-8.7 per 100 thousand population). Most often, this pathology is recorded at the age of 15-19 years (2001-4.2, 2005-2.1, 2010-2.7, 2015-3.1 per 100 thousand population).

The detection of malignant neoplasms

of CNS in this contingent tends to increase (2001-4.8, 2005-5.2, 2010-11.4, 2015-14.2 per 100 thousand population). In 2010 this pathology is mostly detected in the children group of 0-4 years - the incidence rate is 5.6. In 2015 in the children group of 5-9 years - 5.5; 10-14 years - 6.2 per 100 thousand of the population.

In the dynamics of girls, the morbidity of leukemia tends to decrease: 2001-23.8; 2005-13.4; 2010-17.9; 2015-17.5. In general, leukemia occupies the first place in the structure of the malignant morbidity in girls.

The only multi-sectoral Pediatric center for specialized and high-tech care for children and adolescents operates in the Sakha Republic. Annually the PC enters 7,234 children (2000) to 10,228 children in 2015. The proportion of patients from the village is from 37.4% in 2000 up to 33.5% in 2015, due to the fact that 45% of the total child population lives in rural areas. About 60% are planned patients entering the profile departments. Emergency patients account for 40% of all hospitalized patients.

The structure of hospitalized patients in PC of the Republican hospital №1-NCM is presented in Table 6. The increase indicator of the total hospitalized morbidity in 2010 by 2015 was 337.8 per 100,000 children and adolescents (in 2010 - 3610.0, 2015 - 3947.8). The rate of hospitalized morbidity in children and adolescents has increased since 2010 for the following classes of diseases: diseases of the nervous system (by 185.6); diseases of the digestive system (22.2); diseases of the genitourinary system (79.9); diseases of the endocrine system, nutritional and metabolic diseases (14.7); neoplasms (57.8), including malignant ones (14.9). The structure of the hospitalized morbidity of children in 2015 has diseases of the nervous system (669.6 per 100,000 children's population) at the first place, respiratory diseases (511.9), respiratory diseases (503.8) at the second place, injuries and poisoning - the third place (5th place), diseases of the genitourinary system (403.5)- the fourth place, diseases of the digestive system (371.8) - the fifth.

In the structure of hospitalized morbidity, neoplasms has increased from 75.2 in 2001 up to 273.8 per 100 000 children in 2015, malignant neoplasms increased from 81.2 in 2010 up to 96.1 per 100,000 of the child population in 2015. This increase is most likely due to the multiplicity of children enrolling for diagnostic and therapeutic purposes

According to the oncology department data of the Pediatric Center of the Republican Hospital № 1-NCM, about 30 children and adolescents turn to a newly

diagnosed disease every year. The most frequent localizations are leukemia, CNS tumors (Table 7).

#### Conclusions

The data of official medical statistics on the population's appeal to the medical and prophylactic institutions of the Sakha Republic are very contradictory and determine some morbidity dynamics. The data of hospitalized morbidity tend to increase and are mainly associated with the repeated income of children and adolescents contingent with a diagnostic and therapeutic purpose. The most real picture of the oncological morbidity extent in children and adolescents is given by the number of newly diagnosed neoplasms according to the data of the department in the Sakha Republic for children with oncological pathology. Annually about 30 cases of newly diagnosed tumors are noted. In the dynamics of the number of children and adolescents with oncopathology has a tendency to increase.

Table 4

The rate of malignant neoplasms morbidity in children and adolescence females [1-3]

Age	2001	2005	2010	2015
0-4	6,3	6,0	19,6	24,9
5-9	10,7	12,2	12,2	8,2
10-14	21,2	15,5	6,1	15,5
15-19	8,5	10,5	8,0	20,2
Total	46,7	44,2	45,9	68,8

Table 5

The most frequent localizations of malignant neoplasms in children and adolescent females [1-3]

Age	2001	2005	2010	2015
Bone and cartilage				
0-4	...	...	2,8	2,5
5-9	...	...	...	...
10-14	2,1	7,7	...	3,1
15-19	4,2	2,1	2,7	3,1
Total	6,3	9,8	5,5	8,7
CNS				
0-4	...	...	5,6	2,5
5-9	2,7	3,1	...	5,5
10-14	2,1	...	3,1	6,2
15-19	...	2,1	2,7	...
Total	4,8	5,2	11,4	14,2
Leukemia				
0-4	3,1	...	5,6	5,0
5-9	8,0	9,2	9,2	2,7
10-14	8,5	...	3,1	3,1
15-19	4,2	4,2	...	6,7
Total	23,8	13,4	17,9	17,5

Table 6

Hospitalized children morbidity in the Sakha Republic according to the data of the Pediatric Center RH № 1-NCM(per 100,000 children's population)

Name of diseases classes according to ICD X	2001	2010	2015
Total, incl.	2387,6	3610,0	3947,8
J00-J99			
Diseases of the respiratory system	383,4	528,8	511,9
S00-T98			
Injury, poisoning and certain other consequences of external causes	327,0	514,8	503,8
G00-G99			
Diseases of the nervous system	228,9	484,0	669,6
Q00-Q99			
Congenital malformations, deformations and chromosomal abnormalities	150,4	372,8	356,3
K00-K93			
Diseases of the digestive system	286,6	349,6	371,8
N00-N99			
Diseases of the genitourinary system	226,6	323,6	403,5
E00-E90	112,9	232,4	247,1
Endocrine, nutritional and metabolic diseases			
C00-D48	75,2	216,0	273,8
Neoplasms	-	81,2	96,1
Incl. malignant neoplasms			
L00-L99			
Diseases of the skin and subcutaneous tissue	161,6	193,2	168,1
H60-H95			
Diseases of the ear and mastoid process	118,9	171,2	52,7
I 00-I99			
Diseases of the blood and blood-forming organs	67,2	149,2	127,0



Table 7

The structure of newly diagnosed neoplasms

Localization	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Leukemia	9	9	12	5	15	4	11	9	8	12
Tumors of the CNS	6	6	12	6	7	5	11	4	3	9
Neuroblastoma	1	1	2	4	2	1	3	1	1	2
Kidney formation	1	1	2	3	1	2	-	2	1	2
Soft tissue tumor	3	3	-	-	1	1	-	3	1	2
Lymphoma	-	2	-	1	1	1	2	2	2	2
Osteosarcoma	2	1	1	2	1	-	-	2	1	1
Retinoblastoma	-	-	1	-	-	1	1	3	2	2
Hepatoblastoma	1	1	-	1	1	-	2	1	2	
Tumor of germic etiology	1	1	1	1	-	-	-	2	1	1
Thyroid gland swelling	-	-	-	-	-	2	-	1	1	-
Tumors of the pancreas	2	-	-	1	-	1	-	-	-	-
Swelling of the ovary	1	-	-	-	-	2	-	-	-	-
Ewing's sarcoma	-	-	-	-	1	-	-	1	-	-
Total	27	25	31	24	30	20	30	31	23	33

In our opinion, the real picture of oncological morbidity extent in the Sakha Republic (Yakutia) can be given by a single register of cancer patients created by using information technologies, which will take into account the personal data of patients with a mandatory indication of residence place, ethnicity, age, sex and other characteristics of the child.

#### References

1. Davydov M.I. Statistika zlokachestvennykh novoobrazovaniy v Rossii i stranakh SNG v 2005g.-Prilozheniye zhurnala RONTs im. N.N. Blokhina
2. [Statistics of malignant neoplasms in Russia and CIS countries in 2005-the Application log, through. N. N. Blokhin]- T. 20.-2007.- P.156.
3. Zlokachestvennyye novoobrazovaniya v Rossii v 2010g. (zabolevayemost', smertnost')
4. [Malignant neoplasms in Russia in 2010. (morbidity and mortality)]/V. I. Chissov, V. V. Starinsky, G. V. Petrova.- M., 2012.- P. 260.
5. Zlokachestvennyye novoobrazovaniya

v Rossii v 2015g. (zabolevayemost', smertnost')

6. [Malignant neoplasms in Russia in 2015 (morbidity, mortality)] /A.D. Kaprin, V. V. starinsky, G. V. Petrov.- M., 2017.- P. 250.
7. Kosykh N. Uh. Zlokachestvennyye novoobrazovaniya u detey na Dal'nem Vostoke: Populyatsionnoye epidemiologicheskoye issledovaniye [Malignant neoplasms in children in the far East: a Population-based epidemiological study]: the author's abstract dis. ... doctors of medical Sciences : 14.00.14 / Khabarovsk state institute.-Tomsk, 1996.- P. 47.
8. Polyakov V.G. Klinicheskiye proyavleniya onkologicheskikh zabolevaniy u detey [Clinical manifestations of cancer in children] /V. G. Polyakov, M. Yu. Rykov, M. Yu.- SPb, 2017.- P. 9.

#### The authors

1. Burtseva Tatyana Egorovna - doctor of medical sciences, professor of Medical Institute of North-Eastern Federal University, head lab. Yakut Science Center

A.Z. Mestnikova, I.I. Gogolev, Kh. M. Diab, A.S. Machalov, E.E. Fedotova, E.M. Vasilieva

## RESULTS OF COCHLEAR IMPLANTATION IN THE REPUBLIC OF SAKHA (YAKUTIA)

#### ABSTRACT

The article discusses the priorities of cochlear implantation (CI) in the RS (Ya). The results of the CI in Yakutsk to 11 children are presented. All patients in the preoperative period underwent general clinical examination, examination of ENT organs, earmicroscopy, acoustic impedance measurement, a study of otoacoustic emission and short-latency auditory evoked potentials research. A computed tomography of temporal bones with a 2 mm cut thickness was also performed. All patients were examined by a speech therapist and the faculty for the purpose of determining the level of general development, auditory and speech perception and development of speech.

All patients were operated using Neurelec implants (France).

The need for further introduction of high-tech care for children to improve the quality of life was noted.

**Keywords:** cochlear implantation, sensorineural hearing loss, inner ear.

of Complex Medical Problems, 8 (914) 294-32-44, bourtsevat@yandex.ru

2. Lena Nikolaevna Afanasyeva, MD, head physician of YAROD, associate professor of MI SVFU, lenanik2007@mail.ru,
3. Argunova Elena Filippovna, PhD, MI SVFU, eargunova@mail.ru,
4. Nikolaeva Lyudmila Alekseevna, PhD, director of the Pediatric Center RH№ 1-NCM, nla20ncm@yandex.ru,
5. Kondrateva Sargylana Afanasyevna - head of oncology department of the Pediatric Center RH № 1-NCM, gematologia@mail.ru
6. Kharabaeva Elena Mikhailovna - children's oncologist of the oncology department of the Pediatric Center RH № 1-NCM, gematologia@mail.ru
7. Nikolaeva Sargylana Afanasyevna - children's oncologist of the oncology department of the Pediatric Center RH № 1-NCM, gematologia@mail.ru
8. Evseeva Sardana Anatolievna – researcher of Yakut Science Center of Complex Medical Problems, sarda79@mail.ru, contact. phone: 89679111195
9. Chasnyk Vyacheslav Grigorievich - MD, professor of St. Petersburg State Pediatric Medical University, 89062296831, chasnyk@gmail.com
10. Ivanov Peter Mikhailovich - MD, professor of Medical Institute of North-Eastern Federal University, senior researcher of YSC of CMP
11. Fedorov Fedor Fedorovich - 6th year student of the Pediatric Department of the Medical Institute of Medical Institute of North-Eastern Federal University, f.f.fedorov\_1993@mail.ru
12. Burnasheva Karina Ilyichna - 6th year student of the Pediatric Department of the Medical Institute of North-Eastern Federal University, karivin2015@mail.ru.

### Introduction.

Officially, in the world implantation of multichannel cochlear implants began to be carried out to children since 1990. In Russia, CI has been implemented since 1997 [2].

The urgency of cochlear implantation in the territory of the Republic of Sakha (Yakutia) is determined by the high percentage of births of deaf children. On average, 106 children with hearing impairment are diagnosed in the Surdological Center every year, of which about 30 children are sent to primary hearing disability by hearing (Figure 1). Through the audiological screening test since 2008 [1], an early diagnosis of hearing loss is performed, where small patients are selected for CI. In Yakutia there are 170 children with CI.

The relevance of conducting CI in the republic is conditioned by the presence of needy patients, and it is also economically feasible to perform surgery and rehabilitation in the region.

In Yakutia there is a surdologic service that meets high standards, specialists are working, who have been carrying out rehabilitation of children after CI performed in central cities for several years. The need is to train surgeons to perform surgery and purchase expensive implants. In 2017 in Yakutsk conducted 11 CI. What can be considered the beginning of the CI in our region.

The **purpose** of the study is to increase the effectiveness of CI in Yakutia.

### Materials and methods

In "RH №1-NCM" in June 5 CI operations were performed, in December - 6. The age of implanted children was from 1 to 6 years. Table 1 shows that the main contingent is children from one year to 2 years - this is considered a good indicator of early detection of hearing loss in children and timely rehabilitation.

Table 2 lists the factors that contribute to the development of hearing loss. Of the 11 patients, three children had acquired hearing loss after suffering meningitis and taking ototoxic drugs. One of them lost his hearing at the age of 3 and had a lean vocabulary. Of all 11 children, the hereditary nature of hearing loss was found in 2. 2 patients were born at week 28, one of whom was somatically severe with bronchopulmonary dysplasia and post-indubation stenosis of the larynx, was the carrier of the tracheostomy [4].

All patients in the preoperative period underwent general clinical examination, examination of ENT organs, earmicroscopy, acoustic impedance measurement, a study of otoacoustic emission and short-latency auditory evoked potentials

research. A computed tomography of temporal bones with a 2 mm cut thickness was also performed. All patients were examined by a speech therapist and the faculty for the purpose of determining the level of general development, auditory and speech perception and development of speech.

All patients were operated using Neurelec implants (France).

### Results and discussion

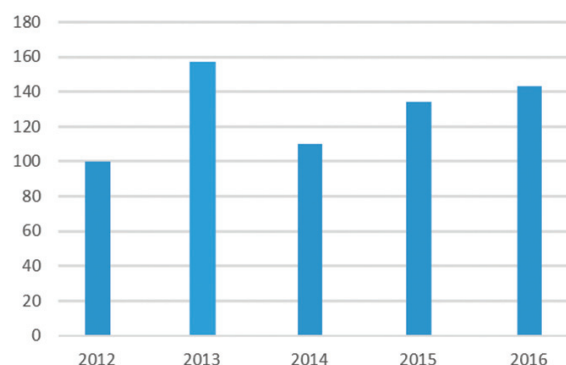
The result of CI depends both on the timely operation, and on the technique of surgical intervention and postoperative auditory rehabilitation of young patients.

The world has accumulated sufficient experience in creating the most secure access to the cochlea, inserting electrodes to the required depth and ensuring a prolonged location of the implant in the temporal parietal region [3]. The procedure for performing the CI is as follows: a skin incision is made parallel to the transitional fold of the auricle. Skin-periosteal flaps are formed. Access to the tympanic cavity is performed through the mastoid process, then a posterior tympanotomy is performed in the area of the facial pocket. Drill removes the canopy above the window of the cochlea, the membrane of the snail's window is exposed. The Neurelec implant is installed in the parietal region, the proximal part of the active electrode is fixed by a drilled tunnel, then the electrodes are completely inserted into the cochlea through the mastoid cavity, posterior tympanostoma and the pre-opened membrane of the cochlear window. The telemetry of the nervous response of the implant is performed intraoperatively by obtaining stapedal reflexes. The behind-the-ear wound is sewn in layers. Tight bandage in the postoperative wound and implant bed.

Among the children operated on, two were found to have ossification of the cochlea 3 mm and 4 mm after the meningitis had been transferred [5], with telemetry of the nervous response, the stapedal reflexes were not obtained. However, with intraoperative radiography of CI, it is seen that the electrodes were in the cochlea (Fig. 2).

The postoperative period in 10 patients proceeded without any peculiarities. One child - had a postoperative hematoma in the implant area, which disappeared on the 7th day after 4 times aspirating the contents.

*Results of auditory rehabilitation.* Pa-



**Fig. 2.** Intraoperative radiography of CI. The arrow shows that the electrode is in the cochlea, repeating its shape.

**Table 1**

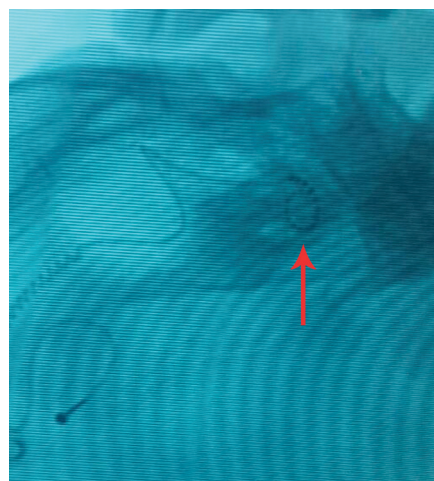
### Age of CI patients

Age group	Amount of children
Up to 1 year	0
From 1 year to 2 years	7
From 2 years to 3 years	2
Older than 3 years	2

**Table 2**

### Factors contributing to the development of hearing loss in children.

The main factors	Frequency of occurrence, n (%)
Prematurity 28-30 weeks	2 (18)
Hereditary weighting	2 (18)
Meningitis in anamnesis	3 (27)



**Fig. 2.** Intraoperative radiography of CI. The arrow shows that the electrode is in the cochlea, repeating its shape.

tients who received CI in June 2017 had the following results: during the connection of speech processors, all children responded to loud sounds. The first training session was conducted 5 months after the operation. All children constantly wear a speech processor and switched to the fourth program. 3 people are asked

to put the processor on in the morning and report the need to replace the batteries. 4 children clearly respond to the name. 3 distinguish sounds by volume and its presence. 2 began to discern the parents by their voices. 4 respond well to household sounds: a knock on the door, the sound of running water, the sound of a drill, a vacuum cleaner, a hair dryer, a phone ring. They hear the sounds of the street, the barking of a dog, the sound of a car. 1 patient hears the creaking of snow.

4 children began to publish various voiced sounds, voice of animals, a typewriter. One boy clearly pronounces the words-appeals "Mom, Dad."

Conditionally-motor reaction is developed in all patients.

In a girl with ossification of a cochlea, after having had meningitis with bilateral implantation, the period is slower compared to other children. CI was conducted in two stages with a difference of 1.5 months. In the development of speech there is a slight dynamics. The girl seldom uttered babbling words.

On February 6, 2018 the specialists of the Clinical Research Center of otorhinolaryngology Russia and Republic hospital №1 NCM for the first time jointly conducted a remote connection of speech processors to 6 children, whom the CI performed on December 16-17, 2017. When connected, 5 children gave a clear reaction to loud non-verbal sounds. One of the girls with the ossification of the cochlea was in doubt. Within a week of rehabilitation sessions, this patient developed a clear conditioned-motor reaction. At low frequencies, the reaction is from 6 meters, at medium frequencies - 2.5 meters, at high frequencies - 0.5 meters.

### Conclusion

The performance of CI in the first

years of life shows significantly better results in the rehabilitation of patients. This is an important motivational factor for conducting this operation in the territory of Yakutia, where no time will be spent on solving paramedical issues. From the economic point of view, the operation in the region, both for the patient and for local government is preferable. In addition, the emergence of new candidates and the presence of implanted patients dictate the need for staffing and training specialists involved in this pathology.

### References:

1. Tavarkiladze G.A. Markova T.G. Chibisova S.S. [et al.] Rossijskij i mezhdunarodnyj opyt realizacii programm universal'nogo auiologicheskogo skringa novorozhden-nih [Russian and international experience in the implementation of universal auological screening of newborns] Vestnik otorinolaringologii [Bulletin of otorhinolaryngology]. Moscow, 2016, Vol. 81, №2, P. 7- 12.
2. Tavartkiladze G.A. Istoriya kohlearnoj implantacii [History of cochlear implantation] Vestnik otorinolaringologii [Bulletin of otorhinolaryngology]. Moscow, 2016, Vol.81, №6, P. 4-7.
3. Fedoseev V.I. Dmitriev N.S. Ehvoluciya hirurgicheskogo vmeshatel'stva pri kohlearnoj implantacii v Rossijskom nauchno-prakticheskom centre audiologii i sluhoprotezirovaniya [Evolution of surgical intervention in cochlear implantation at the Russian Scientific and Practical Center for Audiology and Hearing Aid] Vestnik otorinolaringologii [Bulletin of otorhinolaryngology]. Moscow, 2014, №2, P.17-20.
4. Cejas I. Outcomes and benefits of pediatric cochlear implantation in children with additional disabilities: a review and report of family influences on outcomes / I. Cejas, M.F. Hoffman, A.L. Quittner // Pediatric Health Medicine Ther. – 2015. –Vol. 6. – P.

45-63.

5. Tokat T. Cochlear Implantation in Postmeningitic Deafness / T. Tokat, T. Catli, F. Bayrak [et. al.] // J. Craniofac. Surg. – 2018. – Vol.10. – P. 1097.

### The authors

1. Mestnikova Aina Zakharovna – PhD, otorhinolaryngologist, otorhinolaryngological department of Pediatric Centre of State Autonomous Institution «Republic hospital №1- NCM», Yakutsk, Russia, e-mail: Ain-o4ka\_13@mail.ru;
2. Gogolev Innokentiy Ivanovich – head of otorhinolaryngological department of Pediatric Centre of State Autonomous Institution «Republic hospital №1-NCM», Yakutsk, Russia, e-mail: innokentiy.gogolev@mail.ru;
3. Diab Khassan – MD, head of Clinical Research Department of ear disease of Federal State Budgetary Institution of Clinical Research Centre of Otorhinolaryngology of the Federal-Medico-Biological Agency of Russian Federation, Moscow, e-mail: Hasandiab@mail.ru;
4. Machalov Anton Sergeevich, a surdologist-otorhinolaryngologist, Head of the Scientific and Clinical Department of Audiology, Hearing and hearing rehabilitation of FGBU NKTSO FMBA RF, the senior lecturer of faculty of otorhinolaryngology of faculty of the additional vocational education Russian national research medical university named after N.I. Pirogov;
5. Fedotova Elvira Egorovna – PhD, audiologist of the Republican Audiology Centre, Yakutsk, Russia, e-mail: sakhasurdo@mail.ru;
6. Vasilyeva Lena Maksimovna – audiopedagog of the Republican Audiology Centre Yakutsk, Russia, e-mail: vasilevalena70@mail.ru.





M.B. Suvyrina, I.D. Ushnitsky, A.V. Iurkevich, A.R. Kobets,  
A.A. Ivanova, A.V. Ivanov

## FREQUENCY AND STRUCTURE OF PATHOLOGICAL PROCESSES OF PERIODONTAL TISSUES IN THE POPULATION OF THE FAR EASTERN REGION

DOI 10.25789/YMJ.2018.63.24

### ABSTRACT

The prevalence and intensity of parodontium diseases among the population of the Far East of Russia has been studied. At the same time, an unfavorable morbidity situation was identified, associated with an increase in the severity of the clinical course of periodontal disease with age. The high prevalence of pathological processes of periodontal tissues of inflammatory-destructive nature dictates the need to develop and implement a comprehensive program for the prevention of periodontal diseases.

Clinical-epidemiological examination of the population has been performed to study the prevalence of pathological processes of periodontal tissues with the analysis of possible risk factors of their development. The obtained data have proved the existence of certain features. Thus, young patients have inflammatory processes of marginal gingiva without dentogingival attachment deformation but pathological processes of tissues of inflammatory-destructive character become more expressed with age. At the same time, these examined groups of the population showed insufficient level of dental hygiene that leaves a negative impact on the level of frequency and intensity of inflammatory process of periodontal tissues. Moreover, a part of the examined patients were diagnosed with various somatic diseases mainly chronic, affecting the clinical course of pathological processes of periodontal tissues. Meanwhile, age, physiological changes in organs and systems of the organism become the cause of substantial increase of sensitivity of periodontal tissues to infectious agents, aggravating the course of inflammatory processes. People over 45 have moderate and severe stage of periodontal diseases and rapidly progressing pathological process with the loss of externally intact teeth promoting dysfunction of the temporal-mandibular joint and all dentoalveolar system in general. That requires obligatory systemic approach of medical prevention of pathological processes in periodontal tissues of inflammatory-destructive and metabolic-dystrophic character.

The obtained data confirmed an unfavorable clinical-epidemiological situation with periodontal diseases in the population of the Far East. Such situation necessitates the development of a complex preventive program of periodontal diseases in various age groups of the population including better availability and improvement of the parodontological care in dental clinics of the Far Eastern Federal District. Those preventive measures are aimed at the improvement of patients' quality of life.

**Keywords:** parodontium diseases, prevalence, intensity, risk factors, somatic diseases, level of sanitary hygiene, quality of life, treatment, prevention.

Periodontal diseases are one of the most common and complicated pathologies of the oral cavity organs and tissues. Those pathologies deteriorate with age leading to a severe disease requiring complex therapeutic, surgical and prosthetic treatment [10, 18]. In addition to well-known local factors determining incidence, chronic damage of periodontal tissues, there are other harmful factors such as: climate, fluoride content in drinking water and food, gastrointestinal diseases and endocrine disorders, age changes of the dento-maxilla system [3, 9, 11, 12, 21]. At the same time, morbidity rate and diseases incidence are directly affected by sanitation, hygiene, patients' education and lack of motivation, on the patients' side, to prevent oral diseases [1, 17, 18].

It is necessary to emphasize that the main factors of destructive changes in periodontal tissues may be soft food, poor oral hygiene, saliva secretion decrease, poor marginal restoration, orthodontic appliances, anomalies of the frontal part of the oral activity and teeth location, mechanical trauma, prosthetic treatment mistakes, accompanying pathologies of internal organs [2, 3, 4, 5, 6, 10, 14, 22]. Consideration of etiologic factors and their prevalence with age helps prevent and stop the development and progress-

ing of periodontal pathology that will apparently lead to morbidity rate decrease and patients' life quality improvement [9, 12, 14, 15, 18, 19].

Improvement of complex dental care as a rule is based on the knowledge of clinical-epidemiological peculiarities of pathological process in the oral cavity organs and tissues. That is why studies aimed at those problems that have an important theoretical, scientific and practical application.

**The goal of the research.** To work out recommendations aimed at the improvement of dental services to the population based on complex clinical-epidemiological studies of periodontal diseases.

**Materials and methods.** The object of the research was patients with periodontal pathologies. The research was being performed in the dental clinic of Medical institute of Northern-Eastern federal university named after M.K. Amosov, dental clinic "Eurodent" (Yakutsk), and a dental clinic "Uni-stom" of the Far Eastern state medical university (Khabarovsk). The study included 467 patients. They were divided into 5 age groups: : 15-19 – 88 people, 20-34 – 93 patients, 35-44 – 85 persons, 45-64 – 134 people, 65 and older – 67 people Gender distribution: males– 251, females– 216.

A clinical examination was performed

according to a standard procedure including complaints on tenderness, swelling, gums bleeding, unpleasant odor from the oral cavity, dental necks and roots exposure, teeth mobility, adentia, loss of teeth, periodontal pockets, presence or absence of accompanying somatic diseases ( blood pathologies, cardio-vascular diseases, gastrointestinal disorders, endocrine pathologies.) To assess periodontal tissues the authors used the following indexes: periodontal index PI (Rassel A., 1956), bleeding index according to Mülleman (Mülleman H.R., 1971). Incidence and severity of the disease and periodontal tissues damage were evaluated on the basis of indexes of common periodontal index CPI (1995). The depth of periodontal pockets was measured with a graduated periodontal probe.

The examination was performed according to the ethical principles of research including humans approved by Helsinki Declaration of the WMA (1964, ed. 2000), and the requirements of the Russian Federation documents on clinical studies.

Statistical processing of the findings was conducted according to the standard methods of variable statistics calculating average value, error ratio, the arithmetic average, standard square deviation, variation ration with packages of stan-

dard software «Microsoft Excel» 2009 (Microsoft Corporation, 2000-2016). The received findings were grouped according to the set of similar characteristics

**The results and discussion.** The conducted research revealed several peculiarities. The overall average index of periodontal diseases incidence in the studied groups comprises  $62,76 \pm 0,28\%$ , out of them, males – 179 ( $59,45 \pm 0,31\%$ ), females – 113 ( $40,55 \pm 0,45\%$ ). At the same time, data of epidemiological indexes of periodontal diseases vary in different age groups. In the group 15-19 the incidence of periodontal tissues pathologies was  $89,15 \pm 0,08\%$ , and there is a tendency of its going up with age up to the group 35-44 and it declines in the group of 65 years and older. The frequency of periodontal diseases incidence in the age group 20-34 was  $94,35 \pm 0,04\%$ , in the age group 35-44 and 45-64 the findings were  $96,67 \pm 0,02\%$  and  $79,81 \pm 0,15\%$  respectively. At the same time, the minimum incidence index was observed in the age group of 65 and older where it ranged  $64,53 \pm 0,27\%$ .

It is necessary to underline that in the age groups 15-19, 20-34 and 35-44 there are maximum indexes of sub and undergingival tartar ranging from  $43,25 \pm 0,45\%$  to  $48,12 \pm 0,39\%$ . In the age groups 45-64, 65 and older findings reveal their significant decrease with the indexes  $30,87 \pm 0,52\%$  and  $12,78 \pm 0,67\%$ . The finding characterizing pathological periodontal pockets demonstrate oppositional changes connected with the tendency of its depth increase with age. In the age group 15-19 the index was  $9,54 \pm 0,73\%$ , but in the group 65 and older –  $81,96 \pm 0,14\%$ . At the same time, in the dynamics of the indexes of bleeding and healthy gums there are certain clinical features that decrease with age. In the group 15-19 the indexes of a healthy gum and bleeding comprised  $10,85 \pm 0,69\%$  and  $36,36 \pm 0,49\%$ , whereas in the group of 65 and older they were  $0,70 \pm 0,09\%$  and  $4,56 \pm 0,73\%$  respectively.

We should emphasize that in the dynamics of indices concerning the severity of periodontal tissue damage according to CPI index certain clinical characteristics were demonstrated. In the parameters of healthy gums and bleeding we also observed the same tendency – their decline with age when in the group 15-19 the index was  $0,58 \pm 0,76$  and  $2,14 \pm 0,74$ , but in the group 65 and older they were at the level of  $0,02 \pm 0,01$  and  $0,14 \pm 0,04$  ( $p < 0,05$ ) respectively. However, the parameters of the parts having tartar above or under gingiva demonstrated an apparent decrease with age. In the group 15-19, the index was  $2,87 \pm 0,02$ , but in

the patients of 65 and older it reached  $0,54 \pm 0,04$  ( $p < 0,05$ ). The data characterizing pathological periodontal pocket and unrecorded sextants revealed the following data, a significant increase in the group 15-19 where they comprised  $0,39 \pm 0,04$  and  $0,02 \pm 0,01$  respectively, but in the group 65 and older they made up  $2,95 \pm 0,02$  and  $2,35 \pm 0,03$  ( $p < 0,05$ ).

It is important to stress that in the morbidity structure of periodontal diseases there are certain features associated with age manifestations. In the age group 15-19,  $84,61 \pm 0,33\%$  had chronic catarrhal gingivitis but hypertrophic gingivitis comprised  $4,54 \pm 2,06\%$ . Less frequently, in all examined groups paradontosis was diagnosed –  $3,87 \pm 0,73\%$ . The cause determining the severity of the periodontal diseases in the patients of 65 and over ( $64,53 \pm 0,27\%$ ) is a polymorbid character of underlying and accompanying somatic diseases. The received data show that in the young age the most common periodontal pathologies are mild, sometimes moderate and very rarely severe. With age, the patients usually have pathological changes of periodontal tissues predominantly of inflammatory-destructive or rarely of metabolic-dystrophic character.

It has to be said that paradontomas and idiopathic diseases of periodontal tissues were not revealed during our study.  $58,32 \pm 0,31\%$  of examined patients had poor oral hygiene. An average value of hygiene index according to Green-Vermilion was 3,15, a periodontal index – 1,54, bleeding index according to Mullemann H.R. – 1,2. Such situation results in an unfavorable tendency causing a negative effect on the diseases' incidence.

### Conclusion

The received data characterize the incidence of periodontal diseases in different age groups of population. Low level of sanitary culture results in a poor oral hygiene. It necessitates a further development and improvement of dental services and working out and implementation of a complex program of periodontal diseases prevention.

### References

1. Semenov A.D. Ushnitsky I.D. Rogaleva A.S. [et al.]. Analiz i ocenka potrebnosti v stomatologicheskoy pomoshchi zhitelej promyshlennykh rayonov Yakutii [Analysis and assessment of need for dental care of inhabitants of industrial regions of Yakutia]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. Yakutsk, 2016, №1, V.53, P. 40-42.
2. Mukhlayev S. Yu. Pervov Yu. Yu. Yurkevich A.V. Vliyanie akrilovykh basisnykh plastmass razlichnykh proizvoditelej na parametri immunnogo gomeostaza slisistoi obolochki rta [Influence of acrylic basic plastic of

various manufactures on parameters of immune homeostasis of oral mucosa]. Tichookeanskij medicinskij zhurnal [Pacific medical journal]. 2014, №3, P. 56-58.

