1(61) `2018

ЯКУТСКИЙ МЕДИЦИНСКИЙ ЖУРНАЛ

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

YAKUT MEDICAL JOURNAL

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

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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"

The founder
The Yakut Science Centre of Complex Medical Problems

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
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ORIGINAL RESEARCHES

N.A. Solovyova, Kh.A. Kurtanov, N.I. Pavlova, E.Yu. Sizykh, M.N. Mikhaylova

RESEARCH OF THE ROLE OF POLYMORPHIC OPTIONS OF INTERLEUKINS GENES IN DEVELOPMENT OF ASTHMA IN THE YAKUT POPULATION

ABSTRACT

The purpose of this study was to investigate the polymorphic loci of interleukins genes *IL4 (C589T, G/C3'UTR), IL4R (Q551R, I50V), IL5 (C703T), IL5RA (G80A), IL9 (T113M)* in patients with asthma and in the control group of individuals. As a result of the analysis, we showed that the markers of an increased risk of developing asthma in the children-Yakuts are the *C* allele and the *CC* genotype *(G/C 3'UTR)* of the *IL4* gene, the *T* allele and the genotype *TT (C589T)* of the *IL4* gene, the allele of the *R (Q551R)* gene *IL4RA*, allele *I (I50V)* of *IL4RA* gene, allele *M (T113M)* of *IL9* gene. Thus, this study for the first time shows the association of polymorphic variants of I*L4, IL4RA, IL9* genes with the development of asthma in the Yakut population.

Keywords: asthma, association analysis, genes, Yakut population.

INTRODUCTION

Comparative epidemiological researches of the last years constantly confirm the high prevalence of the bronchial asthma (BA) around the world which is followed by broad variability [9] that is connected not only with problems in diagnostics, but also with structure of susceptibility to this disease in various populations. In view of the fact that the crucial role in development of inflammation at BA belongs to cytokine system, namely *IL4*, *IL5, IL9*, being initiators of the cascade of the reactions leading the most active researches to emission of mediators and migrations of cells in the center of atopic inflammation [2, 10] are conducted in the field of studying of genes of *IL4, IL5, IL9* interleukins and their receptors of *IL4RA, IL5RA* which are carrying out transmission of signals of these ligands in cells targets [3, 5, 14]. In many works on mapping of genes – candidates of BA close coupling of a disease with a locus located on a chromosome 5q31 – 33 [6, 7, 8, 13] is shown. Despite visible progress on studying of the BA molecular mechanisms, the reproduced results are received only for a half of them. The increasing number of publications indicates value of ethnic specifics in determination of allergic diseases, there are suggestions that these specifics can be the cornerstone of interpopulation variability of incidence BA [4], and it assumes need of further studying of genes of interleukins as BA predictors taking into account ethnic origin.

Identification of biological predictors of BA susceptibility allows forming reasonably risk groups for realization in them of actions for prevention of development of this disease. Use of the molecular predictors associated with clinical and also laboratory - functional indicators of BA allows carrying out therapy taking into account ethnic and genetic features of patients.

In our research we analyzed association of one-nucleotide polymorphisms of genes of *IL4 (C589T, G/C3'UTR), IL4R (Q551R, I50V), IL5 (C703T), IL5RA (G80A), IL9 (T113M)* with bronchial asthma in the Yakut population.

Materials and methods

Work consisted of a one-stage open research in the comparative groups created by the principle "case - control". The research has included 150 patients suffering BA (group 1, 2) and 289 conditionally healthy people (group 3, 4). For a weight influence exception BA on differences in structure of genetic susceptibility ad hock the analysis is carried out, the group 5 corresponding on weight BA to group 2 is created from group 1(Tab. 1).

The group 1 has included patients of pulmonary office of the PC of RHN№1 (Yakutsk) in group 2 patients randomized of the DISPAN database of regional children's hospital (Tomsk), at the age of 4 - 15 years, the blood having the level of the general IgE in serum 100ME/ml with the confirmed diagnosis easy, medium-weight, heavy BA for 12 months until inclusion in a research. The diagnosis was verified on the basis of the following criteria: existence of the anamnesis characteristic of BA, typical clinical symptoms of a disease (short wind, cough, suffocation), data of FVD (the proved reversibility of a bronchial obstruction), an atopiya (the atopic anamnesis, positive skin allergic test (SAT), level of the general IgE>gt; of 100 ME/ml). The severity of a disease was established according to classification, all patients received basic therapy of a disease with use of inhalation glucocorticosteroids according to the document GINA 2010 [11].

Groups 3 and 4 included conditionally healthy children who are living in Yakutsk and Tomsk respectively, not having allergic diseases with the level of the general IgE in blood serum <100 ME/ml.

The protocol of a research is approved by local ethical committee at YSC KMP. Parents (trustees) of all included children have signed the informed consent to par-

Table 1

Comparative characteristics of the groups of research

Major group (sick BA)	Monitoring group (conditionally healthy)	The group further statistical analysis (ad hoc)
Group 1 The Yakuts, n = 103, The average age of 9,9±0,2 years Boys, n = 67 (65%), Girls, n = 36 (35%)	Group 3 The Yakuts, n = 223 The average age of 10.1±2.0 years Boys, n = 135 (60.5%), Girls, n = 88 (39.5%)	Group 5 The Yakuts, n = 47 The median age of 9.8±1.6 years Boys, n = 30 (63,8%) Girls, n = 17 (36, 2%)
Group 2 Russian living in the city of Tomsk and Tomsk region, n = 47 The average age of 9.21±0,4 years Boys, n = 30 (63,8%), Girls, n = 17 (36, 2%)	Group 4 Russian living in the city of Tomsk and Tomsk region, n = 66 The average age of 21.2±2.0 years Men, n = 40 (60.6%), Women, n = 24 (39.4%)	

ticipation in the real research.

Clinical examination was conducted on the basis of pulmonary office of PC of RHN№1 (Yakutsk) and the Children's center of clinical immunology and allergology (Tomsk). To all participants of a research allergological examination with application of a method of scarification skin tests with extracts household, the epidermal, pollen allergens, determination of content of the general IgE in blood serums by method of the solid-phase immunofermental analysis and also assessment of maintenance of eosinophils in a nasal secret by L.A. Matveeva [1] technique, assessment of the function of external breath (FEB) by a standard technique (the analysis a curve stream volume and spirometry indicators) on the device MasterScope ("Erih Jaeger GMBH", Germany), the molecular and genetic analysis of 7 polymorphisms of 5 genes of interleukins (*C589T, G/C3'UTR* of a gene of *IL4, Q551R, I50V* of a gene *IL4RA, C703T* of a gene of *IL5, G80A* of a gene *IL5RA, T113M* of a gene of *IL9*) is conducted.

For genotyping used samples of the genomic DNA emitted from blue blood with method phenol - chloroformic extraction [12]. Genotyping was carried out by the analysis of the polymorphism of lengths of restriction fragments (PLRF) of products of amplification of the polymerase chain reaction (PCR) of specific sites of a genome [5].

Statistical processing was carried out by means of the software package of "Statistica for Windows 13.0". Data are presented in the form by X ± x where X – an arithmetic average, x – an average error. Applied Mann-Whitney's U-criterion to assessment of difference of averages in in pairs not the connected selections, considered a difference of values significant at p<0,05. Distribution of genotypes on the studied polymorphisms was checked for compliance to the Hardy-Weinberg's balance (HWB) by exact test of Fischer. For comparison of frequencies of alleles between various groups we used χ2 criterion with Yates's amendment on continuity. For assessment of probability of development of an event the method of the relation of chances with use of the "Statcalc" software product is used.

Results and discussion

By results of ad-hock testing it is revealed that the BA demonstration at the Yakuts children arose later, than at the Russians (Tab. 2). Frequency of the burdened heredity significantly didn't differ and met in 30–40% of cases. The raised indicators of the general IgE in serum of blood were noted both at Yakuts, and at the Russian patients, but the analysis of his level has shown significant distinctions. So, for Yakuts the average level of IgE in serum of blood was 523 ± 40,36 ME/ml whereas for Russians it was twice lower.

Indicators of OFV_1 were within norm both at Yakuts with BA, and at russians that is connected with application of basic therapy and confirms controlled and partially controlled course of a disease. When comparing level within two populations it is revealed that lower OFV_1 level is characteristic of Yakuts. The comparative analysis of level of eosinophils between Yakuts and Russians has shown that at the Russian patients he was twice higher, than at Yakuts. The analysis of the frequency BA which is combined with atopic dermatitis, allergic rhinitis and an allergic conjunctivitis hasn't shown differences between Yakutы and Russians. Comparable results are gained in the analysis of triggers developments of BA symptoms. So, at Yakuts the sensitization household allergens (93,6%) prevailed, it occurred among the Russian patients less often (p = 0,001). Among triggers for the Russian patients epidermal allergens (53,2%), a sensitization pollen allergens also more often were significant met among Russians (p = 0,04).

The analysis of the studied genes of interleukins at Yakuts (group 1) has allowed to establish BA association and its clinical-functional manifestations with all polymorphic options of genes. The probability of BA formation is 3 times higher at carriers of a genotype of a TT of polymorphism *C589T* of a gene of *IL4* (OR = 2,81; CI:95 of % 1,69 - 4,68), is twice higher at carriers of alleles of *T* of polymorphism *C589T* of a gene of *IL4* (OR = 1,97; CI:95 of % 1,35 - 2,87) and *M* of polymorphism of *T113M* of a gene of *IL9* (OR = 1,92; CI:95 of % 1,23 - 2,98) and also genotype of the *CC* polymorphism of *G/C 3'UTR* of a gene of *IL4* (OR = 2,28; CI:95 of % 1,38 - 3,79), is one and a half times higher at carriers of alleles. From polymorphism of *G/C 3'UTR* of a gene of *IL4* (OR = 1,62; CI:95 of % 1,1 - 2,39), *R* polymorphism of *Q551R* of a gene of a receptor of *IL4RA* (OR=1,66; CI:95 of % 1,15 - 2,4) and *I* polymorphism of *I50V* of a gene of a receptor of *IL4RA* (OR = 1,61; CI:95 of % 1,14 - 2,28). Genotypes of the *CC* polymorphism of *G/C 3'UTR* (p = 0,001) a gene of *IL4, GG* (p = 0,012) polymorphism of *G80A* of a gene of *IL5RA* and *MM* (p = 0,019) polymorphism of *T113M* of a gene of *IL9* are BA associated with heavy. Higher level of the general IgE was noted at patients with genotypes of *CC* (p = 0,001) polymorphism of *G/C 3'UTR* of a gene of *IL4, II* (p = 0,015) polymorphism of *I50V* of a gene of a receptor of *IL4RA* and *MM* (p = 0,013) polymorphism of *T113M* of a gene of *IL9*. Lower indicators of OFV1 are registered at carriers of genotypes of a *TT* (p = 0,002) polymorphism of *C703T* of a gene of *IL5*, QR (p = 0,03) polymorphism of *Q551R* of a gene of a receptor of *IL4RA* and *MM* (p = 0,04) polymorphism of *T113M* of a gene of *IL9*. The analysis of distribution of alleles and genotypes of the studied genes of interleukins in groups 5 and 2 has revealed significant distinctions for polymorphic *C589T* and *G/C* options *3'UTR* of a gene of *IL4, Q551R* of a gene of *IL4RA* and *G80A* of a gene *IL5RA*. So in group of Yakuts with carriers allele *T* of polymorphism of *C589T* (p =0,01), allele from polymorphism of *G/C 3'UTR* of a gene of *IL4* (p =0,03), and allele and polymorphism of a gene of *IL5RA* BA prevailed (p =0,01). An allele *Q* polymorphism of *Q551R* of a gene of *IL4RA* prevailed both at Yakuts, and at Russians with BA, but with a different frequency (p =0,04).

Conclusion

It is established what BA at children of Yakuts is characterized by heavier current, a late demonstration, lower indicators of quantity of eosinophils of a nasal secret and OFV1, higher level of the general IgE in blood serum that is caused by clinical-functional effect of the alleles prevailing in this population. So the genotype of the *CC (G/C 3'UTR)* gene of *IL4*, a genotype of the *II (I50V)* gene of *IL4RA*

Table 2

Comparative clinico-laboratory and functional characteristics of groups additional statistical (ad hock) analysis

Test Parameters	Group 5, n = 47	Group 2, n = 47	p
Age (years)	9,87 ± 0,23	9,21 ± 0,39	0,161
Age of manifestation (years)	6,16 ± 0,1	3,93 ± 0,3	0,001
** Weighed down heredity, n (%)	29,8%	38,3%	0,386
IgE, (IU / ml)	523 ± 40,36	243 ± 35,19	0,001
FEV1 (% of due)	99,5 ± 1,86	125 ± 6,95	0,002
Eosinophils of nasal secretion, (%)	1,14 ± 0,06	2,8 ± 0,37	0,001

Note. To assess the differences in pairwise unrelated samples, the Mann-Whitney U test was used, * - to evaluate the difference, a two-sided exact Fisher test was used.

and a genotype of *MM (T113M)* of a gene of *IL9* is associated with higher level of the general IgE in serum of blood. The genotype of a *TT (C703T)* of a gene of *IL5,* a genotype of *MM (T113M)* of a gene of *IL9* and a genotype of *QR (Q551R)* of a gene *IL4RA* is associated with lower indicator of OFV1. Genetic markers of the increased probability of development heavy BA at Yakuts is the genotype of the *CC (G/C 3'UTR)* gene of *IL4*, a genotype of *GG (G80A)* of a gene *IL5RA* and a genotype of *MM (T113M)* of a gene of *IL9*.

Thus, we have defined for the first time in children of the Yakut ethnicity genetic structure of BA susceptibility, but markers of the increased probability of asthma development in the Yakuts are the genotype of *CC* and an allele of *C (G/C 3'UTR)* of a gene of *IL4*, a genotype of a *TT* and an allele of *T(C589T)* of a gene of *IL4*, an allele of *R (Q551R)* of a gene of *IL4RA*, an allele of the *I (I50V)* gene of *IL4RA*, an allele of the *M (T113M)* gene of *IL9.*

REFERENCES

1. Matveeva L.A. Mestnaja zashhita respiratornogo trakta u detej: 2-e izd. [Local protection of the respiratory tract in children: 2nd ed.]. Tomsk: izd-vo Tomskogo un-ta, 1993, 275 p.
2. Namazova L.S. Rol' citokinov v patogeneze allergicheskih reakcij [Role of cytokines in the pathogenesis of allergic reactions] Allergicheskie bolezni u detej pod red [Allergic diseases in children]. Ed. M.Ja. Studenikin, I.I. Balabolkin. Moscow: Medicina, 1998, p. 70-78.
3. Baranov V.S. Ivashhenko T.Je. Lavrova O.V. i dr. Nekotorye molekuljarno – geneticheskie aspekty jetiopatogeneza atopicheskoj bronhial'noj astmy [Some molecular genetic aspects of pathogenesis of atopic bronchial asthma] Med. Genetika [Med. Genetics]. Moscow, 2008, № 10, p. 3-13.
4. Puzyrev V.P. Frejdin M.B. Kucher A.N. Geneticheskoe raznoobrazie narodonaslenija i bolezni cheloveka [Genetic diversity of the population and human diseases]. Tomsk: Pechatnaja manufaktura [Printing manufactory], 2007, p. 86-94.
5. Frejdin M.B. Bragina E.Ju. Ogorodova L.M. Genetika atopii: sovremennoe sostojanie [The genetics of atopy: current status] Vestnik VOGiS [Bulletin of VOGiS]. 2006, V. 10, № 3, p. 492-503.
6. Cytokines: co-ordinators of immune and inflammatory responses / K.I. Arai, F. Lee, A. Miyajima et al. // Ann. Rev. Biochem. – 1990. – Vol. 59. – P. 783-802.
7. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5 / D.A. Meyers, D.S. Postma, C.I.M. Panhuysen et al. // Genomics. – 1994. – Vol. 23, № 2. – P. 464-470.
8. Genetic susceptibility to asthma: bronchial hyperresponsiveness coinherited with a major gene for atopy / D.S. Postma, E.R. Bleecker, P.J. Amelung et al. // New Eng. J. Med. – 1995. – Vol. 333. – P. 894-900.
9. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC) / C.K. Lai, R. Beasley, J. Crane et al. // Thorax. – 2009. – Vol. 64, № 6. – P. 476-483.
10. Hamelmann E. Development of eosinophilic airway inflammation and airway hyperresponsiveness requires IL5 but not IgE or B-lymphocytes / E. Hamelmann, K. Takeda // Am. J. Respir. Cell. Mol. Biol. – 1999. – Vol. 21. – P. 480-489.
11. Masoli M. The global burden of asthma: executive summary of the GINA Dissemination Committee report /, D. Fabian, S. Holt, R. Beasley // Allergy. – 2004. – Vol. 59, № 9. – P. 469-478.
12. Mathew C.C. The isolation of high molecular weight eukaryotic DNA / C.C. Mathew // Methods in Molecular Biology; ed. by J.M. Walker. – N.-Y. : Human Press, 1984. – Vol. 2. – P. 31-34.
13. Positionally cloned genes and age-specific effects in asthma and atopy: an international population-based cohort study (ECRHS) / F. Castro-Giner, R. de Cid, A. Gonzalez et al. // Thorax. – 2010. – Vol. 65, № 2. – P. 124-131.
14. Sandford A.J. Candidate genetic polymorphisms for asthma in Chinese schoolchildren from Hong Kong / A.J. Sandford, H.W. Chan, G.W. Wong // Int. J. Tuberc. Lung Dis. – 2004. – Vol. 5, № 5. – P. 519-527.

The authors:

Solovyova Natalya Alekseevna - candidate of medical sciences, the leading researcher - the head 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";

Kurtanov Khariton Alekseyevich - candidate of medical sciences, the chief researcher – head of department of molecular genetics of YSC CMP;

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;

Sizykh Elena Yurevna - junior researcher of laboratory of population genetics of department of molecular genetics of YSC KMP, the doctor of the highest qualification category, the manager policlinic of YSC CMP Hospital.

Mikhaylova Ulyana Nikitichna - junior researcher of laboratory of population genetics of department of molecular genetics of YSC KMP, attending physician of therapeutic office of YSC CMP Hospital.

Kh.A. Kurtanov, L.A. Sydykova, N.I. Pavlova, N.P. Filippova,
G.A. Apsolikhova, N.A. Solovyova, V.V. Dodokhov,
M.A. Varlamova, A.T. D'jakonova, L.M. Neustroeva, N.V. Borisova

RESEARCH OF ADIPONUTRIN GENE *(PNPLA3)* IN INDIGENOUS PEOPLE OF THE REPUBLIC OF SAKHA (YAKUTIA) WITH TYPE 2 DIABETES

ABSTRACT

Polymorphism of the *I148M G*ene of the *PNPLA3 G*ene was studied in patients with type 2 diabetes of the Yakut nationality. The predominance of the *GG G*enotype (58.5%) with a *G*-allele frequency of 74.1% was revealed. The normally functionin*G* protein of the *PNPLA3 G*ene re*G*ulates the activity of tri*G*lyceride hydrolase and lysophosphatidic acid acyltransferase. It is likely that the hi*G*h frequency of the mutant allele *G* in the Yakuts with type 2 diabetes may be one of the causes of the lipid metabolism mechanism disorder in the liver.

Keywords: diabetes mellitus type 2, insulin resistance, adiponutrin *G*ene, polymorphism, *PNPLA3*, rs738409, *I148M*.

INTRODUCTION

The most significant indicator of a person's adaptation to living conditions is the duration of his life. The same indicator is one of the generally accepted for assessing the quality of life in general. On the inhabitants of the North, the 20th century had a strong influence in the form of a drastic change in the social and environmental conditions of residence, the image and diet of traditional food. Undoubtedly, these changes have led to changes in the quality of health of its indigenous inhabitants. In particular, among the causes in the medical and social disadaptation of man, a large proportion is occupied by so-called diseases with complex inheritance (caused by a combination of genes and environmental factors).

One of the most socially significant pathologies in the Republic of Sakha (Yakutia) is type 2 diabetes mellitus (DM 2). According to Rosstat, the total number of patients with diabetes in the republic is 21,677 people, of which 20,508 with type 2 diabetes, 1099 with type 1 diabetes, and 70 with diabetes of other types [7].

Epidemiological data indicate the frequent combination of type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) [1]. Patients with CD2 are insulin resistant, often obese, have dyslipidemia and increased activity of liver enzymes, they tend to accumulate fat in the liver regardless of BMI (body mass index), thus they have a higher risk of developing severe liver disease compared to patients without diabetes [15].

Non-alcoholic fatty liver disease refers to the most common chronic liver disease. The incidence of this disease is 20-30 % in the general population and 67-75 % in the population of obese people [2]. The prevalence of non-alcoholic steatosis of the liver among residents of the economically developed countries of the world is on average 20-35 %, non-alcoholic steatohepatitis – 3 %. In the United States, 34 % of the adult population has liver disease, 29 % in Japan. In Russia, according to the screening program for detecting the prevalence of NAFLD and its clinical forms, conducted in 2007 and covering 30,754 people, NAFLD was detected in 27 % of the examined, 80.3 of whom had steatosis, 16.8 - steatohepatitis and 2.9 % - cirrhosis of the liver [3].

The prevalence of NAFLD among patients with type 2 diabetes is 60-80 %, and the incidence of NASH is 12-40 % [8].

Genetic, as well as environmental factors play an important role in the development of NAFLD [19]. One of the candidate genes involved in the pathogenesis of NAFLD is the PNPLA3 gene, which codes for the synthesis of the adiponucleus protein. In this case, this genetic feature is most common in Latinos and rarely in representatives of the Negroid race [5]. The association of the PNPLA3 gene with the development of NAFLD revealed a number of studies [14].

The full-genomic search for associations (GWAS) has shown that SNP in the PNPLA3 gene affects the levels of liver enzymes in the plasma. The G allele of polymorphism rs738409 of the PNPLA3 gene is strongly associated with NAFLD, as well as with increasing AST and ALT, ferritin level and fibrosis stage in patients with NAFLD [11].

The most significant polymorphism in the PNPLA3 gene is I148M. It consists in replacing the nucleotide cytosine by guanine, leading to a change in the amino acid isoleucine to methionine at position 148. This replacement leads to a violation of the mechanism of lipid metabolism in the liver. Polymorphism I148M is associated with susceptibility to NAFLD and affects the histological pattern and development of fibrosis in children and adolescents with obesity [17].

According to the National Center for Biotechnological Information (NCBI), the frequency of the allele G of the polymorph I148M of the PNPLA3 gene (rs738409) varies from 19.6 % (African population AFD_AFR_PANEL ss24098326) to 43.2 % (Asian population HapMap-JPT ss76896972) (Fig. 1).

The polymorphism association rs738409 I148M with type 2 diabetes mellitus and NAFLD was confirmed in several ethnic and geographical groups, but to date no frequency assessment has been performed in the populations of Yakutia. The Yakuts are one of the many peoples of the Far East and Siberia. The Yakut population is very interesting in a genetic sense. It is remarkable that this population is formed by an admixture of two or more ancestral populations, so it gives a unique opportunity to study the interaction between gene polymorphisms, ethnic genetic background and ecological contributions to the disease. The aim of the study was to investigate the relationship between the variants of the PNPLA3 gene (rs738409 C> G) and type 2 diabetes mellitus in patients of the Yakut nationality.

Materials and methods of research. The study was conducted in the laboratory of hereditary pathology of the department of molecular genetics of the YSC of the ILC. Informed consent to genetic research was obtained from each patient. For the study, DNA samples from the YMC KMB biomaterial collection were used. The sample includes 106 pa-

tients of the Yakut nationality of the endocrinology department of the Republic of Belarus No. 2-Center for Emergency Medical Care diagnosed with diabetes 2 (79 women and 27 men) aged 31 to 82 years. All patients underwent polymorphism rs738409 of the PNPLA3 gene. Samples of genomic DNA were isolated from the whole blood of patients by a standard phenol-chloroform method. The single nucleotide polymorphism (SNP) of rs738409 I148M was determined by a PCR-RFLP method.

Amplification of the region of the PNPLA3 gene containing the polymorphic variant was carried out by standard primer pairs (forward primer: 5’-CCGGCCTGAAGTCCGAGTTT-3 ‘and reverse primer: 5’-GCGACACCAAAGCCCTGCGG-3’) (Biotech-Industry Ltd., Moscow). The composition of the reaction mixture for PCR (total volume of the reaction mixture is 25 μl): 13 μl ddH2O, 2.5 μl 10x PCR buffer, 2.5 μl 25 mM MgCl2, 2.5 μl 2.5 mM dNTP Mix, 1.5 μl 10 pkmol / μl) of each oligonucleotide primer, 0.3 units. (1.5 units) of the «hotstart» Taq polymerase and 3 μl of DNA. PCR was carried out in a thermal cycler MJ Mini Gradient Thermal Cycler («BioRad»).

Temperature conditions PCR: 95° C - 5 min, then 37 cycles at 94° C - 30 s, 66 ° C - 30 s, and 72 ° C - 40 s and the final elongation at 72° C - 5 min. The PCR products were then cut with a BstF5 I restriction enzyme (SibEnzyme LLC, Novosibirsk) overnight at 65 ° C. The cut PCR products were subjected to horizontal electrophoresis in 1.5 % agarose gels stained with ethidium bromide in 1 x TBE buffer at 120 V for 1 h and visualized using a gel documenting system (Vilber Lourmat, France).

The detection of RFLP products was carried out by horizontal electrophoresis in a plate of 4 % agarose gel stained with ethidium bromide, using a standard tris-acetate buffer at 120 V for 1 h. Visualized in UV-rays using a gel documenting system (Fig. 2).

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

Statistical analysis of the results of medical genetic research was carried out with the help of programs: «Office Microsoft Excel 2010», «Statistica 8.0». The frequency rs738409 was determined by direct counting. The results are considered significant when the value of «p» is less than 0.05 (p <0.05).

Results and discussion. A comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic gene PNPLA3 (rs738409) in the sample of Yakuts suffering from type 2 diabetes revealed a prevalence of the GG genotype (58.49 %), significantly less often the CC genotype (10.38 %). The heterozygous genotype GC was observed in 31.13% of patients. Analysis of the allele distribution of the polymorphic locus PNPLA3 (rs738409) showed a higher allele frequency G of 74.1 %. Allele C is found in Yakuts with a frequency of 25.9 %. Population-genetic analysis of the distribution of polymorphisms of the adiponuclear gene PNPLA3 (rs738409) in the Yakuts showed that the level of observed heterozygosity was Ho = 0.311 level of the expected heterozygosity He = 0.387. The distribution of the rs738409 polymorphism genotypes in the sample (p> 0.05) was in the Hardy-Weinberg equilibrium (Table 1).

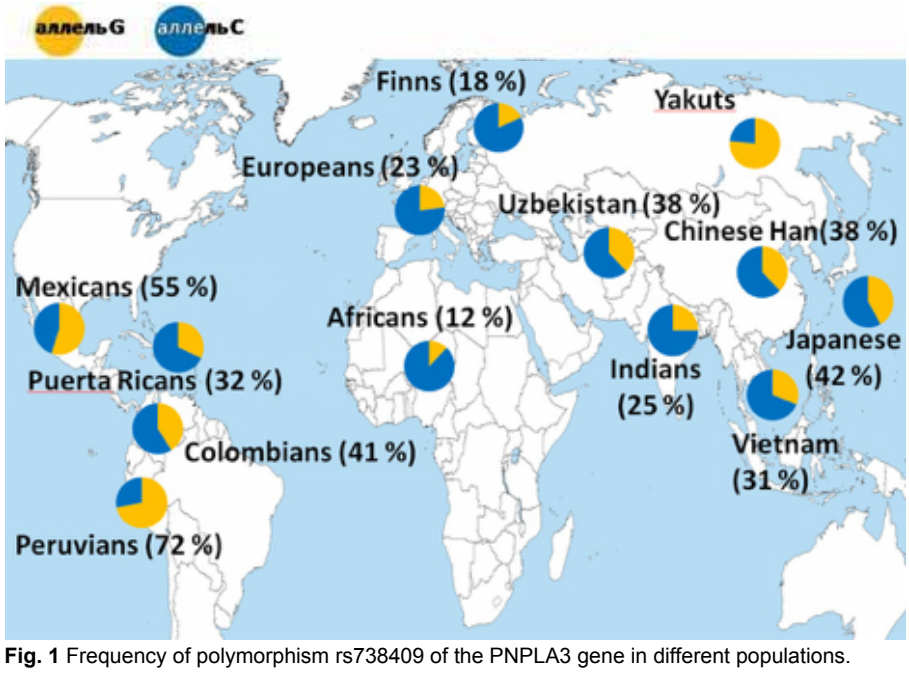


Fig. 1 Frequency of polymorphism rs738409 of the PNPLA3 gene in different populations. Note: yellow color - allele G, blue color - allele C. The data are obtained from the database of the project «1000 genomes» and from literary sources.

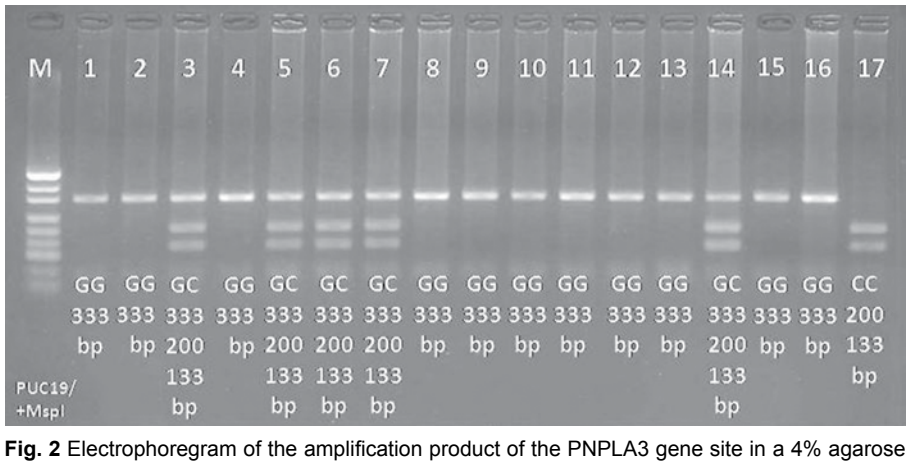


Fig. 2 Electrophoregram of the amplification product of the PNPLA3 gene site in a 4% agarose gel. 17 - genotype CC, 3, 5, 6, 7, 14 - genotype GC, 1, 2, 4, 8, 9, 10, 11, 12, 13, 15, 16 - genotype of GG. M - marker PUC19 / + Msp I. bp - base pairs.

High frequency of allele G (74.1 %) in patients with type 2 diabetes is associated with a high frequency of its occurrence among a healthy population of Yakuts (76.8 %) [4]. According to the “1000 genomes” project, in Asia the high frequency of G allele is found in Japanese (43.2 %). In studies of the Japanese population of patients with type 2 diabetes, M. Ueyama, N. Nishida (2015) and Kan H. et al. (2016), note the high incidence of allele G (48-48.8 %) [13, 16]. In the African American population, the frequency of the G allele is low (19 %) [18], and it is also low (13.7 %) at a genotype GG frequency of 1.5 % in patients with type 2 diabetes [10]. In the European population, the G allele frequency is on average 22.6 % [20], in patients with type 2 diabetes - 29.6 % [12].

As many domestic and foreign re-

searchers note, patients with type 2 diabetes mellitus carry PNPLA3 gene allele (rs738409) as a whole are more susceptible to liver diseases (NAFLD, NASH) with a high risk of developing cirrhosis and hepatocellular carcinoma [6].

The distribution of the frequency of alleles and genotypes of polymorphism rs738409 of the PNPLA3 gene in patients, depending on age, revealed a high frequency (83 %) in the groups of patients up to 35 and up to 65 years (Table 2). The high prevalence rate of the homozygous genotype GG was observed in the group of patients from 55 to 65 years old and was 70 %.

Patients with type 2 diabetes and NAFLD have a higher risk of cardiovascular disease, as well as mortality, due to the depletion of hepatic glycogen stores and a decrease in reserve regulation of glucose homeostasis, and the acceleration of the development of vascular complications. According to the pathogenesis of NAFLD, in the issue of pathogenesis, researchers adhere to 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.

In his studies, Jean-Michel Petit et al. [12], found the relationship of polymorphism PNPLA3 rs738409 with the fat content in the liver independent of general and visceral obesity and insulin resistance. They believe that adiponadine can be an important clue to understanding the mechanisms associated with the difference between fatty liver and fatty liver without metabolic effects, so the accumulation of fat in the liver can be metabolically benign.

The conclusion

As a result of the investigation of the PNPLA3 gene in the Yakuts with type 2 diabetes, it was established that the frequency distribution of alleles and genotypes of the PNPLA3 gene (rs738409) is in accordance with the Hardy-Weinberg law. In patients with type 2 diabetes, a high frequency of G allele (74.1 %) was found with a predominance of the GG genotype (58.49 %).

Thus, it has been established that the frequency of the mutant allele of functional polymorphism rs738409 of the PNPLA3 gene is higher than in other populations of the world. The normally functioning protein of the PNPLA3 gene regulates the activity of triglyceride hydrolase and acyltransferase of lysophosphatidic acid. Therefore, it can be assumed that the high frequency of the mutant allele G of the polymorphism I148M of the PNPLA3 gene in the Yakuts with type 2 diabetes may be one of the causes of the disturbance of the lipid metabolism mechanism in the liver, which requires careful research on larger samples of the populations of Yakutia, and further investigation of the gene is necessary PNPLA3 in Yakuts with type 2 diabetes mellitus.

Table 1

Distribution of frequencies of alleles and genotypes of polymorphism rs738409 of *PNPLA3* gene

Genotypes	Observed	Expected	Alleles		Ho	He	X^2	p
GG	58,49	54,91	*G*	0,741	0,311	0,387	4,123	0,05
GC	31,13	38,38	*C*	0,259				
CC	10,38	6,71						

Note: p> 0.05; X2 is the chi-square; Ho - observed heterozygosity; He is the expected heterozygosity.

Table 2

Frequency distribution of alleles and genotypes of polymorphism rs738409 of the *PNPLA3* gene in patients, depending on age

Age	n		Genotypes, %			Alleles		X^2	Ho	He	p
			CC	*GC*	*GG*	*C*	*G*				
under 35 years old	3	H	0,00	33,33	66,67	0,167	0,833	0,000	0,333	0,278	0,729
		O	2,79	27,82	69,39						
under 55 years old	24	H	16,66	41,67	41,67	0,375	0,625	0,535	0,417	0,469	0,586
		O	14,06	46,88	39,06						
up to 65 years	50	H	4,00	26,00	70,00	0,170	0,830	1,100	0,260	0,282	0,578
		O	2,89	28,22	68,89						
after 65 years	29	H	17,24	31,03	51,73	0,328	0,672	2,872	0,310	0,441	0,112
			10,76	44,08	45,16						

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

The study was supported by Federal Agency for Scientific Organizations program for support the bioresource collections (0556-2017-0003).

REFERENCES

1. Biryukova E.V. Rodionova S.V. Sakharnyy diabet 2-go tipa i nealkogol'naya zhirovaya bolezn' pecheni – bolezni sovremennosti [Diabetes mellitus type 2 and non-alcoholic fatty liver disease – diseases of the present] Meditsinskiy al'manakh [Medical almanac]. Moscow, 2017, № 6 (51), P.130-135.
2. Karimov M.M., Dalimova D.A., Sobirova G.N., Saatov Z.Z., Hamdamova Sh.Zh. Issledovanie associacii polimorfizma gena PNPLA3c nealkogol'noj zhirovoj bolezn'ju pecheni v uzbekskoj populjacii [The association study of polymorphism gene PNPLA3 with non-alcoholic fatty liver disease in the Uzbek population]. Evrazijskij zhurnal vnutrennej mediciny [Eurasian Journal of Internal Medicine]. Moscow, 2015, № 02 (02), P.25-27.
3. Komshilova K.A., Troshina E.A., Butrova S.A. Nealkogol'naja zhirovaja bolezn' pecheni pri ozhirenii [Non-alcoholic fatty liver disease for obesity]. Ozhirenie i metabolism [Obesity and metabolism]. Moscow, 2011, № 3, P.3-11.
4. Kurtanov H.A., Pavlova N.I., Filippova N.P. Molekuljarno-geneticheskij analiz markera rs738409 gena adiponutrina (PNPLA3) v populjacii jakutov [Molecular genetic analysis of the marker rs738409 of the adiponuclear gene (PNPLA3) in the Yakut population]. Genetika cheloveka i patologija: sbornik nauchnyh trudov [Human Genetics and Pathology: a collection of scientific papers]. Tomsk, 2017, №11, P.82-84.
5. Maev I.V., Andreev D.N., Dicheva D.T. [et al.] Nealkogol'naja zhirovaja bolezn' pecheni: posobie dlja vrachej [Non-alcoholic fatty liver disease: a manual for doctors]. Prima Print [Prima Print]. Moscow, 2017, P.64.
6. Mohort T.V. Nealkogol'naja zhirovaja bolezn' pecheni i saharnyj diabet: aspekty patogeneza, diagnostiki i lechenija [Non-alcoholic fatty liver disease and diabetes mellitus: the aspects of pathogenesis, diagnostics and treatment]. Medicinskie novosti [Medical News]. Minsk, 2012, №4, P.4-10.

7. Nikolaeva L.A., Bureva T.B., Chasnyk V.G. Sovremennye predstavlenija ob jetiologii i pervichnoj profilaktike jessencial'noj arterial'noj gipertenzii [Modern ideas about the etiology and primary prevention of essential hypertension]. Jakutskij medicinskij zhurnal [Yakut Medical Journal]. Yakutsk, 2007, № 3, P.57-59.
8. Petunina N.A., Tel'nova M.Je. Nealkogol'naja zhirovaja bolezn' pecheni [Non-alcoholic fatty liver disease]. Medicinskij sovet [Medical advice]. 2016, № 04, P.92-95.
9. Sharonova L.A., Verbovoj A.F., Verbovaja N.I. [et al.] Vzaimosvjaz' nealkogol'noj zhirovoj bolezni pecheni i saharnogo diabeta 2-go tipa [Interrelation of non-alcoholic fatty liver disease and type 2 diabetes mellitus]. Russkij medicinskij zhurnal [Russian Medical Journal]. 2017, №22, P.1635-1640.
10. Association of *PNPLA3* SNP rs738409 with liver density in african americans with type 2 diabetes mellitus / AJ. Cox, MR. Wing, JJ. Carr, [et al.]Diabetes & metabolism. 2011. – Vol. 37,№5. – P.452-455. doi:10.1016/j.diabet.2011.05.001.
11. Association of the rs738409 polymorphism in *PNPLA3* with liver damage and the development of nonalcoholic fatty liver disease / K. Hotta, M. Yoneda, H. Hyogo [et al.] // BMC Med. Genet. – 2010. – Vol. 11. – P.172.
12. Specifically *PNPLA3*-Mediated Accumulation of Liver Fat in Obese Patients with Type 2 Diabetes / J-M. Petit, B. Guiu, D. Masson, L.[et al.] // The Journal of Clinical Endocrinology & Metabolism. – Vol. 95.– №12.– P.E430–E436 https://doi.org/10.1210/jc.2010-0814
13. 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.– Vol.46– E146–E153. doi: 10.1111/hepr.12552.
14. Morbid obesity exposes the association between *PNPLA3* I148M (rs738409) and indices of hepatic injury in individuals of European descent / S. Romeo, F. Sentinelli, S. Dash [et al.] // Int. J. Obes. (Lond). – 2010.– Vol.34.– P.190–194.
15. Costs and consequence associatiated 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.
16. 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.
17. Day CP: Homozygosity for the patatin-like phospholipase-3/adiponutrin I148 M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease / L.Valenti, A.Al-Serri, AK.Daly [et al.]// Hepatology.– 2010. – Vol.51.– P.1209-1217. 10.1002/hep.23622.
18. Association of*PNPLA3* with non-alcoholic fatty liver disease in a minority cohort: the Insulin Resistance Atherosclerosis Family Study/ LE.Wagenknecht, ND.Palmer, DW.Bowden [et al.] // *Liver international: official journal of the International Association for the Study of the Liver*.– 2011.– Vol.31(3). – P.412-416. doi:10.1111/j.1478-3231.2010.02444.x.
19. Wilfred de Alwis N.M. Genetics of Alcoholic Liver Disease and Nonalcoholic Fatty Liver Disease / N.M.Wilfred de Alwis, C.P. Day // Seminars in Liver Disease.– 2007.– Vol. 27.– P. 44-54.
20. http://www.internationalgenome.org/

The authors:

Yakutsk, Republic Sakha (Yakutia), Russia:

Kurtanov Khariton Alekseevich - Candidate of Medical Science, Chief Researcher, Head of the Department of Molecular Genetics;

Sydykova Lyubovy Akhmedovna - Candidate of Medical Science, Head of Department of propaedeutic and faculty therapy with endocrinology and physical therapy, North-Eastern Federal University, Medical Institute;

Pavlova Nadejda Ivanovna – Candidate of Biological Sciences, Leading Researcher, Head of the Laboratory of Hereditary Pathology;

Filippova Natalya Pavlovna – Candidate of Biological Sciences, Senior Researcher of the Laboratory of Hereditary Pathology;

Dodokhov Vladimir Vladimirovich – Candidate of Biological Sciences, Senior Researcher of the Laboratory of Hereditary Pathology;

Apsolikhova Galina Aleksandrovna – junior researcher of the laboratory of hereditary pathology;

Solovieva Natalya Alekseevna – Candidate of Biological Sciences, Leading Researcher, Head of the Laboratory of Population Genetics;

Dyakonova Aleksandra Timofeyevna – researcher of the laboratory of hereditary pathology; Neustroyeva Lena Mikhaylovna – researcher of the Laboratory of Population Genetics;

Varlamova Marina Alekseyevna – researcher of the Laboratory of hereditary pathology;

Natalya Vladimirovna Borisova - doctor of Medical Sciences, Professor of the Department «Normal and Pathological Physiology», North-Eastern Federal University, Medical Institute.

Sofronova S.I.

ARTERIAL HYPERTENSION AND METABOLIC SYNDROME IN SMALL INDIGENOUS PEOPLE OF THE NORTH OF YAKUTIA

ABSTRACT

The research was conducted in the north of Yakutia in places of compact residence of indigenous people of the North. High prevalence of hypertension in the adult population was revealed, its highest rate was observed in Anabarsky district. We studied the frequency of metabolic syndrome (MS) in the indigenous people of Yakutia. The highest frequency of MS was identified in the Evenks and the lowest among the Chukchi. In women MS was observed significantly more often than in men.

Keywords: small indigenous people of the North, arterial hypertension, metabolic syndrome.

Cardiovascular diseases are the first leading cause (45.4%) of mortality of the population in Yakutia, as in Russia in total. According to the Federal State Statistics Service from 2013 to 2015 the circulatory diseases morbidity rate of the population remains on the same level, and the mortality decreases slightly by 0.9% that makes 45.4% [2]. Despite the fact there is

a tendency of reduction in the circulatory diseases mortality rate (403.7 per 100 thousand people of the population in 2013, 406.5 in 2014, 386.7 in 2015), the ischemic heart disease mortality rate tends to rise (152.3 per 100 thousand people of the population in 2013, 162.7 in 2014, 167.5 in 2015), including the myocardial infarction mortality rate (23.6; 23.2; 37.7 respectively). A certain role belongs to the metabolic syndrome (MS). This syndrome is one of widely discussed problems in modern medicine. The urgency is caused by high prevalence rate in the world: according to different authors, it is from 20 to 40% and the high frequency of early development of atherosclerosis and its complications as a myocardial infarction and a cerebral stroke. The prevalence of MS is enlarged with age, especially in an average age group (30-40%) [2, 6, 7], depends on gender, age, ethnic origin and widely ranges: among male population – from 8% in India to 25% in the USA, among women's – from 7% in France to 46% in Iran [4, 5]. According to the conducted researches, at the beginning of the 2000-s among indigenous people of Evenkia there is a significant increase in prevalence of hypertension (44.6%) and overweight (men have 42.4% and women have 51.7%) [3]. Except Yakuts, aboriginal residents, there are representatives of small indigenous nations (Dolgans, Evenks, Evens etc.) in Yakutia. In earlier researches of MS prevalence, the allocation of them as separate ethnoses was not carried out. But such research in small indigenous people of the North has important clinical value considering changes of traditional life, nutritional habits, and high prevalence of arterial hypertension.

Research objective -studying of frequency of arterial hypertension and metabolic syndrome in small indigenous northerners of Yakutia.

Materials and methods of the research

Material for the research is recruited in forwarding conditions in the places of residence of indigenous people of the North: in Kolymskoye and Andryushkino rural localities of the Nizhnekolymsky District, Yuryung-Haya and Saskylakh rural localities of the Anabarsky District, Topolinoe rural locality of the Tomponsky District, Nelemnoye rural locality of the Verkhnekolymsky District. In total 686 people aged from 20 up to 70 years in 4 districts are examined: Anabarsky (Anabar), Nizhnekolymsky (N. Kolyma), Verkhnekolymsky (V. Kolyma), Tomponsky (Tompo) (table 1). In the studied women were identically more than men ($p<0.05$). Average age had no special differences.For the comparative analysis, we created five (Table 2). Inclusion criteria: Representatives of indigenous minorities of the North of Yakutia (Dolgans, Evens, Evenks, Chukchi, Yukaghirs).

Exclusion criteria: representatives of non-indigenous nationalities and Yakuts.

Hypertension is present at the 140/90 mmHg (The Russian references developed by Committee of experts of Society of cardiology of Russian Federation (VNOK), 2004, 2009). Selection was formed according to the lists of workers, which are in administration of settlements. The response made 76%.

The program of a research included the following sections: a questionnaire survey for assessment of an objective state; the informed consent of the respondent to carrying out the researches, blood donation (according to the Ethics Committee protocol); anthropometric inspection with measurement of body height and body weight; blood sampling from a basilic vein in the morning on an empty stomach with 12-hour fasting; measurement of waist circumference in centimeters was taken below a thorax over an omphalus, in the middle of distance between the bottom lateral edge of ribs and top of iliac crest (NIH,1998); circles of hips at the level of breeches, where the biggest circle is.

Laboratory methods of the research included the definition of blood lipids (TC, TG, HDLC, LDLC), glucose test.

The Metabolic Syndrome was diagnosed by criteria of VNOK, 2009: main sign: AO (WC ≥80 cm women, have ≥94 cm at men); additional criteria: HT (ABP>130/85 mm Hg.), the TG level is ≥1,7 mmol/l; the HDLC level <1,0 mmol/l over men; <1,2 mmol/l over women; LDLC level >3,0 mmol/l; a hyperglycemia on an empty stomach (a glucose in a blood plasma on an empty stomach ≥ 6,1 mmol/l) or glucose intolerance (a glucose in a blood plasma in 2 hours after glucose loading within ≥7,8 and ≤11,1 mmol/l).

Statistical data processing was carried out by means of standard methods of mathematical statistics, using the software package of SPSS (version 17.0).

The research was conducted within research projects of YSC CMP "A contribution of a metabolic syndrome to development of atherosclerosis of coronary arteries in residents of Yakutia", R & D "Development of new technologies of treatment and risk prediction of hypertension and insult in the Republic of Sakha (Yakutia)" (Government contract No. 1133).

Results and discussion

During the conducted research we found out prevalence of HT in adult population in the northern districts of Yakutia living in peer climatic conditions. So, in all districts there is the high prevalence of HT, and the highest frequency of HT is in the Anabarsky District.

Considering that the main criterion of MS is abdominal obesity (AO) by criteria of VNOK (2009), we determined the frequency of AO at various ethnic groups of the population. In all groups a high frequency of AO - 47,5% at Chukchi

Table 1

Gender characteristics of small indigenous people of the North on districts of Yakutia

	Anabar	N. Kolyma	V. Kolyma	Tompo
Total	274	182	89	141
Men	81(29,6)	66 (36,3)	35(39,4)	51 (36,2)
Women	193 (70,4)	116 (63,7)	54 (60,6)	90 (63,8)
Average age, years	46,33±0,81	47,04±0,87	47,3 ±2,5	43,02±0,98

Table 2

Gender characteristics of small indigenous people of the North of Yakutia on ethnicity

	Dolgans	Evens	Evenks	Chukchi	Yukaghirs
Total, n	85	141	67	40	77
Men, n (%)	26 (30,6%)	51 (36,2%)	13 (19,4%)	20 (50%)	34(44,2%)
Women, n (%)	59 (69,4%)	90 (63,8%)	54(80,6%)	20 (50%)	43(55,8%)
Average age, years	44,93±1,56	43,02±0,98	48,37±1,64	39,73±1,93	46,49±1,54

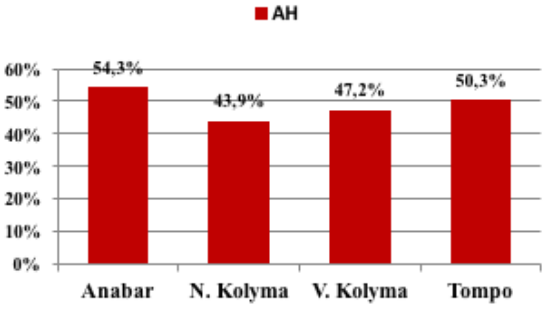


Fig.1. A frequency of arterial hypertension in small indigenous people of the North of Yakutia

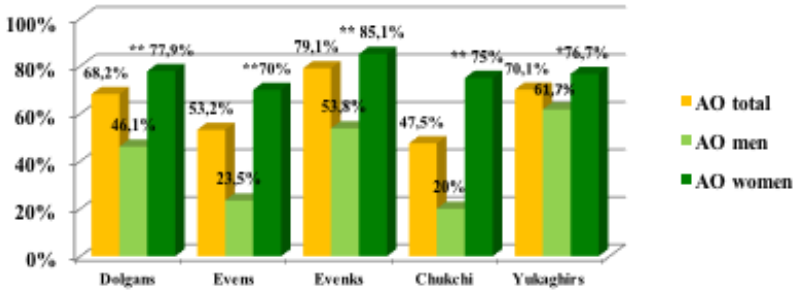


Fig.2. A frequency of abdominal obesity in small indigenous people of the North of Yakutia
* p<0,05, ** p<0,0001 - significant differences on gender characteristics

and 79,1% at Evenks are noted (fig. 2). Statistically significant differences are noted over women in the frequency of the AO in comparison with men. It is necessary to notice that there is equally high frequency of AO overboth men and women of Yukaghirs in comparison with other ethnoses.

Metabolic syndrome frenquency comparison of the examined ethnoses by criteria of VNOK (2009) was carried out (fig. 3). Metabolic syndrome largest frequency was found out of Evenks (56,7%), the smallest of Chukchi (20%). So wide difference in MS frequency is caused by gender differences in these groups, particularly high frequency of AO in women.

Considering the traditional, historically developed essential differences in the level of physical activity and other characteristics of the way of life between men and women, the MS frequency assessment in the compared groups was carried out separately for them (fig. 4). The essential contribution to MS frequency among adult population was made by women. Among them MS is frequent, sometimes superior at three and more times than in men Evens and Chukchi; difference between them are statistically significant (p<0,001), meanwhile there is equally high frequency reaching 85.1% in female Evenks.

Thus, we determined high prevalence of hypertension in the remote north areas of the Republic of Sakha (Yakutia) where representatives of small indigenous nations of North live. Sometimes hypertension is hardly corrected by monotherapy by hypotensive drugs. The high risk of development of cardiovascular complications points to the necessity of further enhanced education of all factors influencing formation of population health in districts of habitat of small indigenous people of Yakutia. Also, the high frequency of Metabolic Syndrome at the examined ethnoses was found out caused by change of traditional life, nutritional habits, low physical activity. Women have the highest frequency of a Metabolic Syndrome. This research confirms the statement of scientific community about Metabolic Syndrome as "pandemic of the XXI century".

REFERENCES

1. Ametov A.S. Ozhirenie – aepidemija XXI veka [Obesity – epidemic of the XXI century]. Terapevticheskij arkhiv [Therapeutic archive]. Moscow, 2002, №10, P.5-7.
2. Zdravookhranenie v Respublike Sakha (Jakutia): Statisticheskij sbornik. Sakha (Jakutia) stat. [Health in the Republic Sakha (Yakutia): statistical collection / Sakha (Yakutia) stat.]. Yakutsk, 2016, 159 p.
3. Khamnagadaev I.I. Rasprostranennost arterialnoj gipertonii, ishemicheskoj bolezni serdtsa I ikh faktorov riska sredi selskogo korennogo i prishlogo naselenija Severa i tsentralnoi Sibiri: avtoref.diss…dokt.med. nauk [Prevalence of arterial hypertension, cardiac ischemia and risk factors of the rural indigenous population of North and Central Siberia: Abstract of diss. of doctor of medical sciences]. Tomsk, 2008, 49p.
4. Assmann G. Harmonizing the definition of the metabolic syndrome: comparison of the criteria of the Adult Treatment Panel III and the International Diabetes Federation in United States American and European populations / G. Assmann [et al.] // Am J Cardiol.- 2007.-Vol. 99(4). - P.541-548.
5. Ford E.S. Prevalence of the metabolic syndrome in US populations / E.S. Ford // Endocrinol Metab Clin North Am. - 2004. - Vol. 33. - P.333–350.
6. Grundy S.M. Diagnosis and management of Metabolic Syndrome. An American Heart Association / S.M. Grundy // Circulation. – 2005. – Vol.112. – P.2735-2752.
7. Zimmet P. Preventing type 2 diabetes and the dysmetabolic syndrome in the real world: a realistic view / P. Zimmet, J.A. Shaw // Diabetic Medicine. – 2003. – Vol.20(9). – P.693-702.

The author:

Sofronova Sargylana Ivanovna – PhD, leading researcher – head of the department YSC CMP, Yakutsk, Russia, sara2208@mail.ru.

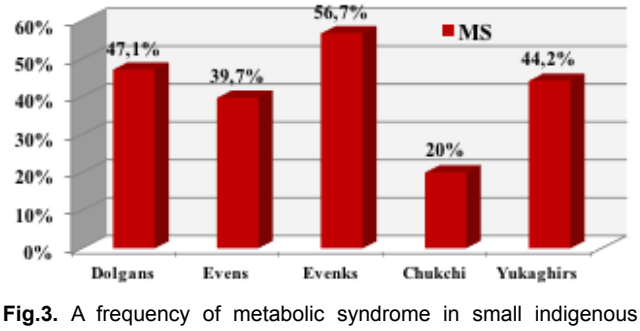


Fig.3. A frequency of metabolic syndrome in small indigenous people of the North of Yakutia

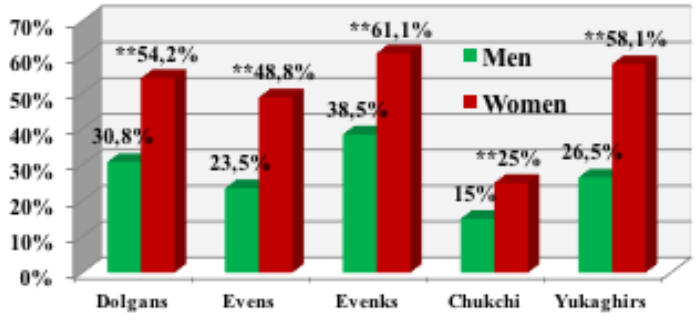


Fig.4 A frequency of metabolic syndrome in small indigenous people of Yakutia depending on gender (by criteria of VNOK, 2009)
** p<0,001- significant differences on gender characteristics

M.A. Varlamova, I.A. Nikolaeva , E.E. Gurinova, A.L. Suhomyasova, A.N. Nogovitsyna, N.R. Maximova

DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY IN THE SELECTION OF UNIDENTIFIED SPINOCEREBELLAR ATAXIES IN YAKUTIA

ABSTRACT

A clinical genealogical and molecular genetic analysis for the presence of mutations in the *DRPLA* gene in patients with an unidentified form of cerebellar syndrome in Yakutia was carried out.

Expansion of CAG repeats in the *DRPLA* gene was found in four members of the Yakut family. Clinical symptoms of patients with dentatorubral-pallidoluysian atrophy (DRPLA), a rare form of autosomal dominant spinocerebellar ataxia, from the Yakut family – ataxia, extrapyramidal and psychiatric disorders – it can be attributed to a later debut with a small degree of expansion of CAG repeats.

Keywords: dentatorubral-pallidoluysian atrophy (DRPLA), expansion of trinucleotide repeats, autosomal dominant disease.

INTRODUCTION

Dentatorubral-pallidoluysian atrophy (MIM 125370) is an autosomal dominant neurodegenerative disease characterized by the variability of combinations of progressive ataxia, epilepsy, myoclonus, choreoathetosis and dementia. The disease can begin at the age of 1 to 6 years of life. The cause of the disease is the expansion of CAG - repeats in the gene of *DRPLA* localized on chromosome 12p13 coding protein with an unidentified function (atrophin) [3]. Normally, the number of tandem CAG repeats is ≤36, and for pathologies from 40 to 100 [1, 2].

An important diagnostic sign of DRPLA is the detection of cerebrum in MR tomograms, in addition to nonspecific atrophic changes in the cerebellum, brainstem and the cerebral hemispheres, foci of demyelination in the white matter of the periventricular region, and the seminal center of the cerebral hemispheres [1]. In families burdened with DRPA, there is often an anticipation and the phenomenon of "father's transfer." The duration of the disease usually does not exceed 15 years. Morphologically, DRPLA is characterized by degenerative changes in the jagged nucleus, the outer segment of the pale ball and their projection zones in the red and lyus cores, and atrophy of the cortex of the cerebral hemispheres [4].

Analysis of clinical-genetic correlations showed that the different degree of expansion (CAG) -repeat of the gene of DRPLA leads to the manifestation of two phenotypes of the disease, different in clinical syndrome and severity. With a small degree of expansion (CAG) repeats of the *DRPLA* gene, a later debut and the development of choreoathetosis, ataxia, and mental disorders ("pseudo chorea") are observed, while in patients with the maximum repeat length of the *DRPLA* gene, the disease manifests itself at an earlier age with a severe syndrome of progressive myoclonus-epilepsy and dementia [5, 8].

Currently, DRPLA is considered an ethnic disease of the Japanese, the prevalence ranges from 0.2 to 0.7 per 100 000 [8], while in Europe and America only single cases are described [3, 4, 7, 8]. According to the Republican genetic register, in Yakutia, there are 519 patients with cerebellar syndrome, 80% of them are the autosomal dominant spinocerebellar ataxia (AD SCA) of the 1st type, with 20% of the forms remaining unidentified [2]. As is known, the Republic of Sakha (Yakutia) is a cluster of accumulation of SCA1, its prevalence rate for SCA1 has doubled over the past 21 years, reaching 46 cases per 100 000 population [6]. Given the prevalence of DRPLA in East Asia (Japan), it seems relevant to study this form of cerebellar ataxia in Siberian populations where unidentified forms of blood pressure of the AD SCA are recorded.

The aim of the work is a clinical genealogical and molecular genetic analysis for the presence of mutations in the *DRPLA* gene in patients with an unidentified form of cerebellar syndrome in Yakutia.

Materials and methods of research

In the period from 2008 to 2012, samples of biological material were sent to the Laboratory of Hereditary Pathology of the Department of the Molecular Genetics Yakut Scientific Center CMP, 80 patients, including 66 with sporadic form of SCA and 7 family cases with SCA (2 patients) were sent to genetics. Molecular-genetic part of the research was carried out jointly with colleagues from the Research Institute of the brain of the University of Niigata (Japan). On the basis of the department of molecular genetics of the YSC CMP, the work continued on the genetic analyzer Applied Biosystems 3130. The results of the sequencing were processed using the GeneMapper software.

DNA was isolated from 10 ml of peripheral blood by a standard method using proteinase K and subsequent phenol-chloroform extraction (Medical Laboratory Technologies, 1999). Previously, all informed subjects received written informed consent.

Results and discussion

Differential diagnosis of 80 patients with an unidentified form of cerebellar syndrome was performed on five forms of blood pressure in the SCA. Expansion of CAG repeats in the *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17) genes was not detected in the sample. The expansion of CAG repeat in the *DRPLA* gene (DRPLA) in four patients from one Yakut family was detected (Fig. 1). The proband and the brother have 63 mutant CAG repeats, the mother and sister of the proband have 62 (normal repeat ≤ 36).

III-5 proband R., born in 1969, first applied to the Medical Genetic Consultation in 2005 with a violation of coordination. In status: a patient of high stature, asthenic physique. Pupils D = S, photoreaction alive, left eye faint a little narrower. The volume of movement of the eyeballs is slightly limited in sides, horizontal bilateral nystagmus. The face is symmetrical. The soft palate is mobile, symmetrical. Swallowing is not broken. A voice with a nasal hue. The tongue is on the middle line, without fibrillation and atrophy. Light symptoms of oral automatism. There is no sharp paresis of

the extremities. Muscle tone is diffusely reduced. Hand dynamometry: D = 29 kg, S = 30 kg. Deep tendon reflexes from the hands and feet are slightly reduced, with no difference in sides. There are no pathological signs. The sample coordinator performs with intent and ataxia from both sides. Easy dysmetry and adiadochokinesia. In the Romberg position it is difficult, ataxia of the trunk. Gait is ataxic. Scale for the assessment and raiting of ataxia (SARA) was 25 points. Surface and deep sensitivity are not violated. MRI of the brain of 13.10.2010.

Conclusion: MRI-signs of cerebral atrophy, with the predominant lesion of stem structures and the cerebellum. EEG on February 20, 2012. Conclusion: Unexpressed diffuse changes. Moderate dysfunction of subcortical-stem structures. During the entire recording, rare bursts of epiactive ("acute-slow wave") are recorded along the anterior parts of the brain for up to 1 second.

II-1 mother of proband K., born in 1945, first applied to the Medical Genetic Consultation in 2006 with complaints about gait violation. She considers herself to be a patient from the age of 50, since 2001 she has had a speech disorder, and occasionally she has turned a blind eye. The pedigree is unknown, was brought up in the orphanage. In the status: in consciousness, the situation is compulsory, the facial features are pointed. The pupils are rounded, equal, and the photoreaction is weakened. The volume of orbit movement is limited when looking up, nystagmus is not present. Nasolabial folds are symmetrical, deep. The soft palate is symmetrical and mobile. Swallowing is not broken. The voice is nasal. Language - easy deviation to the right, without atrophy and fibrillation. Moderate proboscis reflex, symptom Marinescu - Rodovici on both sides. Speech is a rough dysarthria. The patient cannot stand and sit down unassisted, sits with support. In rest there is a tremor of the head and trunk, violent movements of the lower jaw, lips. Muscle tone is diffusely reduced. Hand dynamometry: D = 10 kg, S = 9 kg. Hypotrophy of hypotenor brushes. In the legs, strength is reduced to 3.5 b. Contracture of the right knee joint. Tendon reflexes from the hands: carporadial living, D = S, with biceps and triceps slightly reduced. Knee and Achilles reflexes are low, S> D. There are no pathological signs. Patient K. performs finger-to-nose test with intention, mild choreoathetosis. Scale for the assessment and raiting of ataxia (SARA) was 33 points. Hyperesthesia of the extremities. Deep sensitivity is slightly broken. There are no pelvic disorders. She is confused in date and in the names of grandchildren. It is worth noting that in the mother of proband cerebellar syndrome is combined with extrapyramidal insufficiency and dementia. These clinical symptoms coincide with the literature data on DRPLA.

