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

1(69) `2020
YAKUT MEDICAL JOURNAL

YAKUT MEDICAL JOURNAL

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

Quarterly

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

Registration number PI No.TU 14-00475

Subscription index: 78781
Free price

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

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

The founder
The Yakut Science Centre of Complex Medical Problems

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The articles are given in the authors' translation

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EDITOR-IN-CHIEF COLUMN

Dear colleagues!

The editorial staff of the "Yakut Medical Journal" is pleased to welcome you to the pages of our publication. Every year the first issue of our Journal is published in early spring, when we all make special plans for a better future after a long winter. We live and work in a very dynamic time, which demands more and more in all areas of life. New diseases are emerging that require fast study and development of the latest effective methods of diagnosis, prevention and treatment. This is only possible with the consolidation of medical science and practice.

The main goal of the "Yakut Medical Journal" is to bring current information on a particular medical problem, the results of modern scientific research and translational medicine. In 2019 and in the beginning of this year, the editors of the journal received a large number of interesting materials from different regions of Russia. And the new issue of our journal, as before, turned out to be polythematic, containing articles of different clinical orientation. In particular, the results of clinical and genetic study of the Yakut family with hereditary spastic paraplegia are given, which confirmed the genetic heterogeneity of this pathology. Clinical and anatomical analysis of cases of various types of myocardial infarction is presented and evaluation of peculiarities of diagnostics and frequency of myocardial infarction development is given. The medical-demographic situation in the Republic Sakha (Yakutia) in dynamics for 2010-2017 is considered, an attempt is made to predict the possibility of achieving indicator values in accordance with the strategic objectives of development of the Russian Federation up to 2024. In addition, the reader will get acquainted with an interdisciplinary approach to the study of nutrition of the Yakuts from the XVII to XIX centuries. The authors have described the advantages and disadvantages of using ethnographic, archaeological and biochemical methods of research. Traditionally, we publish descriptions of clinical cases. This issue presents two cases of congenital central hypoventilation syndrome in children and a case of spontaneous pneumothorax in a 17-year-old boy with bronchial asthma.

In 2020, the editorial staff of "Yakutsk Medical Journal" will continue to work on improving the quality of published materials in accordance with the list of scientific specialties, for which the Journal is included in the List of peer-reviewed scientific publications recommended by Higher Attestation Commission (VAK) for publication of the main scientific results of dissertations for the degree of candidate and doctor of sciences, as well as for those scientific specialties, which the Journal will apply to the Ministry of Education and Science of Russia in the future. The work on improving the journal's website will also be continued.

I cordially congratulate my dear colleagues from the Institute of Clinical and Experimental Medicine on a remarkable date - the 50th anniversary of its foundation! The first director of ICEM was an outstanding scientist, Academician of the Academy of Medical Sciences V.P. Kaznacheev. The main directions of scientific activity of the Institute are the study of physiological, biological and immunological changes in the human body in the process of adaptation; development of systems of prevention and treatment of acute and chronic diseases of various systems of the body arising in the process of adaptation. Over the years, the ICEM Clinic has won well-deserved recognition and respect among both patients and colleagues, has established itself as a modern medical institution providing highly qualified medical care. Dear colleagues, let your work bring you inspiration, new breakthroughs, recognition in the scientific community, and success always comes with you in everything!

Dear readers and authors, may the coming spring bring you sunny mood, bright positive emotions, creative inspiration and professional achievements! The editorial staff of the Journal expresses its sincere hope that our publication will continue to be an inseparable and useful companion of your professional activity!

Editor-in-Chief ***Anna Romanova***

ORIGINAL RESEARCH

T.M. Sivtseva, L.G. Goldfarb, T.K. Davydova, N. Sambuughin, C. Toro , A.C. Sundborger, F.A. Platonov, N.M. Renwick, Kh. Kurtanov, A.T. Diakonova, E.E. Konnikova, M.A. Varlamova, A.E. Adamova, O.G. Sidorova, J.E. Hinshaw, V.L. Osakovsky

AUTOSOMAL DOMINANT SPASTIC PARAPLEGIA IN FOUR GENERATIONS OF YAKUT FAMILY LINKED TO DYNAMIN 2 MUTATION

DOI 10.25789/YMJ.2020.69.01

УДК 616.8-009.11-031.58 (=512.157)

The article presents the results of a clinical and genetic study of a Yakut family with hereditary spastic paraplegia (HSP). 5 patients with clinically diagnosed HSP and 4 unaffected family members were studied. The disease is clinically characterized as progressive spastic paraplegia of the lower extremities combined in advanced cases with peripheral neuropathy. Whole exome sequencing, molecular modeling of dynamin-2 and experimental reproduction of the key elements of HSP pathogenesis were conducted. Genetic analysis revealed a novel missense c.2155C> T, p.R719W mutation in the highly conserved GTP-effector domain of the dynamin-2 gene (*DNM2*). In experiments on HeLa cells, it was shown that mutant dynamin-2 affected endocytosis process. *In-silico* modeling determined that the identified mutation is located in the *DNM2* bundle-signaling element and potentially disrupts the assembly and functional properties of the protein. Testing of this mutation in other Yakut families with HSP showed a negative result, which once again confirms the genetic heterogeneity of this pathology.

Keywords: Spastic Paraplegia, HSP, dynamin, *DNM2*, Neuropathy, exome sequencing, endocytosis.

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Hereditary spastic paraplegia (HSP) comprises a group of clinically and genetically heterogeneous diseases that affect the upper motor neurons and their long axonal projections. Various forms of HSP are associated with mutations in more than 60 genes [10]. HSP is a result of mutational changes in the genes that regulate various functions: the efficiency of transmembrane metabolism, the formation of the endoplasmic reticulum, myelination, lipid metabolism, and the speed of movement of molecules in the endosomal and microtubule systems [5, 20]. Despite the variety of pathogenetic mechanisms, the typical manifestations of HSP are progressive degeneration of the corticospinal tract and fasciculus gracilis [10]. The key diagnostic findings are lower limb weakness, increased muscle tone, hyperreflexia, extensor plantar responses, and gait spasticity [26]. The earliest pathological changes are noted in the long fibers of the spinal cord, they predate changes in the cell bodies. In this regard, HSP may be viewed as a counterpart of the axonal form of Charcot-Marie-Tooth (CMT) neuropathy [18].

Chronic neurological disorders are highly prevalent in the Sakha (Ya) Republic, Russian Federation [1]. In the Yakut population, we identified 6 family HSP cases with the number of patients from 2 to 5 people with different types of inheritance. The aim of this study was to identify the genetic variants associated with HSP in Yakut families. This work describes a new type of autosomal dominant HSP associated with a heterozygous mutation in the dynamin-2 gene (DNM2) that we identified in the Yakut family. Dynamins are highly conserved enzymes GTPases, which hydrolyze guanosine triphosphate (GTP). In the process of endocytosis they participate in the forming a vesicle, fill it with the necessary load, pass through the cell membrane, and release the contents into the cytoplasm [17]. In developing neurons, both endocytosis and exocytosis are critical for delivery of nutrients and building materials. This process plays a particularly important and specialized role at neuronal synapses [19]. Dynamin-2 is found ubiquitously, participating in several other cellular processes, while its isoforms dynamin 1 and dynamin 3 are expressed only in neurons [22].

Methods. Family pedigree and patient evaluation.

In the process of systematic ascertainment of patients with Viliuisk encephalomyelitis and related disorders, a family N. with pronounced spastic paraplegia syndrome was identified. This family included 9 patients. The family member (I:2, Fig. 1) had stiff gait and progressive muscle weakness of the lower extremities from about 50 years old before his death at 63. His 3 sons from two marriages (II:1, II:4, and II:6) inherited the disease and diagnosed with hereditary spastic paraplegia. In the third generation, three sons of patient II:4, also from separate marriages, and a daughter of patient II:6 developed

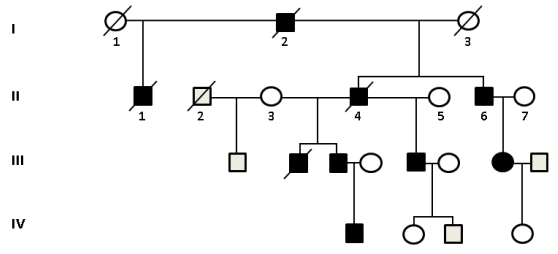

Fig. 1. Domain structure of dynamin 2 and location of known disease-causing mutations. Dynamins contain a GTPase domain that binds and hydrolyses GTP; a middle domain (MD); pleckstrin-homology (PH) domain for lipid attachment; a GTPase effector domain (GED) that is involved in oligomerization and stimulation of GTPase activity. A proline-rich domain (PRD) at the carboxyl terminus interacts with Src-homology-3 domains. Mutations associated with central nuclear myopathy are shown in the upper set; mutations associated with subtypes of Charcot-Marie-Tooth neuropathy are shown at the bottom of the diagram. *sign indicates a homozygous mutation associated with lethal Congenital Contracture Syndrome. The p.R719W mutation identified in the Siberian family with Hereditary Spastic Paraplegia is underlined.

the same disease (III:2, III:3, III:5, and III:7). Finally, the youngest patient (IV:1) was diagnosed as HSP. Pedigree was constructed based on cross interviews of patients and closest family members.

The study was approved by the Institutional Review Boards of the Yakutsk Research Center of complex medical problem (protocol №39, 26.06.2014). A written informed consent was obtained from each participant.

After obtaining informed consent, 5 affected and 4 unaffected family members underwent a neurological exam that included assessment of mental status, cranial nerves, muscle strength (MRC scale), coordination, tendon reflexes, muscle bulk, muscle tone, plantar responses, foot deformity, and gait features. Evaluation of sensory impairment included clinical testing for pain and temperature sensation, vibration and position sense. Electrophysiological investigation conducted in 3 patients (III: 3, III: 5 and IV: 1), included motor and sensory nerve conduction velocities (NCV), compound muscle action potential (CMAP) amplitudes, distal motor latencies (DML), sensory NCV and sensory nerve action potential (SNAP) amplitudes recorded under standard conditions from the median, ulnar, peroneal, tibial, and sural nerves. Routine clinical MRI of the spinal cord was also obtained in three cases. Blood for DNA extraction was drawn from 9 family members.

Exome sequencing. Whole exome sequencing (WES) was performed using genomic DNA extracted from peripheral white blood cells of 2 patients: II:6, III:3. Exome capture utilized TruSeq Kit v1 (Illumina, Sand Diego, California) in accordance with manufacturer's instructions. Library construction, sequence generation, sequence alignment to the reference genome (UCSC GRCh37/hg19), variant calling and potential pathogenic variant identification were performed as recommended by the US National Institutes of Health's Genome Research Center for autosomal dominant genetic model [4]. Mutations in other genes causing HSP or similar diseases were excluded. The selected candidates genes were validated by segregation analysis in 5 patients with a confirmed diagnosis of HSP and 4 unaffected family members using standard Sanger sequencing of amplified DNA fragments.

Experimental reproduction of endocytosis disorders in HeLa cell culture. To determine the mechanism of the damaging effect of the p.R719W mutation, the effectiveness of clathrin-dependent endocytosis in HeLa cells expressing mutant and normal dynamin-2 was tested. HeLa cells were grown in Eagle medium (Life Technologies, Grand Island, NY) supplemented with 10% fetal bovine serum. Human DNA fragments were introduced into the pmM2 pmCherry-N1 plasmid (Agilent Technologies, Santa Clara, CA). Plasmids containing the studied mutation p.R719W, or a non-mutated dynamin-2 gene, were introduced into the grown HeLa cells using the HilyMax transfection reagent (Dojindo Molecular Technologies, Rockville, MD). Cells were incubated in growth medium. 20 h after transfection, HeLa cells were treated with 25 μg / ml Alexa-Flour 488 with conjugated transferrin (Life Technologies, Frederick, MD) for 15 min at 37 ° C. Then, cells labeled with fluorescent transferrin were fixed with 4% paraformaldehyde and photographed using a Zeiss LSM 510 confocal microscope. Immunofluorescence signal was measured using ImageJ software (Image Processing and Analysis in Java, National Institutes of Health). The fluorescence intensity was first measured in the background; the adjusted total transferrin fluorescence signal was then compared between cells expressing mutant and normal dynamin-2. The statistical significance of the differences was evaluated using Student's t-test. A level of P <0.05 was considered significant.

The study of the protein structure of mutant dynamin-2. Molecular models of the mutant and normal dynamin-2 were obtained using I-TASSER [12, 25, 29], using the more studied dynamin-1 as a matrix [7]. The nucleotide sequences of dynamin-1 and dynamin-2 are 78% identical, and the GTPase domain is 87% identical. The tetrameric image of the protein is based on the analysis of the crystal structures of dynamin-1 [28].

Genotyping of the mutation c.2155C> T, p.R719W in the *DNM2.* To search for the identified mutation in other Yakut families, DNA samples from 9 patients and 6 healthy from 7 families with HSP were studied. Genotyping was performed using the following primers: F: GGGTTGGGGTGATACACAAG and R: ATGCTTGAGGGTAGGGGAAC. As a result of amplification, a 315 bp fragment was obtained. When processing with restriction enzyme Fau I in the control sample, 4 fragments were obtained: 108, 87, 69 and 50 bp. The mutant allele gives 3 fragments: 195, 69 and 50 bp.

Results and discussion. Clinical characteristic. The pattern of disease inheritance in this family was autosomal dominant (Fig. 1). Clinical information obtained at evaluation of 5 personally examined affected family members (II:6, III:3, III:5, III:7, and IV:1) was generally identical. But there were differences in the severity of paresis, progression of the disease, and violation of vibration sensitivity, the presence of cognitive impairment and spastic dysarthria. The disease began gradually at the age of 10 to 37 years with impaired gait and muscle weakness in the lower limbs. Further progression of illness in patients II: 6 and III: 5 led to severe disability at 28 and 23 years after the onset of the disease. Three patients (I: 2, II: 1 and III: 2) died after an illness lasting 23-32 years, and one (II: 4) died as a result of an accident.

At examination a single patient (III:5) had mild developmental cognitive delay (25 points on the MoCA scale). All patients had a "Friedreich's foot" and moderate hypotrophy of the lower extremities. Cranial nerves were intact, bulbar functions preserved until late in the illness. In the lower limbs, typical features of spastic paraplegia were present in all patients. Only a single patient (III:3) had moderate spastic dysarthria and spastic tetraparesis with predominant involvement of the lower extremities. Deep tendon reflexes were

increased in the all patients with clonus in 3 patients (III:3, III:5, III:7) and bilateral Babinski sign in 4 patients (III:3, III:5, III:7, II:6). All patients had profoundly spastic gait. Sphincter control abnormalities manifesting as urinary urgency were observed late in the illness in two patients (II:6 и III:5). At the same time, low Achilles reflexes were found in III:3 and IV:1. Patient II:6 revealed flexion contracture of the leg muscles. Pain, temperature and joint-muscular sensitivity are not impaired. In patients II:6, III:3 and III:5, a slight weakening of vibrational sensitivity on the feet was found. Scoliosis was present in one patient. Spinal cord MRI performed in patients III:3, III:5 and IV:1 did not reveal signs of compression, atrophy, or any other changes in the spinal cord.

In summary, the clinical course in five affected individuals over a multi-decade observation period was overwhelmingly consistent with the picture of progressive spastic paraplegia. Only late in the course of illness symptoms suggestive of a mild peripheral involvement in the form of mild sensory changes and distal muscle atrophy became apparent.

Motor and sensory nerve conduction studies were performed in patients III:3, III:5, and IV:1 at the 17th, 32nd and 7th years from disease onset. Stimulation of n. peroneus profundus and n. tibialis posterior showed a decrease in conductivity (NCV) and suppression of motor activity potential (CMAP), expressed in patients with the longest disease. Amplitudes of sensory activity potential (SNAP) in n. suralis is significantly reduced in the same two patients. Thus, an electrodiagnostic study showed a violation of axonal conduction in the motor and sensory peripheral nerves of the lower extremities.

The presented clinical and electrophysiological data are according to the picture of the HSP. Axonal peripheral neuropathy in the distal lower limbs does not contradict the diagnosis of HSP, it is described in the other subtypes of this disease [23]. Other diagnoses are excluded based on the results of clinical and routine laboratory tests.

Genetic analysis. Exome sequencing was performed in two affected individuals, II:6 and III:3 (Fig. 1). A number of filtering steps were used to prioritize sequence variants, beginning with the requirement that the variant had to be shared by two studied affected members of the family N. in heterozygous state. Variants in non-coding regions and synonymous SNPs were excluded. Also variants found in healthy were excluded (based on data from available directories: ClinSeq (www.genome.gov/20519355), проекта 1000 геномов (http://browser.1000genomes.org) и ExAC (http://exac.broadinstitute.org). Variants were additionally examined based on the functional disruption predicted by PolyPhen-II (www.genetics.bwh.harvard.edu/pph2), SIFT (http://sift-dna.org/sift4g), MutationTaster (www.mutationtaster.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar) and CADD (https://cadd.gs.washington.edu). Considering that in our patients a neurodegenerative disorder occurred in adulthood, we also excluded genes that are not expressed in the central nervous system and are involved exclusively in early embryonic development. Four heterozygous variants in the genes listed below met all of the above requirements: DLGAP2, DSCAML1, DNAH10, DNM2 (dynamin-2). These four selected candidates were tested for segregation in family N. (Table 1). The only p.R719W in the dynamin-2 gene of the four genetic variants studied is present in each HSP studied patients. Affected family members II:6, III:2, III:3, III:7 and IV:1 are heterozygous for the p.R719W mutation, while non-affected III:1, IV:2, IV:3 and IV:4 are not have this mutation (Table 1). Sequencing did not reveal pathogenic mutations in previously known HSP-associated genes.

Segregation analysis of candidate variants in the HSP family

ID (Fig. 1)	Phenotype	Мутация: Ген/Вариант			
		DLGAP2/p. D758N	*DSCAML1*/ p.I1742N	*DNAH10*/ p.V3539M	*DNM2*/ p.R719W
II:6	Affected	mut	mut	mut	mut
III:2	Affected	mut	ref	ref	mut
III:3	Affected	mut	mut	mut	mut
III:7	Affected	mut	mut	mut	mut
III:1	Unaffected	mut	ref	ref	ref
IV:2	Unaffected	mut	ref	ref	ref
IV:3	Unaffected	ref	nd	ref	ref
IV:4	Unaffected	ref	nd	ref	ref

mut – mutated; ref – reference allele; nd – not done

Genotyping of the identified mutation in other Yakut families did not reveal the c.2155C> T, p.R719W variant in DNM2. So far, the described family is the only case of HSP associated with this mutation.

Variant c.2155C>T, p.R719W in *DNM2* gene. The identified missense substitution is located at NM_001005360:c.2155C>T; Chr19(GRCh37):g.10939808C>T at exon 19 of the DNM2 gene, which replaces Arginine (R) with Tryptophan (W) (p.R719W) in the encoded dynamin (Fig. 2A). Arginine in this position is highly conserved in evolution up to the worm to the human (Fig. 2B), and is also invariably present in dynamin 1 and 2. A search for the p.R719W variant in three catalogs revealed only one healthy carrier in Southeast Asia among 60 thousand

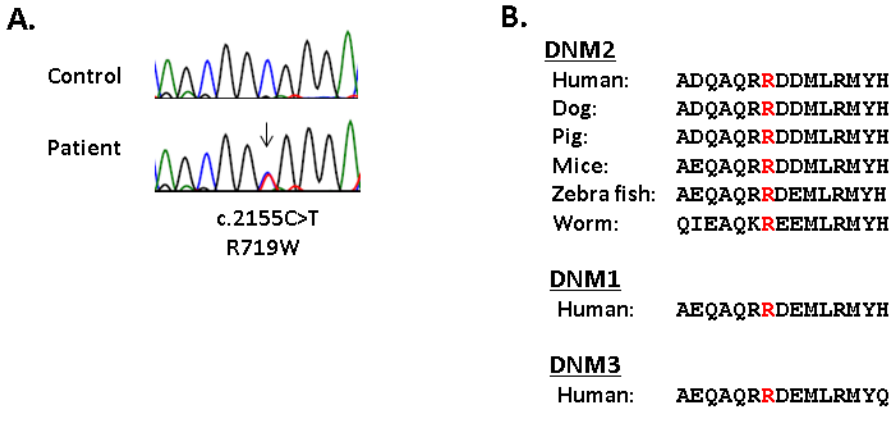

Fig. 2. Pedigree of the Siberian family with Hereditary Spastic Paraplegia. Filled symbols indicate individuals affected with HSP; open symbols represent unaffected family members. The p.R719W mutation was identified in individuals II:6, III:2, III:3, and III:7, and the test for the mutation was negative in III:1, IV:2, IV:3, and IV:4.

people studied (http://exac.broadinstitute.org). Dynamin 2 is a 100kDa multidomain protein composed of a catalytic N-terminal GTPase domain, a middle domain MD, driving dynamin oligomerization, a domain PH for the interaction with membrane phosphoinositides, a effector domain GED that activates GTPase upon assembly of dynamin oligomers into higher order structures, and a C-terminal proline/arginine rich domain PRD a major site for interacting with other proteins [8, 13] (Fig. 3). The p.R719W mutation is in the GED effector domain, which guarantees the activation of GTPase and, even more important in the context of our study, is responsible for the formation of a full-fledged dynamin-2 structure. Distinct mutations in dynamin 2 have previously been associated with other phenotypes including two forms of Charcot-Marie-Tooth disease: axonal CMT2M (MIM# 606482) and intermediate form CMTDIB (MIM# 606482) and centronuclear myopathy ADCNM (MIM# 160150). The mutations responsible for both forms of Charcot-Marie-Toots (indicated in blue under the diagram in Fig. 3) are located mainly in the PH domain, while a separate set of mutations (marked in black) causes central nuclear myopathy.

Functional study. The mutant p.R719W dynamin-2 causes a prominent punctate staining in the cytoplasm of HeLa cells (Fig. 4A, indicated by arrows). Similar morphological phenomena were observed with other mutations in dynamin-2 [14]. The cells expressing mutant dynamin-2 show a significant decrease in transferrin uptake in cells, compared with cells expressing normal dynamin-2. This decrease was evident in all transfected cells and was especially pronounced (more than 50%, Fig. 4B) in the cells marked by arrows. The granules are localized most prominently in the perinuclear area, likely in the endosomal compartment. These results show that inhibition of endocytosis is a factor in the pathogenesis of HSP in the studied family.

Protein structure. The mutation p.R719W is located in the GTPase domain of dynamin-2 protein, its signal element preceding the three-helix bundle (BSE) (Fig. 5A). Mutations in protein molecules with a complex helical configuration are known to lead to the most serious structural disturbances during assembly. A defect in the signal element can change the conformation of the whole molecule [3, 11]. In addition, the p.R719W mutation is located near the critical connection point between the BSE and the stalk. Further, arginine in a normal

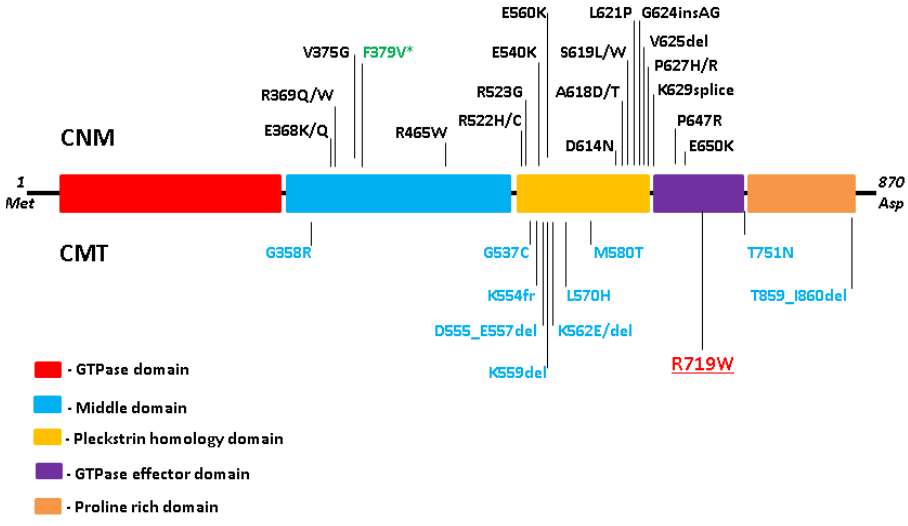

Fig. 3. A. Sequence chromatograph of a fragment of the DNM2 gene showing the position of nucleotide substitution (arrow) responsible for the p.Arg719Trp (R719W) mutation. B. Protein alignment of the GTPase effector domain in various dynamins. Mutated residue is colored red.

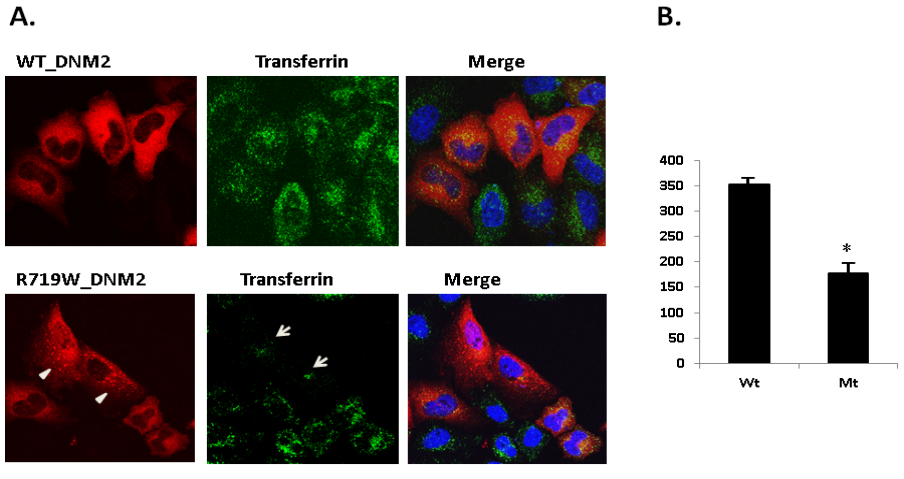

Fig. 4. A. HeLa cells transiently transfected with vectors containing the wild-type (upper panel) and mutant (bottom panel) DNM2. The p.R719W mutant exhibits punctate pattern of DNM2 expression (arrowheads), whereas cells transfected with wild type DNM2 show diffuse staining of the cytoplasm. Uptake of transferrin is reduced in cells expressing mutant DNM2 (arrows). Transferrin is labeled by Alexa-Flour 488 (green); nuclei are labeled with blue stain. B. Quantification of transferrin uptake. The histogram represents the mean +/- standard error (N=25 cells). *P<0.001.

protein provides 3 hydrogen bonds in this place, while mutant tryptophan has only one (Fig. 5B), which leads to additional instability. Structural changes associated with the p.R719W mutation prevent the formation of a normal tetramer (Fig. 5C). Compared to the mutations that cause Charcot-Marie-Tooth peripheral neuropathy and centronuclear myopathy, the mutation p.R719W, which causes HSP, is located in a diverse structural domain and leads to instability of the protein molecule by another mechanism (Fig. 5A).

To date, more than 40 pathological mutations associated with various diseases have been found in dynamin-2. Mutations in this gene are responsible for the autosomal dominant motor and sensory peripheral neuropathies CMT2M (MIM # 606482) and CMTDIB (MIM # 606482). CMT2M and CMTDIB belong to a large group of diseases under the general name Charcot-Marie-Tooth neuropathy. Both forms are characterized by slowly progressing muscle weakness and atrophy, mainly in the distal lower extremities; pulling up the foot while walking; decreased or absent tendon reflexes; a decrease in pain, temperature and vibration sensitivity in the distal extremities. Skeletal abnormalities,

including scoliosis, pes cavus, and malleus fingers, are often found [21, 27]. In some patients with CMTDIB, moderate decrease in the conduction rate and axon degeneration in the peripheral nerves was found [13]. An admixture of signs of peripheral neuropathy in our patients gives some originality in studied case of HSP, typical in other respects. The presence of signs of peripheral neuropathy, however, does not contradict the diagnosis of HSP. When discussing the presence of signs of spastic paraplegia and peripheral neuropathy in the same patient, a commonality of the mechanisms of damage to the spinal cord and peripheral axons is mentioned in the literature (see review [18]).

Another disease associated with DNM2 mutations, ADCNM centronuclear myopathy (MIM # 160150) is a congenital myopathy characterized by progressive muscle weakness, including muscles of the neck, trunk and extremities [16]. The severity varies from a neonatal form with generalized muscle weakness, hypotension, and contractures to a milder disease with a late onset [9, 15]. Some patients show signs of peripheral neuropathy [24]. A skeletal muscle biopsy reveals hypotrophy of type 1 myofibers and abnormal nuclear centralization [6].

Functional analysis of dynamin-2 indicates its important role in the process of clathrin-dependent endocytosis. The p.R719W mutation significantly disrupts this process, which is necessary to ensure synaptic connections between neurons [19]. The results of our experiments on transcribed HeLa cells confirm the etiological role of dynamin-2 in HSP.

Now it remains to determine why various mutations in dynamin-2 lead to pathological changes either in the motor neurons of the spinal cord and corticospinal paths, or in the axons of peripheral nerves or in skeletal muscles. The existing hypotheses are based on the nature of the destruction of the protein molecule dynamin-2 by mutations in various domains. Mutations that cause both forms of Charcot-Marie-Tooth neuropathy are located in the PH domain, while ADCNM mutations are located on the boundary between the Stalk and PH domains [12]. The p.R719W mutation causing HSP is the only known mutation that is uniquely located in the BSE signal element that is stably preserved in evolution, which is structurally and functionally different from regions where other mutations are localized [22]. In-silico modeling showed that a mutation in this region causes a conformational change in the helical configuration and affect the dynamin assembly. The fewer hydrogen bonds around the 719th position also introduce the instability of the protein molecule [3, 11]. The destruction of different dynamin-2 domains leads to the development of various neurodegenerative diseases.

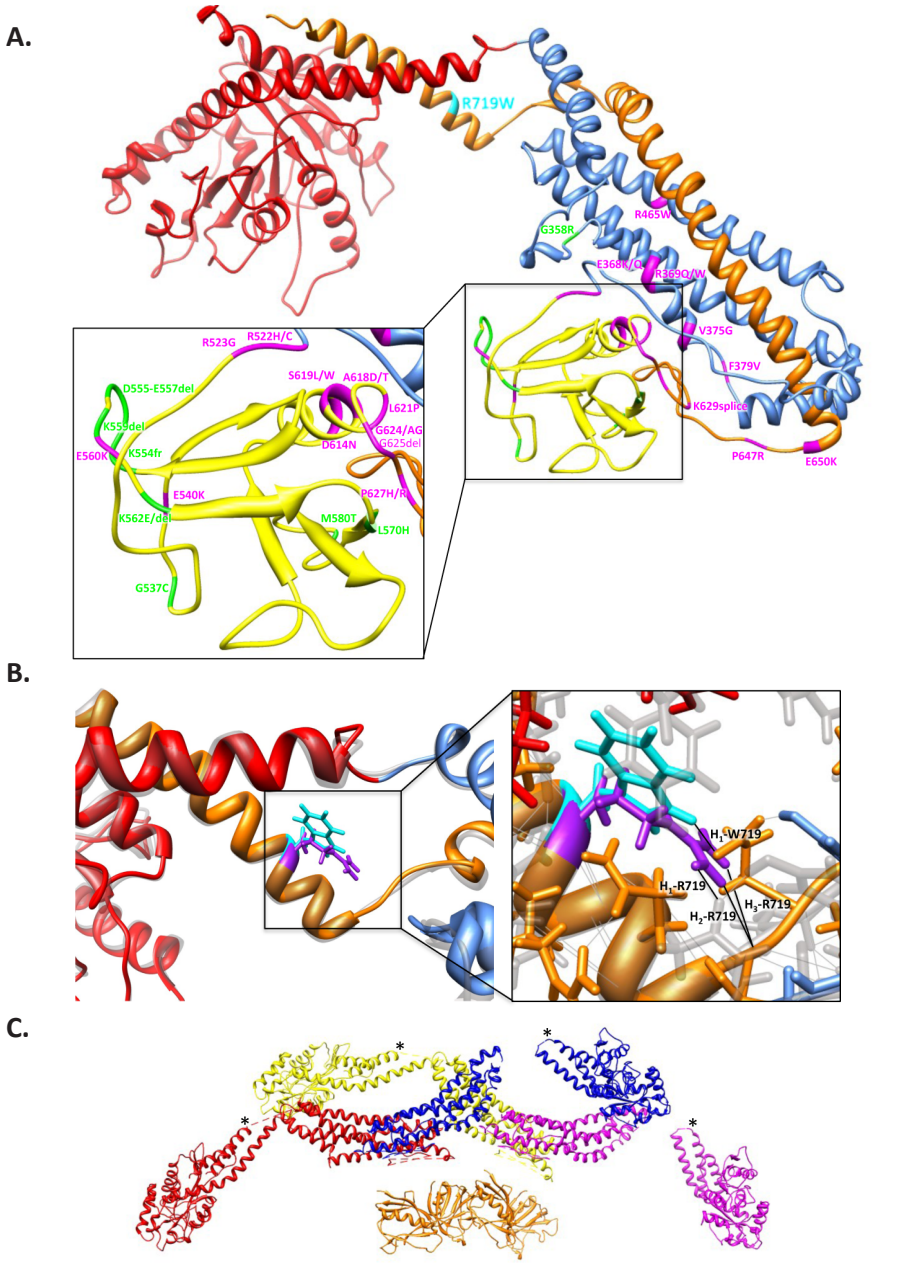

Fig. 5. A. Molecular model of dynamin 2 based on the crystal structure of dynamin 1 [7] indicating the HSP p.R719W mutation (cyan), CNM mutations (magenta) and CMT mutations (green). Dynamin domains are colored as follows: GTPase domain (red), Middle (blue), PH (yellow) and GED (orange). p.R719W is located at the hinge region between the three helix bundle and stalk of dynamin. Generated by I-TASSER. B. Overlay of wild-type and p.R719W dynamin 2 molecular models with R719 (purple) and W719 (cyan) side chains shown. On the right panel: there are three putative H bonds connecting R719 to the rest of the molecule (labeled H1-3-R719) compared to only one for W719 (H1-W719). C. The assembled tetramer of dynamin 1 was generated from docking crystal structures into a 3D density map of K44A-dynamin 1 [2]. Dynamin monomers are colored red, yellow, blue and purple. Asterisks indicate the location of R725W (equivalent to R719W in dynamin 2) in the assembled dynamin 1.

Conclusion. Members of four generations of the Yakut family suffer from a progressive form of hereditary spastic paraplegia. Our molecular, functional, and molecular structural studies have allowed us to identify the c.2155C> T, p.R719W mutation in the DNM2 gene coding dynamin-2 as the cause of this disease.

A mutant protein becomes unable to fulfill the function of endocytosis. The results show that inhibition of endocytosis is a factor in the HSP pathogenesis in the studied family. The mutation is located in a functionally and structurally unique fragment, potentially disrupting the configuration and synthesis of dynamin-2. Identification of the mutation causing HSP with an admixture of peripheral neuropathy will guide future research towards a better understanding of the cellular biological processes involved in these partially overlapping clinical syndromes and will help identify the causes of such disorders in other families. Clarification of the involvement of mutant dynamin-2 in the etiology of HSP and the pathological mechanisms of the development of this disease provides the basis for development in the direction of preventing the HSP development in carriers of mutations.

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (Project "Wide-genome studies of the gene pool of the indigenous population of the Arctic coast of Yakutia" 2020-2022 years).

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POLYMORPHIC VARIANTS OF GENES TYPE I COLLAGEN (*COL1A1*), CALCITONIN RECEPTORS (*CALCR*) AND VITAMIN D (*VDR*) AND THE PARAMETERS OF TEENAGERS MUSCULOSKELETAL SYSTEM IN THE PRIMORSKY TERRITORY

DOI 10.25789/YMJ.2020.69.02

УДК 616.71-007.1-053(571.63)

The physiological parameters of the musculoskeletal system status and the prevalence of nucleotide sequence variants genes collagen *COL1A1* rs1800012 IVS1 c.2046 G> T, and receptors of calcitonin *CALCR* rs1801197 c.1377 T> C and the intracellular vitamin D *VDR* rs731236 c.1056 T> C in healthy teenagers of the Primorsky Territory was studied. It was shown that the homozygous TT genotype of the gene TaqI VDR is 5 times more prevalent among girls than among boys (19.6% and 3.9%, respectively). Moreover, in carriers of homozygous TT and heterozygous CT genotypes of this gene, fractures were more common (p = 0.051, p = 0.012) than in carriers of SS genotype. It was established that, in carriers of the heterozygous genotype GT of the gene *COL1A1* fractures and impaired posture were significantly more. No correlation was found between the presence of fractures and carriers of the genotype TT of the *CALCR* calcitonin receptor (p = 0.143). In the examined cohort of the teenagers are predominant the carriers of the heterozygous genotypes Ss (GT) (87.3%, the collagen gene *COL1A1*) and CT (80% - the calcitonin receptor gene and 66, 7% - the intracellular vitamin D receptor gene). In carriers of the heterozygous Ss (GT) *COL1A1* gene, the presence of the heterozygous CT genotype of calcitonin receptor genes (*CALCR*) and vitamin D *VDR* was more common. Thus, genetic testing made it possible, firstly, to identify the prevalence of “unfavorable” alleles and their combinations in the studied genes (from 3.8% to 50%) that regulate calcium metabolism in teenagers; secondly, to determine the relationship between genotypes and the presence of fractures and impaired posture, which makes it possible to distinguish a group of subjects with a high risk of developing MSS diseases.

Keywords: gene of type 1 collagen, gene of calcitonin receptor, gene of vitamin D receptor, musculoskeletal system.

Introduction. In adolescence, along with the restructuring of the hormonal system, the final formation of the musculoskeletal system occurs, which is accompanied by a maximum increase in the mineral density of bone tissue [1, 6]. It has been shown that metabolic contravention in bone formation lead to inhibition of the linear growth of children and can cause scoliosis and juvenile osteoporosis [3, 9]. In the structure of functional and chronic diseases in children, the frequency of disorders and diseases of the musculoskeletal system (MSS) is in the I – III place, and according to some data, 67% determine the second group of health associated with its disorganization [5, 10]. The activity of bone remodeling that occurs during prepubertal period depends on the degree of expression of genes initiating the synthesis of various proteins [2]. Such proteins include matrix proteins (type I collagen), regulatory proteins that take part in calcium metabolism, cytokines, growth factors and their receptors, as well as bone metabolism enzymes.

One of the main regulators of calcium-phosphorus metabolism in the body is calcitonin, which is synthesized in parafollicular cells of the thyroid gland and has an inhibitory receptor-mediated effect on the activity of osteoclasts, reducing the rate of bone resorption [8]. The calcitonin receptor gene CALCR is located on chromosome 7q21.3 and encodes isoform 1 of the G protein subfamily (G protein-coupled receptors) [18]. Replacing cytosine with thymine (C> T) in exon 17 of the CALCR gene at position 1340 (rs1801197) leads to the replacement of proline amino acid (CCG) with leucine (CTG) at position 463 of the receptor protein molecule and, as shown, is in positive correlation with bone density [11]. Vitamin D also takes part in the process of bone tissue calcium and phosphate metabolism, the hormone-active form of which is calcitriol 1.25 (OH) 2 D3 interacting with receptors of target cells [25]. The calcitriol receptor (VDR) or NR1I1 belongs to the family of intracytosolic, nuclear, takes part in transcription and mechanisms of protein synthesis, and is encoded by a gene located on the 12th chromosome (12q13) [16, 25]. The degree of expression of this receptor determines the effect of calcitriol on bone mineral density and skeleton formation [22]. Moreover, the kinetics and degree of calcium accumulation in the puberty period depends on the presence of various variants of this VDR gene [19]. The most promising diagnostic way in determining the mechanisms of osteoporosis development is the identification of VDR gene variants in exon 2 of FokI (rs10735810), between 8 and 9 exons of BsmI (rs1544410) and TaqαI (rs731236) [23].

The interest are also data on the combination of the genes number expression involved in the post-translational modification of the bone tissue structure-forming protein — type I collagen, consisting of two polypeptide chains α1 and α2, [13, 17]. Two genes carry information about its structure: COL1A1 (gene of the α1 chain) and COL1A2 (gene of the α2 chain). It was shown that polymorphism

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variants gene COL1A1 can cause a wide range of diseases, from osteoporosis to lethal forms of imperfect osteogenesis in Ehlers-Danlo syndrome [14, 15, 17]. Thus, the role of variations in the nucleotide sequences of genes type 1 collagen, receptors calcitonin and vitamin D in the development of various osteopathologies in the adult population has been proved, and it has been demonstrated that these diseases are age-dependent [7, 20, 23, 24]. While, the ratio of the variants these genes with the parameters of the adolescents musculoskeletal system physical examination makes it possible to obtain additional information about the development of possible pathological changes. Given the known data on the predominant presence in children aged 7-17 years of the second health group associated with disorders and diseases of the MSS, there is a need to study the distribution of these genes variants. On the other hand, since a significant ethnic difference in the distribution of genetic determinants associated with the acquisition of peak bone mass and the architecture of the MSS and / or osteoporosis has been demonstrated, such a comparative study is also of certain interest [8, 14, 19, 20, 21, 23]. The purpose of this study: to determinate the prevalence of genes polymorphic variants type I collagen (COL1A1) and calcitonin receptors (CALCR) and vitamin D (VDR) in relation to the parameters of physical examination of MSS in adolescents of the Primorsky Territory.

Materials and research methods. The selection for the study was formed from the number of students undergoing planned medical inspection in the Primorsky Territory general education schools (April-May 2018). After the informed consent of the use survey data for scientific purposes was signed by parents, guardians or trustees, a clinical examination was carried out with the definition of a health group (recommendations of the Institute for Hygiene of Children and Adolescents, orders of the Ministry of Health of the Russian Federation No. 621 dated 12/30/2003 and No. 514n dated 08/10/2017). The child's development stories were also studied (form 112 / u). Assessment of physical development was carried out using regional percentile type tables. The measurement of height and weight, the shape of the chest examining the front, back and profile, posture (the difference between the measurements of the cervical and lumbar sagittal bends of the spine), the shape of the legs, physiometric indicators (vital capacity of the lungs, compressive strength of the hands, number pull-ups on the high bar for boys on the low bar for girls) was determined. Additionally, photoplantography was performed to study physical development.

Molecular genetic research. For genetic analysis, which was carried out on the basis of the Central Research Laboratory of Pacific State Medical University, DNA samples isolated from whole venous blood (volume 4 ml) by phenol-chloroform extraction using the kit DNA-sorb (AmpliSens biotechnologies, Russia). PCR amplification of DNA samples with a purity of A260/280 = 1.8 ± 0.1 and a concentration in the range of 50-100 ng/μl was performed in a volume of 25 μl. The purity index of the DNA preparation was calculated by the ratio of the optical density values at the absorption wavelengths of the samples 260/230 nm, the coefficient value from 1.8 to 2.2 was taken into account.

The identification of gene variants the collagen chain α1 COL1A1: pp.104–441G> T (rs1800012), calcitonin receptor CALCR: c.1377C> T CALCR (rs1801197) and intracellular vitamin D receptor VDR: c.1056T> C (rs731236) was carried out by polymerase chain reaction (PCR) in real time on a PicoReal amplifier (Finland). The reagent kits COL1A1-test, CALCR-test and VDR-test (GenoTehnologiya, Russia) were used. At the end of PCR amplification, according to the protocols in the instructions for the kits, the threshold cycle value (Ct) was determined from the fluorescence curve of the sample. Used oligonucleotide probes labeled with 6-carboxy-4 ', 5'-dichloro-2', 7'-dimethoxyfluorescein (6-JOE). The value of the standard deviation Ct for repetitions of each analyzed sample did not exceed 0.5.

Statistical methods. Quantitative indicators of the bodily characteristics of MSS were evaluated using Student's t-test, regression analysis of the data, and the Fisher test was calculated. The association between the variants of the studied genes and the parameters of the bodily examination was calculated by calculating the odds ratio (OR) and the corresponding 95% confidence interval (CI). Data uniformity was determined using the χ-squared Q-test, the significance of the combined OR was determined using the Z-test at $p < 0.05$. The Fisher test was used to assess agreement with Hardy-Weinberg equilibrium at a significance level of $p < 0.05$. Statistical analysis was performed using Review Manager 5.1 software.

Results and discussion. A comprehensive assessment of growth factors (106 teenagers aged 15-17 years) revealed significant gender differences in terms of length and body weight, chest circumference (OCH, $p \geq 0.005$). The distribution by the health groups of the examined individuals showed that only 2 people (1.8%) corresponded to the first group, while all the others made up the second (Table 1). Correct posture was observed in 69 children (63%), and in boys this indicator prevailed and amounted to 79 people (73%) compared to 59 (54%) in girls. Kyphotic, hyperlordosis and hyperkyphotic posture were more often observed in girls than in boys, 16 and 10 (15% and 9%) people, respectively. A straightened back (low severity of bending of the spine, with reduced mobility of the ribs, the presence of lateral curvature of the spine) was also noted more often in girls (24 people, 22%) than in boys (15, 14%). The results of photoplantography showed the presence of transverse flatfoot of the 1st degree in 29 people (27%), 2nd degree in 39 (63%), and 3rd degree in 5 (5%) of the subjects (Table 1). Longitudinal flatfoot of the 1st degree was detected in 42 people (39%), of the 2nd degree in 9 subjects (8%) and of the 3rd degree was not detected. The presence of normal foot development was noted only in 10 (9%) of the subjects. Thus, our data demonstrate the need to study the physiological parameters of the musculoskeletal system in adolescents in order to obtain timely information. Photoplantography data are of particular importance, since flat feet are known to have a negative effect on the rational distribution of load on overlying joints and lead to more serious postural disturbances [3, 5]. It is also shown that when the anthropometric parameters and indicators of the circulatory system are conjoined, children suffering from flat feet and scoliosis show an increase in heart rate and an increase in stroke and minute blood volume [6, 9].

Polymorphism of the gene COL1A1: pp. 104–441G> T in replacing guanine with thymine is functionally manifested by the disturbance of the transcription factor binding in the region of the first intron. The inheritance of the COL1A1 gene mutation is autosomal dominant and is found in men and women with the same frequency. The probability of the occurrence of MSS disease (osteoporosis, a history of bone fractures) in children, subject to the inheritance of a mutation of this gene from one of the parents, is 50%. According to the data of the genetic study, we divided the subjects into groups according to the SS (GG, genotype 0), ss (TT, genotype 2), and Ss (GT, genotype 1) genotypes. The number of carriers

of the heterozygous genotype (Ss) was 37.3% in boys and 53.0% in girls; the homozygous SS (GG) genotype in 2.0% and 7.8%, respectively, and the ss (TT) genotype was not detected (Table 2). It was shown that the carriers distribution of genotypes depending on the presence of the knee joint ligaments break (GG-82.2% GT-16.7%, TT-1.1%) significantly differed (p = 0.036) from the group of subjects without this pathology (GG -71.4% GT-26.5%, TT-2.2%) [22]. In our study, carriers of the heterozygous Ss (GT) of the gene COL1A1 were significantly more likely to have fractures (p = 0.12, Table 3) than carriers of the homozygous Ss (GT) genotype. The distribution of carriers genotypes COL1A1:pp. 104–441G> T, respectively of the incorrect posture also showed a significant difference between the groups of subjects (p = 0.07 and p = 0.0003, table 4).

The single nucleotide replacement of thymine with cytosine (T> C) in 17 exon of the calcitonin receptor gene (CALCR) at position 1340 (rs1801197) can lead to a change in the functional activity of the encoded protein. This change in osteoclastic receptors is manifested by activation of the bone resorption process and the development of osteoporosis, the presence of which is more often observed among carriers of the variant polymorphism of the homozygous form of SS [16]. The predominance of heterozygous TS (80.4%) in the study of the gene calcitonin receptor polymorphic variants rs 1801197 CALCR: c.1377C> T p. P447L was determined, while homozygous CC and TT genotypes were found in 13.7% and 5.9% (Table 2). Despite the known data on the predominant disease with osteoporosis by carriers of a homozygous form of SS, we did not establish a relationship between the presence of fractures and carriers of this genotype, while a significant relationship (p = 0.14, Table 3) was found for carriers of TT genotype. The distribution of carriers of genotypes taking into account incorrect posture showed that it was significantly more often found in carriers of two genotypes of homozygous TT (p = 0.0001) and heterozygous CT (p = 0.0005, Table 4).

Regarding the polymorphism of the gene intracellular vitamin D receptor VDR , it was found that the TT genotype is associated with a tendency to delay growth rate associated with impaired bone metabolism and osteosynthesis during activation of bone resorption [19]. When studying the distribution of rs731236 TaqI VDR alleles: c.1056T> C, we found that carriers of the C allele made up 94% of the subjects (Table 5). The homozygous

Table 1

Parameters of the state of the musculoskeletal system in teenagers

Age	15,607 (15;17)
Gender	Man - 38.4% Woman - 61.6%
Health group	1 – 1,8 %; 2 – 98,2 %
Body length, cm	163,4 (140;180)
Body weight, kg	60 (40;80)
Body mass index	22,4 (16;30)
Types of posture	without violations - 40.2%; kyphosis - 15.2%; lordosis - 3.6%; straightened - 42%
Body type	normosthenic - 79.5%; hypersthenic - 8.5%; asthenic - 12%
Scoliosis, classification by V.D. Chaklin	no - 63.3%; 1 degree - 34%; 2 degree - 2.7%
Leg shape	correct - 68.9%; X-shaped - 30.1%; O shaped - 1%
Valgus / Varus	valgus – 7,1 %; varus – 1,8 %
Hallux valgus valgus deformity (Hallux valgus)	S – 66,1 %; D – 60,7 %
Flat feet - transverse - longitudinal	 1 degree - 33%; 2 degree - 54.5%; grade 3 - 2.7% 1st degree - 28.6%; 2nd degree - 7.1%
Pelvic bone displacement	no - 82.2%; right - 8.8%; left - 8.8%
Joint hypermobility	no - 79.8%; availability - 20.2%
Fractures,% depending on the amount: 0-no; one; 2; 3 and more	0 – 67,9 %; 1 – 25,9 %; 2 – 4,5 %; 3 – 1,8%
Dislocations:% depending on the amount: 0-no; one; 2; 3 and more	0 – 88,4 %; 1 – 9,8 %; 2 – 1,8 %

TT genotype of the TaqI VDR gene was more common among girls than among boys (19.6% and 3.9%, respectively), with a predominance of 5 times (Table 2). Moreover, in carriers of heterozygous CT and homozygous TT genotypes, the presence of fractures was more often noted (p = 0.09, Table 3; p = 0.01, Table 4).

According to the researchers, the carriage of the polymorphism variants genes type I collagen (COL1A1 (rs1800012)), calcitonin receptors (CALCR 1340 (rs1801197)) and vitamin D (TaqI VDR (rs 731236)) is associated with the development of diseases associated with a rapid loss of bone mineral density tissue and the development of osteoporosis [2, 11, 15-17, 20, 23, 24, 25]. There was a correlation between the gene polymorphism calcitonin receptor C1377T and a decrease in bone mineral density in the lumbar spine in the postmenopausal period in women [12]. Also a direct relationship between the TaqI rs731236 variant of the VDR gene the allele TT and the presence of osteoporosis, and heterozygous CT genotype more common in women with fractures [4]. The results of our study revealed that from 3.8% to 50% of the examined had such combinations in various variants, and a combination of two “unfavorable” alleles was found

Table 2

The genotype distribution in examined teenagers

Collagen gene rs1800012 COL1A1:c.104–441G>T, (n=88)			
Genotype options	SS (GG)	ss (TT)	Ss (GT)
Male	2.0	0	37.3
Female	7.7	0	53.0
Gene of calcitonin receptor rs 1801197 CALCR:c.1377C>T (n=88)			
Genotype options	CC	TT	CT
Male	8	2.0	29.0
Female	6	4.0	51.0
Gene of intracellular vitamin receptor D rs731236 TaqI VDR:c.1056T>C (n=88)			
Male	3.9	3.9	31.4
Female	5.9	19.6	35.3

Примечание. В табл. 3 и 4 различие статистически значимо при p<0,5.

Table 3

Table 3. Correlation coefficient between the presence of fractures and variants of genotypes

Genotypes	N	Fisher coefficient	
		Empirical	Critical, α=0.05
COL1A1:c,104–441G>T			
SS (GG)	88	0,79; p=0,072	1,31
Ss (GT)	88	2,47; p=0,123*	
rs 1801197 CALCR:c,1377C>T			
CC	88	1,63; p=0,211	1,31
TT	88	2,125; p=0,141*	
CT	88	0,36; p=0,851	
rs731236 TaqI VDR:c,1056T>C (n=88)			
CC	88	0,52; p=0,473	1,31
TT	88	0,53; p=0,471	
CT	88	2,88; p=0,091*	

in 46.15%: the G allele of type I collagen polymorphism (rs1800012 COL1A1) and the T allele TaqI polymorphism of the vitamin D receptor gene, and 33.3% of the examined had a combination of 3 "predisposition" alleles at once (Table 5).

Our comprehensive assessment of the MSS health status in teenagers of the Primorsky Territory showed a harmonious development in 109 (47.3%) of 200 people in the surveyed group. Mostly, teenagers have a second health group. Kyphotic, hyperlordosis and hyperkyphotic posture and the presence of lateral curvature of the spine were more often observed in girls than in boys, and photoplantography showed the presence of normal foot development in only 9% of the subjects. Our data demonstrate the need to study the physiological parameters of the teenagers musculoskeletal system state, since it is known that in children suffering from flat feet and scoliosis, there is a violation of blood circulation and the development of concomitant diseases [6, 5]. Such studies will allow the implementation of preventive measures aimed at preventing the development of diseases.

Simultaneously, we conducted genotyping of study participants for the presence of gene variants single-nucleotide substitutions for rs1800012 IVS1 c.2046 G> T collagen COL1A1 rs1801197 c.1377 T> C calcitonin receptor CALCR and rs731236 c.1056 T> C intracellular vitamin D receptor VDR. In the examined cohort of the teenagers Primorsky Territory, carriers of the heterozygous Ss (GT) genotypes (87.3%, the collagen gene COL1A1) and CT (80% - the calcitonin receptor gene and 66, 7% - the intracellular vitamin D receptor gene, respectively) are predominant. In carriers of the heterozygous Ss (GT) COL1A1 gene, the presence of the heterozygous CT genotype of calcitonin receptor genes (CALCR) and vitamin D VDR was more common. The genetic testing also revealed a relationship between the frequency of genes variants distribution that regulate the mineralization process in teenagers and the presence of fractures and impaired posture (from 6.1 to 79.2%). The interest is the revealed relationship between the homozygous genotypes TT of the studied gene polymorphisms calcitonin receptor and the heterozygous CT gene of the intracellular vitamin D receptor VDR with the presence of breaks and impaired posture, especially in girls. In general, the results indicate a combined effect of genes on mineral metabolism in the body, which begins to manifest itself in the teenage period at the phenotypic level. In our opinion, special attention should be paid to the subjects with a combination of several "unfavorable" gene polymorphisms, since it is for them that the risk of metabolic disturbance is highest.