3. Oskolsky G. I. Nepomnyashchy L.M. Yurkevich A.V. [et al.]. Issuchenie strukturno-proliferativnykh processov v epiteliu desni pri ismeneniyakh sostojanij parodonta [Study of structural and proliferative processes in gingiva epithelium at parodontium condition changes]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. Yakutsk, 2011, №4, P.92-94.
4. Ushnitsky I.D. Ivanov A.V. Ivanova A.A. [et al.]. Kliniko-epidemiologicheskaja charakteristika patologicheskikh processov tkanej parodonta vospalitelno-destruktivnogo charaktera [Kliniko-epidemiolo Clinical-epidemiological characteristic of pathological processes of parodontium tissues of inflammatory-destructive character]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. Yakutsk, 2018, V.61, №1, P.83-86.
5. Yurkevich A.V. Oskolsky G.I. Shcheglov A.V. [et al.]. Klinicheskaja ocenka rezultatov lechenija bolnykh posle uvelichenija mezhalveolarnogo rasstojanija [Clinical assessment of treatment results of patients after augmentation of interalveolar distance]. Fundamentalnye issledovanija [Basic researches]. 2013. №7-1, P. 204-206.
6. Ushnitsky I.D. Rogaleva A.S. Chizhov Yu.V. Klinicheskaja charakteristika sostojanija organov i tkanej polosti rta u liz pozhilogo vozrasta Respubliki Sasha Yakutija [Clinical characteristic of condition of organs and tissues of the oral cavity at elderly people of the Sakha Republic]. Klinicheskaja gerontologija [Clinical gerontology]. 2013, №1-2, V.19, P. 48-52.
7. Masheyko A.V. Khristenko A.S. Masheiko A.V. Osobennosti stomatologicheskogo statusa zhenchin v razlichnykh trimestrykh beremennosti. Stomatologija – nauka i praktika, perspektivi razvitiya. Materialy nauchno-prakticheskoi konferensii posvjashchennoi 50 letiju so dnja rozhdenija L.P.Ivanova (v ramkakh Vserossiiskoi studencheskoi olimpiadi s mezhdunarodnim uchastiem "Stomatologija Yuga-2017") [Features of the dental status of females in various trimesters of pregnancy. Dentistry – science and practice, prospects of development. Materials of the scientific and practical conference devoted to the 90 anniversary since the birth of L.P. Ivanov (Russian student's Olympic Games with the international participation "South-2017 Odontology"). 2017, P.104-107.
8. Ushnitsky I.D. Semenov A.D. Nikiforova E.Yu. [et al.]. Mediko-geograficheskaja charakteristika Severa i sovremennije aspekti sovershenstvovaniya stomatologicheskoi pomoshchi [Medical-geographical characteristic of the North

- and modern aspects of improvement of the dental care]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. 2016,V.55, №3, P.49-53.
9. Yurkevich A.V. Oskolsky G.I. Pervov Yu.Yu. Morfologicheskie i molekulyarno-geneticheskie aspekty jadrishkovogo organisatora ribosom [Morphological and molecular and genetic aspects of the nucleolar organizer of ribosomes]. Tichookeanskii medicinskii zhurnal [Pacific medical journal]. 2005, №1, P.85-87.
  10. Oskolsky G. I. Yurkevich A.V. Morfometricheskaja charakteristika strukturi epiteliya desni v norme i pri chronicheskikh sabolevaniyach parodonta [The morphometric characteristic of structure of gingiva epithelium at normal and chronic diseases of parodontium]. Dalnevostochni medicinski zhurnal [Far East medical journal]. 2004, №1, P. 19-23.
  11. Yurkevich A.V. Matsyupa D.V. Oskolsky G.I. Patomorfologicheskoe issledovanie slisistoi obolochki desni pri jasvennoi bolesni zheludka [A pathomorphologic research of gingiva mucosa at peptic ulcer of the stomach]. Sibirski konsilium [Siberian Consultation]. 2005, №4, P. 37-40.
  12. Dybov D.A. Yurkevich A.V. Mikhailchenko A.V. [et al.]. Primenenie preparatov selena v lechenii vospalitelnykh sabolevani parodonta [Use of selenium medication in treatment of inflammatory diseases of parodontium]. Klinicheskaja stomatologija [Clinical odontology]. 2017,V.84, №4,P.26-29.
  13. Sadulayeva A.S. Ushnitsky I.D. Klinicheskaja charakteristika ortopedicheskogo statusa liz starshei vozrastnoi gruppi prozhivayushchikh v usloviyakh Severa [Clinical characteristic of orthopedic status of senior age group patients living in conditions of the North]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. 2011, №2,P.53-55.
  14. Ushnitsky I.D. Semenov A.D. Nikiforova E.Yu. [et al.]. Sovershenstvovanie organizatsii stomatologicheskoi pomoshchi v promyshlennykh rayonakh Respubliki Sasha Yakutiya. Aktualnie voprosy stomatologii i chelustno-lizevoi chirurgii. Materialy kraevoi nauchno-prakticheskoi konferentsii stomatologov i chelustno-lizevzhch chirurgov [Improvement of the organization of the dental care in industrial regions of the Sakha Republic. Topical issues of odontology and maxillofacial surgery. Materials of regional scientific and practical conference of dentists and maxillofacial surgeons]. Chita, 2016,P.116-123.
  15. Oskolsky G. I. Yurkevich A.V. Pervov Yu.Yu. Sovremennye predstavleniya o strukturnykh reaktsiyakh slisistoi obolochki polosti rta v prozesse ontogenesa [Modern issues of structural reactions of oral mucosa in ontogenesis]. Tichookeanskii medicinskii zhurnal [Pacific medical journal]. 2005, №2,P.17-19.
  16. Sadulayeva A.S. Ushnitsky I.D. Trifonov S.A. Sozialno-gigienicheskie aspekty formirovaniya stomatologicheskogo statusa u liz pozhilogo i starcheskogo vosrasta v Yakutii [Social-hygienic aspects of dental status development at patients of old and senile age in Yakutia]. Yakutskiy medicinskij zhurnal [Yakut medical journal]. 2012,V.38, №2,P. 27-30.
  17. Suvyrina M.B. Masheyko A.V. Khristenko A.S. [et al.]. Stomatologicheskij status beremennzhch zhenschchin v rasnye sroki beremennosti [Dental status of pregnant women in different periods of gestation]. Dalnevostochni medicinski zhurnal [Far East medical journal]. 2017, №4, P.104-108.
  18. Semenov A.D. Ushnitsky I.D. Egorov R.I. Stomatologicheskij status zhitelei promyshlennykh rayonov Respubliki Sasha Yakutiya. Aktualnie problemy i perspektivy razvitiya stomatologii v usloviyakh Severa. Sbornik statei mezhhregionalnoi nauchno-prakticheskoi konferentsii, posvyaschchennoi 95-letiyu stomatologicheskoi sluzhbi Respubliki Sasha Yakutiya [The dental status of inhabitants of industrial regions of the Sakha Republic. Contemporary issues and prospects of odontology development in the conditions of the North. The collection of articles of the regional scientific and practical conference devoted to the 95 anniversary of dental service of the Sakha Republic]. Yakutsk, 2015,P. 86-90.
  19. Baginsky A.L. Chizhov Yu.V. Ushnitsky I.D. [et al.]. Stomatologicheskij status i sozialno-gigienicheskaja ozenka korennykh zhitelei Dolgano-Nenetskogo meditsinskogo rajona Krasnojarskogo kraja i Respubliki Sasha Yakutiya [The dental status and social-hygienic assessment of aboriginals of the Dolgan-Nenets municipal district of Krasnoyarsk Krai and the Sakha Republic (Yakutia). Contemporary problems and prospects of odontology development in the conditions of the North. The collection of articles of the regional scientific-practical conference devoted to the 95 anniversary of dentistry of the Sakha Republic]. Yakutsk, 2015,P. 100-107.
  20. Suvyrina M.B. Kliniko-laboratornoe obosnovanie stomatologicheskoi pomoshchi zhenschchin v perimenopauze: avtoreferat diss.kandidata meditsinskikh nauk [Clinical laboratory data of dental care to women in perimenopause: thesis...candidate of medical sciences]. Ekaterinburg, 2002, 23 p.
  21. Yurkevich A.V. Patomorfologicheskij analiz slisistoi obolochki desni pri sacharnom diabete i jasvennoi bolesni zheludka avtoreferat diss.doktora meditsinskikh nauk [The pathomorphological analysis of gingiva mucosa at diabetes mellitus and peptic ulcer of the stomach: thesis...doctor of medical sciences]. Novosibirsk, 2005, 36 p.
  22. Yurkevich A.V. Strukturno- proliferativnye protsessy v slisistoi obolochki desni pri insulinnesavisimom sacharnom diabete avtoreferat diss.kandidata meditsinskikh nauk [Structural and proliferative processes in gingiva mucosa at non-insulin-dependent diabetes mellitus: thesis...candidate of medical sciences]. Novosibirsk, 1999, 22 p.

#### The authors

1. Suvyrina Marina Borisovna, Head of therapeutic dentistry department of Far Eastern State Medical University, candidate of medical sciences, associate professor. Address: Khabarovsk 680000, Muravyev-Amursky St., 35 Phone (4212)761-374, e-mail address: [drsuwirina@rambler.ru](mailto:drsuwirina@rambler.ru);
2. Ushnitsky Innokentiy Dmitrievich
3. Head of the department of therapeutic, surgical, prosthetic and children dentistry of Medical institute of NEFU, Yakutsk (Russia), doctor of medical sciences, professor. Phone 89241708940, e-mail address: [incadim@mail.ru](mailto:incadim@mail.ru);
4. Iurkevich Alexander Vladimirovich, Dean of dental faculty, head of the department of prosthetic dentistry, doctor of medical sciences, associate professor. Address: Khabarovsk 680000, Muravyev-Amursky St., 35. Phone (4212) 625-888, e-mail address: [dokdent@mail.ru](mailto:dokdent@mail.ru);
5. Kobets Alina Radiyevna, Clinical intern of department of therapeutic dentistry. Address: Khabarovsk 680000, Muravyev-Amursky St., 35 Phone: (4212) 761-374, e-mail address: [a\\_dsf@fesmu.ru](mailto:a_dsf@fesmu.ru)
6. Ivanova Aytalina Alekseevna, assistant of therapeutic, surgical, prosthetic and children dentistry department of Medical institute of NEFU, Yakutsk (Russia)
7. Ivanov Andrian Vladimirovich, dentist of clinic "Dentalika".



Lebedeva U.M.

# NUTRITION AND IRON DEFICIENCY STATES AMONG WOMEN AND CHILDREN OF REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2018.63.25

## ABSTRACT

Actual nutrition of pregnant women was studied on a basis of epidemiological research. It is established that rations of a majority of the pregnant women are profoundly deficient in an energy value and all nutrients. Parameters of «red blood» (RBC, HGB, Ht, MCH, MCHC, MCV, RDW and PLT) and iron metabolism (serum iron, ferritin and transferrin) of the pregnant women, puerperas and newborns were studied. A high frequency of iron deficiency states among the pregnant women, puerperas and their newborns is determined. Iron deficiency anemia is diagnosed among 26.8% of expectant mothers in the first trimester, 61.7% in the second one and 70% in the third one of pregnancy, 62.9% in a puerperium and 47.3% of the newborns in an early postnatal period. The latent iron deficiency was discovered among 87.4% of women in the first trimester, in 29.8% in the third one of the pregnancy and among 77.9% of the newborns in the early postnatal period. It is proved that the iron deficiency negatively affects a course of the pregnancy, childbirth, a condition of a fetus and newborn. A conducted canonical correlation analysis revealed a significant interrelation between the blood parameters in the first and second trimesters with a protein content (Canonical  $R = 0.46$ ,  $\chi^2 = 32.29$ ,  $p < 0.04$ ) and minerals (iron, sodium, potassium, calcium, magnesium and phosphorus) (Canonical  $R = 0.45$ ,  $\chi^2 = 35.63$ ,  $p < 0.05$ ) in the mother's ration.

**Keywords:** pregnant women, puerperas, newborn children, actual nutrition, micronutrients, red blood parameters, serum ferritin, iron deficiency states (IDS), iron deficiency anemia (IDA).

## Introduction

Until now, a problem of the micronutrient deficiency has not been resolved. 2 billion people suffer from microelement insufficiency, and a maximum risk group consist of the pregnant women and children under 5 years of age [5]. The iron deficiency occupies one of leading places in prevalence in all countries of the world. According to data of the World Health Organization (WHO), published in 2008, 42% of the pregnant women, 30% of the reproductive age women in the nonpregnant state, 47% of the children under 5 and 12.7% of men suffer from the anemia, in half of cases associated with the iron deficiency [6, 8]. According to N.J. Kassebaum et al. (2014), the prevalence of the anemia in the 187 studied countries was 32.9%. A decrease of the prevalence was noted among all age and gender groups, with an exception of the children under 5 years of age, among whom this disease was detected more often in 2010 compared with 1999 [7]. The frequency of occurrence of the iron deficiency in the world is inhomogeneous and primarily depends on socioeconomic reasons. In materials of the Fourth Report of the World Nutrition Situation of the United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition and the International Food Policy Research Institute it was noted that in the countries with a low socioeconomic level among the children with the various deficient states, the iron deficiency (ID) is the most frequent micronutrient deficiency. In the industrialized countries, despite the fact that the deficiency states

in the recent years began to occur much less frequently, the iron deficiency anemia (IDA) remains the most common form of the anemia among the young children [9, 10].

The youngest children, adolescents and pregnant women are the most "vulnerable" to developing the IDS. Thus, in Russia, according to various authors, the IDA frequency varies from 6% to 40% among the children [1, 2, 3] and from 15% to 56% among the pregnant women [4].

In this regard, rational provision of the

women and children with the essential micronutrients, including the iron, acquires particular relevance under the conditions of the Far North, where there are many families with low social status, and a population nutritional structure has its own national characteristics. In the Republic of Sakha (Yakutia), the IDA prevalence among the women of reproductive age and infants does not decrease, the parameters of maternal and infant mortality remain high. Therefore, a **purpose** of this study is to assess the

Table 1

Types and volume of studies

Type of research	Pregnant woman				Puer- pera	New- born	Total
	Trimesters of pregnancy			Before childbirth			
	I	II	III				
Blood test							
RBC, $\times 10^{12}/\text{л}$	138	125	118	92	118	118	709
HGB, г/л	138	125	118	92	118	118	709
Ht, %	138	125	118	92	118	118	709
MCV, фл	138	125	118	92	118	118	709
MCH, пг	138	125	118	92	118	118	709
MCHC, г/л	138	125	118	92	118	118	709
RDW, %	138	125	118	92			
Serum iron, mmol/L			42			42	84
Serum ferritin, ng/mL	86		86			86	258
Serum transferrin, g/L			42			42	84
Study of energy and nutrients in pregnant women							
Energy, kcal	122	Iron, mg/d					122
Carbohydrates, g/d	122	Calcium, mg/d					122
Proteins, g/d	122	Phosphorus, mg/d					122
Lipids, g/d	122	Potassium, mg/d					122
Ethanol, g/d	122	Magnesium, mg/d					122
Vitamin C, mg/d	122	Mono- and disaccharides, g/d					122
Vitamin B1, mg/d	122	Starch, g/d					122
Vitamin B2, mg/d	122	Dietary fiber, g/d					122
Vitamin PP, mg/d	122	Sodium, mg/d					122
Retinol, retinol equivalent	122	Vitamin A, mg/d					122
		Beta-carotene, mg/d					122

prevalence of the iron deficiency states (IDS) and iron deficiency anemias (IDA) among the pregnant women, puerperas and newborn babies of the Republic of Sakha (Yakutia) in conjunction with the actual nutrition of the pregnant women.

#### Materials and methods of research

Within the framework of this study, 138 pregnant women (the average age is  $27.6 \pm 0.41$  years), 118 puerperas and their newborn babies were complexly examined. The groups of the women were formed by simple randomization from among the women who had consulted a maternity welfare clinic in connection with the real pregnancy. All women and children were examined according to one protocol. A total volume of the conducted studies is presented in Table 1.

The study of composition of the peripheral red blood was carried out in the Laboratory of the Republican Hospital No. 1 of the National Center of Medicine of the Ministry of Health of the Republic of Sakha (Yakutia) (MH RS (Y)) on a hematological analyzer Coulter counter (Switzerland). An anemia severity estimate was conducted according to the level of hemoglobin: a light degree - HBG 112-90 g/L, the medium one - HBG 90-70 g/L, the heavy one - HBG is below 70 g/L (Shekhtman M.M., 1999). In the newborns on the first day after the birth, a lower limit of the hemoglobin level in the blood, according to WHO recommendations, is considered the level of 194 g/L (Johnson T.R., 1982).

A determination of the serum iron, ferritin and transferrin in the pregnant women and their newborns was carried out in the Laboratory of Membranology of the Research Center for Children's Health, Moscow. The serum iron concentration was determined using a Synchron cx diagnostic system (Beckman). To assess the iron content in a depot of the women and children, the serum ferritin content was determined by the method of a solid-phase enzyme-linked immunosorbent assay using reagents and commercial kits (EIA-ferritin) from the "Alcor Bio" company, Russia. The serum transferrin was determined by the method of immunoprecipitation on a Konelab analyzer from the Thermo Electron Corporation.

The estimation of the actual nutrition, calculation of a food set and chemical composition of the rations, energy value and nutrients were carried out on the basis of a questionnaire of the pregnant women in the second half of the pregnancy. The questionnaire was

Table 2

#### Average daily consumption of certain food groups

Food products	Recommended amount, g/d	Actual consumption,		
		M	m	s
Meat and meat products	180	156,0	9,8	108,9
Fish and fish products	100	34,5	7,0	77,7
Milk and milk products	250	435,6	39,1	431,4
Butter	20	15,5	1,8	20,3
Cooking fat and vegetable oil	25	15,6	0,9	10,9
Bread and bakery products, macaroni products	100	185,1	10,2	113,4
Potatoes	300	164,8	12,3	136,1
Vegetables (except potatoes)	500	127,5	9,1	100,7
Fruits and berries	250	143,5	14,15	156,3
Sugar and confectionery	50	77,7	6,4	71,1
Eggs	47	30,2	4,1	45,2

developed by the Federal Research Center of Nutrition, Biotechnology and Food Safety (Moscow) and it was adapted in accordance with the regional characteristics of food traditions of the population in the North.

#### Results of study and discussion of them

It is discovered that the rations of the majority of the pregnant women are profoundly deficient in the energy value and all nutrients. Consumption of products containing the animal protein (meat, fish, eggs), vegetables, fruits and berries was significantly below the

Table 3

#### Average daily intake of essential vitamins and iron

Vitamins and minerals	Recommended amounts	Actual consumption		
		M	m	s
A, mg	1,5	0,8	0,2	2,1
B1, mg	1,7	0,9	0,03	0,4
B2, mg	1,8	1,3	0,1	0,8
PP, mg	19	13,1	0,5	5,7
C, mg	90–100	63,3	4,5	49,4
Beta-carotene, mg	3,5	1,9	0,2	1,9
Retinol, Retinol Equivalents (RE)	1200–1400	1087,6	193,6	2137,9
Iron, mg	38	14,7	0,5	5,4

Table 5

#### Parameters of red blood in puerperas

Parameter	n	M	s	m	Min	Max	95% CI	Reference values
RBC, $\times 10^{12}/\text{л}$	118	3,7	0,5	0,05	2,0	5,1	3,6–3,8	3,5–4,5
HGB, г/л	118	113,8	15,6	1,4	73	156	110,9–116,7	115–130
Ht, %	118	32,3	3,7	0,4	20,8	40,2	31,5–33,0	36–42
MCV, фл	118	91,4	5,9	0,7	76,3	101,3	90,1–92,7	80–95
MCH, пг	118	30,7	2,4	0,3	20,6	35,6	30,1–31,2	24,5–39,2
MCHC, г/л	118	33,5	2,1	0,2	29,2	39,3	32,9–33,9	30–36
PLT, $\times 10^9/\text{л}$	118	246,7	69,6	7,8	139	467	231,1–262,3	140–400

Table 4

#### Dynamics of hemoglobin parameters (HBG) of blood in different periods of pregnancy

Observation period	n	Hemoglobin, g/L						Reference values
		M	s	m	Min	Max	95% Confidence Interval (CI)	
1 trimester	138	121,3	12,4	1,1	81	147	119,2–123,4	120–145
2 trimester	125	114,7	10,1	0,9	86	144	112,9–116,5	115–130
3 trimester	118	111,8	9,9	0,9	85	133	109,9–113,6	112–130
Before childbirth	118	111,6	9,9	1,0	82	128	109,6–113,7	112–130

ANOVA: Fridman  $\chi^2=73,37$ ,  $p<0,00000$ .

Table 6

#### Parameters of red blood in newborn children

Parameter	n	M	s	m	Min	Max	95% CI	Reference values
RBC, $\times 10^{12}/\text{л}$	118	5,0	0,8	0,1	3,0	6,7	4,9–5,1	5,3–5,9
HGB, г/л	118	186,9	26,5	2,5	97	256	181,9–191,9	194–208
Ht, %	118	49,3	7,9	0,9	29,1	69,5	47,4–51,3	56–58
MCV, фл	118	108,5	6,3	0,8	81,4	124,6	106,9–110,1	108–110
MCH, пг	118	36,5	2,5	0,3	26,7	44,6	35,8–37,1	35–37
MCHC, г/л	118	33,8	2,1	0,3	30,4	44,3	33,2–34,3	33–36
PLT, $\times 10^9/\text{л}$	118	284,9	79,1	9,7	70	492	265,4–304,3	273

Table 7

Content of ferritin in serum at different times of observation

Observation time	n	M	s	m	Min	Max	95% CI	Reference values, ng/mL
10-12 weeks of gestation	138	29,0	27,2	2,3	1,0	144,3	24,4–33,7	55–90
34–36 weeks of gestation	118	13,7	12,4	1,3	0,9	71,3	11,0–16,4	10–16
Umbilical blood	118	153,0	100,4	10,8	13,9	532,5	131,5–174,5	200–400

recommended values (Table 2). The insufficient provision of macronutrients (the proteins, fats and carbohydrates) was discovered in 80% of the pregnant women; minerals - in 90%; vitamins - in 75%, iron - in 100%. It was found that, in relation to a norm for the pregnant women, the consumption of the proteins was 75%, fats – 96%, carbohydrates – 68%, the vitamin B<sub>1</sub> – 55%, vitamin B<sub>2</sub> – 72%, vitamin PP – 72%, vitamin C – 63%, vitamin A (retinol) – 77%, magnesium – 60%, phosphorus – 88%, potassium – 83%, calcium – 59% and magnesium – 60% (Table 3). All examined women consumed the iron 3 times less than the recommended norm.

Clinical manifestations of the iron deficiency in the IDA form up to 13 weeks of pregnancy were diagnosed in a third of the examined pregnant women, in the period of 14-26 weeks – in more than 70%, in the third trimester - in 77.5% (Cochran Q-Test=89.75; p<0.000000).

All examined women, according to the standard of management of the pregnant women in the Republic of Sakha (Yakutia), were prescribed iron preparations (Sorbifer Durules). Despite this, the decrease of the hemoglobin content in the peripheral blood was noted during the pregnancy (ANOVA Fridman  $\chi^2 = 73.37$ , p<0.00000) (Table 5). The hemoglobin level below the norm was registered in 26.8% in the first trimester; in 61.7% in the second one; in 70.0% of the women and more in the third one and before the childbirth (Table 4).

A similar pattern was revealed for the parameters of hematocrit, mean erythrocyte volume and mean corpuscular hemoglobin concentration. A number of erythrocytes below the norm was noticed in 17.4% of the women in the first trimester, 54.4% in the second one, 61.5% in the third one and 64.1% before the childbirth. The hematocrit parameters below the norm were observed in 78.9% of the women in the first trimester, in 34.4% in the second one, in 41.9% in the third one and in 42.4% before the childbirth. The MCV values below the norm were observed in 15.2% of the women in the

first trimester, in 12.0% in the second one, in 17.1% in the third one and in 19.6% before the childbirth. The MCHC parameters during the corresponding observation periods were registered at the below normal level in 4.4%, 2.4%, 0.9% and 1.1% of the women. The MCH level below the norm was in 3.6% in the first trimester and 2.4% in the second one. Anisocytosis (RDW) is diagnosed above the norm in 59.4% of the women in the first trimester, in 64.0% in the second one, in 73.7% in the third one and 76.3% before the childbirth.

The parameters of the red blood of the puerperas are presented in Table 5. The number of erythrocytes below the normal values was observed in 47.9% of the puerperas, the low hemoglobin content in 62.9%, the hematocrit in 84.9%, the MCH in 1.3%, the MCHC in 2.5%, the PLT in 1.3% of the women after the childbirth.

As for the newborns (Table 6), 56.6% had the number of the erythrocytes below the norm, 47.3% had the low content of the hemoglobin, in 65.7% - the hematocrit, in 40.9% - the MCV, 24.2% - the MCH, 95.4% - the MCHC and 4.6% - the PLT.

Thus, in the first trimester the average number of erythrocytes, the content of the hemoglobin and hematocrit corresponded to the norm. From the second trimester until the childbirth time, the above listed indicators decreased. For example, the decrease of the erythrocytes in the first trimester was in 17.4% of the women, in the second one - in 54.4%, in the third one - in 61.5% and before the childbirth - in 64.1%. The corresponding pattern is noted for the hemoglobin and hematocrit. At the same time, the frequency of detection of the anisocytosis in the peripheral blood increased with a rise of the pregnancy period (from the first trimester until the childbirth).

The parameter of the serum iron below the norm was in 21.7% of the women at 34-36 weeks of the pregnancy and in 4.9% in the newborns. The level of the serum ferritin below the norm was diagnosed in 87.4% of the women in the first trimester, in 29.8% in the third one

Table 8  
Content of transferrin in serum at different times of observation

Observation time	n	M	s	m	Min	Max	95% CI	Reference values, ng/mL
34–36 weeks of gestation	118	4,9	1,39	0,22	2,3	7,6	4,5–5,4	3,05
Umbilical blood	118	2,2	0,51	0,08	1,3	3,2	2,0–2,3	1,3–2,75

and in 77.9% of the newborns (Table 7).

The values of the serum transferrin were higher than the reference ones in 66.7% of the pregnant women in the third trimester (Table 8).

Thus, the latent iron deficiency (according to the ferritin level) was detected in 87.4% of the women in the first trimester, in 29.8% in the third one of the pregnancy and in 77.9% of the newborns in the early postnatal period, which indicates the very high frequency of the iron deficiency states of the mother and child in the Republic of Sakha (Yakutia).

### Conclusion

The decrease of the red blood parameters prognostically adversely affects the course of pregnancy, childbirth, the condition of the fetus and newborn. It is found that 47.3% of the newborns in the early postnatal period have the iron deficiency (according to the hemoglobin level). The latent iron deficiency (according to the serum ferritin level) was diagnosed in 87.4% of the women in the first trimester, in 29.8% in the third one of the pregnancy and in 77.9% of the newborns in the early postnatal period. The conducted canonical correlation analysis shows the interrelation of the parameters of the composition of the peripheral red blood with the provision of the mother's ration with the proteins (Canonical R = 0.46,  $\chi^2 = 32.29$ , p < 0.04), mineral substances (iron, sodium, potassium, calcium, magnesium and phosphorus) (Canonical R = 0.45,  $\chi^2 = 35.63$ , p < 0.05). The strongest contribution to the correlation coefficient is made from the composition of the peripheral red blood - the Ht in the I and II trimesters, and from the micronutrients in order of importance it is made by potassium (R = 0.68, p < 0.05), iron (R = 0.38, p < 0.05), phosphorus (R = 0.32, p < 0.05), calcium (R = 0.27, p < 0.05) and sodium (R = 0.23, p < 0.05). The contribution of magnesium (R = 0.03, p < 0.05) to the correlation coefficient with Ht turned out to be less than the ones of all indicated microelements. The conducted canonical correlation



analysis revealed the relation close to the statistically significant one between the hemoglobin (HGB) in the puerperas and newborn children and the energy value of the ration of the pregnant woman, the group B vitamins (B<sub>1</sub>, B<sub>2</sub>) (Canonical R = 0.87,  $\chi^2 = 37.92$ ,  $p < 0.09$ ). The significant positive relation between the HGB (R = 0.60,  $p < 0.05$ ) and the energy value of the ration (R = 0.56,  $p < 0.05$ ) and vitamins B<sub>2</sub> (R = 0.68,  $p < 0.05$ ) and B<sub>1</sub> (R = 0.35,  $p < 0.05$ ). So, it is determined the statistically significant canonical correlation of the MCHC in the first and second trimesters with the proteins, the Ht in the first and second ones with the minerals (iron, sodium, potassium, calcium, magnesium and phosphorus), the HGB of the puerpera and newborn with the energy value of the ration of the pregnant woman and group B vitamins. The results of the conducted logistic regression analysis allow determining that the state of the newborn is most closely related to the provision of the mother's ration with the beta-carotene (B=1.015,  $p < 0.05$ ), the hemoglobin level of the woman in the first trimester (B=-0.573,  $p < 0.018$ ) and before the childbirth (B=0.423,  $p < 0.014$ ).

Thus, knowledge of the statistically significant relations of the nutrition parameters of the pregnant woman with disorders of the pregnancy period, complications of the childbirth and fetal pathologies and the health of the newborn is recommended for the correction of the ration of the mother and child nutrition in order to prevent the IDS and IDA.

*The author of the article confirmed the absence of a conflict of interests, which must be reported.*

Lebedeva Ulyana Mikhailovna, ORCID <https://orcid.org/0000-0002-8990-3876>

*The article is written within the framework of the State task of the Ministry of Education and Science of the Russian*

*Federation, a state registration number is 17.6344.2017/BCh and an RFBR grant for the implementation of the scientific project No. 17-21-08001-OGN*

## References

1. Zakharova I.N. Korovina N.A. Malova N.E. Sovremennye aspekty diagnostiki i lecheniya zhelezodefitsitnykh sostoyaniy u detej [Modern aspects of diagnostics and treatment of iron deficiency states in children]. Voprosy sovremennoj pediatrii [Current Pediatrics]. 2002, Vol. 1, No. 1, pp. 60–62.
2. Korovina N.A. Zaplatnikov A.L. Zakharova I.N. Zhelezodefitsitnye anemii u detej. Rukovodstvo dlya vrachej [Iron deficiency anemias in children. Handbook for doctors]. Moscow, 2001, 64 p.
3. Khotimchenko S.A. Alekseeva I.A. Baturin A.K. Rasprostranennost' i profilaktika defitsita zheleza u detej i beremennykh zhenshchin: vliyanie pishchevogo faktora [Prevalence and prophylaxis of iron deficiency in children and pregnant women: effect of food factor]. Rossijskij pediatricheskij zhurnal [Russian Pediatric Journal]. 1999, Vol. 1, pp. 21–29.
4. Shekhtman M.M. Zhelezodefitsitnaya anemiya i beremennost' [Iron deficiency anemia and pregnancy]. Ginekologiya [Gynecology]. 2000, 2: 6, pp. 164–171.
5. Bailey R.L., West K.P. Jr., Blac R.E. The Epidemiology of Global Micronutrient Deficiencies // Ann. Nutr. Metab. 2015. Vol. 66 (suppl 2). Pp. 22–33.
6. Benoist B., McLean E., Egli I. et al. Worldwide Prevalence of Anaemia 1993–2005. Geneva, Switzerland: World Health Organization, 2008.
7. Kassebaum N.J., Jasrasaria R., Naghavi M., Wulf S.K., Johns N., Lozano R., Regan M., Weatherall D., Chou D.P., Eisele T.P., Flaxman S.R., Pullan R.L., Brooker S.J., Murray C.J. A systematic analysis of global anemia burden from

1990 to 2010 // Blood. 2014. Vol. 123 (5). Pp. 615–624.

8. McLean E., Cogswell M., Egli I., Wojdyla D., de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005 // Public Health Nutr. 2009. Vol. 12. Pp. 444–454.

9. United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition and International Food Policy Research Institute. Fourth Report of the World Nutrition Situation. Geneva, Switzerland: United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition; 2000.

10. Sherry B., Mei Z., Yip R. Continuation of the decline in prevalence of anemia in low-income infants and children in five states // Pediatrics. 2001; 107 (4).

## The author

Lebedeva Ulyana Mikhailovna, Candidate of Medical Sciences, Head of the Center of Nutrition of the Scientific Research Institute of Health of the M.K. Ammosov North-Eastern Federal University, Chief Dietitian of the Ministry of Health of the Republic of Sakha (Yakutia) and the Ministry of Health of the Russian Federation in the Far East Federal District, Chairman of the Yakut Regional Branch of the All-Russian Public Organization "Russian Association of Dietitians, Nutritologists and Food Industry Specialists".

## For correspondence

Phone: +79246629041.

Lebedeva Ulyana Mikhailovna.

The Scientific Research Institute of Health of the M.K. Ammosov North-Eastern Federal University.

Address: 28 Yaroslavsky Street, 52, Yakutsk, 677007.



S.I. Sofronova, A.N. Romanova

## ASSESSMENT OF TOTAL CARDIOVASCULAR RISK AMONG INDIGENOUS POPULATION OF YAKUTIA'S ARCTIC ZONE

DOI 10.25789/YMJ.2018.63.26

### ABSTRACT

Data on the high frequency of arterial hypertension in the indigenous population of the Arctic zone of Yakutia, reaching 57.5% in the Anabar region, were obtained. It is established that the 10-year risk of death from cardiovascular complications increases in people with arterial hypertension. The high risk of developing cardiovascular complications dictates the need for further in-depth study of all factors affecting the formation of public health in hard-to-reach areas of Yakutia.

**Keywords:** arterial hypertension, total cardiovascular risk, indigenous population, Yakutia.

Cardiovascular diseases in Yakutia, as well as in general across Russia, hold a leading position in the pattern of population mortality causes (45,4%). According to Goskomstat data, from 2013 to 2015 the circulatory diseases rate of all population remains on the same level, and the mortality decreased slightly (by 0,9%) [1]. In spite of the fact there is a declining trend of the mortality rate of circulatory diseases (403,7 in 2013, 406,5 in 2014, 386,7 in 2015 on 100 thousand people of the population), the mortality from coronary artery diseases tends to increase (152,3 in 2013, 162,7 in 2014, 167,5 in 2015 on 100 thousand people of the population), including a myocardial infarction (23,6; 23,2; 37,7 respectively).

Nowadays, there are more than 200 risk factors of atherosclerosis development and progression. For complex accounting of their influence and possible interactions, the strategy of assessment of total cardiovascular risk was widely adopted. In clinical practice, the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE) are used the most frequently. The scale of Systematic Coronary Risk Evaluation (SCORE) is developed for fatal cardiovascular disease risk assessment within 10 years. Data of the cohort studies are served like a basis for a scale in 12 countries in Europe (including Russia), with the total number of 205,178 people [2, 3].

**Research objective:** to assess total cardiovascular risk among indigenous population of Yakutia's Arctic zone.

### Materials and methods of the research

In the furtherance of the goal, an expedition to the remote districts of the Arctic zone of the Republic (Tomponsky, Nizhnekolymsky, Srednekolymsky, Verkhnekolymsky, and Anabarsky) was organized. Screening of adult population

with participation of the cardiologist, neurologist, endocrinologist, primary care physician, gastroenterologist, ultrasonographer, endoscopist is carried out. In total, 686 people aged from 20 up to 70 years are examined. From among the examined persons 529 people – representatives of indigenous people of Yakutia (Yakuts, Yukaghirs, Evens, Evenks, Dolgans, Chukchi) were selected (Table). Conditionally, these districts were divided into three zones: Tomponsky District (Tompo), Kolyma group of uluses (Kolyma), and Anabarsky District (Anabar). The selection was formed according to the lists of workers which are in administration of the settlements. The response made 76%. Average age of the respondents was 45,59±0,55 years.

Inclusion criteria: representatives of indigenous people of Yakutia (Yakuts, Dolgans, Evens, Evenks, Chukchi, Yukaghirs).

Exclusion criteria: representatives of non-indigenous nationality.

The research took place according to the YSC Ethical Committee Protocol of the informed consent of the respondent to processing of personal data and the research.

Arterial hypertension is present if blood pressure is at 140/90 mmHg (according to the Society of cardiology of Russian Federation Committee of experts, 2004, 2009).

The program of the research includes the following sections: the questionnaire

poll for assessment of an objective state; the informed consent of a respondent to carrying out researches, blood donation; anthropometric examination with measurement of body height and body weight; blood sampling from basilic vein in the morning on an empty stomach with 12-hour continence from nutrition.

Laboratory methods of the research included blood lipids test (TC, TG, HDL Cholesterol, LDL Cholesterol), glucose test.