III-3 sibs of proband, N., born in 1966, female, first applied in December 2010 with complaints of gait disturbance, speech changes, handwriting, sharp vision loss, coordination disorder, forgetfulness. After 40 years the husband of the patient noticed a violation of her gait, and then joined the change of speech and forgetfulness. Her surrounding begins to make comments that she forgets specially. Since the beginning of 2011, she has noticed outbursts of anger. Since 2010, there are attacks of severe headache in the frontal region with a feeling of nausea and vomiting, connects to stressful situations, a frequency of 1 time in 2-3 months, at this time does not accept anything, does not seek medical help, while there is a decrease Blood pressure to 60/40 mm Hg. Art. Within two years does not work, has the 2nd group of disability. In 2000, the patient received a craniocerebral injury in a car accident, received no timely treatment. Family history: the patient is divorced, has one healthy daughter and granddaughter, which she takes from the kindergarten. The mother and native siblings have a similar disease. Objectively: patient with normostenic constitution, height 164, weight 55 kg. Neurological status: vision is reduced (presbyopia), pupils and eye slits are equal. The volume of motion of the orbits is complete, the nystagmus is horizontal in both directions. Less clearly right nasolabial fold. The soft palate is symmetrical in phonation, the voltage is weakened. Reflexes from the soft palate and posterior pharyngeal wall are preserved. She has mild difficulty swallowing solid food rarely. The tongue in the cavity and when protruding along the middle line, atrophy and fibrillation of the muscles there. Reflexes of oral automatism are negative. There are no sharp paresis of the extremities. Tendon and periosteal reflexes from arms and legs are high, uniform from both sides. There are no pathological stop signs. Muscle tone is diffusely reduced. Sensitive violations are not clear. Easy dysmetry and disidiasis. The coordinating tests are performed with intent. A slight tremor of the head during excitement. During the conversation, she smacks her lips. In the Romberg position, the ataxia of the trunk, in tandem is not worth more than 10 s. Gait is ataxic, does not perform 10 consecutive steps in tandem. . Scale for the assessment and raiting of ataxia (SARA) was 16 points. Speech - dysarthria, cerebellar syndrome with mild extrapyramidal insufficiency. A consultation of a psychiatrist was recommended in connection with memory impairment.

III-6 Junior sibs of proband G., born in 1975. The man first applied to the medical genetic consultation on January 19, 2012, he does not present any complaints. From the words of his wife, her husband's speech became slow, the walk became uncertain, there are attacks of dizziness, occasionally choking with saliva during sleep. He applied for donating blood for DNA diagnosis on carrying a mutation in the *DRPLA* gene. Works as a teacher in the center of technical creativity. He is married, has two children, the eldest son from the first marriage of his wife. Head trauma with concussion of the brain in the anamnesis, without adequate treatment. From words, alcohol does not cause. Smokes, 1 pack is enough for 3-4 days. Objectively: asthenic physique, high growth. In neurological status: sight and hearing are preserved. Lachrymation OU. Pupils of rounded shape, equal,

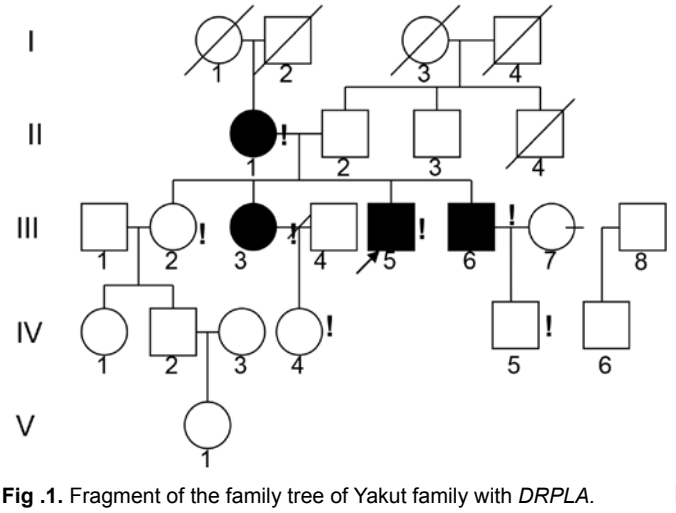


Fig .1. Fragment of the family tree of Yakut family with *DRPLA*.

photoreaction alive. The right eye gap is narrower. The volume of motion of the orbits is complete, nystagmus is absent. Less clearly right nasolabial fold. The soft palate is symmetrical and mobile. Language - a rough deviation to the right, without atrophy and fibrillation. ROA - easy proboscis reflex. There are no sharp paresis of the extremities. Muscle tone is normal. Tendon and periosteal reflexes from the hands and feet of medium liveliness, no difference in sides. When performing a finger-sap sample: on the right it performs uncertainly, on the left it is satisfactory. Easy dysmetry. There may be an easy restriction in the right shoulder joint with the raising of hands upwards, in dilution to the sides (shoulder injury in September 2011). The heel-to-shin test - satisfactory. There are no sensory disturbances. In the Romberg pose, easy rocking. In tandem is <10 seconds. Tandem gait works with difficulty. Scale for the assessment and raiting of ataxia (SARA) was 8 points. Speech is an easy dysarthria. MRI of the brain from 29.02.2012 . Conclusion: MRI-signs of cortical atrophy of cerebellar hemispheres on both sides. Post-traumatic encephalopathy. EEG on 02/07/2012. Conclusion: Unexpected diffuse changes in brain BEA. Focal paroxysmal activity is not present.

IV-5 nephew of the proband, born in 2000. Complaints: increased fatigue. In the clinic: a light pyramidal syndrome. EEG on February 18, 2012 - without any special features.

Thus, the clinical symptoms of DRPLA patients from the Yakut family - ataxia, extrapyramidal and psychiatric disorders - coincide with the literature data on DRPLA and can be attributed to a later debut with a small degree of expansion of CAG repeats.

The conclusion

Among the sample of Russian patients, dentarubroparidotoid atrophy, a rare form of autosomal dominant spinocerebellar ataxia, this pathology was revealed for the first time with the help of molecular genetic methods of diagnosis. Expansion of CAG repeats in the *DRPLA* gene was found in four members of the Yakut family. The proband and mother of the proband had a late form of ataxia, and a mutation in the *ATXN1* gene (SCA 1 type) was first eliminated, followed by other more frequent ataxia types: *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17) . Due to the fact that the mother of the proband is an orphan, was brought up in the Olekma children's home (Yakutia), it is difficult to identify other close relatives of the family. Yakutia is a cluster of accumulation of SCA1 type, and there are also unidentified forms of SCA [2]. In our work, a molecular-genetic method of investigation in 80 patients with unidentified form of SCA excluded a mutation in the genes: *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNL1A4* (SCA6), *TBP* (SCA17).

The clinical symptoms of DRPLA patients from the Yakut family - ataxia, extrapyramidal and mental disorders - coincide with DRPLA literature data and can be attributed to a later debut with a small degree of expansion of CAG repeats [4, 5, 7]. As for other polyglutamine diseases in the Yakut family with DRPLA, there are: reverse correlation between the degree of expansion of the repeats in the mutant allele and the age of manifestation of the symptoms of the disease, a direct relationship between the degree of expansion of repetitions and the severity of clinical manifestations, the phenomenon of anticipation.

Currently, blood pressure in the SCA is becoming particularly relevant, both in the medical and social terms, due to the rather widespread prevalence, difficulties in clinical diagnosis, the absence of an etiotropic treatment method, a steadily progressing course, a high incidence of disability and fatal outcomes. Therefore, the timely identification and direction of patients with cerebellar syndrome in medical genetic counseling, the development of the most effective methods of counseling, including DNA diagnostics, are of great social and economic importance.

REFERENCES

1. Illarionishkin S.N. Rudenskaya G.E. Ivanova I.A. [et al.] Nasledstvennyye ataksii i paraplegii [Hereditary ataxia and paraplegia]. Moscow: MEDpress inform [MEDpress info], 2006, p.416.
2. Platonov F.A. [et al.]. Spinotserebellyarnaya ataksiya pervogo tipa v Yakutii: rasprostranennost' i kliniko-geneticheskiye sopostavleniya [Spinocerebellar ataxia first type in Yakutia: prevalence and clinical and genetic association] Meditsinskaya genetika [Medical genetics]. Moscow, 2004, No. 5, p.242-248.
3. Dentatorubro-Pallidoluysian Atrophy (DRPLA) among 700 Families with Ataxia in Brazil Cerebellum / Braga-Neto, P., Pedroso, J.L., Furtado, G.V. [et al]. – 2017. - 16: 812.
4. Dentatorubropallidoluysian atrophy in a Spanish family: a clinical, radiological, pathological, and Genetic study / Muñoz, MMilà, ASánchez [et al] // J Neurol Neurosurg Psychiatry. – 1999. – 67. – P.811–814.
5. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA) / Koide R, Ikeuchi T, Onodera O [et al] // Nat Genet. – 1994; 6: 9–13.
6. Genetic fitness and selection intensity in a population affected with high-incidence spinocerebellar ataxia type 1 / Platonov FA, Tyryshkin K, Tikhonov DG [et al] // Neurogenetics. 2016;17(3):179-185. doi:10.1007/s10048-016-0481-5.
7. Portuguese families with dentatorubropallidoluysian atrophy (DRPLA) share a common haplotype of Asian origin / S. Martins, T. Matama, L. Guimara [et al] // European Journal of Human Genetics. – 2003. – 11, 808–811.
8. Sugiyama A., Sato N., Nakata Y. [et al] J Neurol (2017). https://doi.org/10.1007/s00415-017-8705-7
9. Radiologic and Neuropathologic Findings in Patients in a Family with Dentatorubral-Pallidoluysian Atrophy / Sunami Y., Koide R., Arai N. [et al] // AJNR Am J Neuroradiol 32:109-14. – 2011. – P. 109-114.

The authors:

Varlamova Marina Alekseevna - research associate of the laboratory of hereditary pathology of the Department of molecular genetics of the Yakut science center of complex medical problems, neurologist at the hospital of the Yakutsk Scientific Center CMP, Yakutsk, the Republic of Sakha (Yakutia).

Nikolaeva Irina Averevna - geneticist of the Medical Genetic Consultation of the Republican Hospital №1 – National Medical Centre, Ministry of Public Health of the Sakha, Yakutsk, the Republic of Sakha (Yakutia).

Gurinova Elizaveta Egorovna - geneticist of the Medical Genetic Consultation of the Republican Hospital №1 – National Medical Centre, Ministry of Public Health of the Sakha, Yakutsk, the Republic of Sakha (Yakutia).

Sukhomyasova Aitalina Lukichna - candidate of Medical Science, geneticist of the highest category, head of the Medical Genetic Center of the Republican Hospital №1 – National Medical Centre, Ministry of Public Health of the Sakha, Yakutsk, the Republic of Sakha (Yakutia).

Nogovitsyna Anna Nikolaevna - candidate of Medical Sciences, research associate of the Educational and Scientific Laboratory «Genomic Medicine» Clinic of the Medical Institute of North-Eastern Federal University in Yakutsk, the Republic of Sakha (Yakutia).

Maksimova Nadezhda Romanovna - doctor of Medical Sciences, research associate of the Educational and Scientific Laboratory «Genomic Medicine» Clinic of the Medical Institute of North-Eastern Federal University in Yakutsk, the Republic of Sakha (Yakutia).

S.K. Kononova, O.G. Sidorova, M.A. Varlamova, Kh. A. Kurtanov, F.A. Platonov, V. L. Izhevskaya,, E.K. Khusnutdinova, S.A. Fedorova

THE ISSUE OF THE FATE OF A FOETUS WITH A MUTATION AFTER A PRENATAL DIAGNOSIS OF SPINOCEREBELLAR ATAXIA TYPE I IN COMPARISON WITH MYOTONIC DYSTROPHY IN THE SAKHA REPUBLIC (YAKUTIA)

ABSTRACT

We discuss one of the issues of prenatal diagnostics – the bioethical dilemma of the fate of a foetus with a mutation. We believe that prior to the onset of the disease, the individuals-carriers of SCA1 gene mutation cannot be called diseased, as they are completely healthy in their physical and intellectual development.

The phenomenon of DM anticipation depends heavily on inheritance from diseased mothers and increases the risk of birth of an almost completely unviable baby with a severe congenital DM. An ethical dilemma arises: «Should we classify spinocerebellar ataxia type 1 as a 'less serious' genetic disease for prenatal diagnostics, and myotonic dystrophy as a more serious disease for prenatal diagnostics?» This is a very complex issue and requires discussion not only among the specialists, but also lawyers, psychologists and the general population of the republic.

Keywords: bioethical issues, prenatal diagnostics, spinocerebellar ataxia, myotonic dystrophy, Sakha Republic (Yakutia).

INTRODUCTION

Prenatal diagnosis (PD) of hereditary diseases is a complex set of modern diagnostic procedures performed at various stages of prenatal development with an aim of identifying possible pathologies that a foetus might have. In Russia, PD saw widespread use only recently, starting with PD of chromosome pathologies using non-invasive methods of ultrasound detection with biochemical markers. At present, PD can identify almost all single-gene disorders with determinable causes: the known mutations of damaged genes. Methods and capabilities of genetic PD are constantly improving, as listed by V. Baranov (2015), who identifies five main modern approaches to PD:

1. molecular diagnosis of chromosomal disorders;
2. microdeletion analysis using microchips (comparative genomic hybridisation – array CGH);
3. pre-implantation diagnosis of chromosomal and genetic disorders;
4. non-invasive PD (NIPD) of chromosomal and genetic disorders by screening foetal DNA obtained from maternal blood (new generation sequencing – NGS);
5. preventive genetic testing (PGT) to identify mutations in married couples when planning a pregnancy [1].

Nevertheless, despite all the advantages of PD as an effective means of preventing hereditary pathologies, with the real possibility of reducing the so-called "evolutionary baggage" of population, there is "another side of the coin" to it: complex bioethical issues that accompany the reproductive decision of a couple – prenatal medical-genetic consulting, obtaining informed consent, making a difficult decision about the fate of an unborn child.

Bioethics researchers P. Tischenko and B. Yudin (2006) emphasize the principal bioethical issues of using genetic technologies:

- involvement of patient's relatives in the process of genetic testing that undoubtedly raises the question of information confidentiality;
- the gap between the theoretical possibility of diagnosing any presently known hereditary disease and the ability to effectively treat it;
- the use of obtained information for carrying out future prenatal diagnosis in a family to prevent the risk of birthing a second sick child;
- probabilistic nature of the appearance of certain genetic disorders in the subject [10].

S. Deryabina (2015), researching the specifics of medical-genetic consulting in the field of neonatal screening, asks: "Do the parents have the right to know about the genetic state of a child with a late-onset disease? Knowledge is not always beneficial to the one who strives for it. All people are different, and for some, forewarned is really forearmed, while the others buckle under the pressure of impending and inevitable fate, forever losing the ability to enjoy life today and tomorrow, not considering the possibilities of the future" [3].

It seems very natural for a family burdened with a hereditary disease to want to have a healthy child; however, the most pressing bioethical issues arise when deciding whether to keep or to abort a foetus diagnosed with a gene mutation that is responsible for the development of the disease. Let us consider the two most widespread hereditary diseases in the Sakha population, for which PD is possible or is already being practiced.

Materials and methods

Genealogical method of research, collection of medical-social data using genetic maps of patients. Molecular-genetic research methods. Sociological research methods (sociological monitoring, interviews).

The article uses data from the republican genetic registry of hereditary and congenital diseases. According to the genetic registry, 252 patients with spinocerebellar ataxia type 1 diagnosis

and 185 patients with Rossolimo-Curschmann-Batten-Steinert myotonic dystrophy diagnosis were registered in medical-genetic consultation [8].

Results and Discussion

In the year 2000, molecular-genetic methods of research and prenatal diagnosis of five widespread single-gene disorders were introduced for the first time to the medical practice of the Sakha Republic (Yakutia) [4]. From 2000 to 2018 the number of hereditary diseases available for DNA diagnosis increased to 30 conditions [6]. It seems that for each disease it would be possible to conduct PD during the early stages of pregnancy and to prevent the birth of a sick child, however, there are numerous bioethical concerns about the appropriateness of PD in each specific case of prenatal assistance.

Spinocerebellar ataxia type 1 (SCA1)

The disease is characterised by a late onset. On average, the disease develops at the age of 35, although there are significant outliers depending on the number of CAG repeats in mutated *SCA1* gene. There are cases when the disease developed at the age of 26 and the age of 55. Clinical signs of SCA1 are characterised by extreme polymorphism, cerebellar syndrome with pyramidal signs. The disease progresses in 5 clinical stages, defined by the severity of motor and speech dysfunctions. The severity of the disease in the later stages is defined by the development of bulbar paralysis [7].

We believe that prior to the actual onset of the disease, the individuals-carriers of SCA1 gene mutation cannot be called diseased, as they are completely healthy in their physical and intellectual development. Among the carriers of SCA1 gene mutation there were and there are many well-known sportsmen, political and public figures, scientists etc. Let us think for a moment: by suggesting a termination of pregnancy to parents of carriers of SCA1 disease, we are, in essence, suggesting to get rid of a productive member of society. The main reasons why termination of pregnancy can be suggested to parents are the incurable nature of the disease and the suffering of the individual in the future. On the other hand, many laboratories are working on finding a treatment for neurodegenerative diseases and may one day be successful.

In our experience, there were several cases when pregnant women refused to terminate pregnancy when the foetus had SCA1 mutation. Their difficult and informed choice was accepted, just like the choice of the women who decided to terminate pregnancy after receiving positive results of DNA testing. We have also observed that about half of all the women who came to us for SCA1 PD did not return for the actual PD procedure after attending the first prenatal genetic consulting session. This fact shows the moral and psychological difficulty of the challenge to decide the fate of a foetus. There is another example when a woman carrier of SCA1 told us about her apprehension of the disease and expressed her wish to give birth to a child, preferably a girl (even if she inherits the mutation), so that the child could look after her in the future.

Let us look at international documents on the issue: “if the parents are set against the abortion, the test data will not benefit them nor their child, but can cause extreme harm to the child from stigmatisation in the family or society. If, after consultation, the parents still refuse the possibility of an abortion, it would be more ethical to abandon the prenatal test. In this case, testing a foetus for a disease with late onset becomes similar to testing a child, the procedure that WHO experts recommend postponing until the child reaches the legal age” [13, 14].

Myotonic dystrophy (DM)

It is a hereditary neuromuscular disease, characterised by multisystem involvement with a large diversity of clinical symptoms, principal of which are myotonia, myopathy, cataract, cardiomyopathy, endocrine disorders, and, in severe cases, psychoneurological disorders and lowered intelligence. DM mutations, like in SCA1, are considered dynamic and are expressed in the expansion of CTG repeats [2].

Myotonic dystrophy manifests in general by asthenia of a patient and the relative lowering of his or her intellect, due to which it can be difficult for a pregnant woman with DM to make an informed decision about undergoing PD. Similar cases are described in literature in connection with prenatal genetic consultation of teenage girls. The authors identified differences in methods of communication with teenagers and adult women. Teenagers have difficulties in understanding information relating to the risks to foetus [12]. We have also encountered complex ethical and legal issues relating to prenatal diagnosis of DM, as well as conditions that could lead to violation of patient’s rights. With an official disability, many patients with DM are considered legally competent, i.e. they don’t have official caretakers and thus have the right to make an independent decision about PD and the right to give informed consent. However, in almost all cases, patients with myotonic dystrophy depend greatly on their relatives, they and their children are taken care of by the healthy members of their families. It is not unreasonable that in such cases relatives actively influence the decisions made by DM patients. The principle of confidentiality also loses all significance within such a family. We have observed that a considerable number of women who came to us for DM PD were representatives of two large families of R and D. A key role in this was played by the most active members of these families, mostly women, who informed all their relatives of the possibilities of prenatal diagnosis.

Unlike SCA1, DM has a type that causes birth defects. The phenomenon of DM anticipation depends heavily on inheritance from diseased mothers and increases the risk of birth of an almost completely unviable baby with a severe congenital DM, and, at the same time, the mother is also at risk due to the weakness of labour [9].

Conclusion

Doctors and bioethics specialists are in discussions about the seriousness of indications for carrying out PD for hereditary diseases. There is an opinion that the period of full healthy life before the development of late-onset diseases such as SCA1 makes these diseases “less serious” for PD. Overall, the doctors agree that the seriousness of indications for carrying out PD depends on the magnitude of risks, early onset and severity of symptoms [5,11]. Therefore, it is clear in this context that DM is a more serious indication for PD and that families should be strongly recommended to undergo it.

It is not possible to fully discuss the complexity of this issue in a small article. Each case of prenatal diagnosis that identified a mutation in a foetus is a psychological stress and a moral dilemma for a pregnant woman and her family. Prenatal medical-genetic consultation should be carried out in accordance with international bioethics principles:

- voluntary nature of prenatal diagnosis;
- completely and fully informing families about all the possible consequences;
- assistance for a family in making a reproductive decision;
- the choice of families regarding a pregnancy with an affected child should be respected and protected by the respective country’s legislation.

REFERENCES

1. Baranov V.S. Kuznecova T.V. Novye vozmozhnosti geneticheskoj prenatal’noj diagnostiki [New opportunities of genetic

prenatal diagnosis] Zhurnal akusherstva i zhenskih boleznej [Journal of obstetrics and women’s diseases]. Moscow, 2015, V.LXIV, vyp.2, p.4-12.
2. Gorbunova V.N. Savel’eva-Vasil’eva E.A. Krasil’niko V.V. Zabolevanija nervno-myshechnoj sistemy. Molekuljarnaja nevrologija [Diseases of the neuromuscular system. Molecular neuroscience] SPb.: «Intermedika » [SPb “Intermedica”], 2000, 320 p.
3. Derjabina S.S. Neonatal’nyj skrining: jeticheskie voprosy rasshirenija spektra skriniruemyh zabolevanij [Neonatal screening: ethical issues, expand the range screening diseases] Voprosy sovremennoj pediatrii [Issues of modern Pediatrics]. Moscow, 2015, V.14, №6, p.714-723.
4. Kononova S.K. Fedorova S.A. Maksimova N.R. Diagnostika spinocerebelljarnoj ataksii 1 tipa v mediko-geneticheskoj konsul’tacii Nacional’nogo Centra Mediciny Respubliki Saha (Jakutija). [Diagnosis of spinocerebellar ataxia type 1 in the MGK NCM RS (Yakutia)] Tez.dokl. 2-oj mezhdunarodnoj nauch.-prakt. konf. “Problemy Viljujskogo jencefalomielita, nejrodegenerativnyh i nasledstvennyh zabolevanij nervnoj sistemy”[II international science.-practice. conf. thezis “Problems of Vilyui encephalomyelitis, neurodegenerative and hereditary diseases of the nervous system”]. Yakutsk, 2000, p.84-85.
5. Izhevskaja V.L. Jeticheskie problemy prenatal’noj diagnostiki [Ethical problems of prenatal diagnosis] Zhurnal akusherstva i zhenskih boleznej [Journal of obstetrics and women’s diseases]. Moscow, 2011, V. LX, vyp.3, p.203-211.
6. Stepanova S.K. Zaharova V.A. Tapyev E.V. Suhomjasova A.L. Maksimova N.R. Molekuljarno-geneticheskie metody diagnostiki monogennyh boleznej v Respublike Saha (Jakutija) [Molecular genetic methods of diagnosis of monogenic diseases in the Republic of Sakha (Yakutia)] Geneticheskie issledovanija naselenija Jakutii: sb.nauch. tr. pod red. V.P. Puzyreva, M.I. Tomskogo [Genetic studies of the population of Yakutia: under the editorship of V. P. Puzyrev, M. I. Tomsky]. Yakutsk: CIP NBR Saha, 2014, 336 p.
7. Platonov F.A. Nasledstvennaja mozzhechkovaja ataksija v Jakutii [Hereditary cerebellar ataxia in Yakutia]: dis… d-ra. med. nauk [dis... d-ra. med. sciences’]. Moscow, 2003, 178 p.
8. Suhomjasova A.L. Maksimova N.R. Nogovicyna A.N. Gurinova E.E. Nazarenko L.P. Raznoobrazie nasledstvennoj patologii v Respublike Saha (Jakutija) po dannym respublikanskogo geneticheskogo registra nasledstvennoj i vrozhdennoj patologii [The diversity of hereditary pathology in the Republic of Sakha (Yakutia) according to the national hereditary register of hereditary and congenital pathology: Genetic studies of the population of Yakutia] sb.nauch. tr. Geneticheskie issledovanija naselenija Jakutii [Genetic studies of the population of Yakutia] pod red. V.P. Puzyreva, M.I. Tomskogo. Yakutsk: CIP NBR Saha, 2014, 336 p.
9. Suhomjasova A.L. Korotov N.M. Miotonicheskaja distrofija [Myotonic dystrophy] sb.nauch.tr. Geneticheskie issledovanija naselenija Jakutii pod red. V.P. Puzyreva, M.I. Tomskogo [Genetic studies of the population of Yakutia under the editorship of V. P. Puzyrev, M. I. Tomsky]. Yakutsk: CIP NBR Saha, 2014, 336 p.
10. Tishhenko P.D. Judin B.G. Moral’nye problemy sovremennoj genetiki. Rabochie tetradi po biojetike [Moral problems of modern genetics. Workbooks bioethics] sb.nauch. st. Biojeticheskie problemy genomiki i jetnogenetiki [Collected articles on bioethical issues in genomics and ethno-genetics]. Moscow:MGU, 2006, vyp.3, 41 p.
11. Holmes-Siedle M. Parental decisions regarding termination of pregnancy following prenatal detection of sex chromosome abnormalities / M.Holmes-Siedle, M. Ryyanen, R. H. Lindenbaum // Prenat. Diagn. - 1987. - Vol. 7. - P. 239–294.
12. Genetic counselors’ experiences with adolescent patients in prenatal genetic counseling / M.G. Catherine [et al.] // J Genet Couns.-2011.-№20.-P.178-191.
13. Proposed International Guidelines on Ethical issues in Medical Genetics and Genetic Services. Report of WHO Meeting on Ethical Issues in Medical Genetics. Human Genetics Programme. - Geneva: WHO, 1997. - 15 p.
14. Wertz D. C. Review of ethical Issues in medical genetics / D.C. Wertz, J. C. Fletcher, K. Berg. - Geneva: WHO, 2001. - 103 p.
15. The study was supported by Ministry of Education and Science of Russian Federation #6.1766.2017, FASO (BRK_0556-2017-0003).

The authors:

Kononova Sardana Kononova - senior researcher of the laboratory of molecular genetics , Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; konsard@rambler.ru;

Sidorova Oksana Gavrilina - researcher of the laboratory of hereditary pathology Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; okssi66@mail.ru

Varlamova Marina Alexeevna – junior researcher of the laboratory of hereditary pathology, Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; Varlamova.m@yandex.ru

Kurtanov Khariton Alexeevich – PhD, chief researcher Department of molecular genetics Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; HARITON_KURTANOV@mail.ru

Platonov Fedor Alexeevich, MD, chief researcher Institute of Health, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; platonovy@mail.ru

Izhevskaya Vera Leonidovna- MD, professor, Deputy Director for scientific work of Medical Genetic Research Center, Russian Academy of Science, Moscow, Russian Federation; izhevskaya@med-gen.ru.

Khusnutdinova Elsa Kamilevna- doctor of biological sciences , professor, academician of the Academy of Sciences of the Republic of Bashkortostan, Director of the Institute of biochemistry and genetics, Ufa Federal Research Center, Ufa, Russian Federation; elzakh@rambler.ru

Fedorova Sardana Arkadyevna- doctor of biological sciences, head of the laboratory of molecular biology, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; sardaanafedorova@mail.ru

I.D. Ushnitsky, L. S. Mironova, I.I. Gogolev, M.M. Davydova

CLINICAL-GENETIC ASPECTS OF CONGENITAL CLEFT LIP AND PALATE AMONG CHILDREN OF YAKUTIA

ABSTRACT

The comparative analysis of prevalence and structure of congenital cleft lip and palate (CCLP) among children living in Yakutia for the last decade has been carried out. At the same time the assessment of the direct and indirect interrelation has been carried out according to medical-genetic consultation of patients and their parents. Studying of congenital anomalies frequency of maxillofacial area at children characterizes an unfortunate trend of their increase during observation.

The obtained data demonstrate that unilateral clefts of the upper lip and palate and also the isolated clefts of the hard and soft palates prevail in their structure. The uranostaphyloschisis was revealed more often in CCLP structure, further there were unilateral through cleft lip and palate, bilateral through clefts, hidden cleft palate, isolated cleft lip and alveolar process where children with syndromes of hemifacial microsomia, Pierre Robin and Gorlin-Goltz are the hardest in holding complex treatment-and-prophylactic actions and medical-social rehabilitation. Some examined children had severe forms of congenital malformation, due to syndromes of hemifacial microsomia and Pierre-Robin's syndrom. Meanwhile some children were revealed to have the inherited forms of malformation of maxillofacial area and also Van der Woude syndrome.

The analysis of pathological sign or syndrome among direct and indirect relatives characterizes the existence of some features where the main congenital malformation of maxillofacial area is traced from indirect relatives, and the direct genetic interrelation from mother or father. Our analysis has revealed the existence of features by gender. So, palate clefts were often found at girls in comparison with boys. At the same time boys prevailed on the contrary in indexes of unilateral clefts lip and palate. The dominance of left-side localizations of congenital clefts of the upper lip and palate was revealed by localization among these pathologies.

The analysis of the obtained data characterizes that the first stage of perfecting of complex medical-social rehabilitation is the creation of the uniform regional database of children with congenital clefts of the upper lip and palate.

Keywords: congenital clefts of the upper lip and palate, relevance, heredity, Pierre-Robin's syndromes, Van der Woude syndrome, hemifacial microsomia.

INTRODUCTION

The congenital cleft of the upper lip and palate is a heavy malformation of maxillofacial area, shown gross anatomic and functional disorders [3, 6]. It should be noted that congenital malformation of the face is not only medical, but also social problem; therefore a complex treatment approach allows us to achieve the good remote results [1, 2]. Congenital lip and palate clefts have multifactorial origin with negative impact of teratogens, heredity, etc. [7]. Despite constant perfecting of surgical and orthodontic methods of treatment of children with congenital clefts of the upper lip and palate, complex rehabilitation of such patients continues to remain one of the most difficult tasks for a maxillofacial surgeon, a dentist, a pediatrician, a logopedist and a psychologist [4, 5].

It is known that perfecting of health care system is based on knowledge of clinical-epidemiological and etiological features of case incidence. In this regard the researches directed to studying of these problems are relevant. We don't have similar researches in the conditions of Yakutia for the last period.

Materials and research methods

The retrospective and prospective analysis of registration cards and case histories has been carried out. Collecting of clinical material and medical-genetic analysis has been carried out on the basis of children's maxillofacial surgery at otorhinolaryngological department and medical-genetic department at Republic hospital № 1 – National center of medicine». Totally 281 children aged from 3 months up to 14 years and teenagers up to 18 years were examined during 2000-2016 years. There were 136 boys and 145 girls. All children were operated concerning congenital clefts of the upper lip and palate. They took a course of medical-social rehabilitation. The clinical-genealogic research of the families having the child with congenital pathology of maxillofacial area was done for the establishment of family relations, tracing the pathological symptom or syndrome among close and distant, direct and indirect relatives. At the same time we made a family tree and carried out the genealogical analysis. A consulting person and a proband (consulting – the person coming for doctor's consultation; a proband – the patient himself). Collecting information included the common questions: surname, name, proband middle name, date of birth, nationality of a proband, his mother and father, birthplace of a proband and parents, existence of kinship marriage in a family tree.

Statistical processing of clinical material was carried out with the use of standard methods of variation statistics.

Results and discussion

The carried-out dynamic analysis of birth rate of children with CCLP during observation characterizes the existence of some features in indexes. So, since 2000 to 2016 in the region there were born 281 children with congenital clefts lip and/or palate. There were 16.53±0.30 cases on average in a year. In 2014 there were maximum quantity (31 cases) of the birth of children with CCLP (CCLP frequency was 1:548 [1.82±0.02 – on 1000 newborns]), and the minimum index (3 cases) was revealed in 2001 (CCLP frequency was 1:4420 [0.22±0.05 – on 1000 newborns]). At the same time a dynamic increase in the line of a trend during observation was defined that characterized a negative tendency of frequency increase of congenital malformation.

It should be noted that CCLP structure has revealed clefts of hard and soft palates (37.82±0.66%), further there were unilateral through clefts lip and palate (30.33±0.74%). Meanwhile, the data of bilateral through clefts and also hidden clefts of the palate, the isolated clefts lip and alveolar process made 8.23±0.98, 7.49±0.99 and 7.52±0.99% respectively. At the same time, minimum indicators of frequency were the isolated clefts of the upper lip (4.13±1.01%), transversal clefts lip – 0.37±1.07%. As a rule, medical-social rehabilitation children with syndromes of hemifacial microsomia, Pierre Robin and Gorlin-Goltz are the hardest in holding complex treatment-and-prophylactic

actions. The carried-out assessment and analysis revealed these syndromes at 4.11±1.03% of children.

It is necessary to emphasize that the carried-out analysis revealed the existence of features by gender. So, girls have palate clefts more often (64.35±0.71%) whereas boys have 35.65±1.26%. At the same time boys on the contrary prevailed in indexes of unilateral clefts lip and palate (55.56±1.01%). The dominance of left-side clefts localizations was revealed by localization among these pathologies where the indicator was 61.72±0.87%.

At the result of analysis we revealed 31 children with the tainted heredity. 9 children were with a through cleft of the upper lip and palate: 4 - with left-side and 5 – right-side cleft. The quantity of cases with a palate cleft was 13 children, 4 of them with the latent form of a palate cleft. The medical-genetic analysis revealed a presence of bilateral clefts of the upper lip and palate at 5 children, including one child with Van der Woude syndrome. 4 examined children were revealed the hereditary tainted of the isolated clefts lip and/or alveolar process.

The analysis of tracing of pathological symptom or a syndrome among direct and indirect relatives characterizes the existence of some features. So, 35.48±2.81% have the direct genetic interrelation from mother or the father, and 64.52±1.55% - congenital malformation of maxillofacial area from indirect relatives.

Conclusion

The received results have demonstrated a negative tendency of frequency occurrence increase of congenital clefts lip and/or palate among children of the region for 2000-2016. At the same time some of the examined patients showed the genetic interrelation of congenital pathologies. Such situation needs the development and deployment of the complex regional program directed to the perfecting of treatment-and-prophylactic help and medical-social rehabilitation of children with congenital malformation of maxillofacial area with the creation of the unified electronic database.

REFERENCES

1. Ljubomirova E.O. Tagirova A.G. Mitropanova M.N. Zemlin I.A. Analiz dejatel’nosti centra lechenija detej s vrozhdennoj patologiej cheljustno-licevoj oblasti v Krasnodarskom krae za 2012-2014 gody [The work analysis of the center of treatment of children with congenital pathology of maxillofacial area in Krasnodar Krai for 2012-2014 period] Materialy V Vserossijskoj nauchno-prakticheskoj konferencii. Vrozhdennaja i nasledstvennaja patologija golovy, lica i shei u detej: aktual’nye voprosy kompleksnogo lechenija [Materials of V All-Russian scientific and practical conference. Congenital and heritable pathology of the head, face and neck of children: topical issues of complex treatment] [otv. red. prof. O. Z. Topol’nickij]. Moscow, 2016, p.182-184.
2. Malimon T.V. Shheglova A.P. Zaharova N.I. i dr. Kompleksnoe lechenie i reabilitacija detej s vrozhdennoj rasshhelinoj guby i neba v otdelenii detskoj stomatologii im. T.V. Sharovoj [Complex treatment and rehabilitation of children with a congenital cleft lip and palate in children’s odontology department by T.V. Sharova] Materialy V Vserossijskoj nauchno-prakticheskoj konferencii. Vrozhdennaja i nasledstvennaja patologija golovy, lica i shei u detej: aktual’nye voprosy kompleksnogo lechenija [Materials of V All-Russian scientific and practical conference. Congenital and heritable pathology of the head, face and neck of children: topical issues of complex treatment] [otv.red. prof. O. Z. Topol’nickij]. Moscow, 2016, p.204-205.
3. Mamedov A.A. Kucherov Ju. I. Zhirkova Ju.V. i dr. Mezhdisciplinarnyj podhod v lechenii detej s rasshhelinoj guby i neba v sovremennyh uslovijah razvitija zdravoohranenija Rossii [Cross-disciplinary approach in treatment of children with a cleft lip and palate in the modern conditions of the development of health care in Russia] Materialy V Vserossijskoj nauchno-prakticheskoj konferencii. Vrozhdennaja i nasledstvennaja patologija golovy, lica i shei u detej: aktual’nye voprosy kompleksnogo lechenija [Materials of V All-Russian scientific and practical conference. Congenital and heritable pathology of the head, face and neck of children: topical issues of complex treatment] [otv.red. prof. O. Z. Topol’nickij]. Moscow, 2016, p.185-192.
4. Porubova E.S. Volkov Ju. O. Harlamov D.A. i dr. Opyt raboty i perspektivy razvitija otdelenija detskoj cheljustno-licevoj hirurgii ODKB [Experience and prospects of development of children’s maxillofacial surgery department] Materialy V Vserossijskoj nauchno-prakticheskoj konferencii. Vrozhdennaja i nasledstvennaja patologija golovy, lica i shei u detej: aktual’nye voprosy kompleksnogo lechenija [Materials of V All-Russian scientific and practical conference. Congenital and heritable pathology of the head, face and neck of children: topical issues of complex treatment] [otv.red. prof. O. Z. Topol’nickij]. Moscow, 2016, p.225-226.
5. Sviridov N.N. Masevkin V.G. Chernomorec Ja.V. Sravnitel’nyj analiz hirurgicheskogo lechenija rasshhelin verhnej guby u novorozhdennyh i detej grudnogo vozrasta [The comparative analysis of surgical treatment of clefts of the upper lip at newborns and infants] Materialy V Vserossijskoj nauchno-prakticheskoj konferencii. Vrozhdennaja i nasledstvennaja patologija golovy, lica i shei u detej: aktual’nye voprosy kompleksnogo lechenija [Materials of V All-Russian scientific and practical conference. Congenital and heritable pathology of the head, face and neck of children: topical issues of complex treatment] [otv.red. prof. O. Z. Topol’nickij]. Moscow, 2016, p.233-238.
6. Isakov L.O. Ushnickij I.D. Piksajkina K.G. Vinokurova A.E. Faktory riska, okazyvajushhie vlijanie na sroki reabilitacionnyh meroprijatij u detej s vrozhdennymi rasshhelinami verhnej guby i neba [The risk factors that influence the timing of rehabilitation activities in children with congenital lip and palate clefts] Jakutskij medicinskij zhurnal [Yakut medical journal]. Yakutsk, 2008, №4 (24), P.21-24.
7. A comparative study of quality of life of families with children born with cleft lip and/or palate before and after surgical treatment / Emeka CI, Adeyemo WL, Ladeinde AL, Butali A // Korean Assoc Oral Maxillofac Surg. – 2017. – №43 (4).
8. Common Mutations of the Methylenetetrahydrofolate Reductase (MTHFR) Gene in Non-Syndromic Cleft Lips and Palates Children in North-West of Iran / S. Abdollahi-Fakhim, M. Asghari Estiar, P. Varghaei [et al.] // Iranian Journal of Otorhinolaryngology. – 2015. – №78. – P.7-14.

The authors:

North-Eastern federal university named after M.K. Ammosov, Yakutsk (Russia), Republic hospital № 1 – National center of medicine», Yakutsk (Russia):

Ushnitsky I.D, MD, PhD, professor, head of the department “Therapeutic, surgical, orthopedic odontology and odontology of the children’s age»;

Mironova L.S., maxillofacial surgeon, 3 year post-graduate student, E-mail: mironovals@bk.ru;

Davydova M.M., student of the NEFU named after M.K. Ammosov;

Gogolev I.I., head of otolaryngologic department of Pediatric Medical Centre.

METHODS OF DIAGNOSIS AND TREATMENT

V.V. Saveliev, M.M. Vinokurov, M.A. Vinokurov, A.V. Parfenova

EXPERIENCE OF LAPAROSCOPIC APPENDECTOMY IN THE MULTIDISCIPLINARY SURGICAL CENTER OF THE REPUBLIC SAKHA (YAKUTIA)

ABSTRACT

The **aim** of the study was to evaluate the results of surgical treatment of patients with uncomplicated forms of acute appendicitis using the laparoscopic method in conditions of the multidisciplinary surgical Center of the Republic Sakha (Yakutia).

Material and methods. The work is based on the analysis of the results of complex treatment of 582 patients with uncomplicated forms of acute appendicitis, in 287 (49.3%) of whom, laparoscopic appendectomy was performed.

Results. The first experience of laparoscopic appendectomy demonstrated the promise of the method, as well as its high efficiency and safety.

Conclusion. The introduction of the method allowed reducing the number of postoperative complications by 3,0% and shortening the length of stay in the surgical hospital by 42,8%.

Keywords: acute appendicitis, laparoscopic appendectomy.

INTRODUCTION

Currently, laparoscopic appendectomy has taken a strong place in emergency surgery of the abdominal cavity [1, 3, 8]. However, the number of studies aimed at studying the results of its use everywhere, especially with regard to complicated forms, remains insufficient, which leads to an active discussion of this topic on the sites of various forums, surgical congresses and congresses [1, 9].

According to a wide range of researchers, the incidence of acute appendicitis varies within 10-15% [2, 5], lethality does not exceed 0.1-0.5% [1, 2, 4, 6], and the number of postoperative complications remains stable high and reaches 30-40% [2, 6] with complicated forms. Thus, the above facts dictate the need for more in-depth and comprehensive study of various aspects of surgical treatment of patients with acute appendicitis.

The study of the possibility of reducing the number of intra- and postoperative complications, as well as the reduction in the time of stay of a patient with acute appendicitis in the multidisciplinary surgical center of the Republic of Sakha (Yakutia), through the introduction and wide application of laparoscopic appendectomy in everyday practice, was **the objective** of our study.

Materials and methods of the research. The presented work is based on the analysis of the results of the complex treatment of 582 patients with acute appendicitis at the age of 18 to 73 years, men - 265 (45,5%), women - 317 (54,5%), who were treated in the emergency surgical department of the Republican Hospital № 2 - Center for Emergency Medical Care of the Republic of Sakha (Yakutia) in the period from 2015 to 2017. The diagnosis of acute appendicitis and its complications is verified on the basis of a modern multi-level complex examination.

Patients were divided into study groups. The main group included 287 (49.3%) patients who underwent laparoscopic appendectomy (LA), the control group included 295 (50,7%) patients who underwent traditional appendectomy (TA). Patients who have been diagnosed with an appendicle infiltrate at the stage of a general examination, an appendicle abscess, a common or diffuse purulent peritonitis are not included in this study.

All operations were performed using the endoscopic Karl Storz Endovision® DCI® system with an autorotation system (ARS) - a digital single camera, PAL color systems, NTSC with an integrated digital image processing module. A set of DCI® HOPKINS®II laparoscopes (large-format optics - 10 mm), trocars, forceps, scissors, dissectors, Karl Storz Click'Line® extractors under combined endotracheal anesthesia.

Points of administration and diameter of trocar: paraumbilical - 10 mm, left iliac region - 5 mm and left mesogastric region - 10 mm. After the installation of trocars, a revision of the abdominal cavity was carried out with the diagnosis and evaluation of the degree of inflammatory changes in the peritoneum. Appendectomy was performed antegrade with treatment of mesentery with the electrosurgical apparatus "LigaSure™» from Valleylab (Smart technology) and clipping of the base of the appendage with tantalum clips without peritonization.

The statistical processing of the material was carried out using the StatPlus 2007 statistical program for the Microsoft Office 2007 operating system, as well as the IBM.SPSS.Statistiks.v22 software package. When estimating the whole population, the mean values (μ) and the standard deviation (σ) were calculated, the reliability of differences (p) was determined by the Newman-Keils criterion.

Results and discussion. In the course of LA, forced transition to laparotomy (conversion) was required in 7 (2.4%) patients. In two clinical cases, the reason for the conversion was the perforation of the appendix, with the development of diffuse purulent peritonitis. In the other three - in the formation of an appendicle infiltrate and typhlitis. And finally, in the last two cases, the cause of the conversion was the appendicle abscess that was not diagnosed at the stage of the general examination. In all cases of conversion, we used laparotomy access of Volkovich-Dyakonov. Immersion of the stump was carried out in the "pouch" and Z-shaped stitches, followed by drainage of the abdominal cavity with silicone drains and / or a Penrose-Mikulich tampon, the amount of which was individual and depended on the severity of the inflammation, the nature of the exudate in the abdominal cavity, and pathomorphological changes vermiform appendix.

From the moment of admission of the patient into the surgical hospital (taking into account the necessary comprehensive examination) and before the surgical intervention, no more than 120 min passed. The time of operative intervention in the performance of the aircraft ranged from 35 to 75 min and averaged 45.2 ± 20.1 min. TA took from 25 to 120 min. An average of 55.8 ± 22.8 mi. The difference in time was statistically significant ($p < 0.05$).

Another important parameter, this is confirmed by other researchers [7, 10], is the average time of activation of patients after performing an operative intervention. In our case, the activation time after the LA was 1.1 ± 0.5 days. After the TA - 2.5 ± 0.7 days ($p < 0.01$). The increase in

the time of bed rest after TA was largely due to postoperative pain syndrome.

Along with the time of activation of the patient, one of the important parameters is the time of the appearance of active intestinal peristalsis [2, 7]. Possibilities to take liquid and solid foods in order to maintain energy balance and maintain the plastic function of the body. In our case, after the operation of LA, this time was 1.3 ± 0.5 days, and after TA – 1.7 ± 0.8 days.

The total number of complications in the main group was 4 cases (1.4%). In 2 (50%) cases there was an intraoperative bleeding from the mesentery of the appendix, in 1 (25%) in the early postoperative period patient was found to have a limited fluid accumulation along the right lateral canal. In 3 described cases no re-operative treatment was required, conservative and operative measures of a corrective nature produced a positive result. In 1 (25%) of the treated patients after LA, in the early postoperative period, continued peritonitis was observed, on which, on the 3rd day, a mid-laparotomy with sanation and drainage of the abdominal cavity was performed. The patient recovered and was discharged on the 15th day of the first operation.

In the control group, the total number of complications was 11 (3.7%) cases. In 4 (36.3%) patients after TA, an infiltration of the area of the postoperative wound was formed. Conservative treatment of these patients was supplemented by physiotherapeutic procedures, which allowed preventing the development of infectious complications, and ended safely. The postoperative period was complicated by hemorrhage from the muscles of the laparotomy wound seam line in 2 (18.2%) patients, suppuration of the postoperative wound was detected in 5 (45.5%) patients. There were no lethal outcomes in both groups.

The average length of stay in the hospital after the LA was 4.0 ± 1.0 bed-days, after TA – 7.0 ± 2.0 bed-days. Patients after the LA were in the surgical hospital on average 3.0 ± 0.1 bed-days (42,8%) less than the patients with TA. The difference in the length of stay is statistically significant ($p < 0.01$).

Thus, we can draw the following **conclusions:** LA is a less traumatic type of surgical intervention. Patients of the LA group were significantly more active than in the TA group. Almost 2.5 more quickly left the surgical hospital, and accordingly significantly reduced the period of incapacity for work and the consumption of medicines. With this method of operative intervention, a significantly lower number of postoperative complications was observed – 0.7% after LA, compared with 3.7% after TA. All this allowed us to continue the wide introduction into surgical practice in the multidisciplinary surgical center of the Republic of Sakha (Yakutia) LA and set the goal of further training this technique for surgeons in the emergency surgical departments of the Center.

REFERENCES

1. Kochukov V.P., Lozhkevich A.A., Ostroverkhova O.G. Laparoskopicheskaya appendektomiya pri ostrom appenditsite [Laparoscopic appendectomy at acute appendicitis] Klinicheskij vestnik [Clinical Herald], 2011, №4, p. 36-38.
2. Drobyshev A.S. [i dr.] Laparoskopicheskaya appendektomiya – prioritetnoe napravlenie v ekstrennoj khirurgii [Laparoscopic appendectomy - a priority in emergency surgery] Vestnik Tambovskogo universiteta [Bulletin of Tambov University], 2014, №6, p. 1983-1985.
3. Panenkov A.N. [i dr.] Laparoskopicheskaya appendektomiya pri retrotsekal'nom retroperitoneal'nom raspolozhenii cherveobraznogo otrostka [Laparoscopic appendectomy at retrocalcular retroperitoneal location of the appendix] Dal'nevostochnyj meditsinskij zhurnal [Far Eastern Medical Journal], 2013, №4, p. 33-35.
4. Levitskij V.D. [i dr.] Sovremennye podkhody k diagnostike i lecheniyu ostrogo appenditsita [Modern approaches to the diagnosis and treatment of acute appendicitis] Endoskopicheskaya khirurgiya [Endoscopic surgery], 2011, №1, p. 55-61.
5. Soroka A.K. Laparoskoriya v provedenii klinicheskikh i morfologicheskikh parallelej appendektomij [Laparoscopy in conducting clinical and morphological parallels of appendectomy] Endoskopicheskaya khirurgiya [Endoscopic surgery], 2013, №1, p. 12-15.
6. Tashpulatov Z.F., Akhmedov A.I. Otsenka effektivnosti optimizirovannogo sposoba appendektomii [Evaluation of the effectiveness of the optimized appendectomy method] Molodoj uchenij [Young Scientist], 2015, №10, p. 467-468.
7. Efficacy of emergency laparoscopic appendectomy in treating complicated appendicitis for already patients / T.C. Wu [et al.] // Saudi. Med. J. – 2017. − № 38 (11). – P. 1108-1112.
8. Laparoscopic appendectomy for acute appendicitis: How to discourage surgeons using inadequate therapy / T. Hori [et al.] // World. J. Gastroenterol. – 2017. − №23 (32). – P. 5849-5859.
9. Laparoscopic appendectomy protocol expedites management of uncomplicated acute appendicitis / A.M. Bada [et al.] // Am. Surg. – 2017. − №83 (6). – P. 673-676.
10. Laporoscopic appendectomy versus open appendectomy for acute appendicitis: a prospective comparative study / S.Kumar [et al.] // Kathmandu Univ. Med. J. – 2017. − №14 (55). – P. 244-248.

The authors:

Savelyev Vyacheslav Vasilievich - MD, associate professor of the Department of Faculty Surgery, Urology, Oncology and Otorhinolaryngology, Medical Institute, Federal State University "M.K. Ammosov North-Eastern Federal University". 677018, ul. Krupskaya 37, Yakutsk, Russia, e-mail: vvsavelievv@mail.ru;

Vinokurov Mikhail Mikhailovich - MD, Professor, Head of the Department of Faculty Surgery, Urology, Oncology and Otorhinolaryngology, Medical Institute, Federal State University "M.K. Ammosov North-Eastern Federal University". 677000, st. Dzerzhinsky 41, apt. 26, Yakutsk, e-mail: mmv_mi@rambler.ru;

Vinokurov Mikhail Andreevich - Post-graduate student of the Department of Faculty Surgery, Urology, Oncology and Otorhinolaryngology, Medical Institute, Federal State University" M.K. Ammosov North-Eastern Federal University". 677000, Yakutsk, st. Bilibin 46/4, apt. 24;

Parfenova Anastasia Vasilievna - clinical resident of the Department of Surgical Diseases and Dentistry of the Federal Pedagogical Institute of the Medical Institute of the Federal State University "M.K. Ammosov North-Eastern Federal University". 677000, Yakutsk, st. Mozhayskogo 21/2, Apt. 27, e-mail: parfenovaaanastasia@mail.ru.

V.N. Pestereva, L.M. Atlasova, P.P. Bessonov, N.G. Bessonova, T.V. Scriabin, D.V. Kopylova, A.D. Makarov

PROSPECTS AND RISKS OF LIVER TRANSPLANTATION IN THE REPUBLIC OF SAKHA (YAKUTIA)

ABSTRACT

In order to study the condition of patients after liver transplantation the histories of patients who were on inpatient treatment at the RHN№1 - NCM department of therapy, Yakutsk in 2003 – 2017, were analyzed. Transplantation was performed in the stage of decompensation of liver cirrhosis of viral and non-viral etiology. Timely transplantation of the liver prevents fatal outcome and prolongs the life expectancy of patients.

Keywords: liver transplantation, re-transplantation, chronic viral hepatitis, liver cirrhosis, decompensation, immunosuppressive therapy, complications, mortality.

In the course of many diffuse and focal liver diseases there comes a period when traditional therapeutic methods of treatment or surgical interventions become ineffective, and the out-of-control disease continues to progress, leading the patient to imminent death. Such patients until recently were considered to be incurable, i.e. «hopeless.»

There is a large number of patients with terminal liver diseases, as evidenced by our medical practice and published papers of Russian researchers, in whom the conservative management of hepatic insufficiency, portal hypertension syndrome or cholestasis is practiced, including mostly ineffective chemotherapy in inoperable tumors. The majority of specialists recognize the palliative nature of these methods, which, at best, can only temporarily stabilize the patients' condition. A radical way to treat terminal liver disease is liver transplantation [4, 6-8].

The Republic of Sakha (Yakutia) (RS (Ya)) has one of the highest rates of viral hepatitis B, C, D and mixed forms in Russian Federation. In recent years, the number of young patients with liver cirrhosis (LC) due to chronic mixed hepatitis has increased.

At a certain point of LC course, decompensation begins which leads to bleeding from the enlarged veins of the esophagus. Therefore, until 2005, endoscopic sclerotherapy of varicose veins of the esophagus and stomach was performed at the Therapy department of «The Republic Hospital №1– The National Center of Medicine" (RHN№1 - NCM) in cooperation with physicians of the endoscopy department, which allowed to prevent relapses of bleeding and prolong the life of patients [1, 3].

In 2004 the Clinical Center of the RHN№1 - NCM has become an associate of the FGBU "Academician V.I. Shumakov Federal Research Center of Transplantology and Artificial Organs" (FRCTAO). On December 29, 2004, for the first time in the history of Yakutia, Professor Y.G. Moisiuk has successfully transplanted the cadaveric liver to a patient from the Dzhebariki-Khaya village, who had primary biliary cirrhosis (PBC). In 2005, two more transplantations of cadaveric liver were successfully performed by Professor Y.G. Moisiuk to patients from our republic [1, 2, 5].

The main areas of work in the field of clinical transplantology are: identification and selection of potential recipients of donor organs; performing appropriate surgical intervention; conducting adequate immunosuppressive treatment to maximize the life of the graft and recipient [7].

Due to the permanent scarcity of cadaveric organs, the liver transplantation program in the Russian Federation has developed and is currently developing in two directions: transplantation of the cadaveric liver and transplantation of liver fragments from living related donors. It was the latter direction that made it possible to significantly increase the number of performed liver transplantation operations to patients in our republic. Thus, since 2010, we sent 24 patients with LC of various etiologies to FRCTAO and State Research Center Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency (SRC-FMBC) (Moscow). All patients underwent transplantation of a liver segment from a living related donor.

The indisputable advantage of transplantation from a living donor is independence from the system of cadaver organs supply, and thus, the possibility of scheduling the operation depending on the condition of the recipient (and not the short "on ice time" period of cadaver liver). The modern level of hepatic surgery allows getting a quality transplant from a living donor with minimal ischemic and mechanical damage. The liver is considered the most convenient organ transplant in terms of immunological compatibility. This is due to the known immunocompetence of the liver, which to some extent suppresses the immune response of the recipient organism. Therefore, the selection of a donor liver to a particular patient is not difficult from the immunological point of view. The use of related transplants greatly simplifies the conduct of drug-induced immunosuppression [4, 8].

Materials and methods

The analysis of the disease history of 41 patients (25 women, 16 men), age range 27 to 61 years, who were hospitalized after liver transplantation (LT) in the department of therapy RHN№1 - NCM in the 2004-2017 period. Ethnic composition of patients: 33 Yakuts, 8 patients of other ethnicity (Russians et al.). Age groups: less than 30 years old - 8 patients, 31-40 - 12, 41-50 years - 11, 51-60 - 9, 61 years and older - 1. The average age was 37 years. The primary conditions that led to LT: chronic viral hepatitis B, D, C (CHB, CHD, CHC, respectively); primary biliary cirrhosis (PBC); primary and secondary sclerosing cholangitis, LC of toxic and alimentary origin (i.e. alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH)). In two patients with CHB and CHD LC, the transplantation was performed at the stage of hepatocellular carcinoma.

All patients underwent general clinical, laboratory and instrumental methods of diagnosis, as well as consultations of specialists, in accordance with national guidelines and standards of care for patients who underwent LT. A prerequisite was to obtain informed consent from patients to participate in the study and conduct additional diagnostic interventions.

Results and discussion

High incidence of chronic hepatitis and LC in the RS (Ya) procured the

implementation of liver transplantation (LT) in the RHN№1 - NCM.

Since 2013, 14 patients underwent segmental LT from a living related donor in RHN№1 - NCM. In August 2016 for the first time in the history of medicine of our republic, transplantation of cadaveric liver was successfully performed in RHN№1 - NCM.

There is an annual increase in the number of LT in Yakutia (Fig. 1) and surgeries carried out in the RHN№1 - NCM (Fig. 2). LT from a living related donor is preferred in Yakutia due the scarcity of cadaver organs. It is also more feasible for the patient and his or her relatives, because there is no need for the recipient and the donor to travel to Moscow. Moreover, the waiting times for the LT are significantly reduced.

The primary conditions leading to LT in Yakutia: CHD - 24 patients (58.3%), PBC - 6 (14.6%), CHC - 5 (12.1%), secondary sclerosing cholangitis - 2 (4.8%), CHB - 2 (4.8%), primary sclerosing cholangitis - 1 (2.4%), LC of toxic and alimentary origin - 1 (2.4%).

The vast majority of operated patients are females aged 30-50 years of indigenous ethnicity with cirrhosis of the viral etiology. Patients with LC due to CHD (58.53%) were mostly young people under 40 years old, infected in childhood during invasive medical procedures. It should be noted that the number of patients with autoimmune liver diseases has increased in recent years. They are mostly middle-aged women.

It should be emphasized that among patients who underwent LT, three patients successfully underwent liver retransplantation:

1. Patient N., female, born in 1959, the transplantation of cadaveric liver was performed in the Shumakov FRCTAO due to decompensated PBC on December 29, 2004. The postoperative period proceeded smoothly. 3-component protocol of immunosuppression was chosen for this patient, which included tacrolimus (Prograf®), methylprednisolone (Medrol®) and mycophenolic acid (Myfortic™). Later the patient developed PBC in transplanted liver. The only way to improve patient's condition was to perform liver retransplantation. Prior to surgery, several plasmaphereses were performed to lower bilirubin levels. On April 1, 2010, transplantation of cadaveric liver was successfully carried out at the same institute. Currently, the patient continues to receive drug-induced immunosuppression according to protocol. Patient is feeling well and continues to work.

2. Patient I., male, born in 1973, required an orthotopic transplantation of a liver segment from a living related donor (brother) due to CHB LC, which was performed in SRC FMBC on September, 12, 2013. Postoperative period was complicated by cicatricial stricture of end-to-end choledochocholedochostomy, which led to the development of mechanical jaundice and, ultimately, graft dysfunction. Liver retransplantation was the only feasible option. On September 2, 2017 the transplantation of cadaveric liver was successfully performed in the same institute. Currently, the patient is receiving a standard 2-component drug immunosuppression, the overall condition is satisfactory.

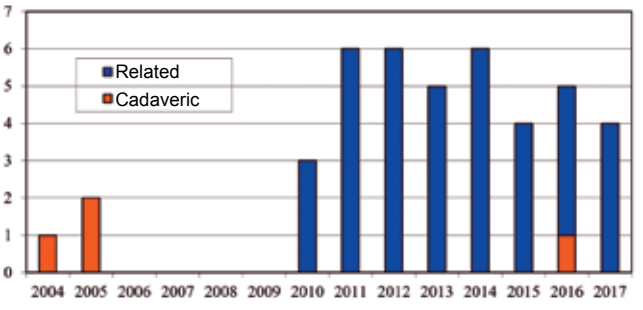


Fig. 1. The number of liver transplantations in the RS (Ya)

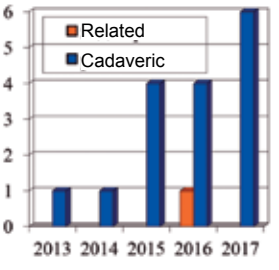


Fig. 2. The dynamics of liver transplantations' growth in the GAU RS (Ya) "RH №1- NCM"

3. Patient T., male, born in 1989, required the orthotopic transplantation of a liver segment from a living related donor due to CHD LC, which was performed by surgeon from FRCTAO who is also a graduate of the Medical Institute of Medical Institute, Yakut State University (currently North-Eastern Federal University named after M.K. Ammosov). An operation was performed on June 28, 2013 at the RHN№1 - NCM for the first time in Yakutia. The postoperative period was complicated by thrombosis of the anastomosis of the hepatic artery and urgent life-saving operation was performed on July 8, 2013: relaparotomy, retransplantation of a liver segment from a second related donor. Following postoperative period proceeded smoothly. Drug immunosuppression was carried out with 2-component protocol - Prograf® and Myfortic™. At present, the patient's condition is satisfactory.

During the period from 2004 to 2017, 7 (17%) of the 41 patients who underwent liver transplantation died: 5 in early postoperative period, 2 patients died within one year after the transplantation due to the infection caused by immunosuppressive therapy (Table).

Survived patients receive immunosuppressive therapy with Prograf® (one patient receives cyclosporine (Sandimmune®) due to adverse reaction to Prograf®). Tacrolimus concentration in the blood serum is continuously monitored. All patients who underwent liver transplantation are followed-up at the polyclinics, in the Clinical-Consultatory Department of RB1 NCM and in the Department of Therapy of the RHN№1 - NCM, periodically undergoing in-patient examination and treatment once or twice a year, depending on the severity of the condition, the timing of the operation and the presence of complications.

Currently, 34 patients who underwent LT are monitored in Therapy Department of the RHN№1 - NCM. In addition, there are 30 patients with chronic diseases of liver at the stage of cirrhosis, 22 of whom are included in the waiting list for the transplantation of the cadaveric liver.

Conclusions. 1. Considering the large number of patients with severe liver diseases in the RS (Ya), good survival after LT, it is necessary to develop state program for the development of transplantology in the RS (Ya).

2. Further development of transplantation (both the transplantation of the liver segment from the living related donor and cadaveric liver) is necessary, because it is one of the most accessible and effective ways of management of patients with terminal liver diseases.

3. Special attention should be given to the quality of HBV vaccination with a 100% coverage of the child population.

4. Foundation of Hepatology Center in RS (Ya) may potentially improve early diagnosis of patients with chronic liver diseases and quality follow-up of patients with chronic liver diseases and patients who underwent LT.

REFERENCES

1. Bessonov P.P. Bessonova N.G. Pestereva V.N. [et al.] Analiz sostojanija pacientov

Analysis of mortality after liver transplantation in the RS (Ya)

Ds	Operation date	Death date	Cause
Patient P., 1966, LC Outcome chronic viral hepatitis B, D	15.12.11 Transplantation of a fragment of a liver from the daughter (Shumakov FNTST and IO)	In the early postoperative period	Accession of infection against IT
Patient S., 1954, PBC	28.10.10 Transplantation of a fragment of a liver from the daughter (Shumakov FNTST and IO)	04.2011	Accession of infection against IT
Patient S., 1989 , LC Outcome chronic viral hepatitis B, D	10.07.11. Transplantation of a fragment of a liver from brother (Shumakov FNTST and IO)	In the early postoperative period	Graft dysfunction
Patient B., 1982, secondary sclerosing cholangitis	10.06.2014г. Transplantation of a fragment of a liver from brother (Burnazjan FMBA)	In the early postoperative period (July)	Aspergillosis
Patient P., 1982, LC Outcome chronic viral hepatitis B, D	04.07.2015 Transplantation of a fragment of a liver from brother (GAU RH№1-NCM	In the early postoperative period	Bleeding from the splenic vein
Patient B., 1961, secondary sclerosing cholangitis	25.06.16 Transplantation of a fragment of a liver outcome SSC from brother (GAU RH№1-NCM) Complication: portal vein thrombosis	In the early postoperative period	Portal vein thrombosis, acute graft rejection
Patient L., 1980, LC of toxic and alimentary origin	28.02.17 Transplantation of a fragment of a liver from son LC of toxic and alimentary origin (GAU RH№1-NCM). Complication: hemoperitoneum. Relaparotomy 28.02.17	In the early postoperative period	Graft dysfunction Acute liver failur

posle transplantacii pecheni v Respublike Saha (Jakutija) [Analysis of the condition of patients after liver transplantation in the Republic Sakha (Yakutia)] Jakutskij medicinskij zhurnal [The Yakut Medical Journal].Yakutsk, 2015, №4 (52), P.81-82.