Currently, there is numerous evidence that under the influence of "variable" factors acting in prenatal, childhood or adolescence, the programmed peak bone mass decreases, which can cause the development of not only a juvenile form of systemic osteoporosis, but also its postmenopausal and senile forms [4, 12]. It has been demonstrated that the presence of fractures in parents (in particular, a hip fracture) increases the risk of fractures regardless of the bone mineral density [13]. Carriage of unfavorable alleles in the genes of type 1 collagen (rs 1800012 Col1A1), G-1997 (rs 1107946 Col1A1), calcitonin receptor (rs1801197 CALCR) and vitamin D (TaqI rs 731236 VDR) is connected with the development of diseases associated with loss of bone mineral density and the development of osteoporosis [7, 16, 24]. It has also been shown that, in carriers of the collagen COL1A1 heterozygous genotype, fractures and impaired posture are more common, which is consistent with other studies of the relationship between the presence of

Table 4

Table 4. Distribution of the genotypes of the subjects (%) depending on the presence of fractures, flat feet and impaired posture

	COL1A1:c,104–441G>T		rs 1801197 CALCR:c,1377C>T			rs731236 TaqI VDR:c,1056T>C		
	SS (GG)	sS (GT)	CC	TT	CT	CC	TT	CT
The presence of fractures (N=27)	23.1	53.85	3.85	15.4	57.7	7.7	23.1	46.2
No fractures (N=61)	22.95	16.4	3.28	27.7	8.23	8.2	1.6	29.5
t-criterion emp.	2.01 *p=0.561*	2.0* *p=0.073*	1.99 *p=0.111*	2.0 *p=0.984*	2.01* *p=0.062*	2.0 *p=0.431*	2.02* *p=0.054*	2.0* *p=0.012*
Flat feet, longitudinal (N=36)	19.4	69.4	13.9	30.6	47.2	8.3	22.2	61.1
No flat feet detected (N=78)	23.1	65.4	10.3	24.3	55.1	11.5	18.0	60.3
t-criterion emp.	1.99 *p=0.662*	2.0 *p=0.674*	2.0 *p=0.621*	2.0 *p=0.655*	2.0 *p=0.654*	2.0 *p=0.653*	2.0 *p=0.612*	2.0 *p=0.933*
Impaired posture (N=48)	31.25	18.75	4.2	39.6	6.25	10.4	2.1	37.5
No impaired (N=37)	8.1	56.7	5.4	2.7	56.75	8.1	18.9	37.8
t-criterion emp.	1.99* *p=0.0008*	1.99* *p=0.0003*	1.99 *p=0.95*	1.99* *p=0.0001*	1.98* *p=0.0005*	1.98 *p=0.354*	2.0 *p=0.182*	2.0 *p=0.931*

the T allele and bone strength in school-aged children [14]. Thus, in the presence of certain risk factors and timely diagnosis of early preclinical stages of osteoporosis, it is possible to prevent life-threatening complications such as fractures of the vertebral bodies and femoral neck. At the same time, testing of allelic variants of these genes opens up great opportunities for the prevention of bone system pathology, as it allows one to effectively identify individuals with a high risk of disease long before signs of pathological changes in the musculoskeletal system appear and is an area of preventive medicine research.

Conclusions. Thus, genetic testing made it possible, firstly, to identify the prevalence of "unfavorable" alleles and their combinations in the studied genes (from 3.8% to 50%) that regulate calcium metabolism in teenagers; secondly, to determine the relationship between genotypes and the presence of fractures and impaired posture, which makes it possible to distinguish a group of subjects with a high risk of developing MSS diseases. In our opinion, the special attention require from pediatricians the adolescence of children, which is characterized not only by a sharp change in the hormonal status of the organism, but also by a maximum increase in the growth of tubular bones and vertebrae with an increase in the mineral density of bone tissue and muscle mass. During this period, the influence of various exogenous and endogenous stimuli on the formation of peak bone mass and, possibly, the risk of developing osteopenic syndrome is decisive. The data of the analysis confirm the need for the introduction of dynamic studies of the health indicators of the MSS in the socio-hygienic monitoring of children's health as an indispensable element. Despite the small sample size of our study, its results make it possible to assess the contribution of genetic polymorphisms to the development of MSS, which in the future will make it possible to use such data as predictive indicators for organizing personalized prevention programs.

Compliance with ethical standards. *The study protocol was approved by the independent interdisciplinary ethics committee of the Pacific State Medical University (protocol No. 2 dated 10.24.2016).*

Financing. *The study was financially supported by the Pacific State Medical University as part of the implementation of the university grant.*

Conflict of interest. *The authors confirmed that there is no conflict of interest to report.*

Table 5

Table 5. Distribution of polymorphisms and alleles of genes in examined adolescents and a combination of the genes variants

Polymorphisms		Distribution in % (n=88)
rs1800012 COL1A1:c.104–441 G>T	SS (GG) Ss (GT) ss (TT) S	9.7 90.3 0 100
rs 1801197 CALCR:c.1377 C>T	CC TT CT C T	11.5 29.5 59 44.4 55.6
rs731236 TaqI VDR:c.1056 T>C	CC TT CT C T	12.8 20.5 66.7 56.1 43.9
The combination of variants of the studied genes	**Genotypes, %**	
Ss + CT (rs1800012 COL1A1:c,104–441; rs731236 TaqI VDR:c,1056)	46.15	
Ss + CT (rs1800012 COL1A1:c,104–441; rs 1801197 CALCR:c,1377)	50	
CT + CT (rs731236 TaqI VDR:c,1056; rs 1801197 CALCR:c,1377)	37.2	
TT + TT (rs731236 TaqI VDR:c,1056; rs 1801197 CALCR:c,1377)	3.8	
Ss + CT + CT (rs1800012 COL1A1:c,104–441; rs731236 TaqI VDR:c,1056; rs 1801197 CALCR:c,1377)	33.3	

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THE CONTENT OF SEROTONIN NEUROMEDIATOR IN MENTALLY RETARDED BOYS OF EARLY SCHOOL AGE

DOI 10.25789/YMJ.2020.69.03

УДК 577.175: 612.085.1: 616.89-008.454-053.2

The article presents the research aimed at the content of serotonin neuro mediator in mentally retarded boys (7 to 11 years). It regulates many physiological functions and also the processes of learning, memory, other cognitive processes, which are very important for early schoolchildren.

In the early schoolchildren with mental retardation from all the groups we determined statistically meaningful ($p<0.001$) decrease of serotonin content in blood lymphocytes as compared to control groups disregard upbringing conditions and the stage of severity, that can be regarded as typical feature for mentally retarded children.

As a preventive measure, special attention may be recommended to be drawn to making sure that the diets of mentally retarded children are rich in tryptophan-containing food. Besides, as serotonin synthesis is affected by the duration of sunlight exposure, another aspect to care about is proper insolation of children with mental retardation.

Keywords: serotonin, mental retardation, early school age, boys, neuromediator.

Introduction. The relevance of the mental retardation issue is largely attributed to its high prevalence. Mental retardation in the child population in various countries worldwide is reported to stand at 1-5% [3, 9]. Mental retardation is usually marked by diminished intellectual and cognitive capacities and skills that occur in the process of development (motor, linguistic, social skills, etc.) [19].

Serotonin is a biogenic monoamine that regulates a whole range of reactions and processes in the body (sleeping patterns, appetite, behavior, physical activity, emotional stability, adaptation, etc.). Primary schoolers face difficulties in the period of adaptation to the beginning of their school education. One of the main functions serotonin has in primary schoolers is its role in the cognitive functions (thought, memory, attention, etc.) [1, 8, 20].

Since due to their pathology mentally retarded children experience difficulties in learning, it appears rather relevant to conduct studies into the serotonin levels prevalent in this group.

The purpose of this study is to research the levels of serotonin neurotransmitter in lymphocytes found in the blood of primary schoolboys (aged 7-11) with mental retardation at the end of the academic year.

Materials and methods. The study looked at 119 primary schoolboys (aged 7-11) at the end of the academic year. 46 schoolers had already been diagnosed to have mental retardation and were attending specialized type-8 remedial schools. They were divided into groups according to their family backgrounds. 26 boys with mental retardation came from two parent families (14 were diagnosed with mild mental retardation (F70), 12 were a moderate case (F71)). 20 boys (moderate retardation (F71)) were from an orphanage for mentally retarded children. The control group was made up of 73 mentally healthy boys who studied at a secondary school in Krasnoyarsk and were also divided into groups: 59 came from two parent families, whereas 14 were from an orphanage for physiologically challenged children. The children under study were treated in accordance with the ethical standards imposed by the World Medical Association Declaration of Helsinki (Seoul, 2008). The study was approved by the Committee for Biomedical Ethics of the Research Institute for Medical Problems in the North.

Mental retardation was diagnosed by a medical commission during a regular medical checkup undertaken by the schoolchildren in compliance with the International Classification of Diseases, 10th Revision (ICD-10).

The content of serotonin in lymphocytes in blood smears was measured using luminescent-histochemical method. This method is based on interaction reaction between serotonin and formaldehyde vapours resulting in luminescent complex formation that glows green. Fluorescent glow was captured using Lumam-I3 microscope («LOMO», Russia) with its signal being transmitted to digital multimeter. The fluorescent signal received at multimeter was measured in muV and then expressed in equivalent units of serotonin content (CU). At present, lymphocytes provide a reasonable and informative model to research levels of serotonin in various cases of neuropsychic diseases [13, 18].

Statistica 6.0 software package was used for statistical data processing (Stat Soft Inc., USA). Normality of distribution was tested using the Kolmogorov-Smirnov test. As these data do not conform to normal distribution, statistical differences of the samplings were checked using non-parametric U-Test Mann–Whitney and median and percentiles were calculated (Me, P25-P75). The statistical hypotheses test showed the significance level of $p<0.05$.

Results and discussion. The study into the levels of serotonin at the end of the academic year demonstrated that mentally retarded schoolchildren with family backgrounds are characterized by statistically lower levels of serotonin (23.4

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CU) in comparison to their healthy peers (36.6 CU (p=0.00001)). No differences were found in the levels of serotonin between children with mild and moderate mental retardation (Fig. 1).

The group of mentally retarded orphans was also reported to reveal lower serotonin levels in comparison to mentally healthy orphans (p=0.0003) (Fig. 2).

No significant differences in serotonin levels were found between the groups of the same degree of mental retardation (F71), regardless of their background, however there is a tendency of steadily lower levels of serotonin in mentally retarded orphans, compared to their peers from families.

The conducted study revealed diminished levels of the serotonin neurotransmitter in all groups of boys with mental retardation. However normal learning and memory functions require an optimal level of serotonin [13, 20]. It is well-known that the role of serotonin in the central nervous system is not restricted to cognitive functions only. Serotonin regulates maturation of various structures in the brain [6], has a significant impact on myelination of axons, proliferation of neuroglia, and formation of new fiber connectivity [8]. It was noted that the processes of learning and memory are impacted by a certain number of serotonin-sustained synapses [14].

The revealed marked tendency towards lower levels of serotonin in mentally retarded orphans as compared to their family-raised peers with the same degree of mental retardation (F71) may be attributed to the fact that institutionalized orphans are susceptible to overall deprivation and adverse psychological state caused by the impossibility to satisfy their basic living needs. For a child, it primarily translates into the need for love, tenderness and care from their parents [5]. It is known that deprivation affects their neuropsychic, emotional and physical development [11]. Apparently, the psychological and emotional discomfort caused by a lack of parental care and attention may further have an impact on the level of serotonin in orphaned children with mental retardation. According to Kryzhanovskaya L. I. [2], deprivation is particularly important in mentally retarded children as the combined influence of deprivation and mental retardation is accompanied by graver consequences than those found in the mentally healthy children population.

At the same time our data demonstrate that the bodily functions in primary schoolers with mental retardation, even those that are raised in their families, and have not only moderate (F71) but also mild forms (F70) of mental retardation, apparently fail to sustain sufficient levels (as those in their mentally healthy peers) of serotonin that influences the processes of learning and affects cognitive function (memory, attention, etc.).

Since the diminished levels of serotonin in primary schoolers with mental retardation are reported regardless of the background they are raised in, or the degree of their mental retardation, the low serotonin levels may apparently be viewed as a peculiarity of primary schoolers with mental retardation that stands in the way of their cognitive activity. Diminished levels of serotonin in mentally retarded children have been reported by other authors as well. For instance, Mulder E. J. et. al. [15] conducted a comparative analysis of serotonin levels in the thrombocytes of 3 groups of children (in the control group, group of autistic children with impaired mental development, and group of mentally retarded children) – the lowest serotonin levels were found in mentally

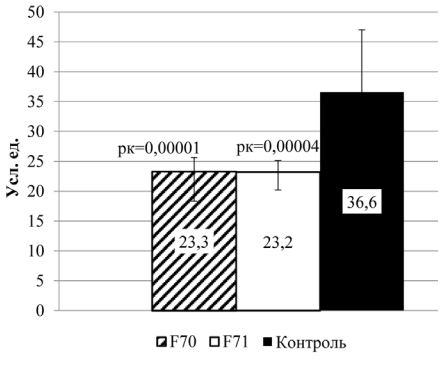

Fig. 1. The content of serotonin in blood lymphocytes (CU) with varying degrees of mental retardation in schoolchildren brought up in the family: F70 - mild severity of mental retardation, F71 - moderate severity of mental retardation

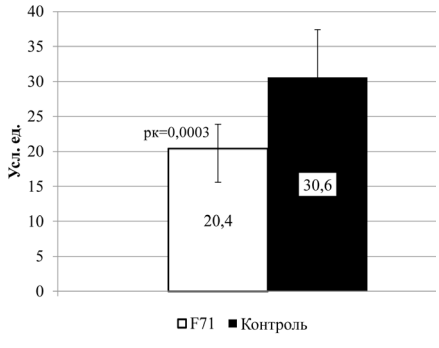

Fig. 2. The content of serotonin in blood lymphocytes (CU) in schoolchildren with mental retardation brought up in an orphanage: F71 - moderate severity of mental retardation

retarded children, even though the statistical significance with the control was not sufficient.

It is worth noting that a number of studies suggested that lymphocytes are reasonable to use as a model of the state of the serotonergic system in the body in the context of neuropsychic disorders [17]. The study conducted by Marazziti D. et. al. [18] claims that lymphocytes that, just as neurons in the central nervous system, serve as transporters of serotonin – SERT – that are a sort of peripheral "mirror" reflecting the activity of serotonergic structures located in the central nervous system. Therefore the study of the levels of serotonin in blood lymphocytes may be considered to be sufficiently relevant for understanding of significance of those levels of this neurotransmitter in primary schoolers with mental retardation.

Conclusion. Thus, mentally retarded primary schoolers are reported to have diminished levels of serotonin. It is known that serotonin is synthesized from the indispensable tryptophan amino acid [7], that is not generated in the body and is normally introduced with food (nuts, cottage cheese, bananas, chocolate, etc.) [16]. As a preventive measure, special attention may be recommended to be drawn to making sure that the diets of mentally retarded children are rich in tryptophan-containing food. Besides, as serotonin synthesis is affected by the duration of sunlight exposure [12], another aspect to care about is proper insolation of children with mental retardation.

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ASSOCIATION BETWEEN *JAK2*V617F MUTATION AND THROMBOTIC COMPLICATION IN PATIENTS WITH CLASSICAL PH-NEGATIVE CHRONIC MYELOPROLIFERATIVE DISEASES

DOI 10.25789/YMJ.2020.69.04

УДК 612.13-15;22-23

The main clinical problem of patients with chronic myeloproliferative diseases (CMPD) is venous and arterial thrombosis. *JAK2*V617F mutation was recognized as one of the main thrombogenic factors among this group of patients.

The objective of the study was to assess the effect of clinical and laboratory parameters and *JAK2*V617F mutation on the incidence of thrombotic complications.

Materials and research. The study included 70 patients with confirmed diagnoses of essential thrombocytemia, polycythemia vera and primary myelofibrosis. The analysis included analysis of clinical and laboratory data of outpatient consultatuion and molecular genetic study to detect the *JAK2*V617F mutation by the allele-specific polymerase chain reaction.

Results. During follow-up time thrombotic complications were registered in 28,6% (20/70) patients. Thrombosis of arterial vessels were seen more commonly (80%) – acute myocardial infarction and acute cerebrovascular accident. According to the results of patient genotyping, the *JAK2*V617F mutation was detected in 90,9% of patients with polycythemia vera, 61,3% of patients with essential thrombocythemia and 64,7% of patients with primary myelofibrosis. Thrombotic complications were significantly more often observed in carriers of the *JAK2*V617F mutation and in patients with cardiovascular risk factors.

Conclusion. Carriage of the *JAK2*V617F mutation and the presence of cardiovascular risk factors significantly increase the risk of thrombotic complications. Early detection of *JAK2*V617F mutation will reduce the number of life-threatening complications.

Keywords: chronic myeloproliferative diseases, *JAK2*V617F, thrombosis.

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Introduction. The main clinical problem of patients with chronic myeloproliferative diseases (CMPD) is vascular complications, including microcirculatory disorders, venous and arterial thrombosis, as well as hemorrhagic complications [2]. Currently due to progress of understanding of diseases molecular mechanisms and development of a new class of drugs – janus kinase inhibitors, it has been possible to reduce clinical symptoms of polycythemia vera (PV) and primary myelofibrosis (PMF) who are resistant to hydroxyurea or with drug toxicity [8]. Thrombotic complications are highly prevalent in patients with CMPD, causing a high risk of mortality and disability. According to published data, prevalence of thrombosis in patients with PV is 3.8 per 100 patient-years, in patients with essential thrombocythemia (ET) from 2 to 4 per 100 patient-years, and in PMF, 2.23 per 100 patient-years [1]. The leading place in the structure of thrombotic complications is represented by arterial thrombosis – myocardial infarction, ischemic stroke and transient ischemic attack.

Thrombosis has a complex multicomponent pathogenesis. Genetic abnormalities, qualitative and quantitative disorders of blood cells, endothelial dysfunction make a certain contribution to the formation of a blood clot [10]. The most significant risk factors for thrombotic complications among patients with CMPD include age over 60 years old, previous thrombosis, cardiovascular risk factors, and the presence of the JAK2V617F mutation. Currently, due to the widespread use of a personalized approach to the treatment of many diseases, the study of molecular markers of thrombogenic risk is gaining particular relevance. It has been proven that carriers of the JAK2V617F mutation are characterized by an increase in the pool of activated leukocytes and platelets with a more thrombogenic potential and an increase in their aggregation ability. In addition, muatation plays role in development of endothelial dysfunction and coagulation link of hemostasis [6,10].

The aim of study was to evaluate the effect of clinical and laboratory parameters and JAK2V617F mutation on the incidence of thrombotic complications.

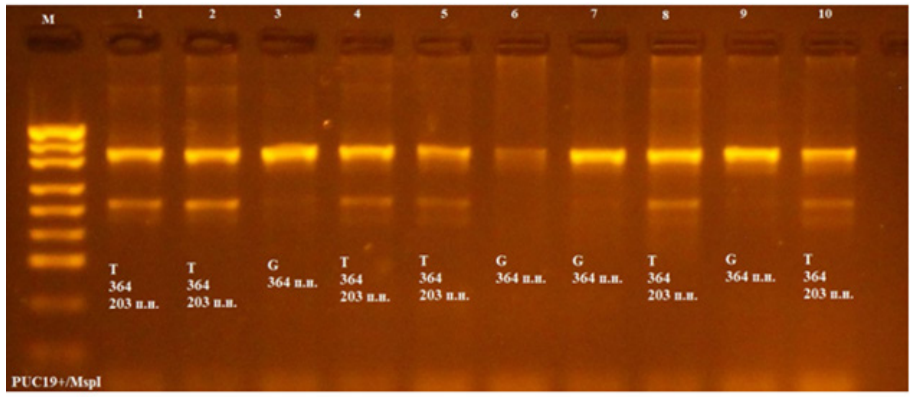
Materials and methods of the research. The study included 70 patients with previously confirmed diagnoses of ET (n = 31, 44,3%), PV (n = 22, 31,4%) and PMF (n = 17, 24,3 %). The median follow-up time was 48 months (from 2 to 252 months). All patients underwent a molecular genetic study to identify the JAK2V617F mutation (rs77375493) by

allele-specific polymerase chain reaction (AS-PCR) using standard pairs of primers manufactured by SybEnzime, Novosibirsk [4]. The reaction mixture with a total volume of 25 µl per 1 sample included: direct allele-specific primers (AGCATTTGGTTTTAAATTATGGAGTATATT), direct (ATCTATAGTCATGCTGAAAGTAGGAGAAAG) 0.5 µl each and reverse (CTGACACCTAGCTGTGATCCT); Dream Taq PCR master mix – 12,5 µl; 9,5 µl of deionized water and 1 µl of DNA. Optimized PCR temperature conditions are presented in Table 1.

Table 1

Condition for AS-PCR

№	Step	t, °C	Time	Number of cycles
1	Initial denaturation	95	10 min.	1
2	Denaturation	95	30 sec.	36
3	Annealing	56	30 sec.	
4	Elongation	72	1 min.	
5	Final elongation	72	10 min.	1



PCR results electrophoregram

Detection of PCR products was performed using electrophoresis on 3% agarose gel stained with ethidium bromide and standard Tris-acetate buffer at 120 V for 45 minutes. The amplification length for the G allele was 364 nucleotide pairs (bp), T - 364 and 203 bp (Figure).

When analyzing the prevalence of thrombotic complications and risk factors, clinical and laboratory data obtained from outpatient patient counseling were used. The statistical significance of the differences was assessed using the χ-square test with Yates correction. Differences were considered significant at $p < 0.05$. To assess the impact of risk factors on the incidence of thrombotic complications, odds ratios (OR) were calculated. Results are presented as OR and 95% confidence interval (CI).

Results and discussion. During the observation period, thrombotic complications were registered in 28,6% (20/70) patients, of which 7,14% (5/70) had two or more episodes. The prevalence of thrombosis among patients with PV was 36,4%, ET - 16% and PMF – 35,2%. 55% (11/20) of thrombotic events were observed before diagnosis. The median time of follow-up from the development of thrombosis to diagnosis was 9 months (from 1 to 78 months). It is known that patients with PV are characterized by more thrombogenic potential associated with an increase in hematocrit and blood viscosity. Estimated prevalence of thrombosis in this group of patients is 12-39% at the time of diagnosis and 10-25% during follow-up time. For patients with ET, microcirculatory disorders are more common than thrombosis of large vessels, and in patients with PMF, thrombotic complications occur with a frequency of 4–7% in the onset and 2–4% during follow-up time [3, 9]. In most cases, thrombosis was localized in the arterial vessels (80%) – acute myocardial infarction (58,8%), stroke (35,3%) and deep femoral artery (5,9%). Venous thrombosis were less common (20%) and represented by deep vein thrombosis (DVT) of lower extremities (10%) and portal system veins (10%).

According to the results of genotyping, the T allele of JAK2 gene (JAK2V617F) was detected in 90,9% of patients with PV, 61,3% of patients with ET, and 64,7% of patients with PMF. When comparing JAK2V617F-positive and JAK2V617F-negative patients, thrombosis were significantly more often observed in carriers of JAK2 mutations – 45% and 10%, respectively ($p = 0.008$).

Next we analyzed the presence of main (age 60 years and over, the presence of JAK2V617F mutation, cardiovascular risk factors) and additional (hypertrombocytosis, leukocytosis) risk factors for thrombotic complications (Table 2). Cardiovascular risk factors included hypertension, diabetes mellitus, and smoking.

Thrombotic complications were significantly more common in carriers of the JAK2V617F mutation ($p = 0,036$) and in patients with cardiovascular risk factors ($p = 0,014$). The OR of the development of thrombotic complications in carriers of the JAK2 mutation was 11,645 (95% CI 1,440-94,191), and 3,605 in patients with cardiovascular risk factors (95% CI 1,213-10,715). There is no significant difference in the frequency of thrombosis between patients aged older 60 years and younger ($p = 0.242$) which is probably related to the fact that the share of those examined over 60 years was only 30,4%.

According to most authors, the most significant independent risk factors for thrombosis among patients with PV, ET, and PMF are age and thrombosis [5]. However, with the gaining of new knowledge about molecular pathogenesis of diseases, prognostic scales based on the mutational status of patients become more relevant. Currently, it has been proven that carriage of JAK2V617F mutation increases the risk of thrombosis among ET patients by up to 45%, and also can be a predictor of recurrent thrombosis. Similar results were obtained in many large studies, which allowed to include presence of JAK2V617F mutation in IPSET-thrombosis scale (a universal tool for assessing the risk of developing ET patients) as an independent thrombogenic risk factor for ET patients [10]. Knowledge about effect of JAK2 mutational status on frequency of thrombosis in patients with PV are contradictory. Some studies have shown that a high allele burden is associated with an increased risk of thrombotic complications. In group of patients with PMF, the greatest risk of thrombosis is associated with JAK2V617F mutation and leukocytosis [7].

In performed research, more than half of thrombotic complications were observed before the diagnosis of the disease. Cases of prolonged latent course of CMPD, when the clinical feature is represented only by thrombosis, are difficult to diagnose. An early molecular ge-

Table 2

Association of thrombosis with risk factors

Risk factor	Patients with chronic myeloprolyferative diseases, % (abs. n)		χ2 criteria	significance, p	OR (95% CI)
	with thrombosis (n=20)	without thrombosis (n=50)			
Age 60 +	65 (13)	46 (23)	1.374	0.242	2.180 (0.745-6.382)
Cardiovascular risk factors	65 (13)	34 (17)	4.411	0.036	3.605 (1.213-10.715)
JAK2V617F mutation	95 (19)	62 (31)	6.092	0.014	11.645 (1.440-94.191)
Leukocytosis >11*109/l	45 (9)	36 (18)	0.182	0.67	1.455 (0.507-4.171)

Note: χ2 - χ-square criteria with Yates correction, p – significane, OR – odds ratio, CI – confidence interval

netic study among people with borderline polycythemia will improve the diagnosis of masked forms of CMPD and prevent the development of fatal complications, and the determination of indications for the detection of the JAK2V617F mutation among patients with thrombosis requires further study.

Conclusion. The occurrence of thrombotic complications is an important factor affecting the survival and quality of life of patients with CMPD. In most cases, thrombosis is the first clinical symptom of disease or manifests before the verification of diagnosis. Carriage of JAK2V617F mutation and the presence of cardiovascular risk factors significantly increase the risk of thrombotic complications. An early molecular genetic study will improve the diagnosis of masked forms of CMPD and prevent the development of fatal complications.

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DIAGNOSTIC AND TREATMENT METHODS

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INITIAL CLINICAL MANIFESTATIONS AND PREMORBID FEATURES OF VARIOUS PHENOTYPIC VARIANTS (II, III) OF SPINAL MUSCULAR ATROPHY

DOI 10.25789/YMJ.2019.2020.69.05

УДК 616.832-009.54-053

Relevance. Spinal muscular atrophy (SMA) is one of the important problems of practical public health due to diagnostic errors and late verification of the initial symptoms of the disease. Insufficient attention is paid to the study of various aspects of the early clinical diagnosis of SMA. An unqualified approach to the interpretation of normal and abnormal neurological status, unidirectional and “stereotyped” actions of a doctor lead to an erroneous interpretation of semiotics and syndromology of motor disorders.

Purpose. To study the initial symptoms and premorbid background in children with SMA II and III types.

Material and methods. On the basis of the Republican Neurorehabilitation Clinical Center (Donetsk), 95 children with SMA were examined, including 66 boys (69.4%) and 29 girls (30.6%). In order to study the possibility of early diagnosis and taking into account the importance, we retrospectively studied the features of the SMA onset in children. In studying life and disease anamnesis, attention was paid to the premorbid features in the clinical and neurological status of early childhood. The concomitant neurological symptoms were studied.

Conclusions. Careful assessment of family history, clarification of manifestations, rate of progression and interpretation of motor disorders in the disease onset are leading factors in early clinical diagnosis of SMA.

Keywords: spinal muscular atrophy, children, initial symptoms, premorbid features.

Introduction. Spinal muscular atrophy is a severe progressive disease developing in the early childhood, the leading etiological factor of which is homozygous deletion of the telomere copy of the SMN gene [1]. The disease is characterized by progressive degeneration and irreversible loss of the spinal cord motor neurons, associated with severe motor disorders and disability [5]. Over the past two decades, significant progress has been made in the study of the molecular-genetic foundations of SMA, which has significantly improved the diagnosis and treatment of these diseases and served as a platform for the development of innovative therapeutic approaches to SMA with the ability to modulate the genetic defect [4]. Nevertheless, there is a great heterogeneity in terms of clinical response to currently available treatment methods, ranging from lack of response to impressive results [6]. There is the generally accepted point of view, that efficacy is improved when treatment is initiated before symptom onset [9]. Thus, research on the problems of hereditary neuromuscular diseases in the leading European centers, including the Department of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; MDUK Neuromuscular Center, Department of Pediatrics, University of Oxford, Oxford, UK, show that innovative therapeutic approaches, regardless of the pathogenetic routes of action, are more effective when patients are treated before or shortly after symptoms rather than later in the disease [3, 4]. It has been suggested that this concept is relevant for all types of treatment, including a variety of drug and non-medical interventions [8]. Therefore, early identification of basic clinical and neurological symptoms, the study of potential factors that inspire the debut of the disease from the perspective of proactive measures aimed at preventing accelerated progression and development of disability is one of the priorities in the segment of SMA.

Research Objective: to study early symptoms and premorbid features of the clinical and neurological status of SMA types II and III children.

Research material and methods. Study was conducted at Republican Neurorehabilitation Clinical Center (Donetsk), 95 children with SMA were examined, including 66 boys (69.4%) and 29 girls (30.6%). Clinical and neurological (anamnesis of the disease, study of neurological status), molecular genetic, functional (electroneuromyography) and statistical methods of study were used.

Inclusion criteria - age from 1 to 12 years, genetically verified form of proximal SMA with autosomal recessive type of inheritance, compliance with clinical phenotype of intermediate SMA (II) or Kugelberg-Welander disease (III), absence of severe concomitant somatic pathology. Exclusion criteria - age under 1 year and over 12 years, absence of molecular genetic testing or genetically non-verified proximal form of SMA with autosomal recessive type of inheritance, patients with SMA of Werdnig-Hoffmann (I) and SMA IV, presence of severe somatic pathology, refusal by the child's parent or legal representative to participate in study.

According to modern recommendations for verification of the SMA phenotype [4, 5] SMA type II was found in 54 (56.8%) children and type III - in 41 (43.2%) patient.

We also reviewed current literature on features of SMA onset in children to establish possible methods of early diagnosis.

According to the consensus statement by international experts from SMA Europe, the European Neuro-Muscular Consortium, the genotype of mutation and the number of copies of SMN2 must be studied in patients as part of genetic screening. Furthermore, parents of patients must also be screened for carrying SMN1 deletion mutation. Molecular and genetic studies were carried out at the "Medico-Genetic Scientific Center" (Moscow), Medico-Genetic Centre "Genomed" (Rostov), Institute of Molecular Biology and Genetics of NASU (Kyiv, Ukraine).

Electromyographic study, including surface, stimulating, needle electromyography ("Neuro-MVP-micro", "Neurosoft", Russia) was conducted to clarify the pathophysiological mechanisms of the

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formation of motor disorders in patients with SMA.

The statistical analysis was carried out by methods of variation statistics on PC using Statistica 10.0 application package (Statsoft Inc., USA). For quantitative indicators the average value (M) and its standard error (±m) were calculated, for qualitative values relative shares (P, %) were calculated.

The study was approved by the local ethical committee of Republican Neurorehabilitation Clinical Center (Protocol № 3-9/19 dated 13.04.2011). Parents or legal representatives of patients were acquainted and informed about the aims, nature, diagnostic procedures and gave voluntary informed consent.

RESULTS AND DISCUSSION. The results of molecular genetic studies are presented in Tables 1-3.

The features of SMA onset in children were retrospectively studied in order to study the possibility of early diagnosis and taking into account the importance. The first symptoms occurred in the age range from 7 months to 7 years. In our studies the development of SMA at the age under 1 year (8.4±1.1 months) was noted in 22 children (23.2%), from 1 to 3 years (20.1±7.5 months) - 53 (55.8%), over 3 years (41.9±4.0) - 20 children (21%). Thus, the first symptoms of the disease more often occurred at the age of 1 to 3 years.

Parents associated the development of clinical manifestations of the disease with recent acute respiratory viral infection, in 28 children (29.5%), with DPT vaccination in 19 patients (20%), in 3 (3.2%) the first symptoms were preceded by anxiety, stressful situations in kindergartens or at home. In the remaining 45 children (47.4%), the onset could not be linked to any external cause.

Thus, the immune response dysregulation factor played a role in the disease onset, which necessitated further research in this direction for preventive purposes in order to delay the SMA onset, thus determining a higher level of functionality before the onset of the disease.

The study of life and disease anamnesis focused on pre-morbid features of clinical and neurological status (Table 4).

According to the draft of the study, early clinical and neurological manifestations of various phenotypic SMA variants were specified (Table 5).

At present, doctors have quite a wide range of diagnostic possibilities [2, 7], but unfortunately, the frequency of diagnostic errors and late verification of initial symptoms of the disease remains high. These problems are determined by a lack of awareness among primary-care practitioners, which in turn is attributed to absence of definite clinical pattern specifically developed for primary care environment that would lead to suspecting early manifestations of SMA and identifying leading symptoms [4]. Children are often observed for a long time at home for perinatal encephalopathy with motor disorders or muscle hypotension syndrome, hip

Таблица 1

Mutation genotypes in patients with SMA type II and III

SMA type, number of patients	Gene mutation type	
	genotype 0/0	genotype 0 / SMN1^{m}
SMA type II (n=54)	51 (94.4 %)	3 (5.6 %)
SMA type III (n=41)	40 (97.6%)	1 (2.4%)

Note: Genotype 0/0 - homozygous deletion (conversion) of exon 7 and/or 8 exon SMN1; genotype 0 / SMN1^{m}- deletion on one allele and intragenic mutation on the other allele.

Table 2

Number of SMN2 copies in children with SMA II and III types

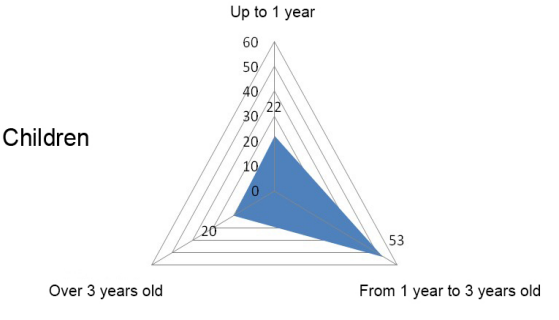
SMA type, number of patients	Число копий SMN2, n (%)		
	2	3	4
SMA type II (n=54)	3 (3.9 %)	46 (85.2 %)	5 (10.9 %)
SMA type III (n=41)	-	15 (36.6 %)	26 (63.4 %)

Table 3

Genetic analysis of parents of type II and III SMA patients

Number of surveyed parents of SMA patients	Вариант носительства делеции SMN1, n (%)	
	Heterozygous exon 7 SMN1 deletion	Presence of two or more copies of exon 7 SMN1 on one chromosome (cis configuration)*
122	115 (94.3 %)	7 (5.7 %)

Note: * Diagnosed using multiplex probe amplification.



The dependence of the incidence of SMA on age

Table 4

Clinical and neurological symptoms before the initial manifestations of SMA (n=95)

Clinical manifestations	Number	%
Hip dysplasia	90	94.7
Hypermobile joint syndrome	88	92.6
Valgus/varus foot	75	78.9
Early speech development	56	58.9
Poor weight gain	45	47.3
Slowly starting child	36	37.9
Slumped when seated	44	46.3

Table 5

Initial manifestations of SMA different variants in children (n=95)

Symptoms	SMA II type (n=54)		SMA III type (n=41)	
	абс.	%	абс.	%
Limited range of active movements in the extremities	50	92.6	18	43.9
Restrictions and movement disorders, frequent falls, tripping, fatigue	23	42.6	41	100
Hard to go up and down the stairs	6	11.1	32	78
Tongue fasciulation + intention tremor	48	88.9	7	17.1
Reduced hand agility	49	90.7	6	14.6
Weakness and hypotrophy of shoulder belt and upper torso muscles	49	90.7	3	7.3
Weakness and hypotrophy of thigh and pelvic belt muscles	11	20.4	34	82.9
Muscle cramps	3	5.6	27	65.9
Spinal column deformity	47	87	22	53.4

dysplasia, flatfoot or valgus foot deformity [1]. Such mistakes in diagnostics, on the one hand, can be explained by untimely examination, absence of dynamic follow-up, wrong differentiation of normal and abnormal neurological status, insufficient knowledge of primary semiotics and SMA syndromology by primary care neurologists, erroneous interpretation of anamnesis data, and on the other hand - unidirectionality and cliché actions of doctors are also associated with erroneous interpretation of semiotics and syndromology of motor disorders.

Conclusions. Careful assessment of family history, clarification of manifestations, rate of progression and interpretation of motor disorders in the disease onset are the leading factors of early clinical diagnosis of SMA, that allow consider the further development of motor symptoms and complications that aggravate condition of a sick child and affect the vital prognosis.

Information about the source of support in the form of grants, equipment, medicines.

The authors did not receive financial support from companies producing medicines and medical equipment.

Conflict of interest: none.

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TWO-STAGE SURGICAL TREATMENT TACTICS IN MECHANICAL ICTERUS OF NEOPLASTIC GENESIS WITH APPLICATION OF ANTEGRADE PERCUTANEOUS BILIARY DRAINAGE

DOI 10.25789/YMJ.2020.69.06

УДК 616.361-089-006

The aim of the study was to analyze the results of two-stage surgical tactics for mechanical icterus of neoplastic genesis using antegrade percutaneous biliary drainage. Material and methods. The study is based on a retrospective analysis of the results complex treatment of 52 patients with mechanical icterus of neoplastic genesis who were treated in surgical departments of the Republican Hospital №2 - Center for Emergency Medical Care from 2015 to 2019. The diagnosis of malignant neoplasm complicated by mechanical icterus was verified on the basis of a complex clinical examination. The structure of the variants of diseases that caused the development of mechanical icterus was as follows: cancer of the liver and intrahepatic bile ducts – 4 (7,8%), cancer of the gallbladder and extrahepatic bile ducts – 2 (3,8%), cancer of the large duodenal papilla – 1 (1,9%), pancreatic cancer – 43 (82,7%), stomach cancer – 2 (3,8%). At the first stage of treatment, with the goal of biliary decompression, percutaneous cholecystostomy was performed in 3 (5,8%) patients and percutaneous transhepatic cholangiostomy in 49 (94,2%) patients. At the second stage, in order to finally restore the passage of bile (which were objectively possible in a particular clinical situation), the following surgical interventions performed: hepaticoejunostomy – 1 (1,9%) patients, cholecystoenterostomy – 3 (5,8%), external drainage of the bile ducts – 2 (3,8%) and pyloroduodenal resection – 7 (13,5%) patients. Results. The use of antegrade percutaneous drainage for the purpose of biliary decompression with the proper technical level and adequate preoperative preparation is accompanied by a relatively low percentage of complications and mortality. Conclusion. The clinical experience we have presented of using two-stage surgical treatment tactics for mechanical icterus of neoplastic genesis allows us to recommend its widespread use in the practice of urgent surgical clinics.

Keywords: mechanical icterus, antegrade percutaneous biliary drainage, two-stage therapeutic tactics.

Introduction. The problems of diagnosis and treatment of mechanical icterus (MI) syndrome of neoplastic genesis remain to date difficult to solve problems of modern surgery [3]. Based on literature data [6,7,9], as well as official statistics [4], over the past decade, there has been a gradual increase in the number of diseases, especially malignant neoplasms (MN), in which MI develops, which cannot but alarm and do not address some issues of the provision of surgical care for this category of patients.

It has been established that the most common cause of neoplastic obstruction of the bile ducts is: cancer of the liver and intrahepatic bile ducts, cancer of the gallbladder and extrahepatic ducts, cancer of the stomach and pancreas [8]. At present, in the Russian Federation (RF), the proportion of cancer incidence of these localizations is 10,98%. The specific gravity of gastric cancer is 5,91%, liver, intrahepatic bile ducts – 1,41%, gallbladder and extrahepatic bile ducts – 0,59%, pancreas – 3,07% [4]. For comparison, as well as the actualization of the study, we present the estimated incidence rates of MN of the pancreatoduodenal zone per 100,000 populations in the RF and the Republic of Sakha (Yakutia) (RS (Y)). In the RF with gastric cancer, this indicator is 13,5, in RS (Y) – 16,4, cancer of the liver and intrahepatic ducts in the RF – 3,3, RS (Y) – 15,3, cancer of the gallbladder and extrahepatic bile ducts in the RF – 1,2, RS (Y) – 1,4, pancreatic cancer in the RF – 7.0, RS (Y) – 7,4 [4]. The above figures cause genuine concern, and create the need to search for new, as well as improving the existing principles and methods of surgical treatment of this category of patients at all stages of medical care, taking into account regional characteristics.

With a low percentage of resectability of tumors of the pancreatoduodenal zone, which according to some reports is not more than 20% [3, 5], and also taking into account the high postoperative mortality and a large number of complications of surgical operations at the height of icterus in MN, it has been used for many years throughout the world the so-called staged treatment [14]. According to [13,15], in this case, biliary drainage (BD) allows you to interrupt the cascade of developing pathological processes, and above all, the development of liver failure, and the final restoration of the passage of bile is performed after its relief. This tactic is also justified by the fact that it is not uncommon for minimally invasive surgical interventions in patients with MN to become the final treatment option [9]. However, there are also opponents of the use of two-stage therapeutic tactics in patients with MN complicated by MI, who argue that due to the widespread use of modern and technological methods of hardware imaging, more advanced methods of radical surgical treatment and pharmacotherapy, good treatment results can be achieved in a short time [3].

For this reason, the aim of our study was to analyze the results of two-stage surgical tactics for mechanical icterus of neoplastic genesis using antegrade percutaneous biliary drainage.

Material and methods. The presented work is based on a retrospective analysis of the results of complex treatment of 52 patients with mechanical icterus of neoplastic genesis who were treated in emergency surgical departments of the Republican Hospital №2 - Center for Emergency Medicine (RHN№2-CEM) of the Republic of Sakha (Yakutia) in the period from 2015 to 2019 years. The

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average age of patients was 67,6 ± 6,5 years, with 17 men (32,7%) and 35 women (67,3%). The diagnosis of MN disease complicated by MI was verified on the basis of a comprehensive examination. The structure of the nosological forms of diseases that caused the development of the breast was as follows: cancer of the liver and intrahepatic bile ducts – 4 (7,8%), cancer of the gallbladder and extrahepatic bile ducts – 2 (3,8%), cancer of the large duodenal papilla (LDP) – 1 (1,9%), pancreatic cancer – 43 (82,7%), stomach cancer – 2 (3,8%). Moreover, stage II disease was detected in 2 (3,8%) patients, stage III – in 23 (44,3%) and stage IV – in 27 (51,9%) patients. We considered the main laboratory criteria for the development of MI: an increase in the level of total bilirubin to more than 21,5 μmol / l, direct, more than 5 μmol / l. Instrumental – expansion of extrahepatic bile ducts > 8 mm, and intrahepatic bile ducts > 4 mm. To determine the severity of the MI and the risk of upcoming surgery, the classification of E.I. Halperin et al. [2]. Ultrasound investigation was performed on an HDI 5000 echo sounder from «Philips» and Elegra from «Siemens» in gray scale, tissue harmonic, color and energy doppler imaging according to standard methods. The study upon admission to the clinic was carried out without prior preparation. Endoscopic examination was performed using a GIF Type 2 T 160 gastrofibroscope «Olympus» (Japan). Retrograde cholangiopancreatography (RCHP) was performed according to the standard method using an «Olympus» TJF type 160 R duodenovideoscope with an EVIS EXERA video system and a set of endovideotherapeutic tools. X-ray surgical interventions were carried out on a universal x-ray machine POLYSTAR T.O.P. company «Siemens». Computed tomography was performed on a 64-slice computer tomography Somatom Definition AS, Siemens Medical Solutions using the AbdomenMultiPhase program with a layer thickness of 5 mm in two stages, before and after bolus contrast enhancement (Ultravist 370 mg / iodine per 100 ml with an injection rate of 3,0 ml / s). In some cases, as a rule, for the purpose of differential diagnosis, radiation studies were supplemented by magnetic resonance imaging (MRI).

In order to decompress the biliary system at the first stage, the following types of surgical interventions were performed: percutaneous cholecystostomy (PC) – 3 (5,8%), percutaneous transhepatic cholangiostomy (PTC) – 49 (94,2%). PC and PTC were performed under the control of ultrasound with subsequent control cholangiography. For the final restoration of the passage of bile in the second stage (if it was possible or appropriate), the following surgical interventions were performed: hepatikoejunostomy – 1 (1,9%), cholecystoenterostomy – 3 (5,8%), external drainage of the bile ducts – 2 (3,8%), pyloroduodenal resection (PDR) – 7 (13,5%).

Statistical processing of the material was carried out using the statistical software package IBM.SPSS.Statistiks.v22. When evaluating the entire population, mean values (M) and standard deviation (m) were calculated.

Results and discussions. We are forced to admit that when choosing a method for eliminating MI during MN, the criteria of resectability were not always taken into account. This was largely due to the urgent profile of the clinic in question. At the same time, palliative interventions in the volume of PC and PTC were performed in all 52 (100%) patients with MI due to MN. Among them, in 39 (75,0%), the chosen method of decompression of the biliary system turned out to be the final treatment option, and 13 (25,0%) patients were subsequently subjected to repeated (second stage) surgical interventions in the amount of hepatikoejunostomy, cholecystoenterostomy, pyloroduodenal resection and external drainage of extrahepatic bile ducts.

Complications after performing PC and PTC were revealed in 9 (17,3%) patients. In this case, directly related to the technical aspects of the operation (intraoperative) – in 6 (11,5%). In three cases, bile leakage was recorded in the postoperative period, which amounted to 5,8%. In two cases, bleeding from the liver parenchyma at the place of passage of the transhepatic drainage was diagnosed – 3,8%, and in one case there was damage to the vessels of the round ligament of the liver, also accompanied by intraperitoneal bleeding – 1,9%. In all cases, laparotomy was required with hemostasis and / or abdominal sanitation. At the same time, two died – 33,3% of patients. Three patients – 5,8%, noted complications not associated with surgery, which arose against the background of disorders in the hemostatic system, and against the background of the underlying disease – acute ulcers of the stomach and duodenum with bleeding. All patients underwent endoscopic hemostasis, with no subsequent recurrence of bleeding.

According to a number of authors [1,9,10,13], whose statements are difficult to disagree with, the main factor in reducing the number of complications and fatalities in performing PC and PTC are the technical aspects of the implementation and the materials used for this. We considered the «two-step» methodology to be the most acceptable and safe [10]. When installing the drains, a Cook kit (USA) was used, consisting of a drain (Ultrathane® material) with an AQ® hydrophilic coating and a pigtail end (diameter from 8,5 Fr) with a MAK-LOC lock and Intro-TipTM fixation ligature, 18G trocar needle, stainless steel conductor, StatLock catheter cutaneous catheter, and «Rusch» kit (Germany). Prevention of possible complications during the performance of PC and PTC was also always inextricably linked with the correction of endotoxemia, liver failure and hemostatic disorders. We considered acceptable blood biochemical values for performing transcutaneous interventions: INR no more than 2 units, APTT no more than 50 sec., fibrinogen no more than 5 g / l, the rest of the patients need intensive preoperative preparation for 5-7 days in order to correct violations homeostasis. In the first 24 hours from the moment of admission, all patients with initial hyperbilirubinemia underwent gravitational therapeutic plasmapheresis, and then they performed PC or PTC. In some cases, 3-4 plasmapheresis sessions were required at intervals of 48-72 hours. Plasmapheresis was also carried out by those patients who subsequently planned a radical operation. This approach allowed normalizing the index of homeostasis 2-3 times faster than with conventional therapy.

Radical surgical interventions were performed by us in two stages, and only with preliminary unloading of the biliary system (PC or PTC), which indicates the presence of a differentiated approach to staging in MN of complicated MI. However, the attitude to the problem of the choice of medical tactics in such cases in the world literature remains controversial, so V.P. Kharchenko [8] reports a two-stage tactic in all patients with breast cancer of neoplastic origin, considering BD a necessary component of complex treatment, while the study by A. Niels [14], on the contrary, it proves inexpediency at the first stage to carry out preoperative biliary decompression. According to the results of our studies, radical surgical treatment was made possible in less than 15% of patients admitted to an emergency clinic, with MN of the hepatopancreatoduodenal zone, complicated by MI (Table).

At the same time, we noted that the prevalence of palliative operations over radical interventions was with all localizations of MN and amounted to 86,5%. So,

The structure of palliative and radical surgical interventions, abs. number (%

Localization of a malignant neoplasm	Palliative	Radical	Total
Cancer of the liver and intrahepatic bile ducts	4 (7.8)	–	4 (7.8)
Cancer of the gallbladder and extrahepatic bile ducts	2 (3.8)	–	2 (3.8)
Cancer LDP	1 (1.9)	–	1 (1.9)
Pancreas cancer	36 (69.2)	7 (13.5)	43 (82.7)
Stomach cancer	2 (3.8)	–	2 (3.8)

with pancreatic tumors, whose share was 82,7%, the possibility of radical treatment was only 13,5%. With similar localization C.C. Ciambella et al. [11] and U. Klaiber [12] report the possibility of a PDR of 20-57%. Such significant differences, in our opinion, are a consequence of the late treatment and admission of patients to the surgical clinic, the progression of the disease, the presence of distant organ metastases, as well as purulent-septic complications of MN. After performing radical surgical interventions in the post-operative period, complications occurred in 2 (28,6%) of the observed patients. In both cases, the failure of pancreatoeunoanastomosis was noted, which required repeated surgical interventions, with one patient subsequently dying from sluggish peritonitis.

Conclusion. Thus, at MI of neoplastic origin, two-stage surgical treatment tactics using antegrade transcutaneous biliary drainage is quite effective and often used in urgent practice. The use of modern materials and proven techniques for the decompression of the biliary system is accompanied by a relatively low level of intra- and postoperative complications. A continuous analysis of the clinical experience of surgical treatment of patients with MI of neoplastic genesis allows the necessary correction of tactics in order to improve treatment outcomes. In addition, given the high incidence rate of malignant necrotizing organs of the pancreatobiliary zone in RS (Y), as well as data on a significant percentage of patients with stage III and IV disease who underwent treatment in the clinic, it is necessary to conduct targeted studies that will determine the main directions of measures for early diagnosis and timely initiation of treatment, including surgery, in this category of patients.

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OPTIMIZATION WAYS TO THE MORPHOLOGICAL DIAGNOSIS OF VARIOUS MYOCARDIAL INFARCTION TYPES

DOI 10.25789/YMJ.2020.69.07

УДК: 616.12-008.1

At present, there are five types of myocardial infarction, depending on the mechanism of disease development, which is consistent with the IV universal definition of myocardial infarction (MI). This article provides a clinical anatomical analysis of 90 cases of various types of MI. Diagnostic features and the incidence of myocardial infarction were evaluated from a clinical and pathological point of view.

In patients with all types of myocardial infarction, a comorbid pathology was recorded, more often with types 2 and 3 of the disease – diabetes mellitus, hypertension, and others. In clinical anatomical analysis, in the interests of the final (posthumous) diagnosis of the indicated types of MI, it is important to have data from intravital studies to compare with the results of the organ section. Under these conditions, the morphometric characteristics of the heart with various types of MI are of particular importance.

Keywords: myocardial infarction, types of myocardial infarction, clinical and pathological analysis.

Introduction. Diseases of the circulatory system occupy a significant place in the doctor's practice [2, 3, 6], and often the initial cause of death is myocardial infarction (MI) [5, 6, 8, 9]. In the Russian Federation and federal districts, myocardial infarction is not most often diagnosed [4]. Moreover, in leading clinics in the world, mortality in this disease is 5-7% [7]. As part of coronary heart disease, myocardial infarction (MI) is largely due to stenotic sclerosis of the coronary arteries [1, 2, 5, 6, 9]. As a rule, the cause of the development of myocardial infarction is a complicated unstable atherosclerotic plaque of the coronary artery of the heart [1, 2, 9]. Complicated unstable atherosclerotic plaque as a combined concept includes: hemorrhage in a plaque; erosion and tears, stratification of the tire, thrombosis and thromboembolism of the distal parts of the affected arteries [2]. According to the "Fourth universal definition of acute myocardial infarction" [9], 5 types of disease are distinguished. At the same time, the authors pay considerable attention to the pathoanatomical diagnosis of acute coronary (sudden) death, MI 2 and 3 types.

Materials and methods. The basis of the work is 90 observations of myocardial infarction, taking into account the types of disease in accordance with the IV Universal Definition of MI [9]. The studies were carried out on the basis of the Central pathoanatomical department of State budgetary institutional of Healthcare of City clinical hospital of RB No. 21 from 2017 to 2018. At the same time, an anamnesis was studied, ECG, Echo-KG data in dynamics, general analysis of blood and urine, indicators of a number of enzymes (KFK-MV, LDH, ALT, AST, ALP), coagulograms, blood biochemistry. An important place in the diagnosis of myocardial infarction is occupied by the determination of the cardiospecific biomarker of troponin, especially fractions I and T. In myocardial infarction, the full pathological autopsy was performed using traditional methods and our modification. At autopsy, a thorough study of the vessels and separate weighing of the departments of the organ were carried out. During the study of the heart, macro-, micromorphometric indicators were taken according to a certain plan. Histological sections were stained with hematoxylin-eosin, according to Mallory, Van Gieson, Masson. To perform the necessary statistical processing of the material, a database was created in the form of static table files using the capabilities of the Statistica 6.0 program (StatSoftInc., USA).