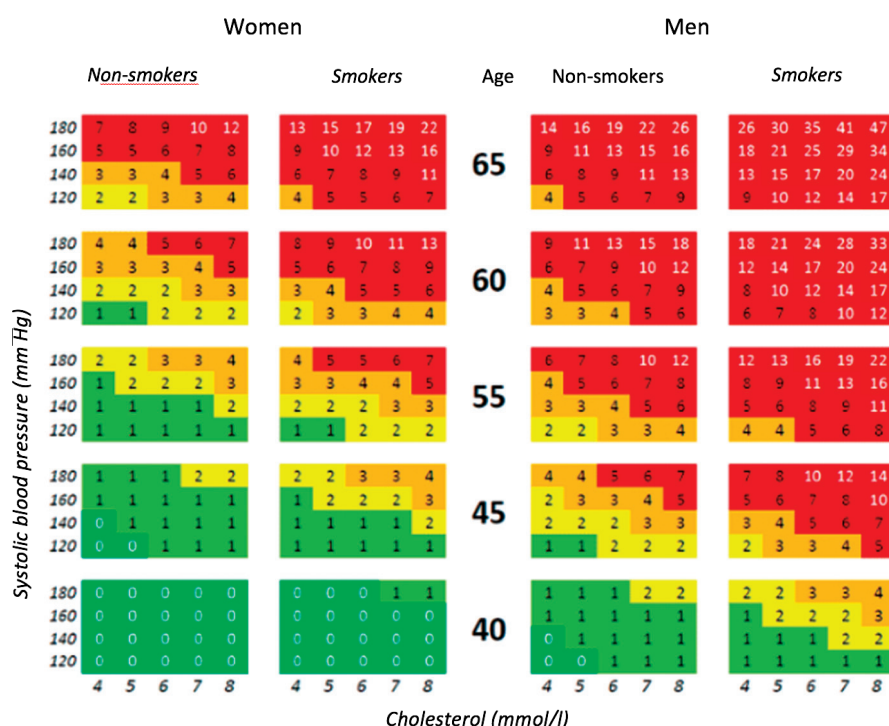
In the poll about smoking, smokers are considered persons who are smoking, at least, one cigarette per day within the last 12 months (Neaton J.D., 1992).

The technique of determination of total cardiovascular risk by SCORE is given in Figure 1. That part of the scale, which corresponds to a gender, age, and the status of smoking of the respondent is chosen. Further, the ABP (mm Hg.) and TC (mmol/l) systolic is considered. The number in the found cell shows the 10-year total cardiovascular mortality risk of the respondent. Level of total cardiovascular risk on the scale of SCORE is considered: less than 1% - low, from >1 up to 5% - average or moderately raised, from >5% up to 10% - high, >10% - very high.

Statistical data processing was carried out by means of standard methods of mathematical statistics, using the software package of SPSS (version 17.0). Data are submitted as  $M \pm m$  where  $M$  – average value of the sign size, and  $m$  – an average error of the sign size. Intergruop

General characteristics of the indigenous population of Yakutia's Arctic zone by ethnicity

	Yakuts	Dolgans	Evens	Evenks	Yukaghirs	Chukchi
Total	119	85	141	67	77	40
Men (%)	30 (25,2)	26 (30,6)	51 (36,2)	13 (19,4)	34 (44,2)	20 (50)
Women (%)	89 (74,8)	59 (69,4)	90 (63,8)	54 (80,6)	43 (55,8)	20 (50)
Average age	48,94±0,99	44,93±1,56	43,02±0,98	48,37±1,64	46,49±1,54	39,73±1,93



**Fig.1** Scale of fatal cardiovascular disease risk assessment within 10 years SCORE (%).

differences were estimated by means of the variance analysis or nonparametric criteria. The differences were considered as statistically significant at  $p < 0,05$ .

### Results and discussion

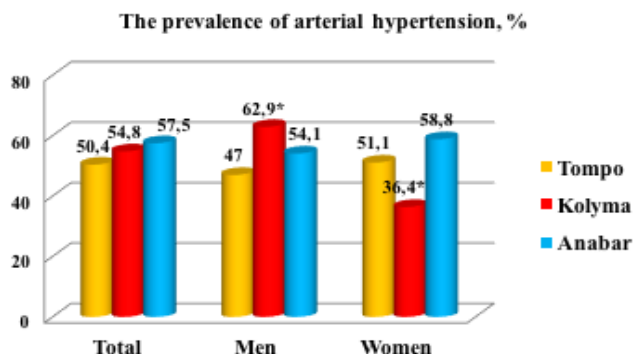
By the results of complex medical examination among more than a half of the population in the explored districts, there is a high prevalence of arterial hypertension from 50,4% in the Tomponsky District up to 57,5% in Anabar (Fig. 2). Arterial hypertension occurs in men of the Kolyma group often than in women (62,9% versus 36,4%). In other districts, hypertension occurs more often in women (difference

statistically insignificant). Generally, essential hypertension stage II was registered. Perhaps, so high frequency of arterial hypertension is caused by low medical literacy of the population, monotherapy priority of antihypertensive drugs, lack of the effective combined antihypertensive drugs of the last generation.

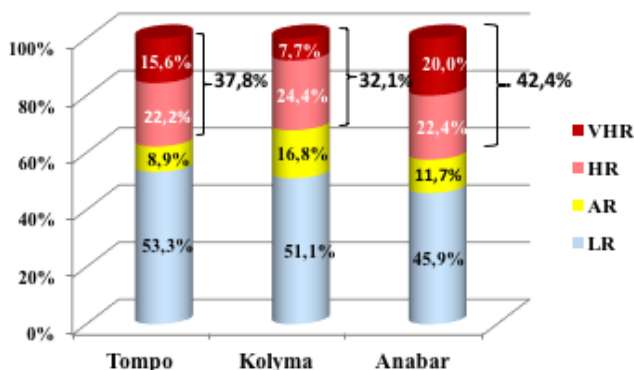
We carried out the assessment of the 10-year mortality risk from cardiovascular complications using SCORE scale in the overall population and the persons with arterial hypertension. For determination of risk from among the respondents, persons aged from 40 up to 65 years were selected: from the Tomponsky District ( $n=89$ ) of the Kolyma group of uluses ( $n=139$ ), the Anabarsky District ( $n=205$ ). Frequency of high and very high mortality risk from cardiovascular complications in the next 10 years ( $>5\%$ ) in the overall population was from 32,1 to 42,4% (Fig. 3). Total mortality risk increases in the persons with arterial hypertension: 54,9% in the Tomponsky District, 45,5% in the Kolyma group, 58,1% in the Anabarsky District (Fig. 4).

### Conclusion

Thus, we obtained data of the high frequency of arterial hypertension among indigenous people of the Arctic zone of Yakutia. Sometimes, arterial hypertension is hardly corrected by antihypertensive drugs monotherapy. It is established that with arterial hypertension is one of the reason for increasing the 10-year mortality risk from cardiovascular complications. Transport remoteness, change of traditional tenor of life, a dreary carbohydrates and fats nutrition, high cost of products of plant-based food, and also the lack of the modern, effective, combined hypotensive drugs lead to the steady increase of the incidence of circulatory diseases, resulting in such terrible complications

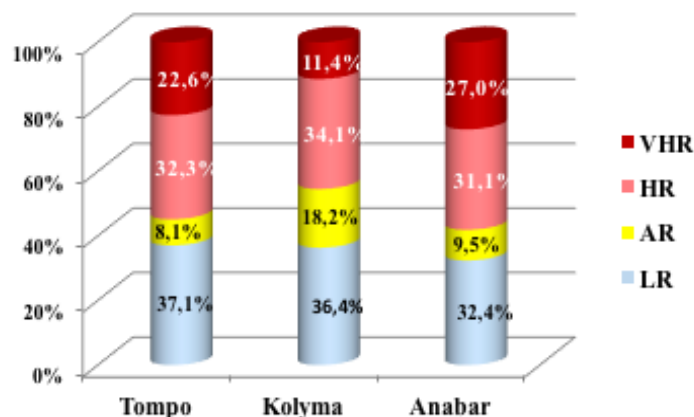


**Fig.2** The prevalence of arterial hypertension in the adult population of Yakutia's Arctic zone.



**Fig.3** Assessment of the mortality risk from cardiovascular complications in the next 10 years on scale SCORE in the overall population.

Here and below: LR – low risk, AR – average risk, HR-high risk, VHR- very high risk.



**Fig.4** Assessment of the mortality risk from cardiovascular complications in the next 10 years on scale SCORE in people with arterial hypertension.



as coronary heart disease and a cerebral stroke. The high risk of development of cardiovascular complications dictates need of further profound studying of all factors influencing formation of health of the population in the remote districts of Yakutia.

*The research was carried out within the framework of the research work of the YSC CMP "The contribution of the metabolic syndrome to the development of atherosclerosis of coronary arteries in Yakutia residents" and the research and development of new technologies for the treatment and prognosis of the risk of arterial hypertension and stroke in*

*the Republic of Sakha (Yakutia) "(State Contract No. 1133)).*

#### References

1. Sakha (Yakutia) stat. Zdravoohranenie v Respublike Saha (Yakutiya): Statisticheskij sbornik [Health in the Republic Sakha (Yakutia): statistical collection]. Yakutsk, 2016, 159 p.
2. Conroy R., Pyörälä K., Fitzgerald A. [et al.] Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project // Eur Heart J. 2003 Jun; 24(11):987-1003.
3. Guy De Backer, Ettore Ambrosioni, Knut Borch-Johnsen [et al.] European guidelines on cardiovascular disease

prevention in clinical practice: Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts) // European Heart Journal, Volume 24, Issue 17, 1 September 2003, Pages 1601–1610.

#### The authors

YSC CMP, Yakutsk, Russia:

1. SOFRONOVA Sargylana Ivanovna - PhD, head of department, sara2208@mail.ru;
2. ROMANOVA Anna Nikolaevna - MD, director, ranik@mail.ru.

## T.K. Sunkharylova, V.V. Dodokhov, N.I. Pavlova, Kh.A. Kurtanov GRAVE'S DISEASE. MODERN REPRESENTATIONS AND DISTRIBUTION IN THE TERRITORY OF THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2018.63.27

#### ABSTRACT

The article presents historical and modern ideas about Graves' disease (GD), new approaches in treatment and diagnostics and the results of studies of foreign and domestic scientists on the role of genetic factors in the development of GD. In the Republic of Sakha (Yakutia), the share of GD in the structure of endocrine pathology ranks 2.3%. The Arctic regions are in the first places by the frequency of occurrence of GD.

**Keywords:** thyroid gland, Graves' disease, thyrotoxicosis, genetic markers, genetic predisposition.

Diffusive-toxic goiter (DTG) is an autoimmune disease with a genetic predisposition. Violations are inherited from parents to children. A persistent pathological increase in the production of thyroid hormones is due to thyroid-stimulating antibodies, which are more active than thyroid hormones, and last longer. In fact, antibodies simulate the action of the natural thyroid hormone, they are able to enhance the synthesis and secretion of thyroid hormones. Antibodies are formed as a result of the development of the body by «incorrect» T-lymphocytes (suppressors), which, instead of controlling the adequacy of the immune response, begin to destroy the thyroid gland.

The first mention of this disease was made in 1722 - the Irish doctor Ives S. and then in 1786, described in more detail the English physician Parry (1786). The most famous description of this disease was made in 1835 by Robert Graves, and in 1840 by the German doctor Karl Bazedov, who described in more detail about 4 cases of the disease and classically classified the so-called «Merzebur tribes», characteristic symptoms of bladder, goiter and tachycardia.

The opinion of researchers about the genetic conditionality of this disease diverge, the authors believe that the days are inherited by the AR type, others by the AD type, and some - by the fact that there is a multi-factor (polygenic) type of inheritance.

Genetic studies show that if one of the monozygotic twins is ill with diffuse toxic goiter, then for another, the risk of getting sick is 60%; In the case of dizygotic pairs, this risk is only 9%.

Outstanding domestic clinician S.P. Botkin (1884) wrote about the role of mental trauma, both on development and the course of DTG. Also, according to the data of the Soviet endocrinologist N.A. Shereshevsky, 80% of patients with this disease had a history of mental trauma. V.G. Baranov and co-authors (1961) established a connection with a trauma in 7.5% of the 480 respondents with this disease. And according to Trotter (1962), etc., the mental trauma has no clear connection with the development of the disease.

Scientists also suggest the relationship between the development of DTG and the provision of the body with zinc. In the studies of D.S. Vinchenko (with co-authors, 2016) showed that in patients

with diffuse-toxic goiter in 70% of cases, the level of zinc in the hair is reduced [12].

Autoimmune diseases of the thyroid gland, including DTG and AIT, are common and affect up to 5% of the population as a whole. Over the past decades, there has been significant progress in understanding the genetic contribution to the etiology of autoimmune thyroid diseases. Several genes of susceptibility to these diseases have been identified and characterized. So the genes of predisposition to DTG, AIT, and genes to both of the above diseases were found.

It is believed that DTG is a disease in which genetic features of immunity are realized against the background of environmental factors such as stress, viral infections, the use of antiviral drugs, excess in the body of iodine.

The first locus of the susceptibility gene to autoimmune thyroid diseases was the locus of the human DR leukocyte antigen (HLA-DR) genome [26].

At present, close cohesion of a number of large histocompatibility complex antigens (DW3, CW4, B8, WHO, B27, A3, AT A28) and DTG has been established. In most cases, the presence

of the alleles HLA-B8 BW-35 in patients with diffuse toxic goiter is described. The link between the disease and antigens of HLA DR3 was also proved. At the same time, the frequency of occurrence of HLA DW3 antigen in people with relapses of thyrotoxicosis is reported [2, 13, 15, 18, 23, 24, 27].

A study of Caucasian patients with DTG showed that the high prevalence of haplotype DRB1 \* 03 DQA1 \* 05 DQB1 \* 02 indicates association with the disease [30].

At studying the distribution of the alleles of the loci HLA-B, C, DRB1, DQA1, and DQB1 among 500 patients and control groups from the UK, it was noted that the strongest link was with HLA \* C, and the next most strongly associated locus was DRB1 [20].

In 2011, Chen et al. published the results of studies of the association of HLA with DTG in the Asian population, in which the authors found that HLA-DPB1 \* 05: 01 was the main gene predisposing to DTG among Han Chinese.

Relatively few studies on HLA-associations with GD were conducted among blacks. And basically the research was done on a limited number of patients, and only in the studies of M.A. Omar (et al., 1990) found an association with variant DRB1 \* 03 [25].

Italian researchers discovered three SNP markers rs13097181, rs763313 and rs6792646 at the 3q locus, which showed little association ( $p < 0.05$ ). There were also significant associations with the thyroid-stimulating hormone receptor gene (TSHR), the cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene and the thyroglobulin (TG) gene [21].

At present, the role of immunological and genetic factors in the development of DTG has been sufficiently studied [7, 5, 1], in recent years, studies in the field of using immunological, genetic and morphological markers in predicting the results of conservative and operative treatment of DTG have become topical [5, 9].

In the course of the research L.V. Trukhina (2006) revealed the most informative risk factors for postoperative relapse of DTG, which include the immunological parameters of AT and RTTG and AT to TPO. She also showed that the polymorphism of genetic markers D6S1271 and D6S2414 (HLA DQ) cannot be used to predict the outcomes of surgical treatment [16].

Diagnosis DTG consists of the study of thyroid hormones, visual-palpatory evaluation and ultrasound. The main complaints of patients are associated with cardiovascular (tachycardia), neurological

disorders and endocrine ophthalmopathy (Graves' ophthalmopathy, autoimmune ophthalmopathy). Upon examination, the thyroid gland is diffusely enlarged, painless, mobile, of moderate density, due to significant blood supply, systolic noise can be heard. In the study of hormones, the concentration of free thyroxine and triiodothyronine is increased, and the production of thyroid-stimulating hormone is reduced. When ultrasound is detected diffuse increase in the thyroid gland, the structure is hypoechoic, a significant increase in blood flow to the tissue. When carrying out scintigraphy with  $^{99m}\text{Tc}$  - diffuse enhancement of the isotope capture by the gland ( $^{131}\text{I}$  and  $^{99m}\text{Tc}$ ). «On the ECG - note the increase in heart rate, observe high pointed teeth P and T, in complicated cases - atrial fibrillation, extrasystole, ST segment depression, negative T wave. In 1/3 of patients, signs of left ventricular functional hypertrophy disappear after elimination thyrotoxicosis» [4].

In 1871 Lister conducted the world's first DTG operation. In Russia, the first surgical intervention on the thyroid gland in DTG was performed by I.D. Sarychev in 1893, Moscow [10]. The resection technique of the thyroid gland, developed by O. Nikolaev (1952) was widespread in the USSR. An effective method of conservative treatment using thyreostatic drugs was proposed by E.V. Astwood (1943).

Currently, there are three main methods of DTG treatment - drug, surgical and radiological. The attitude towards the latter method in different countries is not unambiguous [11]. The main and widespread approach due to the relatively high therapeutic effect is conservative therapy. But therapy with thyreostatics has its drawbacks due to the high risk of recurrence of the disease and the occurrence of complications. In many European countries, in the United States and Canada, the use of artificial radioactive isotope iodine (iodine-131) is becoming increasingly important because it is relatively simple and economical. At the same time, many researchers believe that radioiodine therapy negatively affects the course of endocrine ophthalmopathy (2, 22, 29, 31). In the studies conducted by A.V. Dreval, A.F. Tsyb [et al.] (2007) worsening of the course after was observed in 47.7% of patients. In doing so, they argue that the treatment of ophthalmopathy before the application of radioiodine therapy improves the course of endocrine ophthalmopathy after radioiodine therapy [11].

The use of radioiodine therapy for effective elimination of thyrotoxicosis

is confirmed by Russian and Ukrainian doctors [6, 8]. Studies conducted in 2014-2015 by E.V. Krizhanovskaya and S.A. Nabokov, showed that in the period up to 4 months after therapy only in 6.7% of patients there was thyrotoxicosis, but in the subsequent recurrence of the disease was not revealed, a complication of endocrine ophthalmopathy was noted in one patient [8].

Recently, a number of European countries, as well as in the US, widely used thyroidectomy (complete removal of the thyroid gland) followed by the use of hormone replacement therapy throughout life.

In Russia, unlike in other countries, the treatment of patients with DTC is carried out in a conservative manner, and they are subjected to surgical intervention mainly with relapses of the disease. With relapse of thyrotoxicosis after surgical treatment and conservative therapy, radioiodine therapy is used [28]. In Russia, with surgical treatment of DTG, subtotal resection is used according to O. Nikolaev's technique, leaving 4-6 grams of tissue.

The clinic of the Samarkand State Medical Institute analyzed two methods of surgical intervention for DTG. In the first group of patients after surgery about 8 grams were preserved, and about 2 grams of the thyroid parenchyma was left after the total thyroidectomy in the 2nd group. So relapse of the disease in the first group of operated patients was 11.1%, and in the second group there were no relapses. Thus, the preservation of 2-3 grams of the thyroid parenchyma with total thyroidectomy makes it possible to maintain the hormonal status without the risk of relapse of DTG [17].

In 2012, the results of a study of the use of intravenous ozonotherapy in patients with DTG along with traditional treatment were published, and a comparative analysis showed that the use of infusion ozonotherapy beneficially affects the regression of symptoms and accelerates the rate of occurrence of euthyroidism [14].

In the structure of the endocrine pathology, thyroid diseases are in the second place [19]. In the Russian Federation, the incidence of DTG is about 1%.

It is believed that Yakutia belongs to iodine-deficient regions, on the territory of the republic there are areas with anthropogenic pollution of the biosphere (industrial areas), areas in which underground nuclear explosions were produced with the release of plutonium isotopes into the atmosphere. Also, a huge role in the pollution of the biosphere

was played by the construction of one of the largest reservoirs of Siberia. During the construction of the Viluiskaya HPP, huge areas of the taiga were flooded, the main component of the forest was occupied by coniferous trees, with the decomposition of which a lot of zobogenic microelements are allocated [3].

As of 2017, the number of registered with the diagnosis of DTG was 1274 patients, this is 2.3% of all patients with endocrine pathology (54765 patients).

As can be seen from the table, the greatest number of DTG patients is found in Yakutsk, as well as in industrial areas (Mirninsky, Nyurbinsky, Neryungri), as well as agricultural areas (Table 1). According to V.I. Gagarin (since 2002) this is due to the fact that in this group of regions the only source of drinking water is inaccessible water bodies.

An analysis of the frequency of occurrence of DTG in relation to the average population shows that the highest incidence of DTG is observed in the Arctic (northern) regions of Yakutia: Momsky (0.73), Bulunsky (0.65), Abyisky (0.56) and in the Churapchinsky district (0.50).

### Conclusion

It can be concluded that the development of DTG is the result not only of ecological (environmental) factors, but also genetic ones. According to the State Bank of the Republic Sakha (Yakutia) «Yakut Republican Endocrinology Dispensary» in 2017, the number of patients with diffuse-toxic goiter was 1274 patients, and in 2015 this number was 1298 people, i.e. over the past two years, a significant shift in the number of patients with this disease is not observed. And based on the above data, domestic and foreign researchers, we can say with confidence that the study of genetic factors in the development of diffuse-toxic goiter among residents of the Republic of Sakha (Yakutia) remains relevant.

### References

1. Dedov I.I. Antigeny HLA pri diffuznom toksicheskom zobe [Antigens HLA for Graves' disease] Problemy Endokrinologii [Problems of Endocrinology]. Moscow, 1991, V. 1, pp. 4-5.
2. Balabolkin M.I. Endokrinologiya [Endocrinology] Universum publishing. Moscow: 1998, 416 p.
3. Dreval' A.V. Vliyaniye lecheniya radioaktivnym jodom na techenie endokrinnoj oftal'mopatii [Effect of treatment with radioactive iodine on the course of endocrine ophthalmopathy] Klinicheskaya i eksperimental'naya tireoidologiya [Clinical and experimental in thyroidology]. Moscow, 2007, pp. 33-40.
4. Gagarin V.I., Fedorova M.A., Turkebaeva L.K. Joddefitsitnye zabolevaniya u naseleniya Respubliki Sakha (Yakutiya) [Iodine-deficiency diseases in the population of the Republic of Sakha (Yakutia)] Dal'nevostochnyj medicinskij zhurnal [Far Eastern Medical Journal]. Khabarovsk, 2002, pp. 88-90.
5. Dedov I.I. Mel'nichenko G.A. Endokrinologiya: nacional'noe rukovodstvo. Kratkoe izdanie [Endokrinologiya: nacional'noe rukovodstvo. Kratkoe izdanie]. Moscow, GEOTAR — Media, 2013, 741 p.
6. Sanches M.N. Iz opyta lecheniya tireotoksikoza radioaktivnym jodom [From the experience of treatment of thyrotoxicosis with radioactive iodine] Ukrain's'kij radiologichnij zhurnal [Ukrainian Radiological Journal]. Kiev, 2012, V. 3, pp. 324-326.
7. Kotova G.A. Diffuznyj toksicheskiy zob [Graves' disease] Klinicheskaya Endokrinologiya [Endocrinology]. Sankt-Petersburg: Piter, 2002, pp. 131-150.
8. Krizhanovskaya E.V., Nabokov S.A. Ispol'zovanie fiksirovannoy aktivnosti I-131 500 MBK pri lechenii bol'nykh diffuzno-toksicheskim zobom [The use of fixed activity of I-131 500 MBK in the treatment of patients with diffuse-toxic goiter] Dostizheniya: sb. tezisev VII Vserossiyskogo kongressa endokrinologov. FGBU «Endokrinologicheskij nauchnyy centr» Minzdrava Rossii; Ministerstvo zdoravookhraneniya Rossijskoj Federacii; Obshchestvennaya organizaciya «Rossiyskaya asociaciya endokrinologov» [Achievements: a collection of abstracts of the All-Russian Congress of Endocrinology], 2016, p. 282
9. Latkina N.V., Kuznetsov N.S., Kandror V.I. Prognozirovaniye iskhodov khirurgicheskogo lecheniya diffuznogo toksicheskogo zoba na osnovanii kliniko-immunologicheskikh pokazatelej [Prediction of outcomes of surgical treatment of diffuse toxic goiter based on clinical and immunological indicators] IV Kongress endokrinologov: Tezisy dokladov [IV Congress of Endocrinologists: Abstracts of Reports]. Sankt-Petersburg: Piter, 2001, p. 331
10. Lezhnyov N.V. Zob v Rossii [Goiter in Russia]. Moscow: Tip. M. Borisenko [Printing house M. Borisenko], 1904, p. 34
11. Makarov I.V., Galkin R.A., Andreev M.M. Sovremennyye tendencii i nash opyt lecheniya DTZ [Modern trends and our experience of Graves' disease treatment] Vestnik YUUGU, Chelyabinsk, 2010, V. 4, p. 54-56
12. Vinichenko D.S. O vzaimosvyazi razvitiya diffuzno-toksicheskogo zoba tyazhelej i srednej stepeni tyazhesti s obespechenost'yu organizma cinkom [On the relationship of the development of diffuse-toxic goiter with severe and moderate severity with the provision of the body with zinc] Vrach aspirant [Doctor the post-graduate student]. Voronezh, 2016, V. 3, pp. 71-80.
13. Polozkova N.I. Kliniko-laboratornye, gormonal'nye immunogeneticheskie kriterii vybora metodov lecheniya avtoimunnykh zabolevanij shchitovidnoj zhelezy [Clinical and laboratory, hormonal immunogenetic criteria for the selection of methods for the treatment of autoimmune diseases of the thyroid gland] Diss. ... kand. med. nauk : spec 14.00.03 [The dissertation of the candidate of medical sciences: specialization 14.00.03]. Moscow, 1990, p.136.
14. Logacheva E.G. Rezul'taty primeneniya infuzionnoj ozonoterapii pri diffuzno-toksicheskom zobe [Results of application of infusion ozonotherapy for diffuse-toxic goiter] Zdoravookhraneniye Kyrgyzstana [Health Care in Kyrgyzstan]. 2012, V. 5, pp. 49-50.
15. Semin E.V. Sistema HLA: stroenie, funkci, ochevidnaya i vozmozhnaya svyaz' s avtoimunnymi i

**List of areas of the Republic Sakha (Yakutia) with the highest prevalence of DTG \***

Area	Number of patients	Average annual population	% in relation to the average population
Yakutsk	273	324651	0,08
Mirninsky	133	72914	0,18
Churapchinsky	97	19200	0,50
Nyurbinsky	71	24135	0,29
Bulunsky	55	8404	0,65
Aldan	47	39858	0,12
Neryungri	45	74986	0,06
Tattinsky	44	16358	0,27
Viluysky	39	24719	0,16
Momsky	30	4099	0,73
Abyisky	23	4044	0,56
Ust-May	23	7368	0,31
Total for the RS (Ya)	1274	962 835	0,13

\* for 2017 (according to the State Bank of the Republic of Sakha (Yakutia) «Yakut Republican Endocrinology Dispensary»).



- atopicheskiye zabollevaniyami [HLA system: structure, functions, obvious and possible connection with autoimmune and atopic diseases] Lechebnoe delo [Therapeutics]. Moscow, 2012, pp. 4-9.
19. Trukhina L.V. Immunologicheskie, geneticheskie i morfologicheskie markery prognozirovaniya khirurgicheskogo lecheniya diffuznogo toksicheskogo zoba [Immunological, genetic and morphological markers of forecasting of surgical treatment of diffuse toxic goiter] Diss. ... kand. med. nauk spec. 14.00.03 [The dissertation of the candidate of medical sciences specialization 14.00.03]. Moscow, 2006, p. 141.
  20. Daminov F.A. Khirurgicheskaya taktika lecheniya diffuzno-toksicheskogo zoba [Surgical tactics of treating diffuse-toxic goiter] Akademicheskij zhurnal Zapadnoj Sibiri [Academic Journal of Western Siberia]. Tyumen', 2013, V. 1, pp. 21.
  21. Shabalin V.I. Serova L.D. Klinicheskaya immunogematologiya [Clinical Immunohematology] Medicina [Medicine], 1988, pp. 83-87.
  22. Kuznecov E.V. Endokrinnye zabollevaniya kak mediko-social'naya problema sovremennosti [Endocrine diseases as a medical and social problem of our time] Sovremennyye problemy nauki i obrazovaniya [Modern problems of science and education]. Penza, 2017, Vol. 4.
  23. Simmonds M.J., Howson J.M.M., Heward J.M., Carr-Smith J., et al. A novel and major association of HLA-C in Graves' disease that eclipses the classical HLA-DRB1 effect. Hum. Mol. Genet., 2007, V. 16, pp. 2149-2153.
  24. Lombardi A., Francesca M., Greenberg D. Dissecting the Genetic Susceptibility to Graves' Disease in a Cohort of Patients of Italian Origin. Front Endocrinol., 2016, V. 8
  25. Tallstedt L., Lundell G., Blomgren H., Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment. Eur. J. Endocrinol., 1994, V. 130, pp. 494-497.
  26. Gough S.C. Simmonds M.J. The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action. Curr. Genomics, 2007, V. 8(7), pp. 453-465.
  27. Surg Wld J. Hemithyroidectomy plus contralateral resection or bilateral resection? A prospective randomized study of postoperative complication and long-term results, 1992, V. 16, pp. 765 - 769.
  28. Omar M.A., Hammond M.G., Desai R.K., Motala A.A. et al. HLA class I and II antigens in South African blacks with Graves' disease. Clin. Immunol. Immunopathol., 1990, V. 54, pp. 98-102.
  29. Jacobson E.M. Tomer Y. The genetic basis of thyroid autoimmunity. Thyroid, 2007, V. 17(10), pp. 949-961.
  30. Kisielow P. Boehmer H. Development and selection of T cells: facts and puzzles. Adv Immunol., 1995, V. 58, pp. 87-209.
  31. Wille T., Muller B., Noth D. et al. Long-term follow up after antithyroid drug treatment in Grave's disease. Rundsh. Med. Prax., 2006, V. 95, pp. 1121-1127.
  32. Marcocci C. Bruno Bossio G., Manetti L. The course of Graves' ophthalmopathy is not influenced by near total thyroidectomy. Clin. Endocr., 1999, V. 51, pp. 503-508.
  33. Simmonds M.J. Gough S.C. Unravelling the genetic complexity of autoimmune thyroid disease: HLA, CTLA-4 and beyond. Clin Exp Immunol., 2004, V. 136(1), pp. 1-10.
  34. Wiersinga W.M. Preventing Graves' ophthalmopathy. Engl. J. Med., 1998, V. 338, pp. 121-122.

### The authors

Yakutsk, Russia:

1. Sunhalyrova Tat'yana Konstantinovna - Yakut Science Centre of complex medical problems, junior researcher of the laboratory of hereditary pathology;
2. Dodokhov Vladimir Vladimirovich - PhD, 1) Federal State Educational Institution of Higher Professional Education Yakutsk State Agricultural Academy, Senior Lecturer, 2) Yakut Science Centre of complex medical problems, Researcher of the laboratory of hereditary pathology, dodoxv@mail.ru;
3. Pavlova Nadezhda Ivanovna - PhD, Yakut Science Centre of complex medical problems, Temporary acting chief scientific officer - head of the laboratory of hereditary pathology, solnishko\_84@inbox.ru;
4. Kurtanov Khariton Alekseevich - PhD, Yakut Science Centre of complex medical problems, Chief Scientific Officer - Head of the Department of Molecular Genetics, hariton\_kurtanov@mail.ru.

K.V. Komzin, P.G. Petrova, A.A. Strekalovskaya, S.N. Samsonov, S.S. Parshina, A.A. Andreeva

## SINGLE NUCLEOTIDE POLYMORPHISMS OF ADD1 $\alpha$ , AGT, AGTR1 AND AGTR2 GENES IN DIFFERENT ETHNIC GROUPS OF YAKUTIA ARCTIC ZONE RESIDENTS, SUFFERING FROM ARTERIAL HYPERTENSION

DOI 10.25789/YMJ.2018.63.28

### ABSTRACT

The article presents the results of the study of the frequencies of occurrence of single nucleotide polymorphisms of the genes *ADD1 $\alpha$*  (1378 G> T), *AGT* (704 T> C and 521 C> T), *AGTR1* (1166 A> C) and *AGTR2* (1675 G> A) groups of residents of the Arctic zone of the RS (Ya), suffering from essential arterial hypertension. Subjects of the research were represented by the most widespread ethnic groups in the territory, including the Slavs, Yakuts, Evens and Evenks. To reveal the above mentioned polymorphisms, a real-time PCR method was used with detection of the melting temperature of duplexes. In the course of the study statistically significant differences between the study groups were identified by the points *ADD1 $\alpha$*  1378 G> T; *AGT* 521 C> T and *AGTR1* 1166 A> C.

**Keywords:** arterial hypertension, single nucleotide polymorphisms, *ADD1 $\alpha$* , *AGT*, *AGTR1*, *AGTR2*, real-time PCR, ethnic groups of the Arctic zone.

## Introduction

The Arctic region is unique from many points of view. First, due to geophysical features, the Arctic region is most susceptible to the influence of geomagnetic disturbances, which many authors associate with the development of cardiovascular disorders [1, 2].

This problem is actively studied by the team of authors of this article [10]. In addition, this region has a unique ethnic composition. Now it is known that there are significant differences between people of different ethnic groups, including differences in the course of pathological processes. When studying the pathogenesis of multifactorial diseases, hereditary features are given special attention, because it is the factor that can have significant influence. Primary (essential) hypertension (AH) is a multifactorial disease mainly caused by disturbances in the regulation of arterial blood pressure (BP) at the molecular genetic level. Many researchers attribute these disorders to the presence of point mutations in the genes (single nucleotide substitution) involved in the regulation of blood pressure. If the occurrence of such a mutation exceeds 1% in the studied population, this mutation is called a single nucleotide polymorphism (SNP). In this work, the occurrence of single nucleotide polymorphisms of genes involved in the regulation of BP was studied in various ethnic groups living in the Arctic zone of Yakutia.

Subjects of the research were represented by the most widespread ethnic groups in the territory, including Slavs, Yakuts, Evens and Evenks. Among polymorphisms of genes involved in the regulation of BP, the presence of gene polymorphisms was investigated: *ADD1α* 1378 G> T; *AGT* 704 T> C and 521 C> T; *AGTR1* 1166 A> C; *AGTR2* 1675 G> A.

The role of each of the above polymorphisms in the development of AH and its associated states was examined in the literature. For example, polymorphism of the *ADD1α* gene (1378 G> T), which codes for the α-subunit of the adducin protein, is associated with an increase in sodium reabsorption [6]. In the works of Cusi D. et al. [5] the role of this polymorphism in the development of "salt-sensitive" hypertension was demonstrated. Polymorphisms of the gene encoding angiotensinogen (*AGT* 704 T> C and 521 C> T) are associated with an increase in gene expression and an increase in the plasma level of *AGT* [3, 11, 12]. It is known that angiotensin II interacts with two pharmacologically distinct subtypes of cell surface receptors,

types 1 and 2. Type 1 receptors seem to mediate the cardiovascular effects of angiotensin II [7]. Genotypes *AGTR1* 1166 A> C / C and C/C are associated with a change in the functional activity of the receptor and an increased risk of hypertension [8]. The effects of the receptor for angiotensin II of the second type (*AGTR2*) have not been sufficiently studied to date, but nevertheless, the publications currently available indicate a link between the development of left ventricular myocardial hypertrophy and *AGTR2* polymorphism 1675 G> A [4,9].