2. Bessonov P.P. Bessonova N.G. Lechenie pacientov posle transplantacii pecheni v RS(Ja) [Treatment of patients after liver transplantation in the RS (Ya)] Jekologija i zdorov'e cheloveka na Severe: sb. nauch. tr. VI kongressa s mezhdunar. uchastiem [Ecology and human health in the North: Sat. sci. tr. VI[th] Congress with intern. participation]. Kirov: MCNIP, 2016, p.80-84.
3. Bessonov P.P. Emelyanova E.A. Bessonova N.G. Zheludochno-kishechnye krovotechenija v terapevticheskoj praktike: ucheb. posobie [Gastrointestinal bleeding in therapeutic practice: tutorial]. Yakutsk: Publishing House of the NEFU, 2017, 116 p.
4. Gautier S.V. Konstantinov B.A. Tsirulnikova O.M. Transplantacija pecheni [Liver transplantation]. Medicinskoe informacionnoe agentstvo [Medical Information Agency]. Moscow, 2008, 296 p.
5. Pestereva V.N. Egorova O.T. Atlasova L.M. [et al.]. Otdalennye rezul'taty lechenija pacientov posle transplantacii pecheni [Long-term results of treatment of patients after liver transplantation] Perspektivy razvitija gematologicheskoj sluzhby v RS (Ja): mezhregion. nauch.-prakt. konf [Prospects for the development of the hematological service in the RS (Ya):interregion. scientific-practical. conf.]. Yakutsk, 2013, P.116 - 120.
6. Podymova S.D. Bolezni pecheni [Diseases of the liver]. Moscow: Medicina, 2005, 768 p.
7. Transplantacija pecheni. Nacional'nye klinicheskie rekomendacii [Liver transplantation: national clinical recommendations] Obshheros. obshhestven. org. transplantologov «Rossijskoe transplantologich. obshhestvo» [All-Russian public organization of transplantologists "Russian Transplant Society"]. Moscow, 2013, 43 p.
8. Tsirulnikova O.M. Gautier S.V. Transplantacija pecheni [Liver transplantation] Prakticheskaja gepatologija: posobie dlja vrachej pod red. N.A. Muhina [Practical hepatology / under the ed. ON. Mukhina]. Moscow: The project "We", 2004, P.237-244.

The authors:

GAU RS (Ya) "RH№1 - National Center of Medicine":

Pestereva Vera Nikolaevna – head of Department, e-mail: Pestereva.1960@mail.ru;

Atlasova Lena Mikhailovna - physician-therapist-gastroenterologist;

Skryabina Tatiana Wilhelmovna - physician therapist;

Kopylova Dariya Vasilievna - therapeutist doctor;

Medical Institute of M.K. Ammosov NEFU:

Bessonov Prokopy Prokopievich - Associate Professor, e-mail: bessonovproc@mail.ru;

Bessonova Natalia Georgievna - Associate Professor;

Makarov Albert Dmitrievich - Associate Professor.

O.V. Kalabin, A.P. Spitsin

FEATURES OF THE HEART RATE VARIABILITY OF POWERLIFTERS UNDER THE INFLUENCE OF THE TRAINING PROCESS

ABSTRACT

Objective. To study the peculiarities of heart rate variability in powerlifters depending on the initial type of vegetative regulation under the influence of the training process and the performance of active orthotropic tests.

Material and methods. The study involved 38 men aged 18-25 years, involved in powerlifting. Registration of the cardiorhythmogram was performed using a vegetotester «VNS-Micro», and the treatment was carried out on the basis of the software package «Poly Spectrum» of Neurosoft Company (Ivanovo). The study included several stages: 1) recording the ECG (rhythmogram) in the initial state; 2) after performing the orthotropic test; 3) performing strength training with about maximal anaerobic power; 4) ECG (rhythmogram) recording after training; 5) performing an orthotropic test with subsequent registration of the rhythmogram.

Results. In response to the training load, the powerlifters with normovagotonic regulation have a shift in the vegetative balance toward the predominance of sympathetic activity. In powerlifters with this type of autonomic regulation in response to an orthostatic test before training, there is an increase in sympathetic and a decrease in parasympathetic activity, which indicates a high reactivity of regulatory mechanisms and reliable functional capabilities of the body liftlifters. In powerlifters with normosympathicotonic type of autonomic regulation in response to an orthostatic test before training, the time indices (SDNN, rMSSD, AMo, SI) do not change significantly, which indicates a low reactivity of the autonomic nervous system. At the same time there is an increase in VLF, which indicates the connection of the central department to regulate the rhythm of the heart. High voltage regulatory mechanisms before training, low reactivity of the autonomic nervous system, high centralization in the management of the heart rhythm indicate a low functional capacity of the body powerlifters with normosympotonic type of autonomic regulation.

The conclusion. The peculiarities of temporal and spectral parameters of heart rhythm in athletes engaged in powerlifting are revealed depending on the dominant type of vegetative regulation. It is shown that the same training load leads to different stresses of the regulatory mechanisms (according to the heart rate), depending on the dominance of the VNS department.

Keywords: variability of heart rhythm, type of vegetative regulation, orthostatic test, powerlifting, adaptation.

INTRODUCTION

Intense strength exercises require from the athlete's organism rapid changes in the heart rate (HR) and blood pressure (BP) required to support the metabolic needs of the motor apparatus. The cardiovascular system is given a special role, since it provides the oxygen needs of working muscles and the whole organism.

Despite numerous studies, the interaction between the functioning of the cardiovascular system, autonomic regulation mechanisms and physical activity requires further study. One of the available highly informative methods for studying the cardiovascular system is an orthostatic test [1].

Based on the concept of a two-loop model of cardiac rhythm control, four types of autonomic regulation of the heart rhythm were singled out: two with predominance of central regulation [moderate (type I) and pronounced (type II)] and two with predominance of autonomic regulation [moderate (type III) and expressed (type IV)] [2]. Taking as a basis classification not the divisions of the vegetative nervous system (sympathetic and parasympathetic), but the central and autonomous contours of the vegetative control of physiological functions, thereby confirmed participation in the processes of vegetative regulation of many links of a single regulatory mechanism.

This is a systematic approach to considering the most complex mechanism of regulation of physiological functions, which can be judged from the analysis of HRV. For the rapid assessment of the predominant type of vegetative regulation, quantitative criteria for the HRV parameters SI and VLF [3].

Material and methods of investigation

The study involved 38 men aged 18-25 years, involved in powerlifting. Registration of the cardiorhythmogram was performed using a vegetotester «VNS-Micro», and the treatment was carried out on the basis of the software package «Poly Spectrum» of Neurosoft Company (Ivanovo). The study included several stages: 1) recording the ECG (rhythmogram) in the initial state; 2) after performing the orthotropic test; 3) performing strength training with about maximal anaerobic power; 4) ECG (rhythmogram) recording after training; 5) performing an orthotropic test with subsequent registration of the rhythmogram.

Further, the temporal parameters of the heart rate were calculated and analyzed: heart rate (heart rate, beats / min); rms deviation of successive R-R intervals (SDNN, ms); standard deviation of the

Table 1

Evaluation of autonomic regulation of blood circulation

Moderate predominance of central regulation (Type I - normosympathicotonia)	SI >100 y.e., VLF >240 мс^2
Expressed predominance of central regulation (Type II hypersympathicotonia)	SI >100 y.e., VLF <240 мс^2
Moderate predominance of autonomous regulation (III type - normovagonotony)	20 >SI <100 y.e., VLF >240 мс^2
Expressed predominance of autonomous regulation (Type IV - hypervagonia) (disruption of the sinus node)	SI < 20 y.e., TP > 16000 мс^2, VLF > 500 мс^2

Table 2

Background HRV indices before and after training in normovagotonics (M ± m)

Try	Background (n=22)		p
	Before training	After training	
RRNN	871,10±18,26	688,2±32,39	0,001
SDNN	55,40±4,28	28,1±4,59	0,002
rMSSD	43,80±4,33	17,5±3,95	0,002
pNN50	22,95±4,34	3,23±1,51	0,001
TP	3607,6±605,52	1265,3±356,5	0,005
VLF	1421,5±237,60	449,03±108,14	0,002
LF	1086,7±202,48	511,02±140,29	0,028
HF	1099,6±292,22	305,02±121,04	0,013
LF norm	52,85±4,82	73,34±4,63	0,008
HF norm	47,15±4,82	26,65±4,63	0,008
LF/HF	1,38±0,30	4,99±1,67	0,009
%VLF	41,09±4,65	44,76±6,90	0,880
%LF	31,26±3,48	38,65±4,82	0,273
%HF	27,63±3,63	16,60±3,49	0,076
Mo	0,87±0,02	0,68±0,03	0,001
AMo	36,18±2,53	65,72±6,88	0,001
SI	63,08±7,42	528,71±171,90	0,001

Table 3

HRV indices in performing an orthostatic test before training in normovagotonics (M±m)

Try	Before training (n=22)		p
	Background	Orthotest	
RRNN	871,10±18,26	679,8±13,03	0,001
SDNN	55,40±4,28	46,9±3,11	0,150
rMSSD	43,80±4,33	21,9±2,85	0,001
pNN50	22,95±4,34	3,19±0,87	0,001
TP	3607,6±605,52	3209,9±402,73	0,940
VLF	1421,5±237,60	1099,3±134,98	0,364
LF	1086,7±202,48	1660,1±217,92	0,070
HF	1099,6±292,22	450,6±120,39	0,049
LF norm	52,85±4,82	80,64±3,16	0,001
HF norm	47,15±4,82	19,35±3,16	0,001
LF/HF	1,38±0,30	5,81±1,26	0,001
%VLF	41,09±4,65	36,15±3,66	0,406
%LF	31,26±3,48	51,12±3,01	0,001
%HF	27,63±3,63	12,74±2,60	0,007
Mo	0,87±0,02	0,68±0,02	0,000
AMo	36,18±2,53	45,03±1,62	0,013
SI	63,08±7,42	124,03±15,26	0,001

difference of consecutive R-R intervals (rMSSD, ms); frequency of consecutive R-R intervals with a difference of more than 50 ms (pNN50,%); amplitude of the mode (AMo,%); stress index (SI, condition unit).

The conventional notations for heart rate variability (HRV) indicators are presented in accordance with international HRV assessment standards and the applicable guideline standards. Based on the spectral analysis of HRV, the frequency parameters were calculated and analyzed: the total power of the spectrum (TR), the power in the high-frequency (HF, 0.16-0.4 Hz), low-frequency (LF, 0.05-0.15 Hz) and very low-frequency (VLF, <0.05 Hz) ranges. In addition, the LF / HF coefficient was calculated, reflecting the balance of sympathetic and parasympathetic regulatory influences on the heart. To assess the predominant type of vegetative regulation, quantitative criteria for HRV parameters were taken as the basis: SI and VLF [2].

For statistical processing of the obtained data and presentation of the results, the package «SPSS Statistics v.20» was used. With the normal distribution of the analyzed features, the average value (M) and the standard error of the mean (m) were calculated. When estimating the characteristics of spectral analysis of HRV having a distribution different from normal, nonparametric statistics methods were used. The reliability of the differences was assessed by the criteria of Mann-Whitney and Wilcoxon.

Results of the study and discussion

In response to the training load, the powerlifters with normovagotonic regulation have a shift in the vegetative balance toward a predominance of sympathetic activity, as indicated by a decrease in rMSSD, an increase in AMo and SI, and a shift in the LF / HF balance (Table 1). Characteristic is a significant reduction in power in all frequency ranges (VLF, LF, HF).

In powerlifters with this type of autonomic regulation in response to an orthostatic test before training (Table 2), there is an increase in sympathetic (increase in AMO, p = 0,013; SI, p = 0,001) and a decrease in parasympathetic activity (decrease in rMSSD, p = 0,001; HF, p = 0,049). This indicates a high reactivity of regulatory mechanisms and reliable functional capabilities of the body powerlifters.

Comparison of response rates to orthostatic effects before and after training showed the following. After training the results were significantly different (Table 3). Time indicators (rMSSD, p=0,010; AMo, p=0,008; SI, p=0,004), and spectral indicators (VLF, p=0,013; LF, p=0,005; HF, p=0,019) indicated the continuing tension of the regulatory mechanisms. This may demonstrate a sufficiently pronounced training load.

In normosymphathonics the training load was also accompanied by an increase in sympathetic activity (increase AMo, p=0,046; SI, p=0,024) and decrease parasymphatetic (decrease HF, p=0,016).). In this case equity contributions of VLF and LF don't change (Table 4). Also equity contributions of VLF and LF before training were more HF, which indicates a violation of regulatory mechanisms.

For powerlifters with normosymphathonics type of vegetative regulation in response to an orthostatic test before training. The time indices

Table 4

Background HRV indices before and after training in normovagotonics (M±m)

Try (n=22)	Orthotest		p
	Before training	After training	
RRNN	679,8±13,03	559,9±20,28	0,001
SDNN	46,9±3,11	27,1±3,60	0,003
rMSSD	21,9±2,85	11,6±2,76	0,010
pNN50	3,19±0,87	0,43±0,18	0,005
TP	3209,9±402,73	1359,9±323,12	0,007
VLF	1099,3±134,98	525,6±128,95	0,013
LF	1660,1±217,92	667,6±177,40	0,005
HF	450,6±120,39	166,57±67,96	0,019
LF norm	80,64±3,16	83,18±3,80	0,427
HF norm	19,35±3,16	16,82±3,80	0,427
LF/HF	5,81±1,26	8,67±2,55	0,427
%VLF	36,15±3,66	38,98±3,55	0,597
%LF	51,12±3,01	50,26±3,04	0,880
%HF	12,74±2,60	10,79±2,91	0,496
Mo	0,68±0,02	0,56±0,02	0,001
AMo	45,03±1,62	62,58±5,74	0,008
SI	124,03±15,26	440,95±123,73	0,004

Table 5

Background indicators before and after training in normosymphathonics (M±m))

Try	Background (n=16)		p
	Before training	After training	
RRNN	817,5±37,42	672,38±29,86	0,009
SDNN	35,63±2,22	23,38±3,18	0,012
rMSSD	24,86±2,22	12,63±2,98	0,016
pNN50	5,18±1,71	1,07±0,79	0,021
TP	1555,1±157,43	852,38±208,33	0,016
VLF	516,38±70,10	317,25±55,93	0,021
LF	671,5±101,79	380,98±134,85	0,021
HF	367,25±58,12	154,07±65,50	0,016
LF norm	64,33±3,68	75,23±4,48	0,074
HF norm	35,68±3,68	24,78±4,48	0,074
LF/HF	2,05±0,35	6,20±3,08	0,074
%VLF	33,85±4,33	45,54±6,40	0,074
%LF	42,29±3,26	40,75±4,99	0,834
%HF	23,88±2,92	13,71±3,08	0,036
Mo	0,81±0,04	0,67±0,03	0,027
AMo	48,09±3,06	61,86±5,57	0,046
SI	158,00±30,02	438,00±99,48	0,024

Table 6

Indicators of HRV during orthostatic test execution before training in normosymphathonics (M±m)

Try	Before training (n=16)		p
	Background	Orthotest	
RRNN	817,50±37,42	673,38±39,20	0,036
SDNN	35,63±2,22	42,38±5,86	0,430
rMSSD	24,86±2,22	17,38±2,87	0,092
pNN50	5,18±1,71	2,31±0,99	0,206
TP	1555,1±157,43	2840,3±640,70	0,208
VLF	516,38±70,10	1499,6±373,65	0,046
LF	671,5±101,79	1042,5±266,55	0,294
HF	367,25±58,12	297,93±81,21	0,345
LF norm	64,33±3,68	78,79±2,89	0,009
HF norm	35,68±3,68	21,21±2,89	0,009
LF/HF	2,05±0,35	4,19±0,54	0,009
%VLF	33,85±4,33	51,00±3,45	0,021
%LF	42,29±3,26	38,89±3,46	0,345
%HF	23,88±2,92	10,10±1,17	0,005
Mo	0,81±0,04	0,67±0,04	0,027
AMo	48,09±3,06	46,69±5,05	0,875
SI	158,00±30,02	190,15±49,65	0,916

Table 7

Indicators of HRV during the orthostatic test before training in normosymphathonics (M±m)

Try	Orthotest (n=16)		p
	Before training	After training	
RRNN	673,38±39,20	559,9±20,28	0,001
SDNN	42,38±5,86	27,1±3,60	0,003
rMSSD	17,38±2,87	11,6±2,76	0,010
pNN50	2,31±0,99	0,43±0,18	0,005
TP	2840,3±640,70	1359,9±323,12	0,007
VLF	1499,6±373,65	525,6±128,95	0,013
LF	1042,5±266,55	667,6±177,40	0,005
HF	297,93±81,21	166,57±67,96	0,019
LF norm	78,79±2,89	83,18±3,80	0,427
HF norm	21,21±2,89	16,82±3,80	0,427
LF/HF	4,19±0,54	8,67±2,55	0,427
%VLF	51,00±3,45	38,98±3,55	0,597
%LF	38,89±3,46	50,26±3,04	0,880
%HF	10,10±1,17	10,79±2,91	0,496
Mo	0,67±0,04	0,56±0,02	0,001
AMo	46,69±5,05	62,58±5,74	0,008
SI	190,15±49,65	440,95±123,73	0,004

(SDNN, rMSSD, AMo, SI) don't change reliably (Table 5). This indicates a low reactivity of the autonomic nervous system. At the same time there is an increase of VLF domain (p=0,021), which indicates the connection of the central department for regulation of HR.

Comparison of HRV parameters of orthostatic effect before and after showed the following. A marked decrease of VLF (p=0,016), increase of LF norm (p=0,009), shift balance of LF/HF (p=0,009) towards sympathetic department of ANS (Table 6). High tension of regulatory mechanisms before training low reactivity of autonomic nervous system, high centralization in the management of the heart rhythm indicate a low functional capacity of powerlifter's organism with this type of autonomic regulation.

Conclusion

The most informative method of studying the regulatory systems of the human body at the present time is the analysis of heart rate variability. Holding an orthostatic test before training allows to determine the functional state of sportsmen, and after training to assess the adaptive capabilities of the body. The intensity and severity of reaction of regulatory systems of powerlifter's is determined by the initial vegetative tone.

REFERENCES

1. Mikhailov V.M. Variabel'nost' ritma serdca: opyt prakticheskogo primenenija [Variability of the rhythm of the heart: experience of practical application] Ivanovo: IvGMA, 2002, 290 p.
2. Shlyk N.I. Serdechnyj ritm i tip reguljacii u detej, podrostkov i sportsmenov [Heart rhythm and type of regulation in children, adolescents and athletes: monograph]. Izhevsk: UdSU, 2009, 259 p.
3. Shlyk N.I. Analiz variabel'nosti serdechnogo ritma pri ortostaticheskoj probe u sportsmenov s raznymi preobladajushhimi tipami vegetativnoj reguljacii v trenirovochnom processe [Analysis of heart rate variability in orthostatic test in athletes with different predominant types of vegetative regulation in the training process] Materialy V Vserossijskogo simpoziuma s mezhdunarodnym uchastiem [Materials of the V Russian Symposium with International Participation]. Izhevsk, 2011, P. 348-369.

The authors:

Oleg Vladimirovich Kalabin, assistant of the department, Federal State Budgetary Educational Institution of Higher Education «Vyatka State University», Kirov, Russia;

Anatolij Pavlovich Spitsin, MD, prof., head of the department, Federal State Budgetary Educational Institution of Higher Education «Kirov State Medical University», Kirov, Russia.

Mamaeva S.N., Maksimov G.V., Golderova A.S.,
Munkhalova Ya.A., Pavlov A.N., Fedorov A.L.

INFRARED SPECTROSCOPY OF BLOOD OF CHILDREN WITH MACROHEMATURIA SYNDROME

ANNOTATION

For experimental purposes, the blood of children with hematuria syndrome in acute and chronic glomerulonephritis and IgA nephropathy was studied by IR spectroscopy. The obtained results indicate the possibility of using IR spectroscopy as an additional diagnostic method for differentiating nephropathies.

Keywords: hematuria, IgA-nephropathy, chronic glomerulonephritis, acute glomerulonephritis, IR spectroscopy.

INTRODUCTION

One of the main causes of chronic renal failure is glomerulonephritis, the course and prognosis of which, according to modern concepts, depend on the inflammatory mechanisms of damage of renal tissue. The predominant sedimentation of immune complexes containing immunoglobulin A (IgA) in intraglomerular mesangial cells is known as IgA nephropathy, or Berger disease. This type of glomerulonephritis is the most common in the world: the incidence - 5 cases per 100,000 population [1].

In European, North American and Australian populations its share reaches 10-12% of all glomerulonephritis, and in Asian – up to 30%. IgA-nephropathy leads in terms of prevalence in Japan up to 50% of all cases of glomerulonephritis.

Currently in the Republic of Sakha (Yakutia) there is a tendency of the increasing of renal pathology among children. In the US, the spread of the disease varies from 2-10%, whereas in Asia to 50% (in Japan 18-40%) [3-5].

However, the causes of most hematuria and, in particular, of Berger's disease (IgA-nephropathy) have not been studied at the cellular and molecular levels. IgA-nephropathy is usually detected in children and adults under 30 years of age, most often observed in men.

Usually it is manifested by bouts of macrohematuria with pain in the lower back, growing on the background of pharyngitis. The reasons of the development of IgA-nephropathy can be etiological factors (hepatitis b viruses, herpes viruses, E. coli, fungi, cochlea, etc.), food factors (gluten, alpha-lactalbumin, beta-lactalbumin, casein, etc.) and endogenous antigens (in tumors of lymphoid tissue-lymphogranulomatosis, lymphoma).

There are also evidences of a genetic predisposition to develop Berger's disease [6]. It is known that in IgA-nephropathy there is an increase in the concentration of immune complexes containing IgA, both as a result of an increase in the production of antibodies, and as a result of a violation of their clearance.

The main hypothesis of pathogenesis, widespread at present, assumes abnormal glycosylation and polymerization of IgA with deposition of immune complexes containing abnormal IgA in glomeruli, with activation of leukocytes and inflammation cascade [8].

The main method of diagnosis of the disease is a kidney biopsy with morphological study of biopsy material. At a light microscopy of preparation increase in quantity of cells in a mesangium and a mezangialny extracellular matrix is found. At an immunohistochemical research conglomeration of IgA in a mesangium in the form of the separate granules merging among themselves is revealed [2]. The biopsy of a kidney is highly traumatic research technique giving no more than 90% of reliable results. Searching of new noninvasive and reliable methods of differential diagnosis of diseases of kidneys, in particular difficult diagnosed - IgA nephropathy, is relevant.

The purpose of the real research was assessment of features of blood of children with a macrohematuria syndrome by method of infrared spectroscopy.

Material and methods of a research

15 children aged from 8 up to 16 years with various forms of the nefropathy who had been undergoing inspection and treatment in nephrological office of the Center of protection of motherhood and childhood of Republican hospital No. 1 – National Centre of medicine (Yakutsk) are analyzed. The control group consists of 8 first-year students of MI SVFU and school students of Yakutsk without disease of kidneys.

Material of a research was venous blood which was evenly distributed on dry glass by the standard method. Researches were conducted by dint of an IR-spectrometer of Varian 7000 FT-IR (USA) (range of 4000 - 400 cm-1) by attenuated total reflectance technique (ATRT) in scientific and technological laboratory of «Technologies of Polymeric Nanocomposites» of the Center of collective use of the Arctic innovative center of the NEFU. It should be noted that the obtained data of spectroscopy can be estimated in 3-5 minutes that is an important factor for timely diagnosis.

Results of the research

The IR - spectroscopy of dabs of blood of children and teenagers with a macrohematuria syndrome was for the first time carried out at chronic glomerulonephritis (n=5), at acute glomerulonephritis (n=5) and the IgA - nephropathy (n=5).

The received analysis of these intensity of IR spectrums showed that essential distinctions (at figures 1-2 - averaged curves of comparison groups) are observed in the range of wave numbers from 3600 to 2700 cm-1 to which correspond stretching vibrations of primary amines (N-H) and amides (SN-) the monoreplaced acetylene and also, in the field of wave numbers from 1700 to 900, the main peaks of which show existence of stretching vibrations of - C=C-; stretching vibrations of C=N, stretching vibrations of C=N and C=C-communications.

Apparently from the presented averaged lines of the IR spectrums (fig. 1 a, b and c) forms of peaks are identical, i.e. show of the same chemical compounds. However, peaks of intensity of sick children are higher, than in control group. Essential distinctions of peaks of intensity in comparison with the control group are observed in children with the IgA-nephropathy. 3330 - 2800 cm-1, for example at the intensity maximum of 3286 cm-1 difference compared with the control

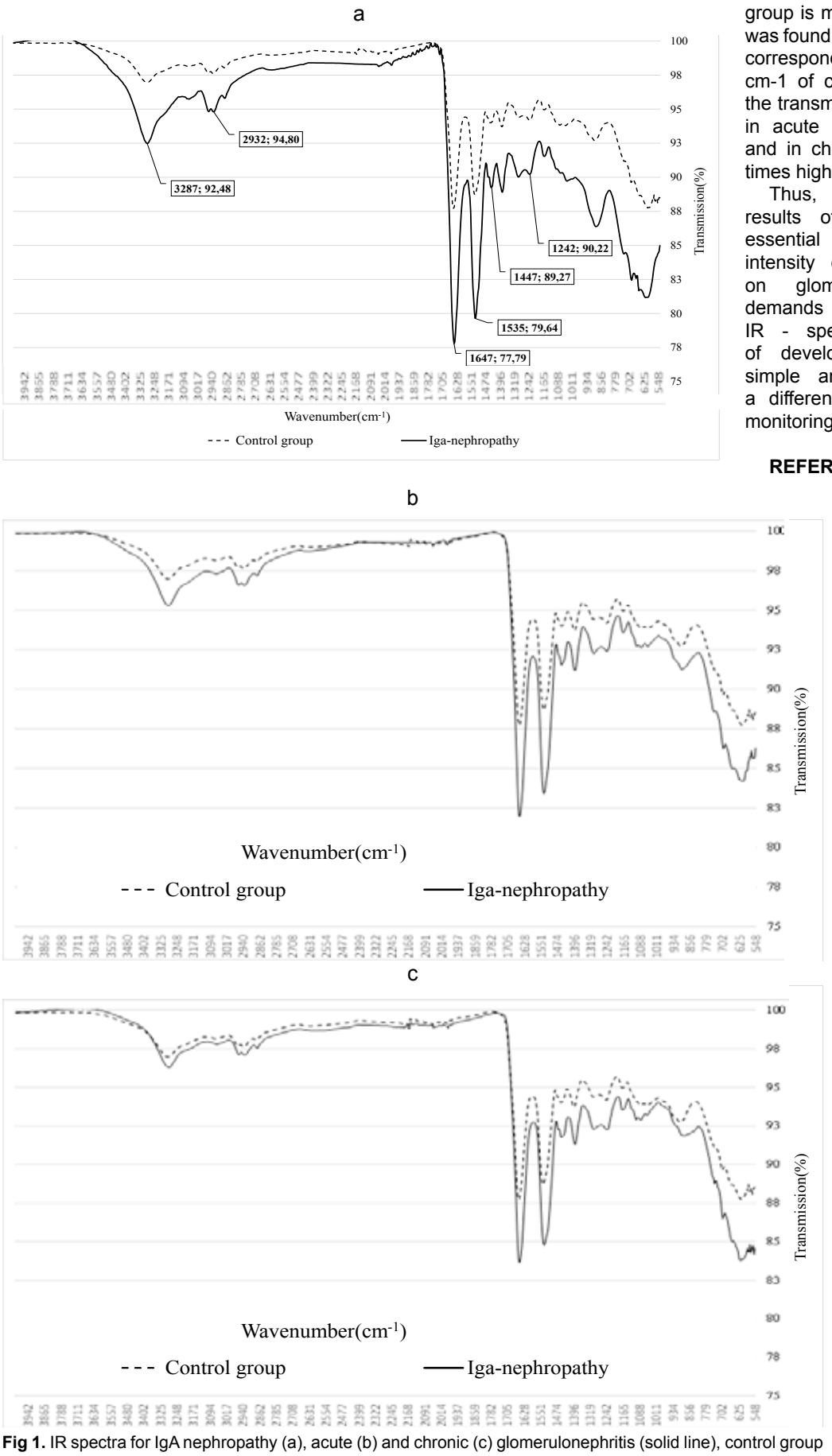


Fig 1. IR spectra for IgA nephropathy (a), acute (b) and chronic (c) glomerulonephritis (solid line), control group (dashed line)

group is more than 2 times (Figure 2). It was found that at an absorbance intensity corresponding to a wave number of 1645 cm-1 of children with IgA-nephropathy, the transmission intensity was 1.8 times, in acute glomerulonephritis. 1.2 times and in chronic glomerulonephritis. 1.15 times higher than with a control group.

Thus, the analysis of preliminary results of a research confirms an essential divergence of peaks of intensity of IR spectrums depending on glomerulonephritis forms that demands more detailed studying of IR - spectroscopy for the purpose of development of less expensive, simple and noninvasive method for a differentiation of the diagnosis and monitoring at this pathology.

REFERENCES

1. Atkins R.Z. Glomerulonefrity [Glomerulonephritis]. Nefrologiya i dializ [Nephrology and Dialysis], 2000, №2 (4), P. 225–229.

2. Varshavskij V.A., Proskurneva E.L., Gasanov A.L. [i dr.]. Ob utochnenii kliniko-morfologicheskoj klassifikacii hronicheskogo glomerulonefrita [On the Clarification of Clinico-morphological Classification of Chronic Glomerulonephritis]. Nefrologiya i dializ [Nephrology and Dialysis], 1999, №1 (2–3), P.100–106.

3. Maksimov G.V., Mamaeva S.N., Antonov S.R. [i dr.] Izmerenie morfologii ehritrocitov metodom ehlektronnoj mikroskopii dlya diagnostiki gematurii [Measurement of erythrocyte morphology by electron microscopy for the diagnosis of hematuria]. Metrologiya. Ezhekvartal'noe prilozhenie k Z. Izmeritel'naya tekhnika. [Metrology. Quarterlyannexto J. Measuringequipment], 2016, №1, P.47-52.

4. Mamaeva S.N., Munkhalova Ya.A., Kononova I.V. [i dr.]. Issledovanie ehritrocitov krovi metodom rastrovoj ehlektronnoj mikroskopii [Study of blood erythrocytes by scanning electron microscopy]. Vestnik Mordovskogo universiteta [Bulletin of the Mordovian University], 2016, T. 26, № 3, P. 381-390.

5. Munhalova Y.A.,

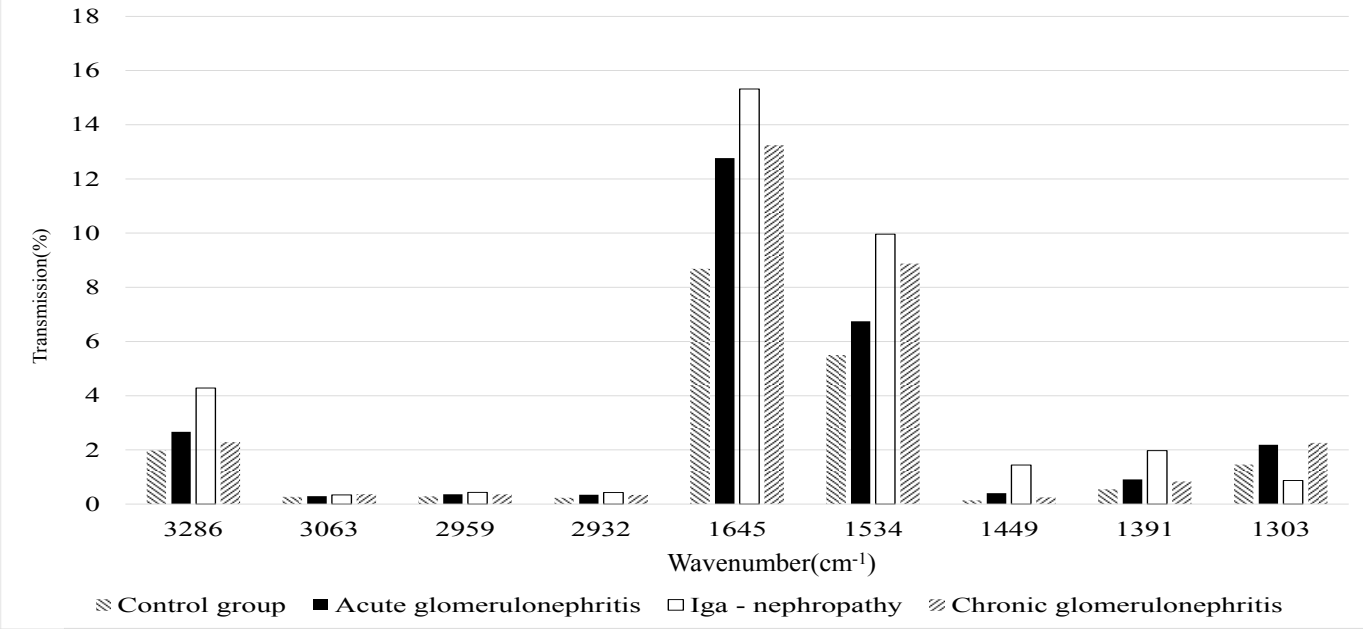


Fig.4. Histogram of comparison of peaks of intensity of spectra for various types of nephropathies with hematuria syndrome with control group

Zaharova N.M., Gorohova A.V. Osobennosti glomerulonefrita associirovannogo s gerpes-virusnoj infekciej [Features of glomerulonephritis associated with herpes-viral infection]. Ehkologiya i zdorov'e cheloveka na Severe: sb. trudov IV kongressa s mezhd. uchastiem (Yakutsk, 2013) [Ecology and human health in the North: Sat. Works of IV Congress with Int. participation (Yakutsk, 2013)] Kirov [Kirov], 2013, 405–409. P

6. Papayan A.V., Soloviev A.A., Styazhkina I.S. IgA nephropathy (Berger's disease in children) [IgA Nephropathy: Progress Before and Since Berger] Lekciya. SPb. [Lecture. SPb,] , 2001, 34 p.
7. Feehally J. / J. Feehally, J.S. Cameron // American Journal of Kidney Diseases. - 2011. - №. 58(2). - P. 310–319.
8. Enhanced Expression of the CD71 Mesangial IgA Receptor in Berger Disease and Henoch Schonlein Nephritis: Association between CD71 Expression and IgA Deposits / E. Haddad., I.C. Moura, M.A. Fajardo [et al.] // Journal of the American Society of Nephrology. - 2003. - №14. - C. 327–337.
9. Race/ethnicity and disease severity in IgA nephropathy / Y.N. Hall, E.F. Fuentes, G.M. Chertow [et al.] // BMC Nephrology. - 2004. - 5:10.
10. Measuring Erythrocyte Morphology by Electron Microscopy to Diagnose Hematuria / G.V. Maksimov, S.N. Mamaeva, S.R. Antonov [et al.] //Measurement Techniques. - 2016. - №59 (3). - P. 327-330.

The authors:

Mamaeva Sargylana Nikolaevna, candidate of physical and mathematical sciences, the associate professor of department of general and experimental physics of Physics and technology institute of North-Eastern federal university named after M. K. Ammosov (58, Belinsky str., Yakutsk, 677000, Republic of Sakha (Yakutia)), Ph.: 8-4112-49-68-32; e-mail: sargylana_mamaeva@mail.ru;

Maximov Georgy Vladimirovich, Dr.Sci. Biol., professor of department of biophysics of Biological faculty of Moscow State University (1, Lenin mountains, Moscow, Russia 119991), ph.: 8-495-939-19-66; e-mail: gmaksimov@mail.ru;

Munkhalova Yana Afanasyevna, candidate of medical sciences, the manager of department of pediatrics and children's surgery of Medical institute of North-Eastern federal university named after M. K. Ammosov (58, Belinsky str., Yakutsk, 677000, Republic of Sakha (Yakutia)), ph.: 8-4112-36-30-46; e-mail: tokmacheva@mail.ru;

Pavlov Alexandr Nikolaevich, candidate of physical and mathematical sciences, the head of the laboratory of "Mechanics. Fluctuations and waves" of department of general and experimental physics of Physics and technology institute of North-Eastern federal university named after M. K. Ammosov (58, Belinsky str., Yakutsk, 677000, Republic of Sakha (Yakutia)), Ph.: 8-4112-49-68-32; e-mail: alpavlov090@mail.ru;

Fedorov Andrey Leonidovich - Cand. tech. Sciences, engineer of laboratory «Technologies of polymer nanocomposites» of the Department of High-Molecular Compounds and Organic Chemistry of the Institute of Natural Sciences of North-Eastern Federal University. M.K. Ammosov. 677000, 48, Kulakovsky str., Yakutsk, Republic of Sakha (Yakutia), Phone: 8-4112-49-69-63; e-mail: gelvirb@mail.ru.

S.M. Tarabukina, E.B. Borisova, S.V. Vladimirova

METHODICAL APPROACHES TO ASSESSING THE AVAILABILITY OF NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES USED IN MEDICAL PRACTICE IN THE REPUBLIC SAKHA (YAKUTIA)

ABSTRACT

The method for assessing the accessibility of analgesic therapy at the regional level with the calculation of the accessibility index based on the integration of logically selected indicators is substantiated. At ranking the municipal districts in accordance with the degree of the generalized index of availability of narcotic drugs and psychotropic substances (ND and PS), the correlation of this index with the level of morbidity and mortality from malignant neoplasms in the regions of the republic was established. In order to assess the availability of ND and PS the nomenclature of the drugs of that group in the municipal areas classified according to the value of the accessibility index of narcotic drugs and psychotropic substances was studied.

Municipal areas with very low availability of analgesic therapy were identified. Low values of the assortment of analgesic therapy are established in these municipal districts. Their common features are geographical affiliation to the Arctic and northern regions of the republic, considerable distance from the center of the republic, low density of residence, lack of a regular land type of transport.

Keywords: assortment, drug provision, narcotic drugs and psychotropic substances, Arctic and northern regions.

INTRODUCTION

Ensuring the availability of medicines, regardless of the place of residence of a citizen, is one of the priority areas of social policy.

A comprehensive analysis of the drug supply system in the Republic of Sakha (Yakutia) has shown that the problem of organizing access to medicinal care for residents of Arctic northern ulus is especially relevant. The availability of medicines in these areas is influenced by such factors as the remoteness of most small settlements from district centers with their infrastructure, low incomes of the population, complicated and expensive transportation, increased costs for maintaining the infrastructure, and extremely low staffing with pharmaceutical personnel [1].

In the nomenclature of drugs, narcotic drugs and psychotropic substances (hereinafter - ND and PS) occupy a special place in respect of which control measures are established in accordance with the legislation of the Russian Federation and international treaties of the Russian Federation [2]. Therefore, the indicator of availability of HD and PS for use in medical practice can serve as an indicator of the definition of accessibility in the drug supply of a single region or an administrative district with remote, inaccessible settlements.

To increase the availability of support for the National Assembly and the Council of Ministers, a plan of key actions (the «road map») aimed at improving the mechanisms for state regulation of the circulation of narcotic drugs and psychotropic medications and providing citizens with modern narcotic and psychotropic medicines for rendering assistance in inpatient and outpatient settings was approved.

One of the benchmarks for the road map is to ensure the necessary level of the range of ND and PS [3].

Materials and methods

In the analysis, the report data of pharmacy and medical organizations for 2014 - 2016, the Ministry of Health of the Republic of Sakha (Yakutia) for 2014-2016, statistical data on the demographic situation in the Republic of Sakha (Yakutia), the structure of morbidity, the results of peer review were used.

Results and discussion

To substantiate methodological approaches to assessing the accessibility of ND and PS, the following factors have been studied: a set of indicators characterizing the level of medical and medicinal assistance provided to the population, allowing to rank municipal districts into groups; the specifics of the use of the National Assembly and the Council of Europe in the provision of primary health care, specialized, including high-tech, medical care; morbidity and mortality from malignant neoplasms; assortment of used ND and PS in the context of municipal districts.

To calculate the generalized index of accessibility of ND and PS, showing the level of availability of ND and PS for medical use, the following signs were selected logically: demographic indicators; the area of the subject of the study; number of medical personnel; number of pharmaceutical personnel; specialization and the profile of the hospital bed.

The index I, showing the level of availability of ND and PS, is defined as

$$I = \frac{\sqrt{\Sigma_{i=1}^{n} k_i}}{n}$$

the average value of the indices of the individual indicator blocks:

ki, - the indicators characterizing the above blocks of characteristics, n - the number of indicators.

Based on the developed methodology, the index of the level of accessibility of ND and PS was calculated in the context of the municipal districts of the Republic of Sakha (Yakutia) and their grouping was carried out (Table). The lowest accessibility index was found to have the Olenek district (0.005), Zhigansky district (0.005), Allayhovsky, Anabar districts (0.00814).

Ranking of territories allows determining the similarity of municipalities in the level of accessibility of analgesic therapy for the population, which makes it possible to justify common approaches to solve existing problems, regardless of place of residence.

To analyze the factors that have a significant impact on the assortment and nomenclature of ND and PS in the municipal formations of the Republic of Sakha (Yakutia), a sociological method was chosen that focused on the collection of internal and external opinions of specialists with pharmaceutical education.

To assess the factors, the main indicators, in our opinion, influencing the availability of analgesic therapy in the republic were selected.

The selected factors were divided into 5 blocks. The first block consisted of factors characterizing the demographic indicators of the territory (area): the population, the average life expectancy. The second block consisted of factors characterizing the data on the structure of the incidence of malignant neoplasms (MN) (primary morbidity, mortality from malignant diseases). The third block included the following factors: indicators of one-year lethality, the presence of palliative departments. The fourth block consisted of such factors as: the presence in the state of the attached treatment and prophylactic institution of oncologists, the number of beds in the hospital. In the fifth block, it was suggested to bring and evaluate other significant factors in the opinion of the respondents.

Ranking of territories by the level of accessibility of analgesic therapy for the population

The index determining the level of availability of HD and PS for use in medical practice	Level	Municipal districts
0,005 – 0,04	Very low level - 4 group	Allaikhovsky, Anabarsky, Bulunsky, Zhigansky, Momsky, Nizhnekolymsky, Olenek, Srednekolymsky, Ust-Yansky, Even-Bytantaisky
0,04 – 0,10	Low level - 3 group	Verkhnekolymsky, Ust-May, Tomponsky, Abyisk, Oymyakonsky, Kobyaysky, Aldan, Olekminsky,
0,10 – 0,50	Average level - 2 group	Gorny, Myrninsky, Lensky, Nyurbinsky, Vilyuysky, Neryungri, Suntar, Verkhnevilyui, Amginsky, Verkhoyansk, Tattinsky, Khangalassky
0,50 – 1,00	High level - 1 group	Ust-Aldansky, Namsky, Churapchinsky, Megino-Kangalassky, Yakutsk city district

The greatest impact on the availability of analgesic therapy in the Republic of Sakha (Yakutia), according to respondents, has: «primary incidence of malignant neoplasms» - 29%, «mortality from malignant neoplasms» - 22%. These factors for the sum of points, estimated by respondents in 9 and 8 points, have a leading position.

The identified on the accessibility index of the ND and PS groups of municipal districts have significant differences in the rates of primary incidence of malignant neoplasms of the population and mortality from malignant neoplasms per 100 000 population in dynamics over the last 3 years.

In Figure, the municipal districts of the Republic of Sakha (Yakutia) on the horizontal axis are arranged in the order of group membership, starting with the smallest value. The largest values of primary morbidity and mortality from malignant neoplasms are in zone 4 of the group with a very low index value.

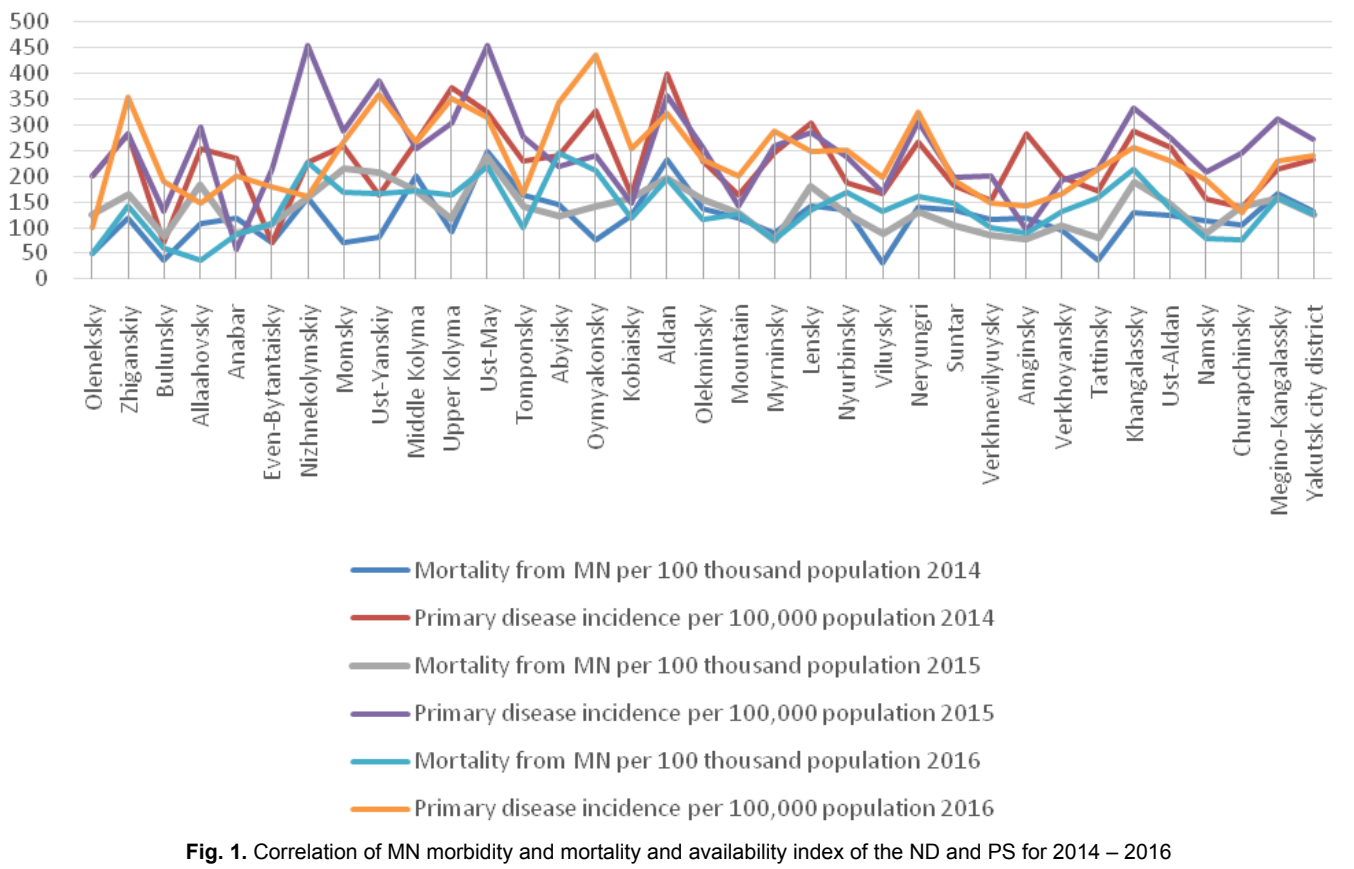


Fig. 1. Correlation of MN morbidity and mortality and availability index of the ND and PS for 2014 – 2016

In the analyzed period, the range of NSs belonging to the list II, in the republic is 66.6% of the nomenclature of registered drugs under the international non-proprietary name.

In the regions of the republic, classified as a cluster with a low level of the accessibility index of the National Assembly and the Parliament, the range of NSs for the international non-proprietary name was 55.5%, for trade names 31.6% of the nomenclature of registered drugs.

The smallest assortment of ND is represented in regions with a very low level of accessibility index of ND and PS -55.5% of the nomenclature of registered medicines in the international non-proprietary name and 26.3% in the trade name.

Analysis of the completeness of the assortment of ND and PS in medical and pharmacy organizations of the Republic of Sakha (Yakutia) showed that there are significant differences in the range of ND and PS present in the municipal districts of the republic. A number of indicators characterizing the state of the assortment of ND and PS, despite the existence of a regulatory framework in the organization of activities related to the provision of ND and PS, has a pronounced range of differences in the municipal regions of the republic. The lowest value of the indicators in the analysis of the assortment of ND and PS was noted in the municipal districts of the republic with a very low level of accessibility index narcotic drugs and psychotropic substances.

The indicators of primary morbidity and mortality from malignant neoplasms for 2014-2016 in municipal areas classified as a group with a very low availability of narcotic drugs and psychotropic substances suggest that the current need for ND and PS is significantly higher than the actual consumption of ND and PS for the last three years.

Thus, a complex of state regulation measures is needed to equalize the availability of analgesic therapy for the population and medical organizations. The ranking of municipal districts by drug provision groups for analgesic therapy creates the conditions for the development of conceptual documents with a set of measures to increase the availability of ND and PS at the level of the subject of the Russian Federation.

REFERENCES

1. Tarabukina S.M. Metodicheskie podkhody k formirovaniyu regional'noj strategii lekarstvennogo obespecheniya naseleniya na primere Respubliki Sakha (Yakutiya) [Methodical approaches to the formation of the regional strategy of medicinal provision of the population on the example of the Republic of Sakha (Yakutia): avtoreferat [the PhD author's abstract]. Moscow, 2011.
2. O narkoticheskikh sredstvakh i psikhotropnykh veshhestvakh [On narcotic drugs and psychotropic substances]: Feder. zakon ot 8 yanvarya 1998 g. № 3 [Federal law, January 8, № 3].
3. Plan meropriyatij («dorozhnaya karta») «Povyshenie dostupnosti narkoticheskikh sredstv i psikhotropnykh veshhestv dlya ispol'zovaniya v meditsinskikh tselyakh [Action plan (road map) «Increasing the availability of narcotic drugs and psychotropic substances for medical use]: Rasporyazhenie Pravitel'stva RF ot 1 iyulya 2016 g. №1403-r. [Order of the Government of the Russian Federation, July 1, 2016, No. 1403-r.].

The authors:

Tarabukina Sardana Makarovna - Candidate of Pharmaceutical Sciences, Associate Professor of the Department of Pharmacology and Pharmacy of the M.K. Ammosov MI NEFU, tcmx@mail.ru, Yakutsk, Republic Sakha (Yakutia), Russia;

Afanasyeva Elena Borisovna - assistant of the Department of Pharmacology and Pharmacy of the M.K. Ammosov MI NEFU, E.Cassi@yandex.ru, Yakutsk, Republic Sakha (Yakutia), Russia;

Lopatina Sargy Vladimirovna - Post-graduate student of MI NEFU, Department of Differential Equations, lopatinasv_1208@mail.ru, Yakutsk, Republic Sakha (Yakutia), Russia.

HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

L.P. Shadrina, A.A. Strekalovskaya, P.G. Petrova, T.A. Androsova, D.V. Bosikov

THE INFLUENCE OF GEOMAGNETIC STORMS ON THE DEVELOPMENT OF HYPERTENSIVE CRISES (AT THE EXAMPLE OF YAKUTSK RESIDENTS)

ABSTRACT

The data of appeal to the ambulance station with hypertensive crises of residents of Yakutsk with a geomagnetic field at the maximum (2013) and a minimum (2017) of the XXIV solar cycle was compared. It is shown that in the years of high solar activity, the effects of geomagnetic storms are manifested in the increase in the number of calls for emergency medical care with a preliminary diagnosis of the hypertensive crisis. At the same time, the majority are elderly and senile people, who, are believed, to have a cardiovascular system more susceptible to the influence of geophysical perturbations. An increase in the number of patients with hypertensive crisis is observed not only on the day of the maximum decrease of the Dst-index (the 0th day of the storm), but also in the interval from the -2th to the 2nd day of the storm. Differences in the reaction time are revealed depending on the type of geomagnetic storm: during sporadic storms, the maximum of calls is most often on the – 1st day, and for recurrent ones – on the 0th day.

Keywords: hypertensive crisis, cardiovascular diseases, geomagnetic storms, geophysical activity.

INTRODUCTION

Cardiovascular disease (hereinafter CVD) is the leading cause of the death all over the world: each year there is not another reason of death for many people but the CVD. One sort of cardiovascular complications and decrease in the working capacity of the population is the hypertensive crisis (hereinafter HC) – inadequate and biologically inexpedient (non-adaptive) response of the organism to the action of various factors, including environmental factors [5]. The main cause of this sort of disease, in the first place, is the state of the human body. In the modern world one can see exorbitant growth of the neuropsychological stresses, which cause a certain reaction

in the body, connected with changes in the blood supply of organs. Each such, albeit insignificant, change in blood circulation is reflected in the cardiovascular system.

In human pathology, hypertensive or hypertensive states play an important role, which is associated, on the one hand, with their high prevalence, and on the other hand, with their participation in pathogenetic mechanisms of CVD and their complications, often leading to a decrease in the working capacity of the population.

Hypertensive crisis (HC) is a patho_ logical reaction, characterized by a sudden increase in systolic and diastolic blood pressure in patients suffering from hypertension or symptomatic (secondary) arterial hypertension. Like any other pathological reaction, HC is the result of disturbances of the organism's reactivity in general or the reactive properties of tissues, organs and their systems, accompanied by a violation of the coronary or cerebral circulation. Sharp sudden increases in blood pressure can pose a threat to the life of the patient and require immediate intervention.

Factors associated with an increased risk of CVD can be divided into two groups: those that a person cannot change, and those that are amenable to change. The first group includes heredity, the aging process and other exogenous factors (psycho-emotional overload, excessive consumption of table salt and water, sudden cancellation of antihypertensive drugs, excessive physical activity). The second group includes such indicators as increased blood lipids (cholesterol and triglycerides), hypertension, smoking, lack of physical activity, excessive body weight, diabetes, stress and other endogenous factors [5].

In recent years, scientists increasingly pay attention to such objective factors as meteorological and geocosmophysical. The first factor includes weather conditions – temperature, wind, atmospheric pressure, precipitation. The geocosmophysical one– changes in the Earth's magnetic field, the level of solar activity, X-ray and other types of radiation caused by active processes on the Sun. By the magnitude of the impact on CVD, these factors are much inferior to those listed above, but their accounting can significantly improve the quality of life. This is especially true for residents of the high-latitude, Arctic zone, where the variations in geophysical activity are much stronger than in the middle- and low-latitude zones, and, consequently, the person is under the influence of more intense fields. It is noted that magnetic storms are dangerous in the first place for those who suffer from arterial hypertension and hypotension or heart disease. In the days of geomagnetic disturbances, the number of heart attacks, strokes and hypertensive crises increases by an average of 15 % [1, 3, 8].

The **purpose** of this work is to study the role of geomagnetic storms in the development of HC for the Yakutsk inhabitants, the determination of specific parameters of geomagnetic disturbances and possible mechanisms for their impact on CVD.

Materials and Methods of the research

The statistical processing of the data of the electronic database of calls to the ambulance because of HCs for 2013 and for the first half (6 months) of 2017 was performed. Medical data are compared with the Dst index of the geomagnetic field. During the geomagnetic storms Dst index has a characteristic variation: first it increases by 5-10 nT within 2-5 hours (the initial phase of the storm), then sharply, during 7-16 hours, falls by tens to hundreds of nT (main phase), and then slowly, within 3-6 days, returns to a calm level (recovery phase). The convenience of using this index is due to the fact that its online values are freely available on the website of the Center for Geomagnetism and Cosmic Magnetism of Kyoto University (Japan) [12]. The day of the main phase of the storm (maximum decrease of the Dst index) is taken as a 0-day of the storm.

Results and discussion

For a detailed study we selected geophysical data in 2013 and the first half of 2017. These years fall respectively on the maximum and minimum of the XXIV solar cycle. Compared with the previous ones, this 11-year cycle proved to be much weaker (Figure 1). If in the XXI (1976-1986) and XXII (1986-1996) cycles the number of sunspots (Wolf numbers, W) reached at the maximum the values W = 155 and W = 157 (respectively, in 1979 and 1989), and in (1996-2009) of the XXIII cycle W = 120 (2000), but in the XXIV cycle the maximum in February 2014 was only W = 71. The average annual number of sunspots in 2014 was W = 75, in 2013 it was slightly less W = 61. In the first half of 2017, the average Wolf number was only W = 15, which is typical for a minimum of solar activity.

In Figure 1, along with solar activity (W), the average annual values of the geomagnetic Dst-index module are shown by dashed lines. As you can see, geomagnetic activity also changes during the solar cycle but usually there are several maxima – one at the growth phase of the solar cycle and one or two at the decline phase. In the XXIV solar cycle, geomagnetic activity was also smaller than in previous cycles. The first maximum was observed during the growth phase of solar activity in 2012-2013 – the module of the average annual | Dst | = 8.0 nT in 2012 and 7.9 nT in 2013. The second maximum was at the decline phase in 2015 – the module of the average annual Dst = 15.5 nT. The first the maximum was much weaker than the second one. Thus, studied 2013 year falls at the growth phase of solar activity and on the first maximum of geomagnetic activity, but in 2017 geomagnetic activity was on decline phase after the second maximum in 2015.

The number of geomagnetic storms: in 2013 there were 43 storms, including 3 large, 19 moderate and 21 weak. According to the accepted classification, we consider storms as a weak if the main phase Dst decrease is 30 nT <| Dst | <50 nT, moderate storm with 51 nT <| Dst | <99 nT, and large storm with | Dst | > 100 nT. In the first half of 2017 there were 25 storms, 1 large, 7 moderate and 17 weak ones were recorded. For comparison – for the same time interval of 2013 there were 24 storms – 3 large, 8 moderate and 13 weak. So, although in the first half of 2013 and 2017 there were roughly equal total number of geomagnetic storms there were more intensive storms in 2013.

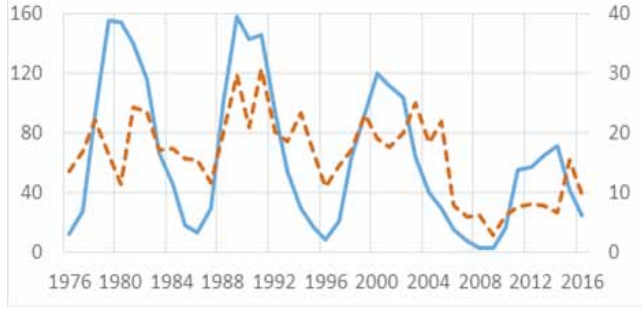


Fig. 1. The mean annual number of sunspots (Wolf numbers W) (solid curve, left scale) and the geomagnetic Dst index (dotted line, right scale) in the XXI-XXIV solar cycles.

In total, during the analyzed period of 2013 and the first half of 2017 there were 3103 ambulance calls for HC (Nhc), 2,267 in 2013 and 456 in 2017 (Table 1). Note that in the first half of 2017 Nhc = 456, which is 2.2 times less than in the same period of 2013 (1006).

In the majority of cases of the HC (2749 out of 3103, or 88.6%) was observed for people older than 50 years, which is quite logical, since pathogenetic factors contributing to the development of HC in elderly and senile people are the high content of angiotensin II circulating in the blood, the deficiency of kininogen, prostacyclin, damage to the vascular endothelium and a decrease in the release of vasodilating substances. At the same time in the vessels there are circulatory disorders of the type of ischemia, stasis or thrombosis, edema of the tissue, diapedesis bleeding. Stability of this indicator testifies its objectiveness: the percentage is almost unchanged both for the 2013 data, and for the first half of 2013 and 2017, and for all registered cases in total (see the third column). The percentage of young people (age younger than 50) is quite low, only 11.4%.

In addition to the age-related criteria in the development of HC and other cardiovascular complications, the sex of patients is an important determining factor too [7]. According to our data, out of 2 647 ambulance calls for HC women make up 78.3% (2 073) in 2013. In 2017, the indicator decreases slightly, to 74.3% (339 out of 456). It should be noted that men predominate among young patients (in 2013, 124 out of 574 or 21.6%, in 2017, 26 out of 117 or 22.2%). For women, this indicator is also stable and amounts to 177 out of 2 073 or 8.5% in 2013 and 27 from 339 or 8.0% in 2017. The frequency of HC for women aged 50 years and older, on the contrary, is several times higher than for men: 1896 against 450 in 2013 (4.2 times) and 312 against 91 in 2017 (in 3.4 times). This fact can be explained by a decrease in adaptive mechanisms in women during menopause, which is accompanied by a deficiency of estrogens due to natural extinction of ovarian function and, apparently, increases their sensitivity to geophysical factors [2, 6, 7].

Figure 2 shows the average daily values of the Dst index and the number of HC in the first half of 2013 and 2017. One can see the number of ambulance calls for HC (Nhc) in 2013 is significantly greater than for the same time interval in 2017 (in numerical terms, respectively, 1005 and 455).

As is known, geomagnetic storms are divided into two types – sporadic and recurrent. On Earth, this is reflected in the morphological characteristics of storms – sporadic storms more often shows a sharp start, more intense mail phase; recurrent storms starts more smoothly,

Table 1

Distribution of ambulance calls for HA by age and sex

Year	Nhc, all	age over 50 / %	woman			men		
			Nhc / %	age over 50 / %	Young / %	Nhc / %	age over 50 / %	Young / %
2013	2647	2346/88,6	2073/78,3	1896/91,5	177/8,5	574/21,9	450/78,4	124/21,6
2013-1	1006	887/88,2	786/78,1	721/91,7	65/8,3	220/21,9	166/75,5	54/24,5
2017-1	456	403/88,4	339/74,3	312/92,0	27/8,0	117/25,6	91/77,8	26/22,2
2013 and 2017	3103	2749/88,6	2749/77,7	2208/91,5	204/8,5	691/22,3	541/78,3	150/21,7

Note: all columns except the first one show the number of calls Nhc / percentage.

Fig. 2. Average daily values of the Dst-index (curve, right scale) and the number of patients with hypertensive crisis (histograms, left scale) from January to June (top to bottom) 2013 (left) and 2017 (right)

Fig. 3. Dst- index during large geomagnetic storms - recurrent (upper row) and sporadic (lower row) and number of patients with hypertensive crisis (columns, right scale).

several intensifications are observed during the main phase, and their duration considerably exceeds the duration of sporadic storms. The differences between these two types of geomagnetic storms are due to the difference in their solar sources – in the first case they are solar flares and associated coronal mass ejections (CME), in the second – long-lived coronal holes and corona high-speed flows (CIR) [4].

It was noted in [9, 10] that there are differences in the response of the cardiovascular system to these two types of storm. The type of storm we determined according to the method [11]. Figure 3 shows data during four large storms: two recurrent on March 17, 2013 (-132 nT) and on June 28, 2013 (-97 nT), and two sporadic on June 1, 2013 (-119 nT) and May 28, 2017 (-125 nT). One can see that during recurrent storms (upper row) Nhc increased 24 hours before the beginning of the storm (on the -1-th day). The increase in Nhc on the 3rd day after the onset of the storm on March 21, 2013 is most likely not related to geomagnetic activity and may be due to the age or individual reactivity of patients to external stimulus, or meteorological factors. During sporadic storms (lower row), Nhc increases on + 1 day after the onset of the storm.