Results and discussion. Those who died from myocardial infarction were between the ages of 42 and 88, with men and women equally distributed (45). Initially, the distribution of types was made according to the results of intravital studies. Moreover, type 1 MI was detected in 28, type 2 in 14, type 3 in 33, type 4 in 4, type 4 in 4, type 4 in 6, type 5 in 1 case. Types of MI according to pathological criteria were distributed as follows: type 1 - 22, type 2 - 37, type 3 - 0, 4a - 2, 4b - 6, 4s-21 and type 5 - 1 case. The largest number of subjects were 75 years of age or older. Acute myocardial infarction in all its types was frequent (85.6%) in old age. It should be noted that MI up to 59 years was registered only in 13 (14.4%) people. In women, type 2 MI was detected 10 times. It is noteworthy that with type 3 MI (33), the distribution of men and women followed equally. Type 4 myocardial infarction was determined in 14 people, and on the "a", "b", "c" variants accounted for 4.4.6 cases, respectively. Only type 5 MI occurred in one deceased. The collection of sectional material continues, which will allow for a more thorough clinical and anatomical analysis in the future, including for types 4 and 5. The criteria for distinguishing types of MI were the results of clinical, radiological, functional, laboratory, instrumental and pathological studies.

For greater clarity, the subjects examined by sex and age composition and types of MI are presented in the diagram (Fig. 1). It was established that type 1 myocardial infarction is most characteristic for men older than 75 years, and type 2 disease was observed mainly in senile age in women. Type 3 myocardial infarction occurred equally often in men (17) and women (16). In women, myocardial infarction was more common over the age of 75 years (62.5%). In men, type 3 MI was detected at the age of 42-88 years. Among them, with 3 types of MI up to 75 years old, there were 13, over 75 years old - 4 people. Short-term hospital stay (up to 1 day) was observed in 77 (85.5%) cases. In the clinic, 2-3 bed days spent 3, 4-6 bed days - 8 and more than 7 - 2. In the history of people with type 1 MI, information about coronary heart disease was absent in 17.8%, type 2 MI 21.4%, 3-type MI in 12% of cases. A history of denial of coronary heart disease has often been established in individuals younger than 59 years of age in 22% of cases. Post-infarction cardiosclerosis was determined at autopsy, which did

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not previously appear in history or was not detected with instrumental methods of research. Diabetes mellitus, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, anemia of various origins and cardiac arrhythmias were more characteristic for patients with MI 2 and 3 types, which were listed as background or concomitant diseases. Hypertension was more often observed in the MI group of types 1.3 and 4. For all types of MI, hemoglobin was reduced, especially in the group with type 3 disease (an average of 122.5 g / l), the erythrocyte content in the blood fluctuated on average 4.3-4.9 * 1012 / l. At the same time, a high content of red blood cells was noted with type 3 myocardial infarction (4.9 * 1012 / l), which was largely explained by blood clotting and manifestations of the dehydration of the body. A biochemical blood test showed high creatinine, when its concentration ranged from 69.3 to 210.5 μmol / L. A high concentration of creatinine was of a nature for individuals of 1,2,3 types of MI. At the end of the disease, there was a negative increase in indicators of general analysis and blood biochemistry, including those confirming a sharp violation of homeostasis of body fluids. On the ECG, ST segment elevation was observed only in 42% of cases of type 3 MI, while other types of MI were detected more often. With type 1 MI, the ST segment elevation was determined in 71%, type 2 in 57%, and type 4 in 85% of observations. With type 4 MI, the clinic performed angiography in 100% of cases. At the same time, with other types of MI, angiography was used much less frequently. Troponin values exceed normal values (> 99th percentile of the upper reference index) for types 1, 4b, and 4c of MI. High rates of troponin were determined in 92.8% for type 1, in 78.6% for type 2 and in 100% of cases for types 4 and 5. The cardiospecific biomarker troponin was predicted to be low in type 2 MI. A similar dynamics was observed in the study of CPK-MV, and for all types of MI, it ranged from 41.8-94 units / liter. In 45 cases, damage to the coronary artery was observed in the form of thrombosis, hemorrhage in the fibrous plaque, stratification and erosion with complete or partial occlusion. Such pathological changes were most often found on the anterior interventricular artery (MAD) (25), then in the descending direction, the right coronary artery (PCA) (10) and the envelope of the artery (OA) (10). Thrombosis was detected at the site of damage to the intima with the destruction of the superficial tire of the fibrous plaque, hemorrhage and narrowing of the lumen of the vessel. When morphologically assessing the degree of atherosclerotic lesion of the coronary arteries, the following gradation was used: narrowing of the lumen of the artery to 25%, 50%, 75% [3]. Narrowing of the lumen of blood vessels without damage to the fibrous plaque was found in half of the observations. In this case, severe stenosing coronarosclerosis without damage to the intima of the vessel (stable fibrous plaque) was recognized as the cause of acute myocardial infarction. In type 1 MI, stenosis was more often recorded in permanent residence (55.7%), somewhat less frequently in OA (48.8%) and PKA (46.5%). Multivascular damage to the coronary arteries of the heart with limiting stenosis was found to be characteristic of types 2 and 4 (Table 3). In case of myocardial infarction of type 4c, an unstable atherosclerotic plaque in the vessels of the organ was presented as follows: PMA-40%, OA-40%, PKA-20%. Most often, an atherothrombotic lesion was detected in permanent residence - 55.5% (Table 4).

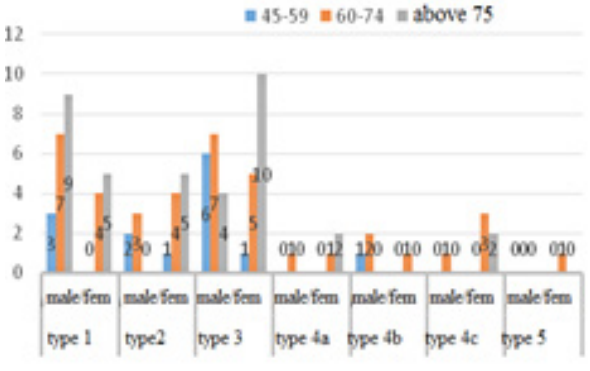

Fig.1. The distribution of types of myocardial infarction in men and women by age. On the abscissa axis there are types of MI; on the ordinate axis is the number of cases.

In our observations, transmural MI prevailed (18). Other localizations, namely intramural (15), subendocardial (7), and suepicardial MI (3) were recorded somewhat less frequently. In this case, IM 4c type was more common with lesions of each of the localizations presented. The average area of the infarcted zone was 28.3 ± 21.2 cm2, and with transmural MI, it was 44.9 ± 21.9 cm2. A recurrent course of MI was recorded in 66% of cases with visible necrosis of the heart muscle of various localization and area. The necrosis zone was mottled with foci of yellowish-brown color. When studying a series of micropreparations, along with the foci of a homogeneous, structureless and eosinophilic mass, bordering zones of granulations were found. In the designated area, significant areas of hemorrhage could be detected due to erythrodiapedesis an area of demarcation inflammation adjacent to necrosis was detected with an abundance of inflammatory cellular elements. Acute myocardial infarction in the anterior wall of the left ventricle (LV) was detected in 3, the lower wall of the left ventricle in 3

Table 1

Distribution of nosological forms identified from the anamnesis depending on the type of MI

Nosological forms identified from the anamnesis	Types of acute myocardial infarction						
	1 type	2 type	3 type	4a type	4b type	4c type	Total
Hypertonic disease, n	18	9	28	3	2	5	65
Diabetes, n	4	8	8	1	0	1	22
Coronary heart disease, n	23	11	29	4	4	6	77
- Postinfarction cardiosclerosis, n	6	3	10	1	0	0	20
- Chronic left ventricular aneurysm, n	2	0	3	0	0	0	5
- Small focal diffuse cardiosclerosis, n	10	1	15	2	1	1	30
Cerebrovascular disease, n	2	3	3	0	0	1	9
History of rhythm disturbance, n	2	1	6	0	0	0	9
Malignant neoplasms, n	1	0	0	0	0	0	1
Анемии различного генеза, n	2	2	9	1	0	2	16
Digestive system diseases, n	2	1	2	0	0	1	6
Chronic obstructive pulmonary disease, n	0	1	3	0	1	0	5
Chronic renal failure, n	1	3	7	0	0	1	12
Total	28	14	33	4	4	6	89

Note: one case of type 5 MI is not included in the table.

Table 2

The characteristics of the sectional material by types of MI and the results of laboratory and instrumental studies

Laboratory and instrumental research indicators	Types of IM					
	1 type	2 type	3 type	4a type	4b type	4c type
GBT: Hemoglobin, g/l	127.3(86-170)	134.1(105-162)	122.5(62-160)	130.8(106-141)	132.6(125-139)	133.4(103-166)
RBC, *1012/l	4.3(2.6-5.9)	4.48(3.1-5.39)	4.9(2.6-21.2)	4.5(3.66-5)	4.4(4-4.99)	4.4(3.2-5.2)
WBC, *109/l	14.6(5.3-31.7)	14.2(7.2-27.9)	12.3(4.8-24.2)	14.3(8.1-24.2)	10.3(7.2-16.9)	19.9(6.8-29)
CAB: CPhK-MB, U/l	68.6(25-271)	41.8(10-93)	66.2(19-184)	53.3(23-83)	94(53-119)	50.5(20-147)
Creatinin, mmole/l	150.9(58-755)	210.5(68-658)	153.1(66-364)	81.7(51-120)	91(74-108)	69.3(64-158)
Troponin pg/ml	2596.5(134.3-10000)	62.9(13.37-120.1)	0	651.4(51.48-1251)	745.3(531.5-982.1)	3124.4(294.7-10000)
ECG: segment lift ST, n	20	8	14	3	4	5
Appearance of pathologic wave Q, n	3	2	0	1	2	2
Fibrillation, n	12	3	15	2	3	1
Echo-CG: left ventricular ejection fraction, %	45.5	47.8	49	0	44	51.7
Angiography, n	10	3	3	4	4	6

Note: CAB is a general blood test. B / Ch - blood biochemistry. ECG - electrocardiography. Echocardiography - echocardiography. In the indicators KLA and b / ch blood indicated average values.

observations (Fig. 2). Moreover, a combination of necrotic changes in the heart muscle in various parts of the organ was a characteristic phenomenon. In the anterior-septal region, myocardial infarction was detected in 16, the posterior-septal region - 9, the circular - in 9, the anteroposterior - in 2 cases. It has been established that damage to the anterior septal region of the left ventricle of the heart is most characteristic of type 4c MI (8). Necrosis in the lower wall of the left ventricle was more common in type 2 MI.

Conclusion: Myocardial infarction was mainly transmural in nature (42%) with a lesion area of 44.9 ± 21.9 cm2 on average. In type 1 myocardial infarction, moderate and severe degree of narrowing was detected in permanent residence (55.7%). Types 2 and 4 of myocardial infarction are characterized by a multivascular lesion in the PMA, OA, and PKA systems with significant stenotic coronary sclerosis (56.1-62.5%). Unstable atherosclerotic plaque with secondary complications was detected in half (45) cases of MI. The latter was more often registered in permanent residence with type 1 disease (80%). According to localization, a mixed type of MI was more common, and the anterior-septal localization was characteristic for type 4c, the lower wall of the left ventricle for type 2 of the disease. Myocardial infarction in 37.2% was localized in the anterior-septal region of the left ventricle. For a clear clinical and anatomical analysis of MI, it seems appropriate to subdivide myocardial infarction into the corresponding types. The greatest difficulty is observed in the characterization of types 2 and 3 of MI. With type 1, this disease most often occurs in men older than 75 years, with type 2 in women of old age. In most (77) cases, a short stay of the examined in the clinic was noted (less than 24 hours), which largely explains a slight deviation from the examination protocol. In some cases, there are no indicators of troponin, KFK-MV and other enzymes, ECG in dynamics, ECHO-KG data and angiography are not presented. In patients

Table 3

The distribution of types of MI depending on the degree of stenosis of the coronary arteries of the heart

Types IM	Coronary arteries of the heart with areas of stenotic fibrous plaque		
	AIVA, %	CA, %	ПКА, %
1 type	55.7	48.8	46.5
2 type	56.1	54.1	48.7
4b type	62.5	54.1	54.1
4c type	56.8	60.8	52.2

Note: 4a and 5 types are not included in the table (for one case)

Table 4

Coronary arteries of the heart with patches of unstable fibrous plaque

Types IM	Coronary arteries of the heart with patches of unstable fibrous plaque			
	AIVA, n	CA, n	RCA, n	Total
1 type	20	7	9	36
2 type	0	0	0	0
4b type	3	1	0	4
4c type	2	2	1	5
Total	25	10	10	45

Note: a complication of unstable atherosclerotic plaque is rupture, hemorrhage, erosion of a fibrous plaque with the formation of a blood clot in the lumen of the vessel, thrombo-atheroembolism of the distal parts of the same artery (according to Zairatyants O.V., Kaktorsky L.V., 2014)

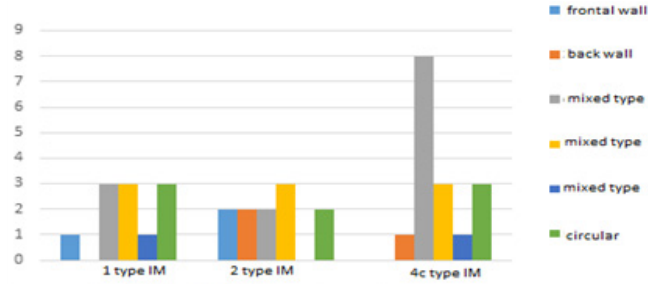

Fig. 2. Distribution of MI types by localization of damage to the heart muscle.

with all types of myocardial infarction, a comorbid pathology was recorded, more often with types 2 and 3 of the disease - diabetes mellitus, hypertension, and others. In clinical anatomical analysis, in the interests of the final (posthumous) diagnosis of the indicated types of MI, it is important to have data from intravital studies to compare with the results of the organ section. Under these conditions, the morphometric characteristics of the heart with various types of MI are of particular importance.

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DOI 10.25789/YMJ.2020.69.08

УДК 616.891.6:616.895.4: 618.19:616-006

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THERAPY OF PATIENTS WITH BREAST CANCER WITH ANXIETY AND DEPRESSIVE DISORDERS

Breast cancer (BC) is one of the leading causes of cancer death worldwide. The problem of mental health and quality of life of such patients is currently particularly relevant. Most patients with breast cancer in the process of adapting to the disease experience certain mental disorders: depressive, anxiety-phobic and psychosomatic disorders.

Purpose. To study the severity of anxiety-depressive disorders in the clinical picture in patients with breast cancer and evaluate the effectiveness of specialized pharmacotherapy using antidepressants in combination with antitumor therapy.

Material and method. The study included 30 patients with a first established diagnosis of breast cancer and 52 patients with a follow-up history of 3-17 years. The main method of work was the clinical, psychopathological, and statistical research methods (a method using contingency tables and the Fechner coefficient, a method using the Chi-square test). To evaluate the effectiveness of psychopharmacotherapy, psychometric data were statistically processed on the basis of statistica 10.

Results. To assess the severity in the clinical picture of anxiety-depressive tendencies and the effectiveness of treatment, special scales were used: hospital scale of anxiety and depression (HADS); general clinical impression scale (CGI) for assessing disease severity (CGI-S "severity") and improvement (CGI-I "improvement"). High antidepressant therapy efficacy indicators were obtained in combination with benzodiazepine drugs and hypnotics in a group of patients with anxiety-depressive nosogenia (15 patients, 88% of respondents with reduction in starting anxiety and depression scores HADS more than 50%, CGI 85%), in the group with chronic hypochondriac dysthymia and cyclotymic endoform depression.

Conclusion. The data obtained in the study confirm the effectiveness of psychopharmacotherapy with antidepressants in breast cancer patients with identified disorders of the anxiety - depressive spectrum.

Keywords: breast cancer, anxiety, depressive disorder.

Introduction. Breast cancer (BC) is one of the common malignant tumors. With early diagnosis and treatment, the 5-year survival rate of such patients is 89% [3, 5, 7, 11]. Most patients with breast cancer during adaptation to the disease and during complex therapy reveal depressive, anxiety-phobic and psychosomatic disorders, which significantly reduces their quality of life, causes a sense of hopelessness, suicidal thoughts [1, 2, 4, 6, 8, 26]. Depression is one of the most common diagnoses for breast cancer patients (from 5% to 40%), side effects of hormone or chemotherapy (menopause, pain and insomnia) lead to the development of depression.

The use of antidepressants is effective in the treatment of depressive disorders and various somatovegetative symptoms that occur in patients with breast cancer [7, 11, 15]. According to Sanjida S. et al. [7] the appointment of antidepressants for cancer patients was 15.6% for breast cancer patients - 22.6%. The most popular antidepressants in the treatment of somatovegetative disorders in breast cancer patients (asthenia, vasomotor symptoms due to ovariectomy or antiestrogen therapy) [13,26,29] are selective serotonin reuptake inhibitors (SSRIs) [25,27]. The use of SSRIs and SSRIs (serotonin and norepinephrine reuptake inhibitors) significantly reduced the frequency and severity of vasomotor flushing in breast cancer patients by 14-58% compared with placebo therapy [29]. For the treatment of vasomotor "hot flashes", the efficacy of paroxetine, fluoxetine, citalopram in a therapeutic dose of 10-20 mg/day, venlafaxine - 37.5-75 mg/day was noted [29]; sertraline (50 mg/day), duloxetine (60 mg/day) are effective in the treatment of vasomotor disorders, the treatment period was 6-12 weeks [11,14,24]. The effectiveness of antidepressants in the complex treatment of neuropathic pain in breast cancer, anxiety-depressive disorders, including anxiety-phobic disorders, major depressive (MDD) and post-traumatic stress disorders (PTSD) has been shown [13, 14, 17, 19, 25]. The use of antidepressants is diverse according to the indications for the appointment and choice of drugs. The appointment of amitriplillin as an agent for the relief of neuropathic pain (from 25-50 mg/day to 150 mg/day) showed high efficiency (59.6%) during 8 weeks of administration, however, anticholinergic side effects were noted in comparison with the drugs of the SOIZS group (19%) [17]. Paroxetine compared with tricyclic antidepressants is the drug of choice for long-term use [10, 23]. SSRIs due to their better tolerance are the drugs of choice for the treatment of anxiety-depressive disorders in breast cancer patients [7, 9, 11, 27]. The appointment of SSRI antidepressants should be correlated with possible cross-drug interactions at the level of metabolism of the cytochrome P450 system and its subunits CYP2D6 and CYP3A4, especially for patients with breast cancer taking tamoxifen and its analogues [16, 19, 20]. Sertraline, escitalopram, citalopram and venlafaxine have the least cross-drug interaction and are the drugs of choice in the treatment of breast cancer patients. Caution is necessary when prescribing high dosages in patients taking aspirin, non-steroidal anti-inflammatory drugs, warfarin or heparin [27].

A study of the effectiveness of sertraline in all types of depression in patients with breast cancer undergoing chemotherapy for 12 weeks (from 25 mg/day to 100 mg/day). showed improvement:> 50% of the points on the Montgomery-Asberg Depression Rating Scale (MADRS); a significant decrease in fatigue, anhedonia, and suicidal thoughts was

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observed [24,27]. The use of escitalopram (10 mg/day for 2 weeks) in a study in palliative cancer patients, including breast cancer, revealed a significant decrease in anxiety-depressive disorders on the HADS anxiety and depression scale, and hopelessness-helplessness, on the scale of mental adaptation to cancer Mini-MAC [22]. Venlafaxine is one of the SSRIs well tolerated by cancer patients, the least active in the CYP450 system and is the drug of choice for patients taking tamoxifen due to the lack of inhibition of CYP2D6. Venlafaxine reduces vasomotor flushing in patients receiving antiestrogen chemotherapy or undergoing ovariectomy [23, 29]. Duloxetine (30-60 mg/day, 4-12 weeks) is an SSRI approved for the treatment of depression and anxiety, neuropathy and chronic pain in patients with breast cancer [14, 28]. In patients with breast cancer, the indicators improved significantly on each of the scales (HADS, general clinical impression (CGI-S) and the Montgomery-Asberg Depression Assessment (MADRS) [26]. Special attention should be paid to antidepressants with a melatonergic effect. Melatonin significantly reduced the risk of developing depressive symptoms in women with breast cancer during a three-month period at a dose of 6 mg/day after surgery, and affected subjective symptoms: anxiety, general well-being, pain, and drowsiness. In stress disorders, in particular PTSD and anxiety-phobic disorders, SSRIs, SSRIs and mirtazapine are the drugs of choice for cancer patients, in combination with benzodiazepines [12, 13, 25]. Mirtazapine was used to treat major depressive disorder in breast cancer patients for 24 weeks, with a decrease in HAM-D score of> 50% was defined as a positive effect [12, 19].

Purpose of the study. To study the severity of anxiety-depressive disorders in the clinical picture in patients with breast cancer and evaluate the effectiveness of specialized pharmacotherapy using antidepressants in combination with antitumor therapy.

Research material and methods. The study was performed in the department of somatogenic psychological pathology (headed by doctor of medical sciences, professor S.V. Ivanov) of the department for the study of borderline mental pathology and psychosomatic disorders (headed by academician of the Russian Academy of Sciences, professor A.B. Smulevich) of Mental Health Research Center (dir. – doctor of medical sciences, professor T. P. Klyushnik) in collaboration with the departments of chemotherapy and combined treatment of malignant tumors (head - doctor of medical sciences,, A.A. Meshcheryakov) and clinical pharmacology and chemotherapy (head - doctor of medical sciences, professor S.A. Tyulyandin), department of chemotherapy (head - doctor of medical sciences A.A. Fedenko), N.N. Blokhin Oncology Scientific Medical Research Center (dir. - corresponding member of the Russian Academy of Sciences, professor I. S. Stilidi). Recruitment of patients in the study sample was carried out on the basis of the departments of the N.N. Blokhin Oncology Scientific Medical Research Center. The study included 82 patients with histologically verified breast cancer. Patients whose condition did not allow a psychopathological examination to be performed to the required extent were excluded from the study. Patients meeting the criteria were included in the study: 1) a verified diagnosis of breast cancer, 2) psychopathological disorders manifesting in connection with the circumstances of the somatic disease (F40 - F48 neurotic stress-related and somatoform disorders according to ICD-10). The study included 30 patients with a first established (6.8 ± 1.2 months from the time of diagnosis) diagnosis of breast cancer who were admitted to the hospital for routine examination and treatment (average age 49.7 ± 4.1 years) and 52 patients (mean age 56.8 ± 6.7 years) with a follow-up history of 3-17 years (mean disease duration 5.7 ± 2.9 years). Patients with higher education prevailed - 50 people. (60.9%), 49 people were married. (59.7%). 20 people worked without reducing the load. (24.3%), with a decrease in load of 25 people. (30.5%), 37 people did not work / were retired. (45.1%). The study was approved by the ethics committee of Mental Health Research Center and N.N. Blokhin Oncology Scientific Medical Research Center.

The main method of work was the clinical - psychopathological and statistical method using contingency tables and the Fechner coefficient, a method using the Chi-square test. A psychopathological assessment was carried out as part of a clinical review involving NCPP staff under the supervision of academician of the Russian Academy of Sciences, professor A.B. Smulevich and doctor of medical sciences, professor S.V. Ivanov. To assess the severity in the clinical picture of anxiety-depressive disorders and the effectiveness of treatment, special scales were used: hospital scale of anxiety and depression (HADS [Zigmond A. S., Snaith R.P., 1983]); general clinical impression scale (CGI [McGuya W., 1976]) for assessing disease severity (CGI-S "severity") and improvement (CGI-I "improvement"). To assess the effectiveness of psychopharmacotherapy, psychometric data were processed statistically based on statistica 10.

Results and discussion. The choice of drugs to ensure the treatment of breast cancer patients with anxiety - depressive disorders, the selection of optimal doses and the duration of treatment courses were determined individually depending on the syndromic structure and in accordance with the dynamics of the somatic and mental status of patients, as well as taking into account potential drug interactions in in conditions of polychemotherapy of antitumor drugs. The sample of patients included patients at all stages of breast cancer (I – IV), with the greatest accumulation of patients of stage IV. There were 69 patients in premenopause, of which 49 patients had a hormone-resistant type of tumor, and 18 patients had a hormone-sensitive type of tumor. There were 15 patients in menopause, of which a hormone-resistant type of tumor was observed in 12 patients, a hormone-resistant type in 3 patients. The most popular chemotherapy regimens included such combinations as FAC / CAF (5-Fluorouracil, Adriablastin, Cyclophosphamide in direct and reverse sequence, with different dosages and administration schedule), CA (Doxorubicin-Cyclophosphamide), CVMF (Cyclophosphamide, Vincristine, Methotrexate 5 – Fluorouracil), as well as various combinations of taxanes (Docetaxel, Paclitaxel) and platinum preparations (Cisplatin, Carboplatin) with Doxorubicin, Gemcitabine, Trastuzumab and other chemotherapy drugs.

Possible undesirable cross-pharmacological effects were evaluated by the degree of interaction of specific drugs with the cytochrome P 450 enzyme system. The effectiveness of therapy was evaluated after 6 weeks of treatment (immediate effect), and after 12 weeks (long-term effect). With the early withdrawal of drugs for any reason (the need for surgery, severe somatic condition, patient participation in the study of antitumor drugs according to the protocol, patient self-cancellation), a renewal of depressive and anxious symptoms was observed on average 2–5 days after withdrawal. In case of discontinuation of antidepressant therapy after several months (from 6 to 12 months), drug withdrawal syndrome did not form. Pharmacotherapy tolerance was good. The first signs of clinical

improvement occurred on the 10-14th day of therapy and reached a maximum level by 6-12 weeks of treatment. In this study, not a single case of adverse drug interactions between psychotropic drugs and drugs used for chemotherapy of breast cancer was recorded.

In the group of patients with newly diagnosed breast cancer (6.8 ± 1.2 months from the time of diagnosis), anxiety-depressive disorders according to clinical examination and psychometric scales were recorded in 17 of 30 patients (56.6%). The average HADS hospital score for these patients was 18–20 points on the anxiety scale (18.2 ± 1.22) and 16–20 points on the depression scale (17.93 ± 1.38), which corresponds to "severe disturbances" (table 1). According to the CGI-S clinical impression scale, the average total score was 4.6, which corresponds to a shift in the degree of impairment to the value of "acute impairment"

In the follow-up group of patients with a breast cancer duration of 3-17 years, chronic hypochondriac dysthymia requiring drug exposure was recorded in 23 patients. In 9 patients, cyclotymic endoform depression was registered against the background of disease progression after prolonged (from 1 year to 7 years) breast cancer remission. The total number of patients requiring psychopharmacotherapy in this group was 32 people. (61.5%). The average HADS score for these patients was 14–16 points on the anxiety scale (15.3 ± 0.76) and 16–18 points on the depression scale (17 ± 0.79) (table 1). The total total score on the CGI-S scale was 4.4, which corresponds to the average value between "clear violations" and "acute violations". The total number of patients in both groups in need of correction by antidepressants was 49 out of 82 patients (59.7%). The choice of drugs was carried out depending on the prevalence of one or another symptomatology in the clinical picture: in the case of a predominance of alarming symptoms, drugs with anti-anxiety and/or sedative effect were prescribed, such as paroxetine (10 - 40 mg/day), mirtazapine (15 - 45 mg/day), amitriptyline (50 - 100 mg/day). In the case of a predominance of melancholy affect with signs of apathy, drugs with a psychostimulating (SSRI group) and / or "double" action (SSRI) were prescribed: sertraline (up to 100 mg/day), venlafaxine (up to 150 mg/day), duloxetine (up to 120 mg/day). In order to stop anxiety and insomnia in patients, in addition to antidepressant therapy, anxiolytic drugs (diazepam, alprazolam, clonazepam) or hypnotics (zopiclone, zolpidem tartate) were prescribed.

In the group of breast cancer patients with anxiety-depressive disorders, a good response to antidepressant therapy was observed after 7-10 days in most patients (15), 88% of responders with a reduction in starting points on the HADS clinical scale of more than 50% (7.86 ± 0, 81 on the anxiety scale and 7.2 ± 1.06 on the depression scale, which corresponds to a subclinical level), on the CGI scale of 85% (table 1). The average total score on the CGI-I scale (to assess improvement) at the last visit was 1.5, which is the average value between grades 1 - "very pronounced improvement" and 2 - "pronounced improvement"). Complete reduction of anxiety - depressive disorders was observed in 2 patients with initial stages of breast cancer (I-II). In most cases (75%), a tangible therapeutic effect developed even when prescribing low starting dosages that did not reach those recommended by the treatment protocol. In a number of signs of improvement, patients noted a significant decrease in anxiety symptoms, normalization of sleep, appetite, decreased depression, restoration of affective background by the 6-th week of treatment.

The stabilization of the clinical effect was observed by the 12-th week of psychopharmacotherapy. In 86% of patients, background manifestations of anxiety that did not reach the clinical level remained due to the features of the diagnosis and prognosis of the underlying disease during subsequent follow-up. In order to consolidate the achieved remission and further improve the condition, the patients underwent maintenance therapy with a partial reduction in dosages, or with the cancellation of psychotropic drugs for 6-12 months, depending on the initial severity and dynamics of the anxiety - depressive symptoms.

In the follow-up group of breast cancer patients with chronic hypochondriac dysthymia and cyclothymic endoform depression, the high effectiveness of specialized pharmacotherapy has been established. The proportion of patients with a reduction in psychopathological symptom complexes (anxiety-phobic, asthenic, somatoform, affective disorders, post-castration vegetative symptoms) more than 50% on the HADS scale was 93.7% (30 people, 8.5 ± 1.61 on the anxiety scale and 6 , 77 ± 1.08 on the depression scale), a significant clinical improvement on the CGI-I scale of 90.6% (29 people, the average total score is 2). A significant effect of the therapy was associated with the combined use of pharmacological agents of a psychotropic effect - benzodiazepines and antidepressants of the SSRIs group, SSRIs, tri- and tetracyclic antidepressants. Clinical improvement occurred on days 10-14, with further gradual reduction of anxiety and depressive symptoms. In 46% (n = 15), anxiety-phobic and somatoform disorders prevailed in the clinical picture. The following psychotropic drugs were used to stop the disorders: alprazolam / lorazepam (0.5-1 mg/day) + paroxetine 20-40 mg/day, amitriptyline 50-75 mg/day, fluvoxamine 50-100 mg/day, mirtazapine 15-45 mg/day, sertraline up to 100 mg/day, venlafaxine up to 150 mg/day). In 53% (n = 17), affective and asthenic disorders predominated. In order to correct them, effective therapy using antidepressants of the IOPSSi group was used: venlafaxine 75 mg/day, duloxetine 60 mg/day. To stop concomitant insomnia in both groups of patients, benzodiazepine drugs (clonazepam, phenazepam) or hypnotics (zolpidem tartrate, zopiclone) were used. In 71% (n = 23) patients, against the background of an anxious depressive state, somatovegetative postcastration (climacteric) phenomena associated with the use of antiestrogen hormone therapy intensified. Hypoestrogenia states, expressed in autonomic dysfunction (hot flashes, increased blood pressure, heart attacks, dizziness, sweating), completely or significantly stopped against the

The dynamics of the severity of anxiety and depression on the HADS scale before and after treatment in patients with anxiety-depressive nosogenia, chronic hypochondriac dysthymia and cyclothymic endoform depression

Disorder	Subscales HADS	HADS rate Before and after psychopharmacotherapy	
		before	after
Anxious- depressive reaction	anxious	18.2±1.22	7.86±0.81
	depressive	17. 93 ±1.38	7.2±1.06
Chronic hypohondrical dysthymia, endogenoform cyclothymic depression	anxious	15.3±0.76	8.5±1.61
	depressive	17±0.79	6.77±1.08

background of combined therapy with SSRI antidepressants and anti-anxiety drugs.

In most cases, clinical improvement occurred on the 10-14th day with a further gradual reduction of anxiety and depressive symptoms to a sub-syndromic level. The affective background was normalized, there was an improvement in sleep and appetite, fears associated with cancer and a quick adverse outcome were deactivated. At the same time, the phenomena of symptomatic and reactive lability (exacerbation of psychopathological disorders under the influence of somatogenic and psychogenic factors) persisted. In these cases, prolonged use of the minimum doses of psychotropic drugs used was recommended.

Conclusion. The data obtained confirm the effectiveness of antidepressant therapy in patients with breast cancer with anxiety - depressive disorders. High efficacy of antidepressant therapy in combination with benzodiazepine drugs and hypnotics has been shown (15 patients, 88% of responders with a reduction in starting anxiety and depression scores by HADS of more than 50%, on a CGI scale of 85%), in the group with chronic hypochondria dysthymia and cyclotymic endoform depression (the proportion of patients with a complete reduction in psychopathological symptom complexes (anxiety - phobic, asthenic, somatovegetative, affective disorders) - amounted to 93.7% (30 patients), according to the CGI-I scale of 90.6% (29 patients). In patients with anxiety-depressive disorders of the asthenic and somatovegetative spectrum, it is advisable to prescribe modern selective serotonin and noradrenergic antidepressants with good tolerance and safety. The drugs and their doses were selected individually taking into account tolerance and drug interactions, according to the principle "benefit ratio exceeds the possible risk for the patient" The results of the study can help optimize specialized care for cancer patients. and the medical and diagnostic stage in an oncological hospital and on an outpatient basis during the subsequent stages of therapy. Patients with breast cancer are psychologically vulnerable for many reasons, including stress due to cancer diagnosis, debilitating treatment, and concomitant chronic pain. Further development of anxiety-depressive disorders without specialized therapy may jeopardize adherence to the treatment regimen and adversely affect the prognosis and survival of patients.

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RESULTS OF STUDY OF PARAMETERS OF BIOCHEMICAL AND ANTIOXIDANT STATUS IN PATIENTS WITH OVARIAN CANCER DURING POLYCHEMOTHERAPY

DOI 10.25789/YMJ.2020.69.09

УДК 618.11-006.04-089.163:615.272.03

The use of chemotherapeutic drugs causes an increase in the formation of free radicals and a change in antioxidant status. As a result, side effects are observed. On the basis of the Oncology Dispensary Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur) there was conducted a controlled randomized open study of parameters of biochemical and antioxidant status in patients with ovarian cancer: 30 patients received chemotherapy (a experimental group); the control group consisted of 20 healthy women, comparable in age. Biochemical status was evaluated by the levels of total protein, albumin, bilirubin and the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase in the blood of patients. Antioxidant status was evaluated by the levels of lipid hydroperoxides, conjugated dienes, and malondialdehyde and by the activity of the main components of the antioxidant system (ceruloplasmin, vitamin E) in the blood of patients. The administration of chemotherapeutic drugs to patients significantly increased the plasma levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, of lipid hydroperoxides by 50%, conjugated dienes by 51%, and malondialdehyde by 46% compared with the women in the control group. An analysis of the effect of chemotherapy on the activity of the antioxidant system components established that the blood concentrations of ceruloplasmin and vitamin E were 55 and 39%, respectively, lower than those in the control group. Thus, the incorporation of antioxidants into the treatment of patients with ovarian cancer should be considered pathogenetically justified, clinically reasonable, and promising.

Keywords: ovarian cancer, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lipid peroxidation, antioxidant system, patients.

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An urgent problem of modern gynecological oncology is an increase in the frequency of malignant ovarian tumors, the bulk of which are stage III-IV processes [2, 10]. Ovarian cancer is the most sensitive tumor to the therapeutic effect of cytotoxic drugs, however, the possibilities of specific therapy are limited due to toxic complications and pronounced metabolic dysfunctions at the level of the whole organism, which largely depend on the activation of lipid peroxidation (LP) [1, 15]. The action of peroxide products under these conditions is manifested in an increase in the membrane ion permeability, dissociation of oxidative phosphorylation, disruption of the structure and function of mitochondria, ribosomes, and a decrease in the activity of membrane-bound enzymes [9]. In addition, according to published data, platinum preparations, used mainly in the treatment regimen for patients with ovarian cancer, are antitumor agents that potentially cause the development of hepatotoxicity [3]. Therefore, there is a need to develop new science-based approaches and pathogenetically substantiated optimization of therapy in patients with ovarian cancer [14].

The purpose of the study was to study the parameters of biochemical and antioxidant status in patients with ovarian cancer during polychemotherapy (PCT).

Material and methods. A prospective, controlled, open, randomized trial was conducted in accordance with the “Rules for Qualitative Clinical Trials (GCP)” (OST No. 42–511–99 of December 29, 1998), with the provisions of the Helsinki Declaration and Guidelines for Good Clinical Practice developed at the International Conference on harmonization of technical requirements for the registration of pharmaceutical products intended for humans (ICH-GCP - International Conference on Harmonization of Technical Requirements for Human Use) and with the permission of the ethical committee of Amur State Medical Academy.

The control group consisted of 20 practically healthy women, comparable in age. The experimental group included 30 patients who are being treated in the oncology clinic of the Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur). Criteria for inclusion in the study: women over 18 years old; verified process (proven morphologically); stage III ovarian cancer; the absence of serious impaired renal, liver and hematopoietic function; adequate indicators of the cardiovascular and respiratory systems;

the absence of primary multiple, synchronous and metachron malignant tumors; voluntary informed consent. Criteria for exclusion from the study: acute infections, including hepatitis B and C, HIV; disease progression against the background of special treatment, identification of distant metastases according to the control clinical examination; history of uncontrolled convulsive disorder; previous neuropathy of any etiology, more than 1 degree of severity; clinically significant uncontrolled disorders: myocardial infarction, stroke, or transient ischemic attack, psychiatric illness / social circumstances that limit the patient's ability to fulfill the requirements of the study. All patients received PCT using platinum preparations: cisplatin, carboplatin (cytostatic antitumor chemotherapeutic drugs of the alkylating type containing divalent platinum (II) in the composition of the molecules according to the scheme: carboplatin AUC6-7 intravenously (iv) on the 1st day 21 -day course, or ATS (cisplatin 50 mg / m2 iv, doxorubicin 50 mg / m2 iv, cyclophosphamide 500 mg / m2 iv on the first day of the 21-day course).

Blood sampling was carried out before treatment and on the 5th day of treatment (in the process of PCT). We evaluated the level of total bilirubin, the concentration of total protein and albumin, aspartate aminotransferase (AcAT), alanine aminotransferase (AlAT), alkaline phosphatase (ALP) on a Clima MC-15 biochemical analyzer (China). The intensity of lipid peroxidation processes was evaluated by examining the content of lipid hydroperoxides, diene conjugates, malondialdehyde, and AOS components (ceruloplasmin, vitamin E) in the blood plasma of patients according to the methods described in our previously published works [8, 12, 17]. The following instruments were used in the work: KFK-2mp spectrophotometer, UNICO spectrophotometer, Solar PV 1251 C photoelectrocolorimeter. The results were statistically processed using Student's t test (t) using the Statistica v.6.0 program. The results were considered reliable at p <0.05.

Results and discussion. The algorithm of clinical and biochemical studies in cancer patients includes the mandatory determination of the content of total protein and albumin in the blood serum, since the development of malignant neoplasms is characterized, as a rule, by the state of severe hypoproteinemia due to a violation of the synthesizing function of the liver, the consumption of albumin as a plastic material for tumor tissue [4]. The results of our study showed a decrease in the concentration of total protein by 15% in the blood of patients with ovarian cancer at the first stage of the study (before treatment) in comparison with the same indicator in the group of healthy women (control), but the differences were not significant (Table 1). It is important to note that the content of total protein and albumin in patients at both I and II stage of the study (during PCT) was in the range of physiological norm, however, the normal concentration of albumin does not always provide adequate transport function of the protein, which may be associated with a violation secondary and / or tertiary structure. That is why T.V. Davydova et al. an opinion was expressed about the need to study in patients with ovarian cancer not only the concentration of serum albumin, but also the conformational transport characteristics of the latter [4]. The study of the total bilirubin content showed a significant decrease of this indicator by 42% in the blood of patients with ovarian cancer compared with the control and allowed us to state hypobilirubinemia (p <0.05). In the process of PCT (stage II treatment), the level of bilirubin in the experimental group tended to increase by 1.5 times, without leaving the range of the physiological norm, relative to the same parameter in stage I (p <0.05).

A study of the activity of hepatic transaminases in patients with stage III ovarian cancer upon admission to the Oncology Center (before treatment, stage I) made it possible to record the level of AlAT and AsAT within normal limits, which did not significantly differ from similar parameters in practically healthy women (control) (Table 2).

In the process of PCT in stage II, a significant increase in the activity of enzymes in the blood of patients was observed in comparison with indicators in stage I and relative to the upper limit of normal (ULN): the level of Alanine

Table 1

The concentration of total protein, albumin (g / l) and total bilirubin (μmol / l) of blood in healthy women and stage III ovarian cancer patients with chemotherapy (M ± m)

Indicator	Rate	Group		
		Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
			Stage I (before treatment)	II stage (5th day of treatment)
Total protein	65.0-85.0	82.5±4.4	70.7±5.6	69.8±6.0
Albumin	35.0-45.0	44.2±2.5	43.0±3.1	41.5±3.6
Total bilirubin	8.5-22.5	11.8±1.2	6.9±0.6*	11.0±0.8 **

Note. Here and in the Table 2 - 4: * - significance of differences in indicators compared with practically healthy women (control group) (p <0.05);
** - reliability of differences in indicators compared with patients at the first stage of the study (before treatment) (p <0.05).

Table 2

Enzymatic activity indices (e / l) in practically healthy women and stage III ovarian cancer patients with polychemotherapy (M ± m)

Indicator	Rate	Group		
		Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
			Stage I (before treatment)	II stage (5th day of treatment)
Alanine Aminotransferase	10-31	22.0±2.1	30.2±2.8	93.7±5.2***
Aspartate Aminotransferase	5-40	26.5±2.8	37.7±3.3	60.2±4.5***
Alkaline phosphatase	50-290	85.4±5.5	153.7±10.8*	258.9±21.1***

Aminotransferase exceeded ULN by 3 times and was 3.1 times higher than the same parameter in stage I (p <0.05), Aspartate Aminotransferase - 1.5 and 1.6 times, respectively (p <0.05), which indicates the development of hepatic cytolysis (or hepatic cell drug-induced liver injury (DILI) [3]) with the introduction of platinum preparations. The data obtained are consistent with the results of studies of E.V. Maximova, who established an increase in hepatic transaminases in 85.2% of cases in patients with ovarian cancer on the background of PCT [5]. The calculation of the de Ritis coefficient (Aspartate Aminotransferase / Alanine Aminotransferase) in patients at stage II made it possible to register a value of less than 1 (0.64), which indicates DILI with an inflammatory type of response [6]. PCT was accompanied by a significant increase in the level of alkaline phosphatase by 68.4% in the blood of patients with ovarian cancer in comparison with the activity of this enzyme at the first stage of research, which significantly exceeded the control by 3 times, but it is important to note that before the treatment and in the process of PCT, the values of alkaline phosphatase out of the range of physiological norms, which correlates with published data [14].

Thus, the study of biochemical status parameters in patients with stage III ovarian cancer indicated the formation of a hepatocellular type of liver injury during PCT, the main pathogenetic mechanisms of which are, firstly, the direct induction of apoptosis; secondly, the formation of toxic metabolites in phase I reactions (mediated by P-450 cytochromes), which leads to an increase in lipid peroxidation in hepatocytes and, as a consequence, a disruption in the structure of cell membranes and necrosis; thirdly, mitochondrial dysfunctions; fourthly, a violation of calcium metabolism in the cell, an increase in the intracellular concentration of Ca2 + ions, leading to injury to the cell wall and its lysis [3]. It is quite logical that under these conditions, the antioxidant system (AOS) experiences extreme stress and tension, since the activity of its components is aimed at stabilizing lipoperoxidation processes and inhibiting the cascade of LPO reactions that have a chain avalanche-like character. In addition, our previous preclinical studies on a model of toxic liver injury induced by the introduction of carbon tetrachloride showed a clear relationship between changes in the biochemical status and the state of the LPO / AOS system of the body [11, 13]. Therefore, it is advisable, in our opinion, to study the parameters of antioxidant status in ovarian cancer in the process of PCT, which is of fundamental importance for the purpose of further pharmacological correction of changes by the appointment of antioxidant agents [16].

Table 3

The content of lipid peroxidation products (nmol / ml) in practically healthy women and stage III ovarian cancer patients with polychemotherapy (M ± m)

Indicator	Group		
	Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
		Stage I (before treatment)	II stage (5th day of treatment)
Lipid hydroperoxides	30.8 ± 2.1	39.0 ± 1.5*	46.5 ± 1.8* **
Diene conjugates	36.0 ± 2.0	48.6 ± 2.2*	54.5 ± 2.0*
Malonic daldehyde	4.8 ± 0.2	5.7 ± 0.3	7.0 ± 0.3* **

Table 4

The content of antioxidant system components (μg / ml) in practically healthy women and patients with stage III ovarian cancer on the background of polychemotherapy (M ± m)

Indicator	Group		
	Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
		Stage I (before treatment)	II stage (5th day of treatment)
Ceruloplasmin	32.6 ± 2.5	20.4 ± 1.8*	14.6 ± 1.0* **
Vitamin E	54.2 ± 3.0	42.5 ± 2.2*	33.2 ± 1.5* **

A study of the content of lipid peroxidation products in the blood plasma of patients with ovarian cancer showed (Table 3) that, against the background of the oncological process, a significant increase in the primary lipid peroxidation products was observed (lipid hydroperoxides were higher by 27%, diene conjugates by 35%, p <0.05) and unreliable - the secondary product of peroxidation of malondialdehyde (19%) in comparison with similar indicators in the group of healthy women. Analyzing the degree of accumulation of lipid peroxidation products in the dynamics of PCT, it is important to note a significant increase in lipid hydroperoxides by 19% (p <0.05), malondialdehyde by 23% (p <0.05) and diene conjugates by 12% on the 5th day of the study (II stage) in relation to these parameters in stage I, which in turn significantly exceeded the control by 50%, 46% and 51%, respectively (p <0.05). Our data are consistent with T.P. Gening et al., Indicating an increase in the level of secondary lipid peroxidation products in the blood plasma of patients with ovarian cancer in clinical stage III according to FIGO 3 days after the first course of PCT according to the CAP scheme and 3 days after the second course [7].

Analyzing the activity of the main components of the antioxidant system (Table 4), it is important to note that at the stage of patient admission to the Oncology Center (before treatment), there was a significant decrease in ceruloplasmin by 38% (p <0.05) and vitamin E by 22% (p < 0.05) compared with similar indicators in the group of healthy women (control), which indicates the tension of the antioxidant system in ovarian cancer. PCT with platinum drugs leads to a progression in the degree of AOS depletion, as indicated by a significant decrease in the concentration of ceruloplasmin (by 29%) and vitamin E (by 22%) in the blood plasma of patients relative to the indicators obtained at stage I of the study (p <0.05). On the 5th day of treatment, the content of ceruloplasmin was 55% lower than in the control group of women, vitamin E -

39% (p <0.05), which allows us to state the fact of a decrease in the activity of the main components of AOS against the background of an increase in the intensity of LPO processes in the conditions of PCT. Thus, the treatment of patients with ovarian cancer with the use of platinum preparations is accompanied by changes in the biochemical and antioxidant status of patients, which makes it necessary to include drugs with hepatoprotective and antioxidant effects in complex therapy.

Conclusions

1. Chemotherapy according to the ATS scheme in patients with stage III ovarian cancer promotes the development of hepatic cytolysis, inducing an increase in the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase.

2. Against the background of polychemotherapy of ovarian cancer with platinum preparations, changes in the antioxidant status of the body are observed, based on the accumulation of lipid peroxidation products and a significant decrease in the activity of the main components of the antioxidant system (ceruloplasmin, vitamin E).

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CEREBRAL AMYLOID ANGIOPATHY: CASE REPORT

DOI 10.25789/YMJ.2020.69.10

УДК 616.8-005

Cerebral amyloid angiopathy (CAA) is a disease of the small cerebral vessels and it mostly affects older people. CAA is characterized by progressive deposition of amyloid-beta in small arteries and arteries of medium caliber, as well as in the capillaries. Sporadic amyloid angiopathy is a cause of recurrent cerebral hemorrhage and cognitive impairment in the elderly. The latest scientific researches and a case report of a patient who suffered from cerebral amyloid angiopathy were used in order to prepare this article. The diagnosis and treatment of CAA are considered.

Keywords: cerebral amyloid angiopathy, spontaneous recurrent cerebral hemorrhages, cognitive impairment.

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Introduction. Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid-beta within cerebral blood vessels and commonly affects the elderly. CAA is associated with the intracerebral hemorrhages (ICH), cognitive disorders (CD) and increases the potential risk of hemorrhage complications for antithrombotic and thrombolytic therapy. CAA combines cerebrovascular and neurodegenerative pathways of brain aging [9]. Pathogenetically, amyloid-beta causes an endothelial dysfunction, disrupts the cerebral blood flow autoregulation and the blood-brain barrier. It leads to the cortical atrophy regardless of the Alzheimer's disease [9].

Autopsy researches show that CAA is associated with aging. There are 21% identified as CAA caused in 61-70 years old group over the 69% in 91 and older group [5]. In Alzheimer's disease brains, CAA is identified in an estimated 85–95% of the cases [11]. It is important to note that only few of them were diagnosed with CAA in life.

The purpose of the research is to explore the significance of CAA as a reason of hemorrhagic stroke and the risk factor of Alzheimer's disease.

Clinical presentation. CAA is characterized by spontaneous lobar ICHs, CD and dementia. It also includes transient focal neurological episodes (TFNEs) caused by subarachnoid hemorrhages (SAHs) [9]. It is also difficult to distinguish a specific CAA's cognitive disorders from Alzheimer's disease because of their comorbidity [7].

The Modified Boston criteria are used in order to incorporate cortical superficial siderosis into the radiological diagnosis of probable CAA (Table 1) [10].

Nowadays, the researchers aimed to explore non-hemorrhagical biomarks in order to modernize the Criteria. There are some of them: 1) hyperintensity of the white matter in T2 images with a tendency to rearward or a spotted pattern; 2) diffusion-tensor parameter changes, such as global mean diffusion and DTI-global efficiency; 3) vascular reactivity to functional stimulation; 4) cortical thickness; 5) point hyperintensity on DWI, indicating microinfarction; 6) increased perivascular space in the centrum semiovale; 7) PET data with PiB; 8) a decrease in the level of Aβ in cerebro-spinal fluid (CSF). Patients with CAA have a reduced concentration of Aβ42-, Aβ40 proteins and an increased concentration of t-tau protein. Patients with CAA differ from patients with AD with a lower level of Aβ40 protein and a higher t-tau / p-tau ratio [8].

A Case Report. Chief Complaint and Past History. 77-year-old man who complained about weakness in the right extremities, periodic headaches, memory impairment and slurred speech. The patient had been suffered from arterial hypertension for a long time, the maximum blood pressure reached 180/100 mm Hg. At the age of 65, he had suffered a hemorrhagic stroke in the left hemisphere with the development of deep right-sided hemiparesis. Conservative treatment was positive as a muscle strength increased in the limbs, but hemiparesis remained. The patient denies having a stroke or transient neurological disorders after the case. At the age of 75, the patient had noticed a gait abnormality and a memory impairment, which slowly progressed. He had been regularly taking amlodipine 5 mg per day and bisoprolol 5 mg per day, atorvastatin 20 mg per day. Previously, he worked as a doctor. He also denied bad habits, head injuries, faintings.

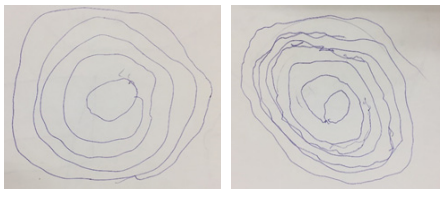
Neurological Examination: cranial nerves – convergence insufficiency,

The Modified Boston criteria (2018)

Definite CAA – full post-mortem examination reveals lobar, cortical, or cortical/subcortical hemorrhage and pathological evidence of severe cerebral amyloid angiopathy – no other diagnostic focuses
Probable CAA with supporting pathological evidence *clinical data and pathological tissue (evacuated hematoma or cortical biopsy specimen) demonstrate:* – lobar, cortical, or cortical/subcortical hemorrhage – mild CAA pathological evidence – no other diagnostic focuses
Probable CAA *Clinical data and MRI/CT demonstrate:* – multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhages allowed) of varying sizes/ages without another cause, or a single lobar, cortical, or corticosubcortical hemorrhage and focal (three or less sulci) or disseminated (more than three sulci) cortical superficial siderosis without another cause* – age ≥55 y.o.
Possible CAA *Clinical data and MRI/CT demonstrate:* – a single lobar, cortical, or corticosubcortical hemorrhage without another cause*, or a focal or disseminated cortical superficial siderosis without another cause; – age ≥55 y.o.

* – traumatic brain injury, hemorrhagic transformation of ischemic stroke, arteriovenous malformation, tumor, taking warfarin with an international normalized ratio> 3, vasculitis.

smoothness of the right nasolabial folds. Dysarthria. The right-sided pyramidal tract disorder in the form of hyperreflection and moderate spasticity. The strength in the limbs is sufficient. The upper Rossolimo's sign on the right is caused. Coordination tests are performed with moderate ataxia. The Romberg test is positive. The patient has a wide-based gait there is no microbasia. Kinetic tremor of the right hand (Fig. 1).



a b

Fig. 1. Archimedes spiral drawing by: a – left hand; b – right hand.

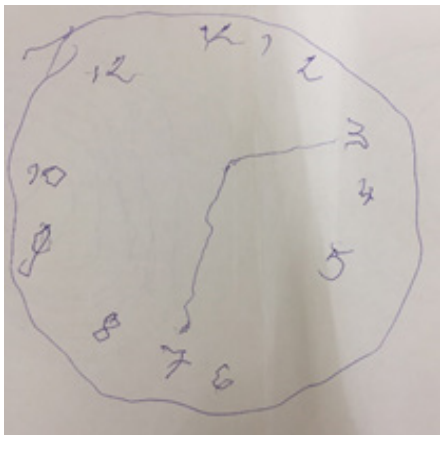


Fig. 2. The "clock drawing" test

The patient was evaluated on a cognitive profile on a 3-CT scale, which includes the "clock drawing" test, assessment of speech activity and visual memory [1]. The "clock drawing" test revealed the incorrect arrangement of numbers on the dial and unequal distance between them (5 points) (Fig. 2).