## Materials and methods of research

A total of 139 volunteers clinically diagnosed with AH participated in this study. Of these, men - n = 42 (30%), women - n = 97 (70%). The average age of the subjects was 50.3 years. The subjects lived in the area of the Arctic zone of Yakutia (Tiksi township). All subjects were divided according to ethnicity into two groups: indigenous (n = 86) and non-indigenous (n = 53) (Table 1).

The group of indigenous inhabitants of the Arctic zone is represented by aboriginal ethnoses who inhabited these territories before the entry of the above-mentioned territories into the Russian state, namely, the Evens, Evenks and Sakha. In turn, as the non-indigenous residents in this study (non-indigenous ethnic groups of the Arctic Zone (NIEGAZ)) comprised of representatives of ethnic groups who migrated to these territories after the annexation, namely Russians, Byelorussians, and Ukrainians who are united in the Slavic ethnos. Also, the group of non-indigenous included subjects of other ethnic groups, namely Uzbeks, Poles, Chinese, and Kyrgyz.

As the study material, samples of whole venous blood were used, obtained by venipuncture in tubes with EDTA. Reagents of PROBA-RAPID-GENETICS (manufactured by LLC "NPO DNA-Technology", Russia Registration Certificate No. FSS 2010/08695) were used to extract DNA from the samples. Amplification and detection of the polymerase chain reaction products was done on «DT Prime» thermocycler (manufactured by NPO DNA-Technology LLC, Russia Registration Certificate No. FSS 2011/10229), using following reagent kits - A reagent kit for determining genetic polymorphisms associated with risk of development of AH, real-time PCR "CardioGenetics of Hypertension" (manufactured by LLC "NPO DNA-Technology", Russia Registration Certificate No. FF 2010/08414).

The study of all volunteers included

the definition of polymorphisms of seven genes at five points, namely: *ADD1α* 1378 G> T; *AGT* 704 T> C and 521 C> T; *AGTR1* 1166 A> C; *AGTR2* 1675 G> A. Polymorphism was studied in real-time mode, with detection of the melting point of duplexes. The results of the samples which contained the internal control sample, after passing the isolation stage, were considered reliable.

The evaluation of the statistical significance between groups of subjects was carried out using the  $\chi^2$  criterion. For descriptive statistics, the software package SPSS Statistics version 13.0 was used. Differences were considered statistically significant at  $p < 0.05$ .

## Results and discussion

First of all, we conducted a comparative analysis of occurrence frequency of polymorphisms associated with AH in Even and Evenk ethnoses. The results of this analysis are set out in Table 2.

As can be seen from Table 2, there were no statistically significant differences between Evenk's and Even's ethnic groups. This allowed us to unite these groups into one - "Indigenous Minorities of the Arctic Zone of the Republic of Sakha (Yakutia)" (IMAZ). The absence of statistically significant differences between these groups, in our opinion, can be explained by the presence of a genetic relationship between them, and probably by mis-self-identification of the subjects.

Next, we analyzed the correspondence of the revealed frequency distribution of the occurrence of genetic polymorphisms associated with AH to the Hardy-Weinberg rule. The results of this analysis are presented in Table 3.

Due to the fact that not all the investigated distributions are described by the Hardy-Weinberg rule, it was decided to use the general model of inheritance for our analysis.

Next, we conducted a comparative analysis between the groups IMAZ and Yakuts, the results of which are presented in Table 4.

As can be seen from Table 4, statistically significant differences between the

**Table 1**

### Ethnic composition of the subjects

	Indigenous ethnic groups of the Arctic zone			Non-indigenous ethnic groups
n	83			56
%	59,71			40,29
	Yakuts	Evens	Evenks	Slavs and oth.
n	35	24	20	56
%	25,18	17,27	14,39	40,29

groups IMAZ and Sakha were found for polymorphisms of the gene ADD1 $\alpha$  (1378 G> T) ( $p = 0.01$ ) and AGT gene (521 C> T) ( $p = 0,03$ ).

Then, we made a comparison between the groups "NIEGAZ" and "IMAZ". The results of this comparison are given in Table 5.

As can be seen from Table 5, the group "IMAZ" statistically significantly differs from the group "NIEGAZ" in two points. The most pronounced differences are observed between the above groups at the points ADD1 $\alpha$  1378 G> T and AGTR1 1166 A> C.

Next, we compared the "NIEGAZ" group and the Yakuts group. The results of this comparison are presented in Table 6.

Table 6 shows that the groups "NIEGAZ" and "Sakha" statistically significantly differ in two points: ADD1 $\alpha$  1378 G> T; AGTR1 1166 A> C.

Summarizing the results obtained in the course of the study, it can be established that statistically significant differences between the study groups are available for occurrence frequencies of following polymorphisms: ADD1 $\alpha$  1378 G> T; AGT 521 C> T and AGTR1 1166 A> C. For these polymorphisms, we calculated the occurrence frequencies of individual alleles, which are presented in Table 7.

As can be seen from Table 7, the unfavorable allele of the T gene ADD1 $\alpha$  (1378 G> T) is most often found in the "IMAZ" group, 1.58 times less frequently, this allele occurs in the Sakha group and 4.04 times less frequently in the NIEGAZ. The unfavorable allele of the T gene of the AGT gene (521 C> T) is most often found in the NIEGAZ and "Yakut groups, the differences between them are minimal, but in the IMAZ group this allele is found 2.92 times less frequently than in the group NIEGAZ. The unfavorable allele of the AGTR1 gene (1166 A> C) is most often found in the "NIEGAZ" group, in comparison with the "IMAZ" group (about 3.39) and the "Sakha" group (about 4.97).

#### Conclusion

The results obtained in this study indicate that there is a statistically significant difference between the different ethnic

**Table 2**  
Occurrence frequency of genotypes variants of the investigated genes in ethnic groups Evens and Evenks

		Frequency of occurrence		$\chi^2$	p
		Evens (n=28)	Evenks (n=20)		
ADD1 $\alpha$	G/G	3	4	1,06	0,59
	G/T	19	11		
	T/T	6	5		
AGT 704	T/T	4	2	0,64	0,73
	T/C	15	13		
	C/C	9	5		
AGT 521	C/C	27	17	2,34	0,31
	C/T	1	2		
	T/T	0	1		
AGTR1	A/A	24	18	0,20	0,91
	A/C	4	2		
	C/C	0	0		
AGTR2	G/G	6	6	0,74	0,69
	G/A	13	7		
	A/A	9	7		

groups of people living in the Arctic zone of the Sakha Republic (Yakutia) in distribution of the occurrence frequency of genes polymorphism involved in the regulation of blood pressure, namely: ADD1 $\alpha$  1378 G> T; AGT 521 C> T and AGTR1 1166 A> C. There were no statistically significant differences in distribution of occurrence frequency of the polymorphisms AGT 704 T> C and AGTR2 1675 G> A. In our opinion, the revealed differences are due to traditionally and historically formed features of the formation of the studied ethnic groups. At the same time, the revealed peculiarities in the distribution of occurrence frequency of

**Table 5**  
Results of a comparative analysis of the occurrence frequency of the investigated genetic polymorphisms in the groups «IMAZ» and «NIEGAZ»

		Frequency of occurrence (N)		$\chi^2$	p
		IMAZ (n=48)	NIEGAZ (n=56)		
ADD1 $\alpha$	G/G	7	41	39,70	3,0E-9*
	G/T	30	15		
	T/T	11	0		
AGT 704	T/T	6	14	2,65	0,27
	T/C	28	29		
	C/C	14	13		
AGT 521	C/C	44	42	5,03	0,08
	C/T	3	11		
	T/T	1	3		
AGTR1	A/A	42	35	9,07	0,01*
	A/C	6	18		
	C/C	0	3		
AGTR2	G/G	12	23	3,34	0,19
	G/A	20	16		
	A/A	16	17		

**Table 3**  
Results of the analysis of the detected frequency distributions of the observed polymorphisms for compliance with the Hardy-Weinberg rule

	ADD1 $\alpha$	AGT 704	AGT 521	AGTR1	AGTR2
KMHA3 (n=48)					
$\chi^2$	3,21	1,92	6,47	0,21	1,24
p	0,07	0,17	0,01*	0,64	0,27
Sakha (N=35)					
$\chi^2$	0,01	1,32	0,76	0,07	6,78
p	0,93	0,25	0,38	0,79	0,009*
NIEGAZ (N=56)					
$\chi^2$	1,34	0,07	3,15	0,12	9,97
p	0,25	0,79	0,08	0,73	0,002*

In table 3-6 \*  $p \leq 0,05$ .

**Table 4**  
Results of a comparative analysis of occurrence frequency of the investigated genetic polymorphisms in the groups IMAZ and Yakuts

		Frequency of occurrence (N)		$\chi^2$	p
		IMAZ (n=48)	Yakuts (n=35)		
ADD1 $\alpha$	G/G	7	15	8,61	0,01*
	G/T	30	16		
	T/T	11	4		
AGT 704	T/T	6	9	3,47	0,18
	T/C	28	14		
	C/C	14	12		
AGT 521	C/C	44	26	6,76	0,03*
	C/T	3	9		
	T/T	1	0		
AGTR1	A/A	42	32	0,32	0,85
	A/C	6	3		
	C/C	0	0		
AGTR2	G/G	12	8	3,13	0,21
	G/A	20	9		
	A/A	16	18		

**Table 6**  
Results of a comparative analysis of occurrence frequency of investigated genetic polymorphisms in the groups NIEGAZ and Yakuts

		Frequency of occurrence (N)		$\chi^2$	p
		NIEGAZ (n=48)	Sakha (n=56)		
ADD1 $\alpha$	G/G	41	15	11,89	0,003*
	G/T	15	16		
	T/T	0	4		
AGT 704	T/T	14	9	1,60	0,45
	T/C	29	14		
	C/C	13	12		
AGT 521	C/C	42	26	2,24	0,33
	C/T	11	9		
	T/T	3	0		
AGTR1	A/A	35	32	9,51	0,009*
	A/C	18	3		
	C/C	3	0		
AGTR2	G/G	23	8	4,65	0,1
	G/A	16	9		
	A/A	17	18		



polymorphisms of genes involved in the regulation of blood pressure can underlie the clinical features of the course of AH in subjects of different ethnic groups. For example, the high frequency of the polymorphism of the gene encoding the adducin protein (ADD1 $\alpha$  1378 G> T) in the IMAZ and the Yakuts can cause a high level of "salt-sensitive" AH which requires special considerations in treatment. We couldn't find any information on the prevalence of "salt-sensitive" AH in these ethnic groups. Polymorphism of the angiotensinogen gene (AGT 521 C> T), associated with an elevated plasma level of this protein, was three times less frequent in IMAZ and Yakuts than in the others. As for the polymorphisms of the gene coding the receptor for angiotensin type 1 (AGTR1 1166 A> C), the unfavorable allele C is much more frequent (about 4 times) in representatives of non-indigenous ethnic groups. These features, in our opinion, can underlie the inefficiency of some types of antihypertensive therapy in members of this ethnic group.

*The work was partially funded by the Russian Foundation for Basic Research. Project number 18-415-140002 p\_a.*

## References

- Samsonov S.N., Sokolov V.D., Strekalovskaya A.A., P.G. Petrova. O svyazi obostreniya serdechno-sosudistykh zabolevaniy s geofizicheskoy vozmushchennost'yu [On the relationship of exacerbation of cardiovascular diseases with geophysical perturbation] Zhurnal nevrologii i psikiatrii im. S.S. Korsakova. Insul't [Journal of Neurology and Psychiatry n.a. S.S. Korsakov. Stroke]. № 14, Moscow, 2005, p. 18-22.
- Strekalovskaya A.A. Petrova P.G. Samsonov S.N. Sokolov V.D. Ivanov K.I. Geomagnitnye vozmushcheniya i oslozhneniya serdechno-sosudistykh zabolevaniy [Geomagnetic disturbances and complications of cardiovascular diseases] Nauchno-teoreticheskij zhurnal «Uspekhi sovremennogo estestvoznaniya» [Scientific and theoretical journal "Successes of modern natural science"]. Moscow, 2004, p.73-74.
- Cai S.Y. Association of angiotensinogen gene M235T variant with essential hypertension / S.Y. Cai, F. Yu, Y.P. Shi // Zhejiang Da Xue Xue Bao Yi Xue Ban. 2004 Mar; 33(2):151-4. Chinese. PubMed PMID: 15067738.
- Carstens N. Genetic variation in angiotensin II type 2 receptor gene influences extent of left ventricular hypertrophy in hypertrophic cardiomyopathy independent of blood pressure / N. Carstens, L. van der Merwe, M. Revera, M. Heradien, A. Goosen, P.A. Brink, J.C. Moolman-Smook. // J Renin Angiotensin Aldosterone Syst. 2011 Sep;12(3):274-80. doi: 10.1177/1470320310390725. Epub 2010 Dec 16. PubMed PMID: 21163866.
- Cusi D. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension / D. Cusi, C. Barlassina, T. Azzani, G. Casari, L. Citterio, M. Devoto, N. Glorioso, C. Lanzani, P. Manunta, M. Righetti, R. Rivera, P. Stella, C. Troffa, L. Zagato, G. Bianchi. // Lancet. 1997 May 10; 349(9062):1353-7. Erratum in: Lancet 1997 Aug 16;350(9076):524. PubMed PMID: 9149697.
- Mische S.M. Erythrocyte adducin: A calmodulin-regulated actin-bundling protein that stimulates spectrin-actin binding / S.M. Mische, M.S. Mooseker, J.S. Morrow. // J Cell Biol. 1987; 105:2837-45.
- Murphy EA. Genetics in hypertension. A perspective / E.A. Murphy// Circ Res. 1973 May 5; 32: Suppl 1:129-38. Review. PubMed PMID: 4576383.
- Niu W. Association of the angiotensin II type I receptor gene +1166 A>C polymorphism with hypertension risk: evidence from a meta-analysis of 16474 subjects / W. Niu, Y. Qi. // Hypertens Res. 2010 Nov; 33(11):1137-43. doi: 10.1038/hr.2010.156. Epub 2010 Aug 12. PubMed PMID: 20703234.
- Schmieder R.E. Effect of the angiotensin II type 2-receptor gene (+1675 G/A) on left ventricular structure in humans / R.E. Schmieder, J. Erdmann, C. Delles, J. Jacobi, E. Fleck, K. Hilgers, V. Regitz-Zagrosek. // J Am Coll Cardiol. 2001 Jan; 37(1):175-82. PubMed PMID: 11153734.
- Strekalovskaya A. Assessment of the Space Weather Effect on Human Health in the Arctic Zone Using the Example of Tiksi Settlement / A. Strekalovskaya, P. Petrova, K. Komzin, L. Malysheva, S. Samsonov, S. Parshina, A. Andreeva // International Journal of Biomedicine 8(1) (2018) 56-59 [http://dx.doi.org/10.21103/Article8\(1\)\\_OA9](http://dx.doi.org/10.21103/Article8(1)_OA9)
- Ying C.Q. Association of the renin gene polymorphism, three angiotensinogen gene polymorphisms and the haplotypes with essential hypertension in the Mongolian population / C.Q. Ying, Y.H. Wang, Z.L. Wu, M.W. Fang, J. Wang, Y.S. Li, Y.H. Zhang, C.C. Qiu. // Clin Exp Hypertens. 2010; 32(5):293-300. doi: 10.3109/10641960903443517. PubMed PMID: 20662730.
- Yuan J. Angiotensinogen T174M and M235T variants and hypertension in the Hani and Yi minority groups of China / J. Yuan, W. Tang, Y. Chun, H. Ying, Y. Yang, C. Xiao. // Biochem Genet. 2009 Jun; 47(5-6):344-50. doi: 10.1007/s10528-009-9237-3. Epub 2009 Apr 14. PubMed PMID: 19365726.

Table 7

**Occurrence frequency of individual alleles for polymorphisms ADD1 $\alpha$  1378 G> T; AGT 521 C> T and AGTR1 1166 A> C in the study groups.**

		Frequency of occurrence (N)		
		NIEGAZ (n=56)	Yakuts (n=35)	IMAZ (n=48)
ADD1 $\alpha$	G	0,866	0,657	0,458
	T	0,134	0,343	0,542
AGT 521	C	0,848	0,871	0,948
	T	0,152	0,129	0,052
AGTR1	A	0,786	0,957	0,938
	C	0,214	0,043	0,063

## NUTRITION IN THE NORTH

U.M. Lebedeva

## EPIDEMIOLOGY OF NUTRITION AND HEALTH OF CHILDREN AND ADOLESCENTS OF REPUBLIC OF SAKHA (YAKUTIA) BASED ON RESULTS OF MONITORING STUDIES

DOI 10.25789/YMJ.2018.63.29

## ABSTRACT

A Center of Nutrition of a Scientific Research Institute of Health of the M.K. Ammosov North-Eastern Federal University has carried out monitoring epidemiological studies since 2001 on actual nutrition and eating habits among children and adolescents aged 10-18. The study uses a food questionnaire developed by a Federal State Budgetary Institution of Science «Federal Research Center of Nutrition, Biotechnology and Food Safety» (FSBIS «FRC of Nutrition, Biotechnology and Food Safety») and Federal State Budgetary Institution «National Medical Research Center for Preventive Medicine» (FSBI «National Medical Research Center for Preventive Medicine») of the Ministry of Health of Russia, adapted in accordance with peculiarities of culture and traditions of the nutrition of peoples of the North. The food questionnaire includes a section on the study of the eating habits and awareness of respondents about the healthy nutrition. Using a method of frequency analysis of consumption of certain products and daily nutrition reproduction from memory, main parameters of consumption of the particular food products including the Yakut national foods and dishes were studied. Daily rations of 5046 children and adolescents were studied by the method of daily nutrition reproduction and were evaluated in accordance with norms of nutrition (methodological recommendations MR 2.3.1.2432-08 «Norms of Physiological Needs for Energy and Food Substances for Various Groups of Population of Russian Federation»). On average, only 62.2% of examined subjects corresponded to an energy value of the rations, almost everyone had a deficiency of micronutrients (vitamins and minerals).

**Keywords:** children and adolescents, regional features, actual nutrition, eating habits, state of health.

## Introduction

The health of the children and adolescents in any society and in various socio-economic and political situations is the most urgent problem and a matter of priority, as it determines the future state of a nation gene pool, providing scientific and technical development of a country, and it is a sensitive indicator of a change of the demographic situation of the state [1]. A European strategy "Health of children and adolescents" (World Health Organization (WHO), 2005), a Concept of development of health service of Russian Federation till 2020 and a Decade of childhood for 2018-2027, declared by an Executive Order of the President of the Russian Federation [13], consider obligations to protect the health of the younger generation as investments in a major resource of social development. The organization of the rational nutrition of the children and adolescents is one of key factors of maintenance of their health, harmonious development and effectiveness of education [10, 11, 12]. The nutrition, which is adequate in qualitative and quantitative senses, contributes to preservation of the physical and mental health of the younger generation [5]. On the contrary, the physiologically inadequate nutrition during childhood and adolescence can lead to serious disorders of organism vital activity, emergence of diseases of a digestive system, endocrine and musculoskeletal systems [7, 9]. In various regions of the Russian Federation, the nutrition of the children and adolescents has its own character-

istics. According to data of Konovalova O. V. (2012), the basic disorders of a diet of adolescents in the Far North are: non-compliance with a nutrition regime, a failure to comply with the drinking regime, non-observance of optimal proportions between main ingredients of food, an excess of refined foods, simple carbohydrates and animal fats, the deficiency of vegetable oils, unsaturated fatty acids, fiber, B vitamins, the vitamins C, A and E, sulfur containing amino acids, fermented milk products, food antioxidants, the disorders of an amount and proportion of dietary mineral elements (iron, calcium, phosphorus, iodine, chromium, selenium, copper, zinc, etc.) [3, 4, 6, 7].

To ensure an optimal course of metabolic processes, to strengthen immunity, it is required a regular balanced intake of several dozen types of macro- and micronutrients. A variety of the nutrition is necessary in connection with the fact that no product contains a full spectrum of nutrients necessary for the normal vital activity of the child organism [2, 8]. In this regard, the study of the actual nutrition and its impact on the children's health is the most urgent problem of the present time.

**An aim** of this paper is a dynamic assessment of the actual nutrition and eating habits among the children and adolescents of the Republic of Sakha (Yakutia) in connection with their health status.

**Materials and methods of research**

The first epidemiological study on the actual nutrition of children in two cities

(Yakutsk and Neryungri) and 6 districts (Aldan, Verkhoyansk, Vilyuisk, Gorny, Megino-Kangalass and Suntar) of the Republic was conducted in 2001 within the context of implementation of a Plan of Activities of the Concept of State Policy on the Healthy Nutrition of the Population of the Republic of Sakha (Yakutia) for the Period till 2005 (2001). A sample was 1324 children aged 10 to 18 years. The subsequent studies were conducted every 5-6 years, in the same areas with the samples of 1569 and 2153 children, respectively. The questionnaires of the FSBIS "FRC of Nutrition, Biotechnology and Food Safety" and FSBI "National Medical Research Center for Preventive Medicine" of the Ministry of Health of Russia were used in the study. These questionnaires were adapted to the maximum extent by staff of the Center of Nutrition of the Scientific Research Institute of Health of the M.K. Ammosov North-Eastern Federal University in accordance with the traditions and culture of the nutrition of the population of the North and Arctic. The frequency of consumption of 12 Yakut national foods and dishes was separately studied. A calculation of a food set and chemical composition of foods and dishes was carried out at the FSBIS "FRC of Nutrition, Biotechnology and Food Safety". Within the context of the present epidemiological studies, the complex assessment of the actual nutrition and health of adolescents aged 15-18 was conducted in 2012-2013. 130 medical cards of schoolchildren were analyzed, the physical parameters (the

parameters of anthropometry and body composition) were studied using a Japanese apparatus "Tanita". The anthropometric parameters (length, body weight) were studied in accordance with methodological guidelines "Standards of Individual Assessment of Physical Development of Schoolchildren of Republic of Sakha (Yakutia)" (2001). Statistical processing of the factual material was carried out using a package Statistica 7.0.

### Results and discussion of them

The analysis of the state of the actual nutrition discovered some features of the nutrition among the urban and rural children and adolescents.

Thus, in the daily ration, the rural schoolchildren had the meat products 1.5-2 times higher than the recommended norms. Of the varieties of meat, children preferred beef (40-50%), colt meat (38.4-52%), pork was rarely consumed (10-14%). Fish was only present in the daily diet of 22.07%, 19.5%, 12.9% of the children in different years of the study, respectively. As of the milk, in all sex-age groups, frequent use of the milk with a low fat content (0.5-2.5%) was noted. In the different years of the studies they consumed 76.0%, 79.9% and 60.3% of the recommended standards, respectively. Sour milk products (kefir, yogurt, cottage cheese) were consumed on average by half of the children and adolescents surveyed, with preference given to the products of local producers.

In the different years of the study, a majority of the surveyed people (92%, 72.8% and 86%) daily consumed wheat bread, and the rye one only 1.8%, 2.5% and 7.5%, respectively. It should be noted that from year to year the consumption of the rye bread increased, and the wheat bread consumption decreased. A significant drawback in the diet of the urban and rural children and adolescents is absence of vegetables in 84%, 76% and 71% and fresh fruits in 86%, 64% and 82%, respectively. Here it should be noted that the imported fruits and vegetables are mainly sold in the Republic of Sakha (Yakutia).

Such products as pasta, cereals, potatoes, fresh fruits and vegetables were consumed several times a week by 42.7% - 53.6% of the urban and rural children and adolescents surveyed, the dried fruits and nuts rarely or never, chips 43.8% - 62.4%. At the same time, there was discovered the increased consumption of sugar and sweets among the urban children on average by 196% and the rural ones by 154%.

When analyzing the qualitative composition and energy value of the daily rations of the urban and rural surveyed

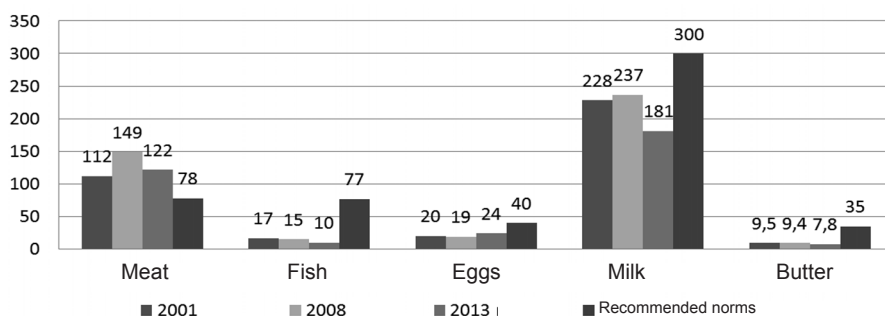


Fig.1. Average daily intake of products containing animal protein.

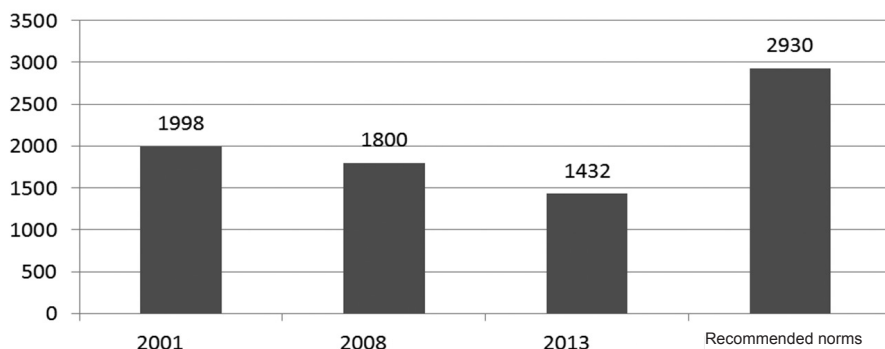


Fig.2. Average daily energy value of diets of children and adolescents of RS (Y).

subjects, the insufficient intake of almost all macronutrients (the proteins, fats and carbohydrates) from the food was discovered. On average, the intake of protein from the ration in the different years of the study amounted to 76%, 58% and 46%, fat 75%, 54% and 52%, carbohydrates 74%, 61.6% and 60.4%, respectively. It is determined that the average volume of fiber intake is much lower than the recommended values. The energy value of the ration of the surveyed subjects corresponded to 71.3%, 64.3% and 51.1% of the recommended food standards.

An energy contribution of the macronutrients is as follows: carbohydrates 52%, 55% and 54%, proteins 15%, 14% and 14%, fats 31%, 31% and 32%. Thus, the inadequate protein contribution to the energy value of the rations in 2008 and 2013 was discovered, the contribution of carbohydrates and fats was slightly higher for the surveyed subjects in the different years of the research (Table 1).

Within the framework of the studies, provision of the rations with the vitamins and minerals (B1, B2, PP, A, C, iron, calcium, magnesium, phosphorus, potassium and sodium) was investigated. The average daily intake of the vitamins among the children and adolescents was as follows: B1 57.1%, 55.7% and 52.8%, B2 43.7%, 56.2% and 56.2%,

PP (niacin) 54.7%, 57.9% and 65.8%, respectively. We also found the insufficient intake of vitamin A (66.0%, 66.0% and 64.3%).

The average daily intake of vitamin C in the dynamics by years corresponds to 48.9%, 83.6% and 48.9% of the recommended values. However, in 2008 due to C vitaminization of third courses, the intake of vitamin C was 2 times higher than in 2001 and 2013. It should be noted that during the study in the rations of children and adolescents in 2008, tea with ascorbic acid was included in accordance with Sanitary Regulations and Standards (SanRaS) requirements for the C- vitaminization of the third courses (Table 2).

A similar situation was noted with respect to the average daily consumption of macro- and microelements for the years of research.

Thus, the average daily consumption of the minerals in the years under study was: iron 80.0%, 86.6% and 64.7%,

Table 1  
Energy contribution of proteins, fats and carbohydrates, %

Macro-nutrients	Recommended values	2001 (n=1324)	2008 (n=1569)	2013 (n=2153)
Proteins	not less than 15	15	14	14
Fats	not more than 30	31	31	32
Carbohydrates	less than 50	52	55	54



Table 2

## Average daily intake of essential vitamins, mg/d

Vitamins, mg	Norms of physiological needs for children and adolescents*	2001 (n=1324)	2008 (n=1569)	2013 (n=2153)
A, $\mu\text{g}$ retinol equivalent	900	594	594	579
B1	1,4	0,8	0,8	0,7
B2	1,6	0,7	0,9	0,9
PP	19,0	10,4	11,0	12,5
C	73,0	35,7	61,0	35,7

\* Norms of physiological needs in energy and nutrients for children and adolescents of the Russian Federation, Methodical recommendations MR 2.3.1.2432—08 (Table 5.4).

calcium 34.7%, 41.5% and 29.7%, magnesium 59.4%, 57.8% and 49.4%, phosphorus 72.7%, 72.3% and 60.2%, potassium 106.0%, 104.7% and 82.4%, respectively, of the recommended norm. As for the sodium consumption, its average daily intake of the surveyed subjects was almost 2.0-2.5 times (244.7, 240.0 and 209.3%) the recommended intake norms (Table 3). The excess sodium intake can be associated with the excess daily average intake of table salt.

During the study, we investigated the eating habits and awareness of healthy nutrition issues. The eating habits were studied with regard to the consumption of the fat, milk and salt. The overwhelming majority of the urban and rural respondents (70-75.5%) noted that in their families the food was cooked using the vegetable oil. 60-66.1% of the respondents use butter for sandwiches, 6.7-10% margarine, 20-27.2% do not use the sandwich butter or margarine.

The study of availability of dairy products (presence in a retail network) with the different fat contents showed that on average up to 70% of the urban children and up to 30% of the rural ones of the total number of the surveyed subjects answered that there was always a choice of milk with the different fat contents in stores. In the different years of the research on the average, half of the respondents answered that there was always the choice of dairy products on shelves of the stores. From 30% to 40% answered that such products were sometimes available, up to 10% answered that such products on the shelves of shops could be rare.

The study of awareness of principles of healthy eating has shown that the children and adolescents have an insufficient level of knowledge in this area. So, with regard to the group of foods that should form a basis of the healthy diet, opinions of the respondents differed from the current recommendations of the World Health Organization (WHO) on the

healthy nutrition. In particular, on average up to 65% of the respondents knew about a benefit of iodized salt, and only up to 46.1% of children rarely consumed it. More than half of the respondents (up to 65.0%) during the years of the studies misused the salt: they added more salt to the food at the table, considering it not salty enough. 50% of the children preferred to consume the milk with the fat content of 3.2%, up to 35.0% of the children chose skim milk and 15% of the children categorically denied the consumption of this product type.

In all cases it was shown that the actual consumption was much lower than the awareness of the children and adolescents of the healthy nutrition (Fig. 3, Fig. 4).

Using the frequency method, the frequency of the consumption of 49 food products was studied including the consumption of the national foods and dishes. It was discovered that about 10% of the schoolchildren had very rarely consumed the national dishes of the peoples of the North (Table 4).

Within the framework of the epidemiological studies during 2012-2013, the comprehensive assessment of the actual nutrition and health of the schoolchildren aged 15-18 was conducted. The medical cards of 130 schoolchildren were analyzed. It was revealed that 53.3% of the children had the eye diseases (myopia, astigmatism, accommodation spasm, retinal angiopathy), 40% had euthyroid goiter, 26.7% had chronic centers of infection (tonsillitis, rhinitis, rhinosinusitis), 16.7% a postural disorder, 13.3% flat feet and 6.7% scoliosis and musculoskeletal system diseases (66.7%), including fractures of bones and spine (30%). These disorders were statistically associated with the poor nutrition, in particular, the eye diseases were associated with the inadequate consumption of the fruits and vegetables, berries, fish and the deficiency of the ration of vitamin B<sub>1</sub> ( $p < 0.05$ ).

Table 3

## Average daily intake of basic minerals, mg/d

Minerals, mg	Norms of physiological needs for children and adolescents*	2001 (n=1324)	2008 (n=1569)	2013 (n=2153)
Fe	15	12	13	9,7
Ca	1200	416	498,5	354,8
Mg	350	208	202,5	172,9
P	1200	872	868	721,9
K	2000	2120,0	2093,5	1647,6
Na	1200	2936,4	2880,5	2511,2

When studying the anthropometric and body composition parameters, actual height of boys and weight of girls did not meet the standard norms (Table 5).

30% of the examined children had the low level of a body mass index. These children were characterized by the low energy value of the ration  $1691.01 \pm 183.4$  ( $p < 0.04$ ), the low protein contribution to the energy value of the ration  $13.4 \pm 0.9$ , the deficiency of calcium  $543.8 \pm 149.5$ , iron  $11.0 \pm 1.9$  ( $p < 0.04$ ), B1  $0.6 \pm 0.04$  ( $p < 0.007$ ), B2  $0.9 \pm 0.2$  ( $p < 0.002$ ), vitamin A  $0.5 \pm 0.2$  ( $p < 0.003$ ), phosphorus  $869.1 \pm 83.2$  ( $p < 0.01$ ), fat  $66.6 \pm 7.8$  ( $p < 0.02$ ) and protein  $53.7 \pm 3.7$  ( $p < 0.05$ ). These children did not eat enough eggs  $35.7 \pm 16.9$  ( $p < 0.002$ ), fruits and berries  $125.5 \pm 83.7$  ( $p < 0.001$ ). They had the low content of calcium in urine  $1.3 \pm 0.2$  ( $p < 0.02$ ), a low percentage of the body fat  $10.5 \pm 1.7$  ( $p < 0.001$ ) and the percentage of water in the body  $65.5 \pm 1.3$  ( $p < 0.002$ ).

### Conclusion

The nutrition of the children and adolescents of the Republic of Sakha (Yakutia) has its regional features, which are characterized by the low energy value of the rations, the presence of the deficiency of basic food components, imbalance of the nutrient composition, as well as insufficient formation of the national traditions and culture of food of northerners among the children. This unsatisfactory nutrition was statistically associated with the prob-

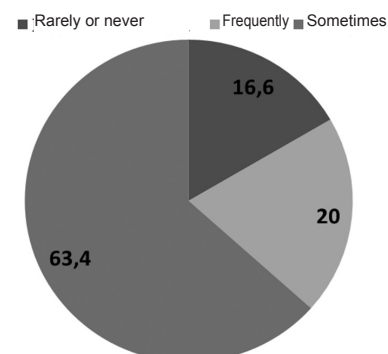


Fig. 3. Frequency of consumption of vitamins and minerals (%).