It was shown in [3, 7, 9, 10] that changes in the cardiovascular system are observed not only on the day of the maximum decrease of the Dst- index (0 day of the storm), but also in the interval from -2 to +2 days of the storm. To test how this manifests itself in our study in the HC, we calculated Nhc (the number of ambulance calls for HC) in a 5-day storm interval (Table 2). There was calculated the number of storms for which the maximum of Nhc was observed, respectively on the -2-nd, -1-st, 0-th, 1-st or 2-nd day of the storm In 2013, at the solar cycle maximum, the number of sporadic storms was almost twice less than number of recurrent storms (15 and 28), and in 2017 (10 and 15).

Table 2 shows that an increase of Nhc is observed during most of geomagnetic storms: in 2013 this is true for 42 of 43 storms, and in 2017 there was no noticeable increase of Nhc in 7 cases out of 25, during weak storms. Of course, not all cases of Nhc increase are associated with a decreasing of the geomagnetic field (see Figure 2), but there is no well amplitude correspondence: during large storms, the Nhc increase may be less than during moderate storms, and sometimes even during weak storms there is a significant increase in Nhc. Hence, the increase in the number of applications for emergency medical care for HC is often associated with storms, but does not directly depend on the intensity of the storm.

As can be seen from the table, the growth of Nhc c during sporadic storms in 2013 more often occur on minus 2-nd and 1-st days (red color), but in 2017 this did not manifests. For recurrent storms, growth of Nhc more frequently occur on the day of the storm begins (0-day) – this is clearly visible in 2013, and in 2017 it is less pronounced. In total, for 25 sporadic and 43 recurrent storm events in 2013 and 2017 (the last 3 rows in the table), the growth of Nhc expressed fairly confidently on one day before the start of sporadic storms and on 0-day for recurrent. Accordingly, for all 68 storms, the maximum number of Nhc occurs on two days – the day before the storm begins (-1-day) and on the day of the maximum decrease of the Dst index (0- day). That is, there is a tendency of a time-differentiated reaction to sporadic and recurrent geomagnetic storms in the increase of the number of requests for medical care for HC (Nhc) in a five-day storm interval. These conclusions agree with results obtained earlier on other data [6-10].

Table 2

The number of storms with a maximum Nhc in the 5-day bore interval (from -2 days before the storm to 2 days after the storm began)

Type of storm	Number of storms	-2	-1	0	1	2	No
2013							
Sporadic	15	4	4	3	3	1	0
Recurrent	28	6	6	8	5	2	1
All	43	10	10	11	8	3	0
2017							
Sporadic	10	1	2	1	2	0	4
Recurrent	15	0	3	3	2	4	3
All	25	1	5	4	4	4	7
2013 and 2017							
Sporadic	25	5	6	4	5	1	4
Recurrent	43	6	9	11	7	6	4
All	68	11	15	15	12	7	8

Note. “No” column shows the number of storms, when there was no increase in Nhc during storm period.

Conclusion

The analysis of the data presented in the study shows the presence of a complicated, ambiguous connection of the number of requests for medical care for HC (Nhc) with geomagnetic activity. Nevertheless, the data studied agree with the previous results [9, 10] and allow

us to state that such a relationship exists.

1. The effects of geomagnetic activity are manifested in an increase in the number of requests for emergency medical care for the HC (Nhc) in years of high solar activity compared to the low.

2. 88.6% of all requests for emergency medical care are elderly and senile people, that is, people whose cardiovascular system reacts more strongly to more weak compared other factor – effect of geophysical activity.

3. The increase of Nhc does not directly depend on the intensity of the storm, but there has been a tendency for a different reaction on the number of calls for HC during sporadic and recurrent storms.

Acknowledgements

This work was made in the frame of project of the Program of Complex Scientific Researches in Republic Sakha (Yakutia) 2016- 2020, Russia and partly supported by RFBR grants № 15-45-05090-p_east_a, and № 15-42-05085-p_east_a.

REFERENCES

1. Gadzhiev G.D. Rakhmatullin R.A. Dorokhova A.N. Ekologicheskie aspekty vozdeystviya solnechnoy i geomagnitnoy activnosti na sostoyanie zdorovia sotrudnicov INC SO RAN [Ecological aspects of the effect of solar and geomagnetic activity on the health of employees of the INC SB RAS] Bulleten Vostochno- Sibirskogo nauchnogo centra [Bulletin of the East Siberian Scientific Center]. Irkutsk: 2010, No 6 (76) Part 1, pp.132-138.
2. Strekalovskaya A.A. Petrova P.G. Samsonov S.N. [et al.] Geomagnytnye vozmushenya i osloshneniya serdechno-sosudisty zabolevanyi [Geomagnetic disturbances and complications of cardiovascular diseases] Nauchno-teorenicheskyi zhurnal «Uspexi sovremennogo estestvoznanya» [Scientific and theoretical journal «Successes of modern natural science»]. 2004, pp.73-74.
3. Gurfinkel Yu.I. Ischemicheskaya bolezn serdsa i solnechnaia activnost [Ischemic heart disease and solar activity]. Moscow: Izd-vo Elf-3, 2004, 168 p.
4. Ermolaev Yu.I. Ermolaev M.Yu. Solnechnie i mezhplanetnye istochnyki geomagnitny buri: aspekty kosmicheskoy pogodyi [Solar and interplanetary sources of geomagnetic storms: aspects of space weather] Geophyzicheskie prosessy i biosfera [Geophysical processes and the biosphere], 2009, T. 8, No 1, pp. 5-35.
5. Zadionchenko V.S. Gorbacheva E.V. Gipertonycheskie krizy [Hypertensive crises] BC, 2001, № 15, pp. 628-633.
6. Petrova P.G. ,Strekalovskaya A.A., Komzin K.V. Reaksiya organyzma cheloveka na vneshnye vozmushenya. Glava 2 [The reaction of the human body to external disturbances. Chapter 2] V knyge «Biopropnoe vozdeystvie kosmicheskoy pogodyi» [In the book «Biotropic impact of space weather»] Ed. M.V. Ragulskaya. Moscow: IZMIRAN, 2010, P. 312.
7. Samsonov S.N. Sokolov V.D. Strekalovskaya A.A. Petrova P.G. O svyazy serdechno-sosudisty zabolevanyi s geofizycheskoy vozmushennostiy [On the connection between exacerbation of cardiovascular diseases and geophysical indignation] Zhurnal nevrologii i psyzianrii im. SS Korsakova [Journal of Neurology and Psychiatry. S.S. Korsakov] Stroke number 14, Moscow, 2005, pp.18-22.
8. Stoilova I. Dimitrova S. Breus T. Zenchenko T. Yanev T. Solnechno-zemnye svyazy i zdorovye cheloveka [Solar-terrestrial connections and human health] Solnechno-zemnya fysica [Solar-terrestrial physics]. 2008, No. 12, T.2, pp. 336-339.
9. Shadrina L.P. Petrova P.G. Samsonov S.N. Manykina V.I. Sravnenye izmenenyi v cardiogramme cheloveka vo vremya sporadycheski i rekurrentny bury (na primere shiteley Jakutska) [Comparison of changes in a human cardiogram during sporadic and recurrent storms (by the example of residents of Yakutsk)] Jakutskij medicinskij zhurnal [Yakutsk Medical Journal]. 2013, No 3, pp. 108-111.
10. Shadrina L.P. Vozdeistvye kosmicheskoy pogodyi na zdorovye shiteley Jakutska [The effect of space weather on the health of residents of Yakutsk] Prykladnya ecologya goroda Jakutska [Applied ecology of the city of Yakutsk]. Sat. works. Novosibirsk: Science, 2017, pp.177-187.
11. Shadrina L.P. Vasilyeva V.G. Chyslennyi parameter dlya opredelenya klassa geomagnytny bury [Numerical parameter for determining the class of geomagnetic storms] Issled. po geomagnetyzmu, aeronomii i fysike Solntsa [Issled. on geomagnetism, aeronomy and physics of the Sun]. Issue. 112, ed. SB RAS, 2001, pp. 163-167.
12. http://wdc.kugi.kyoto-u.ac.jp/dst_realtime/presentmonth/index. html

The authors:

Academy of Sciences of Sakha (Yakutia) Republic, Yakutsk, Russia:

Shadrina Lyudmila Pankratyevna - leading researcher;

Medical Institute of M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia: Strekalovskaya Alena Anatolievna - Candidate of Medical Science, Associate Professor, a_strekalovskaya@mail.ru, Petrova Palmira Georgievna - MD, Professor, Head of Department;

State budgetary institution of the Sakha (Yakutia) Republic, Emergency medical station, Yakutsk, Russia: Androsova Tatyana Antonovna - Chief Physician, Dmitry Borisikov - Deputy Ch. doctor.

O. N. Ivanova, A. S. Golderova

THE STUDY OF IMMUNITY FEATURES IN CHILDREN WITH CHRONIC NASOPHARYNGITIS

ABSTRACT

Immune status was studied in children with chronic nasopharyngitis. It was revealed that in children with chronic nasopharyngitis the content of IgA, CD25 + lymphocytes, CD4 + was reduced. All examined children underwent therapy with lycopid 1 mg per day for 10 days; a second course was performed after 1 month. It was revealed that lycopid therapy in patients with chronic nasopharyngitis lead to normalization of decreased immune status indicators: an increase in CD3 + and CD25 + content, an increase in IgA concentration.

Keywords: chronic nasopharyngitis, children, immunity, immunocorrector.

Nasopharyngitis is an inflammatory disease of the mucous membranes and pharyngitis. It is up to 80% of cases of acute respiratory viral infection accompanied by nasopharyngitis [1,2] .

There are hypertrophic and atrophic forms of chronic nasopharyngitis. Pathomorphological changes in hypertrophic form are characterized by thickening and edema of mucous and submucous layers of the nasopharynx, so the clinical picture observed increased secretion from the nose light transparent liquid, the feeling of rawness and throat irritation, increased lacrimation, and tickling in the nose. The patient coughs constantly, expectorated and sneezing especially in the morning. Atrophic nasopharyngitis is characterized by thinning of the mucosa, since the affected layer is replaced by connective tissue fibers. Accordingly, the clinic is of a different nature and is manifested by dryness in the throat, difficulty swallowing and bad breath. The child of early age the frequency of appearance of virus infections with nasopharyngitis is caused by immune system dysfunction, increased allergic reactions, the presence of chronic adenoiditis [1, 2].

The **purpose** of the study: to study the characteristics of immunity in children with chronic nasopharyngitis and the effect of drug Likopid therapy.

Materials and methods

The study surveyed a group of children (n=30) aged 3 to 5 years with chronic nasopharyngitis: the common rhinitis, sore throat, nasal discharge. We also surveyed a group of healthy children (n=20), and compare groups of children matched for age. The children underwent examination of immune status (CD3+,CD4+, CD8+, CD16+, CD22+, IgA, IgG, IgM, IgE) on the basis of the RH No.1-National center of medicine RS (Ya). Comparison of mean values was assessed by single-factor dispersion analysis using Student T-test for the evaluation of the equality F-Fisher criterion. The relationship between parameters was assessed using the coefficients of the linear and rank correlation.

The **results** of the study: all children with chronic nasopharyngitis had frequent viral respiratory infections, nasal discharge, excessive sweating, fatigue, adenoiditis. There were examined 30 children.

In the group of all surveyed children we have observed a reduced level of IgA (Table).

Also we revealed a decrease in the content of CD25+ cells, activated T cells, T helper (CD4+). In the treatment of chronic nasopharyngitis in the course of immunomodulator Likopid in the dose of 1 mg (1 tablet) 1 times a day 10 days was used, a second course was conducted in a month. At the end of the second course, immunological studies of all treated children were conducted.

Therapy by drug Likopid led to the normalization of some parameters of cellular and humoral immunity: the increase in the content of CD3+ and CD25+, the increase in the concentration of IgA.

Conclusion

1. In children with chronic nasopharyngitis we revealed the immune dysfunction or failure, affecting cellular and humoral immunity (IgA decrease, the decrease in CD25+ lymphocytes, reduced CD4+).

2. Therapy by likopid patients with chronic nasopharyngitis normalizes reduced immune status indices: increase in the content of CD3+ and CD25+, the increase in the concentration of IgA.

REFERENCES

1. Ratnikova L. I. Sten'ko E.A. Novyj podhod k terapii ostryh respiratornyh virusnyh infekcij i grippa [New approach to treatment of acute respiratory viral infections and influenza] Poliklinika. Moscow, 2009, № 2, p. 70–72.
2. Klyuchnikov S. O. Zajceva O.V. Osmanov I.M. Krapivkin A.I. Keshishyan E.S. Blinova O.V. Bystrova O.V. Ostrye respiratornye zabolevaniya u detej. Posobie dlya vrachej [Acute respiratory infections in children. Manual for doctors]. Rossijskij vestnik perinatologii i pediatrii [Russian Bulletin of Perinatology and Pediatrics]. Moscow, 2008, № 3, p. 1–36.

The authors:

Ivanova Olga Nikolaevna - doctor of medical sciences, professor of Department of Pediatrics and pediatric surgery MI NEFU, 89142906125, e-mail: olgadoctor @list.ru, Yakutsk, Russia;

Goldirova Aitalina Semenovna - doctor of medical sciences, chief researcher of the Department study the mechanisms of adaptation, Yakut scientific center of complex medical problems, Yakutsk, Russia.

Table

Indicators of immune status in children of Sakha (Yakutia) in children with chronic nasopharyngitis and healthy children

Indicators	Children with chronic nasopharyngitis (n = 30), M ± m	Healthy children (n = 20), M ± m
CD3+	26,4 ± 1,0	27,2±1,04
CD4+	10,1 ± 0,2*	21,3±0,6
CD8+	11,2 ± 0,5	12,1±2.5
CD16+	12,4 ± 1,4	11,0±1,01
ИРИ	0,8 ± 0,5	1,08±0,02
IgA	1,6 ± 0,1*	2,9±0,6
IgG	18,1 ± 0,2	17,1±0,09
IgM	2,6 ± 0,02	2,2±0,09
CD25+	12,2 ± 1,2*	24,6±0,7
ЦИК	75,1 ± 1,5	70±0,07

*$p < 0.05$ between norms and obtained values in each group.

ARCTIC MEDICINE

R.N. Zakharova., A.I. Fedorov, S.S. Sleptsova, I.I. Podoynitsyna, A.V. Mikhailova, M. E. Baltakhinova

QUALITY OF LIFE OF WORKING-AGE POPULATION OF EAST ECONOMIC ZONE OF YAKUTIA

ABSTRACT

The quality of life (QL) of an able-bodied population of East economic zone (EEZ) of the Sakha (Yakutia) Republic by means of the standardized questionnaire of SF-36 was studied. Researches showed that mean values of scales of the population QL in the zone were at the level lower than 50%. The male population in EEZ had the best indicators of QL on all scales of the questionnaire of SF-36 in comparison with women's. Dynamics of QL indexes of the population of EEZ of the RS (Ya) is comparable to the common regularities of change of QL with age received in other researches. However, it should be noted that decrease in parameters of quality of life generally happens due to deterioration in physical health. The QL psychological component practically does not depend on an age and remains invariable for a long time. These parameters were higher than the population indices in the republic.

Keywords: quality of life, physical and psychological component, East economic zone of Yakutia, population research.

INTRODUCTION

In the modern scientific literature the term «quality of life, the bound to health» was widely adopted and has the following definition: it is the integral characteristic of physical, psychological, emotional and social functioning of the person based on his subjective perception. Value judgment of physical health an individual can be a predictor of the hidden functional violations of systems and bodies, to testify about the disadaptation processes in a human body, which cannot be identified by other method. Therefore, the research of the quality of life (QL) is an early, reliable and efficient method of assessment of the common wellbeing of the person. The method allows giving the quantitative assessment of components of activity of the person – his physical, psychological and social functioning that are defining factors for people of working-age.

It in the way, only the healthy person can be competitive and successful in conditions of the modern market relations and one of methods of early identification of the functional violations in an organism, estimates of psychological wellbeing the technique of evaluation test of human life can serve.

Work purpose - to study the modern level of quality of life of able-bodied population of East economic zone of Yakutia.

Material and research techniques

Work is performed within research: «State assessment, the analysis of the main tendencies of change of a natural and social and economic state, human potential of East economic zone of the Sakha (Yakutia) Republic" within the complex scientific research in the Sakha (Yakutia) Republic aimed at the development of productive forces and the social sphere for 2016-2020 under the government contract No. 5329 of 02.08.2017.

The protocol of population research QL was drafted according to the recommendations of the International project of studying of quality of life [1, 2, 9]. The research included representatives of various social groups of both sexes 15 years living in East economic zone of the Sakha (Yakutia) Republic are more senior. Acquisition was carried out in Tomponsky, Oymyakonsky and Ust-Maysky areas by questioning of respondents by method of direct poll. In Oymyakonsky district 87 respondents, by Tomponsky – 94, Ust-Maysky – 69 were interviewed. In total in the region of a research 250 inhabitants of whom 53% made women, 47% - men are interviewed. Dr. Podoynitsyna I.I. made samples.

As the tool for acquisition we used the questionnaire of assessment of QL SF-36 and the social-demographic card. The questionnaire of SF-36 contains eight scales (concepts) of health most of which often measure in population researches [2, 4, 9, 10]. Numerical values of scales of the questionnaire are expressed in shares from reference sizes, i.e. as a percentage. Indicators of QL were standardized on a universe of the USA according to the recommendations of developers [8, 9, 10]. This questionnaire is suitable for self-contained filling with the respondent, holding computer poll or filling with his trained interviewer at personal contact or by phone. It is applicable aged from 14 years and is more senior [9, 10]. The social-demographic card consists of 14 questions and includes demographic characteristics (a sex, age, employment, education, marital status and the questions of substantial character giving information on the level of income, living conditions, the state of health.

Results of a research and discussion

Results of questionnaire showed that mean values of scales of quality of life of the population are in the region of a research at the level of lower than 50%. The single indicator exceeding 50% level is the scale «vital activity». It demonstrates that the considerable proportion of the population of the East Economic Zone (EEZ) feels in itself forces and energy. On the other hand, on the basis of the analysis of the obtained data by us it is revealed that respondents very often give a low mark to a condition of the health at the moment and skeptically fall into to the prospects of treatment what there correspond the lowest mean values of a scale «the common state of health» (fig. 1) to.

The comparative analysis of indexes of QL of the population of EEZ with population indexes across the Sakha (Yakutia) Republic (fig. 1) is carried out [3]. Results of the analysis established proximity of the compared indexes. Pays an attention that the social activity of the population of EEZ (communication, carrying out time with friends, neighbors, in collective) was much higher than a national average index. Mean values of a scale of psychological wellbeing of

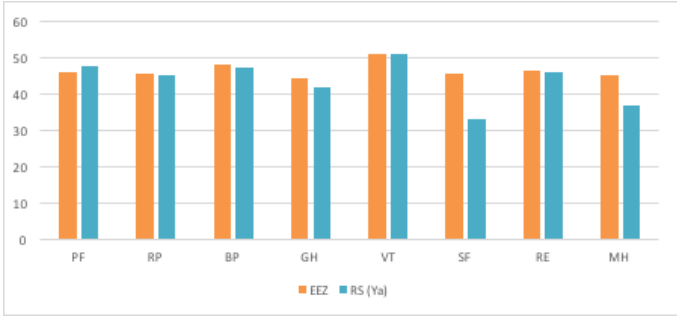


Fig. 1. The standardized population indicators of scales of the SF-36 questionnaire on the populations of East economic zone and the Sakha (Yakutia) Republic in whole.

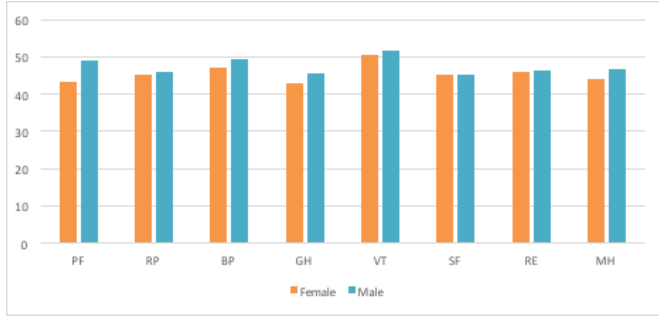


Fig. 2. The standardized population indicators of the scales SF-36 questionnaire on population of East economic zone depending on a sex.

respondents of EEZ also exceeded those on the republic in general.

At women tendencies to decrease in physical activity, volume of a daily exercise stress and an emotional state were noted. The received indicators demonstrate that daily activity of women is limited to their physical and emotional condition that negatively is reflected in their common assessment of the health. Indexes of quality of life of men were statistically significantly above, than at women on all scales of the questionnaire is (fig. 2).

All respondents depending on an age were divided into 6 groups: 18-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65 are also more senior (fig. 3). Results of a research showed that with age there is a decrease in volume of a daily exercise stress since 45-54 years. Restriction of an exercise stress is caused by a health aggravation of symptoms in more senior age groups that is comparable to literary data [5, 10].

The tendency of age dependence was traced also on a scale of role physical functioning. At respondents up to 25 years the pain syndrome had no significant effect on QL (p=0,03). Level of a pain syndrome increases in age groups 25 years are more senior and significantly influences a self-rating of health and activity of respondents. Peak values of pain are noted in groups of respondents 55 years (p=0,04) and more senior.

Respondents aged up to 25 years estimated the common condition of the health above the average level (p=0,004), and from 25 to 44 years gave an average assessment. The population is more senior than 45 years has smaller resistance to diseases and estimates the common state of health below average.

The vital activity of respondents aged up to 55 years remained on more high level, despite decrease in physical health. Low points of a scale of activity in the senior age groups corresponded to increase of exhaustion investigated, to decrease in their biotic activity.

Indexes of scales of social activity, role emotional functioning and psychological health of respondents remained on rather high level irrespective of an age. On reaching the 65 years there is the considerable reduction of volumes and quality of communication with friends and relatives in connection with an aggravation of symptoms of health (p=0,01). Men in all age groups possessed broader social communications in comparison with women. The condition of psychological health of men was much better in comparison with women in all age groups (p=0,02). Age changes of an emotional condition of respondents are not established.

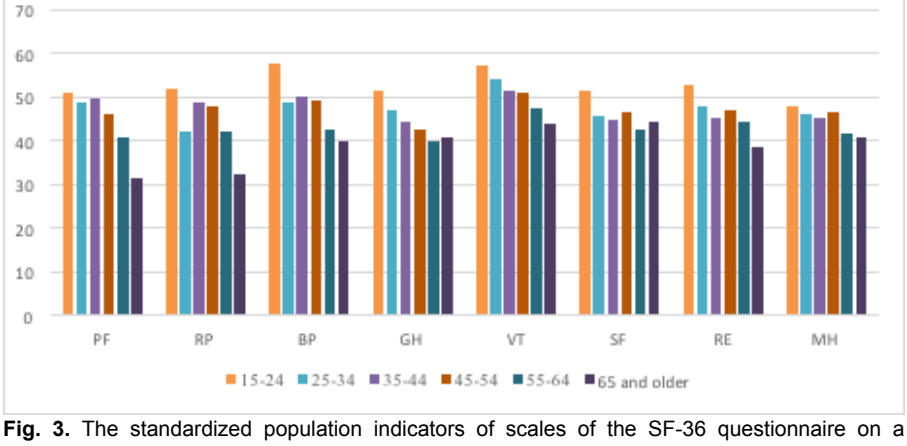


Fig. 3. The standardized population indicators of scales of the SF-36 questionnaire on a population of East economic zone depending on an age.

Conclusion

The analysis of the standardized indicators of QL of the population of three regions of EEZ RS (Ya) showed poor quality of life of the population which is in percentage terms lower than 50% of level of 100% of «ideal» health.

By comparison to the regional indexes of QL of adult population of RS (Ya) developed in 2010, the QL some parameters according to the questionnaire of SF-36 appeared above population indexes, in particular, on rating scales of the common state of health, social functioning and psychological health. The male population in EEZ had the best indicators of QL on all scales of the questionnaire of SF-36 in comparison with women's.

Age dynamics of indexes of QL of the population of EEZ of the Sakha (Yakutia) Republic is comparable to the common regularities of change of QL with age received in other researches [4, 5]. However it should be noted that decrease in parameters of quality of life generally happens due to deterioration in physical health. The QL psychological component practically does not depend on an age.

Thus, the analysis of the standardized indicators of QL of adult population in East economic zone of the Sakha (Yakutia) Republic showed that physical and psychological components of quality of life according to the questionnaire of SF-36 are not interdependent, i.e. at the poor physical health of respondents the psychological component remains high that is not coordinated with results of researches of quality of life of the population in the European countries and the USA [6, 7, 8] that demands further cross-disciplinary researches.

REFERENCES:

1. Kozhokeeva V.A. Razrabotka protokola populyacionnogo issledovaniya kachestva

zhizni vzroslogo naseleniya g. Bishkek s ispol’zovaniem obshchego oprosnika SF-36 [Development of a protocol for the population-based study of the quality of life of the adult population in Bishkek using the general SF-36 questionnaire] Nauchno-prakticheskaya revmatologiya [Scientific and Practical Rheumatology], 2010, №15-16, p. 91-96.
2. Novik A.A. Ionova T.I. Kajnd P. Koncepciya issledovaniya kachestva zhizni v medicine [The concept of life quality research in medicine]. Sankt- Petersburg: “EHLBI”, 1999, p. 30-45.
3. Zaharova R.N. Mihajlova A.E. Ionova T.I. et al. Populyacionnye pokazateli kachestva zhizni u naseleniya Respubliki Saha (Yakutiya) [Population indicators of the life quality among the population of the Republic of Sakha (Yakutia)] Vestnik Mezhnacional’nogo centra issledovaniya kachestva zhizni [Bulletin of the Interethnic Center for the Study of the Life Quality]. St. Petersburg, 2012, №19-20, p. 16-32.
4. Sannikova E.S. Ocenka kachestva zhizni naseleniya na osnove razvitiya promyshlennogo kompleksa regiona: avtoref. diss…. kand. ehkonom. nauk [An estimation of life quality of the population on the basis of development of the industrial complex of region: the author’s abstract. diss. cand. econ. sciences.]. Krasnoyarsk, 1997, 25 p.
5. Fyodorova N.M. Kachestvo zhizni naseleniya goroda v period social’no-ehkonomicheskih transformacij: avtoref. diss…. kand. ehkonom. nauk [Fyodorova N.M. Life Quality of the city’s population in the period of socio-economic transformations: author’s abstract. diss. cand. econ. sciences]. St. Petersburg, 2002, 22 p.
6. Bone M.R. International efforts to measure health expectancy /M.R. Bone //Journal of Epidemiology and Community Health. -1992. - Vol.46. - P. 555- 558.
7. Measuring quality of life in the frail elderly / G.H. Guyatt, D.J. Eagle, B. Sackett, [et al.] // Journal of Clinical Epidemiology.-1993.- Vol. 46. - P. 1433-1444.
8. Fourth Annual Conference of the International Society for Quality of Life Research: Abstracts // Quality of Life Research.-1997.- Vol. 7.- № 8.- P. 613-747.
9. Ware J.E. Methods for testing data quality, scaling assumptions and reliability: The IQOLA Project Approach / J.E. Ware, B. Gandek // J. Clin. Epidemiol.-1998.- Vol. 51, № 11.- P. 945-952.
10. Ware J.E. Overview of the SF-36 Health Survey and the IQUOLA Project / J.E. Ware, B. Gandek // J. Clin. Epidemiol.-1998.- Vol. 51.- №11.- P. 903-912.

The authors:

Zakharova Raisa Nikolaevna, Candidate of Medicine, leading researcher, Research Institute of Health, North-Eastern Federal University named after M.K. Ammosov, 677014, Yakutsk, Kulakovsky Street 46, office 501, phone 89142223002, e-mail: prn.inst@mail.ru

Fedorov Afanasy Ivanovich, Candidate of Biology, senior research associate, Research Institute of Health, North-Eastern Federal University named after M.K. Ammosov, 677014, Yakutsk, Kulakovsky Street 46, office 501, phone 89142332966, e-mail: fedorow@yandex.ru

Sleptsova Snezhana Spiridonovna – MD, Doctor of Medical Sciences, Head of Department of Infectious Diseases, phthisiatrics and dermatovenerology of Medical Institute the North-Eastern Federal University named after M.K. Ammosov, 677016, Yakutsk, ul. Oyunsky, 27, Russia. Tel. 8-914-2718770. E-mail: sssleptsova@yandex.ru

Podoynitsyna Irina Ivanovna, doctor of sociological sciences, Financial and Economic Institute, North-Eastern Federal University named after M.K. Ammosov, Yakutsk, Lenin Avenue 1, office 510, phone 89142977256, e-mail: ii.podoinitcyna@s-vfu.ru

Mikhailova Anna Viktorovna, Cand. econ. Sciences., Head. Department of Sociology and Personnel Management of the Financial and Economic Institute of the NEFU, 677000 Yakutsk, Lenin Avenue, 1, office. 507. Tel. +7 (4112) 49-67-99, e-mail: av.mikhailova@s-vfu.ru.

Baltakhinova Marina Egorovna, research associate, Research Institute of Health, North-Eastern Federal University named after M.K. Ammosov, 677014, Yakutsk, Kulakovsky Street 46, office 501, phone 89142710634, e-mail: bmeg@rambler.ru.

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

MEDICAL AND DEMOGRAPHIC SITUATION IN THE CENTRAL ECONOMIC ZONE OF THE SAKHA REPUBLIC (YAKUTIA)

ABSTRACT

The analysis of the medical and demographic situation has been conducted in the Central Economic Zone (CEZ) of the Sakha Republic (Yakutia). CEZ includes such districts, as Amginsky, Gorny, Kobyaysky, Megino-Kangalassky, Namsky, Tattinsky, Ust-Aldan, Khangalassky, Churapchinsky and Yakutsk - the capital of the republic. According to medical and geographical zoning, these municipalities are part of a group of central and beyond the Lena River districts. The following medical and demographic indicators: fertility, mortality, natural increase, infant mortality, nuptiality and divorce rate were analyzed. At the same time, the indicators of the natural movement of the population were considered depending on the attribution to the urban or rural population. The medical and demographic situation in the CEZ was revealed as generally favorable. Yakutsk and most of the districts are characterized by a relatively high fertility and low mortality, which offers a positive picture of natural increase. Infant mortality does not raise any particular concern. There are negative indicators of nuptiality in a number of districts.

Keywords: medical and demographic situation, fertility, mortality, causes of death, natural increase, natural movement of the population, infant mortality, nuptiality, divorce rate.

INTRODUCTION

Issues of public health and health development have always been among the priorities in the activities of state bodies of Yakutia. For example, in the social and development Strategy of the Sakha Republic until 2030, with defined main directions until 2050 there are sections directly or indirectly affecting the health care: demographic and family policy, innovative healthcare, physical education and sport, social protection of the population. The entire territory of the republic according to the section “Development of territorial planning” is divided into five economic zones: Arctic, Western, Central, Eastern and Southern.

There is a need to assess certain characteristics of public health of the population at this stage, including medical and demographic indicators, since indicator values of expected results are planned by 2030. In this article an analysis of the medical and demographic situation in the Central Economic Zone will be made.

Materials and methods of research. The medical and demographic situation in the Central Economic Zone (CEZ) of the Sakha Republic (Yakutia) for 2000-2016 was examined according to the official statistics of the Federal State Statistics Service (FSSS or Rosstat) and the Yakut territorial department of the FSSS [1, 2].

For the analysis of the medical and demographic indicators, we used the percentile (centile) method, according to this method, the districts with indicators up to the 10th percentile belonged to the territories with a low level of one or other indicator, from 10 to 25th percentile - with a level below average, from 75 to 90 - above average and over the 90th percentile - with a high level. Obviously,

Table 1

Total fertility rate

	Number of births per 1000 population											
	2000	2005	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Total population												
Sakha Republic	13,7	14,2	15,9	16,0	16,7	16,8	17,1	17,8	17,5	17,8	17,1	16,0
Amginsky	17,1	15,5	19,9	20,6	19,2	20,4	20,7	20,2	21,9	22,4	23,0	19,6
Gorny	12,7	19,0	21,4	19,0	18,9	19,5	24,8	22,8	26,1	26,7	24,4	19,6
Kobyaysky	17,1	13,8	15,0	15,8	17,8	15,5	19,4	18,1	20,4	19,9	20,6	15,5
M-Kangalassky	17,6	16,0	19,7	18,6	18,8	17,1	20,5	20,5	24,2	25,4	21,4	21,5
Namsky	17,1	15,5	20,0	19,6	19,7	19,2	19,0	22,9	22,9	23,8	19,3	17,3
Tattinsky	17,4	16,0	16,7	16,7	18,4	21,8	19,8	22,3	22,9	23,6	21,6	18,7
Ust-Aldansky	18,5	16,2	20,2	17,5	16,7	17,8	20,6	19,8	22,6	22,4	20,5	17,0
Khangalassky	12,7	13,3	15,5	16,6	15,6	16,7	16,9	17,0	18,9	19,9	17,5	15,2
Churpachinsky	20,3	16,7	20,4	17,7	20,4	20,6	22,6	23,1	24,0	22,7	21,0	17,7
Yakutsk	13,2	16,0	16,8	17,9	18,8	18,8	16,7	18,2	16,7	16,1	17,0	17,0
Urban population												
Sakha Republic	12,3	13,8	15,1	16,0	16,7	16,5	15,6	16,6	15,5	15,3	15,8	15,3
Kobyaysky	15,0	16,0	19,6	22,6	26,6	24,0	18,9	15,6	18,7	15,3	16,7	12,3
M-Kangalassky	11,0	13,6	13,1	13,1	17,2	12,3	20,5	27,5	28,6	30,4	17,3	22,2
Khangalassky	10,6	13,4	15,5	18,0	17,9	20,9	14,7	16,2	15,9	17,8	16,7	15,1
Yakutsk	13,5	16,3	17,2	19,0	19,6	19,1	16,8	18,7	16,8	16,1	17,2	17,2
Rural population												
Sakha Republic	16,1	15,0	17,5	16,0	16,7	17,4	19,9	19,9	21,1	22,4	19,4	17,3
Amginsky	17,1	15,5	19,9	20,6	19,2	20,4	20,7	20,2	21,9	22,4	23,0	19,6
Gorny	12,7	19,0	21,4	19,0	18,9	19,5	24,8	22,8	26,1	26,7	24,4	19,6
Kobyaysky	18,3	12,8	12,8	12,6	13,6	11,5	19,7	19,3	21,1	22,0	22,4	16,9
M-Kangalassky	18,3	16,3	20,5	19,3	19,0	17,7	27,8	19,6	23,7	24,7	21,9	21,4
Namsky	17,1	15,5	20,0	19,6	19,7	19,2	19,0	22,9	22,9	23,8	19,3	17,3
Tattinsky	17,4	16,0	16,7	16,7	18,4	21,8	19,8	22,3	22,9	23,6	21,6	18,7
Ust-Aldansky	18,5	16,2	20,2	17,5	16,7	17,8	20,6	19,8	22,6	22,4	20,5	17,0
Khangalassky	14,7	13,2	15,5	15,2	13,6	12,9	18,8	17,8	21,6	21,8	18,2	15,3
Churpachinsky	20,3	16,7	20,4	17,7	20,4	20,6	22,6	23,1	24,0	22,7	21,0	17,7
Yakutsk	5,2	10,6	10,7	0,6	5,2	13,7	16,6	9,2	15,6	17,5	12,8	13,0

Notes to the tables 1-7:

	low level for fertility, NI, nuptiality and high for mortality, IM, divorce rate
	level below average for fertility, NI, nuptiality and above average for mortality, IM, divorce rate
	level above average for fertility, NI, nuptiality and below average for mortality, IM, divorce rate
	high level for fertility, NI, nuptiality and low for mortality, IM, divorce rate

Table 2

Total mortality rate

	Number of deaths per 1000 population											
	2000	2005	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Total population												
Sakha Republic	9,7	10,2	9,6	10,0	9,8	9,8	9,4	9,3	8,7	8,6	8,5	8,4
Amginsky	7,7	9,9	10,1	8,5	11,0	9,3	8,1	9,2	8,2	9,1	8,3	7,8
Gorny	9,5	8,7	7,3	7,8	7,5	6,5	7,7	8,0	7,4	8,0	8,0	7,3
Kobyaysky	11,8	10,3	10,8	11,5	10,4	10,8	11,2	11,1	9,4	9,9	9,1	10,4
M-Kangalassky	9,1	9,3	10,5	10,5	9,2	9,5	9,1	10,0	9,4	9,4	9,1	9,0
Namsky	9,3	10,0	8,4	8,8	8,5	7,2	8,3	6,8	7,0	7,8	6,1	7,3
Tattinsky	9,5	9,1	10,1	9,6	9,8	8,4	9,7	10,0	8,6	7,8	8,7	7,8
Ust-Aldansky	9,0	9,0	9,9	9,5	8,1	8,9	7,7	9,7	9,4	8,4	8,0	9,4
Khangalassky	10,6	10,4	9,7	10,1	10,2	10,2	9,7	9,0	10,1	9,0	10,9	9,6
Churpachinsky	9,1	10,5	9,7	8,9	8,7	10,4	9,9	8,2	7,8	7,4	8,3	6,4
Yakutsk	9,9	9,5	8,1	8,4	8,1	8,4	7,3	7,4	7,1	7,0	7,0	6,7
Urban population												
Sakha Republic	9,8	10,1	9,4	10,0	9,9	9,9	9,2	9,2	8,4	8,1	8,3	8,1
Kobyaysky	18,1	15,3	14,9	16,7	16,6	17,6	22,2	15,1	14,0	13,6	10,0	9,7
M-Kangalassky	11,3	10,6	12,8	6,7	7,8	8,6	10,0	9,5	9,4	7,5	8,9	8,1
Khangalassky	10,9	11,5	10,1	10,3	11,9	12,1	11,3	9,2	10,0	8,7	10,1	11,1
Yakutsk	9,9	9,5	8,2	8,8	8,3	8,4	7,2	7,7	7,0	6,9	6,8	6,6
Rural population												
Sakha Republic	9,5	10,2	9,9	9,9	9,5	9,7	9,8	9,7	9,3	9,4	9,0	8,9
Amginsky	7,7	9,9	10,1	8,5	11,0	9,3	8,1	9,2	8,2	9,1	8,3	7,8
Gorny	9,5	8,7	7,3	7,8	7,5	6,5	7,7	8,0	7,4	8,0	8,0	7,3
Kobyaysky	8,4	7,8	8,9	8,9	7,4	7,7	6,1	9,3	7,3	8,3	8,6	10,6
M-Kangalassky	8,8	9,1	10,3	11,0	9,4	9,7	12,2	10,0	9,3	9,7	9,1	9,1
Namsky	9,3	10,0	8,4	8,8	8,5	7,2	8,3	6,8	7,0	7,8	6,1	7,3
Tattinsky	9,5	9,1	10,1	9,6	9,8	8,4	9,7	10,0	8,6	7,8	8,7	7,8
Ust-Aldansky	9,0	9,0	9,9	9,5	8,1	8,9	7,7	9,7	9,4	8,4	8,0	9,4
Khangalassky	10,3	9,3	9,4	9,9	8,7	8,4	8,3	8,8	10,1	9,3	11,7	8,3
Churpachinsky	9,1	10,5	9,7	8,9	8,7	10,4	9,9	8,2	7,8	7,4	8,3	6,4
Yakutsk	11,0	10,1	6,2	1,4	3,4	8,0	9,8	3,7	8,9	9,0	10,2	9,2

Table 3

Deaths by main classes of causes of death in 2016 (per 100 000 population)

	All causes	Class I (infectious disease)	Class II (neoplasms)	Class IX (CSD)	Class X (DRS)	Class XI (DDS)	Class XX (external causes)
Sakha Republic	837,8	15,0	134,6	368,7	26,8	38,1	135,4
Amginsky	784,6	18,0	89,8	293,5	12,0	41,9	203,6
Gorny	730,0	8,4	142,6	402,8	8,4	25,2	117,5
Kobyaysky	1035,2	0,0	118,5	450,4	15,8	23,7	237,1
M-Kangalassky	900,7	16,3	162,6	357,7	32,5	13,0	185,3
Namsky	732,0	16,4	78,1	263,2	32,9	12,3	156,3
Tattinsky	776,9	6,1	165,2	354,8	30,6	30,6	146,8
Ust-Aldansky	936,2	23,9	138,5	339,1	38,2	23,9	210,2
Khangalassky	961,1	21,6	213,2	333,8	46,4	27,8	148,3
Churpachinsky	635,2	9,6	76,4	296,1	14,3	28,7	157,6
Yakutsk	669,8	16,9	127,5	294,8	25,6	21,1	102,5

with the indicators being within the limits of the 25th to the 75th percentile, the districts belonged to a group with average values. After that, nine districts and Yakutsk were grouped for further analysis already within the Central Economic Zone.

Results and discussion.

Fertility. The total fertility rate in nine districts and Yakutsk in the CEZ is presented in Table 1. The situation on the fertility in this economic zone can generally be assessed as favorable, especially in the Amginsky, Gorny, Megino-Kangalassky, Namsky and Churapchinsky districts. Kobyaysky, Khangalassky districts and Yakutsk are apart, but mostly with the average values of this indicator.

The picture is also favorable for the urban population in the three districts and Yakutsk: a high fertility rate for a number of years is common for the Kobyaysky and Megino-Kangalassky districts, for Yakutsk - above average, for Khangalassky district - basically average values. All rural districts are included in the number of territories with high and above average fertility levels. The situation with the fertility of the rural population in Kobyaysky district and Yakutsk, especially in rural settlements of the capital of the republic, is unfavorable.

Mortality. The overall mortality rates of these territories are also characterized positively (Table 2). Only in the Kobyaysky district there are no low and below average mortality rates of all and urban population.

The picture for the rural population of these areas is more encouraging: mortality rates are more frequently low and lower than average mortality rates. The level above average was only once in the Khangalassky district (2015).

Data on the deceased by the main classes of causes of death in 2016 are presented in Table 3. For example, from infectious diseases most people die in the Ust-Aldansky and Khangalassky districts. No mortality from infectious diseases recorded in the Kobyaysky district. High mortality from neoplasms is observed in the Khangalassky district, low - in the Churapchinsky district, below average - in the Amginsky and Namsky districts. Low mortality from circulatory system diseases (CSD) is also common for the Amginsky and Namsky districts, below average for the Churapchinsky district and Yakutsk. Mortality from the diseases of the respiratory system (DRS) is relatively high in the Khangalssky and Ust-Aldansky districts, low - in the Gorny

Table 4

Total rate of natural increase (per 1000 population)

	2000	2005	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
	Total population											
Sakha Republic	4,0	4,0	6,3	6,0	6,9	7,0	7,7	8,5	8,8	9,2	8,6	7,6
Amginsky	9,4	5,6	9,9	12,0	8,3	11,1	12,6	11,0	13,7	13,3	14,7	11,8
Gorny	3,2	10,3	14,1	11,3	11,4	12,9	17,1	14,8	18,7	18,7	16,4	12,3
Kobyaysky	5,3	3,6	4,2	4,4	7,4	4,7	8,2	7,0	11,0	10,0	11,5	5,1
M-Kangalassky	8,5	6,7	9,1	8,0	9,5	7,6	11,4	10,5	14,8	16,0	12,3	12,5
Namsky	7,8	5,4	11,6	10,8	11,2	12,0	10,7	16,1	15,9	16,0	13,2	10,0
Tattinsky	7,9	6,9	6,6	7,1	8,6	13,4	10,1	12,3	14,3	15,8	12,9	10,9
Ust-Aldansky	9,5	7,2	10,4	8,0	8,6	8,9	12,9	10,1	13,2	14,0	12,5	7,6
Khangalassky	2,1	2,9	5,8	6,5	5,4	6,5	7,2	8,0	8,8	10,9	6,6	5,6
Churpachinsky	11,2	6,2	10,7	8,8	11,7	10,2	12,7	14,9	16,2	15,3	12,7	11,3
Yakutsk	3,3	6,5	8,7	9,6	10,8	10,4	9,4	10,8	9,6	9,1	10,0	10,3
	Urban population											
Sakha Republic	2,5	3,7	5,7	6,0	6,8	6,6	6,4	7,4	7,1	7,2	7,5	7,2
Kobyaysky	-3,1	0,7	4,7	5,9	10,0	6,4	-3,3	0,5	4,7	1,7	6,7	2,6
M-Kangalassky	-0,3	2,9	0,3	6,4	9,5	3,7	10,5	18,0	19,2	22,9	8,4	14,1
Khangalassky	-0,4	1,9	5,5	7,7	6,0	8,8	3,4	7,0	5,9	9,1	6,6	4,0
Yakutsk	3,6	6,9	9,0	10,2	11,3	10,7	9,6	11,0	9,8	9,2	10,4	10,6
	Rural population											
Sakha Republic	6,6	4,8	7,6	6,1	7,2	7,7	10,1	10,2	11,8	13,0	10,4	8,4
Amginsky	9,4	5,6	9,9	12,0	8,3	11,1	12,6	11,0	13,7	13,3	14,7	11,8
Gorny	3,2	10,3	14,1	11,3	11,4	12,9	17,1	14,8	18,7	18,7	16,4	12,3
Kobyaysky	9,9	5,0	4,0	3,7	6,2	3,9	13,6	10,0	13,8	13,7	13,7	6,3
M-Kangalassky	9,5	7,1	10,2	8,3	9,6	8,0	15,6	9,6	14,4	15,0	12,8	12,3
Namsky	7,8	5,4	11,6	10,8	11,2	12,0	10,7	16,1	15,9	16,0	13,2	10,0
Tattinsky	7,9	6,9	6,6	7,1	8,6	13,4	10,1	12,3	14,3	15,8	12,9	10,9
Ust-Aldansky	9,5	7,2	10,4	8,0	8,6	8,9	12,9	10,1	13,2	14,0	12,5	7,6
Khangalassky	4,4	3,8	6,1	5,3	4,9	4,5	10,5	9,0	11,5	12,5	6,5	7,0
Churpachinsky	11,2	6,2	10,7	8,8	11,7	10,2	12,7	14,9	16,2	15,3	12,7	11,3
Yakutsk	-5,8	0,5	4,4	-0,7	1,8	5,7	6,8	5,5	6,7	8,5	2,6	3,8

Table 5

Indicators of an infant mortality
(deaths under the age of 1 year per 1000 live births)

	2000	2005	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Sakha Republic	17,6	10,6	10,4	9,1	8,9	7,2	6,3	9,6	9,6	8,0	7,6	7,2
Amginsky	13,8	7,5	15,1	11,5	15,0	8,6	2,8	14,6	5,4	2,7	10,4	5,7
Gorny	6,8	9,1	4,1	4,1	4,6	9,0	10,3	7,5	6,6	9,8	6,7	0,0
Kobyaysky	8,0	15,3	19,5	0,0	21,1	9,4	11,5	12,6	7,6	7,8	23,0	5,1
M-Kangalassky	17,5	13,3	8,5	6,9	6,8	14,8	8,5	7,9	12,1	6,6	6,1	7,6
Namsky	8,5	8,9	11,8	6,8	6,8	13,6	9,1	7,9	11,2	0,0	4,3	6,9
Tattinsky	20,9	0,0	21,0	3,5	12,8	2,7	0,0	13,5	5,3	10,4	8,5	0,0
Ust-Aldansky	21,7	14,0	16,7	12,6	5,4	12,7	2,2	7,0	12,6	2,1	2,1	7,9
Khangalassky	15,9	8,3	9,3	1,8	7,3	8,8	10,6	8,9	9,7	9,3	11,9	6,1
Churpachinsky	21,3	3,0	5,8	8,1	7,3	9,6	7,0	8,4	2,0	2,1	2,3	2,3
Yakutsk	17,0	9,0	6,9	7,9	5,9	5,1	5,1	8,4	12,0	11,3	6,5	6,6

Table 6

IM rates by the main classes of causes of death in 2016(per 1000 live births)

	All causes	Class I (infectious disease)	Class X (DRS)	Class XVI (perinatal causes)	Class XVII (congenital anomalies)	Class XVIII (inaccurately marked states)	Class XX (external causes)
Sakha Republic	72,3	1,9	7,1	37,4	12,3	3,9	4,5
Amginsky	56,7	-	28,3	28,3	-	-	-
Gorny	0,0	-	-	-	-	-	-
Kobyaysky	51,0	-	-	51,0	-	-	-
M-Kangalassky	76,0	-	-	45,6	15,2	15,2	-
Namsky	69,1	23,0	-	46,1	-	-	-
Tattinsky	0,0	-	-	-	-	-	-
Ust-Aldansky	79,4	-	-	-	52,9	-	26,5
Khangalassky	61,1	-	-	61,1	-	-	-
Churpachinsky	23,0	-	-	23,0		-	-
Yakutsk	65,8	-	10,7	40,9	8,9		1,8

district, as well as in the Amginsky and Churapchinsky districts. On deaths from diseases of the digestive system (DDS) a more or less favorable picture is noted in the Megino-Kangalassky and Namsky districts. Low mortality from external causes is common in Yakutsk and below average in the Gorny district; however, in the Kobyaysky district mortality was above average.

Natural increase. The total rate of natural increase (NI) in the CEZ shows generally good situation for this indicator (Table 4). Only in the Kobyaysky and Khangalassky districts are the average values of the rate and only in the Khangalassky district in 2000, the only time the NI was registered below average.

According to the urban and rural population, the picture by the NI is generally favorable, with the exception of the Kobyaysky district (urban) and Yakutsk (rural). For example, the Kobyaysky district had years of low (2000) and below average NI (2011 and 2014) of urban population, and in Yakutsk - respectively in 2000, 2008, and in rural areas in 2005, 2009, 2012, 2014, 2016.

Infant mortality. For infant mortality (IM) in the CEZ, the verdict is mixed: more or less favorable indicators remain only in the Gorny and Churapchinsky districts, in five municipalities (Amginsky, Megino-Kangalassky, Namsky, Khangalassky districts and Yakutsk) the level of IM at least once exceeded the average level (Table 5, Figures 7 and 8). The average level in the Ust-Aldansky district was twice exceeded, but to be fair, it should be noted that there were years with a lower average level of IM (2009, 2011 and 2015). A high level of IM was once in Kobyaysky (2015) and Tattinsky (2007) districts.

The IM rates by the main classes of causes of death in 2016 indicate either high or medium values, or no mortality due to these reasons (Table 6). For example, in the Gorny and Tattinsky districts in 2016, IM was not registered.

Nuptiality and divorce rate. According to the number of marriages per 1000 population, the leading positions occupied by Yakutsk (high level in 2005-2013), Khangalassky (2011, 2013 and 2014), Megino-Kangalassky (2014) and Churapchinsky (2008) districts (Table 7). For a number of years in these areas, marriage rates were above average. Tattinsky district was noted by the average values of nuptiality during the whole period under review. As for the other districts, there was a low level

Table 7

Total nuptiality and divorce rates

	2000	2005	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Number of marriages per 100 population												
Sakha Republic	6,1	7,4	8,3	7,7	8,4	8,7	9,4	8,2	8,6	8,3	8,0	6,5
Amginsky	4,1	6,0	7,2	7,0	8,0	7,2	7,0	7,5	7,6	7,4	6,9	5,9
Gorny	3,9	6,1	6,9	6,1	5,8	7,7	7,9	5,4	7,3	9,2	9,0	5,3
Kobyaysky	7,1	5,2	5,5	6,6	6,1	6,8	6,6	6,5	5,9	8,1	6,2	5,6
M-Kangalassky	5,4	7,0	8,1	7,8	7,8	7,7	9,1	6,3	7,2	9,7	8,4	6,6
Namsky	4,9	5,1	7,1	6,5	6,3	6,7	7,4	5,8	6,5	6,6	5,8	4,7
Tattinsky	6,2	6,8	7,2	6,3	8,2	7,5	7,8	6,8	7,0	8,0	7,1	6,5
Ust-Aldansky	5,9	5,5	8,0	7,0	5,2	5,2	6,0	5,2	5,9	7,2	6,0	4,7
Khangalassky	5,8	7,2	6,7	6,5	7,1	8,9	9,6	8,5	10,7	10,1	8,2	7,2
Churpachinsky	6,4	7,3	7,9	8,4	8,7	9,0	8,7	7,1	7,1	7,8	7,5	5,9
Yakutsk	6,2	8,5	10,1	9,1	9,7	10,4	11,5	10,0	10,0	8,0	8,7	6,7
Number of divorces per 1000 population												
Sakha Republic	4,2	3,9	4,4	4,7	4,9	4,7	5,0	4,5	4,8	4,7	4,3	4,3
Amginsky	1,3	2,3	2,0	3,3	3,6	3,6	2,9	3,0	2,6	3,2	3,5	2,8
Gorny	1,7	2,1	2,0	3,1	2,2	3,5	3,6	2,7	3,5	3,4	3,4	3,1
Kobyaysky	3,6	2,8	2,2	2,9	2,6	2,6	3,8	3,6	3,2	3,6	2,3	4,0
M-Kangalassky	2,0	2,0	2,4	2,3	3,8	3,3	4,0	3,8	4,2	4,2	3,6	3,5
Namsky	2,2	2,7	2,6	2,9	3,2	2,9	2,8	3,3	3,4	2,7	3,4	3,7
Tattinsky	1,8	1,8	3,2	2,7	3,9	3,2	3,2	2,9	4,2	3,3	3,0	2,9
Ust-Aldansky	2,0	1,8	1,8	3,2	2,5	2,4	2,2	2,7	2,1	2,2	2,4	2,3
Khangalassky	2,2	2,8	2,7	3,4	3,8	3,7	4,7	3,9	4,7	4,2	4,2	4,6
Churpachinsky	2,4	2,5	2,4	3,2	4,3	3,7	3,4	2,8	4,1	3,7	2,9	3,2
Yakutsk	4,5	4,0	4,9	5,2	5,0	4,9	5,6	4,6	5,1	4,8	4,3	4,1

of nuptiality: more than others in Ust-Aldansky (five times), Gorny (three) and Namsky (two) districts.

"Leaders" by high divorce rate are Yakutsk (for seven years the divorce rate was above average) and Khangalassky (two) district. In other areas the picture is favorable, because, at least once, there were years with low or below average levels of divorce rates.

Conclusion. Thus, the medical and demographic situation in the CEZ is generally favorable. Most of the districts and Yakutsk are characterized by a relatively high fertility and low mortality, which leads to a positive picture of natural growth. Infant mortality does not cause much concern. There are negative indicators only by nuptiality in a number of districts.

REFERENCES

1. Estestvennoe dvizhenie naselenija Respubliki Sakha (Yakutia) za 2016 god [Natural movement of the population of the Republic Sakha (Yakutia) for 2016] Stat. Collection № 5/261, V. 2, Yakutsk, 2017, 92 p.
2. Statisticheskie ezhegodniki TO FSGS po Respublike Sakha (Yakutia) za 2000 g. i 2006 g. [Statistical yearbooks of TO FSSS for the Republic Sakha (Yakutia) for 2000 and 2006] Elektronnye resursy [Electronic resources].

The authors:

TIMOFEEV Leonid Fedorovich – Doctor of Medical Sciences, Professor, Chair of Public Health and Health Care, General Hygiene and Bioethics, Institute of Medicine, M.K. Ammosov North-Eastern Federal University, 677016 Yakutsk, ul. Oyunskogo, 27. E-mail: tlfnauka@mail.ru.

PETROVA Palmira Georgievna - MD, Professor, Head of the Department of Normal and Pathological Physiology of the Medical Institute of NEFU. 677016, Yakutsk, ul. Oyunskogo, 27, cab. 312 Russia. Tel.: + 7-914-272-74-71. E-mail: mira44@mail.ru.

BORISOVA Natalia Vladimirovna - MD, Professor, Department of Normal and Pathological Physiology, Medical Institute, NEFU. 677016, Yakutsk, ul. Oyunskogo, 27, Tel.: + 7-924-166-96-83. E-mail: Borinat@yandex.ru.

TURKEBAEVA Lena Kimovna - doctor of Medicine, Associate Professor, Department of Pharmacology and Pharmacy. Address: 677016 Yakutsk, ul. Oyunskogo, 27. Tel.: +7-964-415 70 17. E-mail: lk.turkebaeva@s-vfu.ru.

TIMOFEEV Artem Leonidovich– postgraduate student, Chair of Public Health and Health Care, General Hygiene and Bioethics. 677016 Yakutsk, ul. Oyunskogo, 27. E-mail: su-yuol@mail.ru.

A.A.Ivanova, A.F. Potapov, E.P. Kakorina

PREMATURE MORTALITY OF THE POPULATION OF THE REPUBLIC SAKHA (YAKUTIA) FROM EXTERNAL CAUSES

ABSTRACT

A retrospective analysis of the official statistics for the period 1990-2016 was conducted in order to study the level and structure of mortality in the Sakha Republic (Yakutia), It is established that the medical and demographic situation in the Sakha Republic (Yakutia) over the past 25 years is characterized by the high birth rate and high mortality in the young age groups from preventable causes. The mortality of the population by external causes, with a high degree of preventability, leads the causes of mortality in the age categories of children, adolescents, and working-age people. The children deceased from external causes in the age of 1 to 14 years account for 65% of all deaths in this age group, at the age of 15-17 years - 91%, and of working-age persons - 37%. Considering the structure of external causes of death, one pays attention to the high level of deaths by violence. According to 2016 data, the suicide mortality rate (22.7 per 100,000 population) was 34% higher than the average for Russia (14.9), and the murder rate (15.3 per 100,000 population) more than doubled the average one.

Another concerning problem is the death rate resulting from exposure to low natural temperature (cold trauma), which is hardly accounted for in the official statistics. Annually, cold trauma in Yakutia takes more lives than road traffic accidents. According to the 2015data, the cold trauma death rate was 15.1 per 100,000 population, whereas the death rate from road traffic accident was 7.8 per 100,000 population.

Keywords: premature mortality, external causes, Far North regions.

INTRODUCTION

Mortality rate is one of the main indicators characterizing the level of socio-economic development and well-being of territories, health status of the population, and accessibility and quality of medical care provided. Regions of the Russian Federation differ a lot in natural and climatic, economic, social, and environmental conditions; age composition and regional features of mortality rates of the population [1, 3, 5]. The study and identification of removable causes of death in certain regions can contribute to reducing mortality; serve as a basis for developing targeted regional programs to tackle the most significant factors that determine the mortality rate of the population from specific causes at the territorial level.

A comprehensive analysis of the health status of the population in the Sakha Republic (Yakutia), its dynamics in 1990-2016, as well as a study of trends and projections of the future of the republic revealed both some similarities between the processes occurring here and in other regions of Russia (high rates of mortality, morbidity, pathologies becoming chronic, disability, short life expectancy), and the patterns of pathology specific for the Far North, associated primarily with socio-economic and climatic-geographic conditions of living.

During the period 1990-2016, it is possible to single out 2 periods of the increase in the mortality rates in the republic: the first - 1990-1995 (the growth rate at 46%, from 6.7 to 9.8 ‰), the second - 2000-2005 (the growth rate at 5%, from 9.7 to 10.2 ‰). Later, after the period of stabilization of the indicator at the level of 9.3-9.8 ‰ in 2013, its decreased to 8.4 ‰ in 2016 (Fig. 1).

One of the distinctive features of the mortality in the Sakha Republic (Yakutia) is the high level of premature mortality in young age groups by external causes. The human losses due to injuries and poisonings dominate the structure of mortality in children and working-age people, accounting for 65%in the age group from 1 to 14 years, 91% at the age of 15-17, and 37% at the working age [2].

The purpose of this study was to examine the level, structure, and the dynamics of mortality of the population in Yakutia by external causes.

Materials and Methods. A retrospective analysis of the statistical data on mortality of the population in Yakutia in 1990-2016 was carried out. As the source of information, we used data from the Federal State Statistics Service (Rosstat), Territorial Office in the Sakha Republic (Yakutia); medical certificates of death (form 106/y-02); reports of forensic medical examinations; and death certificates of the Registry Office of the Sakha Republic (Yakutia). The study was carried out using statistical, analytical, mathematical methods, as well as methods of comparative analysis.

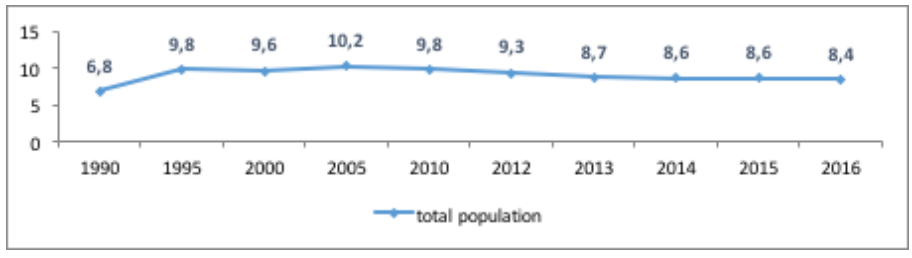


Fig.1. The dynamics of the mortality rate in the Sakha Republic (Yakutia) in 1990-2016.

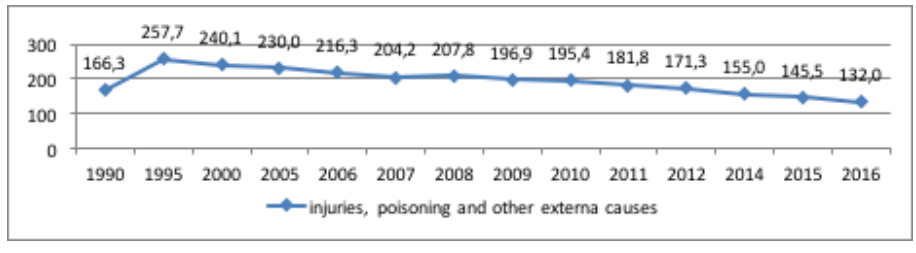


Fig.2. Dynamics of mortality by external causesin the Sakha Republic (Yakutia) in 1990-2016 (per 100,000 population)

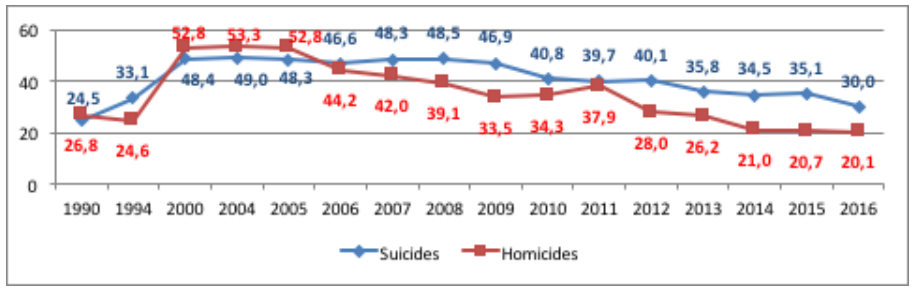


Fig.3. Dynamicsofviolentdeathsrates in the Sakha Republic (Yakutia) in 1990-2016 (per100,000 population)

Results and Discussion. In the dynamics of the main causes of mortality of the republic's population, external causes regularly ranked second following the circulatory system diseases in the period 1990-2014, then moving to the third position after neoplasms in 2015-2016. However, the statistics show that the level of human losses from external causes in the republic is remaining alarming. In 1990, the mortality rate from this class of causes was 166.3 cases per 100,000 population; in 1995 it reached a maximum value of 257.7; later it gradually reduced to 132.0 per 100,000 population in 2016 (by 48.8%), but this level is still quite high and exceeds by 21% the average Russian indicator (104.8 per 100,000 population) (Fig. 2).

According to the Federal State Statistics Service data, suicides predominate in the structure of external causes of death in Yakutia (22.7% in 2016), followed by homicides (15.3%) and accidental drownings (8.7%). In the dynamics of the violent deaths rates in 1990-2016, the period 2000-2005 was especially unfavorable, when the suicide and homicide indicators reached the highest values, almost doubling the 1990-1994indicators, and the suicide rate was more than 2.5 times higher than the extreme critical parameters determined by WHO experts (20 suicides per 100,000 population) (Fig. 3).