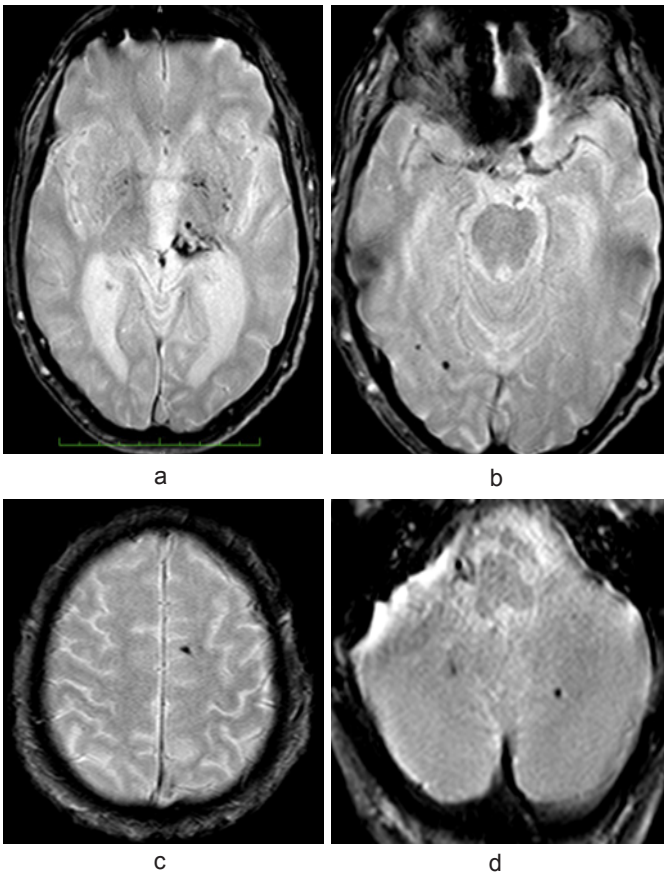
Assessment of speech activity: phonetic speech (naming "L" words) - 2 words per 1 min, semantic speech (naming "animals") - 3 words per 1 min.

Visual memory: delayed playback - 2 out of 12, true recognition - 7 out of 12, false - no.

The patient had no spatial orientation or time perspective's disorder. A memory impairment is determined as the inability to detail recent events. Memory for remote events is saved. As a result, an amnestic cognitive impairment was revealed.

Diagnostic Assessment. The detailed laboratory investigations revealed a normal hemogram. Coagulation workup: prothrombin index 103%, international normalized ratio 1.04. Autoimmune workup (antistreptolysin-O, RF, LE cells, C-reactive protein) are negative.

Urine test: normal. Biochemical blood test: dyslipidemia (cholesterol 6.02 mmol / L, triglycerides 0.58 mmol / L, LDL 3.97



a b c d

Fig. 3. The foci of cerebral hemorrhages in the SWI mode (description above)

mmol / L, HDL 1.97 mmol / L, atherogenic index 2.06). Other parameters (total and direct bilirubin, hepatic transamnases, creatinine, urea, total protein, albumin, glucose) are normal.

ECG: sinus tachycardia with a heart rate of 110 per min. Violation of intraventricular conduction Hypertrophy of the left atrium, left ventricle.

Ultrasound of the carotid and vertebral arteries: the initial manifestations of atherosclerosis, stenotic lesions were not detected.

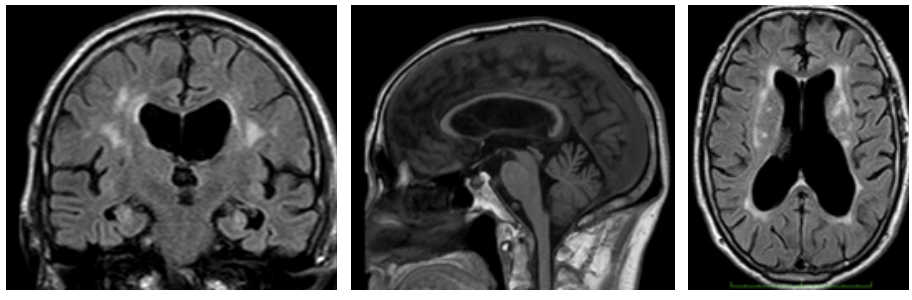
An MRI scan of the brain in the SWI mode reveals a site of cystic-gliosis transformation with deposition of hemosiderin on the periphery in the left thalamus with distribution to putamen and internal capsule on the left (Fig. 3, a). In addition, foci of microhemorrhage in the cerebral hemispheres and in the cerebellum are detected (Fig. 3, b-d).

MRI also determines the atrophy of the hippocampal areas of the temporal lobes, more to the left (Fig. 4, a), mesencephalon atrophy (a 'hummingbird' sign) and moderate atrophy of the cerebellar worm (Fig. 4, b), signs of leukoaraiosis and moderate replacement hydrocephalus due to convexital atrophy of the cerebral hemispheres (Fig.4, c).

According to the presence of hemorrhagic stroke, the foci of hemorrhages in the cerebral hemispheres and cerebellum, amnestic type of cognitive impairments and atactic syndrome, which are explained by hippocampi and cerebellar atrophy and the absence of other causes for cerebral hemorrhages, it's most likely CAA-induced secondary neurodegeneration, as well as Alzheimer's disease.

Conclusion. According to modern data, CAA is not only a histopathological phenomenon, but also a heterogeneous clinical syndrome. The development of clinical and neuroimaging diagnostic Boston criteria has significantly improved the diagnosis of the disease [3]. Further improvement in the diagnosis of CAA becomes possible in view of the introduction of a new MRI mode - SWI (Susceptibility Weighted - images weighted by magnetic susceptibility). In this mode, microhemorrhages are defined as small foci (from 2–3 to 10 mm) of an MR signal with a "flowering effect" [12].

Patients with signs of the CAA have not only an increased risk of dementia, but also a high rate of cognitive decline [7]. Moreover, cognitive impairment in CAA differs from that in AD with relatively preserved episodic memory. Possibly, CAA induced cognitive disorders is due to the combined influence of microinfarctions and disturbance of neuronal connections [9]. In according to the existing pathogenetic classifications, CAA-associated cognitive disorders are more appropriately attributed to vascular ones, although secondary neurodegeneration inevitably joins during the disease [4]. However, amnestic syndrome prevails in the patient's case, which does not allow us to attribute the existing cognitive impairment to the presence of CAA.



a b c

Fig 4. The patient's MRI (description above)

Meanwhile, the presence of cognitive disorders of the amnestic type, which is progressive, affects two cognitive spheres (memory, speech) with the absence of dominant behavioral disorders indicate Alzheimer's disease [2].

Further patient's management includes the appointment of anti-dementia medications due to the high risk of cognitive impairment progression and to control the vascular risk factors.

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HEALTHCARE, MEDICAL SCIENCE AND EDUCATION ORGANIZATION

DOI 10.25789/YMJ.2020.69.11

УДК 616-006.06:614.1

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RELATIONS OF CERVICAL CANCER MORTALITY WITH THE POPULATION'S NUMBER AND DISTRIBUTION IN REPUBLICS, LOCATED IN SIBERIA (2007-2018)

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The statistical relationship analysis' results between the republics' annual values (2007-2018) of age-standardized mortality rates (ASMr) from cervical cancer (CC) and demographic indicators - the population's number and density, the population's distribution on a city-rural basis, are presented. The selected republics are Altai, Buryatia, Tuva, Khakassia and Sakha (Yakutia). A positive correlation us found between CC ASMr and the percentage of republics' rural settlements (Spearman correlation coefficient (r) = 0.7, p≤0.05). With the rest of the demographic data selected for the study, the correlation did not reach the required significance (r <0.7, p> 0.05).

Keywords: cervical cancer, mortality, Siberia, the Far East, Altai, Buryatia, Tuva, Khakassia, Sakha (Yakutia).

Introduction. Cervical cancer (CC) is the second most common type of cancer among women worldwide. More than 90% of deaths from cervical cancer occur in women living in low- and middle-income countries. This is believed to be due to women's inadequate access to screening and treatment services [3].

In the Russian Federation (RF), in the structure of cancer mortality (CM), CC is one of the three main causes of death for women at the highest social activity age (30-59 years) [4].

As well as throughout the world [3], Russian rates of CM, including CC mortality (CCM), have significant territorial variability [4]. The rates' heterogeneity and a high level of CM are characteristic including for residents of Siberia [8]. Researches devoted to a comparative analysis of cancer mortality in Siberia are few. Meanwhile, to do work like that make it possible to assess the contribution of various factors - demographic, geographical, social, racial, ethnic, genetic, etc. - on CM.

In our previous researches, we found disparities in CCM over the Siberia's national territories - the Republic of Altai (RA), Buryatia (RB), Tuva (RT), Khakassia (RKh), Sakha (Yakutia) (RS(Y)) from 2007 to 2017. For the majority of the peoples inhabiting these territories, the fact of genetic kinship has been established [10]. We have shown that the lowest values of annual CC age-standardized mortality rates (ASMr) were observed in RS(Y) [7, 12], the largest - in RB [12]. Differences in CC ASMr between RA, RT, and RKh did not reach a statistical significance [12].

This research goal was to establish a relationship (correlation) between the annual CC ASMr in the long-term (2007 – 2018) and the population's distribution data, namely, the population's number and density, the urban and rural population's number, the number of cities, urban-type and rural settlements in RA, RB, RT, RKh and RS(Y).

Material and Methods. The annual (2007 - 2018) CC ASMr in RA, RB, RT, RKh and RS(Y) were extracted from the annually published books of the Moscow Scientific Research Institute after P.A. Herzen - a branch of the Federal State Budgetary Institution Scientific Research Center for Radiology of the Russia's Ministry of Health, which present the cancer incidence and mortality data of the Russian territories' population [4].

The source of population distribution data in the RA, RB, RT, RKh and RS(Y) was the 2010 All-Russian Population Census (RPC) results, published in the Federal State Statistics Service collection [9].

The study included the following RPC data - the population's number and density, the urban and rural population's number (in absolute terms and as a percentage of the total population), the republics' urban and rural settlements numbers. Based on these data, we also calculated the rural settlements percentage (to the total settlements' number), the rural population's number per one rural settlement, and the urban population's number per one urban settlement (including the cities and urban-type settlements' number).

Since CC ASMr and demographic data did not have a normal distribution,

we applied ranking (from smaller to larger) to them. To identify correlations, the annual CC ACMr ranks' sum (2007-2018) of each republic individually was compared with the RPC's ranked data. To estimate the strength of the relationship Spearman correlation coefficient (r) was calculated using the formula for small sample sizes. Results r ≥0.7 at p <0.05 were considered as significant.

Results and Discussion. To calculate the CC ASMr (per 100 thousand of population) the world standard for the population's age distribution and the Russia's administrative territories average annual population for the corresponding year are used [4].

Having performed the annual (2007 – 2018) CC ASMr ranking in the bundle - RA, RB, RT, RKh, RS(Y), we found that the highest values of the ranks' sum, i.e. the largest CC ASMr were in RB, the smallest - in RS(Y) (Fig. 1). This is consistent with our previous researches [7, 12].

According to RPC, it can be seen that the population's number and density, the urban and rural population's number, the number of cities, urban-type settlements and rural settlements demonstrate a significant differences among republics (table 1).

The difference between the smallest population (RA) and the largest (RB) were 4.7 times. The population is most densely located in the RKh, where the population density is 28 times greater than in RS(Y). The proportion of the urban population that was most marked in RKh exceeds that of the minimum RA by 2.4 times. Accordingly, the republics' rural population's proportion indicators demonstrate the exact opposite.

The smallest number of cities, the absence of urban-type settlements, was typical for the RA, while the same indicators in the RS(Y) showed directly opposite results - the largest number of cities and urban-type settlements. The maximum number of rural settlements is noted in RB, the smallest - in the RT.

If we calculate the republic's rural and urban settlements numbers as a percentage of the total republic's settlements number, we get a similar picture - the maximum distribution of rural settlements (respectively, the minimum of urban) - in RA, the minimal of rural settlements (respectively, the maximum of urban) - in RS(Y) (Fig. 2).

After analyzing the relationship of CC ASMr with the population's number and density, the urban and rural population's number (in absolute values and as a percentage of the total population), the number of urban and rural settlements, and the rural settlement's percentage, it was revealed a significant positive correlation between the annual CC ASMr and the republic's rural settlements' percentage (r = 0.7, p≤0.05). The correlation of the annual CC ASMr with the rest of demographic data did not reach the required strength and probability (r> 0.7, p> 0.05). When calculating the number of rural population per one rural settlement, and the number of urban population per one urban settlement (including the number of cities and towns), the strength and probability r did not also reach the required values (table 2).

The obtained results of the relationship between the annual CC ASMRs with the rural settlement's percentages only, but neither with the rural population's distribution, either with the number of rural population per rural settlement, are somewhat ambiguous. An additional analysis of the relationship between CCM and other demographic data, including the number and ratio of male and female population in the republics, is needed. This is our goal in a future study. It is also possible that a lower quality of care in rural settlements compared to cities influences on CCM [1, 2, 5]. Probably the CC ASMr' transformation over time contributes to the values of r - CC ASMr are calculated on the state statistical reporting basis, in which, compared with the Cancer register,

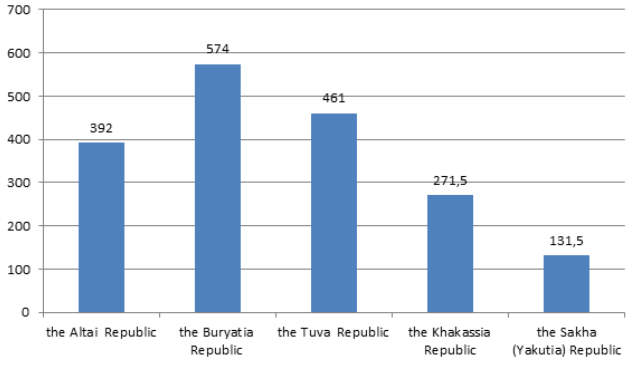

Fig. 1. The sum of CC ASMr annual values ranks in RA, RB, RT, Rkh, RS (Ya) from 2007 to 2018

Table 1

The number and density of the population, the number of urban and rural population, the number of cities, urban-type settlements and rural settlements in RA, RB, RT, Rkh and RS(Ya) according to RPC

	TP	PD	UP	RP	UPp	RPp	UC	US	RS
the Altai Republic	206.2	2.2	56.9	149.3	27.6	72.4	1	0	245
the Buryatia Republic	972	2.8	567.6	404.4	58.4	41.6	6	14	613
the Tuva Republic	307.9	1.8	163.4	144.5	53.1	46.9	5	1	144
the Khakassia Republic	532.4	8.6	358.2	174.2	67.3	32.7	5	8	264
the Sakha (Yakutia) Republic	958.5	0.3	614.5	344	64.1	35.9	13	42	586

Note. TP - total population (in thousands), PD - population density (people per 1 sq.m.), UP - urban population (in thousands), RP - rural population (in thousands), UPp - the urban population as a percentage of the total, RPp - rural population as a percentage of the total, UC - the number of cities, US - the number of urban settlements, RS - the number of rural settlements

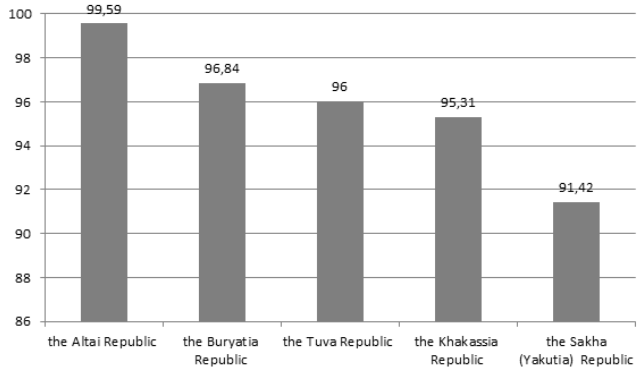

Fig. 2. The rural settlements' percentage of the Russia's constituent entity's settlements' total number in RA, RB, RT, RKh and RS(Ya) based on data from RPC 2010.

Table 2

Spearman correlation coefficient (r) between the annual values of CC ASMr (2007-2018) and the number and density of the population, the number of urban and rural population, the number of cities, urban-type settlements and rural settlements in RA, RB, RT, Rkh and RS(Ya)

	TP	PD	UP	RP	RPp	UC	US	RS	RSp	RPdistr	UPdistr
r	0.1	0.3	-0.3	0	0.5	-0.2	-0.3	0	0.7*	0.5	0.5

Note. *p<0.05, TP - total population, PD - population density, UP - urban population, RP - rural population, RPp - rural population as a percentage of the total, UC - the number of cities, US - the number of urban settlements, RS - the number of rural settlements, RSp - rural settlements' percentage of the total cities, urban-type settlements and rural settlement, RPdistr - the number of rural population per one rural settlement, UPdistr - the number of urban population per one urban settlement (including cities and urban-type settlements)

the mortality rate can be underestimated by up to 10% [6]. It is likely that the calculation features impact on CC ASMRs — into account the average annual populations of the administrative territories of Russia according to the state statistical reporting are taken for the corresponding year, but for demographic data are taken of 2010. At this point of view, the future All- Russian Population Census - 2020 is very relevant for new researches.

Nevertheless, our results on the association of CCM with the rural indicator are supported by researches conducted in Mexico [11], Australia [13], USA [14] and China [15], have shown higher CCM in the rural areas of these countries.

Conclusion. CCM in the 2007 to 2018 in the republics of the Russia, located in Siberia and inhabited by peoples having a close genetic portrait - RA, RB, RT, RKh, RS(Y), it is closely associated with the rural settlements' distribution. The relationship between CCM and the total number and density of the population, the number of urban and rural population and their ratio, the absolute number of cities, urban-type settlements and rural settlements, the number of rural population per one rural settlement and the number of urban population per one urban settlement (including the number of cities and towns) did not achieve the required significance.

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MEDICAL AND DEMOGRAPHIC SITUATION IN THE REPUBLIC OF SAKHA (YAKUTIA) IN THE STRUCTURE OF THE STRATEGIC TASKS OF THE DEVELOPMENT OF THE RUSSIAN FEDERATION TILL 2024

DOI 10.25789/YMJ.2020.69.12

УДК 614.2(571.56)

The article presents the medical and demographic situation in the Republic Sakha (Yakutia) for the period 2010-2017. The assessment of medical and demographic indicators was carried out on the basis of official data of the Federal State Statistics Service of the Russian Federation (FSSS or Rosstat) and the FSSS Territorial Unit of the Republic Sakha (Yakutia). An attempt was made to predict the possibility of fulfilling indicator values in accordance with the strategic objectives of the development of the Russian Federation until 2024. The authors came to the conclusion that the goals would be achievable, but in case that the rates of reduction of total mortality and infant mortality, as well as an increase in life expectancy in the RS (Ya) will be maintained and even improved.

Keywords: medical and demographic indicators, fertility, mortality, natural population growth, total fertility rate, infant mortality, life expectancy, Republic Sakha (Yakutia).

Introduction. In the Russian Federation sufficient attention is paid to demographic policy. So, already in the preamble of the Presidential Decree "On the national goals and strategic objectives of the development of the Russian Federation until 2024" dated May 7, 2018 No. 204, the need to ensure:

- sustainable natural growth of the population of the Russian Federation;
- increase life expectancy to 78 years (by 2030 – up to 80 years).

And when developing national programs in the areas of demographic development and health care, the following tasks are set to improve the medical and demographic situation in the country:

- an increase in healthy life expectancy (HLE) to 67 years;
- an increase in the total fertility rate (TFR) to 1.7;
- decrease in mortality rates of the working age population to 350 per 100 000 of population; deaths from circulatory system diseases (CSD) up to 450 cases per 100 000 population; mortality from neoplasm's, incl. from malignant, up to 185 cases per 100 000 population; infant mortality (IM) up to 4.5 cases per 1000 born children.

It is clear that this Decree made amendments to the resolution of the Government of the Russian Federation "On approval of the state program of the Russian Federation "Healthcare Development" dated December 26, 2017 No. 1640 (by 2025: increase in life expectancy at birth to 76 years, decrease in the mortality rate of the working age population up to 380 per 100 000 population, reducing mortality from CSD to 500 per 100 000 population).

Research material and methods. The official statistics of the Federal State Statistics Service (FSSS or Rosstat) and the FSSS Territorial Unit of the RS (Y) (Sakha (Yakutia) Stat) for 2005, 2010-2017 [1, 2, 4] were used.

When assessing the levels of various medical and demographic indicators, the percentile method was applied. According to this method, regions with indicators up to the 10th percentile belonged to territories with a low level of a particular indicator, from 10 to 25th percentile - with a level below the average, from 75 to 90th - above the average and over 90th percentiles - with a high level. Obviously, that the regions with indicators ranging from the 25th to the 75th percentile, belonged to the group with average values.

Results and discussion. Let's consider the medical-demographic situation in the Republic Sakha (Yakutia) in 2005, 2000-2017 in a comparative aspect with similar average Russian indicators. First, we compare the birth rate, mortality, natural increase and total fertility rate (TFR) (Fig. 1). It should be immediately emphasized that according to these indicators, Yakutia and in the most difficult 1990-2000s was always among the top 10 territories in the whole country.

It is clear that for all the years under consideration the levels of fertility and natural growth in the RS (Ya) were high, and in terms of mortality - low in a comparative aspect with similar data from all 85 constituent entities of the Russian Federation. In addition, all indicators of our republic were in a comparative aspect better than the average in the Far Eastern Federal District (FEFD). By the end of 2017, according to the specified indicators, Yakutia was also among the top 10 territories.

We see quite good indicators in terms of the total fertility rate (Fig. 2). Recall for comparison the indicators of the TFR in 2002: the Russian Federation - 1.286, RS

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(Y) – 1,847. A slightly different picture is observed when considering the mortality rates of the population at working age and infant mortality (Fig. 3, 4).

It can be seen that the mortality rates of the working-age population in the RS (Ya) are quite comparable with the average Russian data. However, there are years in the IM where our republican data were noticeably worse than in the whole country (2013 and 2016). For the last two indicators, the republic is among the subjects of the federation with average levels of these values.

The life expectancy in RS (Ya) compared to the Russian Federation and the Far Eastern Federal District (Fig. 5) is of some interest.

It can be seen that there were years with the level below the average for life expectancy (both sexes) in 2011 and 2012, and 2010-2012 – on life expectancy among women. Comparison of all indicators of the Republic of Sakha (Yakutia) and the Far Eastern Federal District for all the years under consideration is in favor of our republic, with the exception of infant mortality in 2015-2016.

Next, we conducted a correlation analysis between life expectancy (both sexes) and a number of mortality and fertility rates for 2000-2017 (Table 1). It is quite obvious that in order to achieve the goal of life expectancy, it is necessary to redouble efforts to reduce the mortality rate of the population at all ages, but first of all - the infant and working-age population.

Judging by the data of Rosstat in 2018, the vital statistics in the Russian Federation continue to deteriorate (the birth rate is 10.9, the mortality rate is 12.5, the EP is -1.6). True, the indicator IM slightly improved, which decreased to 5.1 per 1000 live births. However, it can be seen that the task of sustainable natural growth in the population of the Russian Federation, however, and reducing mortality from a number of reasons will be difficult. I want to believe that it is relatively easier to solve the problem of increasing the TFR to 1.7.

As for Yakutia, the mortality rates of CSD and neoplasms currently fit into the indicator values of 2024 (Table 2). At the same time, standardized indicators "paint" a slightly different picture. For example, consider the usual data of Rosstat and standardized mortality rates (SMR) from CSD and from neoplasms, presented in Table 3 [3]. It can be seen that standardization immediately worsens the death rates and ranking places of the republic in comparison with

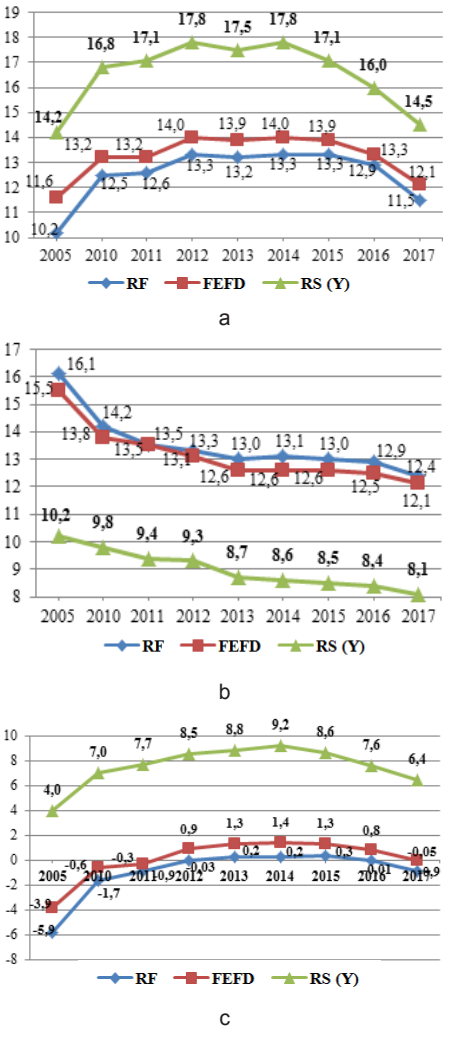


Fig. 1. Dynamics: а – of birth rates, б – of death rates, в – of the coefficients of natural population growth

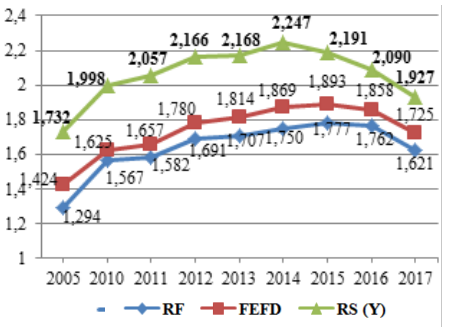


Fig. 2. The dynamics of the total fertility rate

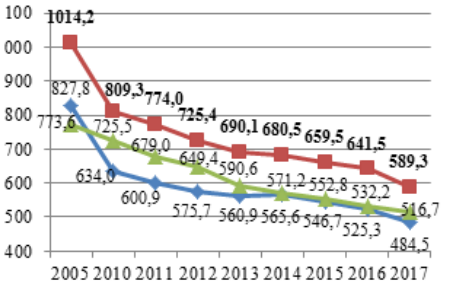


Fig. 3. Dynamics of mortality of the population at working age

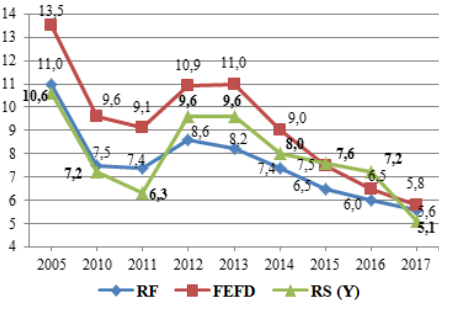


Fig. 4. Dynamics of infant mortality

Table 1

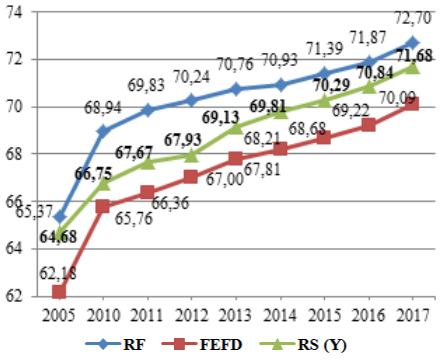
Correlation analysis between life expectancy and mortality and fertility rates (from 2000 to 2017)

Year	Life expectancy	Total mortality	Infant mortality	Mortality of the working population	Fertility
2000	63.66	9.7	17.6	732.9	13.7
2017	71.68	8.1	5.3	516.7	14.4
r		-0.96	-0.83 (-0.94 за 2000-2011 гг.)	-0.97	0.58

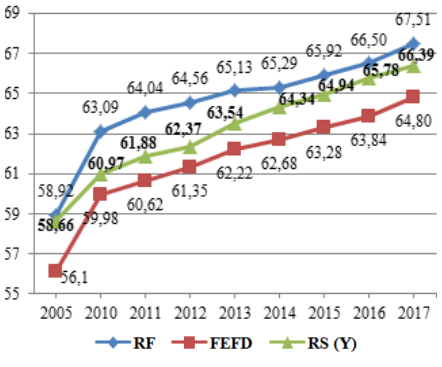
Table 2

Mortality of the population from the main classes of causes of death in the RS (Y) and the Russian Federation in 2017

	Mortality from CSD		Mortality from neoplasms		Mortality from external causes	
	Male.	Female.	Male.	Female.	Male.	Female.
RS (Ya)	423.5	308.2	154.2	119.7	225.5	47.0
RS (Ya) (both sexes)	364.2		136.5		130.0	
RF (both sexes)	587.6		200.6		100.4	



a



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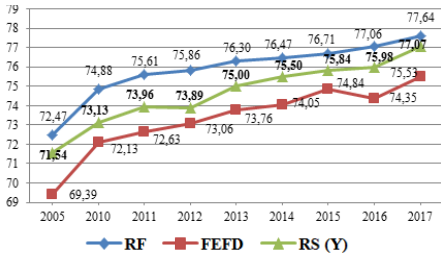

c

Fig. 5. Life expectancy: a- both sex, b – men, c- women

other subjects of the Russian Federation.

It is known that the forecast may not be accurate. So, if even the most important department –- Rosstat – in May 2016 gave a forecast for the TFR (medium variant) for 2017 for 1,786 children per 1 woman, but in reality they received 1,621! However, we tried to do it by HLE, taking into account their growth rates, starting in 2010 (Table 4).

In the Table 5 there are considered comparative indicators of Strategy of social and economic development of the RS (Ya) until 2030 with the definition of the main directions until 2050, approved by the Decree of the Government of the RS (Ya) No. 455 dated December 26, 2016 (Strategy-2030) and the Strategy of Social and Economic Development RS (Y) until 2032 with a target vision until 2050, adopted by Law of RS (Y) No. 45-VI of 12/19/2018 (Strategy-2032).

Table 3

Mortality and standardized death rates from circulatory system diseases and neoplasms in the RS (Y) and the Russian Federation

	Rosstat	SMR from CSD (2016)	Rosstat	SMR from neoplasms
RF	(2010)	495.9	204.4	178.5
RS (Ya)	370.6	485.1	120.3	173.1
Ranked place	4	44	6	27

Table 4

Life expectancy forecast in the Republic of Sakha (Yakutia) by 2024

	2010	2017	2024
Life expectancy (both sexes)	66.75	71.68	76.98
Life expectancy (male)	60.97	66.39	72.30
Life expectancy (female)	73.13	77.07	81.23

Table 5

Indicator values for demography according to the Social and Economic Development Strategies of the Republic of Sakha (Yakutia)

	Strategy -2030	Strategy -2032
Life expectancy	77	80 (78 к 2024 г.)
Total mortality	7.5	7.0* (7.0 к 2024 г.)
Infant mortality	4.4	3.7 (4.5 к 2024 г.)
Total fertility rate	2.6	2.3 (2.07 к 2024 г.)

* standardized indicator

Conclusion. Thus, we reviewed the medical and demographic situation in the RS (Ya) in dynamics and evaluated the possibility of achieving indicator values in 2024. We conclude that they are generally achievable, but on the condition that the rates of decline in the overall mortality of the population and the IM, as well as the increase in life expectancy in the RS (Ya), are maintained and even improved. The effectiveness of measures to reduce the mortality rate of the population of the republic can also be assessed by the results of the implementation of the "Concept for reducing the mortality rate of the population of the Republic of Sakha (Yakutia) from preventable causes and cancer for the period up to 2025".

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

G.A. Usenko, D.V. Vasendin, A.G. Usenko

GAMMA-BACKGROUND ENVIRONMENT DURING MAGNETIC STORMS AND THE CONTENT OF HIGH DENSITY LIPOPROTEIN IN PATIENTS WITH ARTERIAL HYPERTENSION DEPENDING ON THE VARIANT OF ANTIHYPERTENSIVE THERAPY

DOI 10.25789/YMJ.2020.69.13

УДК 550.382.3:612.014.4

Arterial hypertension and coronary heart disease continue to lead in the structure of cardiovascular diseases. In the years of high solar activity and the period of magnetic storms in a healthy and sick body, functional changes occur, which are associated with the exacerbation of cardiovascular diseases. The objective of the study was to establish the relationship between the dynamics of γ-background of the environment in the period of magnetic storms and the blood content of total cholesterol and high-density lipoproteins in patients with hypertension with different temperament and anxiety, taking options for antihypertensive therapy: targeted and not targeted (empirical) on the blockade of psychosomatic characteristics of patients, and to determine the most effective treatment option. The prevailing temperament – choleric, sanguine, phlegmatic and melancholic – was determined using the psychological test John Ayzenk and A. Belov, the presence and severity of depression – psychological tests of Je. Akhmetzhanov. The gamma background of the medium was measured using the dosimeter «Master». It was established that the content of total cholesterol in the blood increased, and high – density lipoproteins decreased in a series of temperamental: choleric – sanguine – phlegmatic–melancholic. During the period of magnetic storms with increased γ-background power (within the regional norm) in healthy individuals and patients with hypertension on the background of any variant of antihypertensive therapy, total cholesterol in the blood increased: a day before the magnetic storm in cholerics, on the 1st day of the magnetic storm in sanguine, and phlegmatic and melancholic on the 2nd day from the beginning of the magnetic storm. The peculiarity of the reaction is that during the magnetic storm, associated with an increase in the γ-background of the medium, the content of high – density lipoproteins in patients with choleric and sanguine against the background of the empirical version of antihypertensive therapy did not change, and in phlegmatic and melancholic patients decreased, while against the background of a targeted treatment option in choleric and sanguine it increased, and in groups of phlegmatic and melancholic patients-did not change, as in healthy individuals of the corresponding temperament. Compared with empirical antihypertensive therapy, against the background of a targeted treatment option, the period of returning the content of indicators to the initial values, as well as their level in the blood and the degree of severity of the reaction (according to the correlation analysis) were the same as in healthy individuals of the corresponding temperament, which indicates the advantage of the treatment option targeted at relieving the psychosomatic features of the patient.

Keywords: arterial hypertension, temperament, magnetic storms, γ-background, lipids, therapy.

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Introduction. Arterial hypertension (AH) and atherosclerosis remain one of those diseases, complications of which lead to disability and (or) death of persons of working age [5, 10, 13, 14]. Intense life activity, occurring in a rapidly changing meteorological factors, combined with an increase in blood lipid content, changes in the flow of the most important physiological processes in the body [4, 7, 8, 11, 16, 17]. The increase in total cholesterol (OH) in blood with a decrease in high-density lipoproteins (HDL) may be associated with the debut and (or) development of atherosclerosis [8]. However, no studies have been found on the relationship between gamma (γ)-background of the environment in the period of magnetic storms (MS) and the content of OH, as well as HDL in the blood of patients with AH with different temperament.

Objective: to establish the relationship between the dynamics of γ-background of the environment in the period of MB and the blood content of OH and HDL in patients with AH-II (HD-II) with different temperament and anxiety, taking different options of antihypertensive therapy (AHT): targeted (TAHT) and not targeted (empirical – EAHT) on the blockade of psychosomatic characteristics of the body of patients.

Material and methods. In the period from 1998 to 2017, 848 engineering and technical workers of men aged 44-62 years (on average 54±1.8 years) were examined in the polyclinic, in whom hypertension in stage II (HD-II, degree 2, risk 3) was established in the cardiology Department. The disease duration is 11.6±1.4 years on average. The presence of essential hypertension was established according to the criteria set out in Russian recommendations [13, 14]. The control was a group of 422 healthy men, compatible with the main anthropo-social indicators. The prevailing temperament – choleric (Ch), sanguine (Sg), phlegmatic (Ph) and melancholic (M) – was determined using the psychological test of John Ayzenk in A. Belov's modification [15] by 3-fold testing before treatment (0)

and after 3, 6, 9 and 12 months of AHT. The presence and severity of depression were determined by the method of E.R. Akhmetzhanov [2]. The value of reactive and personal anxiety was determined by the method described in Questions of psychology [18]. To low anxiety (LA) defined as those who scored 32,0±0,6, and highanxiety (HA) – between 42.8±0.4 points and above. The serum OH content was determined by enzyme methods using proprietary sets «Centrifugal-600», and the cholesterol content of high-density lipoproteins (HDL) was determined after preliminary deposition of the total fraction of low-density lipoproteins (LDL) and very low-density lipoproteins, as well as triglycerides on the autoanalyzer «Technicon-AAII» [6].

Gamma (γ)-background (μr/h) of the medium was measured at the workplaces of the surveyed persons (dosimeter «Master») from 8.00 to 10.00 daily (up to 20 measurements) and compared with the data of the Department of ionospheric-magnetic prediction of the West Siberian Department of Hydrometeorology and environmental monitoring (Novosibirsk). The variations of γ-background power values from 1998 to 2017 did not exceed the normal regional values.

The method of superimposed epochs [9] was used, which takes into account the days before the magnetic storm (-), in the period (0) and after the beginning of MS (+): -7 -6 -5 -4 -3 -2 -1 - 0 - +1 +2 +3 +4 +5 +6- +7 accordingly. The results were processed by the method of variation statistics (M±m) using the standard software package "Statistica 11.0" and parametric t–student test, as well as the calculation of the correlation coefficient (r) Pearson. Values at $p<0.05$ were considered statistically significant. The study was carried out in compliance with the provisions of the Helsinki examination and treatment of people and approved by the ethics Committee of the Novosibirsk state medical University of 20.11.2009, Protocol No. 18.

Features of antihypertensive therapy. According to the method of depression degree [2], a mild degree was noted only in highly anxious phlegmatics (HA/Ph) and melancholics (HA/M). At the conclusion of the psycho in the inpatient treatment they need. Perfectionism choleric (HA/Ch) and sanguine (HA/Sg) received anxiolytic that 96% sibazon 2.5 mg in the morning and at night and HA/fPhand HA/M - antidepressant – 96% coaxil 12.5 mg in the morning and at night (in 4% of the zoloft at 25 mg /day), except for LA-entities [1, 5, 7]. Studies conducted by us using the criteria specified in [3] showed predominant prevalence of sympathetic division (SNS) of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal system (HPAS, cortisol) in Ch and Sg, compared with Ph and M patients, and parasympathetic (PSNS) Department of ANS with predominant activity of renin-angiotensin-aldosterone system (RAAS, aldosterone) in Ph and M, compared to Ch and Sg. Based on the differences above, AHT included drugs that have been approved by order No. 254 of the health Ministry of Russia dated 22.11.2004 for the treatment of hypertension [12]: beta-adrenoblockers (β-AB), ACI inhibitors (aceis), diuretics (hydrochlorothiazide), cardiomagnyl. From β-AB patients in 96% received metoprolol 200 mg / day (in 4% of cases its analogues), and NT/X and NT/S 100 mg/day.) and hydrochlorothiazide: HA/Ch and HA/Sg 25 mg/day, and LA 12.5 mg / day. From ACI, patients in 96% of cases took enalapril 20 mg/day (in 4% of cases its analogues) + veroshpiron 100-200mg/day (in 75% of cases), less often (in 25% of cases) hydrochlorothiazide 25 mg/day, because the potassium content in the blood was lower than in Ch and Sg [7, 12]. LA/Ph LA/M were administered enalapril 10 mg/day + hydrochlorothiazide (hydrochlorothiazide) - 12.5 mg/day. All patients received Panangin 2 tab./day and cardiomagnyl on 1 tab./ day. Since Ch and patients differed from the Ph and M patients with a predominance of the sympathetic division of the ANS, as well as the predominant activity of the hypothalamic-pituitary-adrenal system (HPAS for cortisol), they were prescribed in 96% of cases β-AB + hydrochlorothiazide. Patients Ph and M differed from Ch and Sg patients by predominance of mainly parasympathetic division of ANS and activity of renin-angiotensin-aldosterone system (RAAS by aldosterone). In this regard, the latter was appointed in 96% of cases of ACEI + veroshpiron. All other treatment options are called empirical.

The results of the study and their discussion. The data obtained during the study period showed a significant increase in blood levels of OH and a decrease in HDL in healthy and patients in the temperamental series of HA(LA) Ch–Sg–Ph–M (table. 1, 2). In HA persons, the content of OH was significantly higher, and HDL was lower than in lowanxiety persons of the corresponding temperament, and in HA(LA) healthy OH content was lower, and HDL was higher than in HA(LA) persons of the corresponding temperament. Thus, HA (LA) melancholic the OH content was the highest, and HA(-LA) the choleric is the lowest. On the contrary, the contents of HDL have HA(LA) melancholic was the lowest, and HA(LA) the choleric is the highest from all investigated individuals. the differences can be linked to the prevalence of SNS activity-division of the ANS and HPAS (cortisol) HA(LA) the choleric and sanguine, compared to the HA(LA) phlegmatic and melancholic. The latter, in contrast to Ch and Sg, dominated the activity of the RAAS (aldosterone) and PSNS-section of VNS (index Martinez Felipe and initial vegetative tonus).

The study showed a significant increase in the γ-background of the environment (within the limits of the regional norm) for the day (-1) before the MS, and a return to the initial values was observed on (+4) day from the beginning of the magnetic storm (Table 1- 2). It is most likely that this phenomenon is due to an increase in the concentration of radioactive radon gas, as indicated in [4, 19]. The study showed a significantly higher content of OH in Ch and Sg patients, taking the option of EAHT, compared with the same Ch and Sg, taking the option of TAHT, and, on all days of the method of superimposed eras (Table 1).

In the period of MS in healthy individuals and in patients (against the background of both variants of AHT), an increase in the content of OH in the blood was established (table. 1). In groups Ch, a significant increase in the content of OH was noted one day before the onset of MS, in groups Sg – on the first day, and in groups Ph and M (healthy and patients), an increase in the content of OH was noted on the second day of MS. However, the return of the indicator values to the original (up to MS) against the background of EAHT in group Ch was noted at +3, in group Sg at +4, and in groups Ph and M – at +5 days from the beginning of MS (table.1). On the background of TAHT return to the original values observed on the day before and on the same days as that of healthy persons of corresponding temperament, namely: Ch–Sg–Ph–M: +1 - +2 - +3 - +4 respectively.

In the present study, γ-background variations did not exceed the limit of normal values. However, the influence of γ-background under the conditions of the earth's perturbed magnetic field probably could not but influence the shift of homeostasis towards acidosis of the medium due to the formation of reactive oxygen species [19]. In this regard, the correlation analysis is justified. The data of correlation analysis between the values of the γ-background and content of OH in patients on days the method of

Table 1

Dynamics of γ-background (ur/h) environment, and a cholesterol (mmol/l) in the serum of individuals HA in the background, EAHT (E) and TAHT (T) in the days of magnetic storms during the study period from 1998

Days		-7 - -6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	Всего
γ-background		8.51-8.50±0.01	8.46±0.01	8.58±0.01	8.41±0.01	8.45±0.01	8.70±0.01	8.78±0.01	8.80±0.01	8.65±0.01	8.70± 0.01	8.59±0.01	8.47±0.01	8.62±0.01	8.49±0.01	8.58±0.007
Choleric	E	5.60-5.64±0.04 44-45	5.66±0.04 44	5.60±0.04 43	5.70±0.04 48	5.70±0.04 43	6.40±0.04 49	6.80±0.04 48	6.60±0.04 46	6.67±0.04 47	5.33±0.04 44	5.31±0.04 43	5.60±0.03 44	5.21±0.04 43	5.70±0.04 45	5.83±0.01 676
	T	5.00-5.02±0.04 44 - 43	5.04±0.05 44	5.20±0.05 46	5.10±0.04 44	5.00±0.03 45	5.60±0.03 44	5.80±0.04 46	5.90±0.05 44	5.06±0.04 44	4.55±0.04 48	4.50±0.04 43	5.11±0.03 46	4.37±0.04 43	5.12±0.04 44	5.09±0.02 668
	H	4.99- 5.00±0.05 45 - 44	5.01±0.04 45	4.70±0.05 44	5.10±0.04 46	5.00±0.04 44	5.70±0.03 46	5.80±0.03 44	5.85±0.04 45	5.50±0.03 44	4.62±0.04 46	4.57±0.04 44	5.40±0.04 44	4.40±0.04 46	5.20±0.04 46	5.12±0.02 673
Sanguine	E	6.20-6.22±0.04 46 - 46	6.24±0.03 44	6.20±0.04 47	6.30±0.03 44	6.20±0.04 43	6.10±0.04 48	7.90±0.04 49	8.00±0.03 44	8.10±0.04 43	6.87±0.03 45	6.36±0.03 43	6.40±0.04 46	6.01±0.04 47	6.30±0.03 47	6.63±0.01 682
	T	5.70-5.72±0.03 44 - 46	5.74±0.03 47	5.60±0.04 43	5.80±0.04 44	5.60±0.03 43	5.80±0.03 47	6.30±0.04 48	6.50±0.03 50	6.60±0.04 47	5.36±0.04 44	5.70±0.04 48	5.80±0.03 48	5.41±0.04 45	5.60±0.04 46	5.78±0.02 690
	H	5.55-5.56±0.03 48 - 45	5.78±0.04 44	5.40±0.04 48	5.70±0.05 44	5.40±0.04 44	5.60±0.04 45	6.20±0.04 48	6.30±0.06 46	6.45±0.06 44	5.21±0.04 46	7.09±0.04 48	5.70±0.05 46	5.22±0.05 46	5.70±0.04 49	5.70±0.01 691
Phlegmatic	E	6.78-6.70±0.04 44 - 46	6.57±0.03 45	6.80±0.03 47	6.60±0.04 48	6.57±0.04 48	6.79±0.04 49	6.77±0.04 52	9.00±0.05 54	7.79±0.04 47	8.46±0.05 46	6.30±0.05 49	6.41±0.06 48	7.00±0.05 44	6.40±0.03 48	7.05±0.02 715
	T	5.90-6.00±0.04 44 - 43	6.03±0.03 44	6.10±0.04 46	6.20±0.005 44	6.00±0.05 46	5.90±0.04 46	6.20±0.06 48	6.70±0.06 47	6.80±0.06 49	6.60±0.07 44	6.20±0.07 43	6.40±0.06 44	6.20±0.04 43	6.10±0.04 48	6.23±0.02 679
	H	5.87-5.99±0.04 49 - 49	5.89±0.06 44	6.10±0.06 46	6.00±0.06 44	5.90±0.06 44	5.70±0.04 45	6.00±0.05 49	6.50±0.05 55	6.80±0.05 49	6.60±0.06 46	6.60±0.06 44	6.00±0.06 49	5.80±0.04 48	5.80±0.04 48	6.18±0.02 708
Melancholic	E	6.80-6.78±0.04 44 - 45	6.77±0.03 44	6.83±0.04 43	6.69±0.04 44	6.71±0.04 43	6.82±0.03 44	7.00±0.05 47	8.76±0.04 44	7.84±0.05 43	8.21±0.04 44	8.21±0.04 43	6.74±0.05 44	7.80±0.04 43	6.69±0.04 46	7.18±0.02 661
	T	6.20-6.30±0.04 44 - 47	6.15±0.03 47	6.30±0.04 48	6.00±0.05 45	6.30±0.05 48	6.30±0.04 45	6.25±0.06 48	6.70±0.06 45	6.60±0.05 46	6.00±0.05 44	6.00±0.05 43	6.13±0.05 44	6.46±0.04 46	6.10±0.04 44	6.25±0.02 684
	H	6.10-6.12±0.03 46 - 45	6.14±0.04 46	6.01±0.06 46	6.10±0.07 44	6.20±0.06 44	6.10±0.03 45	6.20±0.05 48	6.60±0.05 49	6.70±0.04 44	6.70±0.03 46	6.70±0.03 47	6.30±0.04 46	6.06±0.04 46	6.20±0.04 44	6.27±0.02 686

Note. In the tables 1-2 H-healthy; the denominator indicates the number of examined.

superimposed epochs showed the presence of significant direct and high (on the background of EAHT) and average (in the background, TAHT) the degree of significance of the relationship. The degree of importance of the background of TAHT coincided with that of healthy persons of corresponding temperament (table. 3). In contrast, EAHT, equality in content, the timing of the return to the original values, and the degree correlations on the background of TAHT with those in healthy persons of corresponding temperament indicates higher efficiency version of TAHT.

In contrast to the dynamics of changes in the content of OH in the period of MS in groups of patients Ch and Sg, taking the option of EAHT, a significant change in HDL content in the blood was not found, and against the background of TAHT, a significant increase in HDL content was found. In the Ph and M groups of patients who took the EAHT variant in the specified period, we found a decrease in HDL in the blood, and in the Ph and M groups who took the TAHT variant, it did not change significantly (Table 2).

Correlation analysis conducted between the dynamics of γ-background in the MS period and HDL content in the blood showed the presence of a significant and weak degree of communication in groups Ch and Sg, taking the option of EAHT. In contrast, in the groups Ch and taking TAHT received authentic video of a high degree of significance of correlation relationship, indicating that the increase in the content of HDL in the blood. The same relationship was obtained in groups Ch and Sg of healthy individuals (Table 3). In the Ph and M groups of patients receiving EAHT, the correlation between the studied parameters was significant inverse and high degree of significance, indicating a decrease in HDL in the blood. On the contrary, against the background of TAHT in the same groups, the relationship was the same direction, but very weak (table. 2). As stated above, by studying the variants of AHT, the authors found that in contrast to EAHT, TAHT essentially brings the value of the indicator and the degree of severity of the reaction of the body during MS (according to the correlation analysis) to those of the HA(LA) healthy persons of corresponding temperament.

Thus, the increase in the power of γ-background of the medium during the day before and during the MS period under the conditions of the earth's perturbed magnetic field was combined with an increase in the blood OH. The increase in the content of OH and decrease in HDL with simultaneous increase in intravas-

Table 2

Dynamics of γ-background (ur/h) environment and content in HDL (mmol/l) in the serum of individuals HA in the background, EAHT (E) and TAHT(T) in the days of magnetic storms during the study period from с 1998 по 2017 г.

Days		-7 - -6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	Всего
γ-background		8.51-8.50±0.01	8.46±0.01	8.58±0.01	8.41±0.01	8.45±0.01	8.70±0.01	8.78±0.01	8.80±0.01	8.65±0.01	8.70± 0.01	8.59±0.01	8.47±0.01	8.62±0.01	8.49±0.01	8.58±0.007
Choleric	E	1.54-1.58±0.03 44 - 45	1.54±0.03 44	1.60±0.03 43	1.52±0.03 48	1.54±0.03 43	1.53±0.02 49	1.60±0.02 48	1.59±0.02 46	1.50±0.02 47	1.58±0.03 44	1.66±0.04 43	1.58±0.03 44	1.53±0.03 43	1.60±0.04 45	1.57±0.001 676
	T	1.76-1.78±0.03 44 - 43	1.80±0.03 44	1.72±0.04 46	1.81±0.03 44	1.82±0.03 45	1.89±0.02 44	1.86±0.02 46	1.89±0.02 44	1.88±0.03 44	1.75±0.06 48	1.80±0.03 43	1.81±0.03 46	1.73±0.03 43	1.83±0.02 44	1.81±0.003 668
	H	1.78- 1.74±0.04 45 - 44	1.79±0.04 45	1.68±0.04 44	1.80±0.03 46	1.81±0.03 44	1.88±0.02 46	1.89 ±0.02 44	1.87±0.02 45	1.90±0.02 44	1.74±0.03 46	1.78±0.03 44	1.83±0.04 44	1.73±0.04 46	1.88±0.03 46	1.81±0.003 673
Sanguine	E	1.47-1.49±0.04 46 - 46	1.50±0.04 44	1.47±0.04 47	1.49±0.05 44	1.48±0.05 43	1.50±0.05 48	1.49±0.03 49	1.50±0.04 44	1.49±0.04 43	1.50±0.04 45	1.51±0.03 43	1.50±0.03 46	1.48±0.03 47	1.47±0.03 47	1.49±0.003 682
	T	1.52-1.50±0.04 44 - 46	1.58±0.04 47	1.56±0.03 43	1.57±0.03 44	1.52±0.04 43	1.54±0.03 45	1.65±0.03 48	1.67±0.04 44	1.65±0.03 46	1.58±0.03 44	1.49±0.04 46	1.59±0.03 48	1.48±0.03 45	1.58±0.03 46	1.57±0.003 690
	H	1.54-1.53±0.03 48 - 45	1.55±0.04 44	1.58±0.04 48	1.57±0.03 44	1.57±0.03 44	1.50±0.04 45	1.63±0.02 48	1.68±0.02 46	1.62±0.02 44	1.60±0.04 46	1.55±0.03 48	1.58±0.03 46	1.50±0.03 46	1.58±0.03 49	1.57±0.002 691
Phlegmatic	E	1.06-1.09±0.03 44 - 46	1.17±0.03 45	1.07±0.03 47	1.15±0.04 48	1.17±0.03 48	1.08±0.04 49	1.07±0.03 52	0.80±0.03 54	0.76±0.02 47	0.78±0.02 46	0.86±0.02 49	0.90±0.03 48	1.06±0.04 44	1.16±0.04 48	1.01±0.005 715
	T	1.33-1.30±0.04 44 - 43	1.27±0.03 44	1.32±0.04 46	1.32±0.04 44	1.34±0.03 46	1.33±0.03 46	1.30±0.03 48	1.27±0.03 47	1.26±0.03 49	1.27±0.04 44	1.30±0.04 43	1.42±0.03 44	1.49±0.04 43	1.32±0.03 48	1.25±0.004 679
	H	1.30-1.34±0.03 49 - 49	1.33±0.03 44	1.39±0.03 46	1.37±0.03 44	1.39±0.03 44	1.35±0.04 45	1.33±0.04 49	1.29±0.03 55	1.27±0.02 49	1.29±0.03 46	1.31±0.03 44	1.29±0.02 49	1.42±0.04 48	1.31±0.03 48	1.27±0.004 708
Melancholic	E	0.90-0.92±0.03 44 - 45	0.94±0.03 44	0.92±0.03 43	0.91±0.02 44	0.92±0.03 43	0.87±0.03 44	0.86±0.02 47	0.65±0.02 44	0.63±0.02 43	0.63±0.02 44	0.84±0.04 43	0.84±0.03 44	0.73±0.04 43	0.90±0.04 46	0.82±0.003 661
	T	1.23-1.20±0.03 44 - 47	1.21±0.03 47	1.20±0.04 48	1.24±0.03 45	1.17±0.03 48	1.24±0.02 45	1.22±0.02 48	1.17±0.03 45	1.20±0.03 46	1.22±0.02 44	1.18±0.02 43	1.24±0.03 44	1.20±0.04 46	1.23±0.03 44	1.21±0.005 684
	H	1.18-1.20±0.02 46 - 45	1.18±0.02 46	1.20±0.03 46	1.20±0.03 44	1.21±0.06 44	1.20±0.03 45	1.17±0.03 48	1.18±0.02 49	1.18±0.02 44	1.20±0.02 46	1.21±0.02 47	1.26±0.04 46	1.29±0.04 46	1.20±0.04 44	1.20±0.004 686

cular hemolysis of erythrocytes (extrapolate – and other cells of the body) in HA(LA) healthy individuals during the MS period was noted by us in an early study [8]. It is known that cholesterol is used as a component for the construction and restoration of cell membranes, and HDL prevent (extract) excessive accumulation of cholesterol in cells. Hence, it can be assumed that due to the damage and (or) destruction of cell membranes in the MS period, an increase in the content of OH in the blood is a consequence of the reaction of the body aimed at increasing the resistance of cell membranes to damaging effects, and OH here is the initial structural material. But sympathotonics Ch and on the background of EAHT the content of HDL did not change, and in the background, TAHT as in healthy individuals, increased. Perhaps it is a feature of the organism's reaction sympathotonic aimed at removing excess OH of blood on the background of TAHT can be regarded as a manifestation of «antiatherogenic» response. Indeed, groups Ph and M of patients with AH, especially HA, are at risk for atherosclerosis and complications [7, 8]. They have in the background holding EAHT the content of HDL declined, pointed to the change in the intensity of lipolytic processes. And only against the background of TAHT, the content of HDL practically did not change, as in healthy Ph and M individuals, which indicates in favor of the effectiveness of TAHT.