Frequency of consumption of national dishes

Table 4

National products and dishes	Daily			Several times a week			1-2 times a week			Rarely or never		
	2001	2008	2013	2001	2008	2013	2001	2008	2013	2001	2008	2013
Elk meat	0	0	0	0	0	0	0	6,7	0	100,0	93,3	100,0
Venison	0	3,3	0	0	0	6,6	12,0	10,0	20,0	78,0	86,7	73,4
Salamat	0	0	0	0	3,3	3,3	6,6	6,7	6,6	93,4	90	90,1
Kuorchekh	0	0	0	13,3	13,3	24,6	10,0	13,4	12,7	76,7	73,3	62,7
Hare meat	0	0	0	0	0	3,3	6,6	13,3	0	93,4	86,7	96,7
Suorat	0	0	0	6,6	3,3	6,6	6,6	10	12,6	86,8	86,7	80,8
Byyrapakh	0	0	0	0	0	0	0	3,3	0	100,0	96,7	100,0
Kumys	0	0	0	0	0	0	0	6,7	0	100,0	93,3	100,0
Blood sausage	0	0	0	0	0	3,3	0	10	0	100,0	90	96,7
Offal	0	0	0	0	0	0	0	10	0	100,0	90	100,0
Pancakes	0	0	0	6,6	3,3	12,6	28,5	46,7	32,5	64,9	50	54,9
Waffles	0	0	0	0	0	3,3	0	6,7	3,2	100,0	93,3	93,5

Table 5

Anthropometric parameters and body composition of schoolchildren surveyed

Parameters	Whole sample M ± m	Recommended norms	Boys M ± m	Recommended norms	Girls M ± m	Recommended norms
Height	166,6 ± 1,4	151-170	174,1 ± 2,2	154-170	162,8 ± 1,1	151-163
Weight	55,5 ± 1,4	37,5-67,5	53,6 ± 1,5	37,5-67,5	40,6 ± 13,5	42,9-59,1
BMI	19,9 ± 0,4	18,5-24,9	19,6 ± 0,7	18,5-24,9	20,2 ± 0,5	18,5-24,9
% of body fat	18,3 ± 1,5	13-25	9,5 ± 1,9	13-17	22,6 ± 1,3	18-25
% of water in body	59,8 ± 1,1	65-77	66,2 ± 1,4	65-77	56,6 ± 0,9	65-77

lems of the health state of children and development of the diseases ( $p < 0.05$ ).

The results of the monitoring epidemiological studies conducted in the Republic of Sakha (Yakutia) are the fundamental scientific, methodological and analytical basis for improving the system of the nutrition of the children and adolescents studying in the educational organizations. This basis is an instrument for the development of the scientifically based recommendations, projects, legislative acts and normative legal documents in the area of optimization of the nutrition of the children and adolescents. This is participation of the Republic in a federal program for modernization of the school nutrition, introduction of the National Program "School Milk", the development of the unified automated food monitoring system in the preschool and school educational organizations with the unified regional food rations.

The results of these studies were the basis for preparation of the Executive Order of the President of the Republic of Sakha (Yakutia) of December 25, 2009, No. 1735 "On Compensatory Payments for Food for Students from Low-Income Families of State General Education Institutions of the Republic of Sakha (Yakutia)" and the Executive Order of the Head of the Republic of Sakha (Yakutia) of May 8, 2015 No. 479 "On Additional Compensatory Payments for Food for Students from Low-Income Large Families of State General Education Organizations of the

Republic of Sakha (Yakutia)", the compensation payments are provided for the students of the state and municipal general education organizations. These Executive Orders allowed improving the structure and social support of various categories of the students of the general education institutions in terms of the organization of the healthy nutrition. To improve the organization of the nutrition of the children and adolescents in the organized groups, it is justified to conduct the monitoring epidemiological studies of the actual nutrition and food habits. The fourth studies are conducted in the dynamics in 2018.

*The author of the article confirmed the absence of a conflict of interests, which must be reported.*

Lebedeva Ulyana Mikhailovna, ORCID <https://orcid.org/0000-0002-8990-3876>

*The article is written within the framework of the State task of the Ministry of Education and Science of the Russian Federation, a state registration number is 17.6344.2017/BCh and an RFBR grant for the implementation of the scientific project No. 17-21-08001-OGN.*

## References

- Andreeva E.E. Otsenka organizatsii pitaniya v obrazovatel'nykh uchrezhdeniyakh goroda Moskvy vedomstvennoj podchinennosti departamenta obrazovaniya goroda Moskvy [Evaluation

of organization of nutrition in educational institutions of Moscow of departmental subordination of Department of Education of Moscow]. Zdorov'e naseleniya i sreda obitaniya [Population Health and Life Environment]. Moscow, 2014, No. 9, pp. 14-17.

- Burtseva T.I. Gigienicheskaya otsenka pitaniya shkol'nikov Orenburgskoy oblasti (v ramkakh eksperimental'nogo proekta po organizatsii pitaniya) [Hygienic estimation of nutrition of schoolchildren in Orenburg region (in the context of experimental project of nutrition organization)]. Voprosy sovremennoj pediatrii [Current Pediatrics]. 2008, No. 6 (Vol. 7), pp. 39-43.
- Vasilovsky A.M. Gigienicheskaya otsenka pitaniya shkol'nikov severnykh malykh gorodov Krasnoyarskogo kraya: avtoref. dis. ... kand. med. nauk [Hygienic assessment of schoolchildren nutrition in northern small towns of the Krasnoyarsk Territory: the author's abstract of dissertation ... Candidate of Medical Sciences]. Kemerovo, 2006, 25 p.
- Dedkova L.S. Gigienicheskaya otsenka pitaniya detej ot 11 do 18 let, prozhivayushchikh v internatakh pri obshcheobrazovatel'nykh uchrezhdeniyakh Nenetskogo Avtonomnogo Okruga [Hygienic assessment of the nutrition of children from 11 to 18 years, living in boarding schools in general educational establishments of the Nenets autonomous district]. Sovremennaya meditsina: aktual'nye voprosy [Modern medicine: topical issues]. Novosibirsk, 2015, No. 1, pp. 71-80.
- Dudenko N.V. Krivko N.P. Obespechennost' vitaminami kulinarnoj produktsii obshchestvennogo pitaniya [Provision of vitamins of culinary products of public catering]. Izvestiya VUZov. Pishchevaya tekhnologiya [News of Higher Educational Institutions. Food Technology]. 1990, No. 2-3, pp. 129-130.
- Istomin A.V. Yudina T.V. Gigienicheskaya otsenka i prognoz sostoyaniya fakticheskogo pitaniya ot del'nykh grupp naseleniya Rossii [Hygienic assessment and prediction of the status of actual nutrition of individual population groups in Russia]. Gigiena i sanitariya [Hygiene and Sanitation]. 1996, No. 4, pp. 17-19.
- Konovalova O.V. Klassicheskaya kontseptsiya ratsional'nogo pitaniya podrostkov na Krajnem Severe [Classical concept of rational nutrition of adolescents in Far North]. Sborniki konferentsij NITS Sotsiosfera [Conference proceedings of Science Publishing Centre Sociosphere]. 2012, No. 8, pp. 360-366.
- Martinchik A.N. Maev I.V. Yanushevich O.O. Obshchaya nutritsiologiya: uchebnoe posobie [General nutritiology: study guide]. Moscow: MEDpress-inform, 2005, 392 p.

9. Moshchev A.N. Gigienicheskaya otsenka fakticheskogo pitaniya i sostoyaniya zdorov'ya shkol'nikov i ikh nutritsionnaya korrektsiya (na primere Vasileostrovskogo rajona Sankt-Peterburga): avtoref. ... dis. kand. med. nauk [Hygienic assessment of actual nutrition and health status of schoolchildren and their nutritional correction (on example of Vasileostrovsky district of St. Petersburg): the author's abstract of dissertation ... Candidate of Medical Sciences]. Saint Petersburg, 2009, 21 p.
10. Onishchenko G.G. Aktual'nye voprosy sanitarno-epidemiologicheskoy bezopasnosti pitaniya naseleniya [Actual issues of sanitary and epidemiological safety of nutrition of population]. Zdravookhranenie Rossijskoj Federatsii [Health care of the Russian Federation]. 2005, No. 1, pp. 3-10.
11. Onishchenko G.G. Zadachi i strategiya shkol'nogo pitaniya v sovremennykh usloviyakh [Tasks and strategy of school nutrition in modern conditions]. Voprosy pitaniya [Problems of nutrition]. 2009, Vol. 78, No. 1, pp. 16-21.
12. Pavlov N.N. Kleshchina Yu.V. Eliseev Yu.Yu. Otsenka fakticheskogo pitaniya i pishchevogo statusa sovremennykh detej i podrostkov [Evaluation of actual nutrition and nutritional status of modern children and adolescents]. Kurskij nauchno-prakticheskij vestnik Chelovek i ego zdorov'e [Kursk Scientific and Practical Bulletin Man and His Health]. 2011, No. 1, pp. 128-132.
13. Ukaz Prezidenta Rossijskoj Federatsii ot 29 maya 2017 goda № 240 Ob ob'yavlenii v Rossijskoj Federatsii Desyatiletija detstva [The Executive Order of the President of the Russian Federation of May 29, 2017 No. 240 On Proclaiming a Decade of Childhood in the Russian Federation].

### The author

Lebedeva Ulyana Mikhailovna, Candidate of Medical Sciences, Head of the Center of Nutrition of the Scientific Research Institute of Health of the M.K. Ammosov North-Eastern Federal University, Chief Dietitian of the Ministry of Health of the Republic of Sakha (Yakutia) and the Ministry of Health of the Russian Federation in the Far East Federal District, Chairman of the Yakut Regional Branch of the Russian Association of Dietitians, Nutritionalists and Food Industry Specialists “.

### For correspondence

Phone: +79246629041 [ulev@bk.ru](mailto:ulev@bk.ru)  
 Lebedeva Ulyana Mikhailovna  
 The Scientific Research Institute of Health  
 M.K. Ammosov North-Eastern Federal  
 University  
 Address: 28 Yaroslavsky Street, 52  
 Yakutsk, 677007

## SCIENTIFIC REVIEWS AND LECTURES

N.A. Solovyova, N.I. Pavlova, Kh.A. Kurtanov, M.A. Varlamova

# CYTOKINOVY MECHANISMS OF FORMATION OF BRONCHIAL ASTHMA AND OBESITY

DOI 10.25789/YMJ.2018.63.30

### ABSTRACT

Considering high prevalence of BA incidence and the progressing growth of number of persons with an excess weight of different degree of expressiveness, today the combination BA and obesity is a current problem of practical health care around the world.

The article examines the results of scientific research on the analysis of clinical and laboratory indicators of bronchial asthma (BA) in obese patients. The analysis of literary data concerning pathophysiological mechanisms of influence of excess amount of fatty tissue on character of a course of bronchial asthma is carried out. It has been established that significant volumes of adipose tissue are a source of pro-inflammatory cytokines, aggravating the course of asthma.

Researches have shown that fatty tissue is metabolically highly active and participates not only in deposition of fats and their mobilization, but also in regulation of a number of exchange processes in scales of the whole organism. Researches of biochemical processes in adipocytes (cells of fatty tissue) have shown that their activity isn't limited to influence on metabolic processes. In researches it is revealed that the high level of an expression of a number of regulatory factors (cytokine) which are taking part in formation and maintenance of inflammatory processes in an organism is characteristic of cells of fatty tissue. This fact allows considering obesity as a disease, one of components of which is the condition of the chronic inflammation covering the whole organism in general. In researches it has been shown that in the presence of obesity such signs as are specific to inflammatory process: inclusion of the intracellular alarm ways which are responsible for inflammatory activation of cells; an expression of the superficial membrane structures and receptors participating in intercellular interactions when forming inflammation; development of the cytokine stimulating further development and maintenance of the inflammatory answer; formation of the markers of a sharp phase characterizing prevalence and clinical value of inflammatory process.

Thus, the understanding of the general mechanisms which are the cornerstone of formation of obesity and BA will promote development of new methods of diagnostics and treatment.

**Keywords:** bronchial asthma, obesity, cytokine, systemic inflammation.

Despite achievements of modern medicine, introduction of new medical technologies in daily work of the practicing doctor there are still a lot of questions demanding studying. A current and complex problem is the choice of tactics of treatment of patients with a syntropy of diseases when diseases are interconnected, have joint or close etiological or / and pathogenetic

factors. Relevant and poorly studied are interfering syntropies, at which the disease developed against the background of previous one, makes heavier its course. A striking example of such syntropy is the bronchial asthma (BA) and obesity.

Both pathologies have gained now character of global epidemics in which various age populations in different

geographical zones are involved. About 10% of resources of public health care, according to some information, are spent for treatment of patients with BA and the states associated with it [7]. By rough estimates, its prevalence in the different countries is from 3 to 15% of the population today, and for the last three decades the number of patients with the diagnosis BA has increased in



economically developed states more than three times. At the same time researches show that in the same regions of the world where there is an increase in BA incidence, also the progressing growth of number of persons with an excess weight of different degree of expressiveness is observed.

Today rather large volume of scientific data which confirm existence of a certain interrelation between BA and obesity is saved up. It is shown that existence of obesity is combined with higher frequency of developing of asthma and also with more expressed weight of its course [6]. It has been revealed that it, as a rule, persons of more advanced age, with existence of various accompanying pathology. There are data that the association BA and obesity is more characteristic of female persons. At the same time this problem is present also at pediatric practice, especially because the combined epidemic of asthma and obesity in the developed countries is shown most visually at children's age [8].

The bronchial asthma at children associated with obesity differs from atopic BA and is characterized by Th1-polarization [15]. Influence of obesity at children on manifestations is BA presented in the table [1].

According to results of immunological mechanisms it is established that the expression of receptors of congenital immunity (Toll-like receptors (TLR)) at the children who are ill BA with obesity and normal body weight was characterized by higher TLR2 and TLR9 level in group of corpulent patients. Besides at the same patients decrease in production Th1-cytokine and a tendency to increase in a profile of the Th2-answer were defined [9].

Clinically the most essential and most significant feature of a current BA both among adults, and among children with obesity the smaller efficiency of basic therapy with use of inhalation glucocorticosteroids (I-GCS)

is considered that quite often demands increase in a daily dose of the applied medicines and interferes with the expected decrease in disease severity in the course of treatment [5]. Moreover, on some observations, existence of obesity, depending on degree of its expressiveness, influences the frequency of hospitalization of patients concerning exacerbation of asthma within a year in comparison with the patients with normal body weight at equal severity of a disease, raising it on average twice. At the same time at such patients not only the lowered response to basic therapy of I-GCS, but also a certain tolerance to effect of the bronchodilator medicines which are intensively used during aggravation is noted [10].

Thus, considering the growing indicators of prevalence of asthma and obesity now there was a need of more profound analysis of pathogenetic mechanisms of leaders to development of this pathology.

Today there are no doubts that fatty tissue is metabolically highly active and participates not only in deposition of fats and their mobilization, but also in regulation of a number of exchange processes in scales of the whole organism. The most known example in this regard is participation of fatty tissue in carbohydrate exchange, namely, in formation of resistance to insulin at patients with an excess weight and diabetes of the 2nd type [16, 18].

Researches of biochemical processes in adipocytes have shown that their activity isn't limited to influence on metabolic processes. In G. Hotamisligil researches with coauthors it is revealed that the high level of an expression of a number of regulatory factors (cytokine) which are taking part in formation and maintenance of inflammatory processes in an organism [4] it is characteristic of cells of fatty tissue allows to consider obesity as a disease, one of components of which is the condition of the chronic

inflammation covering all organism in general.

In numerous researches it has been shown that in the presence of obesity such signs as are specific to inflammatory process: inclusion of the intracellular alarm ways which are responsible for inflammatory activation of cells; an expression of the superficial membrane structures and receptors participating in intercellular interactions when forming inflammation; development of the cytokine stimulating further development and maintenance of the inflammatory answer; formation of the markers of a sharp phase characterizing prevalence and clinical value of inflammatory process [12].

Above-mentioned properties are shown in cells of various types, but generally it concerns cells of fatty tissue and immune system [2, 3]. In particular, it has been shown that at obesity in fatty tissue there is an essential proliferation of cells of macrophages. At the same time in her levels of production of such pro-inflammatory cytokine as a tumor necrosis factor alpha (TNF- $\alpha$ ) and one of factors of a chemotaxis of monocytes increase.

It is supposed that in the conditions of obesity structural elements of fatty tissue are in a condition of the accruing hypertrophy and the constant oxidative stress caused, in particular, by toxic influence of intermediate products of metabolism of fatty acids. It leads to activation of intracellular alarm systems in the adipocytes and an expression of the factors stated above which are carrying out chemotaxis macrophages and promoting their migration in fatty tissue. The last, in turn, activate and further strengthen inflammatory processes in all fatty tissue of an organism [14].

Thus, large volumes of fatty tissue become a constant source of significant amounts of the pro-inflammatory cytokines synthesized by both adipocytes, and the macrophages migrating in fatty tissue that

**Features of a phenotype of the childhood BA with obesity**

Characteristics	usual allergic phenotype BA	phenotype of BA with obesity
The beginning of a disease	Early beginning (aged up to 5 years)	Variable beginning
Atopy	Often	Rare
Nature of inflammatory process	High level of eosinophils, increase in fraction of NO <sub>2</sub> in the exhaled air	Mixed, with prevalence of neutrophils, decrease in NO <sub>2</sub> fraction in the exhaled air
Function of lungs	Incidental bronchial obstruction, variable remodeling	Normal indicators of FVCL, variable decrease in the Tiffno index
Severity	Variable	Variable or more expressed symptoms, decline in quality of life
Answer to the test on a bronchoprovocation	Typical for the majority	It can be reduced
Answer to the test on a bronchodilatation	Mainly fast	It is more often lowered
Response to therapy	Resistance to steroids - seldom	Resistance to steroids - often, the good answer on antagonists receptors of leukotriens
Secondary diseases	Allergic rhinitis, eczema, sinusitis, uneasiness, GER	High level of insulin, increase TG-, LDL, GER

Note. FVCL – the forced vital capacity of lungs, TG-triglycerides, LDL – lipoproteids of low density, GER –reflux of gastroesophagitis.

leads to formation and maintenance in an organism of chronic slow inflammatory process. The feature of this inflammation is that it not quite corresponds to the standard pathophysiological idea of this process. For its description special terms, such as meta-inflammation or para-inflammation have been offered. Its characteristic feature can be considered the low intensity which isn't giving direct clinical symptoms, but, at the same time, the expressed system city, that is the impact on a wide range of bodies and fabrics leading to change of their metabolism, violation of their function and parallel activation of reactions of immune system in them.

Pro-inflammatory cytokines, being products of synthesis of the activated macrophages, have, in turn, ability to stimulate activity of other cellular elements of immune system that leads to the subsequent further strengthening of the inflammatory answer. In this regard one of the most important targets of the pro-inflammatory cytokine synthesized by macrophages and adipocytes is T-helper, the regulatory subpopulations of T-lymphocytes exercising control of character, orientation and intensity of the immune answer.

The inflammation generated by the activated macrophages at obesity isn't connected with penetration into an organism of the alien agent and, therefore, has no specific anti-gene focus and isn't connected with synthesis of specific antibodies. However, one of the cytokine produced by the activated macrophages in fatty tissue, namely SILT-6 has ability to stimulate reactions, controllable T-helper the Th-2 [11] type, thereby influencing pathogenesis of bronchial asthma as the initiator of the chronic inflammation and a factor switching the regulatory T-helper profile in the direction of reactions like Th-2, i.e. the humoral immune answer that leads to disproportionately high synthesis of immunoglobulins of a class E (IgE) - one of the leading factors of development of atopic bronchial asthma.

TNF-  $\alpha$  which level is considerably increased at obesity also plays a role in separate links of pathogenesis of bronchial asthma, strengthening the inflammatory phenomenon in a wall of bronchial tubes. This pro-inflammatory cytokine participates as in development of an acute inflammation due to stimulation of a chemotaxis of neutrophils in the inflammation center, and in synchronization of process due to activation of platelets and induction of synthesis (NO<sub>2</sub>) [13] nitrogen oxide.

Interesting was a fact that the level of the interleukin-10 suppressing production above the listed pro-inflammatory

cytokine of SILT-6 and FNO-  $\alpha$  at obesity is considerably reduced that can be also considered as one of the factors increasing extent of inflammatory reaction in an organism and contributing to heavier course of asthma at corpulent persons [17].

Thus, as show results of researches, both asthma, and obesity represent the diseases forming steady inflammatory process in an organism. In the first case more local, concentrated mainly in walls of airways, in the second case — much more widespread, influencing many bodies and systems. The combination and mutual strengthening of these factors lead to a change in severity of a clinical course of asthma and difficulty of control of a disease. From the practical point of view, the data on interrelation of bronchial asthma and obesity which are available today demand development of new schemes of diagnostics and treatment of these conditions.

## References

1. Astafyeva N.G. Gamova I.V. Udovichenko E.N. [et al.] Fenotip bronhialnoy astmy i s ozhireniem: klinicheskie osobennosti, diagnostika, lechenie [Phenotype of bronchial asthma with obesity: clinical features, diagnosis, treatment] *Astma i allergiya* [Asthma and allergy]. Moscow, 2015, №1, P.3-8.
2. A central role for JNK in obesity and insulin resistance / J. Hirosumi, G.Tuncman, L. Chang [et al.] // *Nature*. - 2002. Vol. 420 - P. 333-336.
3. Adipsin and complement factor D activity: an immune-related defect in obesity. / B. Rosen, K.Cook, J. Yaglom [et al.] // *Science*. - 1989. - Vol. 244 - P. 1483-1487.
4. Adipose tissue expression of tumor necrosis factor- $\alpha$ : direct role in obesity-linked insulin resistance / G.Hotamisligil, S.Shargill, B.Spiegelman [et al.] // *Science*. - 1993. - Vol.259 - P. 87-90.
5. Are overweight asthmatics more difficult to control / P. Saint-Pierre, A. Bourdin, P. Chanez [et al.] // *Allergy*. - 2006 - Vol.61 - P. 79-84.
6. Beuther D. Overweight, obesity and incident asthma: a meta-analysis of prospective epidemiologic studies / D.Beuther, E.Sutherland // *Am. J. Resp. Crit. Care Med.* - 2007 - Vol. 175 - P. 661-667.
7. Burden of comorbidity in individuals with asthma / A. Gershon, C.Wang, J.Guan [et al.] // *Thorax*. - 2010-Vol. 65- P. 612-618.
8. Childhood Overweight and Obesity and Their Association with Asthma/ C. Kier, S.Forde, S. Hom [et al.] // *Journal of Asthma & Allergy Educators*. - 2010; October, 27.
9. Cox L. Sublingual immunotherapy for aeroallergens: status in the United States / L.Cox // *Allergy Asthma Proc.* - 2014. - V. 35. - P. 34.
10. Impact of Obesity on the Severity and Therapeutic Responsiveness of Acute Episodes of Asthma / K.Yeh, M. Skowronski, A.Coreno [et al.] // *J. Asthma*. - 2011. - Vol. 48(6). - P. 546-52.
11. Interleukin-6 promotes the production of interleukin-4 and interleukin-5 by interleukin-2-dependent and -independent mechanisms in freshly isolated human T cells / I.Heijink, E.Vellenga, P. Borger [et al.] // *Immunology*. - 2002 - Vol. 107 - P. 316-324.
12. Hotamisligil G. Inflammation and Metabolic Disorders / G. Hotamisligil // *Nature*. - 2006 - Vol. 444 (7121) - P. 860-867.
13. JNK and tumor necrosis factor- $\alpha$  mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes / M.Nguyen, H.Satoh, S. Favelyukis [et al.] // *Journal of Biological Chemistry*. - 2005 - Vol. 280 (42) - P. 35361-35371.
14. Lang J. Obesity, Nutrition, and Asthma in Children / J.Lang // *Pediatr. Allergy Immunol.Pulmonol* - 2012. - V. 25. - P. 64.
15. Obesity-associated asthma in children: a distinct entity / Rastogi D., Canfield S., Andrade A. [et al.] // *Chest*. - 2012. - V. 141. - P. 895.
16. Protection from obesity-induced insulin resistance in mice lacking TNF- $\alpha$  function. / K. Uysal, S. Wiesbrock, M. Marino [et al.] // *Nature*. - 1997. - Vol. 389 - P. 610-614.
17. Pretolani M. Cytokines involved in the down-regulation of allergic airway inflammation / M. Pretolani, M. Goldman // *Res. Immunol.* - 1997 - Vol. 148 - P. 33-38.
18. Wellen K. Inflammation, stress and diabetes / K.Wellen, G.Hotamisligil // *J. Clin Invest.* - 2005 - Vol.115 (5) - P. 1111-1119.

## The authors

1. Solovyova Natalya Alekseevna - candidate of medical sciences, senior research associate of laboratory of population genetics of department of molecular genetics of YSC CMP, contacts: sonata608@yandex.ru, 8-924- 171-34-89, 677010, Yakutsk, Sergelyakhskoye Highway 4, FGBNU "The Yakut scientific center of complex medical problems";
2. Pavlova Nadezhda Ivanovna - candidate of biology sciences, the leading researcher - the head of laboratory of hereditary pathology of department of molecular genetics of YSC CMP;
3. Kurtanov Khariton Alekseyevich - candidate of medical sciences, the chief researcher - head of department of molecular genetics of YSC CMP;
4. Varlamova Marina Alekseevna - research associate of laboratory of hereditary pathology of department of molecular genetics of YSC CMP.

A.E. Yakovleva, N.R. Maksimova

## MULTIPLE EXOSTOSIS HONDRODYSPLASIA: MOLECULAR-GENETIC CAUSES

DOI 10.25789/YMJ.2018.63.31

### ABSTRACT

Multiple hereditary exostosis (OMIM 133700, OMIM 133701) is a genetically heterogeneous disease manifested by generalized forms of skeletal lesion with numerous progressive deformities of bones and joints. The type of inheritance is autosomal dominant with a high incidence of familial cases. The authors made a review of domestic and foreign literature on the molecular and genetic causes of multiple hereditary exostosis. The main molecular genetic causes of multiple hereditary exostosis are mutations in the genes of exostozin 1 (*EXT1*) (OMIM 608177) and exostozin 2 (*EXT2*) (OMIM 608210).

The study of *EXT* genes, their mutations and the causes of malignant transformation is both a fundamental problem that contributes to understanding the patterns of pathogenesis, and a socially significant task of diagnosing, preventing and predicting this disease

**Keywords:** multiple hereditary exostosis, multiple osteochondroma, exostozin, mutation, *EXT1*, *EXT2*.

Multiple hereditary exostosis (MHE) or multiple osteochondroma (MO) (OMIM 133700, OMIM 133701) is a genetically heterogeneous disease manifested by generalized forms of skeletal lesion with numerous progressive deformations of bones and joints [14, 32].

MHE belongs to the number of common hereditary diseases. According to a number of researchers, the disease occurs mainly among Caucasoid populations. The incidence of the disease in different Caucasoid populations ranges from 1.3 to 2 per 100.000 population or 1 to 7.000 orthopedic patients. High levels of MHE prevalence were found in the populations of the indigenous residents of Guam and Pongassi Indians (Table 1). The incidence of the disease among the Asian population has not yet been identified [42].

Multiple osteochondroma is an autosomal dominant inherited disease with a very large proportion of family cases [11]. Multiple osteochondromas are initially diagnosed before 4 years of age and are represented by generalized forms of skeletal lesion with numerous progressive deformations of bones and joints, shortening and secondary changes in bone-muscular system. By the age of 18-20, the growth of MHE ceases [1, 9, 22, 28]. Osteochondromas (tumors of bone tissue with cartilage) are today the most common among all primary benign bone tumors (50%). In 15% of cases, these tumors arise in the context of a hereditary syndrome called multiple osteochondroplasia (MO), an autosomal dominant skeletal disorder characterized by the formation of multiple bone tumors with cartilage in children's metaphyses. MO is caused by various mutations in *EXT1* or *EXT2*, as a result of which large genomic deletions (single or multiexon) are responsible for up to 8% of MO cases [15, 45].

Beighton et al. (1993) analyzed the skeletons of adults in the Museum of

Pathological Anatomy in Vienna. The museum was founded in 1796 by Emperor Franz II, and now it is in Narrenturm, which was previously the object of detention of persons with insanity. The museum contains 44.000 museum exhibits. Beighton et al. (1993) described the skeleton of a man with multiple exostoses, who died in 1842 from a rupture of an aortic aneurysm (probably syphilitic origin) [20].

Krooth et al. (1961) in his article reports that the first descriptions of the disease were made by Stocks and Barrington (1925), who summarized the clinical description of 1189 cases from literature from around the world and conducted a study of 21 patient from 6 large families with diaphyseal aclasis (multiple exostoses). Patients were from the Chamorro tribe, Micronesians, who live in the Mariana Islands. The frequency of diaphyseal aclasis in the Chamorros, Guam was estimated at 1 in 1000. Among 21 cases from Guam, tumors were found on examination in all men, in women only in half of them [18, 27, 46].

T.P. Vinogradova believes that the endochondral ossification disorder is the basis of this disease. According to M.V. Volkov (1974), this disease accounts for 27% of all primary tumors and tumor-like skeletal dysplasia in children, bone-cartilaginous exostoses among benign bone tumors occur in 40% of cases. The disease is well studied in clinical, radiologic, morphological and genetic aspects. The fact of its hereditary transmission in 75% of all observations was proved [4, 5].

According to A.V. Rusakov (1959), "cartilaginous exostoses - this is not just a tumor-like tissue, but integral parts of the viciously developing bone organs". He, like all other authors, considered exostoses as the dystopia of the skeletal-derived mesenchyme, which determines the growth of bones in length. A.V. Rusakov et al. consider that exostoses

retain the same reactivity as normal germ cell cartilage. This is confirmed by the fact that during periods of increased child's growth there is also an increased growth of exostoses [5].

The disease occurs in two forms: multiple exostosis chondrodysplasia and solitary bone - cartilaginous exostosis.

In the case of solitary lesions, tumors that are immobile in relation to the bone, of various sizes and forms, are revealed; skin over them is usually not changed.

Most authors consider single and multiple exostoses as two forms of a single process in essence. Along with this affirmation in literature and clinical practice, solitary neoplasm is often regarded as a benign tumor - chondroma (achondroma) or osteochondroma. The fact of inheritance of single exostoses is not established [4]. Bone - cartilaginous exostosis of large size can exert pressure on vessels or nerve trunks, causing pain.

MHE is usually detected in childhood and adolescence, most often in the second decade of life. There was a significant predominance of males.

Clinical symptoms of MHE depend on the form of the disease, localization, size of exostoses, their shape and relationship with surrounding organs and tissues. According to S.T. Zatsepin (2001) clinically exostoses can manifest themselves very differently, since they can cause many secondary symptoms. Doctors are well aware that exostoses have different shapes: a relatively wide base and a thin, sharp end; a narrow base, ending with a rounded or spherical tip, mostly cartilaginous; some exostoses almost simultaneously with growth ossify; others have a large cartilaginous non-salient "cap" [5].

At the multiple form of exostosis chondrodysplasia, symptoms such as short stature, slanting, valgus deformity of knee joints are often at the forefront. The location of exostoses in the region of the spine with their growth towards the



Table 1

The prevalence of mhe in different populations

Population	Number of population, per 1.000 of pop.	Geographical location	Population (country)	Reference
Chamorro	32	Guam Isl. (USA)	65 (21 case, 1 :1000)	[30]
Poingassi Indians	0.583	reservation of Poingassi (Manitoba, Canada)	1298 (1:77)	[30]
All Europe	–	Europe	1,3-2	[39,40]
Russian Federation				
Karachaevtsi	194,3	Karachay-Cherkess Republic	0,9	[7]
Tatars	2012,6	Republic of Tatarstan	4,8 (1:20927)	[7]
Bashkirs	1199,7	Republic of Bashkortostan	0,06	[2]
Chuvashi	814,8	Republic of Chuvashia	0,34	
Russian	3795,6	Rostov Region	0,16	
Russian	626,1	Kostroma Region	0,04	
Russian	4522,9	Krasnodar Territory	0,28	
Russian	1199,6	Kirov region	0,11	
Russian	1296,7	Tver Region	0,39	

vertebral canal can cause compression of the spinal cord [11].

The main signs of exostoses are: localization in the metaphyseal or in the metadiaphyseal zone; osteochondral exostosis can have a wide or narrow leg, which is a continuation of the cortical layer of the bone itself and the medullary cavity; the bulk of exostosis represents a bone structure, the outer surface of it can be flat or with subulate outgrowths. The localization of exostoses in frequency corresponds to the growth zones with the greatest potency - this is the lower zone of growth of the femur, upper brachial, tibia, etc. The growth of exostosis continues usually during the period of bone growth, but sometimes the increase in its size is also noted after the closure of growth zones [12].

The most frequent localization of MHE is the metaphysis of long tubular bones. Lesions of the distal metaphysis of the femur, proximal metaphysis of the humerus and tibia occur in 48% of all bone-cartilaginous exostoses [5, 36, 43].

One of the serious complications of the course of bone-cartilaginous exostoses is their malignancy [4, 11]. According to S.T. Zatsepin, L.P. Kuzmina (1971), the transformation of exostoses into chondrosarcoma was noted in 12.5% of patients, according to Adler (1983), about 20%. V.V. Balberkin (1994) notes that among 29 cases of malignant osteochondral cartilage exostoses chondrosarcoma is diagnosed in 25 cases and in 4 - osteogenic sarcoma. More often malignancy of exostoses occurs in patients with a multiple form of exostosis chondrodysplasia (72%). The prevalent localization of malignancy of exostoses is the pelvic bone, less often the scapula, ribs and spine [5, 30].

According to A.M. Gerasimov and A.A. Razzakov (1985), an analysis of the components of proteoglycan aggregates of cartilage extract of exostoses with increased growth activity (with the signs of uniform and uneven bone formation) made it possible to reveal an increase in the content of hyaluronic acid by 5-10 times; the ratio of chondroitin-4-sulfate and chondroitin-6-sulfate was 85:15 at a norm 50:50. The ratio of proteins from proteoglycan cartilage aggregates of exostoses with increased growth activity was close to the ratio characteristic for cartilage of newborns and some other growing tumors, while in the extracts of cartilage of the ilium wing (Lat.: *ala*) of the same patients it corresponded to the age norm [5]. The proteins *EXT1* and *EXT2* form a hetero-oligomer complex, which functions in the biosynthesis of

proteoglycan of heparan sulfate [34]. Pacifici (2017) believes that most HME cases are associated with function loss mutations in *EXT1* or *EXT2* that encode the glycosyltransferase responsible for the synthesis of heparan sulfate (HS), resulting in HS deficiency [38].

The most common cause is mutations in the *EXT* (exostozine) genes, which account for 90% of all cases of MHE [9].

Recently 3 genes have been described: *EXT1*, *EXT2* and *EXT3*, which mutations lead to multiple exostosis chondrodysplasia. Stickens et al. (1996) showed that three genes were identified by an analysis of the genetic linkage in chromosomes 8q24.1, 11p11-13 and 19p [19]. Ahn et al. (1995) defined two main regions, the changes in which lead to MHE: 8q24.1 and 11p11.2. In 1995 in the region 8q24.1, the *EXT1* gene was cloned, coding sequence of which was 2238 bp. (746 amino acids) [16, 35, 37, 43].