Almost throughout the period under study, the violent deaths rates in the republic were significantly higher than in the Russian Federation and the Far Eastern Federal District (Table 1).

Despite a significant improvement in the indicators in 2000-2016 (a reduction in deaths from suicides by 38.0%, homicides - by 62.0%), the situation is still alarming. According to 2016 data, the death rate from suicides (30.0 per 100,000 population) was 48% higher than the average for Russia (15.6) and 34% higher than for the Far Eastern Federal District (19.7). The death rate from homicides in Yakutia (20.1 per

Table 1

Suicide and homicide mortality in the Russian Federation, Far Eastern Federal District and the Sakha Republic (Yakutia) In 2000-2016 (per 100,000 population)

	2000	2005	2006	2007	2008	2009	2010	2011	2012	2015	2016
Suicide mortality											
Russian Federation	38,8	32,2	30,1	29,1	27,1	26,5	23,4	21,8	20,8	17,5	15,6
Far Eastern Federal District	49,9	42,7	40,2	40,4	38,2	35,4	34,0	31,8	30,8	24,9	19,7
Sakha Republic (Yakutia)	48,4	48,3	46,6	48,3	48,5	46,9	40,8	39,7	40,1	35,1	30,0
Homicide mortality											
Russian Federation	28,0	24,9	20,2	17,9	16,7	15,1	13,3	11,7	10,8	8,0	7,0
Far Eastern Federal District	45,2	44,0	35,9	33,4	31,5	28,4	25,6	23,6	21,7	16,2	14,4
Sakha Republic (Yakutia)	52,8	52,8	44,2	42,0	39,1	33,5	34,3	27,9	28,0	20,7	20,1

100,000 population) is almost 3 times higher than the average for Russia (7.0) and 28% higher than in the Far Eastern Federal District (21.7). It should also be noted that the rate of decrease in the mortality rate of the population in Yakutia from suicides from 2000 to 2016 was much lower than in the compared territories: 39.0% against 60.0% in the Russian Federation and the Far Eastern Federal District.

The suicide rates exceed those of the Russian Federation and the Far Eastern Federal District in all main age groups (Table 2).

The presented data demonstrates pronounced disorders in psycho-emotional health of the population, which is an objective reflection of the social unhappiness in the society.

The link between the prevalence of alcoholism in a population and the rate of violent deaths is widely recognized. Alcohol is present in the blood of every second suicide, in 2 out of 3 murdered and in 3 of 4 murderers [4]. According to the data from the Ministry of Internal Affairs of Yakutia, 90% of homicides and 42% of suicides in the region are committed in the state of alcoholic intoxication.

As for the child mortality in the age of 0 to 17 years, in general, most regions of the Far Eastern Federal District face a bad situation, with the indicators that significantly exceed the average for the Russian Federation. By the child mortality rate in the regions of the Far Eastern Federal District, Yakutia ranks fourth (in ascending order) after Sakhalin, Magadan and Amur Oblasts. For both sexes, the mortality rate in Yakutian children aged 0-17 years in 2014 was 108.6 per 100,000of the population of the corresponding age and 20.5% higher than in the Russian Federation (86.0), with the mortality rate among boys being 24% higher than in general across Russia (139.0; RF -105.2).

Among the causes of death in children aged 0 to 17 years, injuries and poisoning lead steadily, with the death rate of boys being 2.1 times higher than that of girls. Accidents rank first in the structure of the causes of death in children from 1 to 14 years (65%) and at the age of 15-17 years (91%).

The mortality of boys in Yakutia by external causes (48.4 per 100,000 population) is 44% higher than in Russia (26.9) and 20% higher than in the Far Eastern Federal District (38.7). The death rate of girls (20.0 per 100,000 population) is higher by 23.5 and 1.5%, respectively (15.3 and 19.7 per 100,000 population). A particularly concerning issue is an extremely high mortality rate in children and adolescents by suicide, whose indicator (9.9 per 100,000 of the population of the corresponding age) is 3 times higher than the average Russian

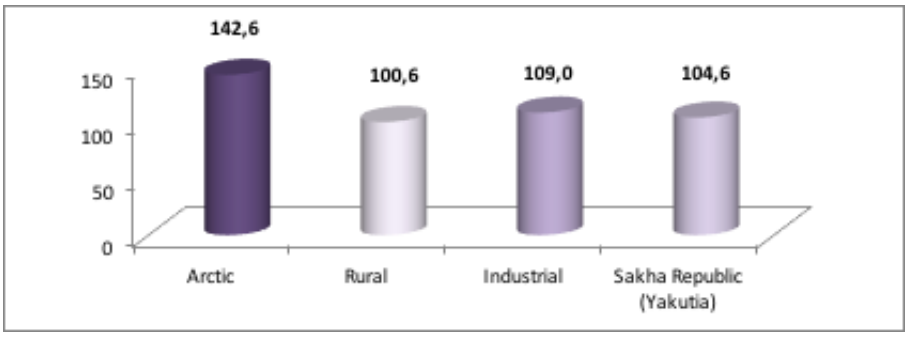


Fig. 4. Children mortality rate in the age 0-17 in different regions of the Sakha Republic (Yakutia) (per 100,000 population of the corresponding age)

Table 2

Suicide mortality in the population by main age groups in the Russian Federation, Far Eastern Federal District and the Sakha Republic (Yakutia) (number of deaths per 100,000 population of the corresponding age

Subjects of the Russian Federation	0-17 years of age	Working age	Over working age
Russian Federation	2.4	26.1	20.6
FEFD	5.5	40.4	25.4
SR(Ya)	9.9	54.4	31.4

Table 3

The number of deaths resulting from road traffic accidents and exposure to low natural temperatures in 2011-2015

Cause of death	2011		2012		2013		2014		2015	
	abs. numb	per 100,000 populat	abs. numb	per 100,000 populat	abs. numb	per 100,000 populat	abs. numb	per 100,000 populat	abs. numb	per 100,000 populat
Road traffic accidents	157	16.4	134	14.0	156	16.3	140	14.6	75	7.8
Exposure to low natural temperatures	195	20.4	164	17.6	150	15.7	158	16.5	145	15.1

one (2.4). In the structure of causes of death in adolescents, suicides account for 51.7%. The problem of adolescent self-aggression is more acute in the rural areas of the republic, with common unemployment, low material security of the families, household drunkenness, which often leads to an uncomfortable psychological climate in families. The child mortality rate has high values in the Arctic group of regions (142.5 per 100,000 of the population of the corresponding age), which is 29% higher than in the rural (100.6) and 24% than in the industrial regions of the republic (109.0) (Fig. 4).

Cold trauma is another pressing issue with the mortality in the regions of the Far North. Under natural and climatic conditions of Yakutia, where the cold season lasts for 7 months a year with the average winter temperature at 35-400C, the mortality by exposure to low natural temperatures (cold trauma) should attract serious attention. In the official statistics of the causes of death of the population, the cold trauma is taken into account among the 'other' causes, and therefore the real scale of the disaster, at least for Yakutia, remains hidden.

The analysis of the statistical data revealed that each year in Yakutia more people die of exposure to low natural temperatures than in road traffic accidents (Table 3).

According to Rosstat, in 2011-2015, the republic saw 662 people died in road traffic accidents, and by 18.5% more of those died due to exposure to low natural temperature (812).

Most of them (over 80%) were people of the working age, including 78% of men aged 16-60 years, and 22% of women aged 16-54 (Table 4).

In the context of the main age groups, the highest mortality rate by general hypothermia and frostbites is observed in the group over the working age (22.0 per 100,000 population) (Table 5).

Thus, the reserve for significant reduction in the preventable mortality of the population in the region depends on, first, by reduction of losses from external causes. It is necessary to take into account the main factors that determine the high level of preventable mortality of the population: low employment and low income of the population, living conditions that fail to meet modern sanitary and hygienic requirements, poor medical institutions infrastructure in the rural areas, lack of self-preserving behavior in people, all negatively affecting the quality of life. A high level of mortality by causes related to psycho-emotional health disorders is an objective reflection of the social and hygienic problems of the population, with this issue being particularly pressing in the Arctic and rural areas, characterized by a low level of socio-economic development.

Table 4

The number of deaths resulting from exposure to low natural temperatures in 2011-2015 by main age groups*

Age group	2011		2012		2013		2014		2015		total	ratio
	men	wom	men	wom	men	wom	men	wom	men	wom		
Under working age	4	1	0	1	2	0	2	0	0	0	10	1.3
working age	108	34	113	24	85	28	91	25	80	35	623	80.3
over working age	21	14	12	8	17	11	20	12	18	10	143	18.4
total	133	49	125	33	104	39	113	37	98	45	776	-
age not specified	13		5	1	6	1	6	2	2		36	-
TOTAL	146	49	130	34	110	40	119	39	100	45	812	-

* under working age – 0-15 years, working age – menof16-59 years, women of 16-54 лет, over working age – men of 60 years and older, women of 55 years and older.

Table 5

Mortality rate by exposure to low natural temperatures in main age groups (per100,000 population)

Age range	2011	2012	2013	2014	2015	total
Under working age	2.2	0.4	0.9	0.9	0	1.1
Working age	23.2	22.7	19.0	19.8	19.9	21.2
Over working age	28.5	15.6	21.1	23.1	19.4	22.0

Conclusion. A high mortality rate in young age groups has a negative impact on the medical and demographic situation in the region, including the life expectancy of the population, the indicators of which are lower than the average Russian data. A high mortality rate in the working age group results in intensive losses in the labor potential of the region and economic damage to the society. From this point of view, the problem discussed in the article requires a comprehensive study to determine the economic effectiveness of the social policy and healthcare development programs, as well to justify the amount of the investments needed.

REFERENCES

1. Bykovskaia T.Iu. Piktushanskaia T.E. Regional'nye osobennosti smertnosti muzhchin trudosposobnogo vozrasta v sovremennykh usloviiakh [The regional trends in the working-age men mortality under the modern conditions] Meditsina truda I promyshlennaia ekologiia [Occupational Health and Industrial Ecology] Moscow, 2011, № 2, P. 28-33.
2. Ivanova A.A. Regional'nye osobennosti prezhdevremennoi smertnosti naseleniia Respubliki Sakha (Iakutiia) i otsenka ekonomicheskogo ushcherba [The regional trends in premature mortality of the population in the Sakha Republic (Yakutia) and the assessment of the economic damage]: MD dissertation: 14.02.03 /Ivanova Al'bina Ammosovna; N.A.Semashko National Research Institute of Public Health. Moscow, 2016, 324 p.
3. Ivanova A.E. Semenova V.G. Antonova O.I. Smertnost' v regionakh Tsentral'nogo okruga Rossii [Mortality in the regions of the Central Federal District of Russia] Demograficheskoe razvitie Tsentral'nogo federal'nogo okruga [Demographic development of the Central Federal District] Ed. Rybakovskii L.L., Iur'eva E.L. Moscow: Ekon-Inform. 2008, P. 86–198.
4. Nemtsov A. V. Alkogol'nyi uron regionov Rossii [Alcohol-related damage in the Russian regions]. Moscow: Nalex, 2003, 136 p.
5. Rogovina A. G. Gendernaia I poselencheskaia differentsiatsiia smertnosti rossiian v 2005-2012 gg. [Gender and settlement differentiation of mortality in Russia in 2005-2012] Bjulleten'

NNII obshhestvennogo zdorov'ja RAMN [Journal of the Research Institute of Public Health, Russian Academy of Medical Sciences]. Moscow, 2014, Issue 1, P.258-261.

About the authors:

Albina Ammosovna IVANOVA, Doctor of Medical Sciences, Associate Professor, Department of Anesthesiology, Reanimation and Intensive Care, Institute of Medicine, Ammosov North-Eastern Federal University. Address: 677005, Sakha Republic (Yakutia), Yakutsk, ul. Sverdlova, 12, kv. 43. Phone: 8-924-762-2916. E-mail: iaa_60@mail.ru.

Aleksandr Filippovich POTAPOV, Doctor of Medical Sciences, Head, Department of Anesthesiology, Reanimation and Intensive Care, Institute of Medicine, AmmosovNorth-Eastern Federal University.

Ekaterina Petrovna KAKORINA – Doctor of Medical Sciences,Director, Department for Monitoring and Strategic Development of Healthcare, Ministry of Health of the RF, Professor, N.A. Semashko National Research Institute of Public Health, Moscow.

Postoev V.A., Menshikova L.I., Usynina A.A., Grjibovski A.M., Odland J.O.

THE ESTIMATION OF PREVALENCE AND STRUCTURE OF BIRTH DEFECTS IN ARKHANGELSK REGION IN 2012-2014: ARKHANGELSK COUNTY BIRTH REGISTRY DATA

ABSTRACT

Introduction

Birth defects (BD) are an important medical and social issue as they represent one of the most important causes of infant mortality and childhood disability. Constant epidemiological surveillance is a core issue in primary prevention of this pathology. The aim of this study was to assess prevalence of birth defects based on population birth registry data.

Materials and methods

The Arkhangelsk County Birth Registry was used in this retrospective cohort study. Database included information on all births at gestational age 22 and more weeks registered in Arkhangelsk County in 2012-2014. Data on variety of perinatal exposures, pregnancy and delivery complications as well as neonatal diseases were available for detail analysis.

Results

In 2012-2014, 1870 various birth defects in 1718 newborns were registered in Arkhangelsk County. The total prevalence of BD was 39,9 for 1000 newborns, and the prevalence after exclusion of co-called minor anomalies was 28,6 per 1000 newborns, that significantly higher than the Federal monitoring data for Arkhangelsk region. The most frequent groups of BD were congenital anomalies of circulatory system, congenital malformations and deformations of the musculoskeletal system as well as congenital anomalies of the urinary system.

When calculating the prevalence of BD that are subject of mandatory registration in Russia, it was found that their prevalence in the Arkhangelsk County was 6,4 per 1000 newborns in 2012-2014.

Conclusion

The total prevalence of birth defects, as assessed by the Arkhangelsk County birth registry, was higher than reported by the Federal monitoring. It can be assumed that this population-based tool allows to estimate the total prevalence of congenital anomalies more completely compared to the current Federal monitoring.

Keywords: birth defects, prevalence, surveillance, population-based medical birth registry.

INTRODUCTION

Congenital malformations (CM) are the direct cause of a significant number of infant deaths, they can lead to disability and can decrease quality of life [19]. In 2015, CM were diagnosed in 130,451 children of the first year of life, they became the cause of disability in 93,788 children. Moreover, it has been reported that CM had been directly connected with 2707 cases of infant deaths in the Russian Federation (RF) in 2015 [6].

According to World Health Organization (WHO) General Assembly's resolution, one of the main action for CM prevention is establishing of an effective national and international surveillance system. At the same time, adequate monitoring of CM should provide an opportunity to determine temporal trends in the prevalence of CM, to identify clusters of CM, to allow en evaluation of both population prenatal screening and preventive programs, and to provide sufficient data for any epidemiological studies of their risk factors [19].

International monitoring systems as a tool for systematic epidemiological surveillance of CM exist in the world from the middle of the last century. The most famous are the International Clearinghouse for Birth Defects Surveillance and Research (ICBDMS), that collects and organizes data from more than 30 regional registers from America, Asia and Europe, and report the prevalence of the most severe and easily visualized 39 forms of CM [12], and the European Registry Network for Epidemiological Surveillance for congenital anomalies (EUROCAT). The later covers almost a third of newborns in the European Union and collects data on more than 80 forms of CM [11].

Definitions of the terms used in the world practice are following: birth defects and congenital anomalies are identical terms and they represent structural and functional developmental abnormalities that present at birth [19]. According to EUROCAT guidelines minor anomalies are a diverse group of isolated anomalies with «insignificant structural, functional or cosmetic effects». They are not considered by EUROCAT when calculating the prevalence of CM [9].

The existing system of monitoring

of the CM in the RF differs from the international registers by the number of anomalies considered and age limits for reporting defects. Twenty-one forms of CM as well as multiple CM are mandatory for reporting, and data collection is organized by medical organizations at regional level [2]. In every case of newborn with CM, information on maternal age, address and parity, as well as sex and birth weight of the child are collected. The total prevalence of all forms of CM is also a subject of surveillance, however, the absence of unified criteria for registration leads to high variation of this indicator between regions of the RF. Thus, the total prevalence of CM in Russia varied from 9.8 per 1000 births in the Stavropol County to 75.4 per 1000 births in Severnaja Osetia-Alania in 2012, with an average All-Russian prevalence of 24.9 [2].

Incomplete registration of cases, the lack of individual data on prenatal risk factors, as well as limited opportunities for temporal analysis requires some changes in the existing monitoring system, which would allow to identify the factors that affect BD occurrence.

Population-based medical birth registries provide possibility for epidemiological surveillance of CM and investigation of their risk factors and allow data collection on both adverse perinatal outcomes and fetal exposures during intrauterine development [13; 14]. An implementation of prospective data collection on CM with medical birth registers reduces the likelihood of selection and information biases [4, 5].

The aim of this study was to investigate prevalence of CM using data of the Arkhangelsk County Birth Registry (ACBR) in 2012-2014 with an assessment of the total prevalence of CM at birth, a proportional distribution of different groups of CM, and birth prevalence of nosological forms that are mandatory for reporting in the RF.

Maternal and methods

The ACBR includes data on all pregnancy outcomes with gestation age of 22 weeks or more. It was implemented in 2012 by the Arkhangelsk Medical Analytic Center with the support of the Northern State Medical University (Arkhangelsk), Norwegian Institute of Public Health (Oslo) and the Arctic University of Norway (Tromsø). The registry contains information about the parents (age, place of residence and occupation); maternal health and lifestyle (smoking before and during pregnancy, signs of alcohol abuse, use of medication during pregnancy, chronic diseases before pregnancy); previous pregnancies and their outcomes, complications of current pregnancy; results of prenatal screening. In addition, the ACBR contains information on deliveries itself, their complications and outcomes. Data on newborns includes status at birth (live or stillborn), Apgar score, anthropometric data, as well as the pathology diagnosed during first days of life, including CM. The ACBR is regulated by the Order of the Ministry of Health care of Arkhangelsk County. The database of the registry is created by using registration forms which are filled in by employees of obstetric departments extracting data from primary medical records [5].

We conducted a retrospective cohort study [7] using data of the ACBR for 2012-2014. It is impossible to include all cases of early spontaneous pregnancy terminations in the analysis and several authors recommend using prevalence at a specified point of time (for example, at birth) as a valid measure of CM's occurrence [15]. Thus, we calculated the prevalence of CM at birth.

Data on 43327 births and 43446 births (livebirth and stillborn) were registered in the ACBR between 01.01.2012 and 21.12.2014. There were 365 cases with missed or incorrect information on the presence or absence of CM and 76 cases had no information on the status at birth. The analysis of CM's prevalence was carried out with a stratification by blocks of anomalies according to the International Classification of Diseases, the 10th revision (ICD-10). The prevalence of defects, which are mandatory for reporting in the RF was also calculated. The newborns with more than one CM diagnosis were included in the analysis only as newborns with multiple defects as their diagnoses were not coded as Q89.7 ("multiple congenital malformations, not elsewhere classified"). These newborns were not included for any specific defects they had. However, all diagnosed malformations in the newborn were used for analysis stratified by group of defects. In addition, the prevalence of CM was recalculated after exclusion of minor anomalies according EUROCAT recommendations [10]. The statistical analysis was done using SPSS 23.0 software package. All rates are presented per 1000 births (livebirth and stillborn) with 95% confidence intervals (CI), calculated by Wild's method [1].

Results and discussion

43,446 live births and stillborn were recorded in the ACBR in 2012-2014. There were 1,718 newborns with 1870 different forms of CM among them. Thus, the prevalence of CM at birth was 39.9 per 1000 births (95% CI = 39.0-40.9). Fourteen (0.8%) were stillborn and 11 (0.6%) died during the first 168 hours of life out of those with CM. The most prevalent groups of defects were the malformations of the kidney and the urinary tract, malformations of the nervous system, the genital tract malformations, malformations of the circulatory system, as well as defects of the musculoskeletal system (Table 1). After excluding minor anomalies according to EUROCAT guidelines [most of them were minor anomalies of the circulatory system (n = 260), the musculoskeletal system (n = 147) and the nervous system (n = 137)] the total prevalence decreased to 28.9 per 1000 births (95% CI = 28.1-29.7). The most prevalent minor anomalies were following: a patient or persistent foramen ovale (Q 21.1), a single cerebral cyst (Q 04.6), congenital metatarsus (primus) varus (Q 66.2). The total prevalence of CM, that are mandatory for registration in the RF was 6.4 per 1000 births (n = 274). Among this group of CM, the most prevalent were hypospadias, clefts lips and/or palate and multiple CMs (Table 2).

Our assessment of CM's prevalence in Arkhangelsk County is the second attempt to apply the medical birth registry for investigation of CM epidemiology. Similar analysis was carried out earlier in Murmansk County [17]. Our data on the total prevalence of CMs were significantly higher in comparison with results of the Federal monitoring for Arkhangelsk County in 2006-2012. (10.1 per 1000 births) [2]. On the one hand, it can be explained by more complete registration of perinatal diagnoses made by the birth registry. On the other hand, we cannot exclude possible overdiagnosis of CM in the early neonatal period.

Data on the total prevalence are similar with international estimates. According to the EUROCAT, the prevalence of CM below 20.0 cases per 1000 births may indicate incomplete detection or poor registration of CM [15]. The prevalence of CM in Arkhangelsk County, calculated after the exclusion of minor anomalies, was higher than EUROCAT data in 2012-2014 (28.9 / 1000 vs. 2 5.8 / 1000). However, the later included pregnancy terminations of about 20% [10], which were not considered in our analysis. In the term of CM structure according to ICD-10 blocks, our data are comparable with the European ones, apart from the significantly higher prevalence of genital defects (4.3 / 1000 vs 2.2 / 1000), malformations of the urinary system (6.3 / 1000 vs. 3, 4/1000),

Table 1

Prevalence of congenital malformations at birth in 2012-2014: data of the Arkhangelsk County Birth Registry (per 1000 births)

Group of congenital malformations according to ICD-10	Total prevalence		Prevalence excluding minor anomalies	
	N	Prevalence (95%CI)	N	Prevalence (95%CI)
Congenital malformations of the nervous system	217	5,0 (4,4-5,7)	80	1,9 (1,5-2,3)
Congenital malformations of eye, ear, face and neck	32	0,7 (0,5-1,0)	24	0,6 (0,4-0,8)
Congenital malformations of the circulatory system	544	12,6 (11,6-13,6)	284	6,6 (5,9-7,4)
Congenital malformations of the respiratory system	24	0,6 (0,4-0.8)	14	0,3 (0,2-0,5)
Cleft lip and cleft palate	70	1,6 (1,3-2,0)	70	1,6 (1,3-2,0)
Other congenital malformations of the digestive system	76	1,7 (1,4-2,1)	57	1,3 (1,0-1,7)
Congenital malformations of genital organs	195	4,5 (3,9-5,2)	184	4,3 (3,6-4,9)
Congenital malformations of the urinary system	277	6,4 (5,7-7,3)	270	6,3 (5,6-7,1)
Congenital malformations and deformations of the musculoskeletal system	306	7,1 (6,3-7,9)	159	3,7 (3,1-4,3)
Other congenital malformations, excluding multiple	79	1,8 (1,4-2,3)	51	1,2 (0,9-1,5)
Chromosomal abnormalities, not elsewhere classified	50	1,2 (0,9-1,5)	50	1,2 (0,9-1,5)

Table 2

Prevalence of congenital anomalies that are mandatory for reporting in the Russian Federation in 2012-2014 (per 1000 birth)

Form of anomaly	N	Prevalence, per 1000 birth (95% CI)
Anencephaly	–	-
Spina bifida	18	0,41 (0,31-0,51)
Encephalocele	1	0,02 (0,00-0,04)
Congenital hydrocephalus	29	0,67 (0,55-0,79)
Anophthalmos, microophthalmos	-	-
Anotia, microtia,	3	0,07 (0,03-0,11)
Transposition of large vessels	1	0,02 (0,00-0,04)
Hypoplastic left heart	4	0,09 (0,04-0,13)
Cleft palate	34	0,78 (0,65-0,91)
Cleft lip with or without cleft palate	28	0,64 (0,52-0,76)
Oesophageal atresia	8	0,18 (0,12-0,24)
Ano-rectal atresia	6	0,14 (0,08-0,20)
Hypospadias	64	1,47 (1,29-1,65)
Renal agenesis or disgenesis	-	-
Epispadias	2	0,05 (0,02-0,08)
Urine bladder exstrophy	-	-
Reducing limb malformations	12	0,28 (0,20-0,36)
Diaphragmatic hernia	2	0,05 (0,02-0,08)
Omphalocele	2	0,05 (0,02-0,08)
Gastroschisis	2	0,05 (0,02-0,08)
Down Syndrome	9	0,21 (0,14-0,28)
Multiple congenital anomalies	46	1,06 (0,90-1,22)
Total	273	6,40 (6,01-6,79)

and significantly lower prevalence of chromosomal abnormalities (1.2 / 1000 versus 4.2 / 1000) in Arkhangelsk County [10]. The described differences can be explained by the possible overdiagnosis of some forms, such as hypospadias and hydronephrosis at the neonatal stage and, conversely, insufficient prenatal and delayed postnatal diagnosis of chromosomal abnormalities or their incorrect classification by ICD-10 blocks. Compared with the study conducted in Monchegorsk (Murmansk region) [18], we can mention more complete detection of cardiovascular defects in the Arkhangelsk County; a likely reason for this is an improvement in ultrasound diagnostics over time (Monchegorsk study is dated 2006 - 2011).

A comparison of our results with other available data from population-based birth registries, shows that the total prevalence of CM in 2011 varied from 52.8 per 1,000 births in Finland to 27.4 per 1000 births and 22.2 per 1000 births in Norway and Sweden, respectively [10, 12, 13]. These differences can be explained by the different time limit for CM registration. For example, it is of 1 year in Finland, while only diagnoses made during the stay of newborns in maternity hospitals are included in the registries in Sweden and Norway [14].

A significant proportion of minor anomalies in the proportional distribution of CM (33.5%) must be emphasized, that is comparable with the results obtained in Monchegorsk. In this study, minor anomalies the cardiovascular system (patient or persistent foramen ovale, additional chords of left ventricular, hypoplasia of umbilical artery) accounted for more than 40% in the structure of all minor anomalies. High frequency of minor heart and vascular anomalies in Arkhangelsk County was demonstrated earlier [3], that, in our opinion, can be associated with high quality of diagnostics, sonographic in particular. The prevalence of malformations which are mandatory for registration in the RF was lower than available data from the Federal monitoring for 2012 (6.40 per 1000 births, compared to 7.07, respectively) [2]. However, statistical comparison of these indicators is impossible due to absence of data on the absolute number of newborns with CM, recorded by the Federal monitoring. Despite the differences in the prevalence of each nosology, the frequency of most forms of CM corresponds with all-Russian data. It was established that the prevalence of such forms of CM as congenital hydrocephalus, cleft palate and hypospadias in Arkhangelsk region is higher than in the RF, however, the prevalence of Down syndrome in Arkhangelsk region was significantly lower than Federal monitoring data.

Use of population-based medical birth registry is one of the method for CM surveillance. Implementation of methodology like in the international registries with the registration of the all CM provides an opportunity for international comparisons. The main advantage of such approach is the possibility of individual link between

exposure and outcome for each child, while the researchers always know exact denominator for the calculation of intensive indicators. As Demikova et al have already reported, inaccuracy in the denominator assessment (or the total number of births in some of regions) is one of the main causes of artificial variation of prevalence in territories of the RF [2].

99.6% of the total number of births in Arkhangelsk County in the study period registered in the ACBR [5], that minimizes the probability of a selection biases. At the same time there are some limitations that can affect the prevalence rates in our study. The main possible limitations of our study pertain to incomplete data on CM and early limit of diagnosing: only diagnoses made in the maternity houses were considered, which could be a reason for underestimation. Both restrictions are likely to lead to an underestimation of the true prevalence rate.

Conclusion

The total prevalence of CM in Arkhangelsk region according to EUROCAT methodology was 28.6 per 1000 births. Cardiovascular anomalies were the most common group in the structure of CM, that is comparable with EUROCAT data and indicates a sufficient detection of CM at birth. The population-based birth registry allows to perform accurate estimation of the total prevalence of CM, especially the prevalence of CM that are not mandatory for monitoring.

REFERENCES:

1. Grjibovski A. M. Doveritelnye intervaly dlja chastot i dolej [Confidence intervals for proportions]. Ekologiya cheloveka [Human Ecology]. Arhangel'sk, 2008;.5:57-60.
2. Demikova N.S. Lapina A.S. Podolnaja M.A. Kobrinskij B.A. Dinamika chastoty vrozhdennyh porokov razvitija v RF (po dannym federal'noj bazy monitoringa VPR za 2006—2012 gg.) [Temporal trends in birth defects in Russian Federation (data of Federal monitoring of birth defects in 2012-2014)]. Rossijskij vestnik perinatologii i pediatrii [Russian bulliten of perinatilogy and pediatry]. Moscow, 2015; 2:72-77.
3. Menshikova L.I. Makarova V.I. Surova O.V. Malye anomaliii razvitija serdca v geneze kardiovaskuljarnoj patologii u detej [Minor anomalies of heart in the development of cardiovascular pathoilogy in children]. Rossijskij vestnik perinatologii i pediatrii [Russian bulliten of perinatology and pediatry]. Moscow, 2001; 2(4): 24-26
4. Postoev V.A. Grjibovskij A.M. Odland J.O. Populjacionnye medicinskie registry rodov kak instrument monitoringa rasprostranennosti vrozhdennyh porokov razvitija i izuchenija ih faktorov riska [Population-based medical birth registries as a tool for birth defects survellence and investigation of their risk factors]. Ekologiya cheloveka [Human Ecology]. Arhangel'sk, 2017;1: 52-62.
5. Usynina A.A. Odland J.O. Pylaeva Zh.A. Pastbina I.M. Grjibovskij A.M. Registr rodov Arhangelskoj oblasti kak vazhnyj informacionnyj resurs dlja nauki i prakticheskogo zdravoohranenija [A birth registry of Arkhangelsk County as a source of information for science and health care system]. Ekologiya cheloveka [Human Ecology]. Arhangel'sk, 2017;2: 58-64.
6. Federalnaja sluzhba gosudarstvennoj statistiki. Dannye o smertnosti detej do 1 goda v 2015 godu po prichinam smerti. [Federal state statistical service. Data on infant mortality in 2015 stratified on cause of death]. URL: http://www.gks.ru/free_doc/2015/demo/t4_3.xls (access date: 25.06.2017)
7. Kholmatova K.K. Kharkova O.A. Grjibovskij A.M. Osobennosti primenenija kogortnyh issledovanij v medicine i obshhestvennom zdravoohranenii [Use of cohort studies in medicine and public health]. Ekologiyja cheloveka [Human Ecology]. Arhangel'sk, 2016; 4: 56-64.
8. Dolk H. EUROCAT: 25 years of European surveillance of congenital anomalies. Arch Dis Child Fetal Neonatal Ed. 2005; 90 (5): 355-358.
9. EUROCAT. Minor malformations for exclusion. EUROCAT guide 1.4, section 3.2. URL: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.2.pdf. (access date: 20.12.2017)
10. EUROCAT. Prevalence tables 2017. URL: http://www.eurocat-network.eu/AccessPrevalenceData/PrevalenceTables (access date: 28.04.2017).
11. EUROCAT. History and funding. URL: http://www.eurocat-network.eu/aboutus/whatiseurocat/whatiseurocat (access date: 20.01.2016).
12. International clearinghouse for birth defects surveillance and research. Annual report — Rome, 2012. URL: http://www.icbdsr.org/filebank/documents/ar2005/Report2012.pdf.
13. Källén B., SpringerLink (Online service). Epidemiology of Human Congenital Malformations. IX, 170 p. 32 illus. in color.
14. Langhoff-Roos J., Krebs L., Klungsoyr K., Bjarnadottir R.I., Kallen K., Tapper A.M., Jakobsson M., Bordahl P.E., Lindqvist P.G., Gottvall K., Colmorn L.B., Gissler M. The Nordic medical birth registers--a potential goldmine for clinical research. Acta Obstetrica Gynecologica Scandinavia. 2014; 93 (2): 132-137.
15. Loane M., Dolk H., Garne E., Greenlees R., Group E.W. Paper 3: EUROCAT data quality indicators for population-based registries of congenital anomalies. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011; 91 Suppl 1: S23-30.
16. Mason C.A., Kirby R.S., Sever L.E., Langlois P.H. Prevalence is the preferred measure of frequency of birth defects. Birth Defects Res A Clin Mol Teratol. 2005; 73 (10): 690-692.
17. Postoev V.A., Nieboer E., Grjibovski A.M., Odland J.O. Prevalence of birth defects in an Arctic Russian setting from 1973 to 2011: a register-based study. Reproductive Health. 2015; 12:3.
18. Postoev V.A., Talykova L.V., Vaktskjold A. Epidemiology of Cardiovascular Malformations among Newborns in Monchegorsk (North-West Russia): a Register-Based Study. Journal of Public Health Research. 2014; 3(2):270
19. Sixty Third World Health Assembly Report. Birth defects. Geneva: WHO, 2010.

The authors:

Postoev V.A., PhD, Lecturer, Department of public health, health care and social work, Head of the International School of Public Health, Federal state budgetary educational organization of high education "Northern state medical university", Arkhangelsk, Russia.

Address: 163001, Arkhangelsk, Troickij,51

Menshikova L.I., Doctor of Science, Professor, Head of the Department of public health, health care and social work, Federal state budgetary educational organization of high education "Northern state medical university", Arkhangelsk, Russia.

Address: 163001, Arkhangelsk, Troickij,51

Usynina A.A., PhD, Associated professor, Department of neonatology and perinatology, Federal state budgetary educational organization of high education "Northern state medical university".

Address: 163001, Arkhangelsk, Troickij,51

Grjibovski A.M., PhD, Research Director, Federal state budgetary educational organization of high education "Northern state medical university", Federal state autonomous educational organization of higher education "North-East federal university named after M.K. Ammosov", professor of the department of public health and heal care, general hygiene and bioethics.

Address: 163001, Arkhangelsk, Troickij,51

Odland J.O., PhD, Professor of public health, Department of community medicine, UiT-The Arctic University of Norway.

Address: N-9007, Tromso, UiT-The Arctic University of Norway.

K.A. Shapovalov, L.A. Shapovalova, M.V. Zaboeva,
T.A. Kalinina, O.E. Toropova

FEATURES OF DISABILITY FORMATION IN A CONTINGENT OF THE CITY CHILDREN'S POLYCLINIC OF THE REGIONAL CENTER OF THE SUBARCTIC TERRITORY

ABSTRACT

Formation of indicators of disability of children of a city children's polyclinic of the regional center of subarctic territory is dictated by necessity of an estimation of results of daily practical work of the pediatrist.

The analysis of the disability of children in 2011-2015 on the basis of the medical documentation of the Syktyvkar city children's polyclinics №3, Komi Republic, Russia was carried out.

In the structure of the causes of disability prevail: diseases of the nervous system - 34.74±3.55% ($p<0.001$); congenital anomalies, chromosomal abnormalities - 29.46±9.63% ($p<0.001$); diseases of the ear and its adnexa - 9.88±2.22% ($p <0.001$); diseases of the endocrine system, eating and metabolic disorders - 8.44±2.07% ($p<0.001$) and neoplasms - 7.21±1.93% ($p<0.001$). The share of these five classes of diseases is 84.69% of the total structure.

The frequency of determination of disability in children annually increases by +1.09 units with a growth rate of + 0.91% and a growth rate of 100.91%.

The incidence of diseases that caused disability in children was highest in the following classes: diseases of the nervous system - 42.06±4.29 ($p<0.001$); congenital anomalies, chromosomal abnormalities - 29.57±3.88 ($p<0.001$); diseases of the ear and its adnexa - 11.96±2.69 ($p<0.001$); diseases of the endocrine system, eating disorders and metabolic disorders - 10.21±2.51 ($p<0.001$) and neoplasms - 8.74±2.33 ($p<0.001$).

A stable annual growth rate of children with disabilities at 4.52% suggests that the process will continue in the future.

Complex treatment carried out within the framework of individual programs for rehabilitation / habilitation of disabled children allowed to completely restore health in 43 children (4.77%), improve the condition - 52 (5.77%), stabilize the pathological process - 90.24%. Weight gain occurred in 4 people (0.44%) due to the progression of the disease.

Keywords: indicators, children, disability, city children's polyclinic, regional center, subarctic territory.

INTRODUCTION

Regional patterns of the formation of children's disability determine not only the basic indicators of public health of the population, but also the prospects for the development of the state as a whole. So in industrial cities with a high man-caused load and rural settlements among the causes of general and primary children's disability 1st rank is occupied by congenital anomalies (Q00-Q99), 2nd place - diseases of the nervous system (G00-G99), 3rd place - disorders of the psyche and behavior (F00-F59), 4th place - diseases of the eye and adnexa (H00-H59). Has its own characteristics and disability in children of subarctic territories, which occupy a significant part of the Russian Federation, which until now remains poorly understood. [2, 3]

Formation of indicators of disability of children of the city children's polyclinic of the regional center of subarctic territory is dictated by the necessity of using a daily statistical tool that:

1) Discloses the role of children's disability indicators for the evaluation and analysis of the health status of the child population;

2) Promotes the adjustment of medical and social programs aimed at improving the health of the child population;

3) Evaluates the perspective of the end results of the pediatric health system;

4) Allows foreseeing both the main tendencies of morbidity and disability of the adult population, and the factors that determine them;

5) Stimulates the adoption of managerial decisions.

Material and methods

The aim of the work was to form the disability indicators of the children of the urban regional center of the subarctic territory, which should become the initial statistical tool for comparing and objectifying such phenomena.

A comprehensive analysis of the disability of 901 children (including primary disability of 112 children) in 2011-2015 was carried out. on the basis of the medical documentation of the SBAH of RK "Syktyvkar Children`s Clinic No 3": the register of directions for ITU; directions for medical and social expertise by the organization that provides medical and preventive care (form No. 0888 / y-06) and return coupons of the FCU «GBE ITU in the Komi Republic» of the Ministry of Labor of Russia Bureau of Medical and Social Expertise No. 4.

The studied contingent does not include children with mental disorders who are sent to a specialized IEC and undergo rehabilitation at the psycho-neurological dispensary, and thus do not appear in the institution's reports.

When working on the material, methodical approaches were used: system, complex, integration, functional, dynamic, process, normative, quantitative, administrative and situational. Methods of analysis included: historical, analytical and comparison. For the analysis, methods were used: grouping, absolute and relative values, average values, dynamic series, continuous and selective observations, detailing and generalization.

Formation of the standard of diseases that caused the emergence and definition of disability in children of the city polyclinic of the regional center of the subarctic territory includes the analysis of the indicators for five years: the determination of absolute numbers, the rank of each class of diseases, the proportion in the overall structure and the frequency factor for 10 000 children. For this purpose, the average annual values were calculated and the statistical significance of the differences was analyzed.

The study was conducted in the SBAH of RK "Syktyvkar Children`s Clinic No 3", which is the basic, specialized polyclinic of the city designed for 600 visits per shift. Currently, the polyclinic serves more than 16,000 children and adolescents. SBAH of RK "Syktyvkar Children`s Clinic No 3" assists: preventive, therapeutic and consultative, organizational, methodological, social and legal. It

Primary and general disability of children in the Children's Clinical Hospital of the Komy Republic «Syktyvkar Children's Polyclinic No.3» in 2011-2015 (in absolute numbers, ranking places,% and frequency per 10 000 children)

Type of disability	Primary							General						
	2011-2015				annually			2011-2015				annually		
	abs. num.	rank.	%	fr. coef.*	abs. num.	rank.	%	fr. coef.*	abs. num.	rank.	%	fr. coef.*	abs. num.	rank.	%	fr. coef.*
Total	112	I-XIII	100,00	15,05	22,40	I-XIII	100,00	15,05	901	I-XIII	100,00	121,08	180,20	I-XIII	100,00	121,08
Infectious and parasitic diseases	1	IX-XIII	0,89	0,13	0,20	IX-XIII	0,89±2,03	0,13±0,30	0		--	--	0	--	--	--
Neoplasms	12	III	10,71	1,61	2,40	III	10,71±6,68	1,61±1,01	65	V	7,21	8,74	13,00	V	7,21±1,93	8,74±2,33
Diseases of the blood and the immune system	4	VI-VII	3,58	0,54	0,80	VI-VII	3,58±4,02	0,54±0,61	14	VIII	1,55	1,88	2,80	VIII	1,55±0,92	1,88±1,12
Diseases of the endocrine system, eating disorders and metabolic disorders	11	IV	9,82	1,48	2,20	IV	9,82±6,43	1,48±0,97	76	IV	8,44	10,21	15,20	IV	8,44±2,07	10,21±2,51
Психические расстройства	--	--	--	--	--	--	--	--	--		--	--	--		--	--
Diseases of the nervous system	34	I	30,35	4,57	6,80	I	30,35±9,93	4,57±1,50	313	I	34,74	42,06	62,60	I	34,74±3,55	42,06±4,29
Diseases of the eye and adnexa	4	VI-VII	3,58	0,54	0,80	VI-VII	3,58±4,02	0,54±0,61	38	VII	4,22	5,11	7,60	VII	4,22±1,50	5,11±1,83
Diseases of the ear and mastoid process	1	IX-XIII	0,89	0,13	0,20	IX-XIII	0,89±2,03	0,13±0,30	89	III	9,88	11,96	17,80	III	9,88±2,22	11,96±2,69
Diseases of the circulatory system	1	IX-XIII	0,89	0,13	0,20	IX-XIII	0,89±2,03	0,13±0,30	13	IX-X	1,44	1,75	2,60	IX-X	1,44±0,89	1,75±1,08
Diseases of the respiratory system	--	--	--		--	--	--	--	9	XI	1,00	1,21	1,80	XI	1,00±0,74	1,21±0,88
Diseases of the digestive system	1	IX-XIII	0,89	0,13	0,20	IX-XIII	0,89±2,03	0,13±0,30	2	XIII	0,23	0,27	0,40	XIII	0,23±0,36	0,27±0,43
Diseases of the skin and subcutaneous tissue	--	--	--		--	--	--	--	0		--	--	0		--	--
Diseases of the musculoskeletal system and connective tissue	7	V	6,25	0,94	1,40	V	6,25±5,23	0,94±0,79	45	VI	4,99	6,05	9,00	VI	4,99±1,62	6,05±1,97
Diseases of the genitourinary system	1	IX-XIII	0,89	0,13	0,20	IX-XIII	0,89±2,03	0,13±0,30	4	XII	0,44	0,54	0,80	XII	0,44±0,49	0,54±0,60
Pregnancy, childbirth and the puerperium	--	--	--		--	--	--	--	0		--	--	0		--	--
Individual states of the perinatal period	--	--	--		--	--	--	--	0		--	--	0		--	--
Congenital anomalies, chromosomal abnormalities	33	II	29,46	4,43	6,60	II	29,46±9,85	4,43±1,48	220	II	24,42	29,57	44,00	II	24,42±3,20	29,57±3,88
Symptoms, signs, revealed during examination	--	--	--		--	--	--	--	0	--	--	--	0		--	--
Injuries, poisonings and other environmental influences	2	VIII	1,80	0,27	0,40	VIII	1,80±2,87	0,27±0,43	13	IX-X	1,44	1,57	2,60	IX-X	1,44±0,89	1,57±1,02

* Frequency coefficient.

includes a city rehabilitation center, an intermunicipal diagnostic center, a health center for children and adolescents. SBAH of RK "Syktyvkar Children`s Clinic No 3" is the holder of the high title WHO / UNICEF «Child-friendly polyclinic» since 2002. In 2004-2006, the polyclinic worked in the International Project «Mother and Child».

Results

The attached children's population of the SBAH of RK "Syktyvkar Children`s Clinic No 3" for 5 years increased by 2,107 people from 13,986 in 2011 to 16093 in 2015, amounting to 14,882.20 children per year. The number of disabled people in these years fluctuated annually from 166 in 2011 to 198 in 2015 (Table No. 1.)

Out of the number of patients in the SBAH of RK "Syktyvkar Children`s Clinic No 3" in 2011, a disability was determined by 166 children. The distribution of ranked classes of disease classes as reasons for determining disability in children was as follows. On the I rank place - diseases of the nervous system, II - congenital anomalies, chromosomal abnormalities; on III - diseases of the ear and mastoid process, IV - diseases of the endocrine system, eating disorders and metabolic disorders, V - diseases of the musculoskeletal system and connective tissue.

In the structure of the classes of diseases that caused the disability in children, prevailed: diseases of the nervous system - 31.33%; congenital anomalies, chromosomal abnormalities - 24.10%; diseases of the ear and mastoid process - 10,84%, diseases of the endocrine system, eating disorders and metabolic disorders - 9.04%, diseases of the musculoskeletal system and connective tissue - 8.43%. These five classes of diseases account for more than every four disabilities out of five (83.74%). The remaining 7 classes were a minority: neoplasms - 4,22%; eye diseases and its adnexa - 3.61%; diseases of the circulatory system and trauma,

poisoning and other environmental effects - by 2.41%; respiratory diseases - 1,81%; blood and immune system diseases - 1.20%; diseases of the genitourinary system - 0.60%.

The incidence of disability by classes of diseases that caused the disability of 10 thousand children in the service area was high: diseases of the nervous system - 37.18; congenital anomalies, chromosomal abnormalities - 28.60; diseases of the ear and mastoid process - 12,87, endocrine system diseases, eating disorders and metabolic disorders - 10,73, diseases of the musculoskeletal system and connective tissue - 10,01. The frequency of the remaining classes did not exceed: neoplasms - 5.01; eye diseases and its adnexa - 4.29; diseases of the circulatory system and trauma, poisoning and other environmental effects - by 2.86; respiratory diseases - 2,15; blood and immune system diseases - 1.43; diseases of the genitourinary system - 0.72.

The number of children with disabilities in 2012 reached 169. The absolute increase in disabled children in 2012 was +3 people with a growth rate of 1.81% and a growth rate of 101.81%.

If the sequence of distribution of ranking places of diseases that caused disability in children has not changed, in their structure the indicators have changed more significantly. There was an increase in the proportion of tumors - 2.88%; diseases of the nervous system - + 1.80%; blood diseases and immune system - + 0.58%; eye diseases and its adnexa - + 0.53%; congenital anomalies, chromosomal abnormalities - + 0.16%. The share of the remaining classes decreased from 1.96% (ear and mastoid disease) to 0.04% (trauma, poisoning and other environmental effects).

The incidence rate of disability in children in 2012 increased by +2.15 units with a growth rate of 1.81% and a growth rate of 101.81%.

The incidence of disabilities in children increased with neoplasms - 1.72 times; diseases of the blood and the immune system - by 1.50 times; eye diseases and its adnexa - 1.17 times; diseases of the nervous system - 1.08 times and congenital anomalies, chromosomal abnormalities - 1.03 times. When injuries, poisonings and other environmental influences remained without dynamics, in other classes it decreased from 1.51 with respiratory diseases to 1.07 times with endocrine system diseases, eating disorders and metabolic disorders.

The number of children with disabilities in 2013 increased by 10 people and amounted to 179. The absolute increase in disabled children in 2013 was +10 people with a growth rate of 5.92% and a growth rate of 105.92%.

There were no significant changes in the distribution of ranked diseases that caused the disability. Leading positions have been preserved: diseases of the nervous system (+9 people), congenital anomalies, chromosomal abnormalities; diseases of the endocrine system (+4), diseases of the ear and mastoid process (+2) and neoplasms (+2).

Structural changes have affected all classes of diseases as causes of disability. Further growth and, accordingly, an increase in the share in the overall structure occurred in classes: diseases of the nervous system - 36.30%; congenital anomalies, chromosomal abnormalities - 24.58%; diseases of the ear and mastoid process - 9.50%, neoplasms - 7.82%, eye diseases and adnexa - 4.47%. The share of these growing four classes of diseases in the overall structure was 82.67%. The proportion of other classes declined from 2.07% (diseases of the musculoskeletal system and connective tissue) to a mild 0.46% (endocrine, nutritional and metabolic disorders).

The incidence rate of disability in children in 2013 increased by +0.07 units with an increase rate of 0.06% and a growth rate of 100.06%.

The incidence of diseases that caused the disability was also insignificant, but nevertheless increased in classes: diseases of the nervous system and neoplasms - 1.10 times; diseases of the ear and mastoid process - 1.07 times and eye disease and its adnexa - 1.06 times. In other classes, this indicator decreased.

With the increase in the total number of children served by the contingent in 2014 by 739 people, the number of disabled children increased to 189.

The absolute increase in children with disabilities in 2014 was 10 people with a growth rate of 5.59% and a growth rate of 105.59%.

It should be noted that within three years a stable annual positive dynamics of the growth in the number of children with disabilities among the serviced contingent was formed in the number of 10 people.

Absolute increase occurred in the following classes of diseases that caused disability in children: congenital anomalies, chromosomal abnormalities; diseases of the endocrine system (+4); diseases of the nervous system (+3 people); diseases of the ear and mastoid process (+2); neoplasms (+1); blood disease and immune system (+1); disease of the endocrine system, eating disorders and metabolic disorders (+1); diseases of the digestive system (+1). In two classes, the absolute increase was negative: diseases of the musculoskeletal system and connective tissue (-2) and trauma, poisoning and other environmental influences (-1). Absolute indicators of diseases as causes of disability in children remained at the 2013 level in three classes: diseases of the circulatory system, respiratory diseases, diseases of the genitourinary system. This distribution of the absolute increase in disability was reflected in the ranking of the first five classes of diseases that caused the disability in children. They remained the same. In the second half of the list, some classes switched places, but no more than a plus-minus one position.

This increase in absolute indicators has made changes in the structure of disability. In this case, the growth in the specific gravity of individual classes did not range from + 0.12% (neoplasms and endocrine system diseases, eating disorders and metabolic disorders) to + 0.82% (congenital anomalies, chromosomal abnormalities, endocrine system diseases) . With negative dynamics, it decreased from -0.03% (respiratory diseases and genitourinary system diseases) to - 1.33% (diseases of the musculoskeletal system and connective tissue).

The frequency of disability determination in children in 2014 increased by +0.69 units with a growth rate of 0.57% and a growth rate of 100.57%.

The intensive indicator of the incidence of diseases that caused the disability of children in the case of growth in 2014 did not exceed + 1.04-1.43%, and at a decrease it reached -1.00-2.11%.

The final 2015 of the period under review was characterized by a continuing steady absolute growth in the number of children with disabilities. The absolute increase in disabled children in 2015 was +9 people with a growth rate of + 4.76% and a growth rate of 104.76%.

Classes of diseases that caused disability and gave an increase in indicators, included: diseases of the nervous system (+4 people); diseases of the endocrine system, eating disorders and metabolic disorders (+3); neoplasms (+2); blood disease and immune system (+1); diseases of the eye and its adnexa (+1); diseases of the ear and mastoid process (+1); diseases of the respiratory system (+1); injuries, poisoning and other environmental effects (+1). Just as in 2014, in only two classes, the absolute increase was negative: diseases of the musculoskeletal system and connective tissue (-4) and congenital anomalies,

chromosomal abnormalities; disease of the endocrine system (- 1). In this case, the class of diseases of the musculoskeletal system and connective tissue for two consecutive years gives a significant reduction from 9 to 3 patients, that is, 3 times.

In the general structure of diseases, as causes of disability, there have been minor changes, both in the direction of increasing and decreasing their shares. The indicators gave positive growth in classes: endocrine system diseases, eating disorders and metabolic disorders (+ 1.15%); neoplasms (0.65%); injuries, poisoning and other environmental influences (+ 0.48%); blood and immune system diseases (+ 0.43%); diseases of the nervous system (+ 0.38%); diseases of the eye and its adnexa (+ 0.32%) and diseases of the ear and mastoid process (+ 0.05%). The proportion of other classes decreased: diseases of the musculoskeletal system and connective tissue (-2.18%); congenital anomalies, chromosomal abnormalities; diseases of the endocrine system (-1.67%); diseases of the circulatory system (-0,05%); diseases of the digestive system (-0.02%) and diseases of the genitourinary system (-0.02%).

The coefficient of frequency of disability determination in children in 2015 increased by +1.43 units with a growth rate of + 1.18% and a growth rate of 101.18%.

The incidence of diseases, as the cause of disability of children in 2015 compared with 2011, has undergone significant changes. She grew 2.11 times with neoplasms; 1,74 - diseases of blood and immune system; , 3 - diseases of the eyes and its adnexa; 1,2 times - diseases of the nervous system; 1,04 - diseases of the endocrine system, eating disorders and metabolic disorders, and 1.02 - congenital anomalies, chromosomal abnormalities. The decrease in the frequency in the other classes was more significant. So, it decreased by 5.38 times with diseases of the musculoskeletal system and connective tissue; 2.3 - diseases of the circulatory system and injuries, poisonings and other environmental influences; 1,73 - diseases of the respiratory system; 1,16 - diseases of the genitourinary system and 1,04 - diseases of the ear and mastoid process.

Discussion

The weak point of the study is the total number of patients who were diagnosed with a disability - 901 children. This figure is not entirely objective, as it reflects the total number of observed disabled children in accordance with annual reports, including Form No. 19 (Order of Rosstat of December 25, 2014 No. 723). But at the same time she does not take into account that most of them are repeated invalids. To objectify the research (Table. No 1) shows the indicators of primary disability for the same years.

In the city polyclinic of the regional center of the subarctic territory 180 children with disabilities are rehabilitated annually. In 2014-2015 years their number is steadily growing. This is due to the increase in the contingent served, both at the expense of increasing the birth rate, and the migration of the population, including children. [4, 5] The absolute increase in disabled children annually makes up +8 people with a growth rate of + 4.52% and a growth rate of 104.52%.

At the first ranked place are diseases of the nervous system (62,60); second - congenital anomalies, chromosomal abnormalities (44,00); the third - diseases of the ear and its adnexa (17,80); the fourth - diseases of the endocrine system, eating disorders and metabolic disorders (15,20); the fifth - neoplasms - (13,00). On the sixth to thirteenth places: diseases of the musculoskeletal system and connective tissue (9.00); diseases of the eye and its adnexa (7.60); blood and immune system diseases (2.80); diseases of the circulatory system (2.60); trauma, poisoning and other environmental effects (2.60); respiratory diseases (1.80); diseases of the genitourinary system (0.80) and diseases of the digestive system (0.40).

In the structure of the causes of disability prevail: diseases of the nervous system - 34.74 ± 3.55% (p <0.001); congenital anomalies, chromosomal abnormalities - 29.46 ± 9.63% (p <0.001); diseases of the ear and its adnexa - 9.88 ± 2.22% (p <0.001); diseases of the endocrine system, eating disorders and metabolic disorders - 8.44 ± 2.07% (p <0.001) and neoplasms - 7.21 ± 1.93% (p <0.001). The share of these five classes of diseases is 84.69% of the total structure. The specific weight of the remaining classes of diseases that caused the disability in children was: diseases of the musculoskeletal system and connective tissue - 4.99 ± 1.62% (p <0.001); eye diseases and its adnexa - 4.22 ± 1.50% (p = 2.813); blood and immune system diseases - 1.55 ± 0.92% (p = 1.685); diseases of the circulatory system - 1.44 ± 0.89% (p = 1.617); injuries, poisoning and other environmental effects - 1.44 ± 0.89% (p = 1.617); respiratory diseases - 1,00 ± 0,74% (p = 1,351); diseases of the genitourinary system - 0,44% and diseases of the digestive system - 0,23%. In the last two classes, the differences in indicators were statistically insignificant. The frequency of determination of disability in children annually increases by +1.09 units with a growth rate of + 0.91% and a growth rate of 100.91%.

The incidence of disability in diseases that caused its occurrence in children was highest in the following classes: diseases of the nervous system - 42.06 ± 4.29 (p <0.001); congenital anomalies, chromosomal abnormalities - 29.57 ± 3.88 (p <0.001); diseases of the ear and its adnexa - 11.96 ± 2.69 (p <0.001); diseases of the endocrine system, eating disorders and metabolic disorders - 10.21 ± 2.51 (p <0.001) and neoplasms - 8.74 ± 2.33 (p <0.001). They significantly exceeded the frequency in the remaining classes: diseases of the musculoskeletal system and connective tissue - 6.05 ± 1.97 (p <0.001); diseases of the eye and its adnexa - 5.11 ± 1.83 (p = 2.792); blood and immune system diseases - 1.88 ± 1.12 (p = 1.679); diseases of the circulatory system - 1.75 ± 1.08 (p = 1.620); trauma, poisoning and other environmental effects - 1.57 ± 1.02 (p = 1.539); respiratory diseases - 1,21 ± 0,88 (p = 1,375); diseases of the genitourinary system - 0.54 and diseases of the digestive system - 0.27 per 10 000 children. In the last two classes, the differences in indicators were statistically insignificant.

As reasons for children to disability in the SB RAS «SDP # 3» for 5 years were not established: skin and subcutaneous tissue disorders; pregnancy, childbirth and the puerperium; individual conditions of the perinatal period; symptoms, signs, revealed during examination.

In solving the problems of preventing childhood disability, priority should be given to the development of fertility planning services, the improvement of antenatal and perinatal care, the preventive work with healthy but deviant children, the development of medical genetic services, and the introduction of screening programs for various pathologies [1].

Conclusions

The formed indicators of the disability of children of the city children's polyclinic of the regional center of the subarctic territory is a statistical tool for everyday use.

In the structure of the causes of disability prevail: diseases of the nervous system - 34.74 ± 3.55% (p <0.001); congenital anomalies, chromosomal abnormalities - 29.46 ± 9.63% (p <0.001); diseases of the ear and its adnexa - 9.88 ± 2.22% (p <0.001); diseases of the endocrine system, eating disorders and

metabolic disorders - 8.44 ± 2.07% (p <0.001) and neoplasms - 7.21 ± 1.93% (p <0.001). The share of these 5 classes of diseases is 84.69% of the total structure.

The frequency of determination of disability in children annually increases by +1.09 units with a growth rate of + 0.91% and a growth rate of 100.91%.

The incidence of diseases that caused disability in children was highest in the following classes: diseases of the nervous system - 42.06 ± 4.29 (p <0.001); congenital anomalies, chromosomal abnormalities - 29.57 ± 3.88 (p <0.001); diseases of the ear and its adnexa - 11.96 ± 2.69 (p <0.001); diseases of the endocrine system, eating disorders and metabolic disorders - 10.21 ± 2.51 (p <0.001) and neoplasms - 8.74 ± 2.33 (p <0.001).

A stable annual growth rate of children with disabilities at 4.52% suggests that the process will continue in the future.

Complex treatment carried out within the framework of individual programs for rehabilitation / habilitation of disabled children allowed to completely restore health in 43 children (4.77%), improve the condition - 52 (5.77%), stabilize the pathological process - 90.24%. Weight gain occurred in 4 people (0.44%) due to the progression of the disease.

The authors state that there are no sources of funding for this article.

The authors state that there are no conflicts of interest, which should be reported in connection with the publication of this article.

Acknowledgments

1. The authors express sincere love to their parents. The authors thank Pikkel MV, Trubina AM, Anisimova LK, Levitina TP, Kudryavtsev VA, Kucherenko VZ, Zhuravlyov SM, Zabin YuL, Novikov PE, Dobrodeeva LK, Udalova LS, Klepikova RA, Bannikova RV, Kalenyuk AF, Sevastyanov AN, Slutskiji SI, Knyazeva N .P., Karakozova NG, Petrova IV, Kaneva LN, Smirnova TV, Chernitsyna I.Yu., Katorkin VI, Arzubova IN, as well as all the anonymous reviewers for their support, useful advice and comments.

INTRODUCTION

The health of women and children is an important indicator of social development and reflects its socio-economic situation. The reduction in maternal and infant mortality rates is included in the main development goals identified by the United Nations [1]. In almost all countries with reliable information, premature birth rates are constantly increasing. This equally affects both rich and less affluent countries [2]. In 2012, Russia moved to the recommended World Health Organization criteria for childbirth, according to the Order of the Ministry of Health and Social Development of Russia №1687n dated December 27, 2011 «On medical birth criteria, the form of the birth certificate and the procedure for its issuance» (registered in the Ministry of Justice of the Russian Federation on March 15, 2012 № 23490) [3]. For the first time in the history of Russian medicine, the term of birth of 22 weeks of gestation and more is established; the body weight of the child at birth is 500 grams or more (or less than 500 grams for multiple births); the length of the body of the child at birth of 25 cm or more (in case the mass of the child's body at birth is unknown). Order of the Ministry of Health of the Russian Federation № 15-4-10 / 2-9480 of December 17, 2013 introduces a clinical protocol on management of early births [4]. In addition, the clinical protocol «Organization of medical evacuation with preterm birth» was developed and recommended for implementation from 21.09.2015. [5]. In each subject of the Russian Federation, monthly monitoring of the performance of these clinical protocols is carried out.

Objective: To analyze the frequency of premature births and very early premature births in the structure of all genera in the Republic of Sakha (Yakutia), to analyze perinatal mortality and its components.

Materials and methods of research. The analysis of the structure of births and perinatal mortality according to the official medical statistics of the State institution «Yakut Republican Medical Information and Analytical Center of the Ministry of Health of the Republic of Sakha (Yakutia)» for 2011-2016.

Results and discussion

According to the results of the analysis, it was shown that before the adoption of the «new live birth criteria», the share of preterm birth in the total delivery structure was 5.4% in 2011, in 2012 this figure rose to 6.9%. This increase of 1.5% is due to early premature births previously registered in the structure of late miscarriages in the period up to 28 weeks. In subsequent years, the proportion of preterm birth remains at the same level (2012 - 0.6%, 2013 - 0.5% 0, 2014 - 0.4%, 2015 -0.5% 2016 - 0.5%).

The frequency of preterm births in the RS (Y) in 2016 was 6.9% in the structure of all genera, early premature births of 0.5%, which is 5.8% and 0.4% higher than in the Russian Federation in 2016 (Table 1-5).

We analyzed the structure of genera in the fields of complex scientific research in the Republic of Sakha (Yakutia), from the group of Arctic district - Verkhoyansk and Eveni-Betantai, Central - Tattinsky and from the group of western district - Verkhnevilyui. In the Even-Bytantaisk district in 2011 there were only 6 births, and all of them are premature, in the following years the number of births is small, and all of them occurred on time. It should be noted that in the Verkhoyansk district the smallest premature birth is observed: in 2011 - 3 (2.02%) out of 148, in 2012 - 10 (0.62%) out of 161, in 2014 - 4 (2.56%) out of 156 in 2016 - 3 (2.6%) out of 115, which is much lower than the Russian indicators. During the entire period, very early premature births were not tolerated. In the Verkhne-Vilyui district in 2011, there were 14 premature births (3.7%) of 378 in 2012. As elsewhere, the increase was 16 (5%) of 338 cases and 1 case (0.26%) of very early premature births. In 2013 and 2014 the rate of early premature births is almost the same at 4% and 3.76%. In 2015 the proportion of premature births decreased 4 (1.6%) and 2 (0.8%) cases of very early premature birth occurred. In 2016 premature birth 4 (2%) and very early 1 (0.5%).

After the introduction of a clinical protocol on the routing of pregnant women with threatening premature births in 2016, 117 pregnant women with threatening premature births were transported in the Perinatal Center of RB № 1 RS (Y). Of the medical organizations of the second level - 58 women, which amounted to 49.57%, of the medical organizations of the first level - 59 women, which amounted to 50.42%. Due to timely routing, the proportion of premature births taken in the Perinatal Center RB № 1 RS (Y) increases annually. The proportion of premature births taken in the Perinatal Center of RB № 1-NCM was: in 2012, - 28.5%, in 2014. - 41.5%, in 2015. - 47%, in 2016. - 49.3% (Table 6).