Conclusion. 1. In the period of MS with an increase in γ-background power (within the limits of the regional norm) the content of total cholesterol in the blood increased, and HDL decreased in a consistent temperamental series from choleric to melancholic: HA(-LA) Ch–Sg–Ph–M.

2. In healthy individuals and patients with hypertension, against the background of both variants of AHT, the blood content of total cholesterol increased: a day before MS in choleric, on day 1 MS in sanguine, and phlegmatic and melancholic on day 2 from the beginning of the magnetic storm.

3. The peculiarity of the body reaction is that during the MS period the HDL content in Ch and Sg patients against the background of

Table 3

Correlation coefficients between the values of γ-background, serum cholesterol and HDL in the blood before, during and after magnetic storms in high and low anxiety patients with AH-II with different temperament against the background of empirical (E) and targeted (T) AHT during the study period from 1998 to 2017.

	Cholesterol, mmol/l				HDL, mmol/l			
	Highanxiety		Lowanxiety		Highanxiety		Lowanxiety	
	patient	health	patient	health	patient	health	patient	health
ChE	+0.588± 0.02	+0.396± 0.01	+0.451± 0.01	+0.255± 0.01	+0.203± 0.02	+0.483± 0.02	+0.476± 0.02	+0.543± 0.02
ChT	+0.403± 0.01		+0.231± 0.01		+0.486± 0.02		+0.558± 0.02	
SgE	+0.682± 0.01	+0.386± 0.01	+0.458± 0.01	+0.258± 0.01	+0.261± 0.02	+0.449± 0.03	+0.478± 0.03	+0.569± 0.03
SgT	+0.439± 0.03		+0.266± 0.01		+0.470± 0.02		+0.572± 0.03	
PhE	+0.693± 0.01	+0.451± 0.02	+0.476± 0.01	+0.267± 0.01	-0.562± 0.03	-0.248± 0.03	-0.438± 0.02	-0.235± 0.01
PhT	+0.479± 0.03		+0.260± 0.01		-0.229± 0.03		-0.246± 0.02	
ME	+0.709± 0.01	+0.459± 0.01	+0.481± 0.01	+0.277± 0.01	-0.658± 0.03	-0.222± 0.02	-0.349± 0.02	-0.252± 0.02
MT	+0.476± 0.02		+0.273± 0.01		-0.214± 0.03		-0.228± 0.02	

EAHT did not change, and in Ph and M decreased, while against the background of TAHT in Ch and Sg it increased, and in groups Ph and M – did not change, as in healthy individuals of the corresponding temperament.

4. Against the background of the TAHT, the period of return of the content of the studied parameters to the initial values, as well as their level in the blood and the degree of severity of the reaction (according to the correlation analysis) were the same as in healthy individuals of the corresponding temperament, which indicates a more effective option of antihypertensive therapy aimed at relieving the features of the psychosomatic status of patients in comparison with EAHT.

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TOPICAL ISSUE

DOI 10.25789/YMJ.2020.69.14

УДК 613.84(571.56)

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Physiological and biochemical aspects of smoking in Yakutia

The article reports the influence of tobacco smoking on the indices of pulmonary function testing and on the biochemical indices (including the some indices of antioxidant system) of the organism of the inhabitants of Yakutsk. The indices of pulmonary function testing (PFT) were determined in accordance with the recommendations of the Russian society of pulmonologists (M., 2003, 2016). The intensity of the peroxide lipids oxidation (PLO) was determined on the concentration in the blood of malonic dialdehyde (MDA). The state of the antioxidant protection of organism was evaluated according to the activity of superoxidedismutase (SOD), catalase and total antioxidant activity of the blood plasma. The concentration of uric acid, total bilirubin and cholesterol in the blood serum was determined on the automatic biochemical analyzer Cobas mira plus of the firm La Roche.

Keywords: smoking tobacco, the chronic obstructive diseases of lungs (COPD), the pulmonary function testing (PFT), malonic dialdehyde (MDA), superoxidedismutase (SODAS), catalase.

Introduction. The respiratory system, being an open one, is one of the first to protect the body from the adverse effects of environmental factors. Smoking as an aggressive risk factor contributes to the development of bronchopulmonary, oncological and cardiovascular diseases. Tobacco smoke is one of the most aggressive smokes, so-termed "pro-oxidant pollutants". It contains a number of chemically active components: nicotine, formaldehyde, benzopyrenes, nitrogen oxide, cadmium, urethane, vinyl chloride, etc. All these components have a direct effect not only on the surface layer of the bronchoalveolar secretion and epithelial cells of lungs, but also on the internal milieu of the body, causing an increase of free-radical oxidation [11, 15, 17, 25].

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It is known that the death rate from lung cancer among smokers is 20 times higher than among non-smokers. Smokers are 13 times more likely to suffer from angina and 10 times more likely to have peptic ulcers than non-smokers. Alveolar macrophages of smoker uptake insoluble particles of tobacco smoke and undergo characteristic morphological changes, which allow them to be classified as biomarkers of a smoker. Another marker is an increased blood nicotine level. Nicotine is a thrombogenic factor that causes damage to the endothelial cells of both large and small vessels. The chemical reaction of nicotine and nitrogen oxide leads to the formation of N-nitrosamines, which have significant carcinogenic properties. Urethane, benzopyrenes, and vinyl chloride are also classified as carcinogens [23]. A smoker has a high percentage of hemoglobin associated with carbon monoxide (CO). With the formation of the CO-hemoglobin complex, the main function of hemoglobin, the transport of oxygen to the tissues, is disrupted.

In the North, the cold factor plays a significant role in the impact on the bronchopulmonary system along with smoking. Inhalation of cold air often causes deterioration of bronchial patency even in healthy people [3]. Data on the effect of smoking on the bronchopulmonary system under the Far North conditions are available only in a few works [8].

The purpose of the research: assessment of the effect of tobacco smoking on the function of external respiration and biochemical indices that characterize the state of antioxidant defense in men in Yakutsk.

Research material and methods: We examined a total of 237 men aged 24 to 50 years. The control group consisted of 140 apparently healthy non-smoking men, mean age 45.28±2.43 (Me-45). Among them, there were 70 men of Yakut nationality mean age 45.71±2.32 (Me-44), and 70 men of Russian nationality with a period of residence in the North of at least five years, without a history of lung diseases mean age 44.86±2.21 (Me-44). There were 97 men with smoking history, mean age 46.78±3.56 (Me-46). Indices of the pulmonary function were estimated by spirometry. The evaluation of the results of pulmonary function, pneumotachometry and respiratory quotient was carried out in accordance with the recommendations of the Russian Respiratory Society [6, 14]. The concentration of malondialdehyde (MDA) in blood serum was estimated by colorimetric method using thiobarbituric acid [28]. The total antioxidant activity of blood plasma was determined using G.I. Klebanov's method [9]. Chemiluminescent methods for estimating the activity of superoxide dismutase (SOD) and catalase were used to evaluate the enzymatic system of the body's antioxidant defense [13]. The content of uric acid, total bilirubin and cholesterol in the blood serum

was estimated using an automatic biochemistry analyzer Cobas Mira Plus, manufactured by La Roche.

The results were processed using the SPSS 8.0 computer software for Windows 95. The data in the tables are presented as M±m, where M is the average, and m is the error of the average. The statistical significance was evaluated using Student's t-Test.

Results and discussion. According to the obtained data, the actual vital capacity (VC) in men of Russian nationality slightly exceeded the upper limit of the norm (85-90%) and was statistically significantly higher than in men of Yakut nationality. Tiffeneau index (the ratio of the volume of forced expiration to vital capacity, i.e. FEV1/FVC) and maximal voluntary ventilation (MVV) were also higher in Russians, and the respiratory reserve was lower than in Yakuts ($p<0.05$). At the same time, the MVV in the indigenous population of the Far North corresponded to the lower limits of the European norm, and the Tiffeneau index even slightly exceeded the generally accepted standards, indicating that there was no disruption of bronchial patency or changes in the elasticity of the pulmonary tissue (Table 1).

The analysis of the PFT results in the two main ethnic groups of the population of Yakutsk indicates the presence of morphological and functional differences in the pulmonary tissue. Differences are associated with maintaining effective respiratory airway in the conditions of permafrost. Thus, the increasement of MV and breathing reserve in Yakuts, compared to the Russians, is related to the reduction in respiratory rate. Pneumotachometry data also confirm this fact. With such pulmonary mechanics' indices, the residual air increases and the contact time of cold air with the respiratory tract reduces. Higher values of the VC, MVV, and Tiffeneau index in men of Russian nationality may be related to an increase in the pulmonary alveolar surface area during the process of adapting to the conditions of the Far North. Literature has evidence that the morphometry of the pulmonary alveolar surface area of the northerners revealed a significant increase in comparison with residents living in Central Russia. The main reason for increasing the alveoli area under the influence of cold climate is their hypertrophy and additional disclosure of previously non-functioning alveoli. According to some researchers, the morphological and functional changes related to physiological defense reactions in response to the low temperature of the inhaled air are developing in two directions. The first direction relates to the compensation of alveolar hypoxia and provides a significant increase in the respiratory lining of the number of type II alveoli. They produce surfactant, which enhances the airiness of the pulmonary tissue. The second direction is related to the development of hypervolemia in response to the decrease of the oxygen partial pressure in alveoli. It is provided by an increased diameter of capillary, size of capillary loops, and a decreased thickness of the endothelium [7, 16].

Comparative analysis of the data in table 1 shows that the surveyed apparently healthy men of Yakut nationality were found to have more effective respiratory airway, despite the decrease in VC, MVV and Tiffeneau index (compared to men of Russian nationality). That is since RQ in Yakut men was higher than in Russians. A. P. Milovanov's fundamental research (1981) showed that the Northern aboriginal people's essential adaptive traits of aero-hematic barrier to the effects of low temperatures is the increasement of the respiratory airway's working zone. Another adaptive trait is structural features of the pulmonary vascular system. In particular, the expansion of pulmonary circulation's arteries [7]. Our results do not contradict the literature data [3, 5, 7, 15, 16].

We analyzed the indices of pulmonary function in 97 men who abused smoking and had smoking history. Many of those subjects started smoking at the age of 16 (30%), and the majority started smoking from 18-19 years old (70%), so people in their 50s had about 30 years of smoking history. All the subjects considered themselves apparently healthy, although in the mornings they were disturbed by coughing with a slight sputum discharge.

According to the obtained data, grouped by smoking history, indices of pulmonary ventilatory function in smokers were significantly reduced (Table 2). Thus, the vital capacity (VC) in young smokers (5 years of smoking history) was statistically significantly lower ($P<0.05$), compared to the control group of healthy non-smokers. With an increase in smoking history (10 years or more), the VC decreased even more, while the average value of this indicator was 84.4±6.2 % ($P<0.05$). The values of the Tiffeneau index, MVV, and FEV1 also decreased with increasing smoking history. Men with smoking history of more than 10 years had worsened indices of pneumotachometry: up to 2.4±0.5 L/sec on an inhale compared to the control group of 3.8±0.1 L/sec ($P<0.001$), on exhalation up to 3.3±0.8 l/sec with the value of the indicator in the control group of 4.3±0.1 l/sec ($P<0.001$). It should be emphasized that in this group of smokers, all indices were significantly reduced. We examined smokers with a smoking history of 5 to 10 years, and they can be considered patients with stage 1 (mild severity) chronic obstructive pulmonary disease (COPD). At this stage of the disease, according to the classification adopted by the Russian Respiratory Society, FEV1 varies from 70% to 80% of the required value. Smokers with more than 10 years of smoking history have signs of stage 2 COPD, since the main symptom of COPD at this stage is that FEV1 is less than 70% of the required value. Thus, all people who abuse smoking need doctor's closest attention, particularly to create a strong motivation for them to quit smoking. The results obtained by us confirm the literature data that smoking has a negative impact on the pulmonary function, which worsens with the age of the smoker and with the number of cigarettes smoked [4,15].

Table 1

Indices of pulmonary function in apparently healthy residents of ethnically different groups of Yakutsk

PF Indices	Groups	
	Yakuts (n=70)	Russians (n= 70)
MV in %	144.6 ± 5.0	142.8 ± 4.8
VC in %	90.8 ± 1.6	96.31.4*
Tiffeneau index in %	81.8 ± 1.9	86.8 ± 0.5*
MVV in %	103.9 ± 3.2	127.6 ± 1.7*
Breathing reserve in %	91.6 ± 0.6	87.6 ± 1.0*
Pneumotachometry L/sec Inhalation Exhalation	 4.31 ± 0.10 4.310.12 ± 0.12	 3.38 ± 0.04 4.52 ± 0.06
RQ ml/L	29.5 ± 1.3	28.9 ± 1.2

* $p<0.05$, statistical significance

Table 2

Indices of pulmonary function in men depending on their smoking history

Показатель	Healthy n=90	Smoking history		
		5 years n= 30	More than 5 years n= 31	10 years and more n= 36
VC, %	94.3 ± 1.3	86.1± 5.0*	88.4 ± 6.1	84.4 ± 6.2*
FEV1, %	80.3 ± 3.4	71.4 ± 6.6	71.2 ± 6.6	63.8 ± 5.8*
Tiffeneau index, %	84.8 ± 0.5	74.8 ± 7.7	71.1± 4.8*	70.5 ± 3.4*
MVV, %	118.6 ± 1.7	87.3 ± 9.1*	84.6 ± 10.4*	87.6 ± 5.8*
Breathing reserve, %	89.6 ± 0.9	79.0 ± 4.4	83.2 ± 3.9	80.8 ± 4.0*
Pneumotachometry Inhalation 1/sec	3.8 ± 0.1	2.9 ± 0.5	3.3 ± 0.8	2.4 ± 0.5*
Exhalation 1/sec	4.3 ± 0.1	3.7 ± 0.7	4.0 ± 0.7	3.3 ± 0.8*
RQ, ml/L	29.1 ± 1.2	15.0 ± 4.0*	18.6 ± 2.4*	10.7 ± 2.1*

* $p<0.05$ compared to healthy subjects

It should be noted that the inverse relationship of pulmonary ventilatory function on smoking history is the most likely cause of an increase in COPD incidence rate among men with age.

It is shown that under the influence of tobacco smoke, alveolar macrophages are destroyed with the release of oxidative substances and lysosomal enzymes from them. Those contribute not only to pulmonary tissue's damage, but also to their infection. A study of bronchoalveolar lavage in smokers showed a 2-3-fold increase in neutrophils. At the same time, the time of their transport through the capillaries increased as a result of reducing the ability to deform under the influence of tobacco smoke oxidants. A big number of polymorphonuclear neutrophils adhered in places of damage to pulmonary blood vessels. Neutrophilia of lavage fluid in smokers plays a pathogenetic role in the development of obstructive bronchitis and pulmonary emphysema due to the increased content of neutrophilic elastase. Its proteolytic effect leads to the development of pulmonary fibrosis and loss of elasticity of the alveolar walls. Moreover, the thin elastic fibers of the interalveolar septum are destroyed faster than their bundles in the bronchial walls. As a result, there is a narrowing of the respiratory tract's lumen, especially pronounced in bronchioles devoid of cartilage. An obstructive syndrome occurs, which is not based on a spasm of the bronchial muscles, but on a disbalance of elastic tension between the pulmonary parenchyma and the bronchi. At the same time, unlike bronchial asthma, the airway obstruction is not paroxysmal, it increases gradually.

Young smokers were found to have squamous cell metaplasia in the respiratory tract's epithelium, chronic inflammatory infiltrates, and small increases in connective tissue in the respiratory tract's walls. Atypical squamous cell metaplasia was also found in older age groups. This is not surprising, considering that tobacco smoke contains substances that damage cell membranes, which was confirmed by experiments with pulmonary fibroblast's culture. When inhaling tobacco smoke, there is a decrease in the synthesis of surfactant phospholipids necessary for the synthesis of surfactant. Prolonged exposure to the chemical components of tobacco smoke leads to metaplasia of epithelial cells, which can become precursors of cancer cells. Dysfunction of muco-ciliary clearance contributes to the bacterial colonization. With the addition of a respiratory infection, the pathological process of the respiratory tract leads to the appearance of typical clinical signs of obstructive bronchitis. A sharp decrease in RQ under the influence of tobacco smoke is the result of a respiratory airway dysfunction, which inevitably leads to tissue hypoxia and disruption of intracellular metabolism, and above all are metabolic processes associated with oxidative phosphorylation reactions.

Therefore, smoking is an important risk factor for developing chronic respiratory diseases. The results of the pulmonary function's study in active smokers indicate significant airways obstruction.

Tobacco smoke is one of the most aggressive, so-termed "pro-oxidant pollutants". It contains a number of chemically active components: nicotine, formaldehyde, benzopyrenes, nitrogen oxide, cadmium, urethane, vinyl chloride, etc. All these components have a direct effect not only on the surface layer of the bronchoalveolar secretion and epithelial cells of lungs, but also on the internal milieu of the body, causing an increase in free radical oxidation.

According to the obtained data, the decrease in all indices of pulmonary function was combined with the intensification of free-radical reactions in the examined men. This is indicated by an increase in the concentration of malondialdehyde (MDA), which is a marker of lipid peroxidation. The count of MDA in the blood of smokers was increased by 30% compared to healthy non-smokers. Hypoxia can also contribute to the intensification of lipid peroxidation, since according to the obtained data, the RQ in smokers was significantly reduced compared to non-smokers (Table 3).

The toxic effect of lipid peroxidation is manifested in the antiproteases inactivation. In this case, oxidative inactivation of α_1-antitrypsin precedes elastase-dependent tissue damage in vivo. This has been demonstrated by studies showing that prior treatment with a small non-damaging dose of hydrogen peroxide significantly increases the sensitivity of isolated lungs to damage caused by perfusion with neutrophilic elastase. Activation of free-radical reactions is accompanied by a decrease in the activity of β-adrenergic and an increase in α-adrenergic and cholinergic receptors, which often leads to the development of bronchospasm in smokers with long history [20].

The intensification of lipid peroxidation in smokers is accompanied by compensatory activation of the endogenous antioxidant body system. The common antioxidant activity of blood plasma, as well as the activity of antioxidant enzymes, was higher in smokers than in non-smokers (Table 3). The level of uric acid (low-molecular endogenous antioxidant) in the blood of smoking men was statistically significantly increased. Bilirubin also has an inhibitory effect at the lipoperoxidation's chain branching stage, the concentration of which also increased in people who abused smoking.

The analysis of the obtained data shows that PFT indices are associated not only with the processes of respiratory airway and oxygen transport blood function, but also with the antioxidant defense of the body. Tissue metabolism, particularly the intensity of free-radical lipid oxidation, depends on the supply of oxygen to tissues. The obtained data on a decrease in pulmonary function indices with a parallel increase in the

Table 3

The impact of smoking on the antioxidant defense indices

Parameters	Healthy	Smokers (smoking history of more than 5 years)
Antioxidative activity, %	51.3 ± 0.7	55.6 ± 1.2
MDA, MDA/ml	1.26 ± 0.06	1.76 ± 0.10*
Superoxide dismutase (SOD), mcg/g, Hb	1.50 ± 0.03	1.96 ± 0.08*
Catalase, mcg/g, Hb	7.36 ± 0.10	7.98 ± 0.36
Uric acid, mmol/L	161.3 ± 7.5	226.5 ± 16.5*
Total bilirubin, mmol/L	5.74 ± 0.30	6.07 ± 0.48
Total cholesterol, mmol/L	4.32 ± 0.05	4.42 ± 0.12

*p 0.05, compared to healthy non-smokers

concentration of MDA in the blood, and an increase in the activity of SOD and catalase in red blood cells, suggest that people who smoke form a higher stationary level of lipid peroxidation. Higher level of LP activates the enzymatic system of antioxidant defense and drains the pool of natural antioxidants. The results of our study are consistent with the literature data. J. Kalra's research [21] showed a spontaneous increase in the generation of hydrogen peroxide from monocytes of smokers in vitro. Alveolar macrophages obtained from the lavage fluid of healthy smokers released more superoxide anion than alveolar macrophages obtained from the lavage fluid of healthy non-smokers.

Conclusion. Human adaptation to the Northern conditions causes morphological and functional changes in the pulmonary tissue, associated with physiological defensive mechanisms responding to the effect of the inhaled air's low temperature. The results of our study indicate that in the process of long-term adaptation to cold climate, the respiratory organs of the two main ethnic groups of the population of Yakutsk acquired some morphological and functional differences that affected the indices of pulmonary function. Thus, in apparently healthy men of Yakut nationality, there was a statistically significant decrease in the VC, Tiffeneau index, and MV, as well as an increase in the breathing reserve and RQ, compared to men of Russian nationality. Features of PFT indices in apparently healthy men of Yakut nationality are probably associated with an increase in the pulmonary airway's working zone and with the expansion of the pulmonary circulation's arteries.

Smoking is an important risk factor for developing chronic respiratory diseases. The results of the pulmonary function's study indicate significant airway obstruction in smokers. There are certain effects due to smoking, such as increased hypoxia, the disruption of blood oxygenation and oxygen transport to the tissues. The effects are evidenced by statistically significant decrease in the value of RQ in smokers, compared to non-smokers.

Tobacco smoke is one of the most aggressive "pro-oxidant pollutants". Our obtained data on the decrease of pulmonary function's indices with a parallel increase of MDA, increase of the contents of SOD and catalase in erythrocytes, suggests that smokers form a higher stationary level of lipid peroxidation. Higher level of LP increases the risk of damaging membrane structures, developing inflammatory process in the pulmonary tissue and forming chronic obstructive pulmonary disease (COPD). The degree of airway obstruction in smokers increases in direct proportion to smoking history. The examined men with smoking history of 5 to 10 years already show signs of stage 1 (FEV1 71.2±6.6%) COPD, and smokers with more than 10 years smoking history have signs of stage 2 (FEV1 63.8±5.8%) COPD. Thus, all smokers need doctor's closest attention, particularly to create a strong motivation for them to quit smoking.

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CONGENITAL AND ADAPTIVE IMMUNITY INDICATORS IN CHRONIC GENERALIZED PERIODONTITIS IN ELDERLY AND SENILE PATIENTS

DOI 10.25789/YMJ.2020.69.15

УДК 616.31-0:612.66

By 2055, the share of elderly people will be up to 40-55% of the total population of the country, which will require significant adjustments in medicine and social insurance of health care in Russia. At the same time, one of the important problems is still the disclosure of regulation mechanisms of dynamic constancy of internal environment of human oral cavity during different age periods. In this regard, the main purpose of the research was to carry out a complex of clinical and laboratory studies with the determination of the dynamics of cellular and humoral immunity indicators, the impact of basic therapy on their recovery in patients with chronic generalized periodontitis (CGP) of the elderly and senile age patients with cardiovascular diseases.

Material and methods.

During 2003-2011, 448 patients with chronic generalized periodontitis aged 60-89 years old were examined and admitted to the Veterans Hospital of War and Labour of Chita and the House of Veterans of Labor "Mercy" village Atamanovka of Transbaikal region for preventive treatment of ischemic heart disease. The criteria for inclusion in the studies were elderly (60 to 74 years old) and senile (75 to 89 years old) patients with moderate CGP and clinical manifestations of IHD (stable effort angina of the I-II functional class, chronic cardiac insufficiency of VA stage, hypertension of the 1-2 stage). Taking into account WHO recommendations, all patients were divided into 2 groups: the 1st group - 204 patients aged 60-74, who were assigned a complex of standard treatment of CGP; 2nd group - 190 people aged 75-89, who were assigned a complex of Standard Medical Treatment of CGP. The control group consisted of 25 practically healthy persons who did not have acute and chronic periodontal diseases, as well as somatic pathology at the time of the study.

All researches were carried out with participants' informed consent and was consistent with the ethical principles set by Law 24 of the Constitution of the Russian Federation, the Helsinki Declaration of the World Medical Association of Helsinki, 1964, 2000.

Results and discussion.

The overall hemolytic activity is reducing in patients of elderly people with CGP in blood and oral fluid. Meanwhile, the content of the C3a complement fragment in blood is increased to control rate up to 59 and 52%, respectively. In addition, there is a suppression of complementary activity, which leads to persistent and irreversible effects of periodontal pathology, in senile age more than in elderly age. To a greater extent, general and local immunity are violated in patients of senile age. Meanwhile, the correction of immunity is insufficient in patients with CGP of moderate severity of the elderly and senile age, under the influence of standard treatment. However, the continued high level of IgG indicates the continued activation of the humoral link of immunity. Changes in immunity after treatment indicated a high antigenic load of local and universal nature. In the oral fluid of patients, signs of hypercoagulation after baseline therapy were maintained. Such a situation was dangerous to the development of thrombogenic complications, and a relapse could easily occur against that background.

Conclusion. The recovery of immunity indicators takes place in insufficient volume in patients with CGP of elderly and senile age by basic therapy. The detected disorders in the immune response of this disease are basic, but not the only pathogenetic mechanism explaining the inflammatory process.

Keywords: periodontitis, oral fluid, elderly and senile age, immunity, hemostasis.

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The State Report of the Russian Federation [4] noted that by 2055 the proportion of old people will significantly increase - to 40-55 % of the total population of the country, which will require significant changes in health care and social security [1, 10, 12].

The ageing process of human undoubtedly affect the state of structures and tissues of the oral cavity [3, 5, 15, 17]. People over 60 years old, due to evolving age changes, develop a mild and prolonged period of dental diseases, often lead to chronic process and require longer treatment than in young and middle-aged patients [6, 9, 11, 13, 14]. In the elderly, these phenomena are exacerbated by a decrease of the re-generative and compensatory capacity of the oral mucosa [2, 7, 14].

In particular, one important problem is the disclosure of mechanisms for regulating the dynamic constancy of the internal environment of the human oral cavity in different age periods [12]. The main role of the local protection factors of the oral cavity is ensuring its normal functioning [8]. At the same time an important link in realization of these processes are the barrier all-organism nonspecific functions providing inclusion of one of protective mechanisms of homeostatic character in response to various pathological states [3, 5].

Purpose of the research. On the basis of complex clinical and laboratory research, the dynamics of cellular and humoral immunity indices, the effect of basic therapy on their recovery in patients with chronic generalized periodontitis (CGP) of the elderly and senile age with pathologies of cardiovascular system are determined.

Research materials and methods. During 2003-2011, CGP 448 patients aged 60-89 years old were examined, at Veterans Hospital of War and Labour of Chita and the House of Veterans of Labor "Mercy" village Atamanovka of Transbaikal region for preventive treatment of ischemic heart disease.

Inclusion criteria: elderly (60 to 74 years old) and senile (75 to 89 years old) patients with moderate CGP and clinical manifestations of IHD (stable effort angina of the I-II functional class, chronic cardiac insufficiency of VA stage, hypertension of the 1-2 stage).

Exclusion criteria: patients under 60 years old with moderate CGP, with acute diseases and exacerbation of chronic somatic diseases, periodontal diseases and exacerbating their severity, as well as endocrine pathology, diabetes mellitus, diseases of the cardiovascular system (except for those specified in the inclusion criteria).

All patients were divided into 2 groups, taking into account WHO recommendations:

- the 1st group - 204 persons at the age of 60-74 years old with a complex of standard CGP treatment;
- the 2nd group - 190 people at the age of 75-89 years old with a complex of standard CGP treatment;

The control group consisted of 25 almost healthy people who had no acute and chronic periodontal diseases, as well as somatic pathology. The values of the indicators obtained during their examination are taken as a norm. Study of innate and adaptive immunity, determination of immunoglobulin level, cytokine level, study of complement system and hemostasis was carried out.

Traditional CGP treatment of patients at the age of 60 – 89 years old included: oral hygiene training; Occupational hygiene and oral sanitation; Anti-septic treatment of periodontal tissues with Romazulan solution, 0.06% Chlorhexidine solution, 1% hydrogen peroxide solution; Applying a non-solidifying bandage comprising Dicain, Heparin, Prednisolon, Synthomycin for 20 minutes; closed curettage of infrabone pockets, mouth oralogy with "Rotocanum" solution - 3 times a day, auto-massage with "Metrogyl Denta" gel - 2 times a day for 5 days. At the same time, rational prosthetics or application of orthopedic splinted crowns were carried out. In addition, patients received anti-inflammatory, desensitizing and antibacterial preparations for 10-12 days.

Statistical processing of the results was performed by STATISTICA 6.0 (StatSoft Inc., USA) determining the statistical significance of the differences at $p < 0.05$. Non-variable methods were used in comparing quantitative values due to abnormal distribution of values in the variation series. The test parameters were presented as a median (Me [25th; 75th percentile]). The differences between groups was evaluated by Mann-Whitney test (U-test). The significance of the differences over baseline was assessed by Wilcoxon test.

Research was carried out with the informed consent of the participants and was consistent with the ethical principles of Law 24 of the Constitution of the Russian Federation and the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, 2000 ed.), "Rules of clinical practice in the Russian Federation," approved by Order of the Ministry of Health of the Russian Federation No. 266 of 19.06.2003, and ethical standards of the Committee on Experiments, Clinical Research Standards GCP (GOST R 52379-2005).

Results and discussion. The overall hemolytic activity is reducing in patients of elderly people with CGP in blood and oral fluid. Meanwhile, the content of the C3a complement fragment in blood is increased to control rate up to 59 and 52%, respectively (Table 1).

However, while C3a increased by 27% in the oral fluid of elderly patients, it decreased by 30% in senile age. Its concentration increase indicates the activation of the complement system and accelerated cleavage of C3 component, which activity increases in the oral cavity with inflammation. The C3a fragment has the ability to induce macrophages with monokine isolation. Perhaps, through this mechanism, the complement system contributes to the increase in the level of anti-inflammatory cytokines in saliva and blood in inflammatory periodontal diseases (Table 2).

Table 1

Indicators dynamics of complement system parameters in patients' blood with chronic generalized periodontitis of elderly and senile age [Me (25–75 0/00)]

Indicator	Control (n = 20)	Elderly age (n = 60)		Senile age (n = 50)	
		before treatment	after treatment	before treatment	after treatment
Blood value complement, c.u	89.75 (89.40; 91.05)	80.40* (80.20; 80.88)	83.10*▲ (82.50; 83.40)	80.10* (78.50; 81.30)	84.20*▲ (81.80; 85.20)
C1- inhibitor, μg/ml	546.17 (536.3; 552.8)	369.70* (348.1; 370.6)	451.65*▲ (446.1; 461.9)	408.50* (402.2; 419.3)	441.70*▲ (437.2; 449.6)
C3a, ng/ml	408.25 (402.4; 415.03)	642.75* (640.1; 667.9)	589.20*▲ (584.3; 597.6)	626.90* (603.5; 643.2)	561.90*▲ (554.9; 572.5)
C5a, ng/ml	4.50 (4.50; 4.60)	5.20* (5.20; 5.30)	4.90*▲ (4.90; 5.10)	5.35* (4.90; 5.73)	4.75 (4.48; 5.10)

Notes. In the Tbl. 1-6 n - number of surveyed; * - distinctions of values in comparison with control (Mann-Whitney's test); ▲ - distinctions of values in comparison with the initial level (Wilcoxon's test); ■ - differences of values between groups.

The concentration of C1 inhibitor in oral fluid in periodontal inflammation in elderly and senile patients is reduced by almost 3 times, and in blood - by 48 and 42%, respectively. Such concentration may indicate a tense adjustment of its activation or insufficient synthesis.

Thus, there is a suppression of complemental activity, which leads to persistent and irreversible consequences of periodontal pathology, in elderly age in patients with CGP of both groups.

Pre-treatment suppression of complementary blood activity in elderly patients and after the course of basic therapy did not undergo major changes, therefore, the non-specific level of protection remained vulnerable. In particular, the overall complementary activity and the level of the C5a fragment of the complement remains low and the levels of the C1 inhibitor and the C3a fragment are elevated, and elderly patients have little or no change except a decrease in the C5a fragment of the complement (Table 1). The activity of complement components in oral fluid was substantially unchanged after standard treatment (Table 2).

Indicators of general and local immunity for CGP in elderly and senile patients are accompanied by a decrease in the number of cells carrying CD4 and CD8 markers, as well as CD4/CD8 and CD3/CD19 rates. At the same time, cell activity (increase in the number of cells CD4 CD25, T-dependent and T-independent NK) and humoral immunity with excessive synthesis of all basic classes of immunoglobulins in blood and oral fluid are observed. To a greater extent, general and local immunity indicators are damaged in senile patients.

Disorders detected in senile patients at different immune units did not undergo significant changes after standard treatment. Thus, the number of lymphocytes, monocytes, CD3/CD19 ratio increased and reached the norm. The number of CD4 increased slightly, decreased - CD3 CD19-, the concentration of IgG decreased, but all of them did not reach the control values (Table 3).

Indicators of cellular and humoral immunity of patients of senile age after treatment slightly differed from those of patients of old age. In private, the absolute number of lymphocytes has increased, and their percentage has exceeded the norm. The quantity of CD3 CD19-, CD4, CD8, CD3 HLA-DR, HLA-DR also became above, but did not reach norm. On the other hand, reduction of quantity of monocytes, granulocytes, CD3 CD16 CD56, CD3-CD16 CD56, CD4 CD25 and also concentration of IgG and IGM was noted. However, their values remained above normal. The ratio of CD3/CD19 to CD4/CD8 increased markedly, and the number of B cells continued to increase, while the IgA level remained unchanged (Table 3). Patients raised, but there was below norm a quantity of CD4, HLA-DR, a ratio of CD3/CD19 and CD4/CD8. Number of CD3 CD16 CD56, CD3-CD16 CD56 and CD4 CD25 - cages and also concentration of IGA, IgG and IGM decreased and got closer to values of norm. In addition, the concentration of IgA and IgG decreased by almost 30%, and the level IgM reached the norm in this group of patients (Table 3).

It has been established that content of IL-1α in plasma blood in the elderly and senile age patients exceeded the norm by almost 7, IL-4 - by 2.5 times, and IL-8 - by 1.5 and by 2 times accordingly. In elderly patients there was a decrease in IL-1α concentration by 2 times in blood plasma on the background of therapy. And even with such a sharp decrease, it exceeded the norm by 3times. IL-4 content continued to increase and exceeded the benchmark by almost 3 times. The concentration of IL-8 decreased slightly, but was also far from normal (Table 3).

The concentration of IL-1α decreased by 1.5 times in blood on the background of therapy in patients of senile age. And even with such a sharp decline, it remained 4 times higher than normal. IL-4 content continued to increase and exceeded the benchmark by almost 3 times. The concentration of IL-8 decreased slightly, but was also far from normal (Table 3).

The concentration of IgA increased by 2.5, IgG by 2, and IgM and sIgA by 3 times as compared to the control (Figure 4) in the oral fluid of patients. The IgM and IgA content in the oral cavity of elderly patients reached controlled values after baseline therapy, and concentrations of sIgA and IgG remained virtually unchanged. IL-4 level, although reduced, remained 9 times above control. IL-1α content was reduced by 2 times and reached reference values, the concentration of IL-8 remained virtually unchanged (Table 4). In senile patients, IgA content after baseline therapy reached a control value. Concentrations of sIgA, IgM and IgG remained high. IL-4 level, although reduced, was 10 times higher than the control. IL-1α fluid content in the oral cavity was reduced twice and reached the norm, the concentration of IL-8 was practically unchanged (Table 4).

Thus, in patients with CGP of moderate severity of elderly and senile age under the influence of standard treatment, the correction of immunity indicators is insufficient. In the oral fluid, the concentration of IgA decreased to normal, while the sIgA content remained high, indicating the need to synthesize the secretory component IgA the mouth mucosa. IgG level has not changed. No significant dynamics of immunity indices occurred in blood, but still decrease of IL-1α content and increase of IL-4 after treatment characterizes partial reduction of inflammatory process. However, the maintained high level of IgG indicates the continued activation of the humoral link of the immunity. Changes in immunity preserved after treatment indicate high antigenic load of local and universal nature.

The conducted researches of indicators of the general and local hemostasis at patients of old and senile age with a chronic generalized periodontal disease of moderate severity hyper coagulation (Tab. 5) is observed that testifies to aPTT shortening and thrombin clotting time, and thrombin clotting time is stronger reduced and extended fibrinolysis in group of patients of senile age. Induced clotting is accompanied by the rise of fibrinogen level, fibrinolysis suppression and high co-centralization of SFC, which are markers of thrombinemia.

Table 2

Values dynamics of complement system in oral fluid of patients with chronic generalized periodontitis of elderly and senile age [Me (25–75 0/00)]

Indicator	Control (n = 10)	Elderly age (n = 60)		Senile age (n = 50)	
		before treatment	after treatment	before treatment	after treatment
Blood value complement, c.u.	6.07 (5.86; 6.20)	3.12* (2.90; 3.12)	4.72*▲ (4.57; 5.23)	3.52* (3.51; 3.52)	3.98*▲ (3.77; 4.28)
C1- inhibitor, μg/ml	32.93 (32.77; 33.16)	12.40* (11.8; 14.85)	22.36*▲ (19.43; 23.25)	13.70* (12.13; 16.73)	23.53*▲ (22.36; 26.12)
C3a, ng/ml	49.14 (49.03; 49.40)	62.09* (60.07; 63.82)	65.80*▲ (64.90; 68.40)	33.60*▪ (30.83; 34.80)	36.50*▲ (35.80; 38.55)
C5a, ng/ml	6.30 (5.33; 6.58)	3.30* (2.90; 3.55)	4.60*▲ (3.80; 4.85)	3.35* (2.90; 4.00)	4.05*▲ (3.80; 5.28)

After standard treatment in blood of elderly patients, hypercoagulation decreased, INR reached a reference value, and frequent thrombin clotting time remained accelerated. The latter indicates that the external clotting activation pathway due to tissue fragments remains initiated. The lysis time of the fibrin clot remained elongated, and the concentration of fibrinogen and pro-ducts of its degradation was high. The dynamics of the hemostasis system in the senile patients after treatment had changes similar to those in the elderly patients, except INR, which remained at the baseline (Table 5).

It has been found out that procoagulant acivity of saliva is higher than in elderly and senile patients than in healthy people (shortened prothrombin and thrombin clotting time, aPTT). No significant differences between age groups were found (Table 6).

The ability of oral fluid to influence fibrinolysis is suppressed with age. This may be due to a decrease in the overall protease activity of saliva and an increase in the concentration of fibrinolysis inhibitors. In oral fluid of patients, hypercoagulation signs after basic therapy were preserved. In particular, the procoagulant potential decreased somewhat and its fibrinolytic activity remained still inhibited (Table 6). Positive dynamics of procoagulant potential of oral fluid is connected not only with reduction of hypercoagulation in blood flow, but also with action of local therapy.

The research results of the hemostasis system show that hypercoagulation is observed in the blood of patients with chronic generalized periodontitis of moderate severity over 60 years of age. The concentration of the compounds having procoagulantive activity in the oral fluid is higher than in healthy individuals, and fibrinolytic activity is suppressed. Such a situation was dangerous to the development of thrombogenic complications, and a recurrence of inflammation could easily occur on that background.

Conclusions. In patients with CGP of elderly and senile age under the influence of basic therapy, the recovery of immunity indicators takes place in insufficient volume. In case of chronic generalized periodontitis of moderate severity in patients of elderly and senile age there is observed systemic polyclonal B-cell activating factor. The reason for this may be bacterial endotoxemia and autoimmune processes. The immunopathology is expressed by imbalance in the system of a complement, malfunction of T-lymphocytes, decrease in intensity cellular and strengthening of humoral immunity, polyclonal activation of V-lymphocytes.

Table 3

Values dynamics of cellular and humoral immunity indices in patients with chronic generalized periodontitis of elderly and senile age [Me (25–75 0/00)]

Indicator	Control (n = 25)	Elderly age (n = 70)		Senile age (n = 80)	
		before treatment	after treatment	before treatment	after treatment
Lymphocytes,%	34.0 (34.0; 35.0)	31.50 (27.0; 34.75)	34.50 (32.0; 37.75)	34.00 (32.00; 34.0)	36.00* (35.0; 38.0)
Lymphocytes, abs./μl	2380.00 (2333.5; 2395)	1723.0* (1575.0; 1847.0)	1878.0▲ (1764; 1998)	2075.50* (2031.8; 2140.0)	2217.00*▲ (2193.8; 2238.3)
Monocytes,%	7.00 (6.0; 7.0)	6.00 (4.00; 7.00)	7.0 (5.00; 8.00)	7.00 (7.00; 8.00)	7.00 (6.00; 7.00)
Monocytes, abs/μl	444.00 (405.5; 460.0)	371.0 (292.5; 410.0)	412.0▲ (342.5; 456.5)	469.00* (454.0; 481.0)	407.50*▲ (396.0; 425.3)
Granulocytes,%	54.00 (51.0; 56.5)	68.0* (64.25; 71.0)	68.0* (62.25; 71.0)	65.00* (63.0; 66.0)	61.00* (59.0; 65.0)
Granulocytes, abs./μl	4270.00 (4205; 4362.5)	3248.0* (2983.0; 3482.0)	3465.0* (3170; 3597)	5124.0* (4985.0; 5245.0)	4652.00*▲ (4532.5; 4748.0)
CD3+CD19-, %	79.40 (78.85; 79.90)	80.10 (76.20; 82.15)	74.85▲ (72.40; 77.80)	70.30* (68.5; 70.9)	70.60*▲ (70.50; 71.25)
CD3+CD19-, PLT./ mql	1832.00 (1785.5; 1932)	1683.5* (1468.3; 1775.5)	1568.0*▲ (1446.0; 1668.0)	1486.00* (1446.0; 1490.0)	1623.50*▲ (1560.3; 1686.0)
CD4+, %	48.20 (47.65; 48.35)	39.75* (37.7; 44.15)	43.8*▲ (41.35; 45.8)	39.10* (38.40; 39.55)	40.40*▲ (39.58; 40.8)
CD4+, PLT./ mql	1117.00 (1080.5; 1135)	859.0* (768.0; 902.5)	964.0*▲ (879.0; 987.0)	822.50* (815.5; 834.0)	909.00* (897.0; 919.0)
CD8+, %	30.10 (29.20; 30.35)	21.20* (18.9; 24.6)	23.75* (22.33; 26.05)	18.45*▪ (16.65; 19.83)	33.75*▲ (32.83; 34.28)
CD4+, PLT./ mql	686.00 (666.0; 714.0)	279.0* (263.5; 315.5)	324.5*▲ (289.0; 346.5)	251.0*▪ (234.0; 289.0)	434.00*▲ (419.5; 453.0)
CD4+/CD8+	1.70 (1.70; 1.80)	3.09* (2.30; 2.80)	2.98*▲ (2.03; 2.40)	3.27 (2.96; 3.58)	2.1 (1.89; 2.24)
CD3+CD16+CD56+, %	4.60 (4.25; 4.80)	6.85* (6.23; 7.63)	6.95* (6.20; 7.28)	9.60* (9.15; 10.4)	8.70*▲ (7.9; 8.9)
CD3+CD16+CD56+, PLT./ mql	110.00 (106.0; 115.0)	170.0* (159.0; 183.25)	168.5* (163.0; 174.75)	197.50* (190.0; 207.25)	161.00*▲ (153.0; 168.0)
CD3-CD16+CD56+, %	10.60 (10.4; 11.0)	10.90 (9.10; 12.30)	11.25 (9.95; 12.80)	21.20* (18.4; 21.7)	14.80*▲ (13.1; 15.7)
CD3-CD16+CD56+, PLT./ mql	252.00 (233.0; 267.5)	223.50 (210.0; 244.50)	231.0 (210.0; 250.25)	513.00* (501.0; 524.0)	435.50*▲ (412.0; 446.0)
CD3-19+, %	8.50 (8.25; 8.7)	6.80* (5.90; 7.70)	7.25* (6.43; 7.60)	12.50* (11.7; 12.8)	11.80* (10.9; 12.4)
CD3-19+, PLT./ mql	210.00 (199.5; 216.5)	102.0* (90.5; 156.5)	116.0* (96.0; 163.0)	226.00* (217.0; 228.0)	234.00* (221.0; 240.0)
CD3+HLA-DR+, %	4.20 (4.10; 4.55)	5.80* (5.00; 6.55)	5.20* (4.65; 6.05)	2.40* (2.10; 2.70)	3.20*▲ (2.60; 3.40)
CD3+HLA-DR+, PLT./ mql	92.00 (88.5; 97.0)	109.50* (95.5; 127.5)	106.0* (93.75; 120.0)	81.00* (81.0; 83.0)	83.00* (82.0; 84.0)
CD4+CD25+, %	8.10 (7.8; 8.45)	19.95* (17.3; 21.35)	16.3*▲ (15.2; 17.1)	21.10* (19.4; 21.9)	18.50*▲ (18.1; 19.28)
CD4+CD25+, PLT./ mql	187.00 (182.0; 193.0)	347.0* (298.75; 366.5)	318.0* (308.0; 329.0)	391.00* (373.0; 398.0)	356.00*▲ (350.0; 371.3)
HLA-DR+, %	80.30 (79.8; 80.65)	74.70* (72.93; 76.40)	76.3* (72.1; 78.9)	63.00* (60.6; 65.4)	67.80*▲ (65.85; 70.85)
HLA-DR+, PLT./ mql		297.00 (288.3; 311.8)	308.0 (293.0; 319.0)	259.00 (237.0; 286.0)	299.00▲ (283.5; 315.5)
CD3+/CD19+	10.70 (10.4; 11.0)	15.40* (14.25; 16.68)	11.6*▲ (11.0; 12.3)	8.40* (7.95; 8.9)	9.30*▲ (8.90; 9.7)
IgA, mg/mL	1.80 (1.70; 1.88)	3.00* (2.90; 3.20)	2.80 (2.6; 3.0)	2.90* (2.80; 3.03)	2.80* (2.80; 3.00)
IgM, mg/mL	1.85 (1.65; 2.05)	2.90* (2.80; 3.15)	2.80▲ (2.55; 2.80)	2.80* (2.6; 2.8)	2.40*▲ (2.2; 2.6)
IgG, mg/mL	12.60 (12.3; 12.7)	21.60* (21.25; 22.10)	16.90*▲ (15.4; 18.1)	21.45* (20.8; 21.8)	16.45*▲ (16.2; 17.2)
IL-1α, pcg/ml	23.50 (23.0; 26.25)	147.00* (142.5; 149.0)	74.6*▲ (72.5; 79.0)	149.00* (140.0; 151.0)	96.6*▲ (94.2; 99.0)
IL-4, pcg/ml	12.00 (10.0; 13.5)	27.90* (27.8; 27.9)	32.4* (31.5; 34.0)	27.0* (26.0; 28.0)	34.1* (32.5; 34.9)
IL-8, pcg/ml	16.50 (16.0; 17.0)	26.30* (25.41; 26.7)	23.4* (22.3; 24.2)	30.0*▪ (29.0; 31.0)	26.5* (24.5; 27.9)

Table 4

Dynamics of the content of immunoglobulins and interleukins in oral fluid in patients with chronic generalized periodontitis of elderly and senile age [(Me (25-750/00)]

Indicator	Control (n = 15)	Elderly age (n = 35)		Senile age (n = 25)	
		before treatment	after treatment	before treatment	after treatment
IgG, mg/mL	0.20 (0.13; 0.21)	0.39* (0.38; 0.41)	0.40* (0.38; 0.42)	0.40* (0.37; 0.41)	0.40* (0.38; 0.42)
IgM, mg/mL	0.026 (0.022; 0.026)	0.072* (0.068; 0.074)	0.032▲ (0.029; 0.037)	0.074* (0.068; 0.078)	0.036*▲ (0.031; 0.037)
IgA, mg/mL	0.040 (0.04; 0.04)	0.099* (0.098; 0.101)	0.047▲ (0.042; 0.052)	0.100* (0.098; 0.102)	0.047▲ (0.044; 0.052)
sIgA, mg/mL	10.98 (10.73; 12.44)	34.50* (33.47; 34.73)	26.80*▲ (26.49; 28.1)	34.96* (33.78; 36.25)	27.15*▲ (26.5; 28.19)
IL-1α, pcg/ml	8.90 (8.15; 9.58)	13.48* (13.48; 14.32)	7.08*▲ (6.6; 7.45)	13.56*	7.08▲ (6.6; 7.35)
IL-4, pcg/ml	20.45 (20.25; 21.4)	320.30* (301.5; 329.45)	182.20*▲ (172.2; 231.8)	327.20* (313.4; 331.8)	216.5*▲ (192.2; 231.8)
IL-8, pcg/ml	15.92 (14.18; 17.14)	26.30* (25.41; 26.7)	23.60*▲ (23.2; 23.9)	28.73* (27.94; 29.55)	26.55* (25.42; 28.8)

Table 5

Dynamics of hemostasis system indicators in patients with chronic generalized periodontitis of old and senile age [Me (25-75 0/00)]

Indicator	Control (n = 15)	Elderly age (n = 30)		Senile age (n = 25)	
		before treatment	after treatment	before treatment	after treatment
INR	1.05 (1.0; 1.10)	1.20* (1.20; 1.20)	1.10 (0.96; 1.26)	1.20* (1.13; 1.20)	1.20* (1.11; 1.21)
aPTT, s	43.10 (40.5; 44.9)	32.90* (29.80; 35.0)	39.00*▲ (38.0; 39.5)	32.50* (28.15; 34.25)	37.60*▲ (36.43; 38.65)
thrombin clotting time, s	17.20 (17.2; 17.3)	15.20* (14.60; 15.6)	15.90*▲ (15.8; 16.5)	14.50*▪ (14.13; 14.60)	15.40*▲ (14.98; 15.58)
fibrinogen, g/l	2.75 (2.3; 3.0)	6.30* (5.9; 6.5)	5.55*▲ (5.5; 5.8)	6.40* (5.83; 6.65)	5.90* (5.80; 6.08)
SFC,mg/100 mL	3.00 (2.9; 3.0)	8.15* (8.00; 9.00)	6.30*▲ (6.00; 6.5)	8.20* (8.00; 8.60)	6.40*▲ (6.13; 6.70)
fibrinolysis, min	141.0 (138.0; 147.0)	191.50* (188.0; 200.0)	178.00*▲ (176.0; 179.0)	195.00* (193.0; 199.5)	177.00*▲ (175.0; 180.0)

Table 6

Effect of oral fluid of patients with chronic generalized periodontitis of elderly and senile age on blood clotting and fibrinolysis after treatment [Me (25-75 0/00)]

Indicator	Control (n = 15)	Elderly age (n = 30)		Senile age (n = 20)	
		before treatment	after treatment	before treatment	after treatment
prothrombin, %	75.80 (74.63;78.6)	61.10* (59.0; 63.0)	65.90*▲ (62.1; 69.5)	59.00* (58.0; 61.35)	67.10*▲ (64.4; 67.9)
aPTT, %	80.10 (79.8;81.80)	60.20* (58.3; 61.0)	70.10*▲ (67.95;70.8)	60.00* (57.2; 60.35)	69.20*▲ (67.3; 70.75)
thrombin clotting time, %	80.28 (78.8;82.81)	63.40* (62.2; 65.3)	68.30*▲ (65.6;70.65)	63.30* (62.2; 63.85)	68.50*▲ (65.7; 70.65)
fibrinolysis, %	73.50 (73.0;75.75)	87.0* (84.0; 89.0)	83.00*▲ (82.0; 83.5)	88.00* (85.0; 89.0)	83.00*▲ (82.0; 84.0)

The findings of the immune response in this disease are fundamental, but not the only, pathogenetic mechanism that explains the course of the inflammatory process.

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NUTRITION IN THE NORTH

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ANALYSIS OF ACTUAL NUTRITION OF FREESTYLE WRESTLERS IN YAKUTIA CONDITIONS

DOI 10.25789/YMJ.2020.69.16

УДК 612[66+821] +616.89

The purpose of the study. Assessment of dietary intake of freestyle wrestlers depending on the season, taking into account the daily energy expenditure.

Material and methods. 63 wrestlers from 20 to 25 years of Yakut State high school sports skills were investigated. Anthropometric measures were taken into account. Daily energy expenditure of the wrestlers was measured in kilocalories (kcal) based on the timekeeping of the training day. The actual nutrition was assessed using the questionnaire (24-hour food recall). Canteen menu where athletes ate was analyzed also.

Results of the study. Analysis of anthropometric data (height 1,67 ± 0,03 m, weight - 69,91 ± 5,68 kg) showed that among 63 surveyed athletes dominated the sportmen with brachymorphic somatotype. This somatotype is characterized by a mean (22% of those surveyed) or low (67% of those surveyed) growth, relatively long torso, broad shoulders, big chest circumference.

Total daily energy consumption of freestyle wrestlers during the training process amounted 5609.28 kcal / day, and during training camps - 5687.16 kcal / day. Daily caloric food ration of the wrestlers depended on food basket. In summer, the caloric intake was highest and amounted to 3571 kcal, in the autumn - 3065 kcal, in winter - 2359 kcal, in the spring - 2878 kcal. The actual weight ratio of proteins, fats, carbohydrates (Protein: Fat: Carbohydrates) in the daily diet of athletes was as follows: in the summer of the year – 1.1: 0.9: 3.7; in the fall - 0.9: 1.05: 4.4; in winter - 1.2: 0.8: 4.5; in the spring - 1: 1: 4.