Mutations of the *EXT2* gene occur 3 times less frequently than in the *EXT1* gene, only single descriptions are known for the *EXT3* gene [27]. *EXT1* and *EXT2* encode glycosyltransferase involved in the synthesis of heparan sulfate. The *EXT1* gene (OMq 608177) (8q24.11-q24.13) contains 11 exons, *EXT2* (OMIM 608210) (11p12-p11) - 16 exons, 438 mutations in the *EXT1* gene and 205 mutations in the *EXT2* gene (OMIM 600209) are described [9, 12, 13, 27] (Table 2).

We analyzed the literature data describing the analyzed mutations in various populations of the world (Table 3).

Wuyts et al. (1998) analyzed the genes *EXT1* and *EXT2* in 26 EXT families from 9 countries. Out of 26 families,

10 had an *EXT1* mutation and 10 had an *EXT2* mutation. 12 of these mutations have not been previously described. From a review of these and previously reported mutations, it was concluded that mutations in the gene *EXT1* or *EXT2* are responsible for most cases of multiple exostoses. Most mutations in these 2 genes cause premature termination of EXT protein, while missense mutations are rare. Therefore, the development of exostoses is mainly due to the loss of the function of the *EXT* genes, which agrees with the hypothesis that the *EXT* genes have tumor suppressor function [39].

In 23 out of 43 examined Japanese families, Seki et al. (2001) found 21 mutations, 18 of which were new. 17 (40%) of the 23 families had a mutation in *EXT1* and 6 (14%) had a mutation in *EXT2*. From 17 families with mutations of *EXT1*, in 13 were those that cause premature stopping of the function of the protein *EXT1*, and 4 showed missense mutations. In contrast to the results of Seki et al. (2001), Xu et al. (1999) found more mutations in *EXT2* than in *EXT1* in Chinese patients (33% and 14%, respectively) [41, 44]. Raskind et al. (1998) re-

Table 2

Mutations in the genes *EXT1* and *EXT2*

Mutation type	Gene	
	<i>EXT1</i>	<i>EXT2</i>
Missens / nonsense	147	70
Splicing	47	24
Regulatory	1	6
Minor deletions	150	57
Minor insertions	51	26
Indel- mutations	9	5
Large deletions	27	17
Complex restructuring	6	0
	438	205

ported that the mutations found in *EXT1* in Caucasoids and in Japanese patients were more identified in family cases than in sporadic ones [19].

In a study of 82 Japanese patients with hereditary multiple exostoses Seki et al. (2001), 4 patients developed malignancy

of the tumor, and their mutations (3 in the *EXT1* gene and 1 in *EXT2*) were different, indicating that the malignant transformation did not directly was associated with a specific mutation in *EXT1* or *EXT2*, but was more likely to be associated with other genetic factors. Loss of heterozy-

gosity was found in chondrosarcoma not only in the *EXT* loci, but also in others, such as 10q (RET, 164761) and 3q [41].

Depending on nationality, about 56-78% of the mutations are found in the *EXT1* gene, and in the *EXT2* gene, 21-44% mutations. Most mutations are

Table 3

#### Mutations in the *EXT1* and *EXT2* genes responsible for MHE in the surveyed populations of the world

Mutations in the <i>EXT1</i> gene	Mutations in the <i>EXT2</i> gene	Method of study	Number of subjects	Population (country)	Reference
	Method of study	MLPA	33 patient	Poland	Jamsheer, et.al., 2014
14	6	Direct sequencing by Sanger on a genetic DNA analyzer	43 families	Japan	Seki, et.al., 2001
45	9	1. MLPA 2. Direct sequencing by Sanger on a genetic DNA analyzer	90 patients	Southern Italy	Ciavarella, et.al., 2013
11	8	Direct sequencing by Sanger on a genetic DNA analyzer	23 patient	Germany	Heinritz, et.al., 2009
29	16	1. MLPA 2. Direct sequencing by Sanger on a genetic DNA analyzer	48 patients	China	Li, et.al., 2017
1	2	Direct sequencing by Sanger on a genetic DNA analyzer	4 probands from 4 families	China	Wu, et.al., 2013
-	1	Direct sequencing by Sanger on a genetic DNA analyzer	25 patients	China	Wang, et.al., 2012
-	1	Direct sequencing by Sanger on a genetic DNA analyzer	23 patients	China	Tian, et.al., 2014
9	4	MLPA	33 patients	Latin America	Delgado, et.al., 2014
2	-	Direct sequencing by Sanger on a genetic DNA analyzer	2 probands	Taiwan	Lin, et.al., 2014
1	-	Direct sequencing by Sanger on a genetic DNA analyzer	4 patients	China	Zhang, et.al., 2013
1	4	Direct sequencing by Sanger on a genetic DNA analyzer	8 patients	China	Xu, et.al., 2017
5	4	Direct sequencing by Sanger on a genetic DNA analyzer	46 patients from 10 families	China	Kang, et.al., 2013
5	4	1. T-NGS 2. Direct sequencing by Sanger on a genetic DNA analyzer	10 probands from 10 families	China	Guo, et.al., 2017
1	-	Direct sequencing by Sanger on the genetic DNA analyzer	9 probands	Iran	Akbaroghli, et.al., 2017
1	-	1. Hiseq2000, Illumina 2. Direct sequencing by Sanger on a genetic DNA analyzer	2 probands, 200 control (100 female, 100 male)	China, province Fuczyan'	Hong, et.al., 2017
28	9	MLPA	39 patients	Spain	Sarrion, et.al., 2013
30	15	Direct sequencing by Sanger on the genetic DNA analyzer	112 patients from 71 family	Japan	Ishimaru, et.al., 2016
-	2	Direct sequencing by Sanger on the genetic DNA analyzer	5 probands from the same family	Zhejiang Province, China	Ruan, et.al., 2018
35	17	1. MLPA 2. Direct sequencing by Sanger on a genetic DNA analyzer	153 patients from 114 families	Brazil	Santos, et.al., 2018
11	5	1. MLPA 2. Direct sequencing by Sanger on a genetic DNA analyzer	14 patients from 9 families	Prague (Czech Republic)	Medek, et.al., 2017
35	12	Direct sequencing by Sanger on a genetic DNA analyzer	92 patients from 26 families		Wuyts, et.al., 1998
			3	Morocco	
			27	Netherlands	
			7	Italy	
			2	Germany	
			1	France	
			3	Turkey	
			1	Great Britain	
			9	USA	
			39	Belgium	

point-like. It is assumed that *EXT1* and *EXT2* genes are carcinogenesis suppressor genes, since their participation in malignant transformation of cartilaginous and bone tissue has been established [6, 8, 10, 19, 21].

With the development of new sequencing technologies, biochip analysis, the search for new mutations has become more extensive and rapid. Hong et al. (2017) have shown that multiple osteochondromas (MO) are an autosomal skeletal disease with an elusive molecular mechanism. To further elucidate the genetic mechanism of the disease, a Chinese family with MO was examined and a new mutation with a change in the structure (c.335\_336insA) in the gene of exotozine 1 (*EXT1*) in one patient with MO was examined by the exom sequencing. This was further confirmed by the method of direct sequencing by Sanger and comparison with 200 unrelated healthy people from the control sample [24].

Lin et al. (2014) in their studies showed that DNA sequencing revealed a mutant *EXT1* gene in both cases in which a mutation of c.447delC (p.Ser149fsX156) arose in exon1 and the nonsense mutation c.2034T>G (p.Tyr678X) in exon 10. No mutation was detected in the control group [31]. Liu et al. (2015) analyzed a large Chinese family of five generations with MHE. Exon sequencing was performed in three individuals with MHE and three healthy relatives. The study confirmed a new deletion of C in codon 442 in the exon 5 of exotozine-1 exon (*EXT1*) as the only cause. Immunohistochemical analysis revealed that the level of the *EXT1* protein in patients with a new mutation in the study was lower than that in patients without an *EXT1* mutation from another family. For a deeper understanding, they analyzed the spectrum of mutations of the *EXT1* gene. The present study should contribute to a further understanding of MHE [25]. Medek et al. (2017) found in five probands various mutations of the *EXT1* gene leading to a premature stop codon (p.Gly124Argfs \* 65, p.Leu191 \*, p.Trp364Lysfs \* 11, p.Val371Glyfs \* 10, p.Leu490Profs \* 31). Two mutants in the *EXT2* genome were found to have a nonsense mutation (p.Val187Profs \* 115, p.Cys319fs \* 46). Five mutations were new and two mutations in probands occurred de novo [23]. Sarrion et al. (2013) conducted a mutation analysis of the *EXT1* and *EXT2* genes in 39 unrelated Spanish patients, most of whom had a mild phenotype, and sought correlation of the phenotype genotype. They found a mutant allele in 37 patients, at 29 in *EXT1* and at 8 in *EXT2*.

Five mutations in *EXT1* were deletions identified by MLPA. Two cases of mosaic were recorded. The authors noted a smaller number of exostoses in patients with a described new mutation compared with other mutations. Mutations in *EXT1* or *EXT2* were detected in 95% of Spanish patients. 18 of 37 mutations were new [33]. Xu et al. (2017) found a new missense mutation (c.1385G>A) in the exon 8 and a splicing mutation (c.725 + 1G>C) in the intron of the 3 *EXT2* gene that are responsible for MO [3, 44].

Our results are useful for expanding the database of known mutations in *EXT1*, *EXT2* and in understanding the genetic basis in patients with MHE, which can improve genetic counseling and prenatal diagnosis.

### Conclusion

Thus, multiple exostosis chondrodysplasia is a fairly common hereditary disease with an autosomal dominant type of inheritance. The disease is characterized by the presence of multiple cartilaginous exostoses in areas of bone growth. The genes responsible for MHE are the carcinogenesis suppressor genes and are located on three different chromosomes: *EXT1* (8q24), *EXT2* (11p12) and *EXT3* (19p). The spectrum of gene mutations, leading to exostosis and malignancy, has not yet been determined. The study of *EXT* genes, their mutations and the causes of malignant transformation is both a fundamental problem that contributes to understanding the patterns of pathogenesis, and a socially significant task of diagnosing, preventing and predicting this disease.

### References

1. Bogolepova N.N. Matyushevskaya E.V. Rentgenodiagnostika dobrokachestvennyh opuholej i opuholepodobnyh obrazovaniy kostej u detej [X-ray diagnostics of benign tumors and tumor-like bone formations in children] Vestnik Chel. Obl. [News of the Chel. Reg.]. Chelyabinsk, 2016, No.4(34), P. 126-128.
2. Bochkov N.P. Nasledstvennye bolezni: nacional'noe rukovodstvo [Hereditary diseases: national leadership] pod red. Akad. RAMN N.P. Bochkova, akad. RAMN E.K. Gintera, akad. RAMN V.P. Puzyreva [ed. Acad. RAMS N.P. Bochkov, acad. RAMS E.K. Ginter, acad. RAMS V.P. Puzyrev]. Moscow: GEOTAR – Media, 2012, P.935.
3. Geneticheskie issledovaniya naseleniya Yakutii / FGBU «Yakut. nauch. centr kompleks. med. problem SO RAMN», FGBU «NII med. genetiki» SO RAMN; [pod red. V.P. Puzyreva, M.I. Tomskogo] [Genetic studies of the population of Yakutia / FGBU YSC CMP SB RAMS, FGBU Institute of Medical genetics SB RAMS; [ed. V.P. Puzyrev, M.I. Tomsky]. Yakutsk, 2014, 333 p.
4. Zotkin A.V. Hirurgicheskoe lechenie detej s ehkzostoznoj hondrodisplaziej kostej verhnih i nizhnih konechnostej: avtoref. dis. ... kand. med. nauk [Surgical treatment of children with exostosis chondrodysplasia of bones of the upper and lower extremities: the author's abstract Dis. ... cand. Med. Sciences]. Penza, 2011, 3 p.
5. Zatsepin S.T. Kostnaya patologiya vzroslykh: rukovodstvo dlya vrachej [Bone pathology of adults: a guide for doctors]. Moscow: Medicine, 2001, 640 p.
6. Lagunova I.G. Kliniko-rentgenologicheskaya diagnostika displazij skeleta: monografiya [Clinical and X-ray diagnostics of skeletal dysplasia: monograph]. Moscow, Medicina, 1989, 31 p.
7. Zinchenko R.A. [et.al.] Mediko-geneticheskoe izuchenie naseleniya Respubliki Tatarstan. VII. Raznoobrazie nasledstvennoj patologii v vos'mi rajonah [Medico-genetic study of the population of the Republic of Tatarstan. VII. Variety of hereditary pathology in eight regions] Medicinskaya genetika [Med. Genetics]. Moscow, 2014, Vol.11, P. 15-29.
8. Fokhtin V.V. [et.al.] Rezul'taty lecheniya detej s ehkzostoznoj hondrodisplaziej slozhnoj anatomicheskoy lokalizacii [Results of treatment of children with exostosis chondrodysplasia of complex anatomical localization]. Sovremennye tekhnologii v diagnostike i lechenii [Modern technologies in diagnostics and treatment]. 2014, №1, P. 13-16.
9. Fedotov V.P. [et.al.] Semejnyj sluchaj segregacii nasledstvennoj motorno-sensornoj nejropatii 1V tipa s mnozhestvennymi ehkzostozami u monozigotnyh bliznecov [Family case of segregation of hereditary motor-sensory neuropathy 1B type with multiple exostoses in monozygotic twins]. Nervno-myshechnye bolezni [Neuromuscular diseases]. Moscow, 2015, № 1, P. 48-52.
10. Shishkina N.S. [et.al.] Sochetanie saharnogo diabeta i sindroma mnozhestvennoj ehkzostoznoj kostno-hryashchevoj hondrodisplazii [The combination of diabetes mellitus and the syndrome of multiple exostosis bone-cartilaginous chondrodysplasia]. Diabetes mellitus, Moscow, 2004, Vol.4, P. 34 - 36.
11. Chesnokova G.G. Izuchenie strukturnykh anomalij i tochkovykh mutacij genov EKHT1 i EKHT2 pri mnozhestvennoj ehkzostoznoj hondrodisplazii i sporadicheskikh zlokachestvennykh novoobrazovaniyah: avtoref. dis. ... kand. biol. nauk: 03.00.15 [Study of structural anomalies and point mutations of *EXT1* and *EXT2* genes with multiple exostosis chondrodysplasia and



- sporadic malignant neoplasms: author's abstract dis. ... cand. biol. sciences: 03.00.15]. Moscow, 1999, 24 p.
13. Shavyrin D.A. Diagnostika i hirurgicheskoe lechenie opuholej i opuholepodobnyh zabolevanij kostej, obrazuyushchij kolennyj sustav, u vzroslyh: dis. ... dok. med. nauk [Diagnostics and surgical treatment of tumors and tumor-like bone diseases forming the knee joint in adults: dis. ... doc. med. sciences: 14.01.15]. Moscow, 2014, 23 p.
14. A broad spectrum of genomic changes in Latin-American patients with *EXT1/EXT2*-CDG / M. Delgado [et. al.] // *Sci Rep*. – 2014. Sep 4:6407. – P.1-7.
15. A. Splice Mutation and mRNA Decay of *EXT2* Provoke Hereditary Multiple Exostoses / C. Tian [et. al.] // *Plos One* – 2014. Vol.9. – P.1-9.
16. Breakpoint characterization of large deletions in *EXT1* or *EXT2* in 10 Multiple Osteochondromas families / L. Jennes [et. al.] // *BMC Med Gen* – 2011. P.1-9.
17. Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (*EXT1*) / J. Ahn [et. al.] // *Nature Genet.* – 1995. Vol.11. – P. 137-143.
18. Deletion of exon 8 from the *EXT1* gene causes multiple osteochondromas (MO) in a family with three affected members / L. Zhuang [et. al.] // *Spr Plus*. – 2016. – P.1-9.
19. Eileen M. Multiple osteochondromas in the archaeological record: a global review / M. Eileen, J. Catriona, McKenzie // *J of Arch Sci.* – 2010. Vol.37. – P. 2255-2264.
20. Evaluation of locus heterogeneity and *EXT1* mutations in 34 families with hereditary multiple exostoses / W.H. Raskind [et. al.] // *Hum. Mutat.* – 1998. – Vol.11. – P. 231-239.
21. Genetic skeletal dysplasias in the Museum of Pathological Anatomy, Vienna / P. Beighton [et. al.] // *Am. J. Med. Genet.* – 1993. Vol.47 – P. 843-847.
22. Hereditary multiple exostoses (EXT): mutational studies of familial *EXT1* cases and EXT-associated malignancies / J. T. Hecht [et. al.] // *Genet.* – 1997. Vol.60. – P.80-86.
23. Hip Joint Osteochondroma: Systematic Review of the Literature and Report of Three Further Cases / A. Makhdom [et. al.] // *Arnd in Orth.* – 2014. P.1-10.
24. Hereditary Multiple Exostoses: Clinical, Molecular and Radiologic Survey in 9 Families / K. Medek [et. al.] // *Prag Med Rep.* – 2017. Vol.118. – P.87-94.
25. Identification of a novel mutation in the *EXT1* gene from a patient with multiple osteochondromas by exome sequencing / G. Hong [et. al.] // *Mol Med Rep.* – 2017. Vol.15. – P.657-664.
26. Identification of a novel *EXT1* mutation in patients with hereditary multiple exostoses by exome sequencing / H. Liu [et. al.] // *Onc Rep.* – 2015. P.547-552.
27. Identification of a novel frameshift mutation of the *EXT2* gene in a family with multiple osteochondroma / P. Xia [et.al.] // *Oncology Letters.* – 2016. Vol.11. – P.105-110.
28. Krooth R. Diaphysial aclasis (multiple exostoses) on Guam / R. Krooth, M. Macklin, T. Hilbish // *Am. J. Hum. Genet.* – 1961. – Vol.13. – P.340-347.
29. Large-scale mutational analysis in the *EXT1* and *EXT2* genes for Japanese patients with multiple osteochondromas / D. Ishimaru [et. al.] // *BMC Gen.* – 2016. – P.17-52.
30. Mutational screening of *EXT1* and *EXT2* genes in Polish patients with hereditary multiple exostoses / A. Jamsheer [et. al.] // *J App Gen.* – 2014. – P.183-188.
31. Mutation Screening for the *EXT1* and *EXT2* Genes in Chinese Patients with multiple Osteochondromas / Q. Kang [et al.] // *Arch. of Med. Res.* – 2013. - Vol.44. – P.542-548.
32. Mutant *EXT1* in Taiwanese Patients with Multiple Hereditary Exostoses / W-D. Lin [et. al.] // *BioMed.* – 2014. Vol.4. – P.23-28.
33. Mutation screening of the *EXT1* and *EXT2* genes in patients with hereditary multiple exostoses / C. Philippe [et. al.] // *Genet.* – 1997. Vol.61. P.520-528.
34. Mutations in the *EXT1* and *EXT2* genes in Spanish patients with multiple osteochondromas / P. Sarrion [et. al.] // *Sci Rep.* – 2013. Vol.3. – P.1-7.
35. Novel mutation of *EXT2* identified in a large family with multiple osteochondromas / X-J. Chen [et. al.] // *Mol Med Rep.* – 2016. Vol.14. – P. 4687-4691.
36. Novel mutations in the *EXT1* gene in two consanguineous families affected with multiple hereditary exostoses (familial osteochondromatosis) / Faiyaz-UI-Haque [et. al.] // *Clin. Genet.* – 2004. Vol.66. – P.144-151.
37. New mutations of *EXT1* and *EXT2* genes in German patients with multiple osteochondromas / W. Heinritz [et. al.] // *Genet.* – 2009. Vol.73. – P.283-291.
38. Novel and Recurrent Mutations in the *EXT1* and *EXT2* Genes in Chinese Kindreds with Multiple Osteochondromas / Y. Wu [et al.] // *J Orthop Res.* – 2013. Vol.9. – P.1492-1499.
39. Pacifici M. Hereditary Multiple Exostoses: New Insights into Pathogenesis, Clinical Complications, and Potential Treatments / M. Pacifici // *Curr Ost Rep.* – 2017. P.142-152.
40. Positional cloning of a gene involved in hereditary multiple exostoses / W. Wuyts [et. al.] // *Hum. Molec. Genet.* – 1996. Vol.5. – P.1547-1557.
41. Pathogenic Gene Screening and Mutation Detection in a Chinese Family with Multiple Osteochondroma / X. Wang [et. al.] // *Genet. Test. And Molec. Biomark.* – 2012. Vol.16. – P.827-832.
42. Seki H. Mutation Frequencies of *EXT1* and *EXT2* in 43 Japanese Families with Hereditary Multiple Exostoses / H. Seki // *Am J of Med Gen.* – 2001. – P.59-62.
43. The putative tumour suppressor *EXT1* alters the expression of cell-surface heparan sulfate / C. McCormick [et. al.] // *Nature Genet.* – 1998. – Vol.19. – P.158-161.
44. The *EXT2* multiple exostoses gene defines a family of putative tumour suppressor genes / D. Stickens [et. al.] // *Nature Genet.* – 1996. Vol.14. – P.25-32.
45. Xu Y. Identification of mutations in *EXT1* and *EXT2* genes in six Chinese families with multiple osteochondromas / Y. Xu, Q. Kang, Z. Zhang // *Mol Med Rep.* – 2017. Vol.4. – P.5599-5605.
46. Zhang F. Exome Sequencing and Functional Analysis Identifies a Novel Mutation in *EXT1* Gene That Causes Multiple Osteochondromas / F. Zhang // *Plos One.* – 2013. Vol.8. – P.1-5.
47. 20 novel point mutations and one large deletion in *EXT1* and *EXT2* genes: Report of diagnostic screening in a large Italian cohort of patients affected by hereditary multiple exostosis / M. Ciavarella [et. al.] // *Gene.* – 2013. Vol.515. – P.339-348.

### The authors

1. Yakovleva Alexandra Eremeevna – Junior Researcher, graduate student III course, Academic Scientific Laboratory “Genomic Medicine” Medical Institute of M.K. Ammosov NEFU, Yakutsk, Russia, e-mail: [alexerem2013@yandex.ru](mailto:alexerem2013@yandex.ru);
2. Maksimova Nadezhda Romanovna – MD, Chief Researcher, Academic Scientific Laboratory “Genomic Medicine” Medical Institute of M.K. Ammosov NEFU, Yakutsk, Russia, [nogan@yandex.ru](mailto:nogan@yandex.ru).

## CLINICAL CASE

S.N. Alekseeva, A.L. Sukhomyasova, G.I. Sofronova, Z.P. Androsova, S.A. Kondratieva, E.E. Gurinova, P.V. Pavlova

## THE CLINICAL CASE OF PROPIONIC ACIDEMIA

DOI 10.25789/YMJ.2018.63.32

### ABSTRACT

The article reports the clinical case of management of a child with a genetic metabolic disease until setting a correct diagnosis. Propionic acidemia is a rare genetic metabolic disease with autosomal- recessive type of inheritance which is related to metabolic disorder of organic acids. The early diagnostics is a difficult task because the clinical symptoms that are caused metabolic disorder, frequently occur by hypoxic - ischemic disorder of central nervous system, brain defects, fetal infections. The full - term child aged 11 days had developed metabolic crisis, which was taken as an expression of neonatal pathology, such as neonatal jaundice, perinatal CNS lesion. On a background of detoxification the patient has the clinical positive dynamic, every two weeks his condition improves. Due to a main disease the child had secondary immunodeficiency, which resulted in recurrent pneumonias. The patient N is examined in three ways: changes of peripheral blood - leukopenia, thrombocytopenia, anaemia; neurological symptoms - soporose condition, lethargy, refusal of meals, oppression of all reflexes, muscular hypotension; in view of anamnesis, impossibility of a comparison all the clinical symptoms to one diagnosis tap genetic research. The absence of the methodology of tandem mass-spectrometer in position extends the time of correct diagnosis establishing and timely treatment. In medical institutions it's necessary to identify levels of metabolites measured in various biological media (e.g. blood, plasma, cerebrospinal fluid and urine), glucose, lactate, pyruvic acid, ammonium, KET of b-hydroxybutyrate and uric acid.

**Keywords:** propionic acidemia, hereditary, metabolic diseases.

### Introduction

Many congenital metabolic disorders in the neonatal period are very acute with the phenomena of metabolic decompensation, acidosis, vomiting, respiratory disorders. This symptomatology imitates the often acute infectious process. The nature of clinical changes is mixed. In addition to neurological disorders, a whole complex of severe changes in various organs and systems is found, i.e. the diseases are polished. According to the peculiarities of the course of the pathological process and the timing of the manifestation of the first clinical signs distinguish: Hereditary metabolic encephalopathies (NME) with manifestation in the period of newborn; NME with manifestation at 4-6 months of life; NME for 1 to 4 years of life; NME with manifestation in children of older ages [2].

Propionic acidemia (aciduria) -CODE ICD-10 E71.1 is a genetically heterogeneous hereditary disease from the group of organic acidemia caused by deficiency of propionyl-CoA carboxylase, which leads to blocking of propionate metabolism at the level of propionyl-CoA transfer into methylmalonyl-CoA and disruption of the metabolism of amino acids (isoleucine, valine, threonine, methionine), fatty acids with an odd number of carbon atoms and cholesterol. The disease occurs in different populations. The frequency among newborns in Europe and the USA is 1: 350,000. In some countries (for example, in Saudi Arabia) the frequency reaches 1: 2000. In the Russian Federation, the frequency of the disease is not defined. The disease is characterized by acute manifestation in the first days of life (with neonatal form), less often - in the

first months of life (with infant form), occurs paroxysmally [3, 4].

Initial signs of the disease - vomiting, dehydration, refusal to eat, weight loss, infantile spasms, respiratory disorders (tachypnea, alternating apnea), generalized muscle hypotension, hyperreflexia, lethargy, drowsiness, coma. In some cases, draws attention to the peculiar face of patients: puffy cheeks, enlarged upper lip. Mortality at an early age reaches 40% [4].

### Materials and methods of research

A pro-and retrospective analysis of the medical record of a stationary patient who was in the department of pathology of newborns and premature infants No. 1 of the Perinatal Center (PNND No. 1 PTC), in the oncohematological and psycho-neurological department No. 2 (PNO No. 2) of the pediatric center of the Republic of Sakha Yakutia "RB # 1-NCM".

### Results and discussion

Child N. was born from his mother 26 years old, by the nationality Sakha, suffering from hearing loss of 3-4 degrees. From the anamnesis of life it is known that the woman has a complicated obstetric and gynecological history: the girl from the first pregnancy and the first marriage suffers from hearing loss, was born through natural birthmarks, during the second pregnancy Lues ill, the pregnancy from the second marriage at 26 weeks culminated in stillbirth. In occasion of Lues it was treated, from the account it is removed or taken off. The third pregnancy ended with a medical abortion at week 8. The fourth pregnancy, proceeded against the background of chorionamnionitis, operative clones in the gluteal the boy died on the 11th day of life in the cen-

tral regional hospital with a clinical and pathoanatomical diagnosis: intrauterine pneumonia.

Child N. from the fifth pregnancy, which was without any peculiarities, the delivery operative on time, head presentation. The indication for surgical delivery was a complicated obstetrical anamnesis, a scar on the uterus. Clinico-histologically confirmed chorionamnionitis. According to the physical parameters, the child corresponded to gestational age, birth weight 3460, height 52. The Apgar score was 8/8. The early neonatal period was uneventful. After receiving the vaccination against hepatitis B and BCG, after audioclearing in the obstetric hospital and neonatal screening for 5 hereditary diseases were prescribed home on day 6 from the obstetric hospital.

On the 11th day of life, he enters the PNND No. 1 PTC with complaints of jaundice and lethargy, refusal to eat. At objective examination, the saffron color of the skin is noted, the weight at admission is 3140 (-320 grams, 9.2%), the cry is weak, the symptoms of CNS depression are noted: general muscle hypotension and hyporeflexia, the child refuses to feed. At admission, the diagnosis is: Bilirubin encephalopathy? In the clinical picture intercurrent infection - acute pneumonia of unclear etiology, neonatal sepsis joins. In a laboratory study, the level of total bilirubin is 280  $\mu\text{mol} / \text{l}$ . A general analysis of blood determines leukopenia, and periodic thrombocytopenia (see Table 1). In the immunogram, cellular immunodeficiency is detected (see Table 2). On the RCT of the lungs at the age of 14 days: bilateral polysegmental pneumonia, subsegmental atelectasis of the

left lung was detected. Against the background of ongoing therapy: phototherapy, detoxification therapy, antibiotic therapy, immunoglobulin replacement therapy, immunomodulatory therapy, the child gives positive dynamics. He becomes quite active, eats milk formula, the mother refuses breastfeeding. When assessing the neurological status, the lack of communication is alarming, when audioclearing it is revealed that the child is at risk for hearing loss. According to the MRI of the brain at the age of 25 days, a small delay in myelination in the substance of the cerebral hemispheres is determined. Easy ventriculodilation of the lateral ventricles without signs of excessive intraventricular pressure. Patient N. is diagnosed with:

Primary: Bronchopneumonia, unspecified. Bacterial sepsis of the newborn.

Concomitant: Perinatal CNS damage of mixed genesis, severe. There's a risk of hearing loss. Neonatal jaundice.

At the age of 1,5 months he is discharged home, with the appointment of a neurologist, a course of pantogam.

In two weeks he enters the Pediatric Center with the diagnosis: Anemia of early age. Neutropenia. Dose-dependent side effect of pantogam? Complaints about drowsiness, oppression, prolonged sleep, refusal to eat. From the anamnesis of the disease it is known that it became sluggish and drowsy on the 15th day after being discharged from the PNSN # 1 of the PTC RS(Y) «RB # 1-NCM». Patient N. is examined in three directions: changes in peripheral blood - leukopenia, thrombocytopenia, anemia; neurologic symptoms - co-morbidity, lethargy, refusal to eat, oppression of all reflexes, muscle hypotension; taking into account the anamnesis, the impossibility of comparing all the clinical symptoms under one diagnosis is connected with genetic research.

Peripheral blood indices determine persistent leukopenia up to  $0.8 \times 10^9 / l$ , a periodic decrease in hemoglobin and platelet levels (see Table 3). The acid-base state of the blood is determined by persistent metabolic acidosis: pH = 7.22, BE = 12 mmol / L. In the myelogram at the age of 2 months 4 days, there was an increase in the proliferation of elements of the megakaryocytic germ with signs of dyspoezia, as well as mild eosinophilia - 7.75%, at the age of 2 months 10 days, severe inhibition of the granulo-megakaryocytopoiesis elements profiling is a manifestation of the hypoplastic process.

The peculiar face of the patient was paying attention: puffy cheeks, enlarged upper lip. During the period of the met-

abolic crisis, there is a sign of soporus, refusal to eat, vomiting, convulsions. Against the background of ongoing detoxification therapy, there is a short-term improvement in well-being. The patient begins to show hunger, the sucking reflex is activated, gaining weight. During periods of stabilization of the state, improvement in the dynamics of blood indices is determined, regression of convulsions.

According to the MRI of the brain at the age of 2 months, 4 days, symmetrical areas of ischemia are defined in the cortical areas of the parietal lobes, in the thalamuses and in the central parts of the cerebellar hemispheres on both sides. MR-signs of perinatal encephalopathy. To all symptomatology the infectious process joins, nosocomial segmental pneumonia: at the age of 2 months 9 days - CT

signs of interstitial infiltration in S6, 9 of the right lung, S 6, 10 of the left lung. According to electroencephalography, the picture of the coma is determined. Primary-genitalized epileptic activity, not associated with tremor attacks. Clearly focal activity was not revealed. EEG at the age of 2 months 9 days: EEG picture of the pattern «flash-suppression». During the treatment period the child was examined by a neurologist, an ophthalmologist, a geneticist, a surdologist, hematologist. At a biochemical blood test: glucose 5.68-5.8 mmol / l, the state of hypoglycemia was not determined by analysis, urea 3.7 moles / l, creatinine 39.1 mkmol / l, lactate 5.24 mmol / l, with load 7.65 mmol / l.

Analysis of clinical and laboratory data made it possible to suspect a hereditary metabolic disease. On the issue

Table 1

Indicators of a CBC in the admission dynamic in Neonatal Pathologies and Special Care Nursery

Days of life	Leukocyte $10^9/l$	RBC $10^{12}/l$	Hb, g/l	Ht, %	Thrombocyte $10^9/l$
11	4,5	4,97	170	51,2	192
12	4,5	4,53	152	46,7	144
13	2,5	4,07	137	41,8	47
15	3	4,2	152	48,5	58
21	6,2	3,2	113	32,1	390
24	8,2	3,29	110	34	494
30	7,9	3,38	109	34,1	324
35	7,2	3,2	111	32,7	474
44	5,8	3,02	105	30,1	191

Table 2

The dynamic of the patient's N immunogram

Age	IgA	IgM	IgG	ЦИК	CD 3+	CD 4+	CD 8+	CD4/ CD8	CD 19+	CD 20+	CD 25+	CD16+ CD 56+
16 days	1,65	0,96	10,5	99,7	87	70	17	2,6	4	3	14	7
1 months 5 days	0,6	0,96	5,27	93,5		52	20	2,6	12	9	9	12
2 months 5 days	1,45	4,11	7,46	91,98	79	55	27	2,04	2	1	5	18
2 months 13 days	1,82	0,82	6,64	93	87	70	17	2,6	4	3	14	7

Table 3

Indicators of a CBC of the patient N in the dynamic at the first time of hospitalization in the Pediatric Center

Age	Leukocyte $10^9/l$	RBC $10^{12}/l$	Hb, g/l	Ht, %	Thrombocyte $10^9/l$
2 months 2 days	1,9	2,85	93	26,1	303
2 months 4 days	1,5	2,55	81	23,1	179
2 months 5 days	1,7	4,14	107	32,2	102
2 months 10 days	1,8	4,22	114	32,4	28
2 months 19 days	3,0	3,58	98	28,7	400
3 months	3,3	3,29	95	25,8	713
3 months 3 days	2,4	3,27	95	27,2	580
3 months 6 days	0,8	2,99	91	25,1	133
3 months 7 days	1,3	3,29	98	27,6	44



of diagnostics and risk of physicians, remote consultation was conducted with the federal scientific and clinical center of pediatric hematology, oncology and immunology named after Dmitry Rogachev, FGBU «Russian Children's Clinical Hospital» of the Ministry of Health of the Russian Federation, FGBU «Medical Genetics Research Center» RAMS. Blood samples were sent to the laboratory of hereditary diseases of the FGBU «Medico-Genetic Scientific Center» RAMN for tandem mass spectrometry. Based on the results of the study, an increase in the concentration of propionylarnitine was detected, the methylmalonic acid test was negative. The significant increase in organic acids in the blood in combination with the characteristic clinical manifestations made it possible to diagnose the propionic acidemia, the neonatal form in the child.