Analyzing the structure of early premature births, we can note the following dynamics: in 2016 the proportion of early premature births in the perinatal center RB1 RS (Y) increased significantly: in 2012 - 23%, in 2013 - 23.7%, 2014 - 47, 9%,

Table 1

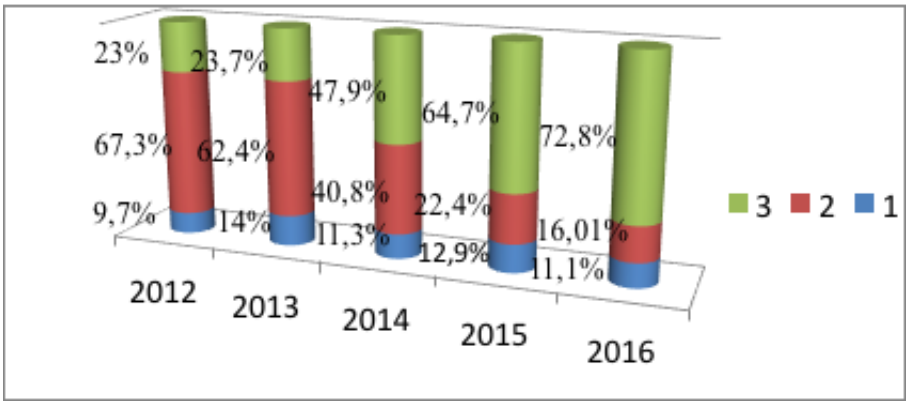
Premature births in the structure of all births in the RS (Ya) districts and the RF for 2011-2016, abs. number (%)

Births	RS (Ya)						RF
	2011	2012	2013	2014	2015	2016	2016
Total	16193	16922	16578	16948	16379	15425	1838559
Birth premature	884 (5,4)	1160 (6,9)	1078 (6,5)	1172 (6,9)	1159 (7,1)	1075 (6,9)	105995 (5,8)
Birth premature very early	-	112 (0,6)	93 (0,5)	71 (0,4)	86 (0,5)	84 (0,5)	8542 (0,4)
Verkhne-Vilyui district							
Total	378	338	299	266	245	201	1706656 (92,3)
Birth premature	14 (3,7)	16 (5)	10 (4)	10 (3,76)	4 (1,6)	4 (2)	105995 (5,8)
Birth premature very early	-	1 (0,26)	0	0	2 (0,8)	1 (0,5)	8542 (0,4)
Verkhoyansk district							
Total	148	161	140	156	133	115	1838559
Birth premature	3 (2,02)	10 (0,62)	7 (5)	4 (2,56)	4 (3)	3 (2,6)	105995 (5,8)
Birth premature very early	-	0	0	0	0	0	8542 (0,4)
Tattinsky district							
Total	262	263	236	224	205	182	1838559
Birth premature	8 (3)	5 (1,9)	5 (2,11)	11 (4,9)	11 (5,36)	4 (2,2)	105995 (5,8)
Birth premature very early	-	1	1	3	0	0	8542 (0,4)
Even-Bytantaisk district							
Total	6	8	2	1	3	3	1838559
Birth premature	6 (100)	0	0	0	0	0	105995 (5,8)
Birth premature very early	-	0	0	0	0	0	8542 (0,4)

Table 2

The frequency of premature births in the RS (Y) for 2011-2016 by groups of medical organizations

	2012	2013	2014	2015	2016
3 group	331 (28,5)	411 (38,1)	487 (41,5)	545 (47)	530 (49,3)
2 group	616 (53,1)	514 (47,7)	528 (45,1)	467 (40,3)	451 (41,9)
1 group	213 (18,4)	153 (14,2)	157 (13,4)	147 (12,7)	94 (8,7)
of all premature births	1160	1078	1172	1159	1075



The frequency of very early premature births in the RS (Y) for 2011-2016 by groups of medical organizations

Table 3

The structure of perinatal mortality in the RS (Y) districts and in the RF in 2011-2016 гг., ‰

Name	RS (Y)								RF
	2006	2010	2011	2012	2013	2014	2015	2016	
Stillbirth %0	6,3	5,2	5,4	8,4	5,22	6,4	6,5	6,4	5,73
Early neonatal mortality %0	5,2	2,9	3,0	4,6	4,5	3,2	3,4	2,5	2,8
Perinatal mortality %0	11,5	8,1	8,4	13,0	10,8	10,0	10,6	9,6	7,9
Verhnevilyui district									
Stillbirth %0	3,2	0	5,2	0	6,7	3,8	16,3	5,0	5,73
Early neonatal mortality %0	3,2	2,6	7,9	3,0	6,7	3,8	4,1	0	2,8
Perinatal mortality %0	6.4	2,6	13,1	3,0	13,4	7,5	20,3	5,0	7,9
Verkhoyansk district									
Stillbirth %0	0	18,6	0	24,8	7,0	12,8	0	0	5,73
Early neonatal mortality %0	0	4,7	6,8	0	14,2	0	7,5	0	2,8
Perinatal mortality %0	0	23,3	6,8	24,8	21,1	12,8	7,5	0	7,9
Tattinsky district									
Stillbirth %0	8,0	6,9	3,8	7,6	0	0	9,7	5,5	5,73
Early neonatal mortality %0	12,1	3,5	3,8	3,8	0	0	9,8	0	2,8
Perinatal mortality %0	20,0	10,3	0	11,4	0	0	19,4	5,5	7,9
Eveno-Bytantai district									
Stillbirth %0	0	0	0	0	0	0	0	3,3	5,73
Early neonatal mortality %0	0	0	0	0	0	0	0	0	2,8
Perinatal mortality %0	0	0	0	0	0	0	0	3,3	7,9

2015 - 64.7%, 2016 - 72.8%. The increase in this indicator was caused by the timely evacuation of pregnant women with very early premature births, who threatened very early on from the second level, whereas at the same level, these rates practically did not decrease in 2012. - 9.7%, 2013 - 14%, 2014 - 11.3%, 2015 - 12.9%, and in 2016 - 11.1%. (diagram 1).

Early neonates with «extremely low body weight» caused a sharp increase in perinatal mortality from 8.4% in 2011 to 13.0% 0 in 2012. This was due to an increase in the rate of early neonatal mortality in 2011 - 3.0% 0, 2012 - 4.6% 0, indicating a lack of timely routing of patients with threatening premature birth in a third-level hospital and inaccessible to intensive care units for admission and care for newborns deeply premature. In addition, there is a decrease in the level of early neonatal mortality (2013 - 4.5% 0, 2014 - 3.2%, 2015 - 3.4% 0, 2016 - 2.5% 0), which, in turn, decrease in perinatal mortality in the republic (in 2013 - 10.8% 0, 2014 - 10% 0, 2015 - 10.6% 0, 2016 - 9.6% 0). Nevertheless, perinatal mortality in the RS (Y) in 2016 is 1.7% higher than in the Russian Federation. (Table 7-11). A similar picture is observed for the regions under study.

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In the growth rate of perinatal mortality contributes to stillbirth, it is not only ante and intranatal loss of fruit, but the termination of pregnancy at a period of more than 22 weeks about congenital malformations of the fetus. Annually, this indicator has a significant part in the structure of stillbirth (2013г. – 1,08%0, 2014г. – 0,4%0, 2015г. – 0,7%0, 2016г. – 0,7%0). This is partly due to the untimely conduct of prenatal diagnosis of congenital malformations of the fetus. To date, the stillbirth rate in the RS (Y) has no tendency to decline and amounted to in 2011 – 5,4%0, 2012 – 8,4%0, 2013 – 6,3%0, 2014 – 6,8%0, 2015 – 7,2%0, 2016 – 7,1%0.

Thus, our analysis shows that only timely carrying out of such activities as pregravid preparation, full examination of a pregnant woman when registering for a dispensary record, accurate compliance with the terms of combined first trimester screening and prenatal ultrasound diagnosis (FMF certificates) can reduce the rate of preterm birth and stillbirth due to timely detection and termination of pregnancy with severe congenital malformation of the fetus. Also, the doctor's watchfulness, strict adherence to clinical recommendations (protocols of treatment) with preterm delivery and routing of pregnant women with threatening premature births, will allow to avoid

premature births at the first level, which is the main task facing the obstetrician-gynecological service of the Republic of Sakha (Yakutia) in 2017 .

The article was prepared based on the results of the project «Multivariate study of the health status of the indigenous and newcomers of the Republic of Sakha (Yakutia) with the aim of optimizing the regional programs to improve the quality of life of the inhabitants of the republic, taking into account territorial, ethnic characteristics in the conditions of modern socioeconomic development.» Programs of comprehensive scientific research in the Republic of Sakha (Yakutia), aimed at the development of its productive forces and social sphere for 2016-2020.

REFERENCES

1. Ailamazyan E.K. Kuzminykh T.U. Diskussionnye voprosy prezhdevremennyh rodov [Discussion issues of premature delivery] Zнurnal akusherstva i zhenskih boleznej [Journal of Obstetrics and Women's Diseases]. Moscow, 2013, № 4, P. 97 - 105.
2. Kulakov V.N. Akusherstvo i ginekologiya [Obstetrics and gynecology] Klinicheskie rekomendacii [Clinical recommendations]. Moscow, 2006, P. 15.

The authors:

Douglas Natalia Ivanovna - MD, Head of the Department of Obstetrics and Gynecology of the Medical Institute of the MI SVFU, e-mail: nduglas@yandex.ru;

Baisheva Nurguyana Semenovna - senior lecturer of the MI SVFU, kosmos80-80@mail.ru;

Burtseva Tatyana Egorovna - doctor of medical sciences, professor MI SVFU, head. lab. YNS CMP, bourtsevat@yandex.ru;

Pavlova Tatyana Urievna - Candidate of Medical Sciences, Chief Obstetrician-Gynecologist of the Ministry of Health of the Republic of Sakha (Yakutia), tatyanaupavl@mail.ru;

Evseeva Sardana Anatolievna - Senior Researcher YNS CMP, sarda79@mail.ru.

P.M. Ivanov, A.F. Abramov, L.N. Afanasyeva, F.G. Ivanova, A.S. Golderova, A.N. Romanova, N.S. Kipriyanova, T.I. Nikolaeva, T.N. Zharnikova, S.A. Myreeva

THE STATE OF THE HYDROSPHERE AND MALIGNANT NEOPLASMS IN YAKUTIA

ABSTRACT

The analysis of hydrochemical factors of the environment with the purpose of finding out the degree of their influence on the incidence of malignant neoplasms of the population living in extreme conditions of the Far North has been carried out.

Keywords: neoplasms, hydrochemical factors of the environment, morbidity.

INTRODUCTION

Annually around 10 million new cases of malignant neoplasm (MN) and more than 6 million deaths from them are detected in the world [6, 7]. In Russia, the overall incidence rate of all forms of MN in men for 2001-2015 increased by 26.8% (from 313,90 / 0000 in 2001 to 398,10 / 0000 in 2015), and in women - by 32,6% (from 306,5 to 406,40 / 0000), and at the end of 2015, there were more than 3.4 million patients registered with specialized oncological institutions in the country with a diagnosed disease, which is 36.5% (over 1.24 million people) 2001 (2.16 million people) [4].

In the Republic of Sakha (Yakutia) (RS(Ya)) in 2015, 2528 people were registered, or 651 (25.7%) people. more compared to 2001 (1877 people). During this period of time, the number of males with the first diagnosis of MN increased by 22.8%, and in women - by 28.4%. The increase in the number of patients was accompanied by an increase in the proportion of people of older age groups, both in men and women.

In Yakutia, the beginning of the third millennium is characterized by a fairly high average annual rate of growth (2.15%) in the number of patients diagnosed with MN for the first time in their life, which was mainly due to relatively high rates of increase in the incidence of women (2.25%) , than for men (1.75%).

Meanwhile, for the analyzed period, according to the State Committee on Statistics RS(Y), in the population indicators there was a negative balance of the average annual number of the population (for men -0.30, and for women -0.05%). The increase in the number of people with a negative dynamics of the demographic situation testifies to the true nature of the growth of the indicators of cancer morbidity in the republic [3]. According to the WHO Committee on Cancer Prevention, 90% of tumors are associated with external causes and 10% depend on genetic factors (7).

A review of the literature on the microelement composition of soils and plants on the territory of the Republic shows that in general Yakutia is characterized by Mo, Se, B deficiency, with a relatively high content of Fe, Cu. In soils of natural forage lands (76%) and in arable (91%), alkaline and strongly alkaline environments predominate.In the valleys of the rivers Amga, Aldan, Vilyui, Lena, chloride-sulfate are common, and in chloride lands, chloride, sulfate, and hydrocarbonate types of salinity. Consequently, according to the physico-microelement composition of soils and plants, which are extremely important for the successful development of a living organism, the territory of the Republic of Sakha can be classified as anomalous geochemical provinces of the country [5].

The **aim** of the study is to assess the degree of influence of hydrochemical environmental factors on the incidence of disease in people living in extreme conditions of the North in the territory of intensive industrial development.

Materials and methods of research. The materials of reporting of the Yakutsk Republican Oncology Dispensary for the period from 2001 to 2015 were analyzed. Materials on the chemical composition of surface waters, presented by the Yakutsk and Tiksinsky territorial departments for hydrometeorology and environmental control, were used for the period from 1979 to 1985. Mathematical analysis 71,800 samples were sampled for each of 28 ingredients taken from 82 observation points for 1979-1985 located throughout the territory of the republic. The statistical data were processed according to the generally accepted methodology, using the «Statistical» software package (Table 1).

Results and discussion

Analysis of cancer morbidity in the

Table 1

Dynamics and rank of malignant neoplasms incidence rates of the RS (Ya) population for 2001 and 2015 (Distribution by average annual growth rate) *

Localization	Incidence on the 100 000 population		Place on morbidity level		Growth (%)	Average Annual, %	Place on growt
	2001	2015	2001	2015			
MEN							
All malignant neoplasms (C00-97)	253,7	265,9	-	-	104,8	0,30	-
Prostate (C61)	5,2	32,2	13	2	619,2	12,95	1
Skin melanoma (C43)	0,5	1,4	20	18	280,0	7,10	2
Other neoplasms of the skin (C44, 46.0)	6,0	16,2	12	5	270,0	6,85	3
Soft tissues (C46- 49)	1,8	3,1	17	15	172,2	3,70	4
Central nervous system (C71, 72)	3,6	5,5	14	13	152,8	2,85	5
Kidneys (C64)	8,0	12,2	10	9	152,5	2,85	6
Rectum, anus (C19-21)	8,9	13,3	7	7	149,4	2,70	7
Pancreas (C25)	8,4	11,6	9	10	138,1	2,20	8
Bones and cartilage (C40, 41)	2,0	2,4	15	16	120,0	1,25	9
Hemoblastosis (C81-96)	11,1	12,9	6	8	116,2	1,00	10
Bladder (C67)	8,8	9,6	8	11	109,1	0,60	11
Colon (C18)	14,3	14,4	5	6	100,7	0,50	12
Testicle (C62)	2,0	2,0	16	17	100,0	0,05	13
Liver (C22)	22,4	20,8	4	4	92,9	-0,50	14
Thyroid (C73)	1,5	1,3	18	19	86,7	-0,95	15
Lungs (C33, 34)	59,5	49,4	1	1	83,0	-1,25	16
Lip (C00)	1,3	1,0	19	20	76,9	-1,75	17
Larynx (C32)	6,9	4,6	11	14	66,7	-2,65	18
Stomach (C16)	37,5	24,3	2	3	64,8	-2,85	19
Esophagus (C15)	30,1	7,5	3	12	24,9	-8,85	20
WOMEN							
All malignant neoplasms (C00-97)	191,6	203,6	-	-	106,3	0,40	-
Soft tissues (C46.1,- 49)	0,6	2,5	20	18	416,7	10,0	1
Bladder (C67)	0,8	2,6	21	17	325,0	8,20	2
Kidneys (C64)	6,0	9,3	14	8	155,0	2,95	3
Central nervous system (C71, 72)	3,2	4,9	16	15	153,1	2,90	4
Body of the uterus (C54)	5,6	8,5	15	9	151,8	2,80	5
Cervix (C53)	13,7	19,2	4	2	140,1	2,25	6
Mammary gland (C50)	29,4	38,2	1	1	129,9	1,70	7
Colon (C18)	9,9	12,6	6	4	127,3	1,65	8
Ovary (C56)	9,5	11,2	7	7	117,9	1,10	9
Rectum (C19-21)	6,8	7,5	12	11	110,3	0,65	10
Thyroid (C73)	7,3	6,9	11	12	94,5	-0,40	11
Liver (C22)	12,5	11,5	5	6	92,0	-0,70	12
Hemoblastosis (C81-96)	9,2	8,0	8	10	87,0	-0,90	13
Other neoplasms of the skin (C44, 46.0)	6,6	5,7	13	14	86,4	-0,95	14
Stomach (C16)	15,1	11,9	3	5	78,8	-1,60	15
Placenta (C58)	1,4	1,1	19	21	78,6	-1,60	16
Pancreas (C25)	7,9	5,9	9	13	74,7	-1,95	17
Skin melanoma (C43)	1,6	1,1	18	20	68,8	-2,45	18
Lungs (C33, 34)	25,2	14,0	2	3	55,6	-3,85	19
Bones and cartilage (C40, 41)	2,2	1,2	17	19	54,5	-3,95	20
Esophagus (C15)	7,3	3,5	10	16	47,9	-4,80	21

* International standard

population of the RS (Y) for 2001-2015. allows to note that Yakutia is still the territory of oncological risk in the Russian Federation as a region that characterizes the positive trend in the indicators of morbidity in the Russian Federation. Thus, in men, the average annual rate of increase in the total morbidity rate of SA was 0.30%, and in women 0.40%. The maximum growth rates in men were manifested in prostate cancer (12.9%), melanoma skin (7.1), skin (6.8), soft tissue (3.7). Further, a relatively high average annual rate of increase was found in patients with MN: central nervous system (2.85%), hemoblastosis (2.8), kidney (2.8), rectum (2.7) and pancreas (2.2%) (table1).

Women have a high average annual growth rate of MN soft tissue (10.0%), bladder (8.20), kidney (2.95), CNS (2.90), MN body (2.80) and cervix 2.25%). The following ranking places in terms of average annual growth rates are: breast cancer (2.8%), colon (3.6), ovaries (1.10) and rectum (0.65%). Dynamics of the annual morbidity rate for the five-year-old population of the RS (Ya), depending on the involvement of their place of residence in the basins of large rivers for 2001-2015 is presented in Table. 2.

For the identification of medical and geographical areas, administrative-territorial units and the involvement of their territory in the basin of the major rivers of Yakutia have been taken into account [3].

The following zones are distinguished: I - Anabar-Olenek (Anabar, Olenek), II - Prilenskaya (Lena River), III - Yanskaya (Yana River), IV - Indigirskaya (Indigirka River), V - Kolyma-Alazeyskaya (basin the rivers Kolyma, Alazeya), VI - Viluiskaya (Vilyui River) and VII - Aldan-Amginskaya (Aldan and Amga rivers). In the Prilenskaya zone (main stream), sub-zones are identified: Verkhnelenskaya, which includes Lensky, Olekminskyuluses, Sredlenskaya - Kobiaisky, Gorny, Namsky, Yakut, Khangalassky, Megino-Kangalassky, and Nizhnelenskaya - Zhigansky, Bulunskyuluses.In the Aldan-Amga zone, respectively: Amga (agricultural) in the Alekseevsky, Amginsky, Ust-Aldansky, Churapchinskiyuluses (the main occupation of the population is agriculture, 96.3% is indigenous), and the Aldan subzone, which includes Aldan, Neryungri, Ust-May, and Tomponsky ulus (non-indigenous population 92.3%).

In the Vilyuisky zone, two subzones are distinguished: the upper current (industrial), which includes the Myrninsky ulus, in which 97.6% of the inhabitants

Table 2

Dynamics of incidence of malignant neoplasms (C00-97) of the population of territories of RS(Ya) involved in basins of the large rivers for 2001-2015, on 100000 population

Zone (subzone)		District	All population			Men			Women		
				2006-2010	2011-2015	2001-2005	2006-2010	2011-2015	2001-2005	2006-2010	2011-2015
I.		I. Anabar-Olenekskaya	Anabar-sky	117,5	158,6	150,4	118,3	189,4	159,4	117,5	128,3
			Oleneksky	156,3	204,6	209,6	214,0	182,6	182,7	98,1	204,6	235,8
II Prilenskaya	IIA-Nizhne-lenskaya		Bulunsky	168,5	160,6	135,4	136,0	140,1	100,7	203,7	160,6	173,5
			Zhiganskiy	201,8	206,2	248,4	163,3	210,3	286,8	238,6	206,2	211,4
	IIБ Среднелен-ская		Kobiaisky	198,1	189,8	177,4	208,2	206,1	168,0	188,2	189,8	186,3
			Namsky	145,7	139,3	176,0	158,5	158,1	179,4	133,8	139,3	172,9
			Yakutsky	214,5	184,8	243,5	215,9	175,7	234,4	213,3	184,8	251,8
			Gorny	147,2	139,8	146,7	150,3	113,0	158,9	144,3	139,8	135,1
			M-Kangalassky	175,6	144,9	278,1	168,2	204,4	273,3	183,6	144,9	283,1
			Khangalassky	189,1	221,8	227,7	215,3	237,7	253,7	164,1	221,8	202,6
	IIB IIV Verkhne-lenskaya		Olekminsky	243,6	289,8	265,0	276,0	287,7	279,5	211,8	289,8	250,7
			Lensky	252,9	191,3	207,6	260,6	182,6	187,2	245,1	191,3	228,0
III Janskaya			Ust-Yanskiy	156,1	190,3	227,8	160,4	182,4	236,0	151,6	190,3	219,7
			Verkhoyansky	168,8	168,7	209,2	192,7	195,8	226,7	144,9	168,7	192,3
			Eveno-Bytantaisky	144,7	143,0	157,3	143,7	146,3	160,9	145,7	143,0	153,9
IVIndigirskaya			Allaahovsky	286,7	277,4	320,1	315,5	325,0	354,6	258,7	277,4	288,1
			Momsky	191,4	265,7	247,1	164,8	261,8	261,8	217,1	265,7	233,5
			Abyisky	229,7	202,3	258,8	190,4	243,4	272,6	267,8	202,3	245,8
			Oymyakonsky	146,6	218,5	251,3	141,7	216,6	269,7	152,2	218,5	230,1
VKolyma-Alazeyskaya			Nizhne-kolymskiy	223,0	252,5	315,7	267,1	284,2	350,6	179,6	252,5	284,0
			Sredne-kolymsky	168,6	204,9	231,2	172,1	224,0	278,7	165,2	204,9	187,2
			Verkhne-kolymskiy	260,3	452,5	365,6	273,7	441,6	303,6	246,7	452,5	426,9
VI Vilyuyskaya	A- Verkhne-vilyuyskaya		Myrninsky	191,4	221,5	238,8	187,9	213,9	213,9	194,9	221,5	263,4
	VI-Б. Nizhne-vilyuyskaya		Suntar	170,8	176,7	182,5	176,5	178,7	189,0	165,4	176,7	176,5
			Nyurbinsky	171,5	180,5	205,7	188,1	200,6	222,3	155,6	180,5	189,9
			Verkhne-vilyuysky	145,5	180,0	183,8	173,3	160,9	176,5	118,5	180,0	190,8
			Viluysky	192,0	166,8	168,4	189,3	189,7	161,1	194,6	166,8	175,2
VIIAldan-Amginskaya	VII-A Leno-Amginskaya		Amginsky	155,1	157,5	179,0	177,0	214,5	179,6	134,3	157,5	178,4
			Tattinsky	192,1	156,6	232,4	189,0	166,9	269,1	195,1	156,6	197,0
			Ust-Aldansky	168,5	187,7	229,5	171,4	201,5	221,0	165,9	187,7	237,4
			Churapchi-nsky	190,1	249,7	174,9	204,9	208,5	176,7	175,6	249,7	173,1
	VII-Б Aldanskya		Aldansky	256,8	353,5	395,0	269,6	345,5	461,9	243,9	353,5	328,2
			Neryungrinsky	212,0	281,7	287,2	211,7	264,1	274,1	212,2	281,7	299,2
			Tomponsky	187,2	267,7	247,3	206,4	285,4	238,3	168,4	267,7	256,1
			Ust-Maysky	197,3	279,2	353,5	198,2	288,2	389,4	196,3	279,2	316,8
The Republic of Sakha (Yakutia)				200,5	210,9	241,3	205,7	212,8	241,1	195,5	210,9	241,6

are visitors, the main occupation is work in the diamond mining industry and the lower current (agricultural) in the Suntar, Nyurba, Verkhnevilyui, Vilyuisky ulus, 95% of the population are people of indigenous nationality, the main occupation is agriculture.

It is likely that an increase in the incidence of heart failure may be due to the presence of close conjugation with negative for homeostasis environmental factors (EF), the nature of nutrition, the provision of the body with important vitamins, harmful household habits, economic conditions of life and, finally, with a change in the number and age structure of the population.

In addition, it is impossible to exclude the possibility of the existence on the vast territory of the republic of provinces, anomalous with respect to the most important for human microelements (Ca, Mg, Zn, Cu, Mo, Se, etc.), which, according to the published data, can have a significant impact on indicators of cancer. In particular, it was found that alkaline (53%) active reaction of the environment prevails in the soils of natural fodder lands of Central and Southern Yakutia [1]. Chloride-sulfate, sulfate types of salinity are common in the valleys of the Lena, Vilyui, Aldan, and Amga rivers, and chloride-sulphate-hydrocarbonate salinity predominates in alas lowlands.

According to A.D. Egorova et al. [2], in the soil of Central Yakutia, despite the sufficient content of total reserves of N, P, K, mobile forms N and P is small, K, Ca and Mn are sufficient. Frequent droughts cause the formation of highly mineralized lakes. In the Lena-Vilyui interfluve (Gornyi Ulus) in meadow pastures, the Mo, Cu, B content is low, and Fe, Mn is high. In the Nyurba region of Co, Fe, Cu - within normal limits, Mn - a reduced amount, and B - insufficient. In the northeastern taiga intermountain river basins and the Kolyma lowland, the B content is low, Mo is low, Cu, Zn is normal, Co is elevated, Fe, Mn, I is high.

It is established that the formation of the chemical composition of the waters of the Lena and Amga rivers plays an important role in their feeding by highly mineralized groundwater. The waters of the rivers Lena, Vilyui, Amga are characterized by a very high average annual content of organic substances and biogenic components. It should be noted that the hydrochemical composition of surface waters varied significantly with the season (winter-summer) and had a fairly wide mosaic in their content over individual rivers (Table 3).

Table 3

The hydrochemical characteristics of surface waters (rivers, lakes), depending on the season in the RS (Ya) [5]

Hydrochemical characteristic	number of samples	during a year	Including by seasons	
			summer	winter
Physical properties				
Suspended substances (mg / l)	653	21,4±1,36	29,0±2,23*	13,4±1,39*
Transparency (cm)	636	64,1±1,66	55,8±2,21*	76,3± 2,30*
The reaction of the medium (PH)	756	7,00±0,54	6,90±0,03	7,07±0,02
Gas composition				
Carbon dioxide (CO2 mg / l) Oxygen (O2 mg / L)	624	9,9±0,27	7,88±0,26*	12,9±0,47*
Carbon dioxide (CO2 mg / l) Oxygen (O2 mg / L)	734	10,1±0,07	9,90±0,09	10,4±0,12
Organic matter, incl. polluting				
Biochromate oxidability (mg / l)	721	29,2± 0,85	28,0±1,06	30, 5± 1,36
BOD5 (mg / L)	671	1,89±0,04	1,63±0,06*	2,17±0,06*
The chromaticity (in degrees P-CO of the scale)	625	41,9±1,27	43,1±1,38	40, 2± 2,41
Petroleum products (mg / l)	4203	0,208±0,004	0,250±0,005*	0,138±0,0064*
Phenols are volatile (mg / l)	3070	0,006±0,0005	0,005±0,0001	0,008±0,0017
Surfactant (mg / l)	3798	0,039±0,001	0,036±0,01*	0,045±0,0016
Biogenic components and polluting inorganic substances (mg / l)				
Ammonia nitrogen	4028	0,12±0,004	0,10±0,003*	0,173±0,0085*
Nitrogen nitrogen (mg / l)	3904	0,043±0,002	0, 024±0,0016*	0,082±0,0039*
Nitrate nitrogen (mg / l)	4019	0,01±0,001	0,009±0,0008	0,021±0,0019
Nitrogen general	2235	0,23±0,005	0,195+0,0064*	0,280±0,0095*
Phosphorus mineral	4373	0,015±0,0027	0,037±0,0030*	0,021±0,0070
Phosphorus total	4368	0,036±0,0033	0,228±0,0060*	0,032±0,0060
Iron (Fe) (mg / l)	3910	0,20±0,004	0,23±0,035*	0,14±0,01*
Silicon (Si)	4364	2,4±0,03	2,3±0,03	2,7±0,07*
Copper (Cu) (mg / l)	3564	2,5±0,04	2,7±0,05*	2,3±0,07*
Zinc (Zn) (mg / L)	3585	10,3±0,19	9,6±0,22*	11,7±0,35*
The main ions (mg / l)				
Carbonate (HCO3)	619	50, 6± 1,67	39,6± 1,63*	65, 5± 3,03*
Sulfate (SO4 +) (mg / L)	571	17,2±0,86	12,7±0,53*	24, 5± 1,98*
Chlorine (Cl	3744	21,82±0,77	11,01±0,52*	44,44±1,96*
Calcium (Ca2 +)	4328	19,81±0,73	15,79±0,71*	31,06± 1,78*
Magnesium (Mg2 +)	3635	5,38±0,11	3,89±0,10*	8,65±0,24*
Mineralization (mg / l)	3459	137,7±3,00	94,71±2,31*	233,94± 7,49*
Total hardness (mmol / l)	572	1,16±0,04	0,90±0,04*	1,54±0,09*

* The difference is statistically significant compared to the average annual values.

Due to the fact that the main part of the republic's population still uses sources of open water as a source of drinking water, it is of some interest to ascertain the strength of the connection between the total incidence rates of organ systems and systems with the components of the chemical composition of natural water bodies, depending on the season of the year.

According to the correlation results, the deserving ingredients from 28 counted substances of surface waters can be in the summer time of year 10, in winter - 15. The exposure time is 20 years.

In the summer, the correlation between the indicators of the total oncological morbidity and the chemical composition of the surface waters of the areas identified by us was revealed: the correlation of the direct average force with the content of nitride nitrogen (0.65), oil products (0.50) and direct low - with mineral content phosphorus (0.36), chlorine (0.26) nitrate nitrogen (0.14), surfactant (0.13) and zinc (0.02). The presence of low feedback of the general morbidity of MN with Fe (-0.39), Mg (-0.17) and total mineralization (-0.15) was revealed.

In Yakutia, malignant tumors of the digestive system, according to the magnitude of the total incidence rates, still remain the leading localizations among other forms of MN organs and systems. The presence of the coefficients of direct correlation with the polluting hydrosphere has been found to differ in degree: nitride nitrogen (r = 0.59), mineral phosphorus (0.33), petroleum products (0.21), nitrate nitrogen (0.13), synthetic surfactants (0.10), chlorine (0.09), and an inverse medium-strength bond was found with the iron content (-0.59).

In the North, the duration of exposure to negative effects on the human body, especially in winter (8 months), significantly increases, both quantitatively and qualitatively, than in the summer (4 months). According to the results of the correlation analysis, the indices of the disease of the digestive system were directly related to nitrate nitrogen (r = 0.61), zinc (0.23), nitride nitrogen (0.19), sulfates (0.19), mineral phosphorus (0,17), synthetic surfactant (0.15), total phosphorus (0.11), chlorine (0.08), and total nitrogen (0.02). Essential was the relationship of the reverse direction with water soluble oxygen (r = -0.56) and iron content (-0.55).

Among organs and systems, respiratory organs in terms of incidence of malignant neoplasms in both groups of population occupy the second place after digestive organs. In this, a certain role is played by the identified ingredients considered to be surface water pollutants and having a direct correlation with the incidence rates.

Among organs and systems, respiratory organs in terms of incidence of malignant neoplasms in both groups of population occupy the second place after digestive organs. In this, a certain role is played by the identified ingredients considered to be surface water pollutants and having a direct correlation with the incidence rates.

In Yakutia, breast cancer (BC) in the frequency of morbidity in the female population has for many years invariably ranked first. According to the analysis, incidence rates regardless of the time of year have a direct strong correlation with nitrogen nitride (r = 0.75 in summer and 0.68 in winter) and a line of medium strength with oil products (r = 0.45 and 0.48, respectively).

In addition, in the summertime there is a direct but weak degree of connection with mineral phosphorus (0.23), nitrate nitrogen (0.14), chlorine (0.12), in winter

with zinc (0.23), nitrate nitrogen (0.20), chlorine (0.19), phenol (0.09), sulfates (0.05), and synthetic surfactants (0.03). In summer, with a content of magnesium (-0.55), mineralization (-0.54), Fe (-0.35) and in winter with water-soluble oxygen (-0.67) magnesium (-0.50), a significant reverse direction correlation relationship.

Of interest are the results of a correlation analysis of the incidence of reproductive organs in women with hydrosphere factors, depending on the season. The presence in the summer of the year of a direct average bond strength with the content of petroleum products (r = 0.55), nitrous oxide (0.41) and chlorine (0.30), direct weak - with mineral phosphorus (r = 0.14), zinc (0.13), nitrate nitrogen (0.09) and the opposite direction with magnesium (-0.37), salinity (-0.34) and iron (-0.03).

It should be noted that in winter, the degree of influence of oil (0.82), nitrate nitrogen (0.77), chlorine (0.41), phenol volatile (0.40), iron (0.34) is greatly enhanced. There is a direct, weak correlation between the incidence rates of malignant neoplasms of the genital organs and the level of contamination of surface waters: surfactants (r = 0.23), total nitrogen (0.16), mineral phosphorus (0.16), sulfates (0.15), zinc (0.14), ammonium phosphorus (0.12). In winter, in women, oxygen deficiency (-0.35) and magnesium (-0.20) contribute to an increase in the incidence of disease of the reproductive organs.

The beginning of the third millennium (2001-2015) in the Republic of Sakha (Yakutia) is characterized by an increase in the incidence of hematological malignancies with an average annual growth rate of 1.0%, which makes it possible to consider work aimed at clarifying the role of pollutants in the environment (primarily the hydrosphere) etiological aspects of this phenomenon.

According to the correlation analysis, the presence (with seasonal fluctuations) of a direct average bond strength with oil content (r = 0.61 in summer and 0.67 in winter), chlorine (0.49 and 0.57, respectively), surfactants (0,40 and 0.57), nitride nitrogen (0.32 and 0.55), mineral phosphorus (0.26 and 0.49), and nitrate nitrogen (0.16 and 0.51). According to the analysis, in order to increase the incidence of malignant neoplasms of the hematopoietic organs and lymphatic tissues, inadequate iron content in water (r = -0.4) in summer and -0.21 in winter) was essential.

In winter, a stronger direct relationship was found between the incidence of hemoblastosis with phenol (0.53), sulfate (0.46), total (0.45) and ammonium (0.42) nitrogen and total phosphorus (0.38) and more a weak direct relationship with the content of zinc (0.03) and oxygen deficiency (-0.19).

In **conclusion**, we note that oncogenic hygiene, being one of the most important areas of primary cancer prevention, is designed to solve the problem of identifying and eliminating the possibility of human exposure to carcinogenic environmental factors. In order to achieve positive results in the work aimed at improving the oncological epidemiological situation in the Republic of Sakha (Yakutia), special attention should be given to the timely detection of risk factors associated with environmental pollution, including the hydrosphere, which contribute to the increase in the incidence of malignant diseases.

REFERENCES

1. Elovskaja L.G. Ivanov I.A. Pitatel'nye jelementy, aktivnaja reakcija sredy, za-solennost' i solonceva-tost' merzlotnyh pochv [Nutrients, active reaction of the environment, salinity and salty content of permafrost soils] Atlas sel'skogo hozjajstva JaASSR [Atlas of agriculture of the YaSSR]. Moscow, 1989, p.96-97.
2. Egorov A.D. Grigor'eva D.V. Kuriljuk T.G. Sazonov N.N. Mikrojelementy v pochvah i lugopastbishhnyh rastenijah merzlotnyh landshaftov Jakutii [Microelements in soils and grassland plants of permafrost landscapes of Yakutia]. Jakutsk, 1970, 287 p.
3. Zlokachestvennye novoobrazovanija v Jakutii (zabolevaemost' i smertnost') [Malignant neoplasms in Yakutia (morbidity and mortality)] Pod red. P.M. Ivanova, L.N. Afanas'evoj, S.A. Myreevoj [Ed. P.M. Ivanov, L.N. Afanasyeva, S.A. Mireeva]. Jakutsk: Sfera, 2018, 180p.
4. Zlokachestvennye novoobrazovanija v Rossii v 2015 godu (zabolevaemost' i smertnost) [Malignant neoplasms in Russia in 2015 (morbidity and mortality)] Pod red. A.D. Kaprina, V.V. Starinskogo, G.V.Petrovoj [Ed. A.D. Kaprin, V.V. Starinsky, G.V. Petrova]. Moscow, 2017, 250 p.
5. Ivanov P.M. Rak pishhevoda i zheludka kak kraevaja patologija na severe [Esophageal and gastric cancer as a regional pathology in the North]. Jakutsk: Bichik, 1999, 197p.
6. Garcia M.B. [et al.]. Rak v mire: fakty i cifry [Cancer in the world: facts and figures]. Atlanta, 2007, 85 p.
7. Estimates of the global burden of cancer in 2008: GLOBOCAN 2008/ J. Ferlay, H.R. Bray, D. Forman, C. Mathers, M.D. Parkin // Int. J. Cancer. - 2010.-№127.-P. 2893-2917.

The authors:

IVANOV Peter M. - MD, prof., Head of course of oncology Medical institute GBOU M.K. Ammosov NEFU, petr_ ivanov_38@mail.ru;

ABRAMOV Alexey Fedorovich - doctor of biological sciences, prof., reseacher FGBNU YANIISK RAAS;

Employees of YAROD:

AFANASIEVA Lena Nikolaevna - Candidate of Medical Science, Chief Physician, IVANOVA Fedosia Gavrilyevna - Candidate of Medical Science, Ch. oncologist MH RS (Ya), NIKOLAEVA Tatiana Ivanovna - Candidate of Medical Science, Deputy head manager, Zharnikova Tatyana Nikolaevna - Candidate of Medical Science, Head of Department, MYREYEVA Svetlana Anatolievna - Candidate of Medical Science, gynecologist-oncologist;

Employees of FGBNU YSC CMP:

ROMANOVA Anna Nikolaevna - MD, Director, GOLDEROVA Aitalina Semenovna - MD, Head of Department; KIPRIYANOVA Nadezhda Sidorovna - MD, prof. FPOV MI NEFU.

SCIENTIFIC REVIEWS AND LECTURES

Neustroeva L.M., Pavlova N.I., Solovyeva N.A., Diakonova A.T., Varlamova M.A., Filippova N.P., Dodokhov V.V., Kurtanov H.A.

NEUROFIBROMATOSIS TYPE I: ETIOPATHOGENESIS, CLINIC, DIAGNOSIS, TREATMENT

ABSTRACT

The relevance of the presented review is due to the high frequency of neurofibromatosis type 1 (NF1) in the population and frequent association with the development of malignant neoplasms. It is mainly characterized by a number of macules, the color of «cafe´-au-lait «, freckles in the skin folds, Lisch nodules and neurofibromas. Because clinical manifestations depend on the patient's age, and there are a number of other overlapping syndromes and diseases, it is usually difficult to put an early clinical diagnosis. At present, there are many molecular methods for diagnosing NF1, the highest sensitivity of any of these methods is ~ 95%.

This article examines the causes, pathogenetic mechanisms of the development of the disease, its complications, molecular genetic methods of investigation.

Keywords: type 1 neurofibromatosis, Recklinghausen's disease, neurofibromin.

Recklinghausen's disease, or Type 1 neurofibromatosis (NF1) is one of the most common monogenic diseases with an autosomal dominant type of inheritance related to phacomatoses. Phakomatosis (Greek phakos - spot) is a group of hereditary diseases united by common links of pathogenesis, which are characterized by a combined lesion of the nervous system, skin, eyes and internal organs. The term «phacomatosis» was first introduced in 1920 by Jan van Der Heve, who described changes in the ocular fundus as spots (phakos-spot) [4].

Neurofibromatosis type 1 (NF1) in 1882 was first described by the German physician Frederich von Recklinghausen. The type of inheritance is autosomal dominant [3, 9]. In the presence of NF1 in one of the parents, the risk of inheriting the mutant gene by the child is 50% and 66.7% in both [6].

Prevalence

According to the literature, the incidence of Type 1 neurofibromatosis in different countries is 1: 3,000-5,000 in the general population. The prevalence in Russia is 1: 2800 - 3300 [5]. In particular, in the Republic of Sakha (Yakutia) among diseases with AD inheritance, Recklinghausen's disease ranks third. According to the Republican genetic register of hereditary and congenital pathology of the The Republic of Sakha (Yakutia) since November 1, 2008. to December 31, 2013 the number of patients from 2008 year is 78, from 2013 year is 136, there is a tendency to increase [1].

Etiology and pathogenesis

The disease is characterized by high penetrance and the emergence of new mutations, almost - 50% of de novo mutation. The cause of NF1 are heterozygous mutations in the NF1 gene. The gene encodes a protein called neurofibromin, which is an onco-suppressor regulating the RAS system. The length and complex organization of the NF1 gene causes a high incidence of spontaneous mutations [3]. The NF1 gene is localized at 17q11.2 and has 62 exons. The rate of occurrence of mutations in the NF1 gene is 2 times higher than in other loci and is 10-4 on the gene [7].

For Recklinghausen's disease, genomic imprinting is characteristic, and 90% of the mutations are of paternal origin. The disease proceeds with a more pronounced clinic when the mutant allele is inherited on the maternal line [7].

NF1 patients described more than 500 different mutations of the gene localized at 17q. The nature of the mutations is quite specific: more than 80% of them lead to the synthesis of a nonfunctional «truncated» protein, or to the complete absence of a transcript (nonsense mutations, mutations in splice sites, deletions and inserts with a «frame» shift, large deletions covering the whole gene or its significant part). The remaining mutations are internal deletions without a «frame» shift and missense mutations affecting functionally important areas of neurofibromin [3].

Protein neurofibromin produces nerve cells, as well as specialized cells of neuroglia (oligodendrocytes, Schwann cells). Neurofibromin contains in its composition the domain of protein-activators of GTPase. Through this domain, the protein - neurofibromin in healthy people interacts with the pro-oncogene product RAS. Inhibits its function and realizes suppression of cell proliferation [10].

Neurofibromin is multifunctional, except for tumor suppression it triggers other signaling pathways and cellular processes. Neurofibromin is ubiquitously expressed during embryonic development and participates in the differentiation of skeletal, cardiovascular and nervous systems [14]. According to various studies, neurofibromin has been implicated in the differentiation of neurons through interaction with a variety of proteins, influences the processes of cell proliferation and adhesion, is involved in wound healing, proliferation of fibroblasts and collagen deposition [7].

At the heart of the pathogenesis of Type 1 neurofibromatosis is a disruption in the regulation of the carrying out of the intracellular signal along the RAS pathway. This path is one of the decisive in the development of the cell and the organism as a whole, regulates such important processes as the cell cycle, growth and differentiation of the cell. Most gene mutations that encode components of the RAS pathway lead to excessive uncontrolled activity. In connection with the foregoing, RAS-party is considered a disease with an increased risk of cancer [10].

Clinical manifestations of the disease

It is characterized by combined lesions of the nervous system (peripheral and central), skin, subcutaneous tissue,

often with disorders in internal organs, endocrine system and bone deformities, iris [9].

Neurofibromas are benign forms, derivatives of the nervous membrane of peripheral nerves, consisting of different types of cells: Schwann cells, fibroblasts, mast cells, endothelial cells, collagen fibers. [1]. It has been established that hormones affect the growth of the neurofibromas [11]. The first neurofibromas appear in the period of prebubertata or pubertal. At palpation, neurofibromas are usually dense to the touch, with a diameter of 1 to 2 cm or more, are painless, but if peripheral nerves are involved, soreness and sensory disturbance appear [10]. A characteristic symptom is the failure of the finger at slight pressure (the phenomenon of «bell button»). Neurofibromas are localized on the trunk and extremities; in women, they usually occur on the areola of the breast [12].

Skin manifestations are the most accessible diagnostic criteria and in most cases are the first symptoms of the disease. So, pigment spots cafe-et-lait - the first and permanent sign of type 1 neurofibromatosis and occurs in 95% of cases. Spots increase in size as the child grows [2]. At the histological analysis of pigmented spots, diffuse deposits are found in the papillate layer of the melanoblast and melanocyte derma with the inclusion of melanin in the cytoplasm [11].

Freckles (Crowe's syndrome) - pigmented spots of light brown color, ranging from 1-3mm, located in the axillary and inguinal areas, under the mammary glands, detected in most cases at 2 years of life. Skin manifestations can be accompanied by itching, which occurs in 20% of cases and reduces their quality of life [2]. Plexiform neurofibroma: are considered pathognomonic sign of the disease. Histologically, they are numerous elongated encapsulated neurofibromas, often mixed with diffuse neurofibroma, which includes the dermis and subcutaneous fat layer. At palpation there is the characteristic sensation of a «bag of worms» [12]. Plexiform neurofibromas can cause disfigurement and can disrupt functions or even endanger life [17].

Approximately 20% of patients have eye symptoms [11] that appear from birth or in the first years of a child's life. At examining the ocular fundus identify of tumor-like bumpy yellow formations in the region of the optic nerve disk or along the periphery of the fundus [4]. Almost all patients older than 20 years on the iris of the eye have «nodules Lisha», which are small whitish spots (hamartomas) on the iris of the eye [11]. The progression of eye pathology decreases visual acuity or leads to total loss of vision [4].

Quite often, in 25-50% of cases Recklinghausen's disease is accompanied by bone deformations in the form of kyphosis, characterized by early manifestation and rapid progression, which lead to irreversible cardiopulmonary and neurological disorders. To prevent them can only timely surgical intervention. In the area of scoliotic deformation, there is a violation of temperature-and-pain sensitivity, manifested by hypesthesia and thermoanesthesia. [8].

The peculiarity of the disease is characterized by a specific sequence of manifestation of clinical signs. So, from birth or from an early age, there are pigmented spots, plexiform neurofibromas, skeletal dysplasia, and other symptoms may appear later, by 5-15 years. In this case, there is a high variability in the clinical manifestations, course and rate of progression of type 1 neurofibromatosis [4]. One of the factors of such variability of manifestations of the disease, there may be individual features of the immune system [7].

Neurofibromatosis of the 1st type also has additional clinical manifestations: endocrine disorders (pheochromocytoma, dysplasia and puberty); changes in the skeleton (scoliosis - up to 15%, deformity of the chest, spondylolisthesis, non-vertebral arches, craniovertebral anomalies, skull asymmetry, pseudoarthrosis), etc. [4].

In addition to the characteristic signs of the disease, patients with Type 1 neurofibromatosis are at increased risk of developing malignant tumors. Thus, neurological tumors consist of glioma of the optic nerve, astrocytoma and schwannoma. Intracranial tumors can cause seizures. Other malignancies that are reported to be associated with this disease are Wilms' tumor, rhabdomyosarcoma, leukemia, retinoblastoma and malignant melanoma [12].

S. Fdil et al. described the case of a rare and prognostically serious complication in type 1 neurofibromatosis, spontaneous hemothorax and recommends attention to high hemorrhagic risk in patients with neurofibromatosis [16]. V.A. Filonov, T.A. Zakharicheva and co-authors in their observation described the case of a 10-year-old boy diagnosed with Type 1 neurofibromatosis complicated by intestinal bleeding. This case shows the need for additional examination of the digestive tract [6]. Patients with type 1 neurofibromatosis are particularly susceptible to internal jugular vein aneurysms due to vascular wall anomalies, which should also be considered when NF1. Thus, according to Delvecchio K et al., a case of internal jugular vein aneurysm measuring 6.9 cm × 3.8 cm × 6.5 cm in a 63-year-old patient with type 1 neurofibromatosis was described [15].

According to retrospective registry studies on congenital anomalies among patients with NF1 in the Finnish population conducted by Leppävirta J, Kallionpää RA.and co-authors, it was found that people with NF1 have an increased risk of serious congenital anomalies. Their study demonstrated results showing that abnormalities in the circulatory system, urinary system and abnormalities in the eyes, ear, face and neck are more common among children with NF1 [14].

Based on Leppävirta J, Kallionpää RA and co-authors of a retrospective analysis of the course of pregnancy of women with NF1, they revealed: increased caesarean section risk, premature birth, complications of pregnancy, including placental abruption, preeclampsia [15].

Diagnostics

Criteria for diagnosis were developed by the International Committee of Experts on Neurofibromatosis in 1988. Diagnosis Type 1 neurofibromatosis can be diagnosed if the patient has at least 2 symptoms [2].

1. Presence of 5 or more pigment macules in the color of « cafe´-au-lait «, more than 5 mm in size, and at least 6 spots with a diameter of more than 15 mm in post-pubertal age.
2. Freckle in the axillary and / or inguinal regions.
3. At least 2 neurofibromes of any type or one plexiform neurofibroma.
4. Dysplasia of the wing of the sphenoid bone or congenital thinning of the cortical layer of long bones with or without pseudoarthrosis.
5. Optic glioma.
6. Two or more Lisch nodules (iris hamartomas);
7. The presence of NF1 in relatives of the first line of kinship.

These clinical criteria are highly specific in adults with NF1 and children 8-9 years of age. In young children, the diagnosis can be more problematic. Only about half of the children with NF1 and

the family history of NF1 meet the criteria for diagnosis by the age of 1 year.

Molecular genetic testing to identify mutations in the NF1 gene assists clinicians in refining the diagnosis to patients who are suspected of type 1 neurofibromatosis, but who do not meet the diagnostic criteria, with an atypical course of the disease. Molecular genetic testing can be useful for a child with a tumor (eg, an optical glioma), in which a diagnosis of NF1 may influence the further management and selection of treatment tactics. Molecular genetic testing of an adult with NF1 is necessary if prenatal or preimplantation genetic diagnosis is expected in pregnancy or in pregnancy planning [17].

Taking into account that the majority of mutations in the NF1 gene lead to the synthesis of a «truncated» neurofibromin, the mutation analysis is carried out primarily on the RNA / protein level of the RTT-method. This method can be supplemented by a number of other traditional technologies of mutational screening, such as: SSCP (conformational polymorphism analysis of single-stranded DNA), heteroduplex analysis, gradient denaturing gel-electrophoresis, blot-hybridization, direct sequencing of individual gene exons, and (taking into account the probability of chromosomal rearrangements), fluorescence in situ hybridization and cytogenetic analysis. The use of various combinations of these methods makes it possible to detect mutations in the NF1 gene in 47% - 95% of cases [7].

Observation and treatment

Treatment is mostly symptomatic and depends on manifestations of type 1 neurofibromatosis.

Surgical treatment is indicated with sharp morbidity and an increase in the size of the tumor, ulceration, compression or displacement of vitally important organs.

Epileptic seizures should be carefully examined, as neurosurgical intervention is sometimes very useful for the patient [12].

In case of complications manifested by malignancy of the tumor, therapy with cytostatic drugs and radiation therapy are indicated.

It is necessary to conduct an annual medical examination, an annual ophthalmological examination, especially in children, regular evaluation of children's development, regular monitoring of blood pressure, MRI to monitor clinically suspicious intracranial tumors and tumors of other localization, medico - genetic consultation. [16].

Diagnostics of the spine is a selection criterion for evaluating a scoliotic curve with Cobb angles in the first place. CT allows a full three-dimensional evaluation of the spine and ribs. MRI is an additional study, especially for the evaluation of root, prevertebral and paraspinal soft tissues [13].

Conclusion

In conclusion, due to the high prevalence of Recklinghausen's disease and the high risk of developing malignant tumors, early detection at the level of the child's service determines the tactics of conducting, monitoring the patient, examining family members and identifying the carriers of the mutant gene. Important vocational training and alertness of primary care physicians. Continuity between specialists of different profiles is of decisive importance in the prognosis and quality of life of the patient. The main aspect of medical care is the medical and genetic counseling of family members to reduce the risk of the birth of patients with severe forms of type 1 neurofibromatosis.

Because an increased incidence of congenital anomalies may also reflect an increased risk of serious anomalies, careful monitoring is required during pregnancy and the neonatal period if the mother or father has NF1. Particular attention should be paid to identifying any signs of anomalies in the cardiovascular or urinary systems, to conduct research and determine the tactics of treatment and follow-up.

REFERENCES

1. Ufimtseva M.A. et al. Kozhnye proyavleniya bolezni Reklingchauzena [Skin manifestations of Recklinghausen's disease] Sovremennye problemy nauki I obrazovaniya [Modern problems of science and education]. Penza, 2016, No.6.
2. Mustafin R.N. Bermisheva M.A. et al. Bolezn` Reklinghauzena v Respublike Bashkortostan, rezul`taty I perspektivy issledovanii [Recklinghausen's disease in the Republic of Bashkortostan, results and prospects of research]. Medicinskii vestnik Bashkortostana [Medical bulletin of Bashkortostan]. Ufa, 2016, No.2 (62).
3. Mustafin R.N., Bermisheva M.A. et al. Osobennosti Neirofibromatoza 1 tipa [Features of type 1 neurofibromatosis]. Medicinskaya genetika [Medical Genetics]. Moscow, 2012, No. 3, p. 3-9.
4. Filonov V.A., Zakharycheva T.A. et al. Neirofibromatoz u rebenka, oslozhnennyi kishechnym krovotecheniem [Neurofibromatosis in the child complicated by intestinal bleeding] Dal`nevostochnyi medicinskiy zhurnal [Far Eastern Medical Journal]. Khabarovsk, 2011, No.3, p. 63-65.
5. Shchurova E.N., Gorbach E.N. et al. Osobennosti sostoyaniya myagkich tkanei na vershine deformacii u bol`nych kifoskoliozom na fone neirofibromatoza 1 tipa [Features of the state of soft tissues at the apex of deformation in patients with kyphoscoliosis against the background of type 1 neurofibromatosis] Nervno – myshechnye bolezni [Neuromuscular diseases]. Khabarovsk, 2017, No. 1.
6. Puzyrev V.P. Tomsky M.I. Geneticheskoe issledovanie naseleniya Yakutii [Genetic studies of the population of Yakutia]. Yakutsk, 2014, p. 336.
7. Pakhomova D.K., Dundukova R.S. et al. Rasprostranennost`Neirofibromato za 1 tipa I znachenie meropriyatii dlya ego rannego vyiavleniia [Prevalence of neurofibromatosis type 1and significance of measures for its early detection]. International Scientific and Practical Conference «WORLD SCIENCE». Ajman, May 2017, No. 5 (21).
8. Sadykova D.I. Safina L.Z. Pozdnyia diagnostika Neirofibromatoza 1 tipa u 14 –letnego yunoshi [Late diagnosis of neurofibromatosis type 1in a 14-year-old young man] Rossiiskii vestnik perinatologii I pediatrii [Rus. Vest. of perinatology and pediatrics]. Moskow, 2017, No. 4, p. 88-92.
9. Faassen M.V. RAS – patologii: sindrom Nuunan I drugie rodstvennye zabolevaniya [RAS-pathologies: Noonan's syndrome and other related diseases. Review of literature] Problemy aendokrinologii [Problems of endocrinology]. Moskow 2014, No. 6, p. 45-51.
10. Tsyrendorzhieva V.B. Nimaeva D.Ts. Neirofibromatoz 1 tipa [Neurofibromatosis type 1] Zabaikal`ski medicinskii zhurnal [Transbaikal Medical Journal]. Chita, 2016, No. 1.
11. Schneider N.A. Neirofibromatoz 1 tipa (Bolezn` Reklingchauzena) [Neurofibromatosis type 1 (Recklinghausen's disease)] Sibirskoe medicinskoe obozrenie [Siberian Medical Review]. Krasnoyarsk, 2007, No. 3.
12. Adil A. Neurofibromatosis Type 1 (Von Recklinghausen) /A. Adil, A.K. Singh // StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2017 Jun-.2017 Oct 19.
13. Chen A.M. Rib head dislocation causing spinal canal stenosis in a child with neurofibromatosis, type 1/ A.M. Chen, J.B. Neustadt, J.N. Kucera //J Radiol Case Rep. 2017 Aug 31;11(8):8-15. doi: 10.3941/jrcr.v11i8.3113. eCollection 2017 Aug.
14. Leppävirta J. Congenital anomalies in

neurofibromatosis 1: a retrospective register-based total population study / J. Leppävirta, R.A. Kallionpää, E. Uusitalo [et al.] //Orphanet J Rare Dis. 2018 Jan 15; 13(1):5.
15. Delvecchio K. Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1 / K. Delvecchio, F. Moghul, B. Patel, S. Seman //World J Clin Cases. 2017 Dec 16; 5(12):419-422. doi: 10.12998/wjcc.v5.i12.419.
16. Fdil S. Spontaneous hemothorax: a rare complication of neurofibromatosis type 1/ S. Fdil, S. Bouchikhi, J.E. Bourkadi /Pan Afr Med J. 2017 Sep 27; 28:85. 10.11604/pamj.2017.28.85.13820. eCollection 2017. French.
17. Friedman J.M. Neurofibromatosis 1 // GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 1998 Oct 2 [updated 2018 Jan 11].

The authors:

Neustroeva Lena Mikhaylovna– Junior researcher of the laboratory of the Laboratory of Population Genetics Tel.: 8 (914) 825 26 01. E-mail: Nlm31@mail.ru.

Pavlova Nadezhda Ivanovna – PhD, temporary acting chief scientific officer - head of the laboratory of heritable pathology. Tel.: +7 (914) 289 39 36. E-mail: solnishko_84@inbox.ru;

Solov'eva Natal'ya Alekseevna – PhD, temporary acting chief scientific officer - head of the Laboratory of Population Genetics. Tel.: 8 (924) 171 34 89. E-mail: sonata608@yandex.ru;

D'yakonova Aleksandra Timofeevna – Junior researcher of the laboratory of heritable pathology Tel.: 8 (914) 238 68 93. E-mail: dyakonovaa@bk.ru;

Varlamova Marina Alekseevna – Junior researcher of the laboratory of heritable pathology Tel.: 8 (914) 298 87 60. E-mail: varlamova.m@yandex.ru.

Filippova Natal'ya Pavlovna – PhD, associate professor, senior researcher of the Laboratory of Population Genetics. Tel.: 8 (914) 303 43 95. E-mail: inniah1970@list.ru;

Dodokhov Vladimir Vladimirovich – PhD, researcher of the Laboratory of Population Genetics. Tel.: 8 (964) 422 02 78. E-mail: dodoxv@mail.ru;

Kurtanov Khariton Alekseevich – PhD, Chief Scientific Officer - Head of the Department of Molecular Genetics. Tel.: +7 (914) 106 00 30. E-mail: hariton_kurtanov@mail.ru.

T.E. Burtseva, T.I. Nelunova, V.G. Chasnyk, S.A. Evseeva, Ya.A. Munkhalova

GENETIC AND EXTERNAL ENVIRONMENTAL RISK FACTORS FOR CONGENITAL HEART DISEASE IN CHILDREN (LITERATURE REVIEW)

ABSTRACT

The article presents a literature review of main risk factors of the development of congenital heart defects in children - genetic and environmental ones.

Keywords: congenital heart disease, children, risk factors, genetics, environment, pollutants.

Genetic risk factors for congenital heart disease in children. Genetically determined mechanisms of formation of congenital anomalies in the fetus include violations of maturation of male and female gametes, as well as pathology of intrauterine development. A variety of mutations (chromosome rearrangements such as translocations, inversions) damage the conjugation of chromosomes in meiosis and the death of maturing germ cells in the meiosis stage. Persons with chromosomal diseases (Down's disease, Klinefelter's syndrome) have severe spermatogenesis disorders associated with the defeat of the AZF locus gene complex located in the long arm of the male Y chromosome, mutations in the CFTR gene or the androgen receptor (AR) gene [6, 3].

The ovum of the female organism is even more sensitive to various exogenous and endogenous factors for several decades, which is associated with the complexity and long duration of hormonal regulation of the processes of oogenesis [1, 21]. Therefore, the prevention of hereditary conditioned congenital pathology should, first of all, be aimed at preserving women's health.

The formation of congenital developmental anomalies can be caused by the influence of damaging factors of different nature during preembryonic development (20 days from the moment of conception), embryonic (up to the 12th week of pregnancy) and fetal development [23]. Critical periods at this stage are implantation and placentation, when the selection of damaged embryos takes place [1].

Anomalies of fetal development, according to some studies, are associated with polymorphism of folate metabolism genes, since mutant genes can cause hyperhomocysteinemia, which has an embryotoxic effect. In addition, the deficiency of methyl groups is thus capable of altering the processes of cell proliferation and differentiation, making it more difficult to divide chromosomes during oogenesis [25]. The study of the polymorphism of folate cycle genes (*MTHFR, MTRR* genes) in families in which births of children with congenital heart diseases were observed showed a significant increase in the frequency of carriage of the MTHFR 677T allele in women and the MTRR 66G allele in men. The authors explain the negative effect of these alleles on embryogenesis by pathological changes in fetal cell division and differentiation during methylation failure [12].

Similar results were obtained in another study of the relationship of MTHFR 677T polymorphism and the risk of developing congenital malformation. The relative risk in fetal analysis was 1.26 without clear evidence of heterogeneity and 1.52 in the analysis of mothers with significant heterogeneity of the results [18].

In the genesis of congenital heart disease, the state of connective tissue in the process of ontogenesis is of great importance, since it is precisely involved in the construction of the heart's framework. The effects of various damaging factors, as well as genetic conditioning, can lead to connective tissue dysplasia and cardiac dysplasia. Atypically located chords of the left ventricle, prolapse of the mitral and tricuspid valves, aneurysm of the

interatrial septum prevail in the structure of congenital heart defects associated with connective tissue dysplasia [11]. Hereditary genesis of congenital developmental anomalies is confirmed by the fact that the risk of developing congenital heart disease significantly increases with twin monochorionic pregnancies [20] and closely related marriages [27].

Genetic and epidemiological studies in recent decades have contributed to the elucidation of the relationship between the prevalence of many diseases and the ethnicity of the population. In the study of hereditary diseases, it was found that differences in incidence rates, clinical picture and disease outcomes are associated with the frequency of alleles of genes responsible for the development of the disease in ethnic groups [24]. It was found that mutations of alleles, detected with a frequency of less than 2%, are, as a rule, specific for individual ethnic groups. For the population of ethnic groups of the Russian Federation, there are also significant differences in adaptation reactions, physiological and morphological indicators [4, 13]. In modern conditions, due to interethnic marriages, the introduction of the European component into the gene pool of ethnic groups of northern peoples is observed, which can change the functioning of physiological systems and predispositions to different classes of diseases [17, 9].