Conclusions. The data obtained conclude that the daily food ration calorie does not reimburse the daily energy consumption of athletes. The chemical composition of nutrients in the daily diet of athletes quantitatively and qualitatively does not correspond to the standards recommended for freestyle wrestlers.

Keywords: Yakutia, wrestling, daily consumption of energy, proteins, fats, carbohydrates.

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Introduction. Modern sports with its extreme physical, mental and emotional loads, long and intensive training is one of the most pronounced stressful effects on the human body. With intense physical activity, the rate of metabolic processes increases sharply, and the need for vitamins, macro - and microelements increases. With the loss of a significant number of elements with sweat, saliva and products of the excretory system, their balance in the body is disrupted, causing certain physiological and pathological shifts. It should be noted that the body of athletes training in the North experiences additional loads, since the existence of a person in extreme climatogeographic conditions is associated with an increase in the basic metabolism, which requires additional energy costs, as a result, the role of fat increases and the so- called "polar metabolic type" is formed [15].

Climatic extremes of human living conditions in Yakutia are created by: the average annual negative temperature; the lack or complete absence (polar night) of solar radiation in winter; the low absolute content of water vapor in the atmosphere; the high level of perturbation of the natural geomagnetic field; the location in the zone of widespread development of permafrost. Studies by a number of authors have shown that micronutrient and electrolyte homeostasis is often disrupted in humans in the North [1,19]. In this regard, the role of nutrition in improving athletic performance and eliminating fatigue in athletes who live and train in the North, increases significantly.

The purpose of this study was to evaluate the actual nutrition of freestyle wrestlers depending on the season of the year, taking into account the daily energy consumption.

Research problem:

1. Calculate the daily energy consumption of wrestlers.

2. To study the actual diet of the wrestlers.

Material and methods. A set of materials for the study was conducted among athletes- wrestlers of the state institution "School of higher sports skill" in Yakutsk. We examined a total of 63 athletes of Yakutia aged 20 to 25 years. Anthropometric indicators were taken into account: height (in meters), body weight (in kg), body mass index (calculated using the formula BMI=body weight in (kg)/height (m)2), Rohrer index.

Daily energy consumption was determined in kilocalories (kcal) based on the timing of the training day with the calculation of energy consumption. At the same time, it was taken into account that the daily energy consumption consists of individual activities of athletes, the main exchange, the specific dynamic action of food and unaccounted energy expenditure [7].

Actual nutrition was assessed using

a questionnaire - based method of daily (24-hour) nutrition reproduction using the Atlas of food consumption developed by the Institute of nutrition of the Russian Academy of medical Sciences with a parallel analysis of the menu layouts of the Institute's canteen where students eat [8,9]. The calculation of the chemical composition of the individual daily diet was carried out using tables of the chemical composition of food, taking into account the loss of food substances, during the culinary processing of food, followed by statistical processing of research results [21].

The obtained data were statistically processed using the SPSS 17.0 statistical software package. Arithmetic mean values (M) and errors of mean values (m) were calculated for all indicators in each group. The significance level was considered reliable at $p \leq 0.05$. The reliability of differences was determined using nonparametric Mann-Whitney criteria. Spearman's linear correlation coefficient was calculated to identify the conjugacy of indicators.

Results and discussion. It is known that anatomical and anthropological features of athletes depend on ethnicity, physical activity and functional systems of the body. Adaptation of the body to various environmental factors is a long process aimed at forming an ecological type that ensures the integrity of the body and optimal conditions for its life. Long-term adaptation of a person to extreme climatogeographic conditions of the North affected his morphometric indicators. Thus, the anthropometric feature of the Northern ecotype is shortness [23].

Analysis of anthropometric data (height 1.67±0.03 m, body weight-69.91±5.68 kg) showed that among the 63 athletes examined by us, persons with brachymorphic somatotype predominate. This type of somatotype is characterized by medium (22% of the surveyed) or low (67% of the surveyed) height, relatively long torso, broad shoulders, large chest circumference.

Relatively high values of the body mass index (BMI-24.65±1.18) and the Rohrer index (14.71±0.58) indicate a large body density, which is associated with high indicators of muscle strength-the flexors of the forearm, the extensors of the hip and trunk of the highly qualified freestyle wrestlers we examined. It was found that wrestlers with large girth sizes and body weight are more effective [10]. The value of body weight (both your own and your opponent's) in wrestling is so great that weight categories are introduced to equalize the chances of winning in this sport.

Wrestling refers to acyclic sports and is characterized by complex motor activity performed in conditions of space and time deficit, often with limited vision and difficult breathing. In the process of intensive muscle activity, athletes spend a large amount of energy, which requires optimal and timely replenishment of energy costs. Freestyle wrestling is an acyclic sport characterized by a large amount of physical activity. According to the standards, the energy consumption of wrestlers should be 4500-5500 kcal (70 kcal/kg of body weight) [17]. In table 1 data reflecting the daily energy consumption of freestyle wrestlers in various types of activities are presented.

From the data presented in the table, it can be seen that the largest percentage of daily energy consumption is accounted for by improving sports skills – about 40% (table 1).Taking into account the main exchange and specific dynamic action of food, the total total daily energy consumption during the training process was 5609,28 kcal/day, and during training camps-5687,16 kcal/day. Some increase in the total daily energy consumption of athletes in June-August is due to an increase in energy consumption during passive and active recreation, which is the specifics of summer training camps. The conversion per 1 kg of body weight averaged 80 kcal. Our results do not contradict the literature data. According to Grigorieva O.V. (2003), the level of daily energy consumption for martial arts students was 4310,2+62,1 kcal, and the conversion per 1 kg of body weight was 59,04+7,12 kcal [5]. But for highly qualified athletes, they can be higher [11,20].

High energy costs associated with the specifics of training highly qualified martial artists should be compensated by optimal nutrition. Rational nutrition is one of the most important directions in improving the physical performance of athletes and their achievement of high results in competitive activities. The athletes we examined were on an organized four-day meal in the School of higher sports skill canteen. However, some wrestlers, in addition to eating in the dining room, had an additional snack, usually 2-3 hours after dinner (late dinner at 21-22 hours). The daily diet of athletes included basic food items: meat and meat products, fish,

Table 1

Daily time budget (per hour) and energy consumption (kcal/hour) for various types of athletes activities

Type of activity	Daily time budget	Energy consumption (kcal)	In % of daily energy consumption	Daily time budget	Energy consumption (kcal)	In % of daily energy consumption
	Training process (September-May)			Training camps (June-August)		
Sleep, lying down	9 hour	581.65	17.13	8 hour	517.02	14.91
The meal	60 minute	90.26	2.66	60 minute	90.26	2.61
Personal hygiene (washing, shower, sauna)	40 minute	97.65	2.87	50 minute	122.06	3.52
Passive recreation (conversation, reading, preparation for classes, TV, Internet)	3 hour 20 minute	307.91	9.06	5 hour 10 minute	477.26	13.76
Household work (washing, cleaning)	1 hour	130.01	3.83	1 hour	130.01	3.75
Active recreation (indoor walking, walking, driving)	3 hour	478.15	14.08	5 hour	796.92	22.99
Study	3 hour	377.12	11.10	-	-	-
Intense physical activity	3 hour	1333.62	39.27	3 hour	1333.62	38.46
TOTAL:	24 hour	3396.35	100%	24 hour	3467.15	100%

Table 2

Actual and recommended daily grocery set freestyle wrestlers of School of higher sports skill

Products	Summer (n=18)	Autumn (n=11)	Winter (n=14)	Spring (n=20)	Norm *
Meat (beef, foal , venison, pork, chicken)	211.4 (40.3)	132.3 (20.5)	160 (18.3)	191.4 (37.4)	300
Meat products (jelly, cutlets, sausages)	100 (13.1)	78.6 (16.5)	81.1 (18.1)	113.2 (9.4)	50
Beef offal (tongue, liver, giblets)	20.9 (2.4)	20 (3.5)	20.8 (3.7)	18.7 (2.8)	100
Fish	100 (8.8)	100 (12.0)	150 (12.5)	97.7 (5.2)	90
Egg	47 (15.5)	47 (11.5)	47 (14.3)	47 (10.2)	47
Butter	20.6 (1.7)	15.5 (1.5)	40 (1.4)	35 (2.5)	80
Vegetable oil	20 (0.8)	20 (1.2)	20 (1.4)	20 (1.1)	-
Dairy products (milk, kefir)	300 (30.0)	300 (27.5)	300 (10.1)	300 (18.8)	600
Sour cream	26.7 (2.2)	16.4 (3.0)	20.8 (2.1)	30.5 (1.3)	30
Cream (whipped with berries)	-	100±27.45	-	-	-
Cheeses	9.8 (1.6)	18.6 (3.0)	10 (2.0)	10 (1.5)	30
Cereals	208.9 (28.2)	284.5 (16.2)	175.0 (14.2)	238.4 (11.4)	90
Vegetables	94.4 (9.7)	160.9 (15.2)	100 (13.5)	65.2 (5.2)	400
Potato	97.8 (8.7)	100 (6.5)	88.4 (7.1)	150.0 (10.9)	300
Fresh fruit	262.8 (11.6)	300 (10.7)	67.2 (3.9)	73.3 (6.1)	500
Sweet (sugar, sweets, etc.)	29.8 (5.1)	29.2 (4.9)	38.2 (3.4)	27.9 (4.2)	100
Flour confectionery products (bun, cupcake, cake, etc.)	110.3 (6.5)	125.5 (3.4)	132.2 (6.5)	65.4 (5.0)	130
Pasta	96.1(5.5)	183.6 (7.9)	186.1 (4.8)	150 (9.1)	-
Bread	237.2 (5.8)	189.1 (7.6)	105.0 (4.2)	154.2 (3.9)	350
Juices (natural, canned, mors, compote from agricultural products)	200 (17.0)	200 (21.3)	125.0 (7.2)	164.5 (6.5)	400
Drinks (black tea, green tea, coffee)	1275.0 (51.5)	1304.5 (72.1)	1019.4 (90.4)	1027.4 (47.0)	-
Water	1750.0 (46.4)	1150.0 (30.1)	3800.00	5600.00	2000
Coca-Cola	100.0 (18.9)	18.2 (1.8)	58.3 (5.5)	45.2 (3.6)	-
Honey	10 (0.8)	10 (1.2)	10 (1.4)	10 (1.3)	-
Nuts	70 (6.0)	70 (6.5)	70 (8.8)	70 (5.7)	-
KCAL	4234.3	4359.6	3999.3	3993.0	

Note - the data is presented in the form of average and standard deviation in the format M (SD);*) – recommended food set for freestyle wrestlers (Appendix No. 10), order No. 325 of 21.10.12 of the Ministry of sports of the Russian Federation.

milk and dairy products, bread and flour confectionery, various types of cereals, pasta, fruits and vegetables. In table 2 presents the main daily set of food products examined by us freestyle wrestlers depending on the season of the year.

Data presented in table 2, indicate that all products of the daily set in all seasons of the year did not meet the recommended standards. Thus, the greatest amount of meat (211,38 (40,3) g) athletes consumed in the summer. However, its content in the summer diet was 1,4 times less than the recommended values. The greatest consumption of dairy products by athletes was noted in the autumn period of the year, however, it was 6,2 times less than the recommended amount per day. It should be noted that dairy products present in the diet of athletes did not differ in diversity. The main dairy products were milk and kefir. Butter, sour cream, cheeses, and fish were consumed by athletes in very low amounts throughout the year. Eggs in sufficient quantities in the daily diet were present only in the spring season.

Fruit during the year, athletes consumed less than the recommended norms. The highest fruit consumption was observed in the summer and amounted to 262,78 (11,6) g, which was 1,9 times less than the norm. Athletes consumed vegetables 5,5 times less than the norm during the year. The total amount of carbohydrates was replenished mainly by cereals, bread and flour confectionery products. Dried fruits, nuts, and honey were consumed by athletes in very small quantities. The daily caloric content of the food ration of wrestlers depended on the food set. In summer, the caloric content of the diet was the highest and amounted to 4234,3 kcal, in autumn-4359,6 kcal, in winter-3999,3 kcal, in spring-3993,0 kcal. According to our data, the average energy value of the daily diet of wrestlers in all seasons of the year was 4146,53 kcal, which is 13% lower than the calculated average for these athletes. Analysis of the seasonal dynamics of the energy value of athletes ' diets showed that the energy value of the actual nutrition of athletes covered the main exchange and energy spent on intensive physical activity only in summer and autumn, and in winter and spring did not correspond to energy consumption. However, it should be noted that using the time-table method, the daily energy consumption can only be obtained approximately. The energy consumption shown in the tables is of relative importance, since the energy consumption when performing even one type of work can fluctuate for various reasons, depending on the state of the body, the level of training and other factors.

The calculation of the chemical composition of the main nutrients showed that the daily intake of their athletes significantly differed from the recommended norms. We found insufficient intake of proteins, lipids and carbohydrates in all seasons of the year. The content of the main food substances in the daily diet of freestyle wrestlers is shown in fig. 1. The training process and participation in competitions (national, national and international) in School of higher sports skill requires significant muscle work, which is accompanied by increased protein breakdown. Therefore, the diet of athletes should contain a sufficient amount of easily digestible high-grade protein. At the same time, animal proteins should make up 55-70% of their total amount in the diet [4.13]. According to the standards for wrestlers per 1 kg of weight per day, it is recommended to use 2,4-2,5 g of protein, 2,0-2,1 g of fat and 9-10 g of carbohydrates. Our athletes' body weight averaged 69,91±5,68 kg, so they should consume 168 g of protein per day. The data shown in fig. 1, show that the lowest amounts of the main components of food fall during the winter period. Thus, the protein deficit in the daily diet of athletes (compared to the recommended values) was 53%. Even in the summer, when the

daily diet included the largest number of food components, the need for protein was met only by 78% (fig.1).

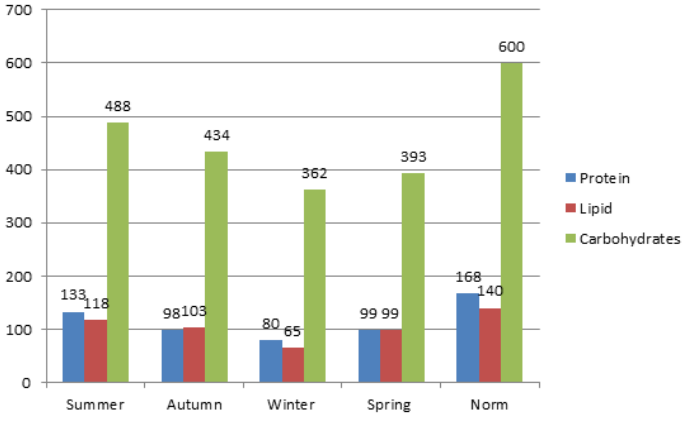

Fig. 1. The content of basic nutrients in the daily diet of freestyle wrestlers (g)

It is known, that protein metabolism is closely related to the exchange of other nutrients, in particular potassium, calcium and some vitamins. When the protein content in the diet is low, the loss of potassium and calcium increases in the body, and the daily urinary excretion of some water-soluble vitamins increases, despite their adequate intake with food [16]. In isolated studies on sports biochemistry, it is shown that the level of magnesium and ascorbic acid in the blood serum of athletes in the Far North is reduced [12].

Insufficient carbohydrate content in the diet is a factor that limits the physical performance of athletes, since muscle fatigue can be associated with depletion of glycogen stores in the muscles. With the body weight of the athletes we examined (69,91±5,68 kg), the amount of carbohydrates in their daily diet should be at least 630 g, but even in the summer, the need for carbohydrates was met only by 78% (Fig.1). The need for lipids in these athletes in winter was met by 46%, in spring and autumn - by 70%, in summer - by 84%, if we consider that the daily need for them at the rate of 2 g per 1 kg of weight is 140 g.

The lack of macro-and micronutrients negatively affects the health of athletes and their sports results. In this regard, it is necessary to use special sports nutrition products and vitamin and mineral preparations, depending on the intensity of physical activity, the stage of the training process and the season of the year.

The ratio of the main components of nutrition – proteins, fats and carbohydrates-is of great importance for adaptation to physical activity. Since even full provision of energy needs of the body due to one or two components (mainly fats or carbohydrates), with insufficient intake of other, for example, proteins, can cause changes in the body's metabolism. Modern research has established that the optimal ratio of protein, lipids and carbohydrates in the diet of athletes should be 1:0.8:4, in percentage terms it corresponds to 15:24:61 (in terms of calories) [2,6,18,22,26]. The actual weight ratio of proteins, lipids, carbohydrates (Proteins: Lipids:-Carbohydrates) of the daily diet of the athletes we examined by season was: in the summer period of the year 1,1:0,9:3,7; in the autumn period – 0,9:1,05:4,4; in the winter period – 1,2:0,8:4,5; in the spring period – 1:1:4. The distribution as a percentage of the daily caloric intake of athletes, depending on the season of the year, was as follows: in the summer – 15:30:55; in the autumn – 13:30:57; in the winter – 14:25:61; in the spring – 14:31:55. These data indicate that the actual nutrition of athletes in terms of quantitative and qualitative composition of food substances (proteins, lipids, carbohydrates) does not meet the standards recommended for wrestlers. The results of our research are consistent with the literature data [20,23,24].

Quantitative and qualitative analysis of daily diets indicates an excess of fat consumption, and at the expense of animal fats, and creates prerequisites for the violation of lipid metabolism in athletes and the occurrence of pathological conditions, such as diseases of the cardiovascular and digestive systems. A relative increase in the proportion of lipid, especially in the autumn period of the year, with a low content of carbohydrates in the daily diets of athletes is associated with a large consumption of oxygen and can lead to the accumulation of ketone bodies in the blood [25]. In addition, physical activity in a cold climate increases the level of oxygen consumption, which leads to an acceleration of oxidative processes. Excessive activation of lipid peroxidation when eating fatty foods is the most important maladaptation factor, reduces the body's motor capabilities, its endurance, reduces physical performance, and, consequently, negatively affects sports performance. In a few studies, it has been shown that the decrease in performance among athletes in Yakutia is associated with the accumulation of peroxidation products in the body of athletes [14].

Conclusion. Among highly qualified freestyle wrestlers of yakut nationality, persons with a brachymorphic somatotype predominate. This type of somatotype is characterized by medium or low growth, a relatively long body, broad shoulders, and a large chest circumference. Relatively high values of the body mass index and the Rohrer index of freestyle wrestlers indicate a large body density, which is associated with high indicators of muscle strength- the flexors of the forearm, the extensors of the hip and trunk.

The total daily energy consumption of freestyle wrestlers corresponds to the standards calculated for wrestlers. The daily caloric content of the diet of freestyle wrestlers was lower than the recommended norms and did not correspond to energy costs in all seasons of the year. The ratio of the main food nutrients: proteins, lipids and carbohydrates is also violated. When analyzing the quantitative and qualitative nutritional value of athletes, a decrease in protein consumption was found, especially in winter, and a relative excess of fat consumption, and at the expense of animal fats, which is unacceptable, since it worsens sports results, and creates prerequisites for a violation of lipid metabolism. At the same time, carbohydrates in the diets were not enough, which is a factor that significantly limits physical performance, since carbohydrates are the main source of energy for the body of athletes. Thus, the basic diets of freestyle wrestlers of the School of higher sports skill in Yakutsk did not correspond to the principles of rationality and balance, which can lead to a decrease in performance and speed of recovery processes and, as a result, to a deterioration in the effectiveness of training sessions, if no correction is made.

When organizing the rational nutrition of athletes engaged in sports in the North, it is necessary to take into account the general principles of nutrition, the specifics of the sport, the season of the year, the intensity of physical activity and the stage of the training process.

The development of nutrition standards for athletes in the Far North should be carried out at the level of Ministries and Departments, which include the School of higher sports skill in Yakutsk, and the approved standards for energy and food

consumption should correspond to the costs of freestyle wrestlers.

In nutrition in the School of higher sports skill of Yakutsk requires the use of special sports nutrition products and vitamin-mineral preparations to optimise the power depending on intensity of physical activity, stage of the training process and season. The use of special sports nutrition products, vitamin and mineral preparations and monitoring the effectiveness of their use should be carried out by a sports doctor. Questions concerning the use of special sports nutrition products and vitamin and mineral preparations should be included in the general educational program for the education of cultural and hygienic skills of healthy nutrition.

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INTERDISCIPLINARY APPROACH IN THE STUDY OF THE YAKUT DIET IN THE 17TH AND 19TH CENTURIES

DOI 10.25789/YMJ.2020.69.17

УДК 392.8+903+550.4

This article investigates the reconstruction of the diet of the ancient Yakuts using ethnographic, archaeological and biological approaches. A synthesis of historical and ethnographic literature on the food of the Yakuts since the 17th century was made. It indicates the importance of dairy and plant foods. Funeral food, consisting of the remains of meat and dairy products, was found in one third (55/145) of the studied burials. Analysis of stable carbon isotopes δ13C and nitrogen δ15N on bone collagen of 61 humans indicates mainly meat and milk nutrition. Significant fish consumption was identified in the Viluy district and Central Yakutia.

A comparative analysis of stable isotopes between the male and female did not show differences in their diet. Individuals with rich burials have low variability of stable isotopes, which indicates that they had a stable diet. Finally, we present the theoretical background of the detection of toxic substances in the hair.

An analysis of 47 buried samples shows an irregular consumption of tea and tobacco by Yakuts from the end of the 17th century.

Keywords: Yakutia, 17th-19th century, food, funeral meal, stable isotope analysis, toxin detection, methodological approaches in food studies.

Introduction. Anthropology of food has been developing since the 30s of the last century and is today an actively developing field of science characterized by an interdisciplinary approach that uses the methods of both the social and biological sciences. Food is an essential element of the people's material culture and is considered a sociocultural phenomenon. Its evolution can be understood in the broader historical, socio-economic, cultural and political context that accompany the development of societies through the centuries. The study of food allows us to infer modifications in lifestyle as well as developments in trade, economy, social structure and relationships, changes in tastes and eating behaviour, popular medicine and traditional customs, the worldview of the people and their interaction with their environment. As such, diet is a fertile study subject from the point of view of both the social and biological sciences.

The case of Yakutia is of particular interest because, on one hand, the exceptional preservation of the tombs makes possible not just the study of artefacts but also biochemical analyses, and on the other hand, a high number of ethnographic and historical documents can be compared to these results. The most important changes in the history of Yakutia occurred in 1620-1630, when Russian Cossacks penetrated the Middle Lena and annexed this new territory to the Russian Empire. This led to the development of local trade with Russians, and through them to international exchange, in particular through Sino-Russian trading points in Kyakhta, and then in Nerchinsk. As a result, the Yakuts, whose food was based on products of animal husbandry, hunting, fishing and gathering, gained access to a variety of goods, including flour, sugar, tea and tobacco. Over the next centuries, under the influence of new products, the role of some traditional food and its preparation was reduced or completely disappeared (for example, with the advent of cereals, the production of flour from pine bark lost its significance, the production of koumiss from mare's milk was significantly reduced, and instead consume large amounts of tea). Changes in nutrition led not only to the evolution of food models, but also to the symbolic meaning of food, its use in religious rituals (for example, salamat, porridge based on flour and cream, became an integral element of the rite of feeding the fire). To date, the study of the nutrition of ancient Yakuts is descriptive, while archaeological and biological approaches will determine the dietary features of specific individuals.

Yakutia underwent an important transformation beginning in 1620-1630, when Russian Cossacks invaded its territory and annexed it to the Russian empire. This led to the development of local trade with Russians, and through them to international contact, via the Sino-Russian trading posts in Kyakhta and Nertchinsk. As a result, the diet of Yakut tribes evolved from its reliance on horses and bovines to a more varied diet including flour, sugar, tea, and tobacco. Previously unknown food products became first accessible to the highest social classes, and then widely integrated in the general diet. Conversely, under the influence of new food products, the role of certain foods and food preparations was reduced (such as kumys, a fermented dairy product traditionally made from mare's milk was significantly reduced and instead tea is widely consumed) or even disappeared (for example, with the development of agriculture, the production of powder from pine bark lost its significance, and was replaced by wheat flour) over the course of the next centuries. Change in modes of food consumption led to changes in consumer tastes as well as in the symbolic value given to different foods and their use in religious rituals (for example salamat, a type of porridge made with flour and cream, was subsequently used in the rite of feeding the spirit of fire). Nowadays, the study of the food of ancient Yakuts is mainly descriptive, while archaeological and biological approaches will determine the dietary features of specific individuals.

Materials and methods. ***Ethnographic studies.*** The Yakut diet has been described in ethnographic publications concerning this region and travellers' records since the 17th century. At the end of the 19th century, the number of ethnographic literature on food increased. They specify the food in certain geographical areas [3] and differences of eating behaviour in social groups (poor and rich) [5]. Food is studied

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as an offering to spirits and in funeral rites [11]. The development of agriculture [8, 10] and traditional activities [9] are described. Two noteworthy studies on the Yakut diet have been conducted by ethnographers more recently. The first focuses on the diet of Yakuts before the development of tillage [6]. The second publication describes rituals and modes of consumption of traditional foods, including foods introduced by the Russians, in particular wheat flour. This study notably compares the Yakut diet with that of other turko-mongol populations [4].

Analysis of archaeological data. In our work, we studied 145 graves excavated by the Sakha-French archaeological expedition from 2002 to 2015 in the Republic of Sakha (Yakutia). All burials were divided into four geographical zones: Central Yakutia, Viluy, Verkhoyansk and Indigirka. Four chrono-cultural periods were defined on the basis of C14 dating, dendrochronology and the study of artefacts: 1) before 1700, when the Russian presence was undetectable; 2) from 1700 to 1750, called the "golden age" characterized by increasing number of artefacts commonly put with the deceased in tombs; 3) from 1750 to 1800, a decline in the population following most likely devastating epidemics and the extermination of fur-bearing animals, which served as goods for trade and for paying yasak, a fur tax. 4) after 1800, when Christianization was widespread if not total, which caused a transformation of funerary practice: burials of this time, apart from some exceptions, do not include any artefacts [15]. The object of our study is the meat and milk residues found in these burials. The presence of permafrost throughout Yakutia contributes to the satisfactory preservation of biological material in burials, which, in turn, allows obtaining complete samples for biochemical analyzes to determine the nutrition of Yakuts.

Analysis of stable carbon and nitrogen isotopes (δ13C and δ15N). The essence of this method is the expression "we are what we eat", in other words, the individual is considered within the food chain. The methodology consists in the extraction of the bone collagen (from the femur in our case) which is then analysed by mass spectrometry. Bone collagen is renewed very slowly, especially in adults, which mean that isotopic data represent the average diet of 5-7 years before the death of the individual [25]. Carbon and nitrogen have two stable isotopes: "light" isotopes containing less neutrons in the nucleus (C12 et N14) and "heavy" isotopes (C13 et N15). The concentrations of heavy isotopes are used to reconstitute the diet of an individual. Differences in the isotopic composition are transmitted along the food chain, with enriching with nitrogen by 3-5 ‰ and carbon by about 1-2 ‰ on each level [13, 14, 16, 19, 20]. Carbon absorption is determined by the type of photosynthesis: plants that use C3 photosynthesis have a lower concentration of the carbon isotopes: their isotopic signature ranges from -24‰ to -34‰, while in C4 plants this ranges between -6‰ and -19‰ [23]. The isotopic value is different for marine and terrestrial plans as the concentration of C13 in ocean water is 7‰ higher than in sedimentary water. As a consequence, C13 concentration is higher in marine plants than in C3 photosynthesis plants [20]. The values of fresh water plants, and hence freshwater fish, can be very diverse depending on local conditions [14, 17]. Variations are due to differences in water temperature, especially in deep lakes, and sunlight [18]. The most commonly measured values are: 2 to 7‰ for terrestrial herbivores, 7 to 12‰ for terrestrial carnivores, and 12 à 20‰ for marine vertebrates [14].

Detection of nicotine and theine in hair. Hair presents a record of molecules with which we are and have been in contact. During its growth, it stores data on our diet and environment within its protein structure. One centimetre of hair gives information on a month of the subject's life [21]. In recent years, hair analysis has been used successfully for the detection of the consumption of drug and other toxic products in clinical and judicial expert reports [24].

Results and discussions. ***Ethnographic data on the Yakuts' food.*** In the first records of travellers, plants, pine bark, game, including a variety of birds and rodents, fish and dairy products are described as food [2]. They remarked on the popularity of tobacco and alcohol in the local population [1, 7]. The end of the 19th century saw an expansion of the ethnographic literature describing the foods consumed (bread, meat, dairy, fish and tea) [12]. Kumys stands out from other dairy products. An important role of plants is highlighted. The widespread of tea and bread is noted [9]. Lake fish (crucian carp and minnow) is considered as food for the poor people while mare meat is the most honorable [5]. Noting the wide variety of geographic conditions in the vast territory of Yakutia, A. Savvin proposes to distinguish four regions according the diet of their inhabitants: 1) The southern regions: Central Yakutia, the Vilui Basin, and the Olyokma Basin. The principal activity is cattle and horse breeding, hence the predominance of dairy products and meat in the diet. 2) The lower plains of Lena and Viluy, as well as the Indigirka and Kolyma rivers. In this region, fishing supersedes herding. Fish and dairy products form the basis of the diet. 3) The mountainous region covering the territories of Verkhoyansk, Moma, Oymyakon and a part of Sakkyryr. The main activities in this region are herding and hunting. Meat and dairy products are consumed more often, but fishing and plant gathering are also important. 4) The extreme North covering the coastline from 68-70° northern latitude. The main foods are fish and game [6].

Funeral food. Food residues were found in one third of all burials studied (55/145). Before the 19th century, food was found from 43 to 69% of burials, then after 1800 only 7% of burials contain food remains. Generally, meat and dairy products placed directly on the soil or in dishes. They could be found either inside or outside the coffin, more commonly near the feet of the deceased but sometimes near their heads. In most cases, meat is put with bones, sometimes pieces of meat without bone are found in dishes or on a wooden skewer. This is generally horse meat, with some cases of bovine or game meat: hare, duck or crane. Dairy products have a thick and / or fatty consistency: fermented milk called *souorat* or *tar* found in *kytyia*, fresh cream, or melted butter poured in birch bark, *mataarchakh* or *tchoron*. Dishes can be covered with leather, birch bark or a plank. Often a wooden spoon is put in a *kytyia*. The Omouk 1 tomb dating from the 19th century, contained a metal plate with a mixture of dairy product and berries. In three children's tombs of the same site a tiny quantity of fish bones was uncovered in the Djarama site.

Food remains in tombs allow us to talk about food as part of the funeral ritual. Yakuts believed that the soul of the deceased had to undergo a dangerous journey to reach the other world where there is life after death, which resembles life on earth, with its material needs. However, it is necessary to take into account the fact that the archaeological finds present a selective picture, and were not necessarily representative of the diet of the living subject. We also don't have access to the totality of the food products originally deposited. In particular, some vessels intended for dairy products were found empty. They

could initially contain milk products of liquid consistency, evaporated over time and did not reach our days.

Possibilities of biochemical analysis in the study of food. When reconstructing human diet, it is first necessary to analyse the isotopic composition of possible participants in the trophic chain. To do this, we have analysed the remains of animal bones from burials, as well as modern river and lake fish. Collagen extracted from the human femur was studied for 61 individuals. The advantage of the stable isotope method consists in a precise quantitative evaluation of the diet of humans and animals. It allows to determine the type of environment in which the subjects lived and their main food sources: plant, fish or terrestrial animal. It doesn't however allow us to distinguish different types of animal protein consumed by a subject, as meat and dairy products have the same isotopic value. It is also difficult to detect a diet based on freshwater fish as the isotopic value of freshwater fish is close to that of terrestrial animals [19]. Analyses confirmed mainly meat and milk based diet of the ancient Yakuts, with some regional features. Thus, the lowest stable nitrogen isotopes were found in the Verkhoyansk and Oymyakon regions, where δ15N is 10.0 10 ± 0.5 (1SD, n = 15), which indicates diet based on animal meat and milk. In contrast to the northern regions, in the Viluy district, high values of δ15N were noted (11.7 ‰ ± 0.9, 1SD, n = 9). Samples from Central Yakutia show a wide range of δ15N values, which varies from 9.5 to 11.9 ‰ (δ15N = 11.0 ‰ ± 0.7, 1SD, n = 34). These data indicate the important role of fish in the nutrition of individuals from these two regions. A comparison of the diet between adult men and women showed no differences. The mean values of both δ15N and δ13C turned out to be the same for men (δ13C = −20.4 ‰ ± 0.4 and δ15N = 10.8 ‰ ± 0.8, 1SD, n = 25) and for women (δ13C = −20.4 ‰ ± 0.3 and δ15N = 10.8 ‰ ± 0.8, 1SD, n = 21), which confirms similar food practices for both sexes. Contrary to ethnographic data, claiming predominantly fish consumption by poor people, isotopic data do not show this. However, the variability of stable nitrogen and carbon isotopes is much lower in individuals from rich burials with a large number of artefacts (δ13C = −20.4 ‰ ± 0.1 and δ15N = 11.2 ‰ ± 0.5, 1SD, n = 9). This suggests that they had a more stable diet than individuals from other social groups [22].

To identify tea and tobacco consumption, we analysed 47 hair samples. We used hair analysis to detect the presence and/or measure the concentration of (i) nicotine or cotinine, its primary metabolite and (ii) three methylxantines (caffeine, theophylline and theobromine). The first analysis allows to determine if the subject smoked or was exposed to tobacco smoke. The three methylxantines are stimulants present in tea which allow to detect and/or measure the consumption of tea by ancient Yakuts. The good preservation of the material and the application of specific detection methods allow us to precisely and reliably detect these toxins. At this stage of the work, we can argue about the occasional consumption of tea and tobacco by Yakuts from the end of the 17th century.

Conclusion. Anthropology of food, situated at the intersection of social and biological sciences, is today an actively developing field of science. Traditionally, the food of past populations was studied by historians and archaeologists relying on written and material sources, but today the possibilities of biological and biochemical analyses on human samples open up a new perspective in the study of living conditions and food practices in the past. Ethnographic literature from the 17th to the 20th centuries testifies to the diet of Yakuts, based on livestock products. Hunting, fishing and gathering have a supporting role and their importance depends on the geographical area. The literature emphasizes the importance of dairy and plant foods. There is a change in the diet of Yakuts with the Russian colonization, when new products were introduced and the agriculture started to develop. An analysis of archaeological material indicates the importance of food in funeral rite before mass christianization in the 19th century. It consists mainly of horse / foal meat and dairy products. Analysis of stable nitrogen and carbon isotopes on bone collagen indicates the trophic level of the individual, i.e. its position in the food chain. The samples studied show the consumption of meat, milk and fish. Finally, for the first time, the consumption of tea and tobacco is becoming the subject of special study. This article provides the methodological basis for the analysis of toxic substances in the hair of the buried, which shows the occasional consumption of these products by Yakuts from the end of the 17th century.

Each of these methods has its advantages and disadvantages, which justifies the interest in a comprehensive study of food. Thus, ethnographic literature provides general information, gives context and is necessary for the interpretation of analysis results. When analysing archaeological material, it is necessary to remember its selective nature, which does not always reflect the daily nutrition during the lifetime of individuals. The method of stable isotopes allows us to determine the diet of specific individuals, and the comparison inside of the group shows differences between sexes and social status. However, he does not distinguish the consumption of meat from the milk, does not show the role of plant foods either. The diversity of these products consumed by Yakuts we can learn only from ethnographic sources. Therefore, comparison of the results of various disciplines helps to trace the evolution of food of Yakuts in all its complexity and diversity.

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ARCTIC MEDICINE

T.E. Burtseva, N.I. Douglas, S.S. Sleptsova, N.M. Gogolev, T.Yu. Pavlova, E.A.Borisova, I.S. Boulshiy, M.P. Slobodchikova

MAIN INDICATORS IN STATE PROGRAM EFFICACY EVALUATION: MATERNAL AND CHILD HEALTHCARE IN THE ARCTIC ZONE OF THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.69.18

УДК 616-053.2(571.56)

The article represents the main indicators of the maternal and child healthcare service in the Arctic regions of the Republic of Sakha (Yakutia), common data for the Republic of Sakha (Yakutia) and the Russian Federation for the period of 2000-2018. Infant and maternal mortality rates are the main indicators and the demographic indices, thus clearly reflecting the development rate of the country, region and healthcare system. The analysis of infant and maternal mortality indices in the Republic of Sakha (Yakutia), including its Arctic regions, is represented in the article. According to the official medical statistics the rate of infant and maternal mortality in the Arctic zone of the Republic of Sakha (Yakutia) has decreased to minimum.

Key words: infant mortality, maternal mortality, Yakutia, the Arctic, an Arctic zone of Russia

Introduction. A regional healthcare development program of the Republic of Sakha (Yakutia) includes the maintenance of modern infrastructure of healthcare service for the period of 2019 – 2024. The main indicators of the program, concerning infant and maternal healthcare, are:

1. Decrease of infant mortality rate to 4.2 per 1000 live births in the Republic of Sakha (Yakutia) by 2024.
2. Reduction of pre-term deliveries at 22-37 weeks of gestation to 55% in the prenatal centers by 2024; which can be achieved by improving efficacy of obstetrics and infant healthcare.
3. Decrease of child mortality rate (under-four deaths rate) to 5.9% per 1000 live births by 2024.
4. Decrease of child mortality rate (from 0 to 17) to 55.0% per 100000 children of the certain age.

The considerable positive results of the efficacy of the main indicators are being noticed at the moment of realization of the regional program.

Materials and methods: The Arctic zone of the Republic of Sakha (Yakutia) is represented by 13 circumpolar (Arctic and Subarctic) regions as: Abiyskiy, Allaikhovskiy, Anabarskiy (Dolgano-Evenkiyskiy national), Bulunskiy, Verkhnekolymskiy, Verkhoyanskiy, Zhiganskiy (Zhiganskiy Evenkiyskiy national), Momskiy, Nizhekolymaskiy, Olenekskiy Evenkiyskiy national, Srednekolymskiy, Ust-Yanskiy, Eveno-Bytantayskiy national regions.

The analysis of medical and demographical indicators, concerning child and maternal healthcare in the Republic of Sakha (Yakutia) and its circumpolar regions for the period of 2000-2018, is represented in the article. The analysis is based on the special database of the state institution ‘Yakut Republican medical center of informatics and analysis under the healthcare ministry of the Republic of Sakha (Yakutia)’ (editions of the statistics “The main indicators of the health status of the population, activities and resources of medical organizations of the Republic of Sakha (Yakutia)” for 2003, 2006, 2008, 2013, 2018 and 2019). This database includes all cases of births, deaths, initial and common disease incidences of the population for the period of 2000-2018. The content-analysis is carried out.

By the present times the Republic of Sakha (Yakutia) still remains most isolated and hard-to-reach regions of the Russian Federation, especially for its circumpolar regions. Among all the substantial tasks the problem of healthcare service organization for the circumpolar regions of the Republic of Sakha (Yakutia) is of principle importance. Most of the normative legal documents in the field of healthcare do not take into account the specificity of the Arctic regions. The Republic of Sakha (Yakutia) is not an exception.

A three-level system of healthcare service for pregnant and parturient women, concerning the region specificity, is described, hospital bed fund is represented.

A detailed analysis of the medical and demographic indicators enables to evaluate the efficacy of organizing the healthcare resources and positive indicators of effective realizing of large scales of federal and regional child and maternity healthcare programs.

Results and discussion. The organization and work of the obstetric and medical healthcare for children of the Republic of Sakha (Yakutia) is represented this way. There are 741 obstetric beds in the Republic of Sakha (Yakutia), obstetric bed provision is 31.0 per 10000 women at the fertile age (31.3 in 2017): among them 339 beds for pregnant and parturient women, with the provision of 14.2 per 10000 (15.0 in 2017)

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and 402 beds for obstetric pathology patients, with the provision of 16.8 (16.3 in 2017). The gynecological profile beds number is 402, the gynecological bed provision is 8.1 per 10000 of female population (8.0 in 2017).

The obstetric bed provision in the Republic of Sakha (Yakutia) by 01.01.2018 was 31.0; the numbers increase a mean index for the Russian Federation (17.99 in the Russian Federation in 2017). It is associated with the huge territory of the Republic of Sakha (Yakutia), remote and hard-to-reach villages located far from healthcare services and absence of transport infrastructure, especially in the Arctic regions of it.

The obstetric and gynecological medical staff provision was 5.7 per 10000 of female population by 2018 (5.6 in 2017). There are 284 obstetricians and gynecologists, 62.7% of them have the qualified category of the specialist (62.7% in 2017), among them the highest category of the specialist is in 38.4% (35.9% in 2017), the first category in 16.2% (14.9% in 2017), and second category in 8.1% (12% in 2017). There are 99.6% certified obstetricians and gynecologists (99.3% in2017).

Since 2011 the Republic of Sakha (Yakutia) practices a three-level system of healthcare service assistance for pregnancy, birth and neonatal periods, according to the Republic of Sakha (Yakutia) Ministry of healthcare order #808n dated 02.10.2009 “On maintenance of obstetric and gynecological medical assistance procedure”. According to the Russian Federation Ministry of healthcare order #572n dated 12.11.2012, the obstetric and gynecological medical assistance is performed by the levels since 2013:

I-st level – 29 maternity departments with 283 beds, which compose 38.2% of the obstetric bed fund.

II-nd level – 6 maternity departments with 218 beds, which compose 29.4% (Aldanskaya central regional hospital, Lenskaya central regional hospital, Megino-Kangalasskaya central regional hospital, Mirninskaya central regional hospital, Nerungrinskaya central regional hospital, Khangalasskaya central regional hospital).

III-rd level – 2 perinatal centers based on Republican hospital #1 National health center, Yakutsk Republican clinical hospital with 240 beds (32.4%).

The pediatric bed fund of the Republic of Sakha (Yakutia) is represented by somatic (pediatric) 719 beds, and 703 specialized day-and-night service beds for each 22 medical profiles. In 2018 the numbers of pediatric beds increased by 3 % from 1380 beds to 1422, if to compare it with 2017. In 2019 the number of somatic pediatric beds increased by 4.8% up to 719 beds; specialized beds number increased by 1.3% up to 703 beds. Thus, a quota of pediatric beds total number has increased to 50.6%, specialized to 49.4%.

The pediatric (somatic) hospital bed provision was 27.2 per 10000 of children population (26.3 in 2017). The specialized pediatric bed provision was 26.6 (26.6 in 2017).

The table 1 shows that the indicators of birth in the Arctic zone of the Republic of Sakha (Yakutia) and the Republic of Sakha (Yakutia) proper are higher than in the Russian Federation. Moreover, the indicator is by 31% higher in the Arctic regions of the Republic of Sakha (Yakutia), than in the Russian Federation. In 2018 the highest indicators of the birth rate were noticed in Olenyokskiy region

Table 1

The dynamics of the birth rate in the Arctic regions of the Republic of Sakha (Yakutia), the Republic of Sakha (Yakutia) proper and the Russian Federation in 2000 – 2018 [1-6]

Regions	2000	2005	2010	2015	2016	2017	2018
Abiyskiy	15.4	10.6	15.1	13.6	9.6	13.6	12.5
Allaikhovskiy	15.3	17.3	12.4	19.6	18.1	14.7	13.6
Anabarskiy	19.7	20.3	17.9	20.5	20.8	21.8	16.2
Bulunskiy	14.6	11.9	15.2	14	14.1	14.3	11.4
Verkhnekolymskiy	10.0	10.1	10.3	11.7	12.0	11.0	8.8
Verkhoyanskiy	15.0	15.5	18.7	19.8	18.3	16.8	13.5
Zhiganskiy	12.6	19.9	22.4	22.8	17.9	18.0	16.9
Momskiy	17.3	19.2	17.9	23.2	18.0	17.6	14.4
Nizhnekolymskiy	11.6	12.8	14.3	17.9	15.5	12.9	14.5
Olenyokskiy	11.6	13.7	24.1	22.1	22.5	22.8	23.6
Srednekolymskiy	13.9	12.8	17.5	19.3	15.1	16.3	13.4
Ust-Yanskiy	9.0	10.3	11.9	17.9	17.6	15.5	13.2
Eveno-Bytantaiskiy	22.6	11.5	16.8	16.1	18.3	17.9	22.0
Mean number by the Arctic regions	14.5	14.3	16.5	18.3	16.6	16.2	14.3
The Republic of Sakha (Yakutia)	13.5	14.3	16.8	17.1	16.0	14.5	13.7
The Russian Federation	8.7	10.2	12.4	13.3	12.9	11.5	10.9

Примечание. Показатели в табл. 1-5 взяты из упомянутых статистических сборников.

Table 2

Dynamics of absolute numbers of the births in the Arctic regions of the Republic of Sakha (Yakutia), the Republic of Sakha (Yakutia)proper, and the Russian Federation for the period of 2000-2018 [1-6]

Regions	2000	2005	2010	2015	2016	2017	2018
Abiyskiy	64	40	57	15	14	21	13
Allaikhovskiy	50	45	27	13	13	5	5
Anabarskiy	51	65	31	15	29	32	6
Bulunskiy	135	107	118	66	74	54	33
Verkhnekolymskiy	57	51	47	23	37	25	21
Verkhoyanskiy	246	184	214	133	115	79	39
Zhiganskiy	42	58	69	59	50	37	34
Momskiy	68	69	54	39	24	33	6
Nizhnekolymskiy	98	68	51	38	42	19	24
Olenyokskiy	58	34	58	16	17	10	12
Srednekolymskiy	117	78	123	89	57	61	30
Ust-Yanskiy	100	78	80	72	50	61	30
Eveno-Bytantaiskiy	26	9	8	3	3	2	2
Total number for the Arctic regions	1112	886	937	581	525	439	255
Part, %	8.4	6.4	5.9	3.5	3.4	3.2	1.9
The Republic of Sakha (Yakutia)	13147	13656	15905	16379	15425	13686	13375

Table 3

Dynamics of the part of the normal delivery in the Arctic regions of the Republic of Sakha (Yakutia), and the Republic of Sakha (Yakutia) proper (2000-2018) [1-6]

Regions	2000	2005	2010	2015	2016	2017	2018
Abiyskiy	50.0	75.0	43.9	86.7	78.6	95.2	76.9
Allaikhovskiy	98.0	71.1	51.9	100.0	53.8	20.0	60.0
Anabarskiy	70.6	49.2	71.0	73.3	75.9	56.3	33.3
Bulunskiy	31.1	37.4	65.3	39.4	75.7	81.5	81.8
Verkhnekolymskiy	71.9	68.6	74.5	43.5	89.2	72.0	71.4
Verkhoyanskiy	78.5	23.4	39.7	85.7	85.2	77.2	33.3
Zhiganskiy	80.9	82.8	71.0	83.1	84.0	78.4	79.4
Momskiy	52.9	26.1	46.3	30.8	45.8	69.7	83.3
Nizhnekolymskiy	81.4	58.8	68.6	84.2	78.6	52.6	91.7
Olenyokskiy	82.8	43.8	79.3	100.0	82.4	70.0	83.3
Srednekolymskiy	81.2	38.5	71.5	67.4	40.4	32.8	26.7
Ust-Yanskiy	15.0	25.6	73.8	94.4	72.0	75.4	90.0
Eveno-Bytantaiskiy	42.3	88.9	100.0	100.0	66.7	100.0	50.0
Total for the Arctic regions	64.3	53.0	65.9	76.0	71.4	67.8	66.2
The Republic of Sakha (Yakutia)	33.7	42.7	50.0	52.3	51.2	48.6	47.9

Table 4

The dynamics of infant mortality rate in the Arctic regions of the Republic of Sakha (Yakutia), and the Republic of Sakha (Yakutia) proper (2000-2018) [1-6]

Regions	2000	2005	2010	2015	2016	2017	2018	‰
Abiyskiy	25.0	20.4	14.9	15.2	25.6	0	0	
Allaikhovskiy	30.8	38.6	0	18.9	0	25.0	0	
Anabarskiy	95.9	47.5	18.2	13.3	0	13.0	0	
Bulunskiy	13.8	17.9	16.0	0	16.0	0	10.5	
Verkhnekolymskiy	15.9	0	0	0	19.6	0	0	
Verkhoyanskiy	20.4	15.4	12.5	8.8	0	5.2	0	
Zhiganskiy	12.5	0	20.8	0	26.3	0	0	
Momskiy	22.7	0	12.0	51.5	10.3	0	0	
Nizhnekolymskiy	22.5	0	41.5	12.7	14.7	0	0	
Olenyokskiy	27.4	17.9	20.2	11.4	22.2	0	0	
Srednekolymskiy	7.1	22.7	7.2	20.7	0	8.2	10.0	
Ust-Yanskiy	22.5	0	20.8	0	17.9	18.0	10.8	
Eveno-Bytantaiskiy	54.1	0	0	0	0	0	0	
The mean number for the Arctic regions	28.5	13.9	14.2	11.7	13.1	5.3	2.4	-26.1
The Republic of Sakha (Yakutia)	17.6	10.6	7.2	7.6	7.2	5.1	5.0	-12.6
The Russian Federation	15.3	11.0	7.5	6.5	6.0	5.6	5.1	-10.2

Table 5

Dynamics of maternal mortality cases in the Arctic regions of the Republic of Sakha (Yakutia), the Republic of Sakha (Yakutia) proper for 2000-2018. [1-6]

Regions	2000	2005	2010	2015	2016	2017	2018
Abiyskiy	-	-	-	-	-	-	-
Allaikhovskiy	-	-	-	-	-	-	-
Anabarskiy	-	-	-	-	-	-	-
Bulunskiy	1	-	-	-	-	-	-
Verkhnekolymskiy	-	-	-	-	-	-	-
Verkhoyanskiy	-	-	-	-	-	-	-
Zhiganskiy	-	-	-	-	-	-	-
Momskiy	1	-	-	-	-	-	-
Nizhnekolymskiy	-	-	-	-	-	-	-
Olenyokskiy	-	-	-	-	-	-	-
Srednekolymskiy	-	1	-	-	-	-	-
Ust-Yanskiy	-	-	-	-	-	-	-
Eveno-Bytantaiskiy	-	-	-	-	-	-	-
Total for the Arctic regions	2	1	-	-	-	-	-
The Republic of Sakha (Yakutia)		4	4	4	-	1	2

(23.6%), Eveno-Bytantayskiy (22.0%) and Zhiganskiy (16.9%) regions. The indicators of the birth rate are twice or more higher than in other regions of the Russian Federation.

Despite the high indicators of the birth rate in the Arctic regions of the Republic of Sakha (Yakutia) the numbers have decreased from 8.4% to 1.9% since 2000; it corresponds to the number of migration from these regions (table 2).

As it is shown in the table 3, the part of the normal delivery in the Arctic regions of the Republic of Sakha (Yakutia) is quite stable, so 64.3% in 2000 is a mean number for the Arctic regions of the Republic of Sakha (Yakutia); 66.2% in 2018. While in the Republic of Sakha (Yakutia) proper the mean number is considerably low, it was 33.7% in 2000, and 47.9% in 2018.

The index of the infant mortality rate for the period of 2000-2018 in the Republic of Sakha (Yakutia) was higher than the indices in the Russian Federation till 2017, since 2018 the indices decreased and became 5.1% in 2017, and 5% in 2018 (see table 4).

If we analyze the only 13 Arctic regions of the Republic of Sakha (Yakutia), taking into account difficulties in transport infrastructure, absence of a neonatologist in the medical staff of the Central regional hospitals, the index of the infant mortality rate will be high till 2016; these numbers will be higher than the ones for the whole Republic. In 2018 this index has decreased its historical minimum of 2.4%. It is well-known that the density of population in the Arctic regions is less than 10000, and when we calculate the indices of the infant mortality rate the law of small numbers makes sense, so even 1 case of the infant mortality will show high numbers in total. Besides that we should underline the positive fact of the absence of the infant mortality cases in 2018 in the following regions of the Arctic zone: Abiyskiy Allaikhovskiy, Anabarskiy, Verkhnekolymskiy, Verkhoyanskiy, Zhiganskiy, Momskiy, Nizhnekolymskiy, Olenyokskiy, and Eveno-Bytantaiskiy regions. It is doubtless that this is the result of a huge work of the whole team of the medical staff in the local regional hospitals, the Perinatal center of the maternity and child welfare, Pediatric center of the Republican hospital #1, National health center, Yakutsk Republican clinical hospital and the air medical service.

As it is shown in the table 5, the maternal mortality rate has sharply decreased in the Arctic regions of the Republic of Sakha (Yakutia) since 2000.

Since 2010 there are no registered cases of maternal mortality. This is also the result of the effectively organized three-level system of healthcare service for pregnant and parturient women; monitoring pregnant and parturient women. While there were 2 cases of the registered maternal mortality in the other regions of the Republic in 2018.

Conclusions. Having analyzed medical and demographic indicators for the period of 2000-2018 in the Arctic zone of the Republic of Sakha (Yakutia), we can constitute the following positive tendencies as:

1. High mean indices for the birth rate (18.4%);
2. Great portion of the normal delivery (66.2%);
3. Permanent decrease of the mean number in infant mortality rate to 2%;
4. No cases of maternal mortality;
5. Ways of effective organizing the healthcare service resources and positive indicators of its efficacy.

Funding. *It is a part of research of the Medical science centre of complex medical problems "Children health condition monitoring in the Republic of Sakha (Yakutia)" (state registration number: 0120-128-07-98); the project of the Ministry of science and higher education of the Russian Federation (2019-1472); and with a financial support from RFBR according to the research project #18-05-60035_Arctica.*

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INDICATORS OF THE CARDIOVASCULAR SYSTEM AND HEART RATE IN YOUNG MALE RESIDENTS OF MAGADAN REGION AT LOCAL EXPOSURE TO COLD

DOI 10.25789/YMJ.2020.69.19

УДК 612.176+612.014.43+612.899

The aim of this work was to study the alterations of cardiohemodynamics and the variability of the heart rhythm at rest and under local cold effects in individuals with different initial types of autonomic regulation.

Methods: In 54 young male people aged 17 to 19, background records of cardiac rhythm and hemodynamics were registered both at rest (lying on the couch) and during immersion of the contact hand in a container with water at a temperature of 4 ° C for 4 minutes.