After confirmation of the diagnosis, the treatment strategy was based on the following principles: limiting the intake of isoleucine, valine, threonine and methionine with food to the minimum requirement; administration of levocarnitine to enhance the binding of the toxic propionyl radical; Exclusion of starvation, prevention of activation of catabolism; controlling the acid-base state of the blood, preventing the development of acidosis, maintaining the water balance; increased therapy during the metabolic crisis [1, 3].

Despite intensive therapy, the child's specific nutrition died from multiple organ failure and toxic encephalopathy due to severe metabolic acidosis. The patient N. lived 3 months 11 days. The pathological diagnosis is exposed: The basic disease: Hereditary illness of an exchange. Propionic acidemia. (E 71.1).

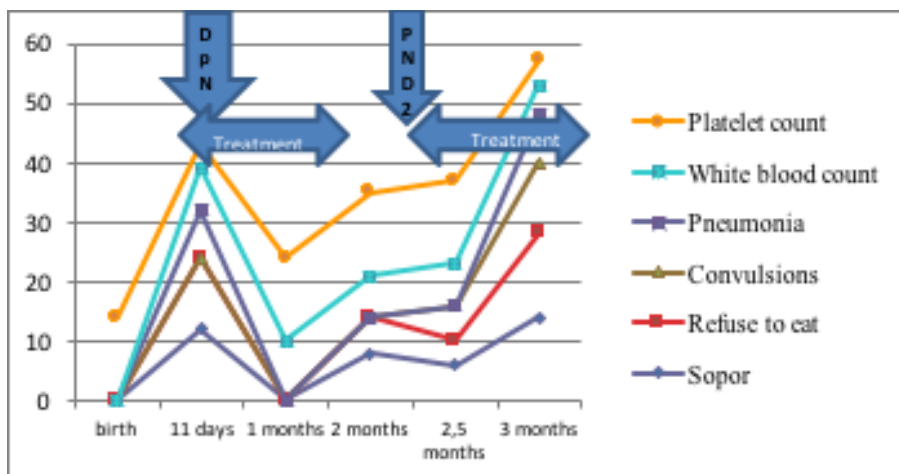
Complications of the underlying disease: Aplastic state of blood: agranulocytosis, anemia, neutropenia, thrombocytopenia (D 60-70). Secondary necrosis of the gastric mucosa, small intestine. Gastrointestinal bleeding. DIC-syndrome: hemorrhage under the epicardium, mucous membranes of the respiratory tract, esophagus, serous membrane of the large intestine. Subarachnoid perivascular hemorrhages.

Focal hydropic and fatty liver. Ascites. Hydropericardium. Cerebral edema.

Concomitant diseases: Simple kidney dysplasia. Hearing loss according to clinical data. Comparison: coincidence. Cause of death: Progression of the underlying disease. Category of difficulty: II.

### Conclusion

This clinical example shows a long diagnostic search, late diagnosis and attracts the attention of neonatologists,



The dynamic of clinical displays of patient N at the second time of hospitalization resuscitators, pediatricians, neurologists to the diagnosis of hereditary metabolic diseases. The absence of a screening diagnostic technique postpones the precious time of setting the right diagnosis and prescribing specific therapy.

A thorough clinical examination of the child and the definition of the symptom complex contribute significantly to the success of the differential diagnostic process, which consists of 4 stages. Each of the stages has its own tasks:

Stage 1 - provides for the examination of children with undifferentiated pathology and the delineation of hereditary and non-hereditary diseases. In this case, special importance is attached to the clinical symptom complex, given genealogy, obstetric anamnesis.

Stage 2 - is characterized by the identification of children with a possible hereditary pathology of amino acid metabolism and the determination of their dominant clinical symptoms. The doctor is recommended to compare by the presence of dominant signs with six groups of hereditary aminoacidopathies: 1 - diseases accompanied by ketoacidosis and vomiting, 2 - diseases accompanied by a change in color and odor of urine, 3 - diseases accompanied by eye pathology and mental retardation, 4 - diseases accompanied by CNS and liver damage, 5 - diseases accompanied by mental retardation and convulsive syndrome, 6 - diseases accompanied by psychoneurological disorders and skin lesions.

Stage 3 - intra-group differential diagnosis is performed.

Stage 4 - a purposeful laboratory examination. Efficacy is determined by the thoroughness of the examination in the first three steps [2].

Thus, at the pre-laboratory level of the survey, the use of purely clinical signs allows to significantly reduce the number of nosological forms for differential diagnosis and determine the nature of subsequent laboratory studies.

### REFERENCES

1. Baranov A.A. Namazova-Baranova L.S. Borovik T.E. Diyetoterapiya pri nasledstvennykh boleznyakh aminokislotnogo obmena. Metodicheskoye pismo [Dietotherapy in hereditary diseases of amino acid metabolism. Methodical letter]. Moscow: 2013, 97 p.
2. Barashnev Yu.I. Baharov V.A. Novikov P.V. Diagnostika i lecheniye vrozhdennykh i nasledstvennykh zabolevaniy [Diagnosis and treatment of congenital and hereditary diseases]. Moscow: 2004, p. 560.
3. Prikaz MZ RF ot 29.12.2012 №1670n «Ob utverzhdenii standartov spetsializirovannoy meditsinskoy pomoshchi detyam pri propionovoy atsidemii» [Order of the Ministry of Health of the Russian Federation from 29.12.2012 №1670n "On approval of the standard of specialized medical care for children with propionic acidemia"].
4. Federal'nyye klinicheskiye rekomendatsii (protokoly) po okazaniyu meditsinskoy pomoshchi bol'nym propionovoy atsidemiyey [Federal clinical recommendations (protocols) for the provision of medical care to patients with propionic acidemia]. Moscow: 2013, p. 24.

### Information about authors:

- Yakutsk, Republic Sakha (Yakutia), Russia:
1. Alekseeva Sargylana Nikolaevna – PhD, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the MI SVFU, sargylanao@mail.ru;
  2. Aitalina Lukichna Sukhomyasova, PhD, Head of educational and scientific laboratory "Genomic medicine" NEFU, head of medical-genetic center of GAU RS (Y) "RB # 1-NCM", AitalinaS@yandex.ru;
  3. Afanaseva Natalya Aleksandrovna – neonatologist of CDN of Nam district.
  4. Sofronova Gulnara Ivanovna - PhD, a neurologist of the highest qualification

category of psycho-neurological department №2 of GAU RS (Y) "RB # 1-NCM", [gulnara-ykt@yandex.ru](mailto:gulnara-ykt@yandex.ru);

5. Androsova Zinaida Petrovna - PhD, a neurologist of the highest qualification category of the psycho-neurological department No. 2 of GAU RS (Y) "RB #

1-NCM";

6. Kondrateva Sargylana Afanasyevna – head of oncohematology department, a pediatric oncologist and hematologist of the highest qualification category, [gematologia@mail.ru](mailto:gematologia@mail.ru).

7. Gurinova Elizaveta Egorovna - doctor-

geneticist of the medical-genetic center of GAU RS (Y) "RB # 1-NCM".

8. Pavlova Paraskovya Vitalievna - 6th year student of the Pediatric Department of the Medical Institute of NEFU named by M.K. Ammosov, [paraskopova@mail.ru](mailto:paraskopova@mail.ru).

## EXPERIENCE EXCHANGE

A.A.Yarovskiy

# MEDICAL AND STATISTICAL ASPECTS OF STUDYING THE INCIDENCE OF ABORTION IN THE SAKHA REPUBLIC (YAKUTIA)

DOI 10.25789/YMJ.2018.63.33

### ABSTRACT

The article represents the results of medical and statistical analysis of abortion in the Sakha Republic (Yakutia) for the long-term period (1991–2015). A decrease in the incidence of abortion and transformation of its structure has been noted. The level of abortions due to social indications and registered criminal abortions has decreased the most. An increase in the proportion of spontaneous and unspecified abortions in total ratio of abortion has been found out. The results of the correlation analysis confirm the influence of the women reproductive behavior on demographic processes in the Sakha Republic (Yakutia).

**Keywords:** abortions, reproductive losses, demographic processes.

### Introduction

One of the most important tasks of the Russian Federation State Program "Health Development" is the ensuring of the prevention in the sphere of health care and the development of primary health care for the population. In the subprogram "Mother and Child Welfare" particular attention is paid to prevent and decrease the number of abortions. Priority of ongoing measures is determined by social and demographic processes characterized by stable depopulation, population aging and health deterioration of all population groups [3, 4, 6].

Under modern demographic conditions the problem of demographic losses is very actual because despite its constant downward trend, abortion takes a leading place in realization of women reproductive function and structure of reproductive losses [1, 2, 5].

**The aim** of the research is medical and statistical analysis of all types of abortions structure and incidence dynamics followed by evaluation of their influence on demographic processes in the Sakha Republic (Yakutia).

### Materials and methods

To achieve the aim of the survey retrospective analysis of abortions structure and dynamics of their incidence in the Sakha Republic (Yakutia) for the long-term period (1991-2015) was carried out. Base material was a Form of state federal statistical observation №13 "Information on termination of pregnancy (up to 22 weeks)" (n=25). The indicators

of abortions frequency calculated for 1,000 women of fertile age and 100 normal births were analyzed. The indicators of abortions frequency and their dynamics in different reproductive age groups for the given period were analyzed. The dynamics of the abortions level in early and late terms of pregnancy termination was compared. The dynamics of abortions among primigravidae was determined.

To analyze the correlation between reproductive-demographic indicators and abortions Pearson correlation analysis was carried out. The base of the analysis was statistical data of the Territorial body of Federal State Statistics Service in the Sakha Republic (Yakutia) for the period 1990-2015. The strength and direction of the relationship between the variables were estimated. The distribution of quantitative variables was under the normal law (p for the Shapiro-Wilk criterion more than 0.05).

### Results and Discussion

The study of reproductive function realization in the Sakha Republic (Yakutia) at 2015 year-end shows 16,379 (59.3%) pregnancies end with childbirth; 11,236 (40.7%) end with abortions. In 2015 the number of abortions for 1,000 women of fertile age was 46.2 (in the Russian Federation – 23.8).

The data on spontaneous, induced and unspecified abortions were analyzed to understand better the nature of pregnancy terminations. As a result, changes in the structure of abortions

types were determined (Figure 1).

The percentage of spontaneous abortions increased by 14% over the period under review, the share of unspecified abortions increased by 5.7%, the share of induced abortions decreased by 19.2%. In 2015, 21.0% of the abortion structure were spontaneous, 7.9%, unspecified abortions, 4% - justifiable abortions, and 67.1% legal medical abortions.

The total number of abortions for the period 1991-2015 decreased from 30,062 to 11,236 mainly due to legal medical abortions, number of which decreased by 64.7%.

Analyzing the incidence of abortions according to their types the uneven dynamics of indicators rates attracted attention. The rate of abortions having the greatest medical and social significance - abortions for social indications and registered criminal ones - decreased to the maximum extent.

The incidence rate of justifiable abortions remained stable at 1.8 per 1,000 women of fertile age for the period under review. The number of unspecified abortions increased by 35.8% (Figure 2).

For the period 1991-2015 the prevalence rate of spontaneous abortion as the main indicator of women reproductive health increased from 7.5 to 10.1 per 1,000 women of fertile age (Table 1). The share of spontaneous abortion in 2015 was about 11% of the number of pregnancies ended with childbirth.

Since 2012 in the structure of abortion

terms there was an upward trend in growth of pregnancy terminations from 12 to 21 weeks, the number of abortion up to 12 weeks was stable (Table 2).

The analysis of abortions according to the method of pregnancy termination revealed that the use of the most safe medical method of abortion was still insufficient: 31% from the number of medical (legal) abortions in 2015.

The analysis of abortions according to the age of women could be made only since 1996, because until 1995 in the statistical form №13 20-34 year old women had been united in one group. This group accounted more than 70% of abortions.

In the structure of age groups, the greatest number of terminated pregnancies fell on 20-34 year old women. In 2015 the figure for 1,000 women of the corresponding age was 71.5 (71.6 in 2011). The next positions were taken by the age groups "35+" with the indicator 26.3 in 2015 (23.4 in 2011) and "from 15 to 19 years" (13.0 in 2015, and 16.8 in 2011). In the age group "up to 15 years" the indicator was relatively stable and amounted to 0.2.

Changes in the age structure of abortions corresponded to changes in the age structure of women giving birth ("aging of the age model of fertility"), which quite naturally reflected a single trend in the reproductive and sexual activity of the female population. Among women terminating pregnancy, the proportion of the age group "25-29 years" increased in the structure of abortions (from 22.4 to 28.9%). The age group "30-34 years" (21.1-24.5%) was a "leaders" among women terminating pregnancy, as well as among women in childbirth. The share of the age group "35-39 years" wasn't changed (15.3-16.6%).

Comparing the age-specific fertility rates (the number of births per 1,000 women of the corresponding age) and the age-related abortion rates (the number of pregnancy terminations per 1,000 women of the corresponding age), it was evident that with the same type of curves women at younger age predominantly gave birth than terminated pregnancy. Up to 34 years the indicator of age-specific fertility rates was significantly higher than the index of age-related abortion rates. The curve of age-related abortion rates was more sloping, shifted to the right along the age axis, that was, at the age of 35 and more, women were more likely to terminate pregnancy than give birth (Figure 3).

In 1991, in the structure of all pregnancies outcomes, the rate of

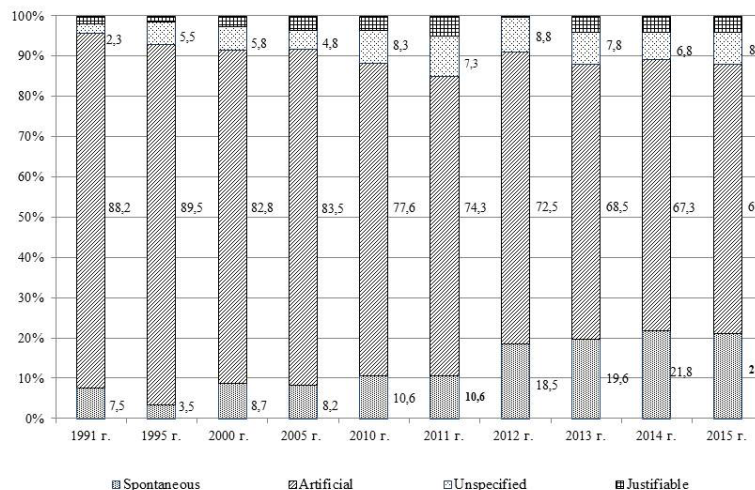


Fig. 1. Structure of abortions types.

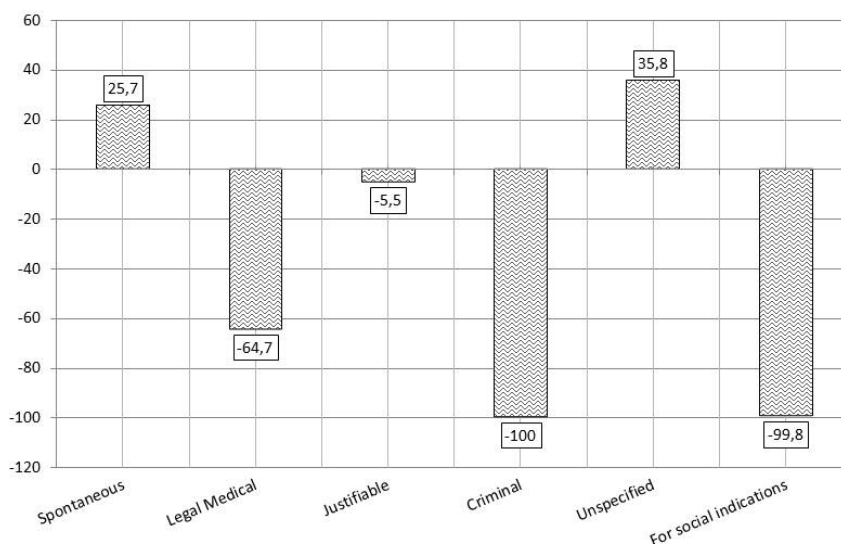


Figure 2. Rate of Growth (Decrease) of abortions for the period 1991-2015.

Table 1

Table 1. Structure of abortions types in dynamics

	1991	1995	2000	2005	2010	2011	2012	2013	2014	2015
<b>Medical</b>										
Per 1,000 women of fertile age	88,0	69,2	60,5	47,9	37,7	35,5	31,7	32,4	31,3	31,0
Per 100 born dead and alive	131,7	124,7	127,9	97,6	67	59,3	52,1	48,8	45,5	45,1
<b>Spontaneous</b>										
Per 1,000 women of fertile age	7,5	2,7	4,6	4,8	5,1	3,8	5,6	9,3	10,1	10,1
Per 100 born dead and alive	11,2	5,0	9,8	9,8	9	6,3	10,4	13,9	14,7	14,2
<b>For social indications</b>										
Per 1,000 women of fertile age	-	-	2,2	0,75	0,55	0,033	0,037	0,01	0,004	0,004
Per 100 born dead and alive	-	-	4,6	1,5	1	0,05	0,06	0,02	0,006	0,006
<b>Justifiable</b>										
Per 1,000 women of fertile age	1,9	1,2	1,9	2,0	1,2	1,3	0,5	1,96	1,9	1,8
Per 100 born dead and alive	2,9	2,1	4,2	4,2	2,2	2,2	0,9	2,96	2,8	2,7
<b>Unspecified</b>										
Per 1,000 women of fertile age	2,3	4,5	3,1	2,8	3,5	2,4	3,1	3,7	3,2	3,6
Per 100 born dead and alive	3,4	7,9	6,5	5,7	6,2	4,1	5,1	5,6	4,6	5,3
<b>Criminal</b>										
Per 1,000 women of fertile age	0,4	0,07	0,03	0,003	0,003	0,003	0,003	0,02	0,01	-
Per 100 born dead and alive	0,6	0,12	0,07	0,007	0,006	0,006	0,006	0,02	0,02	-



abortions made by 15-19 year old girls was 45%. The indicator for 1,000 girls of the same age was 52. In 2015 this indicator decreased to 12.7, and abortions made 27% of all pregnancies (Figure 4).

In the correlation analysis it was found out that with the frequency of abortions the coefficients of total fertility and crude birth rate, fecundity rate, the proportion of normal births and the rate of natural increase were negatively correlated. An increase in the total number of abortions was statistically significantly associated with an increase in stillbirth. The indicators of maternal and infant mortality rate, premature birth, hemorrhage in the consecutive and postpartum period positively correlated with the frequency of abortions (Table 3).

Thus, the analysis of the dynamics and structure of officially registered abortions revealed that the observed decrease in the number of abortions was accompanied by the transformation of their structure in the 1990s. The high prevalence of spontaneous abortion (termination of every 10<sup>th</sup> pregnancy) determined the significance of this pathology in reducing the reproductive potential of the population.

The results of the correlation analysis proved the influence of women reproductive behavior and health on demographic processes in the Sakha Republic (Yakutia).

## References

1. Burdulin G.M., Frolova O.G. Prichiny i tekhnologiya analiza reproduktivnyh poter' [Causes and technology of analysis of reproductive losses]. Moscow, 2008, 128 p.
2. Bushmeleva N.N. Reproktivnye poteri i puti ih snizheniya v region (na primere Udmurtskoj Respubliki) [Elektronnyj resurs] [Reproductive losses and ways to reduce them in the region (the Udmurt Republic as an example)] [Electronic resource]. Social'nye aspekty zdorov'ya naseleniya» [Social Aspects of Population Health], 2014, №4 (38), Rezhim dostupa: <http://vestnik.mednet.ru/content/view/596/30/lang.ru/> [Access mode: <http://vestnik.mednet.ru/content/view/596/30/lang.ru/>].
3. Polunina N.V. [i dr.] Itogi realizacii nacional'nogo proekta «Zdorov'e» v detskih ambulatorno-poliklinicheskikh uchrezhdeniya [Results of the national project "Health" implementation in children's outpatient hospitals]. Pediatriya [Pediatrics], 2012, №3, pp.

Table 2

Table 2. Structure of pregnancy termination terms (%)

Terms of pregnancy termination	1991	1995	2000	2005	2010	2011	2012*	2013	2014	2015
Up to 12 weeks	92,5	93	89,1	94,6	95,2	95,2	95,9	95,2	95,1	95,5
12-21 weeks	5,3	5,2	8,4	3,9	3,1	3,0	4,1	4,8	4,9	4,5
22-27 weeks	2,2	1,8	2,5	1,5	1,7	1,8	-	-	-	-

\*In 2012 Ministry of Health and Social Development approved medical criteria for birth registration from 22 weeks and fetal body weight of 500 g (according to perinatal criteria recommended by WHO)

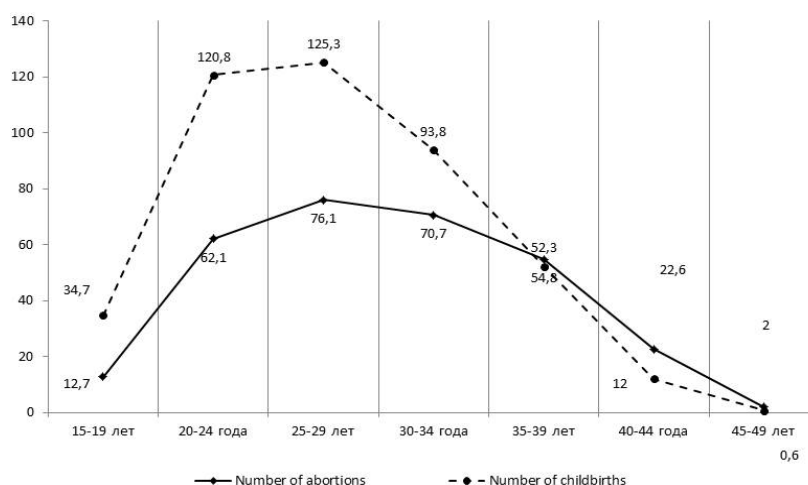


Fig. 3. Correlation of age-specific fertility rate and age-related abortion.

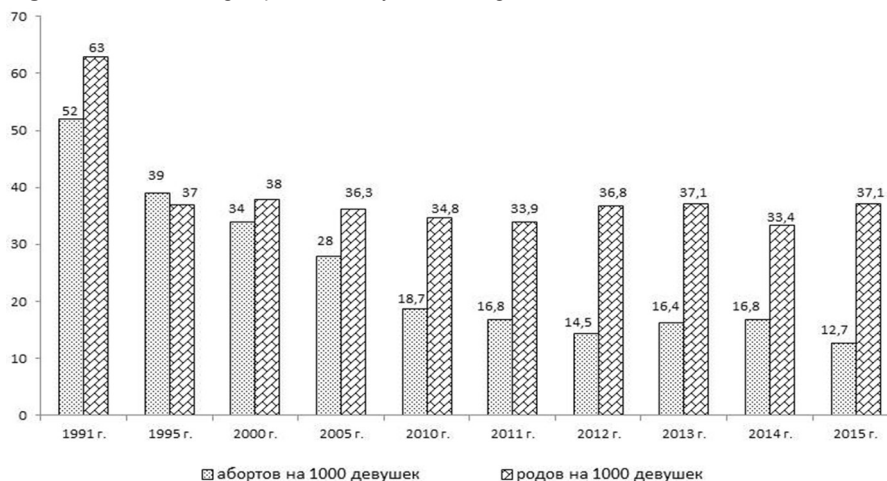


Fig. 4. Correlation of indicators of abortions and childbirths incidence rate among 15-19.

Table 3

Table 3. Correlation coefficients between indicators

indicator	Abortions per 1,000 women of fertile age	
	r	p
Total fertility rate per 1,000 of total population	- 0,816	0,001
Fecundity rate per 1,000 women aged 15-49	- 0,818	0,001
Crude birth rate	- 0,630	0,028
Still-born rate per 1,000 born dead and alive	0,640	0,025
Child mortality rate per 1,000 born alive	0,906	<0,001
Mother mortality rate per 100,000 born alive	0,887	<0,001
Natural increase per 1,000 of population	- 0,838	0,001
The proportion of normal births from the total number of births	- 0,660	0,023

Note: r- Pearson correlation coefficient, p- achieved level of statistical significance

- 21-26.
4. Starodubov V.I., Suhanova L.P., Sychenkov Yu.G. Reproktivnye poteri kak mediko-social'naya problema demograficheskogo razvitiya Rossii [Elektronnyj resurs] [Reproductive losses as a medical and social problem in the demographic development of Russia [Electronic resource]. Social'nye aspekty zdorov'ya naseleniya [Social Aspects of Population Health], 2014, №4 (38), Rezhim dostupa: [http://vestnik.](http://vestnik.mednet.ru/content/view/367/30/)

[mednet.ru/content/view/367/30/](http://vestnik.mednet.ru/content/view/367/30/) [Access mode: <http://vestnik.mednet.ru/content/view/367/30/>].

5. Frolova O.G. [i dr.] Prenatal'naya diagnostika – vazhnejshaya zadacha regional'nyh programm modernizacii zdavoohraneniya [Prenatal diagnosis as the most important task of regional programs of healthcare modernization]. Akusherstvo i ginekologiya [Obstetrics and gynecology], Moscow, 2012, № 5, pp. 75-78.
6. Cybul'skaya I.S. Mediko-social'nye

aspekty formirovaniya zdorov'ya detej [Medical and social aspects of children's health formation]. Tver': Tverskaya Gorodskaya Tipografiya [Tver: LLC Tver City Printery], 2013, 288 p.

#### The author

Yarovskiy Aleksey A., Post-graduate student, Medical Institute NEFU, Yakutsk, the Sakha Republic (Yakutia), Russia, Tel: 8-914-2-74-76-70, E-mail: [yavorskiy2011@mail.ru](mailto:yavorskiy2011@mail.ru).

M.B. Kutsyi, M.S. Karasev, N.Yu. Vladimirova, V.S. Gorokhovskiy, I.A. Stadnikova, N.V. Grishina, A.G. Serebrennikov

## THE EXPERIENCE OF INTEGRATION OF THE EUROPEAN GUIDELINES ON MANAGEMENT OF MAJOR BLEEDING DURING OPERATIVE DELIVERY AMONG WOMEN WITH PLACENTA PERCRETA

DOI 10.25789/YMJ.2018.63.34

### ABSTRACT

The article reflects the experience of transfusion therapy in major obstetric bleeding during cesarean section among women with placenta percreta from 2016 to 2018. A comparative analysis of the applied blood components and blood products is presented in the article. The analysis has shown that integration of The European guidelines on management of major bleeding allows decreasing the average volume of blood loss, reducing postoperative transfusions, reducing the frequency of postoperative mechanical ventilation, as well as reducing duration of stay in the intensive care unit.

**Keywords:** massive hemorrhage, obstetrics, infusion-transfusion therapy.

### Introduction

Despite the rapid development of medical technologies, maternal mortality around the world remains significantly high. Every day about 830 women die from complications related to pregnancy or childbirth [2]. According to the World Health Organization, in 2015, approximately 303,000 women died during and after pregnancy and childbirth [3].

Women die in a result of complications during and after pregnancy and childbirth. Most of these complications are preventable. The main complication leading to maternal mortality is major bleeding [4]. One of the main risk factors for major bleeding is placenta percreta [1].

Major bleeding is often impossible to predict, and often impossible to control, therefore infusion-transfusion therapy in major bleeding is essentially important and it determines the success of treatment of patients with placenta percreta.

### Purpose of the research

Reducing the number of complications

related to infusion-transfusion therapy in major bleeding among women with placenta percreta during cesarean section.

### Materials and methods

During the period from 2016 to 2018, 27 patients with placenta percreta (9 patients per year) were operated in Khabarovsk, KGBUZ Perinatal Center. The caesarean section was performed at 37 weeks gestation. All patients underwent total hysterectomy. During the operation, all patients underwent general combined anesthesia with intubation of the trachea and mechanical ventilation. The operations among all patients were followed with major obstetric bleeding, more than 40% of the total blood volume (TBV).

Complex of preoperative checkup included general clinical tests, ultrasound examination of the uterus, MRI of the uterus, specialists examination. Complex of preoperative patient preparation included: among women with iron deficiency anemia - parenteral iron injections. In the absence of contraindications, the preparation of

frozen autoplasm was done.

During the operation, if there were no contraindications, all patients underwent a reinfusion of auto-red blood cells.

Infusion-transfusion therapy changes every year. In 2018, transfusion therapy was applied according to the European guidelines for major bleeding [5]. The basis of the infusion- transfusion tactics was:

1. Providing transfusion in a restrictive mode - balanced crystalloids in the volume up to 2000 - 2400 ml;

2. Before the achievement of surgical hemostasis, using the concept of acceptable hypotension with a target level of systolic blood pressure 80-90 mm Hg, with correction of hypotension (in case of its development) by early use of noradrenaline;

3. Preventive transfusion of red blood cells components (starting from the moment when placenta percreta was confirmed intraoperative);

4. Targeted use of moderate doses of fresh frozen plasma (FFP) in combination with cryoprecipitate as a source of fibrinogen;

5. Pre-emptive transfusion of platelets concentrate;

6. Widespread and early (when blood loss is more than 50% of total blood volume) use of recombinant factor VIIa - eptactagogue alpha;

7. Minimization of use of colloid solutions until complete cancellation;

8. Preventive injections of tranexamic acid to all patients in a dose of 1000 mg, repetition of the dose when blood loss exceeds 50% of total blood volume.

### Results and discussion

The introduction of the European guidelines has led to significant changes in the intraoperative and postoperative dynamics of the patients' status. So, as criteria for the stability of the patient, we estimated the average duration of postoperative stay in intensive care unit, the frequency of postoperative mechanical ventilation, the frequency of intraoperative and postoperative use of noradrenaline to stabilize hemodynamics, and the frequency of postoperative renal replacement therapy. Also, the frequency of postoperative transfusion therapy became extremely important criteria to estimate the effectiveness of the used tactics (Table 1).

Certainly, due to the small amount of cases, we did not receive statistical reliability of the differences in the criteria listed above; however, the dynamics shown speaks for itself. Management of the patients both during surgery and in the postoperative period is accompanied by a much higher stability of the condition, hemodynamics, early recovered consciousness and spontaneous breathing, absence of clinical and laboratory parameters of hemorrhagic shock.

With the integration of the European guidelines and the beginning of pre-emptive transfusion therapy, the main objection was a possibility of the significant increase of the transfusion volume, potentially leading to the increase of post transfusion complications. However, due to the analyzed research results, we found that the integration of the European guidelines did not lead to an increase of red blood cells and plasma components volume (Table 2). Thus, working according to the European guidelines doesn't lead to an increase of the transfusion volume, but it leads to pre-emptive and preventive transfusion therapy.

But the main result obtained after adding the transfusion of platelets concentrate, cryoprecipitate, and eptactagogue alpha was a significant decrease in the average volume of blood

Table 1

The frequency of major bleeding complications in years 2016-2018

	2016	2017	2018
Duration of postoperative stay in the intensive care unit, days	4,2	3,1	1,3
Postoperative mechanical ventilation, total (%)	3 (33,3)	1 (11,1)	0
Use of norepinephrine during surgery, total (%)	7 (77,8)	5 (55,6)	2 (22,2)
Use of norepinephrine after surgery, total (%)	3 (33,3)	2 (22,2)	0
Postoperative renal replacement therapy, total (%)	3 (33,3)	1 (11,1)	0
Postoperative transfusions, total number of patients (%)	5 (55,6)	3 (33,3)	0

loss compared to 2016 (Fig.).

### Conclusion.

Analyzing the research, it should be noted that the integration of the European guidelines of major bleeding during the cesarean section among women with placenta percreta allows reducing the overall blood loss, reducing the number of postoperative transfusions, the frequency of postoperative mechanical ventilation, and shortening the time of patients' stay in the intensive care unit. At the same time, the infusion-transfusion therapy is not followed by the increase of erythrocyte components and fresh-frozen plasma volume. Thus, based on the obtained results, we can recommend the integration of the European guidelines of major bleeding in third level obstetric hospitals, during the operations among women with placenta percreta.

### References

1. Adamyan L.V. Serov V.N. [et al.]. Profilaktika, lechenie i algoritm vedeniya pri akusherskikh krvotekheniya. Klinicheskie rekomendacii (Protokol) [Prevention, treatment and patient management with obstetric bleeding. Clinical guidelines (Protocol)]. Moscow, 2014, 25p.
2. Alkema L. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group / Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. - Lancet. 2016; 387 (10017): 462-74.
3. Patton G.C. Global patterns

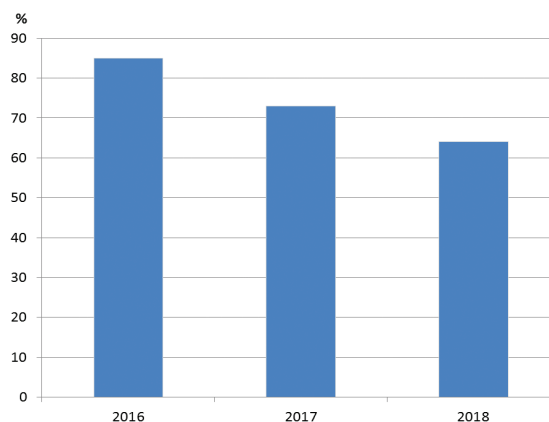
of mortality in young people: a systematic analysis of population health data / Patton GC, Coffey C, Sawyer SM, Viner RM, Haller DM, Bose K, Vos T, Ferguson J, Mathers CD. - Lancet, 2009, 374:881-892.

4. Say L. Global Causes of Maternal Death: A WHO Systematic Analysis / Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels JD, et al. -
5. Lancet Global Health. 2014;2(6): e323-e333.
6. Rossaint R. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition / R. Rossaint, B. Bouillon et al. - Critical Care (2016) 20:100.

Table 2

Dynamics of changes in blood components and blood products introduction

	2016	2017	2018
Auto-red blood cells, ml	5361	11307	6025
Auto-fresh frozen plasma, ml	4700	8170	2500
Donor red blood cells, ml	14708	7409	8772
Fresh frozen plasma, ml	11570	8290	9860
Platelets concentrate, dose	4	4	20
Cryoprecipitate, dose	0	0	17
Eptactagogue alpha (recombinant factor VIIa), mg	0	3,6	15,6



Correlation of the average volume of blood loss with the total blood volume.