External environmental risk factors for congenital heart disease in children. The development of economic activities throughout the world has now led to large-scale environmental pollution of production waste. Toxic substances through the ecological chain enter the human body, having various adverse effects, including teratogenic. The most vulnerable to their impact are the body of pregnant women and children. The issue of the effect of environmental toxic substances and other anthropogenic risk factors on the cardiovascular system of the embryo and fetus is still not fully understood, which is associated with difficulties in establishing threshold exposure and dose dependence of the formation of congenital malformation [22]. The most pronounced teratogenic effect in relation to the cardiovascular system is established for ionizing radiation. At the heart of hereditary disorders in individuals exposed to radiation exposure are chromosomal, genomic and dominant gene mutations in both somatic and sexual cells. Mutational changes in somatic cells cause destabilization of the genome, a decrease in functional and reparative capabilities of DNA, and immunological resistance of the organism. Developmental malformations are caused by genetic changes in the sex cells. Thus, studies conducted on samples including descendants of the first generation of the liquidators of the Chernobyl accident showed a high prevalence among them of congenital anomalies and malformations - 2.5 times higher than in the Russian population as a whole. Among the population living in radiation-contaminated territories, this indicator exceeded the all-Russian level by 2.8 times. 46.1% of the children of the liquidators of the accident with the detected chromosomal aberrations had abnormalities of development, including congenital heart disease [8]. Industrial emissions to atmospheric air due to the operation of industrial enterprises in the chemical and petrochemical industries are also reflected in an increase in the prevalence of congenital heart disease among the population living in contaminated areas. Thus, in a study conducted in industrial regions of the Republic of Tatarstan, a direct correlation was established between the increase in the incidence of congenital heart diseases and the total release of industrial toxic substances described by the regression equation: congenital heart disease = 0.469 + 0.003 x NE [14]. The effect of toxic industrial emissions in the pathogenesis of the development of congenital malformations can be explained by mutagenesis of the sex cells of parents or somatic cells of their descendants, the disturbance of mitotic processes, damage to energy processes and cell membranes in the fetus, which eventually leads to cardiac dysfunction at various stages of organ formation [10].

In the Republic of Sakha (Yakutia) in recent years, the growth of anthropogenic pollution of atmospheric air by solid, liquid and gaseous products of industrial production, in the structure of which solids, carbon monoxide, nitric oxide, sulfur dioxide and hydrocarbons prevail. In the industrially developed regions of the republic, a statistically significant increase in morbidity rates of congenital anomalies, deformations and chromosomal abnormalities, including CHD, was established [2]. These data are consistent with the results of a study in the city of Belgorod. The highest prevalence of CHD was observed in areas with a high content of pollutants, such as nitrogen dioxide, inorganic dust, carbon monoxide, which are unfavorable for the ecological state of the air basin, with a load of 12.0 tons per year per newborn [5].

In the regions of developed agricultural production of the Stavropol Territory of the Russian Federation, land contamination with copper, cadmium, nickel, pesticides, as well as a high content of nitrites and nitrates in drinking water. At the same time, the results of medical and hygienic monitoring indicate a steady increase in the prevalence of congenital malformations in newborns and children, one third of whom are in the CHD [7].

Chinese researchers established a direct relationship between the exposure of pregnant women to ozone and carbon dioxide in the first trimester of pregnancy and the development of interventricular septal defects and tetralogy of Fallot in newborns [26].

Data from twelve epidemiological studies suggest that the risk of developing CHD in newborns increases five to six times when exposed to an industrial solvent of trichlorethylene on the mother's body during pregnancy [19]. The risk of congenital heart diseases increased also with the professional effect of nickel on the body of the fathers (RR = 1.28) [15].

Studies of the etiological association of anthropogenic and occupational factors on the parents' organism and the development of congenital circulatory anomalies in their offspring are important not only for studying the pathogenetic features of teratogenesis, but also for the development and implementation of preventive programs in ecologically unfavorable territories.

Thus, on the basis of literature data, one can conclude that genetic and external environmental factors are one of the main risk factors for the CHD development; are of great importance in assessing and predicting the causes that have a negative impact on the reproductive health of the population and increase the risk of development congenital heart defects in children.

REFERENCES:

1. Ajlamazyan EH.K. Baranov V.S. Prenatal'naya diagnostika nasledstvennyh i vrozhden¬nyh boleznej [Prenatal diagnosis of hereditary and congenital diseases]. Moscow: MEDpress-inform [M.: Medpress-inform]. 2005, 415 p.
2. Astaf'ev V.A. Ushkareva O.A. Semenova N.P. Zagryaznenie atmosfernogo vozduha i zabolevaemost' naseleniya respubliki Saha (Yakutiya) [Pollution of atmospheric air and morbidity of the population of the Republic of Sakha (Yakutia)] Byulleten' VSNC SO RAMN [the Bulletin of East Siberian scientific center SB RAMS]. 2013,

V. 94, №6, P. 92-96.
3. Baranov A.A. Al'bickij V.YU. Il'in A.G. O rezervah snizheniya smertnosti detskogo naseleniya [On the reserves to reduce the mortality of children] Voprosy sovremennoj pediatrii [Issues of modern pediatrics]. 2006, V. 5, №. 5, P. 5-7.
4. Boyko E.R. Fiziologo-biohimicheskie osnovy zhiznedeyatel'nosti cheloveka na Severe [Physiological and biochemical foundations of human life in the North]. Ekaterinburg: UrB RAS, 2005, 210p.
5. Verzilina I.N. Agarkov N.M. Churnosov M.I. Rasprostranennost' i struktura vrozhdennyh anomalij razvitiya u novorozhdennyh detej g. Belgoroda [Prevalence and structure of congenital developmental anomalies in newborn children in Belgorod] Pediatriya [Pediatrics]. 2009, V. 87, № 2, P. 151-154.
6. Ginter E. K. Medicinskaya genetika [Medical genetics]. Moscow: Medicine, 2003, 448p.
7. Dement'eva D.M., Bezrodnova S.M. Problema vrozhdennyh porokov razvitiya u detej v regione s neodnoznachnoj ehkologicheskoj situaciej [The problem of congenital malformations in children in a region with an ambiguous environmental situation] Gigiena i sanitariya [Hygiene and Sanitation] . 2013, № 1.- P. 61-64.
8. Ibragimova A.I. Klinicheskie dannye o genotoksicheskom dejstvii ioniziruyushchej radiacii [Clinical data on the genotoxic effect of ionizing radiation] Ros. vestn. perinat. i pediatrii [Ros. known. perinatum. and pediatrics]. 2003, № 6, P. 51-55.
9. Krivova N.A., Chanchaeva E.A. Antioksidantnaya aktivnost' plazmy krovi u aborigenov nizkogor'ya i srednegor'ya Yuzhnogo Altaya [Antioxidant activity of blood plasma in aboriginal lowlands and mid-mountains of the Southern Altai] Fiziologiya cheloveka [Physiology of man]. 2011, № 2, P. 60-65.
10. Kucenko S. A. Osnovy toksikologii [Foundations of Toxicology] SPb.: OOO Izd-vo «Foliant» [SPb .: Open Company Publishing house "Foliant"]. 2004, 720p.
11. Men'shikova L.I. Surova O.V., Makarova V.I. Displaziya soedinitel'noj tkani serdca v geneze kardiovaskulyarnoj patologii u detej [Dysplasia of the connective tissue of the heart in the genesis of cardiovascular pathology in children] Vestnik aritmologii [Bulletin of arrhythmology]. 2000, №19, P. 54-56.
12. Fetisova I.N. Peretyatko L.P., Dyuzhev ZH.A. [i dr.] Polimorfizm genov folatnogo cikla v sem'yah s privychnym nevynashivaniem beremennosti, porokami razvitiya ploda i anehmbrioniej [Polymorphism of folate cycle genes in families with habitual miscarriages, fetal malformations and anembryonia] Vestnik RUDN, seriya Medicina [Bulletin of RUDN, series Medicine]. 2009, № 6, P. 11-18.
13. Kolesnikova L.I. Darenskaya M.A., Dolgih V.V. [i dr.] Pro- i antioksidantnyj status u podrostkov-tofov i evropeoidov [Pro- and antioxidant status in sub-growths-tophics and Caucasoids] Izvestiya Samarskogo NTS RAS [Proceedings of the Samara Scientific Center of the Russian Academy of Sciences]. 2010, T. 12, № 1-7, P. 1687-1691.
14. Nasyrova K.I. Mirolyubov L.M., Kalinicheva YU.B. [i dr.] Regional'naya zabolevaemost' vrozhdennymi porokami serdca v svyazi s zagryazneniem atmosfernogo vozduha promyshlennymi vybrosami [Regional morbidity of congenital heart defects due to industrial air pollution of atmospheric air] Prakticheskaya medicina [Practical medicine]. 2008, T.28 , №4, P. 72-74.
15. Nikanov A.N. Talykova L.V., Rocheva I.I. [i dr.] Rol' proizvodstvennyh faktorov riska v formirovanii reproduktivnyh ehffektov u rabotnikov nikelevyh predpriyatij krajnego severa [The role of production risk factors in the formation of reproductive effects among employees of nickel enterprises in the Far North] EHkologiya cheloveka [Ecology of the person]. 2009, №6, P. 44-46.
16. Sipyagina A.E. Osobennosti formirovaniya vrozhdennyh porokov razvitiya u detej iz semej likvidatorov radiacionnoj avarii [Features of formation of congenital malformations in children from families of liquidators of a radiation accident]. Ros. vestn. perinat. i pediatrii [Ros. known. perinatum. and pediatrics.]. 2005, №2, P. 53-56.
17. Fefelova V.V. Voprosy proiskhozhdeniya mongoloidov Sibiri i vliyanie otdalennyh posledstvij autbridinga na predraspolozhennost' ehtih populyacij k zabolevaniyam [Questions of the origin of Mongoloidal Siberia and the influence of remote consequences of outbreeding on the predisposition of these populations to diseases] The Bulletin of the Siberian Branch of the Russian Academy of the Medical Sciences: Thesis of the 13th international congress on circumpolar health. Novosibirsk, 2006, P. 88-89.
18. Li.Z, Jun Y., Zhong-Bao R. [et all] Association between MTHFR C677T polymorphism and congenital heart disease. A family-based meta-analysis. Herz. -2015,Vol. 40, Suppl. 2, P. 160-167.
19. 19. Bukowski J. Critical review of the epidemiologic literature on the association between congenital heart defects and exposure to trichloroethylene. Rev Rev Toxicol., 2014, Vol. 44, № 7, P.581-589.
20. Campbell K., Copel J., Ozan Bahtiyar M. Congenital heart defects in twin gestations, Minerva Ginecol., Vol. 61, № 3, P.239-244.
21. Golubovsky M. D. Manton K. Oocytes physically and genetically link three generations: genetic demographic implications. Environment and perinatal medicine, SPb., 2003, P. 354-356.
22. Foster W.G., Evans J.A., Little J. [et all] Human exposure to environmental contaminants and congenital anomalies: a critical review. Crit Rev Toxicol. 2016, №11, P.1-26.
23. Fung A., Manlhiot C., Naik S. [et all] Impact of prenatal risk factors on congenital heart disease in the current era. J Am Heart Assoc. 2013, Vol. 31, № 2: e000064.
24. 24. Kaufman J.S. Cooper R.S. Considerations for the use of racial / ethnic classification in the etiologic research. Am. J. Epidemiol. 2001, Vol. 154, P. 291-298.
25. Martinelli M. Scapoli L., Pezzetti F. C677T variant form at the MTHFR gene and CL . P: a risk factor for mothers?. Am. J. Med. Genet. , 2001.,Vol. 98, P. 357-360.
26. Zhang B. Zhao J., Yang R. [et all] Ozone and Other Air Pollutants and the Risk of Congenital Heart Defects . Sci Rep., 2016, № 6. P. 348-352.
27. Shieh J.T. Bittles A.H., Hudgins L. Consanguinity and the risk of congenital heart disease . Am J Med Genet A, 2012, Vol.158A (5), P.1236-1241.

The authors:

Burtseva Tatyana Egorovna, MD, Professor of the Department of Pediatrics and Pediatric Surgery of the MI SVFU, Laboratory of the YNC CMP, Yakutsk, Russia, e-mail: bourtsevat@yandex.ru, contact. telephone: 89142943244.

Nelunova Tuyara Ivanovna, cardiologist, RB 1-NCM, post-graduate student of SPBGPMU, Yakutsk, Russia, nelunova-ti@mail.ru, tel. 89248718507.

Chasnyk Vyacheslav Grigorievich, MD, professor, head. Department of Hospital Pediatrics SPbGPMU, Saint-Petersburg, Russia, e-mail: chasnyk@gmail.com, contact. phone: 89062296831.

Evseeva Sardana Anatolievna, Senior Researcher YNS CMP, Yakutsk, Russia, e-mail: sarda79@mail.ru, contact. phone: 89679111195.

Munkhalova Yana Afanasyevna, MD, associate professor, head. Department of Pediatrics and Pediatric Surgery of MI SVFU, Yakutsk, Russia, e-mail: tokmacheva@mail.ru, contact. phone: 89142707107.

A.V. Larinskaya, A.V. Yurkevitch, I.D. Ushnitsky, T.E. Kruglov

THE COMPARATIVE CHARACTERISTIC OF MODERN ENDOGERMETICS

ABSTRACT

The epidemiological researches in Russia demonstrate the prevalence of caries among the population that determines the frequency of its complications and endodontic treatment [1, 3, 10, 12, 13]. It needs the improvement of effective endodontic treatment that is a current odontology problem [8, 15- 17].

The efficiency of endodontic treatment depends on quality of preparation and sealing of the tooth root channel. At the same time clinical performance and biological compatibility of widespread endogermetics in dental practice is various since there is a direct interrelation between the choice of sealing material, method of root channel obturation and the favorable prognosis after treatment.

There are many technics of root channel obturation in endodontic treatment complications of caries, each of which has the advantages and disadvantages. The most important of them from the clinical point of view is a method of root channel obturation by gutta-percha points and endogermetics. At the same time various materials are applied to channels sealing obturation. Zincum-oxide-eugenol pasta is the cements modified for endodontic use. Their main property is the bactericidal effect. Sealers containing a calcium hydroxide, have antimicrobial activity, osteogene effect. Meanwhile the sealers containing a formic aldehyde have high toxicity. Nowadays polymers are widely applied in endodontic practice. Advantages of this group of sealers are good handling properties, adhesion, they aren’t dissolved under the influence of tissue liquid, have dimensional stability, are indifferent to periodont. At the same time the analysis of research data of density of root channels obturation by scanning acoustic and optical microscope characterizes the adequate obturation of root channels.

For the last decade a large amount of new materials for root channels was offered. There are still attempts of creation of new germetics, new technologies are being developed, which will have positive effect to more predictable and reliable treatment of caries complications, promoting teeth conservation.

Keywords: complications of caries, endodontics, sealing materials, obturation of root channels, bactericidal action, biocompatibility.

REFERENCES

1. Borovskiy E.V. Sostoyanie endodontii v tsifrah i faktah [Endodontics state in numbers and facts] Klinicheskaya stomatologiya [Clinical odontology], Moscow, 2003, No 1, p.38-40. Goryilev A.A. Laboratorno-klinicheskoe issledovanie effektivnosti plombirovaniya kornevyih kanalov materialom na osnove sinteticheskogo polimera [Laboratory clinical trial of root channels sealing efficiency on the basis of synthetic polymer] : avtoref. diss. … kand.med.nauk [dissertation abstract. … candidate of medical sciences]. Moscow, 2009, 21 p.
2. Dyibov D.A., Kruglov T.E. Izuchenie chastotyi vozniknoveniya retsi-diviruyuschego i vtorichnogo kariesa u zhiteley Amurskoy oblasti [Studying of frequency of developing of recurrent and secondary caries among residents of the Amur region] Stomatologiya – nauka i praktika, perspektivyi razvitiya materialyi nauchno-prakticheskoy konferentsii, posvyaschennoy 90-letiyu so dnya rozhdeniya L. P. Ivanova. [Stomatology – science and practice, the prospects of development, materials of the scientific and practical conference devoted to the 90 anniversary of L.P. Ivanov].Volgograd, 2017, p.47-50.
3. Lutskaya I. K. Obosnovanie vyibora endodonticheskogo lecheniya [Choice of the endodontic treatment] Novoe v stomatologii [New in odontology]. Moscow, 2001, No 2, p.28-30.
4. Makedonova Yu.A. Sravnitelnaya harakteristika effektivnosti materialov pri plombirovanii kanalov korney zubov s intaktnyim pe-riodontom [The comparative characteristic of efficiency of materials for root channels sealing with intact periodontium]: avtoref. diss. … kand. med.nauk [thesis abstract … candidate of medical sciences]. Volgograd, 2012. 23 p.
5. Makedonova Yu.A. Firsova I.V. Germetiziruyuschaya sposobnost novogo obtura-tsionnogo materiala dlya kornevyih kanalov «REAL SEAL» s tehnologiey «RESILON» [The germetic ability of new obturative material for root channels «REAL SEAL» with RESILON technology] Saratovskiy nauchno-meditsinskiy zhurnal [Saratov scientific and medical magazine]. Saratov, 2012, No 1. p.111-113.
6. Malyutina N.N., Taranenko L.A. Patofiziologicheskie i klinicheskie aspektyi voz-deystviya metanola i formaldegida na organizm cheloveka [Pathophysiological and clinical aspects of impact of methanol and formic aldehyde on the human body] Sovremennyie problemyi nauki i obrazovaniya [Modern problems of science and education]. Moscow, 2014, No 2, p.36-37.
7. Shiryak T.Yu. Saleev R.A., Urazova R.Z. Potrebnost v lechenii oslozhnYonnogo kariesa vremennyih zubov u detey [The need for treatment of the complicated caries of temporary teeth at children] Kazanskiy meditsinskiy zhurnal [Kazan medical magazine]. Kazan, 2012, V.93, No 4.p.634-637.
8. Firsova I.V., Makedonova Yu.A., Trigolos N.N. Rol germetiziruyuschey sposobnosti silerov v uspe-he endodonticheskogo lecheniya [A role of the germetic ability of sealers in successful endodontic treatment] Sovremennyie problemyi nauki i obrazovaniya [Modern problems of science and education], 2014, No1; URL: www.science-education.ru/115-11915 (data obrascheniya [date of the address]: 06.10.2017).
9. Baginskiy A.L. ChizhovYu.V. Ushnitskiy I.D. [i dr.] Stomatologicheskiy status i sotsialno-gigienicheskaya otsenka korennyih zhiteley Dolgano-Nenetskogo munitsi-palnogo rayona Krasnoyarskogo kraya i Respubliki Saha (Yakutiya) [The dental status and social-hygienic assessment of aboriginals of the Dolgan-Nenets municipal district of Krasnoyarsk Krai and Republic of Sakha (Yakutia)] Aktualnyie problemyi i perspektivyi razvitiya stomatologii v usloviyah severa. Sbornik statey mezhregionalnoy nauchno-prakticheskoy konferentsii, posvyaschennoy 95-letiyu stomatologicheskoy sluzhbyi Respubliki Saha (Yakutiya) [Current problems and prospects of odontology development in the North conditions. The collection of articles of the transregional scientific and practical conference devoted to the 95 anniversary of dental service of the Republic of Sakha (Yakutia)], Yakutsk, 2015, p. 100-107.
10. Kosilova A. S., Oskolkova D.A., Pleshakova T.O. Sravnitelnaya harakteristika sovremennyih silerov i predpochteniya vrachey-stomatologov [Comparative characteristic of modern sealers and preference of dentists] Problemyi stomatologii [Odontology Problems]. Moscow, 2012, No. 5, p. 26-30.
11. Larinskaya A.V., Yurkevich A.V., Mihalchenko V.F. Covremennyie aspektyi vnutrikanalnoy dezinfek-tsii pri lechenii oslozhnennyih form kariesa [Modern aspects of intra channel disinfection at treatment of the complicated caries]

Klinicheskaya stomatologiya [the Clinical odontology]. Moscow, 2017, V.83. No 3. p.13-16.
12. Oskolskiy G.I., Ushnitskiy I.D., Zagorodnyaya E.B. Stomatologicheskiy status naseleniya Dalnevo-stochnogo regiona [Dental status of the population of the Far East region] Endodontiya Today. [Endodontics Today]. Moscow, 2012, No 3. p.10-14.
13. Severina T.V. Issledovanie kachestva prisoedineniya silerov k stenke kornevogo kanala i guttaperchevyim shtiftam [Research of quality of sealers accession to the wall of the root channel and gutta-percha points] Mezhdunarodnyiy zhurnal prikladnyih i fundamentalnyih issledovaniy [International magazine of applied and basic researches]. Moscow, 2014, No 2. p.154-158.
14. Semenov A.D., Ushnitskiy I.D., Egorov R.I. Stomatologicheskiy status zhiteley promyishlennyih rayonov Respubliki Saha (Yakutiya) [The dental status of inhabitants of industrial regions of the Sakha Republic (Yakutia)] Aktualnyie problemyi i perspektivyi razvitiya stomatologii v usloviyah severa. Sbornik statey mezhregionalnoy nauchno-prakticheskoy konferentsii, posvyaschennoy 95-letiyu stomatologicheskoy sluzhbyi Respubliki Saha (Yakutiya) [Current problems and the prospects of odontology development in the North conditions. The collection of articles of the transrregional scientific and practical conference devoted to the 95 anniversary of dental service of the Sakha Republic (Yakutia)]. Yakutsk, 2015. p.86-90.
15. Suvyirina M.B., Yurkevich A.V. Otsenka rasprostranennosti nekarioznyih porazheniy tverdyih tkaney zubov u vzroslogo naseleniya (na primere Amurskoy oblasti) [Assessment of prevalence of non-carious lesions of firm tissues of teeth among adult population (on the example of the Amur region)] Vestnik Volgogradskogo gosudarstvennogo meditsinskogo universiteta [Bulletin of the Volgograd state medical university]. Volgograd, 2017, V. 64. No 4, p.96-98.
16. Ushnitskiy I.D. Pokazateli porazhennosti kariesom zubov u nase-leniya Yuzhnoy Yakutii [Prevalence indicators of teeth caries among the population of South Yakutia] Dalnevostochnyiy meditsinskiy zhurnal [Far East medical magazine]. Chabarovsk, 2000, No 2, p.55-56.
17. Holodovich O.V. Primenenie endogermetikov na osnove polidimetilsiloksana v kompleksnom lechenii bolnyih s hronicheskimi formami pulpit [Use of endosealers on the basis of polydimethylsiloxane in complex treatment of patients with chronic forms of pulpitis] : avtoref. diss. … kand.med.nauk [thesis abstract… candidate of medical sciences]. Voronezh, 2011, 23 p.
18. Al-Khatib Z.Z. The antimicrobial effect of various endodontic sealers. / Z.Z. Al-Khatib, R.H. Baum, D.R. Morse [et. al] // Oral Surgery, Oral Medicine and Oral Pathology. – 1990. – №70. – P.784-790.
19. Araki K . Indirect longitudinal cytotoxicity of root canal sealers on L929 cells and human periodontal ligament fibroblasts / K. Araki, H. Suda, L.S. Spangberg // Journal of Endodontics. – 1994. – №20. – P.67-70.
20. Araki K. Excretion of 14C-formaldehyde distributed systemically through root canal following pulpectomy / K. Araki, H. Isaka, T.Ishii [et. al] // Endodontics and Dental Traumatology. – 1993. – №9. – P. 234-239.
21. Beltes P. In vitro evaluation of the cytotoxicity of calcium hydroxide-based root canal sealers / P. Beltes, E. Koulaouzidou, V.Kotouala [et. al] // Endodontics and Dental Traumatology. – 1995. – №11. – P.245-249.
22. Cohen B.I. Evaluation of the release of formaldehyde for three endodontic filling materials / B.I. Cohen, M.K. Pagnillo, B.L. Musikant [et. al] // Oral Health. – 1998. – №88. – P.37-39.
23. Ersev H. Cytotoxic and mutagenic potencies of various root-canal-filling materials in eukaryotic and prokaryotic cells in vitro / H. Ersev, G. Schmalz, G. Bayirli [et.al] // Journal of Endodontics. – 1999. – № 25. – P.359-363.
24. Geurtsen W, Leinenbach F, Krage T, Leyhausen G Cytotoxicity of four root canal sealers in permanent 3T3 cells and primary human periodontal ligament fibroblast cultures / W. Geurtsen, F. Leinenbach, T. Krage [et.al] // Orals Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. –1998. – №85. – P.592-597.
25. Huang F.M. Cytotoxicity of resin-, zinc oxide-eugenol-, and calcium hydroxide-based root canal sealers on human periodontal ligament cells and permanent V79 cells / F.M. Huang, K.W. Tai, M.Y. Chou [et.al] // International Endodontic Journal. – 2002. – №35. – P.153-158.
26. Koch M.J. Formaldehyde release from root-canal sealers: influence of method // International Endodontic Journal. – 1999. – №32. – P.10-16.
27. Lin L. M., Gagler P., Langelan K. A histopatologic and hislobacteriologic study of 35 periapical endodontic surgical of specimens / L.M. Lin, P. Gagler, K. Langelan // J. Endod. – 2006. – Vol.3. – №8. – P.58-60.
28. 28. Mickel A.K. Growth inhibition of Streptococcus anginosus (milleri) by three calcium hydroxide sealers and one zinc oxide-eugenol sealer / A.K. Mickel, E.R. Wright // Journal of Endodontics. – 1999. – №25. – P.34-37.
29. Osorio R.M. Cytotoxicity of endodontic materials / R.M. Osorio, A. Hefti, F.J. Vertucci // Journal of Endodontics. – 1998. – №24. – 91-96.
30. Segura J.J. Effect of eugenol on macrophage adhesion in vitro to plastic surfaces / J.J. Segura, A. Jmenez-Rubio // Endodontics and Dental Traumatology. – 1998. – №14. – P.72-74.
31. Spangberg L.SW. AH-26 releases formaldehyde / L.SW. Spangberg, S.V. Barbosa, G.D. Lavigne // Journal of Endodontics. – 1993. – №19. – 596-598.
32. Telli C. Evaluation of the cytotoxicity of calcium phosphate root canal sealers by MTT assay / C. Telli, A. Serper, A.L. Dogan [et.al] // Journal of Endodontics. – 1999. – №25. – P.811-813.

The authors:

Larinskaya Anna Viktorovna - graduate student of odontology department of orthopedic odontology of The Far Eastern State Medical University. Tel: +7-914-159-56-24, e-mail address: nura.lar@mail.ru. Address: 35, Muravyev-Amursky St., Khabarovsk 680000;

Alexander Vladimirovitch Yurkevitch - dean of dental faculty of The Far Eastern State Medical University, head of odontology orthopedic department, PhD, associate professor. Tel: (4212) 625-888, e-mail address: dokdent@mail.ru. Address: 35, Muravyev-Amursky St., Khabarovsk 680000;

Ushnitsky Innokentiy Dmitrievitch - head of the department of therapeutic, surgical, orthopedic odontology and odontology of children's age of Medical institute of NEFU, Yakutsk (Russia), PhD, professor. Tel: 89241708940, e-mail address: incadim@mail.ru;

Kruglov Taras Evgenyevitch - clinical intern of orthopedic odontology department of The Far Eastern State Medical University, tel: 8-965-675-42-40, e-mail address: krooglik95@yandex.ru. Address: 35, Muravyev-Amursky St., Khabarovsk 680000.

N.V. Strelnikova, A.A. Antonova, E.L. Starovoytova, O.L. Shevchenko, I.P. Koltsov, V. B. Turkutyukov, M.I. Elistratova, T.O. Martilova

TEMPORARY TEETH CARIES AND ITS COMPLICATIONS IN CHILDREN AS A SOCIALLY SIGNIFICANT INFECTIOUS DISEASE

ABSTRACT

The article contains the analysis of literature of more than 50 years. It gives the ground to identify the caries of children's temporary teeth as infectious process. Under favorable conditions, it can turn into an infectious disease with natural peculiarities of epidemiology, etiology, pathogenesis, pathomorphology, clinical manifestations, complications, immunological changes, with the possibility of specific and nonspecific prevention. The decay is viewed as the globally common infection with high social value.

Keywords: caries of temporary teeth, children, the carious process, infectious disease, opportunistic infection, cariogenic bacteria, biofilms.

Epidemic of carious illness among the population has enlarged from isolated cases in ancient times to 100% nowadays [1]. According to WHO data, the prevalence of caries in different countries varies from 17 to 94 %. It is a problem of public health in general [14], and according to the data [27] caries of teeth is one of the most widespread infectious diseases, and the most expensive illness in the world. The severity of tooth decay and their complications at an early age is increasing [14], the prevalence of caries of teeth of one year old children is 15 %, by 3 years this indicator reaches 46, by 6 years – 96 % [6, 7, 11, 16].

Terms Caries Status (CS), Caries Free (CF) children, the Early Childhood Caries - ECC, a Severe Early Childhood Caries (S-ECC) are often applied. ECC is characterized by the presence of one or more carious, by a removed tooth because of the complicated caries or the sealed-up surface in any temporary children's tooth at the age of 71 months and earlier [34]. ECC is recognized as a clinical syndrome, described by Beltrami in the 1930th as "Les dents noire de tout-petits" (Black teeth in toddlers) [19]. The susceptibility of enamel to the influence of acids in the period of an incomplete mineralization is the greatest. At the age of 2-3 years after teething the high prevalence of a focal demineralization can take place. The probability of emergence of this disease increases with insufficient hygienic care of an oral cavity and consumption of a large amount of carbohydrates [4, 6, 20]. At this time teeth especially need thorough and effective care [4]. The role of parents increases in ensuring prophylaxis of the oral cavity of the child. Their own sanological culture and their active position in providing a healthy lifestyle to their children is very important, however local all-hygienic and social and economic aspects are important as well [12].

The fact of high prevalence of S-ECC among children of early age is alarming. It leads to notable medical and medico-social consequences, significantly influencing a condition of physical and mental health of a child and also family welfare in general [6]. Society has recognized interrelation between ECC and inadequate childcare [21]. The authors [35] related untreated or neglected caries to the crime basis - child abuse. Mostly ECC is connected with a low economic level in the country of child's accommodation. In such countries small children have weight reduction because of impossibility of good nutrition: children at the age of 3 years with early caries weighed 1 kg less, than children in a control group as the toothache complicates the process of meal taking, promotes a sleep disorder, slowing down metabolic activity [28].

The aggressive course of caries leads to complications, the foci of a chronic infection and their further sensibilization influences the functioning of an organism and growth of the child, defining his psychoemotional state [13, 18].

In modern socially we have recognized the official status of important infections such as: HIV, hepatitis's B, C, D, tuberculosis and others, which in some cases lead to death. The infectious disease of teeth caries is a silent pandemic. It doesn't threaten life, but considerably reduces its quality, leading to global social and economic consequences. It requires - up to 5 percent of expenses on a medical care in the world, up to 70 percent of stomatologists working time [18], and can confidently be recognized as a socially significant infection of the 21st century.

Classifications of caries are made on the basis of clinical and morphological features of a lesion of teeth. According to the classification of ICD-10 caries belongs to: class XI - Illnesses of digestive organs; to section 1.1. - Illnesses of an oral cavity, sialadens and jaws; K02 - Caries of teeth. Also caries is distinguished on lesion depth: initial, superficial, average and deep caries. These classifications allow us to judge a carious lesion of a separate tooth; however the main task is a treatment of the child with caries of teeth, but not only one tooth. Therefore in pediatric dentistry it is important to use one more classification by T.F. Vinogradova. This classification is based on a degree of illness activity: the compensated, subcompensated, and decompensated form [4]. The conceptual framework of an infectology is successfully applied in cariology: according to the clinical state there can be peracute, acute and chronic caries; mild, average, and severe forms; uncomplicated and complicated forms of caries.

Caries is a localized, transmissible pathological infectious process [25]. The targets of a carious infection are the solid dentine and cement of teeth while in other infectious diseases, soft organs and tissues are damaged. Various scientists at various times defined caries first of all as an infectious disease, and only secondly as the progressing destruction of tissues of tooth. Recognition of caries an infectious disease gives the prospect of integration of cariology with the general medicine. Its infectious nature focuses attention of experts on elimination of a microbial plaque on teeth and decrease risk factors promoting acid dissolution of mineral substrate [7].

Treatment-and-prophylactic measures at tooth decay are based on Miller's chemical and parasitological theory however there are "white maculae" in etiology and pathogenesis of "illness of a civilization". There are indisputable data of interrelation between the epidemic of caries and climate-geographical and medico-social factors [7]. The most

reasonable is the concept of ecology of a microbic flora of the dental plaque according to which pathological process develops if there is the interaction of two main cariogenic factors — the influence of substrate for a certain period of time and the existence of acid-forming bacteria [13]. The most recognized and dangerous are cariogenic bacteria, Gram-positive coccuses of phylum *Firmicutes*, species of *Streptococcus mutans*, *Streptococcus sobrinus*, the Kingdom of *Bacteria*, the Class *Bacillaceae*, the Family *Streptococcaceae*, and the Genus *Streptococcus*.

The hypothesis of a role of streptococci in development of caries has been accepted in the USA for practical guidance since 1960 after the research works conducted in the country from the 40th of the previous century [29]. Streptococci make an considerable share of micro flora of a tooth plaque, up to 80 percent of total amount of microorganisms in an oral cavity [5]. They can be met in various quantitative ratios which depend on a diet, individual hygiene, structure and peculiarities of saliva and other factors [20]. Scientists study the role of *S. gordonii, S. sanguinis*, and other Viridians Group Streptococci (VGS), which are the residents of an oral microbiota. We should mention that 7 indigenous species according to modern classification are related to the ecological *mutans* group: *S. cricetus, S. rattus*, *S. mutans, S. sobrinus, S. downei, S. macacae, S. ferus*. Also scientists found in a tooth plaque *S. sanguinis* type. It interacts on a tooth enamel surface with *S. mutans*, making the environment for it less hospitable which is important for caries status of a child [9].

Streptococcus mutans is the key etiological agent initiating infectious cariogenic process. It can have serotypes c, e, f and k. Types f and k are often found in persons with an infectious endocarditis [31]. Specific virulent types of *S. mutans* have unique adhesive proteins SpaP and Cnm which promote their resistance to antibacterial properties of saliva, and children may have “impetuous” or “rampant” caries. It is connected with the increased adhesive ability of *S. mutans* development [9]. It is one more scientific proof of the infectious theory which has great practical value.

Thus, caries is a nonspecific polyetiological infectious process which under certain conditions develops into a chronic infectious disease. It is inapparant (asymptomatic, latent), having the nature of an opportunistic infection which develops and progresses under favorable conditions of external and internal environment. Caries originators are ubiquitous bacteria - the VGS of the *mutans* group. The most virulent of them of *S. mutans, S. sobrinus* are constantly living in an oral cavity of a person from the moment of primary infection and further on during all person’s life. They are opportunistic representatives of an autokhtonny local microbiota of an oral cavity.

The most important factor of virulence of *Streptococcus mutans* is their prosperity in acidic environment [9, 22]. Unlike the majority of microorganisms in an oral cavity such viridans streptococci as *S. sanguis*, *S. mitis*, *S. oralis*, whose metabolism is considerably slowed down by low pH, the metabolism of *S. mutans* and *Lactobacillus spp.* in such conditioned only increases. That makes them the dominating bacteria in cariogenesis [22]. These properties allow streptococci to be the first to occupy various biotopes in an oral cavity of the child [5]. It was considered earlier that *Streptococcus mutans* infect a child in the period between 19 and 31 months, in a so-called discrete window of infection [23]. But nowadays it is proved that infection with cariogenic types of *S. mutans* and their colonization in tongue grooves, are possible before teething [20]. It confirms the way of their transfer from a mother to a child [4]. At the same time Tanzer writes that solid surfaces are necessary for colonization of *S. mutans.* So their fast emergences before babies’ teething lead to the use of obturators for correcting a cleft lip [32].

Research papers have shown that 119 Afro-American children in their early age have 315 genotypes of strains of *S. mutans.* One child had from 1 up to 9 genotypes at the same time. Usually they have more than one genotype. 33 percent of children allocated only one highly transmissible genotype which wasn’t bound to a streptococcus genotype of a mother or any family member, and at least one genotype is identical to maternal or to one of family members. It shows strains’ high ability to transfer. Children attending one and the same kindergarten have identical strains of bacteria in their saliva and children who are on home education have identical strains of streptococci with their mother and father [20]. At the same time the genotypes of strains are different as well as their quantity [30]. Transmission can be direct and indirect. Direct transmission takes place when we have the contact and household mechanism of transfer. Indirect transmission goes through general toys, ware, nutrition, and dirty hands.

The earlier S. mutans appear in an oral cavity of a child the higher the prevalence of caries by 4 years of life. Children, whose mothers have a high level of Streptococcus mutans, have a larger risk of receiving microbes, than children whose mothers have low level [18]. And if food contains a high level of easily fermented carbohydrates, then S. mutans, being in symbiotic interaction with Lactobacillus spp., synthesizes the extracellular polysaccharides helping to stabilize a tooth plaque matrix [34].

Frequent consumption of sugars is recognized as the trigger mechanism: in an etiopathogenesis of caries microorganisms are emphasized as secondary, the main material is sucrose – the only carbohydrate which uses S. mutans. It makes a sticky extracellular polysaccharide on the basis of dextran which allows them to bind with each other and form a dental plaque. S. mutans makes dextran by means of dextransucrase enzyme, decomposing sucrose: n molecules of sucrose (glucose) n + n fructose [31]. Sucrose is the most significant aggressive factor as it transforms anticariogenic products into cariogenic and causes “metabolic explosion” in an oral cavity [4]. It increases the proportion of *Streptococcus mutans* and lactobacilli, at the same time the level of *Streptococcus sanguini* decreases [24, 33]. All this in general leads to a cariogenic situation – acidic environment promotes a → demineralization of highly mineralized tooth enamel, it becomes speckled, and vulnerable for destruction [4].

Streptococcus mutans are supplied with specialized receptors for adhesion to the surface of teeth. Using the enzymes making key matrixes, its glucosyltransferases - GtfB, GtfC, GtfD, produce sticky glucosylglucan polymers which facilitate the attachment of bacteria to the surface of tooth. Glucans are the main components of a biofilm matrix which protects the microbial community from mechanical and oxidizing stresses, and also they organize cariogenic biofilms. Besides, they receive lactic acid in great amount. It is a by-product of bacteria consumption of sucrose, together with the community of mature biomembranula. It finally leads to a demineralization of a surface of teeth and to cariogenesis. Thus, glucosyltransferases B, C and D provide the mechanism of formation of cariogenic biofilms. It is a key factor of *S. mutans* virulence [31]. The formation of a plaque on the teeth surface made of biological biofilms contained microorganisms of a mouth biota prevents the enamel of temporary teeth from physiological maturity. It blocks getting macro elements - and minerals from saliva. Bacteria in a biofilm are always metabolic active, causing fluctuations of pH level in saliva [17]. According to the conceptual model of tooth biofilms by Jill S. Nield-Gehrig (2003) it consists of bacteria: micro colonies, units of

micro colonies of bacteria, extracellular polysaccharide matrix of EPS substance, epitheliocytes, components of saliva and nutrition, blood cells. A microbiological portrait of the healthy biomembranula is associated with the state of health of teeth and parodont (Health-associated dental plaque): *S. sanguinis, S. mitis*, *S. oralis*, *S. salivarium*, *Veillonella spp*., *Actinomycetaceae*, *Haemophilus spp*., *Bacteroides spp.* Biomembranula associated with caries is presented by Disease-associated dental plaque with disturbance of a microbial homeostasis: dominance of acidogenic and acid tolerant species of *Streptococcus spp*. and *Lactobacillus spp*., when losing dominant positions of the main symbiotic microflora and augmentation of representation of a transitional microflora [8]. The "social behavior of microorganisms" received the special name: - "quorum sensing" [3]. It is important to notice that pathogenic bacteria don't show aggression against the owner's body until they reach a certain quantity / a critical dose and the degree of virulence don't reach the necessary level in order to overcome the owner's protection. This fact also strengthens positions of the infectious theory of caries of teeth.

An important series of experiments was conducted in 1950-1960th on the gnotobionts. They proved the interrelation of a carious lesion with biomembranula. Scientists didn't find caries of teeth in the sterile rats receiving a cariogenic diet, but the rats that were artificially infected with *S. mutans* arose and developed caries. O. Fejerskov, E. A. V. Kidd [7, 26] in 2004 proved the infectious theory of caries. According to their research pathological process is initiated within biomembranula, shown in the liable enamel or dentine. Reflecting the activity of biomembranula the lesion can be active or passive, and regular destruction of biofilms can stop a lesion of caries [26].

Thus, children's caries of teeth needs to be viewed as an infectious disease. It is more often chronic, with the appearance of a certain sequence of distinctive signs typical to inherent infection. It has the nature of an opportunistic infection with the contact and domestic mechanism of transfer from an infectious source to healthy child bacteria, residents of an oral cavity. *S. mutans* and other cariogenic microorganisms initially occupy an oral cavity of the child, since the neonatal period and later on. They are normal inhabitants of an oral cavity of a person. Before teething they appear on the mucosa of the mouth, gums, and the root of the tongue and show their pathogenic potential only in the conditions promoting their activation and endogenous diffusion on solid surfaces of an enamel of teeth and further on in organs and body tissues of an individual.

Moreover, the carious infectious disease has its own, epidemic features: it proceeds acyclicly, it has no clear incubation interval, with the distinct etiological factor - an infecting agent - *Streptococcus mutans*, with expansion of the clinical symptoms characteristic only for caries. Also it has formation of pathomorphologic substrate in a target organ - a solid tissue of tooth and no development of specific antibodies. However this infection doesn't come to an end with the originator eradication from a macroorganism. According to the second strategy of a parasitism, acyclic infectious process - AIP [15] the resident flora of an oral cavity perishes together with the owner's organism. AIP begins with penetration of a pathogenic microorganism into a human body but it doesn't come to an end in a habitual time interval - within a week, a month, or a year. It remains until the end of human life. The microorganisms causing AIP belong to different taxonomical groups; they have a different mechanism of penetration into target cells. In this case illness can have different clinical picture. The fundamental difference of AIP from any cyclic infectious mono process is that clinical improvement as the seeming recovery isn't followed by biological recovery. It is shown by decrease or even disappearance of clinical implications of illness, by formation and existence of high levels of specific antibodies in blood serum, but an infecting agent doesn't leave an organism. The existence of a pathogen in a body forms not only a basis for exacerbations and a recurrence, but also it is the evidence of continuous infectious process. Its duration is equal to the life expectancy of the person. The defining factor is a disability of T - and B-cells of immune system to control the infected macrophages and to block infectious process. All herpes virus, viruses of *Rubella*, HBV, HCV and HDV, HIV, the T-cellular leucosis, adenoviruses and other, not yet open microorganisms belong to the pathogens causing AIP [2].

The infectious theory of caries development doesn't contradict to all earlier existing theories, including the neurotrophical, physical and chemical theory of D.A. Entin (1928), the metabolic, proteolysis-chelation, fundamental chemical and parasitological theory of Miller and et al (1890). It does not contradict them, moreover, it enriches them, supplements and synthesizes. The infections caused by the opportunistic microorganisms which are a part of normal microflora of an organism are called opportunistic infections. Opportunistic or potential pathogenic microorganisms, cause diseases when the protective forces of an organism decrease in adverse conditions of the environment. Such diseases can be caused by more than one hundred species of opportunistic microorganisms. Among them there are bacteria, including a genus of streptococci, viruses, mushrooms, protozoa; bacteria: *Staphylococcus spp*., *Streptococcus spp*., *Enterococcus spp*., family *Enterobacteriaceae*, *Pseudomonas spp*., *Acinetobacter spp*.; viruses: *HBV, HCV*; *HSV*-1, 2; *CMV*; *Papovaviruses*; *Adenoviruses*; *Coxsackieviruses* and *ECHO*, etc.; mushrooms: *Candida*; *Histoplasma*; *Aspergillus*, etc.; protozoa: *Pneumocystis*, *Toxoplasma*, *Cryptosporidium*, etc. [2].

Considering caries infectious process as opportunistic, classical approaches such as vaccination, use of antimicrobial chemotherapeutic drugs, antiseptics are restricted and also will not give the expected effect in our fight against caries pandemia. For example, the works on long operating vaccine have been conducted for more than 30 years. The control of an infectious disease – children's caries of teeth is possible on the condition of the use of all potentials of epidemiology and infectology to break the epidemic chain of contact – domestic infection. And now it is necessary to control the mechanisms of endogenic activation of the originator. It is necessary to influence on an etiological factor, after a deep research of its microbiological, molecular and genetic, immunobiological, immunochemical properties as well as on the mechanisms which control the prosperity of cariogenic streptococci in a biological niche; that is their ability to form a tooth plaque on the surface of tooth, to turn digestible carbohydrates into the lactic acid causing damage of a dentine, and their ability to adapt to sudden changes of conditions in a tooth plate [31].

According to the statement of the Director-General of WHO Dr. Tedros Adhanom Ghebreyesus, on December 10, 2017: "The enjoyment of the highest attainable standard of health is one of fundamental rights of every human being without distinction of race, religion, political belief, an economic or social conditions. But when people have an opportunity to be active participants, but not passive recipients in the course of rendering the help to them, results improve, and health care systems become more effective".

On September 28, 2014 in Moscow the Russian experts entered the International alliance for a cavity-free future (ACFF) which urges to recognize caries as continuously proceeding disease, preventable at early stages, and

reversible. They are going to develop comprehensive programs on prophylaxis and treatment [1]. The purposes of Alliance and Russia: by the year of 2020 to integrate a package of measures of prophylaxis suitable to local conditions, to create the system of monitoring of a disease on the local level. One of the tasks is that each child born in 2026 shouldn't get ill with caries throughout the entire life. It inspires hope for decrease of caries and its complications at children of early age [1, 10].

Thus, having recognized the polyetiological and opportunistic nature of carious infectious process, it is necessary to eliminate favorable conditions for the formation of biofilms of a dental plaque, leading to this infectious disease and its complications. The identification of caries as infection will allow us to define the ways of modern nonspecific and specific prophylaxis of an infectious disease – caries of children's temporary teeth. In the absence of effective vaccines, it has the status of an uncontrollable infection with pandemic diffusion. On condition of giving the infection the status of socially important it will be possible to introduce state programs and develop the complex of actions for treatment and prophylaxis for the management of risk factors in caries development. It will help us to involve experts of various profiles and organizers of public health care.

REFERENCES

1. Avraamova O. G. Al'jans za budushhee bez kariesa [Alliance for a cavity free future] Stomatologija segodnja [Dentistry today]. 2014, № 8, P. 68–69.
2. Bogadel'nikov I. V. Smirnov G. I. Osobennosti techenija infekcionnyh i jepidemicheskih processov v nastojaschee vremja [Peculiarities of the infectious and epidemic processes course at present] Aktual'naja infektologija [Actual Infectology]. 2013, № 1 (1), P. 68–72.
3. Gincburg A. L., Il'ina T. S., Romanova Ju. M. «Quorum sensing» ili social'noe povedenie bakterij ["Quorum sensing" or social behavior of bacteria] ZhMJeI [JMEI], 2003, № 5, P. 86–93.
4. Leont'ev V. K., Kisel'nikova L. P. Detskaja terapevticheskaja stomatologija. Nacional'noe rukovodstvo [Children's therapeutic dentistry. national guide]. M.: GEOTAR – Media, 2017, 952 p.
5. Kramar' V. S., Perov Ju. A., Kramar' O. G., et al. Kolonizacija mikroorganizmami polosti rta: metod. rekomendacii [The colonization by microorganisms of the oral cavity: a method recommendations]. Volgograd, 1989, 16 p.
6. Korchagina V. V. Lechenie kariesa zubov u detej rannego vozrasta [Treatment of teeth caries at early age children]. M.: MEDpress – inform, 2008, 186 p.
7. Leus P. A. Real'ny li vozmozhnosti iskorenenija karioznoj bolezni [Whether possibilities of a carious disease eradication are real]. Sovremennaja stomatologija, 2014, № 2, P. 30–35.
8. Masis G. I. Koncepcija celostnogo kharaktera mikrobnyh populjacij «Biopljonka v okruzhajushhej srede i v organizme cheloveka» [The concept of the holistic nature of microbial populations «Biofilm in the environment and in the human body»]. Jendodontija today, 2012, № 2, P. 11–13.
9. Ippolitov Ju. A., Havkin A. I., Aljoshina E. O., et al. Mikrobiota i bolezni polosti rta [Microbiota and oral cavity diseases] Jeksperimental'naja i klinicheskaja gastrojenterologija, 2015, № 6 (118), P. 78–81.
10. Ozhgihina N. V. Reabilitacija detej s aktivnym kariesom zubov [Rehabilitation of children with active caries] Vserossijskij kongress «Stomatologija Bol'shogo Urala». III Vserossijskoe rabochee soveshhanie po problemam fundamental'noj stomatologii. Sbornik statej [Russian Congress "Dental Big Ural". III all-Russian workshop on fundamental dentistry problems. A collection of articles] ed. by O. P. Kovtun – Ekaterinburg: UGMU, 2015, 168 p.
11. Shevchenko O. L., Elistratova M. I., Germash V. I., et al. Osobennosti lokalizacii karioznyh porazhenij vremennyh zubov u detej Dal'nevostochnogo regiona [Features of localization of carious lesions of carious teeth in children of the Far East region]. Zdorov'e i obrazovanie v XXI veke, 2017, volume 19, № 12, P. 228–233.
12. Starovojtova E. L., Antonova A. A., Strel'nikova N. V., et al. Sanologicheskaja kul'tura roditelej kak osnova stomatologicheskogo zdorov'ja detej [Sanology culture of parents as the basis of the children dental health]. Zdorov'e i obrazovanie v XXI veke, 2017, volume 19, № 10, P.157–162.
13. Knajst S., Maslak E., Tsare R., et al. Social'nye faktory, vlijajushhie na razvitie rannego detskogo kariesa: rezul'taty issledovanija v pjati stranah [Social factors influencing the development of early childhood caries: results of a study in five countries]. Sociologija mediciny, 2012, № 1 (20), P. 41–45.
14. Kuz'mina Je. M. Stomatologicheskaja zabolevaemost' naselenija Rossii. Sostojanie tvjordyh tkanej zubov. Rasprostranjonnost' zubocheljustnyh anomalij. Potrebnost' v protezirovanii [Dental morbidity of the Russia population. The status of hard teeth tissue. Prevalence of dentoalveolar anomalies. The need for prosthetics]. M.: MSMSU, 2009, 236 p.
15. Supotnickij M. V. K voprosu o meste VICh – infekcii i VICh/SPID – pandemii sredi drugih infekcionnyh, jepidemicheskih i pandemicheskih processov. Vnutrikletochnye parazity i simbionty mnogokletochnyh organizmov [To the question about the place of HIV infection and HIV/AIDS pandemic among other infectious, epidemic and pandemic processes. Intracellular parasites and symbionts of multicellular organisms]. Jenvajronmental'naja jepidemiologija, 2007, volume 1, № 2, P. 183–258.
16. Shakovec N. V. Rezul'taty trjohletnej profilaktiki kariesa zubov u detej rannego vozrasta [The results of three – year dental caries prevention in early childhood]. Vestnik VGMU, 2016, volume 15, № 2, P. 93 – 101.
17. Allais G. The biofilm of the oral cavity / G. Allais // New in dentistry. — 2006. — T. 136. – № 4. — P. 4–15.
18. American Academy of Pediatric Dentistry. Symposium on the prevention of oral disease in children and adolescents. Chicago, Ill, November 11 – 12, 2005: Conference papers. Pediatr Dent. – 2006. – № 28(2). – P. 196–198.
19. Beltrami G. [Black teeth in toddlers.] Siècle Medical 1932 Apr 4. Cited in Beltrami, G. La mélanodontie infantile [Infantile Melanodontia]. Marseilles, France: Leconte Editeur, 1952. [Book in French].
20. Berkowitz R. J. Cause, treatment and prevention of early childhood caries / R. J. Berkowitz // J. Can Dent Assoc. – 2003. – № 69. – P. 304–307.
21. Beyond the dmft: The human and economic cost of early childhood caries / P. S. Casamassimo, S. Thikkurissy, B. L. Edelstein [et al.] // J Am Dent Assoc. – 2009. – № 140. – P. 650–657.
22. Burt B. A. Sugar Consumption and Caries Risk: A Systematic Review / B. A. Burt, S. Pai // Journal of Dental Education. – 2001. – № 65. – P. 1017–1023.
23. Caufield P. W. Initial a acquisition of mutans streptococci by infants: evidence for a discrete window of infectivity / P. W. Caufield, G. R. Cutter, A. P. Dasanayake // J Dent Res. – 1993. – P. 37–45.
24. Douglass J. M. Response to Tinan off and Palmer: Dietary determinants of dental caries and dietary recommendations for preschool children / J. M. Douglass // J Public Health Dent. –2000. – № 60(3). – P. 207–209.
25. Harald. H. Stardevants Art and Sciences of Operative Dentistry / H. Harald, E. Swift, R. Andre // 6th ed., Mosby company, Elsevier, 2013. – 568 p.
26. Kidd E. A. What Constitutes Dental Caries? Histopathology of Carious Enamel and Dentin Related to the Action of Cariogenic Biofilms / E. A. Kidd, O. Fejerskov // J Dent Res. – 2004. – № 83. – P. 35–38.
27. Marsh P.D. Are dental diseases examples of ecological catastrophes? / P.D. Marsh // Microbiology. – 2003, Vol. 149. – № 2. – P. 279–294.
28. Petersen P. E. WHO Global Policy for improvement of oral health – WH Assembly 2007. Geneva: WHO. J Int Dent. – 2008. – № 6. – P. 115–121.
29. Shafer W. G. A textbook of oral pathology / W. G. Shafer, M. K. Hine, B. M. Levy // Saunders, 1974. – 853 p.

30. Sharing of a bacterium related to tooth decay among children and their families / American Society for Microbiology // Science Daily. – 2016. – Mode of access: www.sciencedaily.com/releases/ 2016/06/ 160620100329.htm.
31. Structure-Based Discovery of Small Molecule Inhibitors of Cariogenic Virulence / Qiong Zhang, Bhavitavya Nijampatnam, Zhang Hua, Thao Nguyen3, Jing Zou1, Xia Cai4, Suzanne M. Michalek4, Sadanandan E. Velu & Hui Wu1 // Scientific Reports. – 2017. – № 7, Article number: 5974.
32. Tanzer, J. M. The microbiology of primary dental caries in humans / J. M. Tanzer, J. Livingston, A. M. Thompson // J Dent. Edu. – 2001. – № 65. – 1028–1037.
33. The Role of Sucrose in Cariogenic Dental Biofilm Formation – New Insight / L. Paes, H. Koo, C. M. Bellato [et al.] // J Dent Res. – 2006. – № 85(10). – P. 878–887.
34. Tinanoff N. Current understanding of the epidemiology mechanisms, and prevention of dental caries in preschool children / N. Tinanoff, M. J. Kanellis, C. M. Vargas // Pediatr Dent. – 2002. – № 24. – P. 543–550.
35. Valencia – Rojas N. Prevalence of early childhood caries in a population of children with history of maltreatment / N. Valencia-Rojas, H. P. Lawrence, D. Goodman // J Public Health Dent. – 2008. – № 68. – P. 94–101.

The authors:

Strelnikova Natalia Viktorovna - Candidate of Medical Sciences, Associate Professor of the Department of Microbiology, Virology, Immunology FGBOU Far-Eastern State Medical University of the Ministry of Health of Russia, head of the bacteriological laboratory of KGBU "Regional Clinical Hospital No. 1 named after Professor S.I. Sergeev,.

Address: 680020, Khabarovsk, ul. Sheronova, 3, Apt. 89.

Contact phone: + 7924-925-89-85, e-mail: jpdom@mail.ru

Antonova Alexandra Anatolievna - Doctor of Medical Sciences, Professor, Head of the Department of Childhood Stomatology FGBOU Far-Eastern State Medical University of the Ministry of Health of Russia,

Address: 680021, Khabarovsk, ul. Vladivostok, 22, Apt. 49.

Contact phone: + 7962-586-29-37, e-mail: alex.antonova@rambler.ru

Starovoitova Elena Leonidovna - assistant of the Department of Children's Dentistry FGBOU Far Eastern State Medical University of Russia, the dentist-therapeutist, Address: 680510, p. Topolevo Str. Lugovaya, 7, kv.12

Contact phone: + 7914-543-82-98, e-mail: doc-el@mail.ru

Shevchenko Olga Leonidovna - assistant of the Department of Childhood Stomatology FGBOU Far-Eastern State Medical University of the Ministry of Health of Russia, a dentist

Address: 680054, Khabarovsk, ul. Strelnikova 27, apt. eleven.

Contact phone: + 7924-201-69-50, e-mail: olgash.1985@mail.ru

Koltsov Igor Petrovich - Candidate of Medical Sciences, Head of the Department of Microbiology, Virology and Immunology of the State Public Health Service of the Far-Eastern State Medical University of the Ministry of Health of Russia.

Address: 680009, Khabarovsk, ul. Demyan Bedny, d. 21, Apt. 129.

Contact phone: + 7914-204-86-60, e-mail: koltcov-55@mail.ru

Turkuyukov Vyacheslav Borisovich - Doctor of Medical Sciences, Professor, Head of the Department of Epidemiology and Military Epidemiology of the FGBOU VO TGMU of the Ministry of Health of Russia,

Address: 690002, Vladivostok, Ostryakova Ave., 2.

Contact phone: + 7914-734-75-00, e-mail: vyach12593@mail.ru

Elistratova Marina Ilinichna - Associate Professor of the Department of Childhood Stomatology FGBOU in the Far Eastern State Medical University of Russia, the dentist-therapeutist, a child dentist, candidate of medical sciences.

Address: 680000, Khabarovsk, ul. Frunze, 1, Apt. 40.

Contact phone: + 7914-400-92-29, e-mail: m_elistratova@rambler.ru

Martilova Tatyana Olegovna - a student of the Pediatric Faculty of the State Pediatric University of Russia in the Far Eastern State Medical University of the Russian Ministry of Health.

Address: 680038, Khabarovsk, ul. Volochaevskaya, 180, apt.

Contact phone: + 7914-168-90-41, e-mail: MartilovaTanushka5800@mail.ru.

I.D. Ushnitsky, A.V. Ivanov, A.A. Ivanova, A.V. Yurkevitch, E.M. Seydalova, A.A. Novogodin

CLINICAL-EPIDEMIOLOGICAL CHARACTERISTICS OF PATHOLOGICAL PROCESSES OF PERIODONTAL TISSUES OF INFLAMMATORY-DESTRUCTIVE NATURE

ABSTRACT

Today according to Russian and foreign researchers the prevalence of parodontium diseases is high and does not tend to decrease. A wide range of etiological factors and pathogenetic mechanisms of the development of parodontium inflammatory diseases influence on the carrying of complex treatment-and-prophylactic actions. At the same time parodontium diseases often lead to teeth loss, contributing to formation and development of dentoalveolar system disorders and further digestive tract diseases. In this regard, pathological processes of parodontium tissues have both medical and social value as patients are usually of the working-age.

According to the WHO data the prevalence rate of parodontium diseases among various groups of population is characterized by particular features. So, worldwide more than half of the examined patients at the age group of 12-15 years have parodontium diseases, at the same time at the age of 35-44 years it has total character. At the same time in Russia 12-year old patients make 1/3, and 15-year-old teenagers have slightly lower than a half surveyed, at the age of 35-44 years only 1/5 part has rather healthy parodontium. Meanwhile, the high level of parodontium diseases was noted among the North inhabitants due to severe climatic conditions and specific regional environmental and biological risk factors.

It should be noted that quite often treatment of periodontal disease of inflammatory and destructive processes can take several years, and in certain cases it continues during all life. A desire of the patient and dentist to gain most expected clinical effect without damage of the functional activity of dentoalveolar system that demands carrying out further researches for the perfecting of the periodontal help to the population is explained.

Keywords: parodontium diseases, prevalence rate, dentoalveolar system, treatment, prevention.

Nowadays despite broad studying of periodontal diseases, there are still problems of their treatment and prophylaxis [7, 11, 14, 37]. A wide range of etiological and pathogenetic aspects of pathological processes of periodontal tissues and a high level of prevalence among various age groups of the population make particular treatment-and-prophylactic difficulties [9, 17, 19- 21]. In this regard scientists are researching new effective methods of

complex therapy of periodontal diseases which is not only the main odontology problem but as well as the national objective priority directed to preservation and promotion of health of the population [18, 22].

Due to level of prevalence periodontal diseases take the second place after caries and its complications [14, 38, 40]. At the same time various pathological processes of periodontal tissues of inflammatory and destructive character cause assumptions of developing of chronic infection in the oral cavity, teeth loss, psychoemotional and working disorders of patients which is urgent medical and social problem [42].

According to the World Health Organization teeth loss of periodontal diseases in 5 times more often promotes the functional disorders of dentoalveolar system in comparison with teeth loss at caries [12]. The prevalence of pathological processes of periodontal diseases is characterized by same features worldwide. Thus, in age group of 12-15 years the average index varies from 61 to 96% whereas in age group of 35-44 years within 96-100%. At the same time the complex research has established what in age group of 29 to 44 years only 4-5% of the examined have been found clinically healthy periodont [12, 24, 25].

The researches of children of school age of 8-12 years in Italy defined a high level of periodontal diseases which reached the level of 97% [1, 14, 16, 21]. The largest frequency of inflammatory periodontal diseases of various severity in age group of 15-19 years were found in Africa and South-Eastern Asia where indexes reached respectively 90-95%. 18-20% of this age group in America and Europe has healthy periodont [27].

In age group of 35-44 years the average world index of periodontal diseases varies from 65 to 98%, in the USA – 70% where a third loss of teeth happened according to periodontal diseases. In Europe 15% of this age group have deep periodontal pockets with affection of 5 and more sextants [5].

It is necessary to emphasize that researches of the population of the Russian Federation have reveled certain features. Thus, 12-year-old children showed the prevalence of periodontal diseases at 34%, and 15-year-old teenagers reached the level of 41%. At the same time in these age groups there are symptoms of inflammation as following: gums bleeding (23 and 22%), dental calculus (11 and 19%). Meanwhile the average indicator of the affected sextants was 1.14 at 12-year-old children, 1,42 at 15-year-old teenagers. Among adult population at the age of 35-44 years signs of tissues periodontal lesion were 81% where 16% of them had pathological periodontal pockets. But, at the same time, 2.28 intact sextants were noted in indicators of intensive periodontal tissues lesion among adult population. With the age older than 65 years and more the natural tendency to teeth loss becomes perceptible and the prevalence level respectively decreases where only 0.57 healthy sextants are defined in indicators of intensive periodontal diseases [6, 36, 39].

The clinical-epidemiological researches showed that 12% of the Russia population have intact periodont where 53% have initial inflammatory phenomena and 12% more expressed inflammatory and destructive processes of early and severe degree. Meanwhile in the Central European, Southern European and West Siberian regions in the age group of 35-44 years from 15 to 16% population have healthy periodont and bleeding - 24%. Whereas in the Ural Federal District these indicators are respectively 11 and 51%. In the Far Eastern Federal District patients of this age group have about 40% healthy periodont and gums bleeding reaches 8%, indicator supra and sub gingival calculus – 34% [9]. In the surveyed regions the share of patients with deep periodontal pockets is in limits of digital values (1-4%) [5].

Numerous researches showed that climate-geographical conditions of population's accommodation can influence on indicators of frequency and intensity of periodontal diseases. So, in the Volgograd region the prevalence of periodontal diseases is 37 and 57% at 12-year-old children and 15-year-old teenagers, Chita region - 46 and 62%, the Republic of Sakha (Yakutia) and the Kemerovo region 89 and 84% at 15-year-old teenagers [33, 36]. Meanwhile, 15-year-old children of Armenia 73% of frequency of pathological processes of periodontal tissues where the quantity of the affected sextants for the last period has grown 3 times up [15].

Climatic conditions of the Northern region are characterized by the long periods of low temperature, long snow cover, sharp differences of atmospheric pressure, ultraviolet deficiency, close permafrost layer, essential strain of body functions in living conditions adaptation, reflected in functional dislocations of various organs and systems, including dentoalveolar system [3, 10, 23, 28, 29, 32]. Children of the high latitudes living in such conditions have signs of inflammation of the regional periodont at school age. So, at 7-year-old children the prevalence of periodontal diseases averages 39%, then with the age the indicator augmentation tendency reaches the level of 84% by 14 years old. There are, usually, gingivitis, more seldom periodontal diseases of mild, rare moderate severity revealed. Meanwhile among adult population, including elderly people the prevalence of periodontal diseases averages 90% where more expressed inflammatory and destructive processes of periodontal tissues promoting loss of teeth. At the same time at the population living in Subpolar and Arctic areas of the North, the frequency of periodontal diseases reaches maximum values and average indicator reaches the level of 96% [31, 32].