Results of the work. It was found that the analyses of heart rate variability in vagonormotonic young men can neither at rest nor at the peak of the cold test provide an opportunity to adequately analyze the changes in the cardiorhythm index in response to the test. Whereas in the differentiation of the examined subjects according to their initial types of autonomic balance it was shown that in the sample of young men with the initial normotonic type of autonomic regulation at rest, higher values of arterial blood pressure and heart rate were observed with a pronounced hypertensive reaction in response to the cold test. In this case, the pattern of changes in the indices of the heart rate variability at a cold test indicates a statistically more pronounced activation of the sympathetic link of the autonomic nervous system. In the meantime, in the vagotonics group, the local cold effect did not change the character of autonomic regulation of cardiac rhythm against the background of significant dynamics of systolic and diastolic arterial pressure.

Conclusions: The obtained results indicate that young men with a predominance of parasympathetic orientation in the heart rhythm regulation demonstrate high stability of autonomic regulation to the presented cold test, which was manifested by the absence of statistically significant shifts in all studied cardiorhythm indicators and may indicate the cold resistance of this contingent.

Keywords: young men, cold test, cardiovascular system indicators, heart rhythm.

The significant material on the physiology of humans and animals with various forms of adaptation to low ambient temperatures [4, 10, 14] has been available now. Cold test is one of the common tests used for functional assessment of the microvascular state. It is associated with the creation of local tissue hypothermia in the zone of its contact with a cooling object of a small area, the low temperature of which is maintained for the required period of time [11]. Analysis of the references indicates a sufficient degree of study of the structure of the peripheral component of vasomotor reactions to relatively short-term acute local cooling of various body segments, as well as neurohumoral and local mechanisms of vascular tone regulation [3]. Also, at a sufficiently high level, the physiological mechanisms of the response of the cardiovascular system to the cold have been studied [5]. Moderate general cooling usually leads to an increase in systemic arterial blood pressure, cardiac output, and heart rate, which is associated with increased sympathetic ANS activity and general vasospasm at the periphery of the body [9]. In this regard, the peculiarities of rearrangements of systemic cardio hemodynamic parameters and heart rate variability at rest and during local cold exposure in individuals with different initial autonomic regulation types were studied.

Materials and methods. In total, 54 young men aged 17 to 19 years old, students of Northeastern State University (Magadan) were surveyed. Background records of heart rate, hemodynamic parameters were carried out while lying on the couch. After that, another contact brush was immersed in a container with water at a temperature in the range of 4 Cº for 4 minutes.

The cardiac rhythm was recorded using the Varicard instrument and the VARICARD-KARDi software, taking into account the guidelines of the group of Russian experts [1]. The following indicators of HRV were analyzed: mode (Mo, ms) - the most common value of the R-R interval; the difference between the maximum and minimum values of cardiointervals (MxDMn, ms); the number of pairs of cardiointervals with a difference of more than 50 ms in% of the total number of cardiointervals (pNN50, ms); standard deviation of the complete array of cardiointervals (SDNN, ms); mode amplitude with a class width of 50 ms (AMo50%, ms); index of tension of regulatory systems (SI, standard units); the total power of the heart rate spectrum (TP, ms2), the power spectrum of the high-frequency component of heart rate variability in the range of 0.4-0.15 Hz (respiratory waves) (HF, ms2); spectrum power of the low-fre-

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quency component of heart rate variability in the range of 0.15–0.04 Hz (LF, ms2); the power of the spectrum of the very low-frequency component of heart rate variability in the range of 0.04–0.015 Hz (VLF, ms2). Systolic (MAP, mmHg) and diastolic (DBP, mmHg) blood pressure and heart rate (HR, beats / min) were recorded with a Nessei DS – 1862 automatic blood pressure monitor (Japan) at rest (lying) and at the peak of the cold test.

The types of autonomic regulation were determined at rest on the basis of the values of the following indicators: MxDMn, SI, TP, where the range of eutonia (normotonia) for MxDMn we considered equal to 200 to 300 ms, for SI - from 70 to 140 conv. units, for TP - from 1000 to 2000 ms2 [6]. If the studied indices of MxDMn and TP were below these ranges, then the autonomic balance was assessed as sympathotonic, with an increase in the values of this corridor - as vagotonic. On the contrary, relative to the SI, with an increase in its values of more than 140 services. units (taking into account 2 other indicators) vegetative balance was assessed as sympathetic, and a decrease of less than 70 const. units, - vagotonicheskoy. Due to the small number of sympathotonics in the sample, the functional indicators of young men of this type in this series of studies were not analyzed. The sample for statistical analysis included individuals with normotonic and vagotonic types of vegetative regulation. All examinations were conducted in a room with a comfortable temperature of 19-21 ° C, in the morning. The study was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Ethical Committee for Biomedical Research at the NESC of the Far-Eastern Branch of the Russian Academy of Sciences (No. 004/013 dated December 10, 2013). Prior to inclusion in the study, all participants received written informed consent.

The results were subjected to statistical processing using the software package Statistica 7.0. The check for the normal distribution of the measured variables was carried out on the basis of the Shapiro – Wilk test. The results of non-parametric processing methods are presented as a median (Me) and interquartile range in the form of 25 and 75 percentiles, and parametric methods as an average value and its error (M ± m). In the case of a comparison of related samples, the statistical significance of differences was determined using the t – Student criterion for dependent samples with a normal distribution and the non-parametric Wilconson test for samples with a distribution other than normal. When comparing unrelated samples, the statistical significance of differences was determined using Student's t-test for independent samples with a parametric distribution and the non-parametric Mann – Whitney test for samples with a non-normal distribution. The critical level of significance (p) in the work was taken to be 0.05; 0.01; 0.001 [2].

Results and discussion. The main indicators of heart rate variability in young men - wagon-monitors in the city of Magadan at rest and at the peak of the cold test are presented in table 1. The obtained results did not allow us to conduct an adequate analysis of the rearrangement of heart rate indicators in response to the sample, because of the different heart rate indicators. Based on this, we carried out differentiation of the examined group according to the initial type of vegetative balance, as a result of which two groups of young men were distinguished: the 1st group is normotonics (n = 19) and the 2nd group - vagotonics (n = 35).

From the above data it can be seen (Table 2) that the examined young people of the two groups, differing in the initial type of autonomic balance at rest, have a number of differences in both the background indicators of the heart rate and the indicators at the peak of the cold test. When analyzing the results, it was found that the group of normotonics with respect to the tested vagotonics in the background state is characterized by statistically significant differences in almost all analyzed characteristics of HRV, which causes differentiation according to the initial autonomic type.

It can be seen from the above data that at the peak of performing a cold test of a young man — normotonics, compared with vagotonics, they are characterized by lower values of MxDMn, RMSSD, pNN50, Mo, all spectral indices of heart rate: TP, HF, LF, VLF and higher HR and SI. Changes in the indices of heart rate variability for the cold test had pronounced differences in the two groups examined. Thus, representatives from the number of normotonics in response to the cold sample presented were characterized by a decrease in RMSSD, pNN50, Mo, TP, HF, LF, VLF against the background of an increase in HR and SI. In the group of young men - vagotonics, no one analyzed cardiac rhythm index in response to the cold test showed significant dynamics.

Table 3 presents the main indicators of the cardiovascular system in the young men examined by us at rest and at the peak of cold exposure, taking into account the initial type of vegetative balance. From the above data it can be seen that in young men – normotonics at rest, statistically significantly higher indices of systolic, diastolic blood pressure and heart rate were noted. Short-term cold exposure in representatives of the two groups caused a significant increase in systolic and diastolic blood pressure, where a more pronounced hypertensive reaction of MAP was characteristic of normotonics with a simultaneous increase in heart rate, and an increase in DBP was more pronounced in the vagotonic group.

Analysis of the dynamics of the main characteristics of heart rate variability revealed a number of differences in the response to short-term cold exposure in groups with differences in the initial type of autonomic balance: thus, in the group with the initial normotonic type of autonomic balance, marked dynamics of al-

Таблица 1

Indicators of the Heart Rate Variability at rest and under local cold effects (Vagonormotonic)

Изучаемый показатель	Stage of Experiment		Significance of difference
	at rest	local cold effects	
HR, bpm	65.3 (59.5;72.9)	68.2 (62.9;74.8)	p<0.001
MxDMn, ms	344.0 (303.0;447.0)	384.0 (324.0;450.5)	p<0.05
RMSSD, ms	63.5 (46.1;82.9)	58.8 (45.7;76.1)	p=0.25
pNN50, %	40.2 (21.2;57.2)	36.0 (21.4;46.7)	p<0.001
SDNN, ms	71.1 (53.7; 86.8)	75.7 (62.8;92.8)	p<0.01
Mo, ms	888.0 (825.0; 1034.0)	856.0 (766.5;962.5)	p<0.001
AMo50, ms	30.3 (23.2; 37.5)	27.5 (23.8;33.1)	p<0.05
SI, arb. units.	44.9 (28.6; 73.3)	46.1 (27.3;61.2)	p=0.17
TP, ms ^{2}	3463.2 (2540.0; 4893.6)	3968.4 (2527.0;4973.5)	p=0.41
HF, ms ^{2}	1466.5 (769.9; 2415.8)	1491.2 (790.5;2226.5)	p=0.40
LF, ms ^{2}	1171.0 (703.8; 1827.9)	1380.1 (931.3;2112.5)	p=0.18
VLF, ms ^{2}	647.3 (395.0; 839.6)	650.6 (391.9;1270.3)	p=0.08

Таблица 2

Indicators of the Heart Rate Variability at rest and under local cold effects with different initial types of autonomic regulation, Me (25; 75-percentile)

Studied parameter	Нормотоники		Significance of difference baseline-Local cold effects	Vagotonic		Significance of difference baseline-Local cold effects	Significance of difference baseline normotonic – baseline vagotonic	Significance of difference local cold effects normotonic – local cold effects vagotonic
	at rest	local cold effects		at rest	local cold effects			
MxDMn, ms	344.9 (272.2;374.1)	325.1 (263.4;401.0)	p=0.37	378.0 (328.0;479.1)	423.1 (353.0;496.0)	p=0.17	p<0.05	p<0.05
RMSSD, ms	57.8 (38.8;61.3)	36.1 (26.7;64.1)	p<0.05	71.1 (47.1;88.5)	65.8 (54.5;75.3)	p=0.33	p<0.05	p<0.05
pNN50, %	33.2 (15.5;38.3)	13.1 (6.8;30.3)	p<0.05	44.9 (21.6;59.9)	40.8 (30.4;48.2)	p=0.23	p<0.05	p<0.05
SDNN, ms	67.7 (53.6;71.2)	70.4 (47.5;94.6)	p=0.23	75.1(64.6;92.3)	81.2 (70.2;99.1)	p=0.22	p<0.05	p=0.55
Mo, ms	831.1 (751.6;912.4)	709.6 (657.7;715.1)	p<0.05	915.3 (791.2;979.3)	878.0 (773.0;962.0)	p=0.18	p<0.05	p<0.001
AMo50, ms	33.4 (28.1;37.1)	35.9 (18.0;52.2)	p=0.87	26.2 (22.3;37.5)	26.0 (20.5;30.6)	p=0.49	p<0.05	p=0.68
SI, arb. units	76.8 (39.8;80.7)	92.8 (30.7;146.9)	p<0.05	37.6 (24.2;67.3)	33.5 (24.5;48.6)	p=0.53	p<0.05	p<0.05
TP, ms^2	3201.9 (2379.2;4670.1)	1814.9 (1003.1;4813.2)	p<0.05	3897.0 (3376.1;4938.8)	3969.9 (3097.4;4775.2)	p=0.96	p<0.05	p<0.05
HF, ms^2	1523.6 (521.1;1862.0)	813.2 (342.9;2193.7)	p<0.05	2049.1 (829.2;2805.2)	1705.6 (1007.3;2279.7)	p=0.11	p<0.05	p<0.05
LF, ms^2	1418.1 (908.3;1646.9)	853.6 (623.6;2026.3)	p<0.05	1200.1 (728.1;1882.5)	1299.9 (955.3;2051.5)	p=0.48	p<0.05	p<0.05
VLF, ms^2	516.2 (477.7;677.1)	276.2 (157.2;577.3)	p<0.05	565.7 (379.1;1293.2)	712.0 (418.9;1187.8)	p=0.43	p=0.73	p<0.05

most all the studied heart rate characteristics in response to the cold trial. A decrease in the activity of parasympathetic regulation was noted, as evidenced by a statistically significant decrease in MxDMN, RMSSD, pNN50 and Mo, which was manifested against the background of an increase in the activity of the sympathetic division of the autonomic nervous system, as indicated by a statistically significant increase in SI and HR. Analysis of the spectral parameters of HRV indicates a decrease in all those leaving the total power of the spectrum and, accordingly, the TP index in response to the cooling of the hands of the representatives of the 1st group. Thus, a decrease in the HF component of the total spectrum power (by 43%) is a reflection of the decrease in the activity of the respiratory waves and the activity of the parasympathetic division of the ANS during the cold test. Such a decrease in parasympathetic activity during the trial, in accordance with the fundamental provisions of the theory of accented sympathetic-parasympathetic antagonism [17], is aimed at providing sympathetic activation (which is manifested in an increase in SI and HR), as the main function of the sympathetic nervous system is changing blood circulation [7].

Also, in response to this type of exposure, a decrease in the LF and VLF components of the general spectrum was observed in the subjects from the group of normotics. Currently, a decrease in LF components of the heart rhythm with an increase in blood pressure is considered as an indicator of baroreflex dysfunction, which, apparently, due to the activation of the sympathetic link and causes such a pronounced increase in the BPS, as well as an increase in heart rate in people from the number of normotonics. At the same time, a decrease in the load-bearing VLF indicates a post-load energy shortage [8].

Table 3 shows that at rest, the average blood pressure values of both systolic and diastolic and heart rate were significantly lower in the vagotonic group, which can be considered as a more economical and efficient mode of functioning of the cardiovascular system. It should be noted that in the group of normotonic values, the systolic blood pressure values in the lying position approached the upper limit of the norm, which indicates a high normal blood pressure in the representatives of this sample [19].

Conclusion. Thus, studies have shown that the pattern of cardiac rhythm rearrangements, indicators of the cardiovascular system in response to cold exposure depends on the initial type of autonomic balance. In the examined, characterized by the initial autonomic type of vegetative regulation in the process of short-term cold exposure, no significant dynamics of the heart rate characteristics was recorded against the background of increasing BPS and BPD with preservation of HR not different from background values. At the same time, in the group of normotonics, pronounced changes in the cardiovascular system parameters in the form of significant hypertensive SBP reactions and an increase in heart rate were combined with a decrease in the activity of the parasympathetic link and activation of the sympathetic link in the regulation of heart rhythm [13]. At the same time, a decrease in LF components of the

Table 3

Indicators of the cardiovascular system in baseline and under local cold effects with different initial types of autonomic regulation, M ± m

Studied parameters	Stage of Experiment		Significance of difference baseline-Local cold effects
	at rest	local cold effects	
Normotonic			
BPS, mm Hg	137.7±2.9 *	146.3±3.1*	p<0.05
BPD, mm Hg	71.8±3.1*	77.7±3.4*	p<0.05
HR, bpm	72.5±3.9*	81.9±3.1*	p<0.05
Vagotonic			
BPS, mm Hg	129.1±2.1	135.2±2.5	p<0.01
BPD, mm Hg	66.1±2.0	73.3±1.7	p<0.001
HR, bpm	65.6±2.8	67.3±2.7	p=0.67

* Significance of difference normotonic – vagotonic

heart rate with an increase in blood pressure and heart rate may indicate baroreflex dysfunction [15], and a decrease in VLF on the loading effect may reflect the presence of afterload energy deficit in response to the cold sample [8]. Reducing the activity of the parasympathetic link in the regulation of heart rate in the group of normotonics, based on the theory of accented sympathetic-parasympathetic antagonism [17], apparently aimed at providing sympathetic activation to ensure adequate blood circulation in response to the cold test [7]. According to a number of researchers, adaptive changes in the characteristics of heart rate variability during prolonged exposure to cold are manifested by a decrease in sympathetic activity and a concomitant increase in parasympathetic activation [12, 16] and the transition of vegetative balance towards parasympathetic dominance in the regulation of the cardiovascular system, which, according to the authors evidence of increased cold resistance [14, 18]. The results obtained are generally consistent with our data, where it is shown that boys with a predominance of parasympathetic orientation in the regulation of heart rhythm for the cold test presented demonstrate a high stability of autonomous regulation, which was manifested by the absence of statistically significant shifts for all studied heart rate index.

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DISTINCTIVE FEATURES OF GASTRIC AND DUODENAL ULCER UNDER THE CONDITIONS OF THE EXTREME NORTH

DOI 10.25789/YMJ.2020.69.20

УДК 616.3-008.1-022-07

The clinical manifestations of ulcer associated with Helicobacter pylori were compared in patients of various ethnic groups of indigenous and non-indigenous origin living in the Extreme North. Out of 98 patients included in the study, the 1st group consisted of 51 indigenous people (80% of them were Yakuts), the 2nd group consisted of 47 non-indigenous (Caucasians).

The examined groups of patients were homogeneous by age, gender, and ethnicity. There were 27 indigenous men, 24 women, non-indigenous men 34, and 13 women. The age of the examined patients was from 18 to 68 years. When analyzing the clinical and endoscopic aspects of peptic ulcer disease in patients in the studied ethnic groups, a number of features was revealed.

The purpose of the research was a comprehensive study of the main clinical and endoscopic, morphological and functional features of erosive and ulcerative diseases of the stomach and duodenum in various ethnic groups living in the Extreme North.

Duodenal ulcer was detected more often in men of both ethnic groups than in women, $p<0.05$, respectively. In the indigenous group, peptic ulcer disease was detected mainly in middle working age, more often with localization of ulcer in the stomach.

The results obtained suggest that in patients with a long ulcer history, the degree of HP contamination in the mucous membrane is reduced. In the indigenous group with rarely recurring and first detected ulcers, 66.7% of the patients were poorly contaminated, and in the non-indigenous group of patients with rarely recurring ulcers, 44.7% of the patients had a low degree of contamination.

Keywords: gastric and duodenal ulcer, pain syndrome, dyspeptic disorders, gastric mucosa, Helicobacter pylori.

Introduction. The relevance of the study is primarily due to the object of study, which is represented by frequently and long-term ill patients with acid-dependent diseases (gastroesophageal reflux disease, chronic gastritis, peptic ulcer disease).

Recently, numerous studies confirm the presence of a definite relationship between Helicobacter pylori (HP) and associated gastroduodenal diseases. Among adults suffering from chronic gastritis (CG), HP is detected in more than 80% of cases, gastric ulcer (GU) - in 70-85%, duodenal ulcer (DU) - in 90-95% [1,3,4].

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Data from international epidemiological studies conducted about 20 years ago showed that the detection rate of Helicobacter pylori among patients with duodenal ulcer (DU) is 95%. Patients suffering from gastric ulcer are infected with HP in 60% of cases. Correspondingly, HP-negative DU is determined in 5%, and HP-negative GU in 40% of patients with peptic ulcer [2, 6].

The purpose of the research was a comprehensive study of the main clinical and endoscopic, morphological and functional features of erosive and ulcerative diseases of the stomach and duodenum in various ethnic groups living in the Extreme North.

Research methods and material. The clinical manifestations of ulcer associated with Helicobacter pylori were compared in patients of various ethnic groups of indigenous and non-indigenous origin living in the Extreme North. Out of 98 patients included in the study, the 1st group consisted of 51 indigenous people (80% of them were Yakuts), the 2nd group consisted of 47 non-indigenous (Caucasians).

The examined groups of patients were homogeneous by age, gender, and ethnicity. There were 27 indigenous men, 24 women, non-indigenous men 34, and 13 women. The age of the examined patients was from 18 to 68 years. Of these, men - 61 (62,2%), women - 37 (37,8%). Duodenal ulcer was detected more often in men of both ethnic groups than in women, D <0.05, respectively. The age group from 21 years to 40 years is the most representative -62 (63,3%) patients. There were 7 elderly and senile patients (7,1%), and young patients under 20 years old - 29 (29,6%).

The complex of the initial examination included esophagogastroduodenoscopy (EGD). The study was combined with a targeted biopsy, during which at least 2 pieces were taken: from the antrum mucosa and from the corpus gastricum; in case of erosion and ulcers - at least 4 pieces were taken from the mucous membrane.

Histologically, the presence of H. pylori was determined using enzyme immunoassay diagnostic system "HelikoBest antibodies." To confirm the eradication of H. pylori in patients along with the histological method used rapid urease test kits URE-Hp-Test-Pliva-Lachema (Brno, Czech Republic).

In assessing the results of histological examination for H. pylori are three degrees of contamination of the mucous membrane of the stomach, according to the Sydney classification: low - to 20, the average - from 20 to 50, and high - more than 50 microbial cells in the visual field.

Results and discussion. When analyzing the clinical manifestations, the duration of the ulcer anamnesis of the groups of patients under consideration was also approximately the same and ranged from 1,5 to 27 years, an average of 5,9 years. By the duration of the anamnesis, patients were distinguished with a newly diagnosed ulcer, with disease duration of up to 5 or more than 5 years.

In the first group of the indigenous origin, out of the 51 patients there were

8 (15,7%) patients (P>0,05) with newly diagnosed ulcer, 34 (66,7%) patients had a disease duration of less than 5 years (P>0,001), and 9 (17,6%) patients had ulcer for more than 5 years (P>0,01). 24 (47,1%) patients had a relapse once a year, 11 (21,6%) – 2 times a year and 6 (11,8%) – more than 2 times a year.

Out of 47 patients of the second group of non-indigenous origin the PUD was distributed as follows: with a newly diagnosed ulcer - 22 (46,8%); with a disease duration of less than 5 years - 14 (29,8%) and more than 5 years - 11 (23,4%) patients. y 18 (38,3%) patients had a relapse once a year, 21 (44,7%)– 2 times a year and 8 (17%) – more than 2 times a year.

When analyzing the frequency of relapses and the duration of exacerbation of pyloric bulbar ulcers in accordance with the classification of the course of peptic ulcer [5] in group I, a mild course (relapses no more than once a year) was observed in 8 (15,7%) patients; moderate (relapses – 2 times a year) - in 32 (62,7%), severe (relapses more than 2 times a year) - in 11 (21,6%) patients. Out of 47 patients of the 2nd group, a mild course was detected in 7 (14,9%), moderate in y 29 (61,7%) and severe in 11 (23,4%) patients (P>0,05).

The complications pattern analysis revealed that gastrointestinal hemorrhage is one of the frequent complications of peptic ulcer disease. This was observed in 9 (17,6%) patients in group I and in 7 (14,9%) patients in group II, and cases of relapsing hemorrhage were noted in 3 (5,9%) patients of the second group. Clinically, hemorrhage from an ulcer of the pyloric bulbar region manifested itself in 2 (2%) patients in the form of voluminous vomiting with dark blood admixtures, abrupt dizziness, sometimes short-term fainting, in 6 (6,1%) patients - the appearance of tarry stools in the setting of general weakness, dizziness, the appearance of pallor, ailment.

Clinically, stenosis in 2 (3,9%) patients of group I and in 1 (2,1%) patients of group II was manifested by vomiting, pain, weight loss and heaviness in the epigastric region after eating. Loss in body weight of up to 5 kg in all examined patients was noted in 12 (12,2%) cases, from 5 to 10 kg -3 (3,1%), more than 10 kg - 2 (2%).

The main clinical manifestation of peptic ulcer in the patients of the described groups was pain with localization in the pyloroduodenal region, which was detected in 10 people (19,6%), of indigenous group, 28 (59,6%) of non-indigenous group and, respectively, with localization in the epigastric region in 31 (60,8%) and 9 (19,1%) patients.

Along with pain syndrome in the indigenous group of patients, dyspeptic disorders were more pronounced as follows: nausea in 17 (33,3%) patients, vomiting in 10 (19,6%), heartburn in 18 (35,3%), sour belching, bitterness - in 15 (29,4%), belching with the smell of rotten eggs - in 5 (9,8%), a feeling of fullness and quick satiety after eating even a small amount of food - in 13 (25,5%), hypersalivation in 8 (15,7%) patients. Bowel disorders were observed in the form of constipation in 18 (35,3%) patients and in the form of diarrhea in 4 (7,8%) patients.

In the group of non-indigenous patients, heartburn was more often observed - in 18 (38,3%) patients, other dyspepsia symptoms occurred in few patients.

In the non-indigenous group, pain syndrome was more often detected - 80,4% with localization in the pyloroduodenal zone and in the epigastric region; 36.6% of dyspeptic disorders, heartburn was noted in 35,3%. Bowel disorders in both groups were more often manifested by constipation: in group I - 35,3% and in group II - 8,5%.

During endoscopic examination of the gastric mucosa, pathological changes were localized in the antrum and body of the stomach, while the cardiac section in all patients was intact. The non-indigenous group was dominated by hyperplastic changes in the gastric mucosa - 24.7%, erythematous-exudative changes in the stomach - 48.4% and in duodenum - 62.4%, erosions were also detected - 18.3%. In the first group of patients, ulcers in the stomach were found in 38.5%, in the antrum — 12.3%, and in the duodenal bulb — 49.2%. In the II group of patients, the localization of ulcers in the stomach was detected in 21.5%, in the antrum of the stomach - 14% and duodenal bulb - 64.5%.

Most often, ulcerative defects were localized in the lesser curvature of the prepiloric and pyloric segments of the stomach - 22 (43,1%) cases in group I, 16 (34%) cases in group II. Localization of the ulcer in the greater curvature of the pylorus, 6 (11,8%) cases in group I, 9 (19,1%) cases in group II, localization along the anterior and posterior walls of the first part of the duodenal bulb, respectively, were revealed in 11 (21,6%) patients of the group I, and in 14 (29,8%) patients of the group II. In 2 (3,9%) patients of group I and in 4 (8,5%) of group II, “kissing” ulcers of the anterior and posterior walls of the first part of the duodenal bulb were diagnosed.

Taking into account the criteria for the endoscopic section of the Sydney classification, the following degrees of inflammation activity of the gastroduodenal zone were identified in the observed patients.

Grade 1 of inflammation activity was characterized by uneven swelling of the mucosa with patches of hyperemia in the form of spots ("spotted hyperemia") and the presence of mucus (not detected in our studies).

The second grade of activity is characterized by significant diffuse edema of the mucous membrane with severe hyperemia and areas of submucosal hemorrhages, friability, frequent bleeding upon contact; in some places, the mucous membrane is covered with white sticky mucus, this was observed in 22 (43,1%) patients with gastric ulcers, in 33 (70,2%) patients with duodenal ulcers, of which 10 and 12 patients of the group I and 15 and 18 – of the group II, respectively.

The third degree of inflammation activity, in which along with significantly pronounced hemorrhages on the surface of the mucous membrane, local and often multiple defects (erosions) were detected in 34 (34,7%) patients with gastric localization of ulcers and in 54 (55,1%) with duodenal ulcers.

When assessing the endoscopic characteristics of ulcerous defects and gastric and duodenal mucosa, it turned out that 30 (58,8%) patients in group I had a ulcerous defect diameter of 5 to 10 mm and grade 2 gastroduodenal inflammation. Ulcers larger than 10 mm and inflammation of the gastroduodenal zone of grade 3 were noted in11 (21,6%) patients.

In the second group, the diameter of the ulcer defect from 5 to 10 mm and grade 2 inflammation of the gastroduodenal zone were noted in 35 (74,5%) patients; the diameter of ulcers of more than 10 mm and grade 3 inflammation – in 8 (17%) patients.

The sizes of ulcers ranged from 0.3 to 2.5 cm. Giant ulcers of the pyloric bulbar zone (more than 2 cm) were found in 3 (3,1%) patients.

Morphological evaluation of the mucous membrane of the antrum was performed in 21 patients. All patients had lymphoid infiltration of the mucous membrane and in 71,4% had neutrophilic type of infiltration. Foveolar hyperplasia was observed in 52,4% of patients, without significant differences. Thus, in an endoscopic examination of the gastroduodenal zone, the observed patients of the indigenous group were

more often diagnosed with chronic gastritis – 47 (92,1%), where the atrophic form - in 35,4% and erythematous-exudative changes in the stomach - in 24,6 % and in duodenum - 44,6%. There were no ethnic differences in the form and depth of the ulcer defect.

Of undoubted interest are the analysis results of the dependence of the frequency and degree of HP contamination in patients with peptic ulcer in various ethnic groups. A lower degree of HP contamination of the gastric mucosa was detected in 32 (62,7%) examined patients of the indigenous group, while moderate and high were found in 11 (21,6) and 8 (15,7%) patients, respectively. In the II group, the degree of contamination is slightly higher than in the group I: moderate occurred in 22 (46,8%) and high in 17 (36,2%) patients.

An analysis of the dependence of the HP detection frequency in mucous membranes on the duration of the ulcerative history, the pattern and severity of the gastric and duodenal ulcers revealed some particularities.

Thus, a low degree of contamination in young people with a history of the disease up to 1 year in group I observed in 12 (23,5%) patients, in group II - in 8 (17%); with a history of the disease from 1 to 3 years - in 13 (25,5%) and 11 (26,8%) patients; from 3 to 5 years - in 9 (17,6%) and 2 (4,2%) patients, respectively. A high degree of HP contamination is inherent in patients with ulcer history of up to 5 years and was observed in 34,2% of patients in group I, 45,6% of patients in group II.

Conclusion. When analyzing the clinical and endoscopic aspects of peptic ulcer disease in patients in the studied ethnic groups, a number of features was revealed. Duodenal ulcer was detected in both ethnic groups more often in men, than in women, p <0.05, respectively. In the indigenous group, peptic ulcer disease was detected mainly in middle working age, more often with localization of ulcers in the stomach. The history of the disease prevailed by the patients with a disease duration of less than 5 years (52.3%), relapse rate was observed once a year in 67.7%, the course of ulcer prevailed by the moderate course (60%), and in terms of complications, pyloric stenosis was more often detected (24.6%).

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The results obtained suggest that in patients with a long ulcer history, the HP contamination degree in the mucous membrane is reduced. In the indigenous group of patients with rarely recurring and first detected ulcers, 66.7% of patients were poorly contaminated, and in the non-indigenous group with rarely recurring ulcers 44.7% of patients had a low degree of contamination.

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ENZYME ACTIVITY IN THE INDIGENOUS AND NON-INDIGENOUS POPULATION OF THE REPUBLIC SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.69.21

УДК 612.128

In order to assess the metabolic state of the indigenous and non-indigenous population, the activity of certain enzymes in the blood serum was determined in 2259 people living in rural, industrial and Arctic groups of the regions of the Republic Sakha (Yakutia). Differences in the activity of serum enzymes in the indigenous and non-indigenous population of Yakutia are associated primarily with the various energy needs of the body.

Significantly higher activity of enzymes involved in bioenergy in the indigenous population is consistent with the opinion of researchers about a more intense energy exchange of the indigenous population acquired in the process of long-term adaptation to the harsh conditions of the North.

Keywords: North, indigenous and non-indigenous population, adaptation, enzymes.

Preservation of adaptation reserves of the human organism in the conditions of the North becomes a pressing problem of preventive measures for the development of methods of early, pre-nosological diagnosis of pathological conditions, preservation of health and working capacity of the population.

It is known that in conditions of high latitudes, normal human activity is associated with a transition to a new level of energy supply, which requires an increase in the spending of energy reserves to accelerate basic metabolism, which requires quantitative and qualitative transformations of enzyme systems. In the indigenous population, the restructuring of the physiological functions of the body is fixed genetically with the formation of a "systemic structural trace", in the newcomers the adaptive reaction is associated with the formation of a short-term phenotypic variant [2, 3, 5, 7].

Maintaining the constancy of the basic biochemical parameters of blood is achieved by the participation of key enzyme systems that catalyze the main streams of transamination, thermogenesis, gluconeogenesis. Aspartate aminotransferase (AST) (the process of catabolism) is involved in thermogenesis and bioenergy, and alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) (the process of anabolism) are involved in gluconeogenesis [9]. Alkaline phosphatase (ALP) is involved in the processes of transmembrane nonspecific dephosphorylation. The final reaction of anaerobic glycolysis is catalyzed by lactate dehydrogenase (LDH): the conversion of lactate to pyruvate and vice versa. Creatine kinase (CK) is involved in the transport of macroergic phosphates from mitochondria to cellular ATP (Na-K, Ca, myosin, etc.).

The activity of enzymes depends on the adaptive properties of the body. Over the past decades of socio-economic transformation and urbanization, there has been an increasing decline in the adaptation reserves of the North's population.

According to V.I. Khasnulin et al. (2015), objective indicators of the health of northerners are worse than those of residents in more southern regions. The morbidity of northerners by diseases of respiratory, blood circulation systems and malignant neoplasms is 2-3 times higher than in the Russian Federation [12].

One of the factors in the development of metabolic disadaptation observed in indigenous peoples is a moving away from the traditional way of life and the displacement of the northern type of diet with high consumption of carbohydrate products, which changes the northern type of metabolism [4, 6, 11].

In this regard, a comparative assessment of key enzymes' activity in the indigenous and expatriate population becomes important, having not only diagnostic but also metabolic significance. In addition, the frequency of changes in the enzymes' activity is relevant in assessing adaptive and maladaptive reactions of the body.

The purpose of the research is to assess the activity of the main blood enzymes in the indigenous and expatriate population of the Republic of Sakha (Yakutia).

Materials and methods. The material for biochemical research was gathered during biomedical expeditions through a single-stage examination of the population of Yakutia in the spring period. A random sample of 2,229 people aged 20 to 85 years old was examined with the average age of 46.38±0.28 years old. 1421 indigenous people (average age - 47.30±0.37; me-48), 808 expats (average age - 44.78±0.42; Me-46) were examined. Of these, 1,283 were women with the average age of 47.12±0.37 years old, and 1012 were men, their average age was 45.43±0.43 years old.

Blood for biochemical screens was collected in vacutainer tubes from the median cubital vein in the morning on an empty stomach, 12 hours after eating. The activity of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatine kinase (CK), and creatine kinase-MB (CK-MB) was calculated by an enzyme assay on a "Labio" automatic biochemistry analyzer using "Analyticon" reagents (Germany).

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Statistical processing was performed using the "SPSS Statistics 17.0" package from StatSoft Inc. (USA). The equality of sample means was checked using the parametric Student's t-test (in the case of a normal distribution) and the nonparametric Mann-Whitney U test for independent samples (in case of a deviation from the normal distribution). The data is presented as follows: M - mean value, ± m - standard error of the mean value, 95% confidence interval, median (Me), interquartile interval - 25th (Q1) and 75th (Q3) percentiles. Pearson correlation coefficient methods were used to identify the link between the studied indicators. The value $p < 0.05$ was taken as the threshold α-level of significance.

Results and discussion. The conducted analysis of the activity of blood serum enzymes in the entire surveyed population showed that the average activity of enzymes is within normal values, both in indigenous and expatriate population. However, the average activity of ALP, LDH, and GGT in native residents of Yakutia was 25; 9; 17.6% higher than in the expatriate population and had a negative correlation relationship: ALP ($r = - 0.435$; $p<0.01$), LDH ($r = - 0.234$; $p<0.01$), and GGT (- 0.154; $p<0.01$), which indicates a different intensity of adaptive metabolic processes (table 1). There were no significant differences in the ratio of LDH, CK, and AST activity. The higher activity of CK and CK-MB in the expatriate population is probably due to an increased need for energy essential for adaptive adjustment of metabolism in the North. In order to maintain homeostasis, activation of enzyme systems involved in thermogenesis and bioenergetics is required.

In different physiological and pathological conditions, the De Ritis ratio (AST/ALT) is used to determine the predominance of catabolic or anabolic pathways of metabolism. AST/ALT ratio is equal to 1.33– 1.5 at the equilibrium of metabolic pathways [1,9]. The De Ritis ratio (AST/ALT) had no significant differences, since the activity of ALT and AST in indigenous and non-indigenous people was relatively at the same level. For the indigenous population, the median of the De Ritis ratio was 1.50; for the non-indigenous population, it was 1.46, with a normal average of 1.33±0.42 or between 0.91 and 1.75.

A high percentage of cases of increased enzyme activity that does not correspond to the reference values was detected in 43% of the indigenous population for ALP, 35% for LDH and 20% for GGT, which accordingly exceeded the frequency of increased enzyme activity in the expatriate population by 4; 2; 1.4 times (Image 1).

Frequency of the high De Ritis ratio was slightly higher in the indigenous population, while percentage of the low De Ritis ratio was at the same level in both the indigenous and expatriate population (Image 2).

Table 1

Enzyme activity in the population of indigenous and non-indigenous residents of Yakutia

E/l	Groups	N	M±m	95% CI	Me (Q1-Q2)	*p*
Age years	Indigenous	1447	47.30±0.37	46.57-48.03	48.00 (36.00-57.00)	
	Non-indigenous	836	44.78±0.42	43.96-45.61	46.00 (35.00-54.00)	
LDH	Indigenous	1421	394.60±2.07	390.53-398.67	389.00(344.00-436.75)	*0.000*
	Non-indigenous	814	359.37±2.77	353.92-364.83	357.00 (308.00-399.00)	
CK	Indigenous	1419	108.08±1.88	104.37-111.78	91.00 (65.00-127.00)	*0.005*
	Non-indigenous	808	117.28±2.68	112.07-122.54	97.00 (71.25-138.00)	
CK_{MB}	Indigenous	1046	22.22±0.34	21.53-22.90	20.00 (15.00-27.00)	
	Non-indigenous	438	23.13±0.53	22.08-24.19	21.00 (16.00-28.00)	
ALP	Indigenous	1914	252.45±2.13	248.26-256.64	238.00 (196.00-293.00)	*0.000*
	Non-indigenous	804	187.17±2.01	183.21-191.13	180.00 (148.00-214.00)	
GGT	Indigenous	1421	40.14±0.78	38.60-41.68	30.00 (21.00-49.00)	*0.000*
	Non-indigenous	808	33.00±0.90	31.22-34.78	25.00 (17.00-38.00)	
ALT	Indigenous	1421	19.62±0.43	18.77-20.47	15.00 (10.00-22.00)	
	Non-indigenous	808	18.32±0.52	17.30-19.34	14.00 (10.00-21.00)	
AST	Indigenous	1421	25.62±0.34	24.95-26.30	23.00 (19.00-28.00)	
	Non-indigenous	808	24.54±0.48	23.59-25.49	21.00 (18.00-26.00)	
K de Ritis	Indigenous	1421	1.62±0.01	1.58-1.65	1.50 (1.14-2.00)	
	Non-indigenous	808	1.59±0.02	1.55-1.64	1.46 (1.11-1.93)	

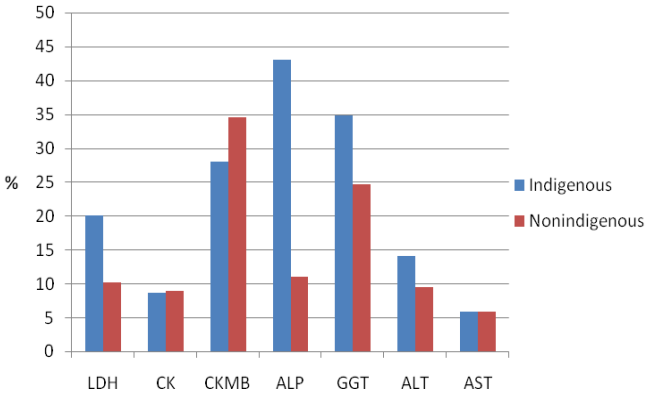

Fig. 2. The frequency of high enzyme activity in indigenous and non-indigenous inhabitants, E/l.

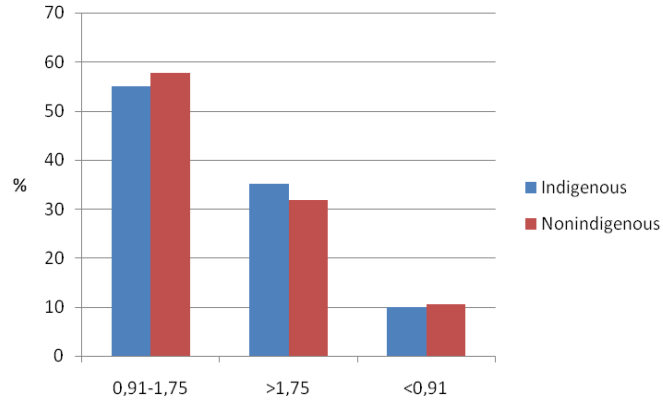

Fig. 2. The percentage of high and low K de Ritis in the indigenous and non- indigenous population

Table 2

Indicators of normal enzyme activity in indigenous and non-indigenous populations within the reference values

Enzymes,E/l	Control values, E/l	Groups	N	M±m	95% CI	Me (Q1-Q3)	$P_{I\text{-}Non\text{-}i}$
LDH	225-450	Indigenous	1116	367.07±1.53	374.07-340.85	370.00 (332.0-408.00)	0.000
		Men	504	368.01±2.29	363.51-372.51	371(333.50-409.00)	
		Women	612	347.76±2.81	342.22-353.29	348 (332.00-407.00)	
		Non-indigenous	723	344.77±1.99	340.85-348.69	345.00 (306.00-388.00)	
		Men	332	366.23±2.06	362.18-370.28	370.00 (312.00-388.75)	
		Women	381	341.39±2.84	335.80-346.99	340.00 (298.00-387.00)	
CK	<190	Indigenous	1293	47.28±0.39	46.51-48.05	48.00 (63.00-116.00)	0.000
		Men	524	110.37±1.78	106.86-113.88	107.50 (80.00-136.00)	
		Women	772	81.30±1.57	78.21-84.39	74.00 (56.25-97.00)	
		Non-indigenous	742	45.23±0.44	44.37-46.10	47.00 (69.00-125.25)	
		Men	320	115.12±2.39	110.41-119.83	111.00 (82.00-146.00)	
		Women	413	89.46±1.90	85.71-93.22	83.00 (63.50-110.50)	
CKMB	<25	Indigenous	763	17.11±0.20	16.70-17.52	17.00 (14.00-21.00)	-
		Men	308	17.65±0.35	16.95-18.35	18.00 (14.00-22.00)	
		Women	454	16.75±0.24	16.26-17.24	17.00 (13.00-21.00)	
		Non-indigenous	294	17.30±0.30	16.71-17.89	18.00 (14.00-21.00)	
		Men	145	18.21±0.41	17.40-19.02	18.00 (15.00-22.000	
		Women	146	16.33±0.43	15.47-17.19	17.00 (13.00-21.00)	
ALP	До 258	Indigenous	827	201.35±1.34	198.71-204.00	204.00 (174.00-228.00)	0.000
		Men	329	208.76±1.98	204.84-212.67	208.00 (184.00-234.00)	
		Women	333	196.85±1.78	193.35-200.36	201.00 (171.00-225.00)	
		Non-indigenous	714	173.20±1.46	170.32-176.09	174.00 (144.00-200.00)	
		Men	333	178.71±2.13	174.52-182.90	180.00 (151.00-206.00)	
		Women	375	167.63±2.00	163.69-171.57	169.00 (138-196.00)	
GGT	women: 7-32; men: 11-50	Indigenous	932	25.02±0.30	24.42-25.63	23.00 (18.00-30.00)	0.000
		Men	416	28.75±0.44*	27.88-29.61	27.00 (22.00-35.00)	
		Women	498	22.08±0.38*	21.33-22.84	21.00 (17.00-26.00)	
		Non-indigenous	624	23.03±0.41	22.22-23.85	21.00 (16.00-28.00)	
		Men	333	27.41±0.69*	26.05-28.78	25.00 (17.00-26.00)	
		Women	375	19.57±0.42*	18.74-20.40	19.00 (14.00-24.00)	
ALT	До 30	Indigenous	1225	14.74±0.19	14.36-15.11	13.00 (10.00-19.00)	-
		Men	515	15.59±0.31	14.98-16.20	14.00 (11.00-19.00)	
		Women	709	14.14±0.24	13.67-14.61	12.00 (10.00-18.00)	
		Non-indigenous	737	14.82±0.22	14.38-15.27	14.00 ()	
		Men	334	15.58±0.34	14.90-16.26	14.00 (11.00-19.00)	
		Women	398	14.28±0.30	13.69-14.81	13 (10.00-18.00)	
AST	До 40	Indigenous	1329	23.25±0.17	22.89-23.60	22.00 (19.00-27.00)	-
		Men	573	23.62±0.29	23.04-24.19	23.00 (19.00-27.00)	
		Women	760	22.98±0.22	22.54-23.42	22.00 (19.00-26.00)	
		Non-indigenous	754	21.73±0.22	21.29-22.17	21.00 (18.00-25.00)	
		Men	338	22.73±0.34	22.06-23.41	22.00 (19.00-26.00)	
		Women	406	20.80±0.29	20.22-31.27	20.00 (17.00-24.00)	
K de Ritis		Indigenous	778	1.33±0.01	1.31-1.35	1.33 (1.13-1.53)	-
		Men	361	1.34±0.01	1.31-1.37	1.35 (1.13-1.55)	
		Women	412	1.31±0.01	1.28-1.33	1.30 (1.11-1.50)	
		Non-indigenous	458	1.33±0.01	1.30-1.35	1.31 (1.11-1.53)	
		Men	213	1.33±0.01	1.30-1.37	1.30 (1.12-1.55)	
		Women	244	1.33±0.02	1.28-1.37	1.30 (1.10-1.50)	

The De Ritis ratio above 2 indicates a cardiac involvement associated with the destruction of cardiomyocytes. On the contrary, below 1 indicates liver damage and is a prognostically unfavorable sign of the course of the disease. In this case, any deviations in the "cardiac" (> 1.5) and "liver" (< 1.5) variations of the ratio mean a change in the direction of metabolic pathways with an according predominance of catabolic or anabolic reactions [1,13].

In laboratory diagnostics, ALP along with GGT is an indicator enzyme of various liver pathologies, and

the presence of a large percentage of individuals with hyperactivity of these enzymes indicates metabolic maladaptation and the development of pathologies. A moderate increase in the activity of ALP, as a powerful regulator of energy metabolism, is an adaptive reaction of the body with changes in the intensity of substrate pathways through the membranes and indicates compensation for a decrease in the level of phosphorus by dephosphorylation. Increased GGT activity indicates more intensive borrowing of amino acids from tissues to maintain gluconeogenesis, but only after spending other sources. In addition to participating in the end reaction of anaerobic glycolysis, LDH regulates the acid-base homeostasis of the blood and is involved in maintaining and preserving a constant pH level.

In order to assess the regional characteristics of the key enzyme activity, a comparative analysis of data from indigenous and expatriate populations (with normal indicators of enzyme activity) has been conducted. Thus, the average activity of ALP, GGT, and LDH in the native population was significantly higher than that of the expatriate population. This difference is also shown by the medians of these enzymes, which accordingly were higher than those of the expatriate population by 14.7, 8.7, and 6.7% (table 2).

During the adaptation to the conditions of the North, increased gluconeogenesis requires optimal intake of free amino acids into the blood as necessary substrates for glucose synthesis. The intake of amino acids from tissues provides GGT, the transmembrane enzyme, but only after utilizing other sources. In addition, GGT is a component of one of the detoxifying systems of the body; it is involved in the destruction of serotonin and histamine, in the metabolism of GABA, and proteolysis of denatured proteins. As one of the key enzymes in bioenergetics, ALP provides a sufficient content of phosphates in the blood, which in turn are consumed to maintain the appropriate circulatory buffer system and to synthesize high-energy bonds (ATP, ADP). Thus, ALP plays an important role in the regulation of transmembrane metabolic pathways. Increased LDH activity provides more intense glycolysis and easier dissociation of oxygen and hemoglobin, which allows more intensive blood circulation and high tissue oxygenation. As a result, substrates pass through metabolic pathways faster and more intensively [10], which requires high activity of all enzymes.

In the expatriate population, a significantly higher level of CK than in the indigenous population may be associated with an increased need for an endogenous membrane protector - creatine phosphate, which plays an important role in maintaining the ATP/ADP ratio in the cell. CK is the most sensitive enzyme of metabolism, an integral part of the CPK-system, which includes creatine, creatine phosphate (CP), and creatinine. CK is a more beneficial form of high-energy's transport than adenosine triphosphate (ATP). In addition, CK is considered a stress enzyme.

Thus, the average activity of enzymes in the entire research population did not exceed the control values. The high frequency of hyperactivity of alkaline phosphatase, gamma-glutamyltransferase, and lactate dehydrogenase among the indigenous population indicates the presence of greater metabolic maladaptation than in the expatriate population. It is possible that changes in the quality of life and Europeanization of the diet of the Northern population have the greatest negative impact on the health of the indigenous population. A regional characteristic of the activity of the main enzymes within the reference values is a significantly higher activity of alkaline phosphatase, gamma-glutamyltransferase, lactate dehydrogenase in the indigenous population, and a higher activity of CK in the expatriate population. This is associated with the various energy needs of the body and indicates a greater adaptation of the indigenous population to the climatic and geographical conditions of Yakutia.

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ASSESSMENT OF CHANGES IN THE DIAMETERS OF COMMON CAROTID ARTERIES AND THICKNESS OF THE INTIMA-MEDIA COMPLEX IN THE EVENS OF THE ARCTIC ZONE OF THE REPUBLIC SAKHA (YAKUTIA) IN THE AGE AND GENDER ASPECTS DURING ULTRASONIC MEASUREMENTS

DOI 10.25789/YMJ.2020.69.22

УДК 611.133

An ultrasound study was conducted to study the anatomical and morphological structure of the common carotid artery and intima-media thickness of the common carotid artery among evens of the Arctic zone of the Republic of Sakha (Yakutia) of different ages and genders. 210 patients were examined, aged from 21 to 74 years, average age is 47 years. The thickness of the IMC was measured along the back side of vessel relatively to the sensor by 1 - 1.5 cm proximal to the CCA bifurcation. Measurements of the CIMT thickness were taken three times, then the arithmetic mean value was calculated. In the presence of thickening, the IMC was measured in the zone of maximum visual thickening. It has been established that the diameter of the left CCA is larger than the diameter of the right CCA; the increase in the thickness of the IMC CCA oc-curs more with age in the left CCA in both genders, average age at which thickening of the inti-ma-media complex to 1.0 mm and more occurs, in general, for all groups was 58.73 years, which is 5,2 years later than for residents of central Russia.

Keywords: common carotid artery, thickness of intima-media complex, brachycephalic arteries, ultrasound scanner, Arctic zone, Evens.

Introduction. The relevance of the study of the carotid arteries is linked to the fact that the thickness of the intima - media of the common carotid artery, according to numerous interna-tional and Russian studies, is an early preclinical marker for the development of coronary athero-sclerosis.

Ultrasound examination of the carotid artery allows non-invasive detection of minimal changes in the arterial wall in the form of a thickening of the intima-media complex [3]. Moreo-ver, even in young patients with a low risk of cardiovascular diseases on the FRS scale (<5%), an initial atherosclerotic change is detected by ultrasound of the carotid arteries, which may be an indirect indication of the presence of coronary atherosclerosis [17].

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The study of the extracranial part of the brachycephalic arteries with the measurement of the thickness of the intima-media complex (IMT) is the method of choice for non-invasive screening to detect subclinical manifestations of atherosclerosis [3]. This technique is easily re-peatable and well reproducible, provides information about the common carotid artery (CCA), the area of the CCA bifurcation, the internal (ICA) and the external carotid arteries (ECA). Measurement of the mean and peak intima-media thickness of the carotid arteries is an important part of the study. The thickness of the intima-media complex (IMC) of the carotid arteries varies according to age, gender and ethnicity. IMT is measured as the distance between two echogenic lines separated by echo-negative space in the artery wall [17].

In 1986, Pignoli together with colleagues reported for the first time connection between thickness of aortic wall and atherosclerosis. Since then numerous studies have proved the link between thickness of the intima – media complex of the carotid artery and development of cardi-ovascular diseases (CVD). According to the results of foreign studies, a proportional relationship has been established with the risk of myocardial infarction and the thickness of the intima – me-dia carotid artery (CIMT) in different groups of the population [13,14]. In particular, a 0.1 mm thickening increased the future risk of a heart attack by 13–18%, and myocardial infarction by 10–15% [13-15].

The average values of IMT averaged over the entire distance are less susceptible to releases, while the maximum value of IMT may reflect advanced stages of focal thickening in the di-rection of plaque formation.

Taking into account the fact, that cardiovascular diseases continue to be a serious public health problem throughout the world and are leading among the causes of death and primary dis-ability of the population, one of the main aims is to prevent the development of the disease. Therefore, the search for new markers of coronary atherosclerosis remains relevant, primarily using instrumental methods of research [11].

The severity and rate of development of atherosclerosis among people living in different climatic-geographical regions, as well as among people of different nationalities of the same re-gion [6], has an unequal frequency and prevalence. At the same time, the features of structure of the arterial vessels in the age and ethnic aspects remain poorly studied [11].

Studying and acknowledging the anatomical and morphological features during life peri-od of the structure of the carotid arteries, distinctive to Evens of the Arctic zone of Yakutia, us-ing ultrasound scanning, would reveal the morphological

structure of the carotid arteries in the age-specific aspect and predict the epidemiological situation regarding CVD. Scientific literature on this topic has not been found.

On the basis of written above, the purpose of the study was to study the diameter of the common carotid arteries and the thickness of the intima-media complex in the Evens of the Arc-tic zone of the Republic of Sakha (Yakutia), depending on age and sex using ultrasound scan-ning.

Methods and materials of study. The study was conducted in the areas of the Arctic zone of the Republic of Sakha (Yakutia) (Anabarsky, Abyisky, Verkhoyansk, Momsky and Eveno - Bytantaysky) in the period from 2015 to 2016. 210 people were examined, of whom 106 men (50.5%) and 104 women (49.5%) aged from 21 to 74 years (mean is 47 years). According to the WHO recommendations, the examined men and women were divided into three age groups (Ta-ble 1).

All examined are permanent residents of the republic, belonging to the Even nationality without mixed blood.

The study of brachiocephalic arteries at the extracranial level was conducted on a VIVID I ultrasound scanner (GE Medical Systems, Israel) with a linear format sensor in the frequency range from 5 to 10 MHz. During the study, the passability of the carotid arteries and the presence of intraluminal formations were

Survey Distribution depending on age and gender

Age groups	Men	Women
1 group	21 – 35 years old	21 – 35 years old
2 group	35 - 60 years old	36- 55 years old
3 group	61 – 74 years old	56 – 74 years old

evaluated. The assessment of status of CCA (qualitative and quantitative parameters) was carried out at B-mode. The structural characteristic included the analysis of echogenicity and the degree of differentiation into layers of the intima-media complex.