### The authors

1. Mikhail Borisovich Kutcyi, M.D., head of department of anesthesiology and intensive care, «Perinatal center» Khabarovsk region. +79142097120 mkutsyy@gmail.com
2. Michail Sergeevich Karasev, doctor anesthesiologist-resuscitator of department of extracorporeal hemocorrection methods «Perinatal center», postgraduate student of «Anesthesiology, resuscitation, transfusiology and ambulance» department of Far Eastern State Medical University. +79098748372 fishop@mail.ru
3. Vladimirova Natalia Urievna, PhD, professor, deputy chief in obstetrics of «Perinatal center», professor of «Obstetrics and gynecology» department of Postgraduate institute for Public Health Workers. +79147723550 Zam.pc@mail.ru
4. Vadim Semenovich Gorokhovskii, PhD, chief of «Anesthesiology, resuscitation, transfusiology and ambulance» of Far Eastern State Medical University. +79241015246 vadsgr@yandex.ru
5. Irina Andreevna Stadnikova, doctor transfusiologist of department of extracorporeal hemocorrection methods «Perinatal center» Khabarovsk region. +79147775258 rinastar06@mail.ru
6. Nina Victorovna Grishina, doctor anesthesiologist-resuscitator of department of extracorporeal hemocorrection methods «Perinatal center» Khabarovsk region. +79242034135 nina.grishina1954@gmail.com
7. Artur Gennadievich Serebrennikov, doctor anesthesiologist-resuscitator of department of anesthesiology and intensive care, «Perinatal center» Khabarovsk region. +79141998249 artur4815@rambler.ru

O. N. Ivanova, E.F. Argunova, T.G. Dmitrieva, Ya.A. Munchalova, V.B. Egorova, S.N. Alekseeva

## THE STUDY OF IMMUNITY IN CHILDREN WITH MULTIPLE PAPILOMAS

DOI 10.25789/YMJ.2018.63.35

### ABSTRACT

This article is devoted to an urgent problem-multiple papillomas in children. A group of children (n=30) aged 9 to 12 years with multiple papillomas was examined. A group of healthy children (n=20) was also examined, compared groups of children are comparable in age. All children (n=30) had positive PCR for HPV, as well as histological study of papillomas. All children were examined for immune status (CD3+, CD4+, CD8+, CD16+, CD22+, IgA, IgG, IgM, IgE) on the base of National Medical centre of Republik Sakha Yakutia. Comparison of mean values was performed by one-factor analysis of variance using student's T-test to assess the equality of Fisher's f-test means. The relationship between the parameters was evaluated using linear and rank correlation coefficients. It was found that in children with papillomas reduced the content of IgA, CD19+ and CD16+ lymphocytes. All examined children received therapy drug groprinosin 500 mg age dose for 10 days, then the drug Likopid in the age dose for 10 days. All children with papillomas were found to have immune dysfunction or insufficiency affecting cellular and humoral immunity (IgA reduction, CD19+ lymphocyte reduction). It was revealed that therapy with groprinosin and lycopid drugs leads to the normalization of reduced immune status indicators: an increase in the content of CD19+, IgA, an increase in the concentration of IgA, and the absence of new papillomas in children.

**Keywords:** papillomas, children, immunity, immunocorrector, immunoglobulins, lymphocytes.

Papillomas are a disease that affects the skin and cells of the mucous membranes. The cause of papillomas is the human papilloma virus, which belongs to the Papoviridae family, the Papillomavirus group. The ability of the virus to integrate its DNA into the genome of human cells is a feature of HPV.

When injected into the blood channel, at the initial stage of HPV affects the basal cells of the epithelium. Microtrauma, scuffs, cracks and other skin damage contribute to the penetration of the papilloma virus into the body. For a long time, the virus may initially multiply without appearing clinically [1].

Papilloma is a neoplasm of the skin or mucous membranes and looks like papillary proliferation that protrudes over the surrounding tissue. Papillomas are localized on the skin, mucous membranes.

When traumatizing papillomas, bleeding is possible, since it consists of connective tissue covered with skin and contains vessels. The tumor grows upwards outward in the form of scattered papillae in different directions and resembles cauliflower [2,3,4].

Skin color may not change, but in most cases, papillomas are white to dirty brown. The favorite localization of papillomas is the skin of the hands and hands. In patients with HPV immunodeficiency infection is manifested in the form of multiple papillomas. The concentration of the virus in the affected areas reaches a maximum by the 6th month from the moment of infection, this period is the most contagious.

PCR diagnosis allows to confirm the presence of human papillomavirus in the body and to determine its type and diagnose how many viruses there are in the body at the time of the analysis.

If the method of treatment is papilloma removal, then a biopsy is performed in parallel with the surgery to conduct a cytological study [1,5,6].

The treatment scheme of papillomas in each case is selected individually. If there are symptoms of HPV on the skin and mucous membranes, depending on the localization and symptomatology are resorting to cryotherapy for warts, electrocoagulation or removal of papillomas of the laser. It should

be borne in mind that the removal of papillomas does not lead to a complete recovery. Therefore, patients with previously diagnosed papillomas need to undergo periodic examination and conduct courses of antiviral therapy. The most effective treatment regimens include antiviral and immunomodulatory drugs.

The purpose of the study: to study the characteristics of immunity in children with multiple papillomas of the effectiveness of the therapy drugs groprinosin and Likopid.

Materials and methods a group of children (n=30) aged 9 to 12 years with multiple papillomas was examined. A group of healthy children (n=20) was also examined, compared groups of children are comparable in age. Informed consent was obtained from the parents of all children. All children (n=30) showed positive HPV DNA. Types of HPV 1,2,3,4,10 were revealed. All children were examined for immune status (CD3+, CD4+, CD8+, CD16+, CD22+, IgA, IgG, IgM, IgE) on the basis of RB No. 1-NCM RS(I). Comparison of mean values was

performed by one-factor analysis of variance using student's T-test to assess the equality of Fisher's f-test means. The relationship between the parameters was evaluated using linear and rank correlation coefficients.

Results: in the study of the disease history in children with papillomas, the appearance of new papillomas was noted weekly. Removal of papillomas did not bring any therapeutic effect, after 2-3 days there were new papillomas. Therefore, it is advisable to use antiviral therapy. In the analysis of the immune status, it was revealed that in the group of all the examined children there was a reduced level of IDA (table 1).

There was also a decrease in the content of CD19+ and CD16+ lymphocytes, that is, normal killers, providing antiviral protection.

Since the causative agent of the infection is detected in the form of proviruses in the epithelial cells of the skin and mucous membranes at the sites of localization of previous recurrences with electron microscopy of histological biopsies, the inclusion of isoprinosine in the treatment complex of antiviral agents is justified and necessary [3]. Likopid is no less important, because along with systemic immune deficiency in HPV infection, there is a decrease in local resistance of the skin and mucous membranes and a weakening of local immune reactions that counteract the development of infection [1].

In the treatment of children with papillomas, a course of combination of 2 drugs was used: the antiviral drug groprinosin at a dose of 250mg ½ tablet 3 times a day for 10 days and then the immunomodulator Likopid at a dose of 1mg (1tablet) 2 times a day for 10 days, 2 courses of therapy were conducted with an interval of 1 month. At the end of the course of therapy, clinical manifestations of papillomas were not observed in any of the children. At the end of the second course, after 3 months, immunological studies were carried out for all treated children (table 2).

Therapy drugs groprinosin and Likopid led to the normalization of some parameters of cellular and humoral immunity: the increase in the content of CD19+, CD16+, the increase in the concentration of IgA and the appearance of new papillomas on the skin.

Discussion: thus, the use of combined treatment of groprinosin and lycopid in multiple papillomas in children is both a timely and necessary component of treatment. Together with

Table 1

**Indicators of immune status in children of Republik Sakha (Yakutia) in children with multiple papillomas and healthy children**

Indicators	Children with multiple papillomas (n = 30)	Health children (n = 20)
CD3+	27,4 ± 1,0	27,2±1,04
CD4+	20,1 ± 0,2	21,3±0,6
CD8+	10,9 ± 0,5	12,1±2,5
CD16+	6,4 ± 1,4	11,0±1,01*
ИРИ	0,8 ± 0,5	1,08±0,02
IgA	0,6 ± 0,1	2,9±0,6*
IgG	18,1 ± 0,2	17,1±0,09
IgM	2,6 ± 0,02	2,9±0,09
CD19+	11,2 ± 1,6*	24,6±0,7*
ЦИК	75,1 ± 1,5	70±0,07

\*p < 0.05 between the standards and the obtained indicators in each group.

immunomodulatory effects towards activation of natural immunity (activation of natural killer cells and cytotoxic T-lymphocytes), groprinosin and Likopid exert an indirect antiviral effect by suppressing intracellular reproduction of pathogens.

#### Conclusion

1. All the children with papillomas were found to have immune dysfunction or insufficiency affecting cellular and humoral immunity (decrease in IgA, decrease in CD16+ lymphocytes, decrease in CD19+).

2. Therapy with Lycopodium in patients with papillomas leads to the normalization of reduced immune status: increased content of CD19+ and CD16+, increased concentration of IgA.

#### References

- Kostava M. N., Prilepskaya V. N. Vozmozhnosti terapii papillomavirusnoj infekcii [Possibilities of therapy of papillomavirus infection] Rus. med. zhurn. 2009; 17 (1), 9–16.
- Mynbaev O. A., Eliseeva M. YU., Doorbar Dzh., Manuhin I. B. Ehpideologiya, molekulyarnaya biologiya, patofiziologiya pi principy immunoterapii papillomavirusnoj infekcii [Epidemiology, molecular biology, pathophysiology PI principles of immunotherapy of papillomavirus infection] Vopr. ginekol., akush. i perinatol. 2009; 8 (3): 69–79.
- Nesterova I. V. Strategiya i taktika immunoterapii vtorichnyh immunodeficitov

Table 2

**Indicators of immune status in children multiple papillomas before and after therapy with groprinosin and lycopid**

Indicators	Children with papillomas before therapy (n = 30) M ± m	Children with papillomas after therapy (n = 30) M ± m
CD3+	27,4 ± 1,0	27,8±0,76
CD4+	20,1 ± 0,2	22,1±0,7
CD8+	10,9 ± 0,5	11,1±0,5
CD16+	6,4 ± 1,4	12,2±0,81*
ИРИ	0,8 ± 0,5	1,32±0,2
IgA	0,6 ± 0,1	2,8±0,4*
IgG	18,1 ± 0,2	19,2±0,1
IgM	2,6 ± 0,02	2,8±0,12
CD19+	11,2 ± 1,6*	22,3±0,8*
ЦИК	75,1 ± 1,5	67±0,09

s infekcionnym sindromom [Strategy and tactics of secondary immunodeficiencies immunotherapy infectious syndrome] Vestnik MEDSI. 2009; 3: 24–32.

- Prilepskaya V. N., Rogovskaya S. I., Kondrikov N. I., Suhin G. T. Papillomavirusnaya infekciya: diagnostika, lechenie i profilaktika [Human Papillomavirus infection: diagnosis, treatment and prevention.] M.: MEDpress-inform, 2007.
- Chan P. K., Chang A. R., Cheung J. L. et al. Determinants of cervical human papillomavirus infection: Differences between high- and low-oncogenic risk types // J Infect Dis. 2002, 185: 28–35.

#### The authors

- Ivanova Olga Nikolaevna -doctor of medical sciences, Professor of Pediatrics and pediatric surgery Department of NEFU, olgadoctor@list.ru;
- Argunova Elena Filippovna – candidate of medical Sciences, associate Professor of Pediatrics and pediatric surgery MI NEFU;
- Dmitrieva Tatyana Gennadiyevna - doctor of medical sciences, Professor of Pediatrics and pediatric surgery Department of NEFU, dtg63@mail.ru;
- Munkhalova Yana Afanasievna - Candidate of Medical Sciences, Head of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of NEFU, tokmacheva@mail.ru;
- Egorova Vera Borisovna - Candidate of Medical Sciences, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of NEFU, veraborisovna@yandex.ru;
- Alekseeva Sargylana Nikolaevna - Candidate of Medical Sciences, Associate Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute of NEFU, sargylanao@mail.ru.

E.N. Sazonova, D.V. Yakovenko, O.A. Lebed'ko,  
A.Yu. Marochko, S.L. Zharskij, V.A. Dobryh,  
M.F. Rzyankina, T.V. Chepel'

## BIOSYNTHETIC PROCESSES IN CARDIOMYOCYTES OF ALBINO RATS AFTER ADMINISTRATION OF DIHYDROQUERCETIN

DOI 10.25789/YMJ.2018.63.36

### ABSTRACT

The aim of the research was to study the effect of dihydroquercetin on DNA synthesis and anabolic processes in the myocardium; to analyze the role of changes in biosynthetic processes in cardioprotective effects during oxidative stress. Materials and methods. Dihydroquercetin ("Ametis", Russia) was injected to newborn and adult albino rats Wistar intraperitoneally in a dose 50 mg/kg during 5 days daily. Oxidative stress was modeled by hypobaric hypoxia. Biosynthetic activity was evaluated by autoradiography with  $^3\text{H}$ -thymidine and morphometry of nucleolo-nucleoli apparatus. Parameters of free-radical oxidation was investigated by chemiluminescence. Results. Administration of dihydroquercetin to intact newborn rats from 2 to 6 postnatal days depressed the DNA-synthetic activity of cardiomyocytes and increased the nucleoli amount in right ventricle cardiomyocytes. Administration of dihydroquercetin to newborn rats, exposed to intrauterine hypoxia, corrected negative cardiac consequences of antenatal hypoxia. In adult male rats injections of dihydroquercetin induce the decrease of cardiomyocytes' nuclei size and total area of nucleoli in cardiomyocytes' nuclei. These changes may reflect the inhibition of cardiomyocytes anabolic activity. Administration of dihydroquercetin to adult male rats preliminarily before hypobaric hypoxia corrected the post-hypoxic changes of heart weight and total area of nucleoli of right ventricle cardiomyocytes. Conclusion. Dihydroquercetin has a positive corrective effect on the biosynthetic processes in the myocardium of albino rats in the presence of oxidative stress. But in «healthy» heart dihydroquercetin induces adverse affects, because it inhibits DNA synthetic processes in the myocardium of newborn animals and significantly reduces the morphometric nucleolo-nucleolar parameters of adult rats cardiomyocytes. The data obtained allow to recommend the using of antioxidants in cardiology only in the presence of pronounced oxidative stress.

**Keywords:** cardiomyocytes, antioxidants, DNA synthesis, nucleoli, free-radical oxidation.

### Introduction

Antioxidants are recommended for the prevention of cardiac pathology [2]. Plant bioflavonoid dihydroquercetin (DHQ) is considered as a reference antioxidant [6] and is used for prevention and treatment cardiovascular disorders [8]. DHQ and it analog quercetin have a positive effects in ischemically-reperfusion [12], post-traumatic [11], diabetic [13] and other myocardial lesions. DHQ reduces the angiotensin II level in the myocardium, decreases the formation of reactive oxygen species (ROS) by inhibiting the NADPH-oxidase activity of cardiomyocytes (CMC) [13].

The aim of the research was to study the effect of dihydroquercetin on DNA synthesis and anabolic processes in the myocardium, to analyze the role of changes in biosynthetic processes in cardioprotection under oxidative stress.

### Materials and methods

Newborn and adult albino Wistar rats were used in experiments. All experimental manipulation were performed according to all institutional and national guidelines for the care and use of laboratory animals. Rats were kept in a well-ventilated cage under standard laboratory conditions. They were fed pellet diet and water *ad libitum*. The permission of the Ethical Committee of the Far Eastern State Medical University

was obtained for carrying out the experiments.

At the first stage of the study, newborn offspring of intact female rats and female rats exposed to hypobaric hypoxia during pregnancy were used. For modeling the hypobaric hypoxia, pregnant females from 14 to 19 gestation days were placed in a hypobaric chamber, in which a low pressure (224 mm Hg) was created. The partial pressure of oxygen was 42 mm Hg, accordingly. The duration of daily hypoxic exposure was 4 hours: decompression and pressure increasing continuance were one hour, the duration of the stationary hypobaric state was two hours. Other group of pregnant rats (control) did not incubate in hypoxic conditions. The offsprings were divided into four experimental groups randomly. The "Control group": animals were subjected to intraperitoneal injection of isotonic sodium chloride solution (0,1 ml) from 2 to 6 postnatal days daily. The "DHQ group": animals were subjected to intraperitoneal injection of dihydroquercetin (50 mg/kg; "Ametis", Russia) from 2 to 6 postnatal days daily. The "Antenatal hypoxia group": animals were exposed to intrauterine hypoxia and were subjected to intraperitoneal injection of isotonic sodium chloride solution (0,1 ml) from 2 to 6 postnatal days daily. The "Antenatal hypoxia+DHQ group": animals were

exposed to intrauterine hypoxia and were subjected to intraperitoneal injection of dihydroquercetin (50 mg/kg; "Ametis", Russia) from 2 to 6 postnatal days daily.

After 24 hours after the final injection, the 7-day-old animals were weighed and withdrawn from the experiment by rapid decapitation under anesthesia. One hour prior to euthanasia, 7-day-old animals were intraperitoneally injected with  $^3\text{H}$ -thymidine at a dose of 1  $\mu\text{Ci}$  per gram to assess the DNA synthesizing activity of CMC.

At the second stage of the study adult (60-days-old) male rats were used. Four experimental groups was formed also. The "Control group": animals were subjected to intraperitoneal injection of isotonic sodium chloride solution (0,1 ml) 5 days daily. The "DHQ group": animals were subjected to intraperitoneal injection of dihydroquercetin (50 mg/kg; "Ametis", Russia) 5 days daily. The "Hypoxia group": animals were exposed to hypobaric hypoxia during 4 hours 5 days daily (partial pressure of oxygen was 42 mm Hg) with prior administration of isotonic sodium chloride solution (0,1 ml) 60 mins before hypoxic exposure. The "DHQ+hypoxia group": animals were exposed to hypobaric hypoxia during 4 hours 5 days daily (partial pressure of oxygen was 42 mm Hg) with prior administration of dihydroquercetin (50



mg/kg; "Ametis", Russia) 60 mins before hypoxic exposure. 24 hours after the final experimental procedure, the adult male rats were weighed and then rapid decapitation after 30-second raush anesthesia with chloroform vapors was carried out. After organ extraction the heart weight was evaluated.

Then the tissue fragment was placed in the Carnoy fixator with standard histological procedure. The autoradiographs of 7-day-old animals' heart was prepared according to the procedure adopted in the laboratory [1]. The index of labeled nuclei (ILN, %) was determined by viewing at least 2,000 CMC nuclei in each investigated area of the myocardium. The intensity index (II), which indirectly characterizes the rate of DNA synthesis, was estimated as the average number of tracks over the nucleus.

In order to analyse the protein-synthesizing activity of CMC, histological sections of heart stained with silver nitrate was prepared [4]. The average number of nucleoli was counted by viewing at least 100 nuclei in the subendocardial zones of the left and right heart ventricles. Computer morphocytometry was performed on the MEKOS-C image analyzer: the area of nuclei and nucleoli of cardiomyocytes, the average number of nucleoli in the nuclei of cardiomyocytes were determined.

Reactive oxygen species generation in heart homogenates were evaluated by chemiluminescence assay (CML). Registration of CML was carried out on a luminescent spectrometer LS 50B "PERKIN ELMER". The standardization of the CML signal was performed using special program «Finlab». The CML study included the determination of a number of parameters for the intensity of spontaneous and activated luminescence: Ssp. – parameter of 1 minute spontaneous CML, which directly correlates with the reactive oxygen species' production; H1 – maximum of amplitude of the Fe<sup>2+</sup>-induced luminescence quick flash, which indicates the content of lipid peroxidation products; Sind 1 – parameter of 2 minutes Fe<sup>2+</sup>-induced CML, reflecting the rate of peroxide radicals generation; H2 – maximum of amplitude of the H<sub>2</sub>O<sub>2</sub>-induced luminol-dependent CML, that inversely correlates with substrate' peroxide resistance; Sind 2 – parameter of 2 minutes H<sub>2</sub>O<sub>2</sub>-induced luminol-dependent CML, which inversely correlates with antioxidant capacity. CML parameters were calculated per 1 g tissue and expressed in relative units.

The statistical analysis was performed using the Statistica software version 6.0 by the t-Student test. Differences between groups were considered significant at  $p < 0.05$ . The total number of animals used in the work was 126 rats.

### Results and discussion

First of all, we studied the effect of DHQ in the myocardium of newborn rats. Five-fold administration of DHQ does not change the body and heart weight of 7-day-old rats (Table 1). When DNA-synthetic processes in the myocardium was studied, a decrease of the amount of CMC in the S-phase of the cell cycle was found in the left atrium myocardium (by 31,4%), in the right atrium myocardium (by 35,1%). Also a decrease of the CMC intensity index of the right ventricle myocardium was registered (by 12,6%) (Table 2). We registered the increase of nucleoli amount (by 9,5%) in the nuclei of the right ventricular CMC of the experimental rats [9]. Thus, DHQ induced inhibition of proliferative and activation of protein-synthetic activity of CMC. This effects can indicate on the stimulation of differentiation processes in the myocardium of newborn animals under the antioxidant influence. It is known, that ROS in developing CMC prevent cell differentiation, and pharmacological reduction of the ROS generation during cardiogenesis stimulates differentiation

of CMC [10].

We analyzed the effect of DHQ on the biosynthetic activity of CMC of newborn rats, exposed to antenatal hypoxia. Antenatal hypoxia induced the decreasing of the body weight (by 24,8%) and the heart weight (by 25,6%) of 7-day-old rats (Table 1), and caused inhibition (by 30,8-34,0%) of DNA-synthetic activity of CMC of the examined heart chambers (Table 2). This results agree with the our early data about the cardiac consequences of antenatal hypoxia [1]. The administration of DHQ to animals, exposed to antenatal hypoxia, corrected the heart weight (Table 1), normalized of DNA synthesis in the myocardium (Table 2). According to data of Petruk N.S. et al. (2014), in newborn rats exposed to antenatal hypoxia, acute myocardial ischemia occurs on the 3rd postnatal day as a result of oxidative stress [7]. Influence of DHQ is able to reduce the intensity of oxidative stress and normalize the proliferative processes in the myocardium. In addition, in 7-day-old animals of this experimental group, we registered an increase of the nucleoli amount in the CMC nucleus of left (by 35,6%) and right (by 35,2%) ventricle (Table 2).

At the next stage of the investigation, we studied the effects of five-fold administration of DHQ in adult male rats. In adult animals, the administration of

**Table 1**

**Gravimetric parameters of 7-days-old albino rats, exposed to antenatal hypoxia and administration of dihydroquercetin (DHQ)**

Parameter	Control	DHQ	Antenatal hypoxia	Antenatal hypoxia + DHQ
Index of labeled nuclei of left atria CMC	14,40±0,36	14,26±0,47	10,83±0,41*	11,08±0,45*
Index of labeled nuclei of left ventricle CMC	95,20 ± 6,43	89,67 ± 8,23	70,86 ± 5,50*	78,64 ± 6,29

\* In tables 1-5 -  $p < 0.05$  compared with "Control".

**Table 2**

**Proliferative and anabolic activity of cardiomyocytes (CMC) of 7-days-old-rats, exposed to antenatal hypoxia and administration of dihydroquercetin (DHQ)**

Parameter	Control	DHQ	Antenatal hypoxia	Antenatal hypoxia + DHQ
Index of labeled nuclei of left atria CMC	5,76±0,67	3,95±0,25*	3,87±0,29*	4,65±0,17
Index of labeled nuclei of left ventricle CMC	8,33 ± 0,67	7,78±0,35	5,60 ± 0,21*	7,60 ± 0,28
Intensity index of left ventricle CMC	21,90 ± 0,93	19,95±0,62	17,44 ± 1,70*	19,74 ± 0,47
Nucleoli amount in left ventricle CMC	2,19±0,05	2,41±0,11	2,24±0,07	2,97±0,07*
Index of labeled nuclei of right atria CMC	5,49±0,67	3,56±0,21*	3,80±0,29*	4,58±0,33
Index of labeled nuclei of right ventricle CMC	6,56 ± 0,64	5,97±0,26	4,33 ± 0,17*	6,10 ± 0,21
Intensity index of right ventricle CMC	21,54 ± 0,71	18,83±0,20*	16,09 ± 1,57*	19,65 ± 0,53
Nucleoli amount in right ventricle CMC	2,10±0,05	2,30±0,07*	2,25±0,05	2,84±0,06*

Table 3

**Gravimetric parameters of adult albino rats, exposed to hypoxia and administration of dihydroquercetin (DHQ)**

Parameter	Control	DHQ	Hypoxia	DHQ + hypoxia
Body weight (g)	236,25±25,6	241,88±20,34	242,5±8,86	232,22±13,02
Heart weight (g)	0,894±0,097	0,919±0,084	1,03±0,075*	0,932±0,068

Table 4

**Nucleo-nucleolar parameters of cardiomyocytes (CMC) of adult albino rats, exposed to hypoxia and administration of dihydroquercetin (DHQ)**

Parameter	Control	DHQ	Hypoxia	DHQ + hypoxia
Size of nuclei of left ventricle CMC	48,80±1,16	41,99±1,44*	43,97±1,23*	36,67±0,92*
Total area of nucleoli of left ventricle CMC	3,69±0,14	2,54±0,12*	3,18±0,12*	3,00±0,11*
Amount of nucleoli of left ventricle CMC	1,97±0,07	1,91±0,05	2,04±0,14	1,88±0,06
Size of nuclei of right ventricle CMC	50,44±1,53	33,67±1,29*	39,95±1,21*	28,8±1,01*
Total area of nucleoli of right ventricle CMC	2,75±0,10	2,38±0,094*	2,02±0,10*	2,94±0,12
Amount of nucleoli of right ventricle CMC	1,93±0,03	2,01±0,07	2,00±0,05	1,89±0,03

Table 5

**Chemiluminescence parameters of homogenate of adult male rats' heart**

	Control	DHQ	Hypoxia	DHQ + hypoxia
Ssp	0,10±0,009	0,071±0,007*	0,301±0,024*	0,138±0,012
Sind-1	0,699±0,053	0,527±0,047*	1,177±0,091*	0,857±0,078
H1	0,465±0,038	0,350±0,024*	1,314±0,063*	0,731±0,066*
Sind-2	4,288±0,277	3,377±0,250*	10,222±0,828*	6,115±0,436*
H2	3,248±0,248	2,017±0,131*	8,538±0,689*	4,467±0,488

DHQ did not change the body weight, the heart weight (Table 3), and the nucleoli amount in CMC nuclei (Table 4). Morphometric studies revealed a decrease of the CMC nuclei size (by 14% and by 33,3%) and the total area of the nucleoli in the CMC nuclei (by 31,2% and by 13,4%) of the left and right ventricles, respectively (Table 4). DHQ inhibits hypertrophy of CMC and protein-synthetic processes in CMC induced by angiotensin II. Moreover, it has been shown that the excess of ROS directly induced the CMC hypertrophy [14]. The role of ROS in maintaining of the structural and functional parameters of CMC is described in the literature [3]. Injection of DHQ significantly reduced the activity of free radical generation and increased antioxidant protection of myocardial tissue (Table 5). Accordingly, the antioxidant effect of DHQ can cause a reduction of the nucleo-nucleolar apparatus parameters of CMC and decrease the activity of protein-synthetic processes in the myocardium.

Further, we analyzed the effect of the preliminary administration of DHQ on the parameters of the CMC of adult male rats, exposed to hypobaric hypoxia. Five-fold hypobaric hypoxia induced an increase of adult rats heart weight (by 15.2%) (Table 3), a decrease of the CMC nuclei size in left and right ventricles (by 9.9% and by 20.8%, respectively) and a decrease of the total area of nucleoli in CMC nuclei in left and right ventricular (by 13.8% and by 26.5%, respectively) (Table 4). Also, in the heart homogenate of this experimental group animals, pronounced stimulation of free radical generation and a decrease of antioxidant activity were observed (Table 5). Preliminary (prior to hypoxic exposure) administration of DHQ corrected the changes of the heart weight (Table 3) and parameter of total area of the nucleoli in the CMC of the right ventricle (Table 4). Also a pronounced antioxidant effect was revealed according to the chemiluminescence data (Table 5).

Thus, the DHQ injections induce a significant decrease of the CMC morphometric parameters in adult animals. This effect shows the inhibition of biosynthetic processes in the heart cells under the antioxidant influence. At the same time, the preliminary administration of DHQ before hypoxic action partially corrects the negative effect of hypoxia.

The effect of DHQ on the albino rats' heart has some ontogenetic features: the DHQ induced more pronounced deviations of the CMC parameters in intact adult animals and less correction

effects during oxidative stress, compared with newborn rats. The reason of this difference may be the low structural maturity (low differentiation) of CMC and a large proportion of anaerobic processes in the metabolic profile of the newborn animals myocardium [5].

#### Conclusion

Dihydroquercetin has a positive corrective effect on the biosynthetic processes in the myocardium of albino rats in the presence of oxidative stress. But in «healthy» heart dihydroquercetin induces adverse effects, because it inhibits DNA synthetic processes in the myocardium of newborn animals and significantly reduces the morphometric nucleo-nucleolar parameters of adult rats cardiomyocytes. The data obtained allow recommending the using of antioxidants in cardiology only in the presence of pronounced oxidative stress.

#### References

1. Zubenko S.I. Lyu Yan'. Zhul'kov M.O. Lebed'ko O.A. Sazonova E.N. Vliyaniye antenatal'noj gipoksii na tkanevoj gomeostaz miokarda bely'x kry's: rannie i otdalennyye posledstviya [The influence of antenatal hypoxia on tissue homeostasis of albino rats myocardium: early and long-

term consequences] Byull. e'ksperimen. biologii i mediciny [Bul. Exp. Biol. Med.]. Moscow, 2014, 157(3), P. 294-297.

2. Afanas'ev S.A. Vecherskij Yu.Yu. Maksimov I.V. Markov V.A. Rebrova T.Yu. Kardioprotekorny'j e'ffekt antioksidanta gistoxroma v kardiologicheskoy i kardiokirurgicheskoy klinike [Cardioprotective effect of antioxidant histochrome in cardiology and cardiosurgery practice]. Tomsk, 2010, 150 p.
3. Kapel'ko V.I. Uchastie aktivny'x form kisloroda v samoregulyacii sokratitel'noj funkcii serdca [Participation of reactive oxygen species in self-regulation of the contractile function of the heart]. Byulleten' VSNCz SO RAMN, Novosibirsk, 2016, № 3(109), P. 156-159.
4. Mamaev N.N. Mamaeva S.E. Struktura i funkciya YaOR xromosom: molekulyarnyye, citologicheskie, klinicheskie aspekty [Structure and function of NOR of chromosome: molecular, cytology and clinical aspects] Tsitologiya [Cell and Tissue Biology]. Spb., 1992, № 10, P. 3-12.
5. Kozlov V.A. Tverdopleb I.V. Shpon'ka I.S. Mishalov V.D. Morfologiya razvivayushhegosya serdca: struktura, ul'trastruktura, metabolizm

- [Morphology of the developing heart: structure, ultrastructure, metabolism]. Dnepropetrovsk, 1995, 220 p.
6. Men'shnikova E.B. Lankin V.Z. Zenkov N.K. Bondar' I.A. Krugovy' x N.F. Trufakin V.A. Okislitel'ny'j stress. Prooksidanty' i antioksidanty' [Oxidative stress. Prooxidant and antioxidant]. Moscow: Firma "Slovo", 2006, 556 p.
  7. Petruk N.S. Ivanchenko M.V. Tverdoxleb I.V. Vzaimosvyaz' reakcij mitoxondrial'nogo apparata i raspredeleniya neksusov sokratitel'ny'x kardiomiocitov v postnatal'nom ontogeneze v otvet na vozdejstvie xronicheskoy vnutritrobnog gipoksii v e'ksperimente [The relationship between the mitochondrial reactions and the distribution of contractile cardiomyocyte nexus in postnatal ontogenesis in response to chronic intrauterine hypoxia in the experiment] Vestnik VolgGU. Volgograd, 2014, 2(50), P. 97-100.
  8. Shakula A.V. Shhegol'kov A.M. Klimko V.V. Yaroshenko V.P. Nekrasov V.I. Dergacheva L.I. Primenenie digidrokvercetina v kompleksnoj medicinskoj rehabilitacii bol'ny'x ishemicheskoy bolezni'yu serdca na gospi'tal'nom i ambulatorno-poliklinicheskix e'tapax [The use of dihydroquercetin in the complex medical rehabilitation of patients with ischemic heart disease at the hospital and outpatient-polyclinic stages]. Consilium Medicum, 2008, 12, P. 44-48.
  9. Shtejn G. I. Kudryavceva M.V. Kudryavcev B. N. Izmenenie morfometricheskix parametrov okrashenny'x serebrom yadry'shek gepatocitov kry's pri cirroze pecheni i v processe ee rehabilitacii [Changes of morphometric parameters of silver-colored nucleoli of rat hepatocytes in liver cirrhosis and in the process of its rehabilitation] Tsitologiya ["Cell and Tissue Biology"]. Spb., 1999, V. 41, № 7, P. 574-579.
  10. Drenckhahn J.D. Heart development: mitochondria in command of cardiomyocyte differentiation / J.D. Drenckhahn // Dev Cell. – 2011. – 21(3). – P. 392-393.
  11. Protective effect of quercetin on posttraumatic cardiac injury / Z. Jing, Z. Wang, X. Li, T. Cao, Y. Bi, J. Zhou, X. Chen, D. Yu, L. Zhu, S. Li // Sci Rep. – 2016. – 6. – P. 30812.
  12. Quercetin attenuates cardiomyocyte apoptosis via inhibition of JNK and p38 mitogen-activated protein kinase signaling pathways / C. Li, T. Wang, C. Zhang, J. Xuan, C. Su, Y. Wang // Gene. – 2016. – 577(2). – P. 275-280.
  13. Taxifolin prevents diabetic cardiomyopathy in vivo and in vitro by inhibition of oxidative stress and cell apoptosis / X. Sun, R.S. Chen, Z.H. Yang, G.B. Sun, M. Wang, X.J. Ma, L.J. Yang, X.B. Sun // Food Chem Toxicol. – 2014. – 63. – P. 221-232.
  14. Taxifolin protects against cardiac hypertrophy and fibrosis during biomechanical stress of pressure overload / H. Guo, X. Zhang, Y. Cui, H. Zhou, D. Xu, T. Shan, F. Zhang, Y. Guo, Y. Chen, D. Wu // Toxicol Appl Pharmacol. – 2015. – 287(2). – P. 168-177.
- ### The authors
1. FGBOU Far-Eastern Federal District of the Ministry of Health of the Russian Federation, Khabarovsk, Muravyev-Amursky Str. 35:
  2. Sazonova Elena Nikolaevna - MD, associate professor, pro-rector for science work, head of Department of normal and pathological physiology, Chief Researcher, Khabarovsk branch of the DNTS FPD - Research Institute for Maternity and Childhood Protection, naukapro@mail.fesmu.ru, sazen@mail.ru,
  3. Yakovenko Darya Valerevna - lecturer, Department of normal and pathological physiology;
  4. Marochko Andrey Yurievich - MD, prof., Department of general and clinical surgery;
  5. Zharsky Sergey Leonidovich - MD, prof., Head of chair of faculty therapy with the course of endocrinology,
  6. Dobrykh Vyacheslav Anatolievich - MD, prof., Head of chair of propaedeutics of internal diseases with the course of phtisiatry,
  7. Rzyankina Marina Fedorovna - MD, prof., Head of chair of propaedeutics of internal diseases with the course of children's infectious diseases,
  8. Chepel Tatyana Vladimirovna - MD, associate professor, pro-rector for educational and pedagogical education work,
  9. Lebedko Olga Antonovna - MD, director of the Khabarovsk branch of the DNTS FPD - Research Institute for Maternal and Child Protection, iomid@yandex.ru.