The researches have established that the clinical course of periodontal diseases has the certain patterns due to age aspects. Thus, at young age the pathology of periodontal tissues is most often of mild severity, rarer than average, rarer than severity level. At the senior age groups the expressed inflammatory and destructive processes are more often and less changes of metabolic and dystrophic process [32]. The complex clinical-epidemiological research for the last period in Russia characterizes that more than a third of children and teenagers have signs of periodontal tissues lesions. With the age the prevalence with inflammatory periodontal diseases fluctuates from 80 to 100% where severe forms are often examined. At the same time the negative tendency of augmentation of prevalence of periodontal diseases among adult population is traced [36].

Undoubted impact on the course of pathological processes in periodontal tissues occurs in the internal organs. Often, somatic diseases are the cause of the inflammatory and destructive phenomena in oral cavity mucosa [2, 34, 35].

High level of prevalence of periodontal diseases among various groups of the population, demanding long and difficult complex therapy causes relevance of their problems in clinical odontology [26]. Quite often the treatment of periodontal disease of the expressed inflammatory and destructive character can take several years, and in certain cases it continues during all life. On the other hand a desire of the patient and dentist to gain concrete clinical effect without injury of functional activity of dentoalveolar system [27] becomes clear.

Due to V.A. Kozhokeeva and et al. data [13] for the last period significant growth in patients' visits with periodontal diseases testified a negative tendency of their prevalence. From the same positions it is possible to explain the high level of teeth loss in patients of old and senile age concerning periodontal diseases, especially of inflammatory and destructive processes [8, 30, 41].

CONCLUSION

The results of our research characterize the prevalence of periodontal diseases which take the second place by frequency after caries of teeth. Meanwhile structural reactions of mucosa in ontogenesis, climatic- social and economic conditions and also dental service potential definitely influence on incidence [21, 43]. At the same time, according to prognosis, this trend will increase [4].

Thus, periodontal diseases are widespread pathologies which define both important medical and social problem. This situation urges complex research work referred to incidence decrease and improvement of dental service and also medical-social rehabilitation of the patients.

REFERENCES

1. Anistratova S.I. Znachenie sotsial'no-ekonomicheskogo polozheniya sem'i v razvitii osnovnykh stomatologicheskikh zabolevanii u detei shkol'nogo vozrasta: dis. … kand .med. nauk [Value of economic and social situation of family in development of the basic dental diseases in children of the school age]. Volgograd, 2015, 166 p.
2. Oskolsky G.I., Nepomnyaschikh L.M., Yurkevich A.V., Lushnikova E.L., Yurkevich N.V. Vzaimosvaz' patologicheskyh proyavlenii v slizistoy obolochke polosti rta (sopr) I zabolevanyi zhelydochno-kishechnogo trakta [Interaction of pathological manifestations in the oral mucosa and gastrointestinal tract diseases]. Dalnevostochnyi medicinskyi jurnal [Far East medical journal], 2010, № 3, pp. 130-133.
3. Vilova T.V. Alekseeva O.V. Ekogenii i stomatologicheskaya patologiya [Ecogeniuses and dental pathology]. Ekologiya cheloveka [Human ecology], 2006, №6, pp.12-17.
4. Vol'f G.F. Rateitskhak E.M. Rateitskhak K. Parodontoloiya [Periodontology]. Moscow: MEDpress-inform, 2008, 548 p.
5. Grudyanov A.I. Bulygina V.V. Kurchaninova M.G. Rasprostranennost' vospalitel'nykh zabolevanii parodonta i podkhody k ikh lecheniyu [Prevalence rate of inflammatory parodontium diseases and approaches to their treatment]. Parodontologiya [Periodontology], 2000, №2, pp. 31-38.
6. Grudyanov A.I. Ovchinnikova V.V. Profilaktika vospalitel'nykh zabolevanii parodonta [Prophylaxis of inflammatory diseases of the parodontium], Moscow: OOO «Meditsinskoe informatsionnoe agentstvo», 2007, 80 p.
7. Grudyanov A.I. Fomenko E.V. Etiologiya i patogenez vospalitel'nykh zabolevanii parodonta [Etiology and pathogenesis of inflammatory diseases of the parodontium], Moscow: OOO «Meditsinskoe informatsionnoe agentstvo», 2010, 96 p.
8. Dmitrieva L.A. Parodontologiya: natsional'noe rukovodstvo [Periodontology], Moscow: GEOTAR – Media, 2013, 126 p.
9. Oskolsky G.I. Nepomnyashchikh L. M., Jurkiewicz, A. V., Lushnikova E. L., Yurkevich N. In. Izuchenie strukturno proliferativnih processov v epitelii desni pri izmenenyah sostoyania perodonta [The study of the structural and proliferative processes in the epithelium of the gums when changes of parodentium]. Yakutsky medicinsky jurnal [Yakut medical journal], 2011, № 4, pp. 92-94.
10. Kaznacheev V.P. Mekhanizmy adaptatsii cheloveka v usloviyakh vysokikh shirot [Mechanisms of human adaptation in the conditions of high latitudes], Leningrad: Meditsina, 1980, 200 p.
11. Kukushkina E.A. Vliyanie immunomoduliruyushchei terapii na pokazateli immuniteta i nespetsificheskoi rezistentnosti bol'nykh parodontitom: avtoref. dis. … kand. med. nauk [Influence of immunomodulatory therapy on indicators of immunity and nonspecific resistance of patients with periodontal disease], Chita, 2004, 19 p.
12. Kruglova N.V. Otsenka effektivnosti kompleksnogo lecheniya vospalitel'nykh zabolevanii parodonta: dis. … kand. med. nauk [Assessment of effectiveness of complex treatment of inflammatory parodontium diseases]. Nizhnii Novgorod, 2011, 155 p.
13. Kozhokeeva V.A. Pavkina T.A. Obrashchaemost' vzroslogo naseleniya s boleznyami parodonta v stomatologicheskie polikliniki g. Bishkek [Incidence of adult population visits with parodontium diseases in dental policlinics of Bishkek], Nauka i novye tekhnologii [Science and new technologies], 2010, №1, pp. 126-129.
14. Malan'in I.V. Sovremennye metody komp'yuternoi terapii zabolevanii parodonta: dis. … d-ra med. nauk [Modern methods of computer therapy of parodontium diseases], Krasnodar, 2005, 363 p.
15. Manrikyan M.E. Analiz effektivnosti profilaktiki i lecheniya zabolevanii parodonta u patsientov s razlichnymi ortodonticheskimi konstruktsiyami: avtoref. dis. … kand. med. nauk [Analysis of effectiveness of prophylaxis and treatment of parodontium diseases at patients with various orthodontic bands], Erevan, 2005, 38 p.
16. Myshentseva A.P. Formirovanie stomatologicheskogo zdorov'ya u detei rannego vozrasta v sovremennykh usloviyakh zdravookhraneniya: dis. … kand. med. nauk [Dental health at children of early age in modern conditions of health care], Samara, 2016, 167 p.
17. Nadeikina O.S. Analiz stomatologicheskoi zabolevaemosti detei Penzenskoi oblasti i razrabotka mer profilaktiki kariesa zubov: dis. … kand. med. nauk [Dental incidence analysis of children of Penza region and development of caries prevention], Nizhnii Novgorod, 2014, 216 p.
18. Oragvelidze M.P. Obosnovanie primeneniya neoselena v kompleksnom lechenii bol'nykh generalizovannym parodontitom: avtoref. dis. … kand. med. nauk [Justification of neoselenium use in complex treatment of patients with generalized periodontal disease], Irkutsk, 2006, 23 p.
19. Oskolskiy G.I., Yurkevich A.V. Morfometricheskaya kharakteristika strukturi epiteliya desni v norme I pri hronicheskih zabolevaniah parodonta [Morphometric characteristics of gingival epithelium structure in healthy and periodontal tissues and in chronic periodontal diseases]. Dalnevostochny medicinskyi jurnal [Far East medical journal], 2004, № 1, pp. 19-23.
20. Oskolsky G.I., Yurkevich A.V., Pervov Yu.Yu. Sovremennye predstavlenya o strukturnyh reakciah slyzistoy obolochki polosti rta v processe ontogeneza [Actual notions of structural responses of oral mucosa in its ontogenesis]. Tihookeanskyi medicinskyi jurnal [Pacific medical journal], 2005, № 2, pp. 17-19.
21. Oskolsky G.I., Yurkevich A.V. Morfologicheskaya kharakteristika epithelia desny pri khronicheskih zabolevaniah perodonta [Morphological characteristics of the epithelium of the gums in chronic periodontal disease]. Sibirskiy konsilium [Siberian consilium], 2005, № 4, pp. 18.
22. Dibov D.A., Iurkievich A.V., Mikhalchenko A.V., Mikhalchenko D.V Primenenye preparatov selena v lechenyi vospalytelnyh zabolevanyi perodonta [The use of selenium in the treatment of inflammatory periodontal diseases]. Klinicheskaya stomatologia [Clinical dentistry], 2017, № 4 (84), pp. 26-29.
23. Rukavishnikov V.S. Efimova N.V. Metodologicheskie i patogeneticheskie problemy identifikatsii ekologicheski obuslovlennykh narushenii zdorov'ya [Methodological and pathogenetic

problems of identification of ecologically caused health disorders]. Sibirskii nauchnyi meditsinskii zhurnal [Siberian scientific medical magazine], 2008, №1, V.129, pp. 52-56.
24. Grudyanov A.I. Tkacheva O.N. Avramov T.V. Sistemnye vospalitel'nye markery kak faktory progressiruyushchego techeniya khronicheskogo generalizovannogo parodontita u patsientov s vysokim riskom serdechno-sosudistykh zabolevanii [Systemic inflammatory markers as factors of the progressing chronic generalized periodontal disease at patients with high risk of cardiovascular diseases]. Parodontologiya [Periodontology], 2015, №3, V.76, pp. 37-41.
25. Tsepov L.M. Nikolaev A.I. Nakonechnyi D.A. Sovremennye podkhody k lecheniyu vospalitel'nykh generalizovannykh zabolevanii parodonta [Modern approaches to treatment of inflammatory generalized parodontium diseases]. Parodontologiya [Periodontology], 2015, №2, V.75, pp. 3-9.
26. Gulyaeva O.A. Bulyakov R.T. Gerasimova L.P. Sovremennye metody v kompleksnom lechenii vospalitel'nykh zabolevanii parodonta [Modern methods in complex treatment of inflammatory diseases of the parodontium], Ufa: Izdatel'stvo «UralPoligrafSnab», 2016, 190 p.
27. Oskolsky G.I., Yurkevich A.V., Scheglov A.V., Mashina N.M., Chubenko O.S. Sostoyanie protezov I nuzdaemost v ortopedicheskom lechenii naselenya Khabarovskogo kraia [State of prostheses and need for orthopedic treatment in population of khabarovsk region]. Fundamentalnye issledovania [Fundamental research], 2013, № 7-2, pp. 370-374.
28. Oskolsky G.I., Ushnitsky D. I., Zagorodnyaya E. B., Jurkiewicz A. V., N. Car.M. Baisheva V. I. Stomatologicheskyi status naseleniya dalvostochnogo regiona [Dental status of the population of the far Eastern region]. Endodontiya Today [Endodontics Taday], 2012, № 3, pp. 10-14.
29. Subanova A.A. Osobennosti epidemiologii i patogeneza zabolevanii parodonta (obzor literatury [Features of epidemiology and pathogenesis of parodontium diseases]. Vestnik KRSU, 2015, №7, V.15, pp. 152-155.
30. Ushnitskii I.D. Zenovskii V.P. Vilova T.V. Stomatologicheskie zabolevaniya i ikh profilaktika u zhitelei Severa [Dental diseases and prevention at inhabitants of the North], Moscow: Nauka, 2008, 171 p.
31. Ushnitskii I.D. Kliniko-fiziologicheskie aspekty sostoyaniya organov i tkanei polosti rta u naseleniya Respubliki Sakha (Yakutiya): dis. … d-ra med. nauk [Clinical-physiological aspects of condition of organs and tissues of the oral cavity at the population of the Sakha (Yakutia) Republic], Arkhangel'sk, 2001, 262 p.
32. Ushnitskii I.D. Zenovskii V.P. Vilova T.V. Stomatologicheskie zabolevaniya i ikh profilaktika u zhitelei Severa [Dental diseases and prevention at inhabitants of the North], Moscow: Nauka, 2008, 171 p.
33. Firsova I.V. Ivanova E.I. Rasprostranennost' zabolevanii parodonta sredi patsientov, obrativshikhsya v stomatologicheskie polikliniki g. Volzhskogo Volgogradskoi oblasti [Prevalence rate of parodontium diseases among patients at dental policlinics of. Volzhsky city Volgograd region]. Dental forum, 2014, №4, pp. 95-96.
34. Yurkevich A.V. Macupa D. V. Oskolskiy G.I. Patomorfologichesky analiz slizistoy obolochki desni pri yazvennoy bolezny jeludka [Pathomorphological examination of the mucous membrane of the gums with ulcers of the stomach]. Sibirskiy konsilium [Siberian consilium], 2005, № 4, pp. 37-40.
35. Yurkevich A.V. Patomorfologichesky analiz slizistoy obolochki desni pri sakharnom diabete I yazvennoy bolezny jeludka: dis. doc. med. nauk [Pathologic analysis of the mucous membrane of gums in diabetes and stomach ulcers]. Novosibirsk, 2006, 160 p.
36. Yanushevich O.O. Stomatologicheskaya zabolevaemost' naseleniya Rossii. Sostoyanie tkanei parodonta i slizistoi polosti rta [Dental incidence of the population of Russia. Condition of tissues of parodontium and mucous oral cavity], Moscow: MGMSU, 2009, 228 p.
37. Yanushevich O.O. Kuz'mina E.M. Sovremennye podkhody k opredeleniyu potrebnosti naseleniya v stomatologicheskoi pomoshchi [Modern approaches to definition of the population need for dental help], Moscow, 2010, 84 p.
38. Clancio S.G. Detection and management of the high risk periapical tissues / S.G. Clancio // Int-Dent-J. – 1991. – Vol.5. – №41. – P. 300-304.
39. Dumitrescu A.L. Etiology and Pathogenesis of Periodontal Disease / A.L. Dumitrescu // Periodontal Microbiology. – 2010. – №5. – P.39-76.
40. Howell T.H. Chemotherapeutic agents as abjuncts in the treatment of periodontal disease / T.H. Howell // Curr-Opin-Dent. – 1991. – Vol.1. – №1. – P. 81-86.
41. Hirotomi T. Longitudinal study on periodontal conditions in healthy elderly people in Japan / T. Hirotomi A. Yoshihara, M. Yano [et al.] // Community Dent Oral Epidemiol. – 2002. – Vol. 30. – №6. – P. 409-417.
42. Mittermayer C. Oralpathologic / C. Mittermayer, W. Sandritter. – Schattauer. – 1984. – 334p.
43. Sheiham A. The prevalence of periodontal disease in Europe / A. Sheiham, G.S. Notuveli // J. Periodontal. – 2002. – Vol.29. – P. 104-121.

The authors:

Ushnitsky Innokentiy Dmitrievitch PhD, professor, head of therapeutic, surgical, orthopedic dentistry and children's dentistry department of Medical institute, North-Eastern federal university named after M.K. Ammosov, Yakutsk (Russia). e-mail: incadim@mail.ru, tel:89241708940

Ivanov Andrian Vladimirovitch dentist-surgeon, implantologist, orthopedist of dental clinic "Dentalika", Yakutsk (Russia). e-mail: andrian_ivanov@mail.ru, tel:89246616569.

Ivanova Aytalina Alekseevna head of dental department of Medical institute, North-Eastern federal university named after M.K. Ammosov, Yakutsk (Russia). e-mail: aitalinalex@mail.ru, tel: 89142258715.

Yurkevitch Alexander Vladimirovitch. – PhD, dean of The Far Eastern State Medical University, head of orthopedic dentistry department, Khabarovsk (Russia). e-mail: dokdent@mail.ru, tel: 89625025888.

Seydalova Evgenia Muratovna student of dental faculty, Medical institute, North-Eastern federal university named after M.K. Ammosov, Yakutsk (Russia). e-mail: andrian_ivanov@mail.ru, tel: 89246616569.

Novogodin Andrey Andreevitch student of dental faculty, Medical institute, North-Eastern federal university named after M.K. Ammosov, Yakutsk (Russia). e-mail: andrian_ivanov@mail.ru, tel: 89246616569.

CLINICAL CASE

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

INTENSIVE THERAPY FOR SEVERE POST-OPERATIVE COMPLICATIONS IN A CAD PATIENT AFTER A BYPASS SURGERY

ABSTRACT

The article presents a clinical case of severe postoperative complications with a clinical death episode in a patient with coronary artery disease after a bypass surgery. On the second day after the surgery, the patient, who had underwent a mammary coronary bypass surgery of the anterior descending artery and an aortocoronary bypass surgery of the right coronary artery and circumflex artery with artificial circulation, developed acute kidney injury, requiring renal replacement therapy. In the following days, there was esophageal-gastric bleeding with the development of DIC-syndrome and hemorrhagic shock, resulting in clinical death registered for 2 minutes. After a successful cardiopulmonary resuscitation, a number of other serious complications were observed: acute respiratory distress syndrome and acute destructive calculous cholecystitis, treated with cholecystectomy.

A comprehensive intensive therapy, including vasopressor/inotropic hemodynamic support, aggressive respiratory therapy, efferent methods of detoxification, resulted in successful management of all the complications, stabilization of the patient's condition, restoration of the functions of organs and systems and recovery of the patient.

Keywords: coronary artery disease, coronary artery and mammary coronary bypass surgeries, acute kidney injury, esophageal-gastric bleeding, hemorrhagic shock, acute respiratory distress syndrome.

INTRODUCTION

Despite the high efficiency of bypass surgeries in the treatment of coronary artery disease (CAD), these operations are associated with a high risk of developing a number of complications, including thrombosis[8], bleeding[3], myocardial infarction [6], acute kidney injury (AKI) [5], acute respiratory distress syndrome (ARDS) [1], and infectious complications [7]. Complications in the perioperative period are most common in people suffering from diabetes, excessive body weight, chronic lung and kidney diseases [2]. The use of artificial circulation (AC) during the surgery, as well as antiplatelet and anticoagulant therapy, can initiate failures in the blood coagulation system with pronounced thrombocytopenia and the development of hemorrhagic syndrome.

The **objective of the research was** to analyze severe postoperative complications with a clinical death episode developed in a CAD patient after a coronary artery and mammary coronary bypass surgeries.

The material of the research was a clinical case of intensive therapy of a patient with the following diagnosis:

Principal: CAD. Stable angina of class 3. Postinfarction cardiosclerosis from 06 September 2007. Coronary sclerosis. Condition after stenting the anterior interventricular branch (AIB) of the left coronary artery (LCA) in 2007, transluminal balloon angioplasty (TBA) and right coronary artery (RCA) stenting in 2012.

Secondary: Diabetes mellitus, type 2 in the stage of decompensation. Diabetic retinopathy OU, nephropathy, polyneuropathy. Obesity of degree 2, body mass index (BMI) - 42, android type. Dislipidemia. Hypertensive disease of degree 3. Arterial hypertension of degree 3, cardiac risk of degree 4. Papillary adenocarcinoma of the left lobe of the thyroid gland $T3N^0M^0$. Condition after radical strumectomy in2012.

Clinical observation. Patient M., 58, was admitted to the Cardiac Surgery Unit RH No.1- NCM for an examination and further CAD treatment.

Complaints at admission: short breath, a burning sensation behind the sternum after little physical exertion (walking for a distance under 50 m, going up one floor), increase in arterial pressure, and blurry vision.

From the *history*, it is known that the patient has suffered from CAD since 2007, when first angina pains appeared after moderate physical exertion. In the same year, he suffered a myocardial infarction of the anterior wall of the left ventricle with the formation of the Q wave. During the examination, an occlusion was identified with stenosis of the coronary arteries, which was treated with stenting of the middle third of the AIB and RCA. In 2015, because of restenosis, stenting of the PCA was performed.

The concomitant diseases included hypertension with the maximum value of systolic blood pressure up to 230 mmHg (since 2010) –the administered antihypertensive therapy was not effective; chronic calculous cholecystitis.

Objective status: State of moderate severity. Alert.

The skin and visible mucous membranes were of normal color, t of body was 36.6 C^0. Excessive type of nutrition, hypersthenic, height 160 cm, weight - 105 kg (BMI - 42). The peripheral lymph nodes were not enlarged.

The lung breathing was vesicular, carried out in all sections, there was no wheezing, respiration rate was 18 per minute.

The heart sounds were muffled, rhythmic, heart rate was 68 per minute. The blood pressure was 140/82 mmHg.

The tongue was clean, moist. The abdomen was soft, painless, enlarged by subcutaneous fat. The liver lied along the costal arch edge. The stool had shape, without pathological impurities.

Diuresis was adequate. Peripheral edema was absent.

On 03 February 2016, with artificial circulation, pharmacological cold cardioplegia and under combined endotracheal anesthesia, the unit surgeons performed the coronary artery bypass surgery (CABS) of the RCA and circumflex artery (CA), as well as the mammary coronary bypass surgery (MCBS) of the anterior descending artery (ADA). The surgery lasted for 04 hours 35 minutes, duration of anesthesia – 05 hours 35 minutes.

The course of general anesthesia: inhalation low-flow anesthesia with Supran (0.2-4.0 % vol.) with central fentanyl analgesia (5-10 μg/kg), without any peculiarities. Antegrade cardioplegia with Custodiol solution 2000 ml, cooled to $+6^0C$, pressure in the aorta about 100 mmHg, asystole on the 2nd minute. The time of

AC – 02 hours 31 minutes, the time of aortic compression– 01 hour 39 minutes. The calculated volumetric perfusion rate – 5.28 ml/min, systemic BP during AC – 62/57 mmHg, the apparatus pressure in the arterial main line of the AC was 130-140 mmHg. Hypothermia down to 34.0^{0}C. During the AC, the partial pressure PaO_2, $PaCO_2$ and sVO_2, as well as the parameters of the acid-base state were within the limits of normal values.

At the end of the main stage of the surgery, after warming the body to 36.1^{0}C, the cardiac activity was restored, external stimulation of the heart was performed, after which there developed ventricular fibrillation. The rhythm was restored by defibrillation with a discharge of 50 J on the open heart. Antiarrhythmic therapy: Lidocaine 1 mg/kg, magnesium sulfate 250 mg. The patient's own rhythm was restored, in the form of sinus bradycardia, heart rate at 45 per minute. The temporary pacemaker (5A, frequency 78 per minute) was connected. The hemodynamics with inotropic support of Dopamine at 3 μg/kg/min, CVP in the 8-12 mmHg range.

The intraoperative blood loss was 150 ml due to the amount blood with tissue wastes and surgical material; the rest of the blood was reinfused with the help of drainage suction of the AC and CellSaver apparatus.

After the surgery, the patient was taken to the Intensive Care Unit. They continued ALV in CMV mode: respiratory volume 730 ml, RMV 9.5 l/ in, PEEP + 5 cm w.c., FiO_2 45%, Paw18-20 w.c., SpO_2 99%.

Days 1-3 (03-05 Feb 2016). In12 hours after admission to ICU, after becoming alert again, gaining the adequate breathing, stable hemodynamics and satisfactory muscle tone, the patient was extubated. However, 30 minutes after the extubation, the patient complained of shortness of breath. Noisy wheezing was noted, as well as dyspnea of a mixed character with a RR at 24 per minute. The skin and visible mucous were pale pink, SpO_2 93% due to administration of moistened oxygen (5 l/min) through a face mask. The gas composition of the blood: PaO_2 110 mmHg, PCO_2 35 mmHg, SvO_2 97%, Shunt 7%. After another 30 minutes, the patient was excited, dyspnea reached 34-36 breaths per minute, cyanosis of the visible mucous membranes appeared, SpO_2 – 88%, AP – 150/87 mmHg, CVP – 13-14 mmHg. Gases of the blood: PaO_2 85 mmHg, $PaCO_2$ 56 mmHg, SvO_2 47%, Shunt15%. Taking into account the respiratory failure and hypoxemia, the patient was intubated and transferred to ALV in the CMV mode with moderate hyperventilation f 16-18 per minute, FIO_2– 60%. The analysis of the blood gases after 10 minutes showed: PaO_2 104 mmHg, SvO_2 85%, Shunt 17%. The hemodynamics was stable, diuresis was adequate 1 ml/kg/hour. Propofol sedation was started at a dose of 2-3 mg/kg/hr.

In the following days, the mechanical ventilation continued; with an attempt to transfer the patient to spontaneous breathing, he quickly got tired, and signs of hypoxia appeared. Gases of blood: PaO_2 102 mmHg, PCO_2 34 mmHg, SvO_2 88.1%, Shunt 24.6%.

The worsening of the patient's condition was noted on 05 Feb 2016: hyperthermia up to 38.8^{0}C, increase in leukocytosis up to 21.2*10^9/l, hyperosmolarity (298 mosmol/l) due to hypernatremia (Na+ - 150 mmol/l) and hyperglycemia (blood glucose up to 19 mmol/l). The signs of acute kidney injury (AKI) manifested: blood urea samples 17.5 mmol/l, creatinine 240 μmol/l; decrease in diuresis 0.8 ml/kg/hour; GFR 24.7 ml/min 1.73 m^2; edema on the face and feet due to stimulation of diuresis by loop diuretics. AVL was continued, antibacterial therapy was changed.

Days 4-8 (06-09 Feb 2016). In connection with the progressing renal failure and oliguria at 0.25 ml/kg/hour, there was started daily renal replacement therapy (RRT) in the regime CVVHDF, ultrafiltration (UF) 100 ml/ h with Heparin 5-10 thousand units. GFR (CKD-EPI) – 41.5 ml/min/1.73m^2.

On day 8 after the surgery, after becoming alert again, gaining the adequate breathing, stable hemodynamics, satisfactory muscle tone, normalized acid-base and blood gases balance, the patient was extubated.

Days 9-12 (10-13 Feb 2016). On day 9, the nasogastric tube showed discharge looking like coffee grounds. EGD revealed an acute ulcer in the body of the stomach in the area of greater curvature, with signs of bleeding (Forrest 1a). The endoscopic injection method of hemostasis was administered. The antiplatelets were canceled. Conservative hemostatic therapy was prescribed: two-component antiulcer therapy – a blocker of the third generation of H_2-histamine receptors (Famotidine 40 mg per day) and Nexium proton pump inhibitor (starting dose of 80 mg IV and then a supporting dose of 8 mg/h IV for 72 hours).

The blood tests showed anemia up to 67 g/l (Table 2), a transfusion of fresh frozen plasma and erythrocyte mass was started.

On day 11, the patient had a relapse of gastric bleeding; endoscopic hemostasis was repeated, conservative hemostatic therapy was continued. Despite the treatment, unstable hemodynamics was observed as a manifestation of the hemorrhagic shock. The ongoing infusion-transfusion therapy (ITT) was supplemented by vasopressor (Norepinephrine 0.5-1.0 mcg/kg/min, Adrenaline 50-100 ng/kg/min) and inotropic supports (Dopamine 10-15 mcg/kg/min). Hemodynamic parameters of the mean arterial pressure (MAP) were ≤ 86 mmHg.

In the setting of complex rhythm disturbances in the multiple ventricular extrasystoles type, ventricular fibrillation was observed. Cardiopulmonary resuscitation (CPR) was started: external cardiac massage, artificial lung ventilation, defibrillation 1 discharge (200 J), followed by restoration of the cardiac activity (2 minutes after clinical death).

In the early postresuscitation period, the patient continued with ALV, medication sedation (Propofol 1-2 mg/kg/h). Due to the development of paroxysmal atrial

Table 1

The dynamics of indices of the excretory function of the kidneys

Days after the surgery	Indicator			
	Urea, mmol/l	Creatinine, μmol/l	GFR ml/ min/1.73m^2	Diuresis, ml
1	7	139	47,7	4840
3	17,5	240	24,7	2400
5	12,7	156	41,5	650
7	22	174	36,4	630
9	21	142	46	700
11	28	201	30,6	600
13	27	274	21	540
15	26	300	18,5	515
23	19	369	14,6	420
35	26	642	7	0
45	26	331	16,7	200
50	27	312	18	5000>
81	24	280	19	4000
109 (day of transfer from ICU)	10	168	38	3000

Table 2

The dynamics of the complete blood count indicators

Days after the surgery	Indicator				
	Erythrocytes, *1012/l	Hb, g/l	Ht, %	Thrombocytes, *109/l	Leucocytes, *109/l
1	3,27	104	26,7	168	16
3	3,22	102	30	130	21
5	5,73	109	53,1	68	10
7	3,06	90	28,5	140	22
9	3	90	28	138	21
11	2,6	68	29	142	24
13	2,6	68	25	90	26
16	3,2	82	26	94	22
28	2,84	81	25,6	248	8,7
81	3,4	84	25,6	287	14
109 (day of transfer from ICU)	3,05	79	27,78	183	7,8

flutter with 1:1ratio, antiarrhythmic therapy was initiated (Amiodarone 1200 mg/day). Given the extremely difficult condition, it was decided to refrain from open surgical intervention; the endoscopic clipping of the bleeding stomach vessel was repeated.

On day 12 after the surgery, the nasogastric tube again showed copious discharge of the dark brown color. An emergency laparotomy and transverse gastrotomy were performed. The revision of the stomach showed sound vascular clips, imposed previously, an ulcer 7-8 mm with active bleeding in the lower third of the body of the stomach along its posterior wall. Sewing (Z-shaped nodular suture) of the bleeding site and ligation of the left gastric artery were performed. With further revision of the abdominal cavity, a destructive gallbladder with necrosis areas was revealed, and therefore a cholecystectomy was executed.

Days 13-15 (14-16 Feb 2016). The patient's condition remained extremely serious; there were no signs of gastrointestinal hemorrhage. The staff continued medication sedation, ALV, ITT, vasopressor/ inotropic support (MAP ≤86 mmHg), RRT (using Calcium citrate instead of Heparin), parenteral nutrition. Through the tube, inserted into the duodenum, enteral feeding was started. Due to prolonged ventilation, the need for adequate sanitation of the tracheobronchial tree was performed with medial tracheostomy.

On day 15, EGD revealed a linear rupture in the region of the nasal esophagus, which was an indication for the installation of the Blackmore tube. In setting of replacement transfusion therapy, anemia remained (Table 2).

There were signs of pronounced ARF (Table 1). The patient had peripheral anasarca edema, fluid in the pleural cavities. Pleurofix system pleural drainage was installed; 700 ml of serous hemorrhagic fluid was evacuated from the both sides.

Days 16-27 (17-28 Feb 2016). The condition of the patient was still extremely serious. There were no signs of gastrointestinal bleeding, but the anemia remained. The patient received enteral feeding through a tube inserted into the duodenum. There were signs of hemorrhagic bronchitis, CKD-EPI – 11.1 ml/min/1.73 m^2. Anasarca. The unstable hemodynamics remained against a background of microfine infusion of norepinephrine 0.25-0.5 μg/kg/min, epinephrine ≤50 ng/kg/min, and dopamine at a dose of 5-10 μg/kg/min (MAP ≥ 89 mmHg).

In the following days, in the setting of the ongoing mechanical ventilation, the patient developed a clinic of acute respiratory failure with a decrease in SpO_2 ≤ 92%, hypoxemia $PaO_2$89-93 mmHg, SvO_2 66-72 mmHg against the background of FiO_2 0.7-1.0 fraction of oxygen. A computed tomography of the chest organs revealed signs of acute respiratory distress syndrome (ARDS).

Days 28-80 (29Feb – 20 April 2016). During this period, vasopressor amines were cancelled, and the dose of Dopamine was reduced to 3-5 μg/kg/min. The patient demonstrated positive dynamics, caused by the restoration of diuresis, and then polyuria in the first 10 days (1.0-2.0 ml/kg/h). GFR was 7-19 ml/min /1.73 m^2. The computer tomography of the chest organs showed positive dynamics – there were no signs of ARDS, there were foci of fibrous changes in the lungs and insignificant stagnation in the small circle of blood circulation. RRT continued under the indications, on average, 1 session every 3 days.

Days 81-108 (**21April – 21May 2016).** The condition of the patient showed positive dynamics. There was a decrease in peripheral edema, GFR 31.9 ml/min/1.73 m^2. Against this background, the RRT was cancelled. A total of 33 sessions of the filtration-dialysis method of detoxification (hemodialysis, ultrafiltration, hemodiafiltration) were conducted.

In the period of polyuria, which lasted for 1 day, the daily diuresis averaged to 3,127 ± 245.6 ml. During this period, the focus of abscess in the retrostenal hematoma was sanitized.

The patient activation started, the medication sedation was cancelled. The patient is without the neurological deficit. Alert, adequate, he understood the phrases addressed to him and performed simple commands. The discontinuation of the patient from mechanical ventilation went for 2 days. The respiratory gymnastics and exercise therapy were done. The patient can take food unassisted. There were no signs of gastrointestinal hemorrhage. There was an improvement in the radiographic pattern in the lungs, normalization of the clinical and biochemical parameters of the blood.

On 22 May 2016, on day 109 after the surgery, the patient was transferred from ICU to the Cardiac Surgery Ward in a state of moderate severity; in 14 days, in satisfactory condition, he was discharged home.

In total, the patient spent 268 days in the hospital, including 109 days in the ICU.

When analyzing this clinical case retrospectively, one can see that the complications were observed from the first hours of the postoperative period. These were signs of laryngospasm with acute respiratory failure, which developed after extubation of the patient and led to a repeated intubation of the trachea and transfer to mechanical ventilation. Another complication was ARF with uremia and hypervolemia, marked in the patient from day 3 after the surgery, in respond to which 33 sessions of RRT were performed. According to the published data [4], the risk of developing AKI in patients after surgical treatment of CAD is highest with concomitant diabetes and metabolic syndrome, which were present in this patient. On days 9-12, the patient had bleeding from an acute stomach ulcer with severe anemia and a hemorrhagic shock, resulting in a two-minute clinical death. The cardiopulmonary resuscitation, started immediately and conducted with taking into account the type of the cardiac arrest, as well as the adequate management of the early postresuscitation period, allowed restoring blood circulation and avoiding a subsequent neurological deficit.

Thus, a comprehensive intensive therapy, including vasopressor/inotropic hemodynamic support, aggressive respiratory therapy, efferent methods of detox-

ification, resulted in the successful management of all the severe complications, stabilization of the patient's condition, restoration of the functions of organs and systems, and the recovery of the patient.

REFERENCES

1. Andrianova M.Ju. Paljulina M.V. Kukaeva E.A. Perekisnoe okislenie lipidov i soderzhanie srednih molekul pri operacijah na serdce s iskusstvennym krovoobrashheniem [Peroxide oxidation of lipids and content of medium molecules in cardiac surgery with artificial circulation] Anest. i reanimatol. [Anest. and reanimat.] Moscow, 2001, vyp. 2, p. 33–35.
2. Bokerija L.A. Goluhova E.Z. Sigaev I.Ju. Keren M.A. Sovremennye podhody k hirurgicheskomu lecheniju IBS u bol'nyh s saharnym diabetom [Modern approaches to the surgical treatment of cardiac ischemia in patients with diabetes mellitus] Vestnik RAMN [Bulletin of the Russian Academy of Medical Sciences] Moscow, 2012, №1, p. 20 – 26.
3. Gladysheva V.G. Vlijanie aktivirovannogo faktora VII na gemostaticheskij potencial pri massivnyh refrakternyh krovotechenijah u kardiohirurgicheskih bol'nyh: avtoreferat kandidata medicinskih nauk: 14.00.29 [Influence of activated factor VII on the haemostatic potential with massive refractory bleeding of cardiosurgical patients: the author's abstract of the candidate of medical sciences: 14.00.29] Gematol. nauch. centr RAMN [Hematol. sci. center of RAMS]. Moscow, 2006, p. 21.
4. Iskanderov B.G. Sisina O.N. Ostroe povrezhdenie pochek i ego prognosticheskoe znachenie u pacientov s saharnym diabetom 2 tipa, podvergshihsja aortokoronarnomu shuntirovaniju [Acute kidney injury and its prediction of significance in patients with type 2 diabetes mellitus who underwent aortocoronary bypass surgery]. Nefrologija [Nephrology] Moscow, 2015, vol. 19, №4, p. 67-73.
5. Miroljubova O.A. Ostroe povrezhdenie pochek posle aortokoronarnogo shuntirovanija na rabotajushhem serdce: prognozirovanie ishodov [Acute kidney injury after aortocoronary bypass surgery on the off-pump method: predicting outcomes], Nefrologija i dializ [Nephrology and dialysis] Moscow, 2014, vol. 16, № 3, p. 350-358.
6. Cardiac troponin I: Its contribution to the diagnosis of perioperative myocardial infarction and various complications of cardiac surgery / M.O. Benoit, M. Paris, J. Silleran [et al.] //Crit Care Med. - 2001. - Vol. 29. - pp. 1880-1886.
7. Mediastinitis after more than 10,000 cardiac surgical procedures / A.M. Eklund, O. Lyytikainen, P. Klemets [et al.] //Ann Thorac Surg.-2006. - 82(5):1784-9.
8. Perioperative activation of hemostasis in vascular surgery patients / C.M. Samama, D. Thiry, I. Elalamy // Anesthesiology. – 2001. – Jan 94(1). – pp. 74–8.

The authors:

KORORSTELEV Aleksandr Sergeevich - anesthesiologist-resuscitator, Department of Anesthesiology, Resuscitation and Intensive Care (Cardiology), State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No.1 - National Center of Medicine" Address: 677000, Sakha Republic (Yakutia), Yakutsk, ul. Oyunskogo, 27. Tel/fax. +7 (4112) 363489. Mob. +7-924-763-9300. E-mail: bezbazaroff@inbox.ru

BULATOV Alkviad Valentinovich – Candidate of Medical Sciences Head, Department of Anesthesiology, Resuscitation and Intensive Care (Cardiology), State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No.1 - National Center of Medicine"

ANISIMOV Sergei Stepanovich – anesthesiologist-resuscitator, Department of Anesthesiology, Resuscitation and Intensive Care (Cardiology), State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No.1 - National Center of Medicine"

ZAKHAROV Petr Ivanovich – Doctor of Medical Sciences, chief external expert in cardiovascular surgery, Head, Cardiovascular SurgeryDepartment, Clinical Center, State autonomous institution of the Sakha Republic (Yakutia) "Republic's Hospital No.1 - National Center of Medicine"

POTAPOV Aleksandr Filippovich - Doctor of Medical Sciences, Head, Department of Anesthesiology, Resuscitation and Intensive Care with Emergency Care Course, Faculty of Post-graduate Studies for Doctors, Institute of Medicine, Federal state educational institution of higher professional education "M.K.Ammosov North-Eastern Federal University".

L.E. Nikolaeva, O.N. Ivanova, E.F. Argunova

CLINICAL CASE OF BRONCHIECTASIS IN THE TEENAGER OF 16 YEARS

ABSTRACT

This article is devoted to the observation during 3 years (2014-2017) of the clinical case of bronchiectasis in a teenager of 16 years. His complaints were shortness of breath during physical exertion, a wet cough with purulent sputum. From an early age he often (about 5 times a year) had bronchitis with an obstructive syndrome. He was hospitalized in the pulmonology department with the diagnosis: community-acquired pneumonia, middle-lobe, moderate severity. According to the results of computed tomography of chest organs, a conclusion was made: bronchiectasis of the middle lobe of the right lung.

Keywords: bronchiectasis, fibrosis, teenager, pneumonia, bronchial asthma.

Bronchiectasis (BE) occurs in about 0.5-1.5% of the population, developing predominantly in childhood and young age (from 5 to 25 yrs). The disease occurs in the form of recurrent bronchopulmonary infections and is accompanied by a constant cough. The lesion of the bronchi with bronchiectasis may be limited to one segment or a lobe of the lung or be widespread (1-2).

Acquired bronchiectasis occurs as a result of frequent respiratory infections, the migrated in childhood - pneumonia, chronic deforming bronchitis, tuberculosis or lung abscess. Sometimes bronchiectasis develops as a result of ingress of foreign bodies in the bronchial lumen.

Chronic inflammation of the bronchial tree causes changes in mucosal and muscular layers of bronchi and in the peribronchial tissue. Becoming malleable, affected walls of the bronchial tubes to dilate. Pneumosclerosis processes in the lung tissue after suffering bronchitis, pneumonia, tuberculosis or lung abscess leads to scarring of the pulmonary parenchyma and dilation, distortion of the bronchial walls. Destructive processes also affect the nerve endings, arterioles and capillaries that feed the bronchi.

Fusiform and cylindrical bronchiectasis affect large and medium-sized bronchi,

saccular –smaller ones. Uninfected bronchiectasis are few and small in size, can long time does not manifest itself clinically. With the accession of infection and development of inflammation bronchiectasis filled with purulent sputum, supporting chronic inflammation in the bronchi modified. The maintenance of a purulent inflammation in the bronchi contributes to bronchial obstruction, the obstruction of self-purification of the bronchial tree, reducing the protective mechanisms of the bronchopulmonary system, chronic suppurative processes in the nasopharynx (1-2). Timely diagnosis and clinical monitoring, sanitation foci of infection achieve long-term remission of chronic disease in children.

The **aim** of the study: to show the clinical course of bronchiectasis in a 16 years child.

Materials and methods of the research

The outpatient (the clinic of the monitoring) and in-patient (pulmonary department of Republican Hospital №1 - National Medical Center) cards of the patient.

The results of observation: from birth the child is concerned about complaints of shortness of breath on exertion, cough with purulent sputum.

From the anamnesis of disease:

From an early age he had episodes of bronchitis with obstructive syndrome (about 5 times a year). The child has burdened heredity: his grandmother along his father's side has diabetes mellitus, his grandmother along mother's side has bronchial asthma. He lives in a damp house without bathroom. In June 2014, he had bilateral pneumonia. In November 2014 - acute bronchitis. He was treated stationary at the place of residence in the hospital. Then the child was urgently hospitalized in the pulmonology department with a diagnosis of community-acquired pneumonia, middle-lobe, moderate severity. He was treated with Cefotaxime 1 gram 3 times a day, and Bromhexine. The results of computed tomography of the chest conclusion: bronchiectasis of the middle lobe of the right lung. Until 2016 he was hospitalized every year in the pulmonology department of the RH № 1- NCM, radiographs of chest organs showed infiltrative changes in the lungs.

In 2016 he was hospitalized and examined at the National Children's Health Center in Moscow with the diagnosis: Q 33.8 Other congenital malformations of the lung. Congenital malformations of the bronchi: bronchiectasis of the middle lobe of the right lung. Chronic bronchitis.

In 2017, the child was hospitalized in the pulmonology department of the RH № 1- NCM, an allergological examination was carried out, as a result, sensitization to allergens of pillow feather, house mites, cat wool, birch, timothy, *cock's foot* pollen and tangarines was revealed. A study of the level of immunoglobulins of blood was performed, the following results were revealed: immunoglobulin A-1.55 mg/ml, immunoglobulin M-1.8 mg/ ml, immunoglobulin G -24.0 mg / ml, immunoglobulin E total -14.7 MU/ml.

The nasal secretion was studied and the following data (per 100 cells) were obtained: neutrophils - 81hpf; lymphocytes - 8 hpf, eosinophils - 11 hpf. Bacteriological culture of sputum was carried out, as a result of which Staphylococcus aureus susceptible to gentamicin, clindamycin, co-trimoxazole, oxacillin, ciprofloxocin and erythromycin was cultivated. X-ray examination was carried out, as a result of which the conclusion was made: deforming bronchitis. Pneumosclerosis of ligulate segments on the left. Spirometry was performed, a conclusion was made - there are no violations in the spirogram. The test with salbutamol is weakly positive.

A computed tomography of the thoracic organs was performed. As a result of the study, subpleurally located foci of the type of frosted glass, prone to fusion in the right lung in S1, have been identified. There is some decrease in the volume of the middle lobe of the right lung. In the segments of the basal pyramid of the lower lobes of the lungs, mainly in the right side in the middle lobe and in the ligament segments on the left, the parenchyma segment compaction by the type of fibrosis is preserved. Bronchi on both sides are with dense walls. Intramammary lymph nodes are not enlarged. There is no effusion in the pleural cavity. Conclusion: During the period 2016-2017, foci appeared in S1 in the right lung.

Bronchial lavage was cultivated. Streptococc pneumonia, resistant to clindamycin, oxacillin, erythromycin, sensitive to levofloxacin, tetracycline was isolated.

As a result of the study, the following diagnoses were made:

Diagnosis clinical J47.0 Bronchoectatic disease, cylindrical bronchiectasis in the S1 lobe of the right lung, moderate severity.

Complications: J96.0 Respiratory failure of the I degree.

Concomitant diagnoses: J 45.0 Bronchial asthma. Atopic form. Easy course. Uncontrolled. The period of remission. J30.4 Allergic rhinitis. Persistent current. The average severity. Period of relapse.

The following measures are recommended: observation of the district pediatrician at the place of residence, dispensary observation at the pulmonologist and allergist, hospitalization in the pulmonology department of the RH № 1- NCM annually for the purpose of dynamic observation and specialized examination, hypoallergenic life (to exclude contact with feather pillows, pets and plants) hypoallergenic nutrition (exclude stone fruits, honey, carrots, cereal products, tangerines), elliptic revert one inhalation 22 mcg + 92 mcg 1 time / day for 3 months, after that pulmonologist and allergist examination, expectorant drugs, peakflowmetry 4 times a day, situational therapy of attacks of bronchial asthma.

Conclusion

Management of patients with bronchiectasis is a difficult task for the district pediatrician, pulmonologist and other specialists, since frequent monitoring of the course of the disease is necessary, which will allow long-term remissions of a chronic disease in children.

REFERENCES

1. Bolezni organov dyhaniya u detej [Diseases of the respiratory system in children] Pod red. S. V. Rachinskogo, V. K. Tatochenko [ed. by S.V. Rachinsky, V.K. Tatochenko]. Moscow, Medicina, 2007, 496p.
2. Paleev N.R. Bolezni organov dyhaniya. Rukovodstvo dlya vrachej [Diseases of the respiratory system. The manual for doctors] pod redak. N.R.Paleeva [edit. N. R. Paleev]. Moscow, Medicina, 2000, V. 3, 4.

The authors:

Yakutsk, the Republic Sakha (Yakutia), Russia:

Nikolaeva Lena Egorovna – head of the Department of pulmonology Republican Hospital №1- National Medical Center;

Ivanova Olga Nikolaevna – MD, Professor MI NEFU, olgadoctor@list.ru;

Argunova Elena Filipovna – docent MI NEFU, eargynova@mail.ru.

A.A. Yakovlev, M.M. Vinokurov, A.V. Vinokurov

REGIONAL THROMBOLYSIS WITH MASSIVE THROMBOEMBOLISM OF THE PULMONARY ARTERY OF WOMEN IN THE FIRST TRIMESTER OF PREGNANCY

ABSTRACT

The article describes a clinical example of successful regional thrombolysis with massive pulmonary arterial thromboembolism of the pulmonary artery of women in the first first trimester of pregnancy. Conducted local thrombolytic therapy saved not only the life of a woman, but also the life of a conceived child.

Keywords: thromboembolism of the pulmonary artery, regional thombolytic therapy, pulmonary artery, posterior tibial vein, international normalized ratio, prothrombin index, inferior vena cava.

The frequency of thromboembolism of the pulmonary artery (TEPA) is determined due to the literature data, during pregnancy – within 0.05-0.1%; in the postoperative period - 3%.Mortality in this pathology ranges from 8 to 30% and depends on the quality of diagnosis, treatment, pregnancy and delivery [1-3,5].The main causes of maternal death of thromboembolism of the pulmonary artery are a reflex drop in cardiac output, ventricular fibrillation and acute respiratory failure [1, 2, 5, 6].

Accepted obstetric tactics in pregnant women with TEPA at the present time depends on the severity of the patient's consciousness, gestation period, fetal condition, joining of other obstetric and extragenital complications.

With the development of TEPA in the first trimester of pregnancy after arresting cardiopulmonary shock, the elimination of thrombosis and stabilization of the woman's condition, pregnancy should be interrupted due to the severity of the disease, fetal radiation in the early stages of pregnancy, the need for prolonged anticoagulant and antithrombotic therapy. With the development of TEPA in the second and third trimesters, the issue of maintaining pregnancy should be addressed individually, depending on the condition of the woman and the viability of the fetus. With successful treatment of pulmonary embolism, satisfactory patient condition and absence of pathology in the fetus, pregnancy can be carried (but not preserved!) [1, 5].

Conditions for bearing pregnancy after pulmonary embolism: integrated management of pregnancy together with related specialists (obstetrician-gynecologists, hematologists, anesthesiologists-resuscitators, vascular surgeons and cardiosurgeons); continuous anticoagulant therapy throughout pregnancy; quality laboratory control of anticoagulant therapy; regular control of echocardiography of pulmonary-cardiac hemodynamics and compression two-dimensional echocardiography of the veins of lower extremities; continuous monitoring of the fetus. Pregnancy should be interrupted in case of a serious condition of a woman (an increase in pulmonary hypertension or the development of severe pulmonary hypertension), a progressive deterioration in the functional state of the fetus, and the addition of other obstetric and extragenital complications.

When treating TEPA in pregnant women, the primary task is to eliminate the obstruction of the pulmonary artery and restore its patency. To date, thrombectomy from the pulmonary artery and thrombolytic therapy have been used for this purpose [4].

Surgical treatment can save the life of a patient with massive pulmonary artery obstruction, but only a very small number of specialized vascular clinics are actually available. At present, the most accessible and most frequently used method of recanalization of the pulmonary artery in pulmonary embolism, despite obvious shortcomings, is the method of selective, regional thrombolysis. Due to simplicity, systemic thrombolysis is often used in almost all vascular centers [1, 2, 5, 6]. With the appearance of an X-ray surgical operation in our clinic, endovascular mini-invasive methods of surgical treatment for patients became possible for everyday practical activities.

We give an example of the successful treatment of a patient during the first trimester of pregnancy with pulmonary artery thromboembolism that took place up to a day-old period in the first surgical department of the Republican hospital No. 2 - Center for emergency medical care, where regional thrombolytic therapy using endovascular mini- invasive methods of surgical intervention was used.

A patient Z., female, 38 years old complained of severe suffocation, lack of air, chest pain. From anamnesis: According to the patient, she came from the village of Khandyga in the morning (she was 12 hours by car), and when she climbed the stairs at 06:00 am, abdominal pain, a feeling of lack of air, the patient fell and hit her head. Before that, for two weeks, the pains and swelling of both lower limbs were disturbed. She did not apply for medical help. The condition is extremely difficult. Consciousness is clear. Skin covers and visible mucous membranes are clean, pale with cyanosis of the face. Breathing is carried out in all the pulmonary fields, there are no wheezing, weakened in the lower parts. Heart tones are rhythmical. Blood pressure 100/50 mm Hg. Pulse is 160 per minute. The abdomen is soft, painless. Intestinal peristalsis is heard. The gases are moving away. Diuresis is normal.

St.localis: There are moderate edema of both shins to the upper third. Symptoms of Homans and Moses are positive.

08.07.2016 Electrocardiography. Severe sinus tachycardia with a heart rate of 162 beats per minute. Electronic Heart Axis SI QIII. Peaks QS in V1-V4 (V5) with (-) peak T in combination with the clinic, anamnesis. Do not exclude thromboembolism of the pulmonary artery. Electrocardiography in dynamics.

General blood analysis. WBC=13 10^9/L; HGB=121 g/L; RBC=4.28 10^12/L; HCT=39.6%; PLT=135 10^9/L; basophils=1%, segment neutrophils=77%; lymphocytes=20%; monocytes=2%; erythrocyte sedimentation rate=34 millimeters per hour. D-dimer=>5000;

08.07.2016 Antithrombin=103%

08.07.2016 Blood chemistry. Total

protein=61.4 g/L; Albumins=31.8%; Total bilirubin=8.4; Blood glucose=5.8; Urea=2.2; Creatinine of blood=87; Amylase of blood=57; Alanine aminotransferase=16; Aspartate aminotransferase=18.

08.07.2016. Ultrasound examination of the heart and blood vessels: Complications in the study: forced position in orthopnea, non-optimal visualization. The maximum anterior-posterior size of the left atrium is 3.3 centimeters. The maximum opening of the valves of the aortic valve is 1.6 centimeters. The diameter of the root of the aorta is -1.8 centimeters. The diameter of the aorta in the bulb area is 2.9 centimeters. The thickness of the interventricular septum in diastole is 1.1 centimeters. The thickness of the back wall of the left ventricle in the diastole is 1.1 centimeters. The maximum antero-posterior size of the outflow tract of the right ventricle is 3.8 centimeters. The diameter of the pulmonary artery trunk is 2.3 centimeters. Blood flow in the trunk of the pulmonary artery: the maximum speed is 50 centimeters per second. The maximum velocity of blood flow on the mitral valve is 83 centimeters per second. Parameters of the aortic blood flow: the maximum speed is 101 centimeters per second. Blood flow in the tricuspid valve is 41 centimeters per second. The diastolic volume of the left ventricle is 84 milliliters. The systolic volume of the left ventricle is 33 milliliters. Fraction of ejection of the left ventricle - 60%. The maximum volume of the left atrium is 55 milliliters, not enlarged. The maximum volume of the right atrium is 42 milliliters, not enlarged. Conclusion: the study was conducted against a background of severe tachycardia. Visualization of the structures of the saddle is difficult, the patient in forced position orthopnea, all dimensions are given approximate, some of the structures could not be visualized. The systolic function of the left ventricle is normal. Ejection fraction 60%. Moderate expansion of the right ventricle. Rough, distinct zones of disturbed local contractility of the left ventricular myocardium were not revealed. The lower vena cava could not be visualized. Indirect signs of pulmonary hypertension. Additional echostructures in the heart cavity are not reliably detected.

08.07.2016 Ultrasound examination of veins of lower extremities. Complication in the study - the forced position in the orthopnea. On left: The large subcutaneous vein, the proximal segment of the common femoral vein, the deep femoral vein are passable, the lumens compression is a complete, pronounced effect of spontaneous contrasting. In the tibial veins, blood flow is not recorded. Subcutaneous vein - it was not possible to visualize. In the lumen of the superficial femoral vein, along the entire length, thrombotic masses of various echogenicity are visualized, completely obturating the lumen. The end of the thrombus is visualized in the distal segment of the common femoral vein (at a distance of about 1.0 to 1.5 centimeters from the bifurcation). No signs of flotation have been identified. Minor edema of surrounding tissues, mainly on the shin level. Right: large saphenous vein, common femoral vein, deep femoral vein, tibial veins - passable, compression of lumens full, pronounced effect of spontaneous contrasting. The total femoral vein is expanded to 1.9 centimeters, the lumen compression is complete. In the lumen of the superficial femoral vein, the parietal thrombotic masses are visualized without signs of flotation, the blood flow is recorded weakly phase. Subcutaneous vein - it was not possible to visualize. Minor edema of surrounding tissues, mainly at the level of the shin.

Conclusion: Echographic features of occlusive thrombosis of the superficial vein vein, left without flotation symptoms, near-wall thrombosis of the superficial femoral vein of the spas without flotation symptoms. The pronounced effect of spontaneous contrasting. Edema of both shins.

Exposed clinical diagnosis:

Primary: Acute ileofemoral thrombosis of the left lower limb.

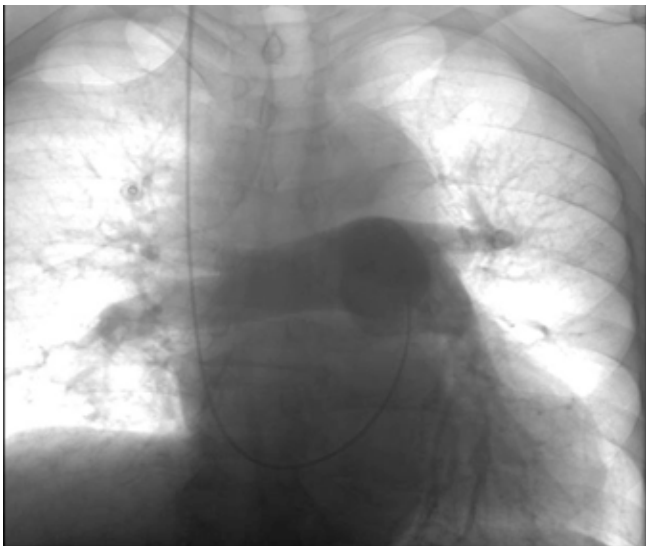

Fig.1. Overview of pulmonography of patient Z. before thrombolysis. Angiopulmonography revealed thrombosis of the lower branch of the pulmonary artery. In the patent-mediated phase, the «mute» zone in the middle third of the lung pattern.

Complication: Massive pulmonary embolism.

Concomitant: Pregnancy 14-15 weeks.

The patient was urgently transported to the X-ray room, accompanied by an anesthesiologist. The patient is warned about possible complications of medical procedures and termination of pregnancy. The woman categorically refused to stop pregnancy, motivating about the desired pregnancy. Before us there was a question on preservation of two lives: a life of mother and the child.

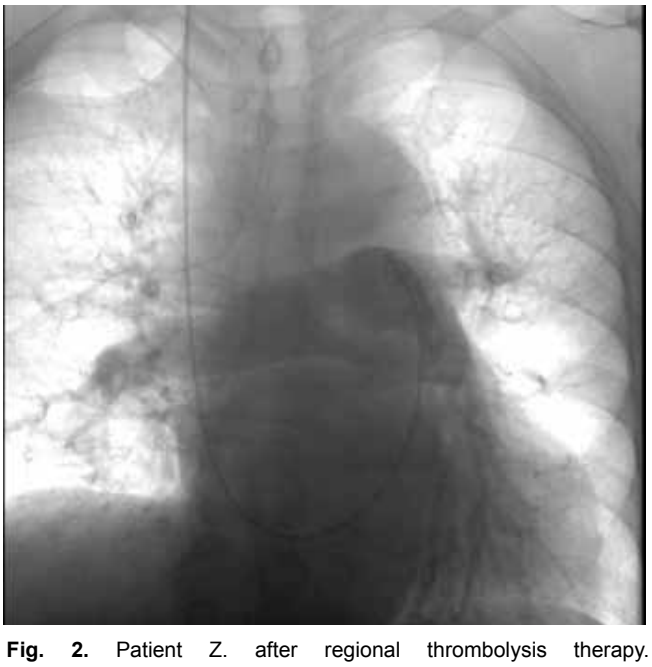

Fig. 2. Patient Z. after regional thrombolysis therapy. Angiopulmonography in dynamics from 08.07.2016 thrombus of the left lower branch of the pulmonary artery was not detected. In the parenchymal phase, all zones are contrasted evenly on both sides.

Coagulogram pattern of patient Z. for 4 hour observation

Parametr	16.03.16	16.03.16	16.03.16	16.03.16
INR	1,62	3,16	2,78	1,55
PTI	60,1	22,7	25,7	48,7
APTT	57	75,4	64,4	33,4

In the X-ray-operative room we installed the pigtail catheter for regional thrombolysis therapy through the jugular vein on the right, cavitation of the inferior vena cava, a detachable cava filter is installed in the lower hollow vein below the renal vein bifurcation, angiopulmonogrophy (Fig.1).

After the catheter was inserted into the pulmonary bifurcation, the patient was transferred to the intensive care unit for regional thrombolysis. The drug of choice for the thrombolytic therapy - Aktelize 100 mg. The first dose of the 10 mg Aktelize solution was introduced into the bolus catheter for 2 minutes. The remaining solution of 90 mg of Actilele is connected to a syringe pump. The drug was administered for 2 hours under the control of a coagulogram. After carrying out thrombolysis therapy, the patient continues therapy with low molecular weight heparins.

As it can be seen from the table, no significant changes in the coagulogram pattern occurred in the 4-hour dynamic observation, which corresponds to the data of the literature sources in the periodic publications on angiology [1, 5, 6].

12 hours after thrombolytic therapy, control angiopulmonography was performed (Fig.2).

The patient continued therapy with low molecular weight heparins Clexane 0.8 mgg x 2 subcutaneously per day. Conclusion of control computed tomography of chest cavity organs with contrast before discharge in comparison with 16.03.16. positive dynamics in the form of the absence of contrast defects in the left pulmonary artery. The installed cava filter was removed on the 14th day after the monitoring of the cava.

Ultrasound examination of the veins of the lower extremities from 07/28/2016. Complications in the study are absent. Conclusion: Echographic signs of occlusive thrombosis of the superficial femoral vein on the left without flotation symptoms in the stage of moderate recanalization, near-wall thrombosis of the superficial femoral vein on the right without flotation symptoms. The pronounced effect of spontaneous contrasting. Edema of both shins. When compared with the study of 22.07.2016 - positive dynamics in the form of recanalization.

Later the patient was transferred to the Perinatal Center of the Republican Hospital No. 1 for further dynamic observation, treatment and maintenance of pregnancy. Continued to study the course of anticoagulant therapy, during pregnancy. Childbirth operative on time. He was a healthy, full-blooded child, without deviations from his health.

Thus, the regional thrombolytic therapy saved the lives of the mother and child in the first trimester of pregnancy. Successfully ended with operative labor with the birth of a full-term healthy child.

Conclusions:

1. The use of X-ray surgical endovascular methods of treatment allows for effective local thrombolytic therapy for pulmonary embolism.

2. With local thrombolytic therapy of recanalization of the branches of the pulmonary arteries occurs due to the direct action of the thrombolytic preparation on the thrombus without significant effect on systemic hemostasis. At that thrombolysis moderately affects the peripheral circulation, without causing bleeding.

REFERENCES

1. Rossijskie klinicheskie rekomendacii po diagnostike, lecheniju i profilaktike venoznyh trombojembolicheskih oslozhnenij [Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboplasy complications] Flebologija [Phlebology]. Moscow, 2010; 4:1:2:2-37.
2. Profilaktika venoznyh trombojembolicheskih oslozhnenij v travmatologii i ortopedii. Rossijskie klinicheskie rekomendacii [Prevention of venous thromboplasty complications in traumatology and orthopedics. Russian clinical guidelines]. Travmatologija i ortopedija Rossii [Traumatology and orthopedics in Russia]. Moscow, 2012; attachment 1 (63):2-24.
3. Rossijskie klinicheskie rekomendacii po profilaktike i lecheniju venoznyh trombojembolicheskih oslozhnenij u onkologicheskih bol'nyh [Russian clinical recommendations for the prevention and treatment of venous thromboembolic complications in cancer patients]. Moscow: Planida, 2012; 32.
4. Profilaktika venoznyh trombojembolicheskih oslozhnenij v akusherstve i ginekologii. Klinicheskie rekomendacii [Prevention of venous thromboembolic complications in obstetrics and gynecology. Clinical recommendations]. Akusherstvo i ginekologija [Obstetrics and gynecology]. Moscow, 2014; 10: attachment: 1-18.
5. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest Am Coll Chest Phys. 2012; 141:2. doi: 10.1378/chest.11-2304.
6. ESC Guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal. 2014; August 29, 2014; 48. Advance Access published. doi: 10.1093/eurheartj/ehu283.

The authors:

Yakutsk, Republic Sakha (Yakutia), Russia:

Yakovlev Anton Antonovich - PhD, doctor angio-surgeon RH №2 – Emergency Medical Centre, jakvlev.antn@rambler.ru;

Vinokurov Mikhail Mikhailovich - doctor of medical sciences, prof., Head of Department of Medical Institute M.K. Ammosov NEFU, mmvmi@rambler.ru;

Vinokurov Mikhail Andreevich - graduate student, michailwork@mail.ru.