The ultrasound image of the arterial wall structures is based on the difference in the acoustic density of the arterial wall tissues and the reflection of the ultrasound beam from the interface of the tissues of different ultrasonic density. The upper edge of the first echo-positive line histologically corresponds to the interface of the vessel lumen - intima, the upper edge of the second echo-positive line corresponds to the border between media and adventitia, the thickness of the far-side intima-media complex can be measured as the distance between the upper borders of the first and second layers of the image. The echogenicity of the tissues surrounding the vessel was taken as the conditional standard in assessing intimal echogenicity, media - vessel lumen echogenicity. The thickness of the intima media was measured along the back wall relative to the sensor to the vessel wall by 1–1.5 cm proximal to the CCA bifurcation [9]. To reduce the opera-tor-dependent measurement error, the scanning plane was oriented strictly perpendicular to the longitudinal axis of the vessel. In the presence of thickening, the IMC was measured in the zone of maximum visual thickening. To assess the compliance of the vessel diameter with a specific phase of the cardiac cycle, ECG monitoring was performed.

Statistical processing of the results was carried out by standard methods. Quantitative data are presented in the form of M + g or mean (depending on the nature of the distribution), as well as the minimum and maximum values of the indicators. Differences were considered signif-icant at p <0.05.

Results and discussion. Analysis of the results of ultrasound examination of morphological structure of common carotid arteries (CCA) among the Evens in the age and gender aspect re-vealed that the average CCA diameter among men was 0.61-0.63 cm (0.06 + 0.09), among wom-en - 0, 51-0.62 cm (0.03 + 0.1). At the same time, in all age groups, diameter of the common ca-rotid arteries on the left was larger than on the right (Fig.1): among men by 0.01 cm, and among women - by 0.02 cm.

A comparative analysis of diameter of left common carotid artery among men in the age aspect showed that this indicator was greater in the 1 age group (21-35 years). The dynamics of changes in diameter of left CCA among men showed that this parameter slightly decreased by the second mature period, and then towards to old age there was a tendency to a slight increase. In the 2 group, this indicator was 0.62 cm, which is significantly less than the 1 group by 0.02 cm, and with the 3 age group by 0.01 cm. At the same time, the indicators of the 3 group re-mained significantly less than those of the 1 group by 0.01 cm (Fig. 1, a). A similar dynamics of changes in the diameter of the common carotid artery was observed among elderly men and to the right. Thus, the diameter of right common carotid artery in the 2 group was 0.61 cm, this pa-rameter was significantly less in comparison to the 1 group by 0.02 cm, and 0.01 cm less than in the 3 age group (Fig. 1, b).

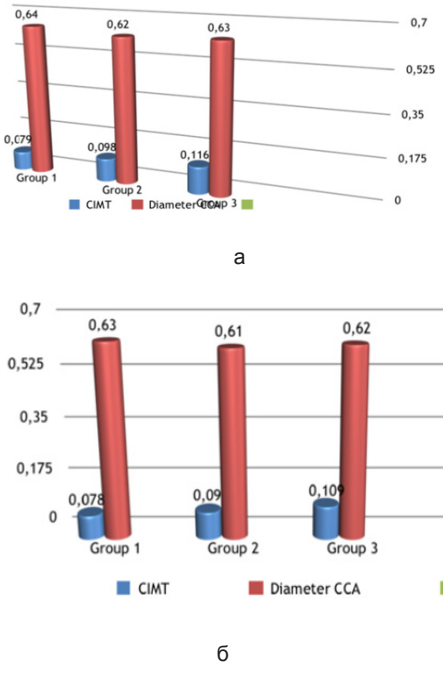

Fig. 1. Diameter of left (a) and right (b) CCA and thickness of left (a) and right (b) CIMT in groups of men

Female analysis of dynamics of parameters of the common carotid arteries in the age aspect showed a gradual increase in their diameters both on the left and on the right. In the 2nd age group, the CCA diameter on left was significantly more (by 0.04%) compared to the 1st age group. By 56-74 years (group 3), diameter of left common carotid artery becomes 0.62 cm, which is more by 0.12% compared with group 1 (Fig. 2). A similar trend was observed in right common carotid artery. Thus, in 1st age group diameter was 0.51 cm, in the 2nd age group it was more by 0.04% than in group 1, and in group 3 it increased by 0.15% (Fig. 2,b).

A comparative analysis of obtained dimensions of thickness of the intima-media complex of common carotid arteries revealed that thickness of the intima-media complex of left common carotid artery is slightly larger than on right, both in male and female population. Among men there were a gradual increase in intima-media thickness which was observed both on left and on right, depending on age. Thus, increase in thickness of the intima-media complex of left common carotid artery in group 2

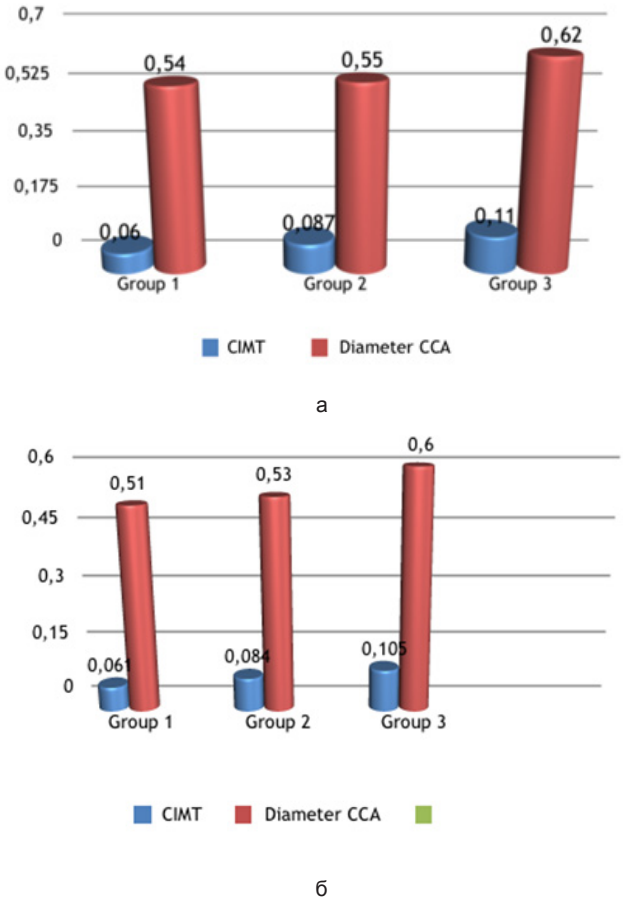

Fig. 2. Diameter of left (a) and right (b) CCA and left (a) and right (b) CIMT in groups of women

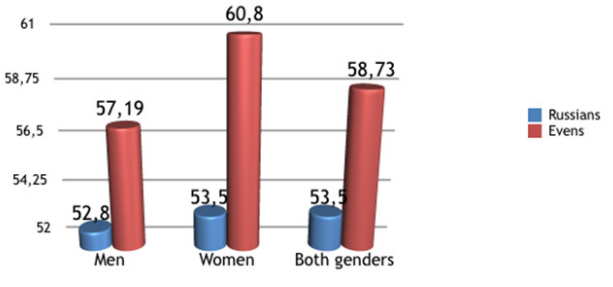

Fig. 3. A comparative diagram of the thickening of the intima - media complex up to 1 mm and more of Evens and Russians, according to V.G. Lelyuk, S.E. Lelyuk.

was 0.19%, and in group 3 it was 0.31% compared to group 1. In right common carotid artery increase in thickness of the intima-intimal-media complex was revealed: by the 2nd group it was 0.13%, and in age group 3 it was 0.28% compared to group 1 (Fig. 1).

Nevertheless, among women increase in thickness of the intima-media complex was faster than among men. Thus, intima-media thickness in left common carotid artery significantly increased by 0.31% (0.027 cm) by the 2nd age group, by 0.45% (0.05 cm) in the 3rd group (compared to 1 group). A similar thickening of the intima-media thickness was observed with age in right common carotid artery. In group 2, increase in IMT compared with group 1 was for 0.22% (0.019 cm), in group 3 for 0.41% (0.044 cm) (Fig. 2).

It should be noted that the average age at which there was a thickening of the intima-media complex up to 1.0 mm and more, for all studied groups was 58.7 years. At the same time, for men the average age of the IMC thickening up to 1.0 mm and more was 57.2 years, for women - 60.8 years. When comparing with the data of V.G. Lelyuk, S.E. Lelyuk (2003) [9] IMC thickening up to 1.0 mm or more among men of even nationality comes later by 4.4 years and among women by 7.3 years compared with residents of Central Russia (Fig. 3).

Summary

1. Diameter of left common carotid arteries in all age groups of recipients of the Even na-tionality of the Arctic zone is larger than diameter of the common carotid arteries on the right, among men it is more for 0.01 cm and among women it is for 0.02-0.03 cm.

2. For men the smallest diameter of the common carotid arteries is observed in the 2nd age period, the largest is in the 1st age group. While among women, diameter of the common carotid arteries gradually increases with age. These changes may be caused by the presence of age-related involutional changes in persons over 60 years of age and the gender characteristics of the organism.

3. There is an uneven gradual increase in thickness of the intima-media complex for both men and women of Evens in the Arctic zone of the Republic of Sakha (Yakutia). Here-with, the IMT of the left common carotid arteries "grows" faster than on right in both groups. At the same time, women revealed a greater thickening of the intima-media com-plex in the older age group, compared to men.

4. For men the average age of IMC thickening up to 1.0 mm and more was 57.2 years, for women - 60.8 years. When comparing to Russian indicators, the thickening of IMC to 1.0 mm or more among men of Even nationality comes later for 4.4 years, but for women later for 7.3 years compared to residents of central Russia.

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SCIENTIFIC REVIEWS AND LECTURES

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MICROBIOME OF THE REPRODUCTIVE TRACT OF WOMEN AND INFLAMMATORY DISEASES OF THE PELVIC ORGANS

DOI 10.25789/YMJ.2020.69.23

УДК 618.17-009-083

The study of the microbiota of the uterus and placenta in clinically healthy women completely refutes the opinion that has existed for many years about their sterility. Recent studies have proved the relationship of the microbiota of the uterus and vagina with the frequency and characteristics of the clinical manifestations of inflammatory diseases of the pelvic organs. The literature review provides modern data on the genital microbiocenosis, describes the role of the most common microorganisms in the initialization of the inflammatory process. Features of the species composition of the microbiota of the uterus and vagina determine the tendency to chronicity of the inflammatory process and the severity of the negative impact on the reproductive health of women. The integral role of opportunistic microorganisms is described in the development of inflammatory diseases of the pelvic organs. A clinically healthy woman is dominated by lactobacilli in a vaginal microbiota, but a few conditionally pathogenic microflora may be present in the normal vaginal microflora: *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum,* yeast-like fungi of the genus *Candidaopobobus*, bacteriidae *Preobobus bacteria*, and bacteria representatives, *Megasphaera, Dialister, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia.* Some recent studies show that about 25% of healthy women have a "non-lactobacillary" type of physiological microbiocenosis, represented by a spectrum of anaerobic bacteria. Conditionally pathogenic microorganisms that are involved in the inflammatory process contribute to the excessive activation of mediators of inflammation of the macroorganism. The development of chronic forms is very often provoked wth long-standing non-specific inflammatory processes, which subsequently are difficult to respond to drug therapy. Untimely treatment of PID is associated with the deterioration of the patient's condition and long-term complications. However, even with timely treatment, distant complications may occur. One study showed that in women with PID, between the ages of 20 and 24, 18% will eventually develop chronic pelvic pain, 8.5% will have an ectopic pregnancy, and 16.8% will have infertility.

Keywords: microbiome, inflammatory diseases of the pelvic organs, chronic inflammatory processes in the pelvic organs, conditionally pathogenic microorganisms, infertility, reproductive health.

The study of the microbiome and its impact on human health has been the subject of active research in recent years. Microbiota is a collection of microorganisms present in a separate human biotope that are in symbiosis with the host organism [31, 33]. There is currently no clear understanding of the role of microbiota in maintaining physiological equilibrium and developing a pathological process in an organ. Studies on healthy volunteers using precision methods to determine the species composition of uterine microbiota and placenta in women show that they have their unique microflora, which completely refutes the long-standing view of their sterility. A W. Adrews study with co-authors of endometrial microflora composition in patients who had spontaneous premature birth and induced premature birth in history showed that there was no significant difference in microbial insemination of the endometrium. *Gardnerella vaginalis, Lactobacillus spp., Streptococcus viridians, Peptostreptococcus spp., Mycoplasma hominis, Ureaplasma urealyticum* were most frequently isolated. By cultural method, the state of microbiota of uterine cavity was evaluated in the work of M.N. Chertovsky and S.I. Kulinich in 2013. Microflora, represented by polymicrobic associations of opportunistic microorganisms, prevailed in most patients [8].

Relatively recently, a new approach has emerged to study the microbiota of the reproductive tract, particularly the uterine cavity, through molecule-genetic methods of study. In the S. Hilier study, in women with clinical signs of chronic pelvic pain, endometritis was confirmed histologically at 40%. As a result, a wide range of bacteria was obtained, represented by 63 different species, including 8 species of opportunistic microorganisms. The presence of true pathogens such as Neisseria gonorrhoeae and/or Chlamydia trachomatis has been associated with endometrite in 29% and 6% of cases. Among opportunistic microorganisms, G.vaginalis 35% and A.vaginae 22% were reliably identified in histologically confirmed endometritis. As a result of a study conducted by Franasiak J.M. et al., 15 bacterotypes of microorganisms were presented. In 90% of patients, a similar composition of uterine cavity microbiota was found, in which Bacteriodes xylanisolvens, B. thetaiotaomicron and B.fragilis dominated [31, 32].

Due to the data of the study of the vaginal microflora, lactobacilli predominate in a vaginal microbiota in a clinically healthy woman, despite this, the normal vaginal microflora may include a small number of conditionally pathogenic microflora representatives: Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum, yeast-like fungi of the genus Candidaopobobus bacterias, Preida mobius, bacterial bacteria, and bacteria representatives, Megasphaera, Dialister, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia. Some recent studies show that about 25% of healthy women have a "non-lactobacillary" type of physiological microbiocenosis, represented by a spectrum of anaerobic bacteria. All women with this type of microflora have a small number of representatives of lactoflora [7, 8].

A study by Mitchell M. et al. examined female uterus samples obtained after a hysterectomy. Microbial contamination of the uterine cavity was detected in 95% of patients, of which only 1 type of microorganism was found in 90% of patients. The most common species were: Lactobacillus iners, Prevotella spp., Lactobacillis crispatus [26]. Colonization of the uterine cavity by microorganisms was significantly lower than the vagina. Markers of inflammation in the endometrium did not differ significantly in women who did not find microorganisms in the uterine cavity compared with those who only found bacilli, or microbes associated with bacterial vaginosis (BV) were present.

Among violations of the microecology of the vagina, bacterial vaginosis occupies a leading position, makes up 30-

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80% of all infectious lesions of the vagina and shows a tendency to spread. Studies in this area indicate the presence of various obligate-anaerobic and facultative anaerobic microorganisms in patients with BV in 96.2% of cases. According to some authors, in 60% of cases, patients with confirmed colonization of the endometrium had violations of the vaginal microecology. The bacterial flora isolated in this case was of microaerophilic, obligate-anaerobic and facultative anaerobic origin. Determination in the microflora of the uterine cavity of such BV-associated representatives as Propionobacterium spp., Eubacterium spp., Peptostreptococcus spp., Bacteroides spp., Prevotella spp., Porphyromonas spp., Fusobacterium spp., Vellonella spp., Corppbacter. spp., Streptococcus spp., Enterococcus spp., Enterobacter spp., E. coli, Klebsiellaa spp., Gardnerella vaginalis, proves their participation in the development of inflammatory changes in the endometrium. It is shown that in the occurrence of inflammatory diseases of the pelvic organs (PID), a significant role belongs to the combined infection, in which 2-6 pathogens are involved with a predominance of representatives of obligate-anaerobic microflora. In 67.2% of cases, asymptomatic persistence of microorganisms occurs. Conditionally pathogenic microorganisms that are involved in the inflammatory process contribute to the excessive activation of mediators of inflammation of the macroorganism. With long-standing non-specific inflammatory processes, the development of chronic forms is very often provoked, which subsequently are difficult to respond to drug therapy. The chronic inflammatory process is an open gate for various viruses, the development of precancerous, cancerous processes due to a decrease in local immunity [1, 8, 33].

Inflammatory diseases of the pelvic organs (PID) are the most common diseases of the reproductive system in modern time in gynecology and have a negative impact not only on the reproductive health of women, but also on the overall incidence and quality of life [2, 3, 10, 12, 19].

Under current conditions, inflammatory diseases of the genital organs have special characteristics: an increase in the value of the conditionally pathogenic flora in the development of the pathological process, the absence of specific clinical symptoms, the transformation of the clinical picture in the direction of the erased forms and atypical course, the growth of antibiotic resistance of microorganisms, multi-focal inflammatory lesions, which creates significant difficulties in the diagnosis. “In mixed infections, some pathogens can create favorable conditions for the penetration, persistence and reproduction of other microbes, thereby increasing their pathogenicity” [4, 9, 11]. For example, the revealed “relationship between gonococcal infection and infection with M. hominis and U. Urealyticum: colonies of mycoplasmas and ureaplasmas grow on the surface of gonococcal colonies” [5, 6]. Also, some authors point to the “possibility of a synergistic action of U. urealyticum and G. vaginalis” [21, 23]. Ureaplasmas and mycoplasmas are often detected in patients with PID, but, despite this, their unconditional role in the development of the inflammatory process requires clarification. It is believed that these microorganisms are indicators of bacterial contamination of the genital tract, and not the main cause of the infectious process. According to some authors, ureaplasmas are found in 80% of women with symptoms of genital tract infection and in 51% of women with reproductive health problems.

The main trigger in the development of PID is microbial invasion. The cervix is one of the important structures that acts as a protective barrier to the spread of bacteria in the internal genital organs. The presence of pathogenic bacteria in the cervical canal can indicate both its syncretism and true colonization [22].

At present, in the etiology of PID, the frequency of occurrence of microbial associations in the form of biofilms is very high, which, according to various authors, is 52-96.7% [13].

Analyzing the situation today, it should be noted that the data on the frequency of STIs in Russia vary, which may be due to the incompleteness of the data provided by paid clinics. Moreover, according to the statement of the President of the Russian Society of Dermatovenerologists and Cosmetologists, director of the State Research Center of Dermatovenerology and Cosmetology Federal State Budgetary Institution of the Ministry of Health of Russia A. A. Kubanova at the XV All-Russian Congress of Dermatovenerologists and Cosmetologists held in 2015, “by 2014 the frequency of STIs for the last 10 years decreased by an average of 64%: syphilis - by 68%, gonococcal infection - by 49% ”[18].

The number of patients with PID in Russia includes about 60-65% who applied to medical institutions and 30% of patients hospitalized in a hospital [17, 18].

The highest PID incidence rate occurs at the age of 18-29 years, and is reliably comparable with an active sex life and with a low use of barrier methods of contraception. Between 2006 and 2013, there was a decrease in the prevalence of PID in the United States. The number of annual visits to emergency departments for PID has also decreased. Nevertheless, as of 2013, this indicator was still significant - 0.41% of all visits to the emergency department or from a total of 7.4 million visits [34]. Although the exact cause of the decrease in the prevalence of PID is unknown, it is believed that increased screening for sexually transmitted infections (STIs), leading to earlier detection and treatment, increased accessibility and adherence to antibiotics, and improved diagnostic testing may be contributing factors [27].

A study of PID in younger populations showed that adolescents are at even greater risk of PID and related complications. It is estimated that one in five cases of PID occurs in women younger than 19 years of age, and in one study, adolescents and young women aged 17–21 years were twice as likely to have PID as in other age groups. It is believed that an increased risk of PID in adolescents is secondary to a combination of behavioral and biological factors. In terms of behavioral risk, adolescents can have several sexual partners, have unprotected sex, and have short-term and high-frequency monogamous relationships [1, 28]. Biologically adolescents have a large fraction of the surface area for infection by microorganisms. Trent et al. also found in a PEACH (PID Evaluation and Clinical Health) study that adolescents under the age of 19 with relapsing PID are five times more likely to report chronic pelvic pain 7 years after the diagnosis of PID. In addition, adolescents in the PEACH study (PID Evaluation and Clinical Health) developed PID relapse in a shorter period of time than in adult women [24].

Inflammatory processes in the endometrium lead to its structural and functional inferiority, a violation of the receptor apparatus, which in turn causes premature termination of pregnancy.

Untimely treatment of PID is closely associated with the deterioration of the patient's condition and long-term complications. However, even with timely treatment, distant complications may occur. One study showed that in women with PID, between the ages of 20 and 24, 18% will eventually develop chronic pelvic pain, 8.5% will have an ectopic pregnancy, and 16.8% will have infertility [29, 30]. The problem of barren marriages has also become more and more relevant recently.

In the Russian Federation, the frequency of female infertility continues to increase and makes 517.5 per 100.000 female population. In addition, the number of ectopic pregnancy in the Russian Federation in the structure of the causes of maternal mortality reaches 3%, and in some years this figure can reach 6-7%.

An inseparable link of the complex mechanism of the onset and development of pregnancy is each organ of the female reproductive system, violations in any of which under the influence of infection can lead to infertility [15].

Inflammatory diseases of the pelvic organs take part in increasing the production of antisperm antibodies (ASAT). They are one of the known immunological factors preventing fertilization, enhancing sperm agglutination and gluing their heads to each other, which prevents them from moving through the cervical canal and blocks capacitation. The study of Yu.A. Petrov, which was conducted among women with infertility of inflammatory genesis, had high ASAT indicators, where the presence of all classes of immunoglobulins in the blood serum was significantly increased, which in turn could reflect the absence of physiological cyclicity among the indicators of the immune system. Elevated levels of IgM, IgA, IgG in cervical mucus cause the development of rejection reactions of the embryo.

Another cause of infertility due to chronic inflammation of the female genital organs is a violation of the receptivity of the endometrium and, as a result, endocrine dysfunction. A.R. Kotikov et al. data indicate the severity of the inflammatory process, which is inversely proportional to the level of expression of steroid hormone receptors - estrogen and progesterone. The inflammatory process inhibits local expression of markers of rapid proliferation. Moreover, a decrease in expression is most significant on the part of progesterone receptors, which explains the failure of the endometrium for blastocyst implantation [13, 14].

The cause of tubal-peritoneal infertility in 30-72% of cases is the pathology of the fallopian tubes of inflammatory genesis. Moreover, the peritoneal factor is present, only in 27% of patients with tubal infertility. Most patients with inflammatory changes in the fallopian tubes present a violation of their patency. As a result of cicatricial and sclerotic changes, obstruction occurs, as a result of the effects of infections on the tubular epithelium. With the progression of inflammatory infiltration of the walls of the tubes and atrophy of the ciliary epithelium of the mucous membrane, the occurrence of inflammatory obstruction of the fallopian tube, an excessively secreted secret stretches the walls of the tube, turning it into a hydrosalpinx. Due to squeezing of the epithelium, necrotic changes occur, which primarily cover the ciliary epithelium: its decylation occurs. If pus accumulates in the lumen of the tube, a pyosalpinx is formed. These anatomical and functional changes in the fallopian tubes significantly disrupt the advancement of the egg into the uterine cavity, and prerequisites for the development of an ectopic pregnancy or infertility arise [16].

Conclusion. Thus, the complex of changes arising in the reproductive organs of women in response to the vital activity of microorganisms can be reversible. However, the characteristics of the microbial landscape often determine the possibility of a manifestation of the inflammatory process, the nature of the clinical manifestations, the severity of pathomorphological disorders and the risk of developing reproductive function disorders, including infertility.

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DOI 10.25789/YMJ.2020.69.24

УДК 613.71:369

ADAPTIVE PHYSICAL CULTURE AS AN INTEGRATIVE SCIENCE ABSTRACT

Adaptive physical culture forms a conscious attitude to one's strength, the ability to overcome not only physical, but also psychological barriers that prevent one from leading a fulfilling life. In article the authors defined adaptive physical culture not only as a method of using physical education for people with health problems, but also as a research task in the general program for studying neurodegenerative diseases at the Yakut Science Centre of Complex Medical Problems.

Keywords: adaptive physical culture, rehabilitation, quality of life, disability.

Introduction. The first attempts to introduce disabled people to sports were made in the 19th century, when, in 1888, the first sports club for the deaf was formed in Berlin. The first "Olympic Games for the Deaf" were held in Paris on August 10-17, 1924. The program of the games included competitions in athletics, cycling, football, shooting and swimming. Disabled people with injuries of the musculoskeletal system began to actively engage in sports only after the Second World War. In 1944, a sports program was developed at the National Spinal Injuries Centre at Stoke Mandeville Hospital as an essential part of comprehensive treatment. Its creator, professor Ludwig Guttman, a neurosurgeon, eventually became the director of the Stoke Mandeville Hospital and the president of the British International Organization for the Treatment of Disabled People with Injuries to the Musculoskeletal System [6].

The extensive long-term history of disabled sports and the rehabilitation of persons with disabilities in foreign countries presents a significant amount of scientific research and publications [22,23,24,27]. Physical activity is inextricably linked with the quality of life and psychological well-being of a person since childhood [21,23]. The social adaptation of the disabled is organized at a high level, innovative methods of physical and psychological rehabilitation are also being developed [24,26,27,32]. In foreign scientific literature, the expression "adaptive physical culture" is not used, terms like "rehabilitation", "exercises or fitness", "physical activity in individuals with disabilities", etc. are utilized instead [21,26,32].

Since 1980, Russia has hosted various sports competitions and tournaments for the disabled. In 1989, the first All-Union Spartakiad of the Disabled was held. But it was only in 1992 in Barcelona that our disabled athletes participated in the Paralympic games for the first time. Until that time, according to the ideology of the Soviet government and the social system, it was believed that there were no problems in the USSR, which meant that there weren't any disabled people as well [9].

Medical and social assistance to the disabled occupies an important, essential part of the overall social policy of any state. Legal regulation of restorative medicine for people with disabilities is based on international treaties and conventions, supplemented by a system of national legislation. Federal Law of 04.12.2007 No. 329-FL "On Physical Education and Sports in the Russian Federation" establishes: physical rehabilitation is the process of restoring impaired or temporarily lost functions of the human body and abilities using the means and methods of adaptive physical culture and adaptive sports. The law states that the regional authorities and local self-governing bodies have the right to assist in the development of physical education and sports for people with disabilities, adaptive physical culture (APC) and adaptive sports [1].

Adaptive physical culture has divided into different areas of research in Russia: educational, sports and fitness, medical, social, psychological.

Scientific research in these areas is diverse and broad. Analyzing the features of physical education of students with health disorders, the authors conclude that the socio-psychological and didactic adaptation of students is poorly developed. They are not characterized by perseverance and determination, the ability to collect themselves and overcome laziness. They have low resistance to colds, suffer from physical inactivity, are skeptical of physical culture. The task of physical culture teachers is to organize classes in such a way that they have a visible healing and training effect, aimed at gradually and sequentially improving physical fitness and increasing the students' functional capabilities [19]. This is possible, according to the authors, only if a number of didactic principles are abided:

- the principle of systematicity (continuous use of any means of physical culture);
- the principle of "simple to complex" (a gradual increase in the physical requirements for students, more complex types of exercises are periodically included in the content of classes and the

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volume and intensity of physical activity increases);

- the principle of accessibility (all means of physical education should be accessible both in structure and in terms of physical activity);

- the principle of alternation, or diffuse muscle load;

- the principle of conscious activity (active participation of the student in classes, their understanding of the tasks and opportunities of physical exercises) [19].

On the study of the social capabilities of the Russian system of rehabilitation and social adaptation of children with disabilities, the authors emphasize that it is not correct to solve the problems of rehabilitation practice for people with disabilities only by medical methods, since adaptive physical culture is an object of interest for various social institutions. Currently existing methods for assessing the health and functional status of this category of the population, for the most part, are limited to the statement of medical problems. At the same time, questions of an emotional, psychological, correctional, pedagogical, and social orientation that make up the quality of life and require the involvement of sociological tools remain open [8].

Adaptive physical culture is a historically established and widely used practice, acquiring the characteristic features of a social institution, using centuries-old achievements and traditions of medical, social and professional pedagogical rehabilitation [8].

The human body, as a self-organizing system, is able to develop and mutate in an unstable environment. The presence of consciousness, the ability to reflect and the presence of will allow one to direct their own development in the desired direction. However, the complexity of the structure of our body, the abundance of possibilities that go beyond our understanding, the presence of compensatory mechanisms, whose work often, due to their multicomponent nature and elusive manifestations can't be comprehended, cause problems in the aspect of control and management. In the course of an organized process that forms the basis of physical training, the marked diversity, variability and multifunctionality of the subject of transformations becomes the cause of complex obstacles that cannot always be overcome blindly relying on the strength of their own design, acting simply and bluntly. Currently available teaching and training methods are quite numerous and diverse, differ from each other in content, effectiveness, and focus. It can also be said about methods, schools, and entire areas of special physical training that they all occupy their own niche, have their own advantages, disadvantages, and characteristic features [14].

The use of diverse means and forms of APC as an innovative educational field is actively expanding, aimed at "... the maximum possible development of the vitality of people with persistent deviations in health status, by ensuring the optimal mode of functioning of bodily-motor characteristics and spiritual forces released by nature or remaining in the process of life, their harmonization for maximum self-realization as socially and individually significant subjects of society "[10]

The use of adaptive physical culture tools and methods in working with people with various developmental disorders, learning difficulties, and difficulties in adaptation allows overcoming these disorders, preventing the development of pathological conditions, and strengthening their mental health. At the same time, many years of experience in the use of physical rehabilitation in a number of foreign countries shows an undeniable improvement in the condition of patients with various degrees of impairment. This improvement is manifested in an increase in overall performance and a greater susceptibility to traditional therapeutic methods, often associated with a reduction in the necessary drug treatment [17].

Adaptive physical culture as an integrative science. Currently, a person is considered not only as an instrument of one or another activity for the transformation of nature and society, but as the goal, result, meaning of these transformations and the existence of society itself. This is due to the emergence of a new conceptual system of views, according to which it is the person with all its unique properties and characteristics that forms the center of theoretical understanding of social phenomena. Such a reassessment of the role of the individual in the development of our society is associated with the processes of humanization, democratization, liberalization, and increased publicity. It is these processes that have revealed one of the most complex problems of our time - the problem of disability, and attracted the attention of the general population of our country, including politicians, scientists, public figures, secondary and higher education workers. In Russia, the greatest experience in the application of physical education tools and methods in working with people with health problems is accumulated in the medical and educational fields (especially in special education). Therefore, very often adaptive physical culture is interpreted as part of physical therapy or is reduced to adaptive physical education in special (correctional) educational institutions for children with developmental disabilities. Recognizing the indisputable achievements of domestic specialists in these areas, it is not necessary to narrow the functions of such a capacious and wide social phenomenon as APC [2, 3, 5,7, 12].

For example, many researchers of the problems of rehabilitation for traumatic spinal cord injury believe that substitutional compensation methods, which are based on an increase in the patient's motor abilities due to segments of the spinal cord that partially retained their structure and were not previously involved in such movements, as well as the involvement of weakened muscles of the transition zone above the level of trauma in motor acts together with healthy muscle groups are most important. These mechanisms are the theoretical justification for the use of physical culture means in the complex. The tactic of rehabilitation is based on the general principles of long-term, continuous and systematic exposure to a complex of restorative means, the leading place among which is given to physical exercises (kinesitherapy) and the formation of regularity in physical activity. Methodological techniques have been developed that allow you to make the patient perform the movement and believe in the possibility of rehabilitation, measures to restore the functions lost as a result of spinal cord injury. The effectiveness of kinesitherapy is increased if it is used in combination with physical methods of treatment and targeted medications. The restoration of lost functions under the influence of physical exercises is achievable only in patients with eliminated spinal cord compression, restored anatomical integrity of the spinal canal and stabilization of the vertebrae. In other cases, only adaptation to the defect is possible [11].

Studies on APC in children with visual impairment showed their poor physical development, impaired coordination and accuracy of movements, functional disorders of the cardiovascular and respiratory systems, deviations in the functions of the musculoskeletal system. The adaptive physical education complex consisted of: 1) physical education classes (morning gymnastics to music, outdoor activities, conditioning to the cold, etc.); 2) therapeutic physical culture (TPC) and seasonal intake of age-specific doses of adaptogens and vitamins, phytotherapy;

3) individual classes in various types of gymnastics (special physical exercises for large muscle groups, special gymnastics for eyesight). Particular attention was paid to exercises of the respiratory system, as visually impaired children are prone to frequent respiratory diseases due to reduced immunity. As one of the means of adaptive physical education of children with visual impairment, therapeutic physical culture classes in water were chosen. Universal flexibility exercises performed in water helped to increase joint mobility, since the water's pushing force provides passive stretching, and the drag provided by water limits the speed of movement and reduces the risks of damage to joints and muscles [15].

The theory of APC as a science explores the content, structure, functions of APC, its purpose, principles, tasks and means, features of the activities of students and specialists in this field; develops the conceptual apparatus, and also studies the goals, objectives, methods, content of various components (types) of APC, substantiates and validates in practice its new types and forms aimed at satisfying the diverse needs of people with deviations in health, including persons with disabilities. One of the main problems of the theory of APC is the problem of studying the needs, motives, interests, values of people with deviations in health and disabled people, their personality and individuality; the problem of studying the process of formation and adjustment of the axiological concept of life in this category of the population, overcoming psychological complexes using APC tools and methods [3, 4,12,17].

The theory of APC should reveal its complex relationships with other areas of society's science and practice - healthcare, education, social welfare, PE, etc., and also develop technologies for the formation of society's readiness to accept disabled people as equal members with self-worth and great creative potential in the various types of human activity. The most important problem of the theory of APC is the study of mental, moral, aesthetic and labor education features in the process of physical education [4, 13,18].

APC for neurodegenerative diseases (NDDs). NDDs are characterized by gradually increasing motor disorders and muscle atrophy. Physical exercises for groups of patients with NDDs are necessary for improvement of motor functions, respiration, and general health. A significant body of research supports the view that for people living with various slowly progressive disorders, exercise and physical activity gives positive psychosocial effects and wider therapeutic benefits, such as restoring self-confidence, removing the emphasis on one's physical disabilities, restoring a sense of control over physical health and emotional well-being, preservation of self-identity, restriction of psychological disorders associated with the disease and nurturing a sense of belonging through the establishment of relationships with other people [20,22,24,28,30,31].

Physical exercises that are aimed at pleasant experiences, such as doing exercises for your inner satisfaction and enjoyment, and not for reasons that are simply related to improving physical condition and the development of social support can also have a positive impact on quality of life [25,33].

Significant psychosocial benefits were obtained. Which indicate that multiple interacting psychosocial constructs underlie active participation in physical exercises for people living with progressive NDDs [29].

Conclusion. We believe it is important to study the research field of adaptive physical culture for patients with NDDs as part of the development of the Center for Neurodegenerative Diseases in the Clinic of the YSC CMP. One of the main goals of APE is the problem of studying the needs, motives, interests, values of people with deviations in health and disabled people, their personality and individuality; the problem of studying the process of formation and adjustment of the axiological concept of life in this category of the population, overcoming psychological complexes using APE tools and methods. In this area, APC intersects with bioethical and psychosocial areas of research.

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REGISTER OF BIRTHS AS THE MOST IMPORTANT TOOL FOR FORECASTING OBSTETRIC COMPLICATIONS AND REDUCING OF PERINATAL LOSS LEVEL

DOI 10.25789/YMJ.2020.69.25

УДК 618.4 (470.1 1)

The article provides a review of the literature on the creation and maintenance of the birth register in Russia and other countries. In foreign countries birth registers have been used for more than half a century. Based on the data of their birth registers, perinatal losses were reduced by more than 5 times. There are currently no valid birth registers (BR) in the Russian Federation. There was experience in their implementation and maintenance in Arkhangelsk and Murmansk regions from 2006 to 2011.

In the Arctic zone of Russia, a high risk for perinatal complications is caused by several groups of factors: inaccessibility of perinatal centers, nutrition features (unvaried food), the presence of regional pathologies, the constant exposure to cold temperatures, the absence of a highly qualified medical team on an ongoing basis, the presence of extragenital diseases, and understaffing by narrow specialists in medical institutions of the Arctic regions, seasonal absence of perinatum transport centers with midwife centres, district hospitals and central district hospitals. Women with developed complications of pregnancy and childbirth are evacuated by medical aviation, the departure of which may be delayed or delayed due to bad weather conditions. We need effective mechanisms for predicting perinatal complications in order to take all measures to prevent them in advance.

Based on the above, it becomes relevant to create and introduce a register of pregnancy and childbirth in the Arctic zone of the Republic of Sakha (Yakutia) with a retrospective analysis of all currents and outcomes of pregnancy and childbirth for the timely prediction and prevention of perinatal complications and transportation of pregnant women to level III of obstetric institutions.

Keywords: birth register, perinatal losses, obstetric complications, Arctic regions, prognosis.

Birth Register (BR) is an electronic database that contains detailed clinically and scientifically significant information about the health of all pregnant women and children born in a particular area [3].

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BR is a database for current and future research, due to which it is possible to reduce perinatal losses, develop standards and protocols for providing medical care to pregnant women, women in childbirth and women in childbirth. The use of BP allows to reduce by several times the frequency of sudden infant death [6], to assess the risks associated with IVF [8, 9], to reduce perinatal mortality [9], to more accurately assess the prevalence of congenital anomalies [12] and the influence of genetic and other factors on the etiology of the perinatal complications [13, 18]. Based on the register data, it is possible to analyze complications of pregnancy and childbirth, as well as the causes of perinatal and maternal mortality in a full-term pregnancy, followed by organizational decisions in order to predict and prevent them [1].

Taking into account the potential risk factors that lead to adverse pregnancy outcomes, the birth register allows to evaluate the effectiveness of standards for the provision of medical care in obstetrics and perinatal medicine. The information collected through the registry of births is used for quality monitoring of obstetric care services and neonatology, as well as to identify the causes that lead to a pathological condition. This database allows for quality control of the implementation of certain decisions, orders, standards and clinical recommendations.

BR began to be created in 1960. The first Registry was founded in Norway in 1967 and was a database of medical birth certificates [2]. Gradually, its status changed and today BR carries out continuous registration of pregnancy outcomes (starting from 1999 also with abortions) to monitor birth defects and other perinatal conditions, assess the quality of medical care and provide data for epidemiological studies [10]. By 2016, 2,817,468 pregnancy outcomes were registered in it. Such a quantity of data is a huge research potential, providing constant epidemiological surveillance [12]. Thanks to the work of the Norwegian BR, it was possible to reduce several times the cases of sudden infant death syndrome [15]. During the existence of this registry, perinatal mortality in Norway decreased by 5 times [9]. An assessment was made of the risks to maternal and fetal health associated with IVF [7, 8], as well as the contribution of genetic factors to the etiology [17]. The intake of folic acid in order to prevent congenital malformations was developed and implemented based on data from the Norwegian BR [2].

Today, national birth registries also exist in Finland, Iceland, the USA, Canada, Australia, and Estonia. The largest of them is Swedish BR, with an annual number of births of more than 100,000 [14]. The reason for their creation was the growth of congenital anomalies in the 50-60s [16]. The task was to identify the risk factor for fetal

malformations. A drug with teratogenic effects of thalidomide was identified and discontinued, and this fact went down in history and is described in textbooks on perinatology.

Based on data processing, the Swedish BR revealed 9% of the missing data on the harmful habits of the mother and father, 15-25% - on the body mass index before pregnancy, which allows to identify the defects in the work of the obstetric service.

The first in Russia was the Kolskiy BR, which contained data recorded in 1973-1997. On the basis of studies conducted on the research of this BR, the relationship of preterm birth, low birth weight, a low Apgar score with a low level of education and poor living conditions of the mother was proved [5].

In Russia, the BR was introduced into practice the Murmansk and Arkhangelsk regions. In the Murmansk region, RR functioned from 2006-2011 and was used to study the prevalence of congenital malformations and risk factors.

Studies based on data from the Kolskiy and Murmansk BRs have revealed that the overall prevalence of congenital malformations at birth between 1973-2011 in Monchegorsk was higher compared to EUROCAT data [18].

On the example of Birth Register of Arkhangelsk Oblast, the influence of poor living conditions, bad habits and increased stress on the decrease in body weight of infants was revealed [5]. In BR of Tulskiy region data from more than 11 thousand birth histories were entered, based on the study of which the relationship of socio-demographic factors and adverse outcomes of pregnancy and childbirth was proved [17]. Even a short time of using register data allows to focus on perinatal risks and reduce adverse outcomes of pregnancy and childbirth. The experience of these countries proves the need for the introduction of BR in the Republic of Sakha (Yakutia).

Thus, BR serves as the most important information resource for science and practical health care and is a tool for monitoring perinatal complications and the prevalence of congenital malformations.

Conclusion. The problem of obstetric complications and perinatal losses is one of the most urgent in modern world medicine. Biomedical, socio-economic and psychological factors influence the development of adverse pregnancy outcomes. Urinary tract infection before childbirth is an established risk factor for low birth weight and perinatal death in children born to women aged 20–29 years [5]. Cigarette smoking [1, 4], alcohol consumption [2] and consumption drugs [4] during pregnancy increase the risk of stillbirth. Compared to healthy women, pregnant women with urinary tract infections [4, 5] and genital tract [5] are at a higher risk of preterm labor. Poor antenatal care [11] and maternal infections [16] are associated with early infections in newborns.

In the Arctic zone of Russia, a high risk for perinatal complications is caused by several groups of factors: inaccessibility of perinatal centers, nutrition features (uniform food), the presence of regional pathologies, the constant exposure to cold temperatures, the absence of a highly qualified medical team on an ongoing basis, the presence of extragenital diseases, and understaffing by narrow specialists in medical institutions of the Arctic regions, seasonal absence of perinatum transportation with medical and obstetric centers, district hospitals and central district hospitals. Women with developed complications of pregnancy and childbirth are evacuated by medical aviation, the departure of which may be cancelled or delayed due to bad weather conditions and time of day.

Taking into account all the points made above, it becomes relevant to create and implement a pregnancy and childbirth registry in the Arctic zone of Republic Sakha (Yakutia) with a retrospective analysis of all currents and outcomes of pregnancy and childbirth for the timely prediction and prevention of perinatal complications and transportation of pregnant women to level III obstetric institutions.

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POINT OF VIEW

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OPPORTUNITIES TO IMPROVE THE TREATMENT EFFECTIVENESS IN CHRONIC ENDOMETRITIS AMONG WOMEN WITH EXTRAGENITAL DISEASES

DOI 10.25789/YMJ.2020.69.26

УДК 618.14-002.2

The immune status features were assessed in a sample of women with chronic endometritis (CE) after pregnancy termination against the background of extragenital diseases (EGD) (anemia and chronic pyelonephritis). In women with CE a high frequency of bacterial vaginosis, microbial contamination of the cervical canal (Escherichia coli - in one third), moreover, than endometrium (Enterococcus faecalis and Bacteroides fragilis - in hypoplastic type) was found.

The study of the activity of cellular and humoral immunity links at CE, taking into account the type of inflammation and the presence of infection of the uterine mucosa, allows for rehabilitation of women after pregnancy termination against the background of EGH, which is adequate to the identified disorders.

Keywords: termination of pregnancy, chronic endometritis, extragenital diseases.

Introduction. Research interest in the problem of managing women with chronic endometritis (CE) is explained by the lack of clear ideas about the nature of changes in humoral and cellular immunity in response to persistence in the mucosa of low-virulent or aggressive microorganisms.

Features of the organism immunoreactivity including activation of local anti-infective processes in the uterine mucosa or systemic changes, often - with the induction of autoantibody synthesis are discussed in scientific works with a fair share of doubt [1]. It is believed that the disadaptation of the body on the CE background is realized in various immune responses to antigenic irritation due to the failure of mechanisms protective against bacterial and viral infections. There is an opinion that chronic inflammatory diseases of the pelvic organs should be considered as an autoimmune process, in the outcome of the preserved abnormal immunoreactivity after elimination of infections [4].

The largest number of studies is devoted to the analysis of immune reactions in the sample with miscarriage, due to the conclusion that CE presence among more than 70.0% of women determines the violation of the embryonic development processes, starting with implantation processes [5, 9]. The nature of structural and functional changes resulting from the release of inflammatory mediators in endometrial tissue corresponds to the general indications of any inflammatory process [7].

Obviously, ischemia on the background of sclerotic and microcirculatory changes in the inflamed uterine mucosa, which determines unfavorable conditions for the progression of pregnancy, is associated with abnormal immunoreactivity [6]. However, the nuances of the immune response in CE remain poorly understood, as well as the possibilities of medical correction of autoimmune mechanisms that damage the uterine mucosa among women with pregnancy termination on the CEGD background (chronic extragenital diseases). Ideas about the role of the microbial agent in the genesis of inflammation remain controversial: some authors refer to the low frequency of bacterial contamination of the mucosa, others – to difficulties in identifying anaerobic strains or viruses, or insist on the microbial elimination with the maintenance of the autoimmune process [3].

Objective of the research: To evaluate the nature of immune disorders in a sample of women with chronic endometritis after pregnancy termination on the EGD background.

Materials and methods of the research: A group of 360 women with anemia (n = 216) and chronic pyelonephritis (CP) (n = 144) was prospectively examined. Their pregnancy termination in the first trimester took place on the histologically confirmed CE background. The control group (n = 71) was represented by women whose pathological examination of mucosal biopsy specimens revealed no chronic inflammation. Written informed consent for participation in the study was obtained from all patients.

Criteria for inclusion in the research: the presence of reproductive losses (up to two months after abortion) on the CP and anemia background, histologically verified CE.

Exclusion criteria: multiple pregnancy and the one being the result of assisted reproductive technologies; heavy somatic diseases in the stage of decompensation, precancerous and oncological diseases; stillbirths; chromosomal abnormalities and congenital malformations of the fetus.

Methods of the research: clinical and statistical analysis, sonography, hysteroscopy, pathological and microbiological (assessment of biocenosis, PCR diagnostics, bacteriological examination of discharge from the cervical canal, endometrium) examination of the endometrium. Diagnosis of placental polyp among three women within two months after the intervention excluded them from the study.

Addressing the problem of abortion on the EGD background was associated with difficulties in diagnosing morphofunctional endometrium changes, the choice of timely pathogenetically reasonable rehabilitation. By stratification of endometrial inflammation according to the results of hysteroscopy and morphology, two CE types were distinguished: hyperplastic (n = 203) and hypoplastic (n = 154).

The basis of the hysteroscopic CE types' differentiation – hypoplastic and

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hyperplastic – was the peculiarities of thickness, colour and structure of the mucosa and the vascular pattern.

Determination of immunocompetent cells subpopulations was performed by immunotherapies of peripheral blood lymphocytes, flow cytofluorometry on the machine EPICS-XT company COULTER (USA) and multiparameter two-tone cytofluorimetry. To determine the content of immunoglobulins IgA, IgM, IgG (g/l) by radial immunodiffusion in gel (Manchini et al., 1965) monospecific serum sets were used (Vaccine and Serum Research Institute named after I.I. Mechnikov, N-Novgorod). The number of circulating immune complexes (CIC, opt. units) was evaluated by the method of Haskova V. et al (1978) modified by Yu.A. Grinevich and I.A. Alferova (1981) by the method of selective precipitation in 4.16% PEG 6000 (Serva, Germany).

Mathematical processing of the data was performed using standard software packages for Windows version 20 (SPSS Inc., Chicago, IL). Statistical processing of the studied material included descriptive statistics.

To assess the significance of differences in qualitative features in unrelated groups, $\chi 2$ criteria were used. Differences between the indices in different groups were considered significant at $p < 0.05$.

Results of the research and their discussion. According to the results of a morphological study of the material after uterine emptying, all women with abortion on the CP and anemia background were diagnosed with CE (chronic endometritis) (n = 360). Age categories of women with abortion on the CP (chronic pyelonephritis) and anemia background were as follows: 31.3% were in the 18-24 years group, 40.3 – 25-30 years, 22.9% –31-35 years. The number of 36-40 years old women in the CP group turned out to be 9 times more than with anemia (48.6% versus 5.5% accordingly, p = 0.0005). The average age in the CP group was 27.1 ± 5.7 years, anemia – 26.5 ± 5.2 years.

The number of births was higher in the group with anemia – one and a half times, than in group with CP (58.3% versus 36.1%, p = 0.0006), a history of abortion was indicated by 41.0% of women, spontaneous miscarriages – 30.1%, tubal pregnancy – 9.8%, non-developing pregnancy – 11.1%.

The average term for pregnancy termination in the CP group was 8.4 ± 2.2 weeks, anemia – 7.6 ± 2.5 weeks.

The analysis of the microbial contamination of the urogenital tract loci, comparing the simultaneous occurrence of various strains, was carried out along with the assessment of the organism's immunological reactivity to the persistence of infections in the endometrium.

The conclusion about normocenosis appeared in 6.6% of vaginal discharge samples among women with chronic inflammation of the uterus and 58.1% - without CE ($p < 0.05$). Subnormal cenosis was characteristic of 12.0% of all women with pregnancy termination on the EGD background. Bacterial vaginosis (BV) was diagnosed in 73.4% of women with the hypoplastic CE type, 51.9% - hyperplastic, in 25.7% - was found in the absence of an inflammatory process ($p < 0.05$). Vaginitis was detected in a third of women with the hyperplastic CE variant (32.5%), three times less frequently (10.3%) – among patients with a hypoplastic one.

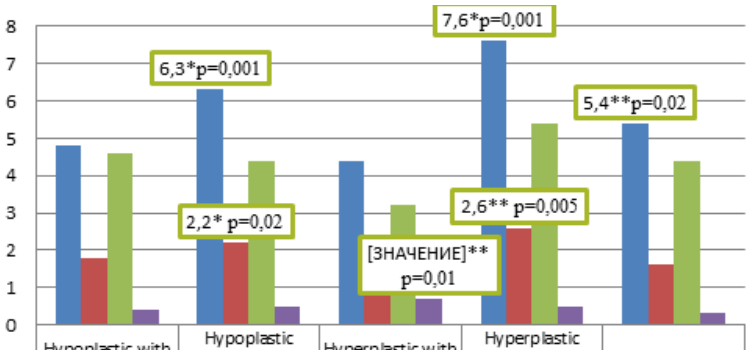
The frequency of infections in the cervical canal in the sample with CE exceeded those in the endometrium – regardless of the type of inflammation. Cultural diagnostics contributed to the identification of a significant contamination of the cervical canal with enteroflora – to confirm the high frequency of vaginal dysbiosis.

The persistence of enterococcus in the endometrium was found in every tenth woman with CE, regardless of the type, in 9.9% on average; the infection in the cervical canal was detected more frequently: in a third of cases with the hypoplastic type of inflammation ($p < 0.05$), a quarter – with the hyperplastic one ($p < 0.05$). The cervical canal contamination with Escherichia coli distinguished a third of all women with CE (32.4% on average), with a greater frequency of its persistence – twice – with the hypoplastic type (18.8% vs. 7.9%) ($p<0.05$). The frequency of bacteroids detection in the endometrium among patients with the hypoplastic CE type exceeded that in the cervical canal by four times (11.0%) ($p<0.05$). The intensity of β-streptococcus colonization (> 104 CFU / ml) in the cervical canal was higher (14.0% vs. 4.9% on average) than in the uterine mucosa of all women with CE.

The analysis of the immunological profile of women with EGD whose pregnancy termination was due to chronic endometrial inflammation included assessment of leukogram (Fig. 1), cellular and humoral reactivity factors, depending on the presence of the uterine mucosa contamination (Fig. 2).

Microbial contamination of the endometrium with infections was accompanied by a lower leukocyte reaction — as compared with the intact uterus mucosa — in both CE types ($p < 0.05$). A similar tendency was revealed in relation to lymphocytes and neutrophils, whose indices, when the mucous membrane of the uterus is contaminated on the background of CE hyperplastic type, were lower ($p < 0.05$). The monocytic reaction was more significant in the group of women with endometrial infection in hyperplastic inflammation ($p < 0.05$).

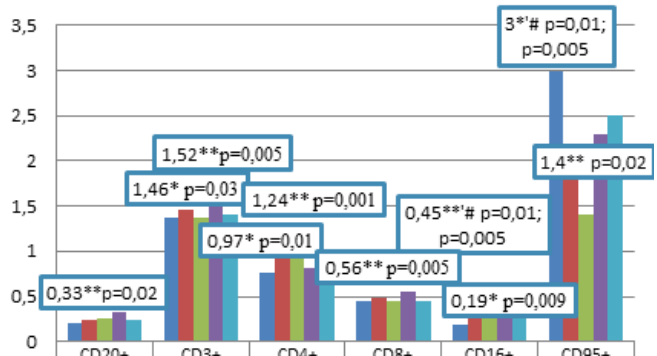
Contamination by uterine mucosal infections in the hypoplastic CE type was accompanied by some inhibition of



	Hypoplastic with contamination	Hypoplastic without contamination	Hyperplastic with contamination	Hyperplastic without contamination	Healthy
Leukocytes	4,8	6,3	4,4	7,6	5,4
Lymphocytes	1,8	2,2	1,5	2,6	1,6
Neutrophils	4,6	4,4	3,2	5,4	4,4
Monocytes	0,4	0,5	0,7	0,5	0,3

Note: * Fig. 1-3 ($p < 0.05$) - the differences in the indices are statistically significant between the groups with / without contamination – for the hypoplastic type, ** - the hyperplastic type, # - for another CE histotype with contamination

Fig. 1. Leukocyte profile depending on the presence of the uterine mucosa contamination



	CD20+	CD3+	CD4+	CD8+	CD16+	CD95+
Hypoplastic with contamination	0,21	1,38	0,76	0,45	0,19	3
Hypoplastic without contamination	0,24	1,46	0,97	0,49	0,32	1,8
Hyperplastic with contamination	0,25	1,37	1,24	0,45	0,45	1,4
Hyperplastic without contamination	0,33	1,52	0,82	0,56	0,25	2,3
Healthy	0,24	1,4	0,83	0,44	0,26	2,5

Fig. 2. Markers of cellular immunity of lymphocytes in various CE types, depending on the uterine mucosa contamination

the production of CD3 +, CD4 +, CD20 +, CD16 + cellular immunity clusters on the background of high proapoptotic directionality (p <0.05). The vectorial character of immune-mediated reactions in hyperplastic CE type with endometrial persistence of infections consisted in the greater activity of individual clusters (CD4 +) (p <0.05) induced by NK CD16 + (p <0.05).

The assessment of humoral immunity depending on the presence of the uterine mucosa contamination is presented in the.

The level of IgA was elevated in the group with the uterine mucosa contamination (Fig. 3), to an irrespective of the CE type (p<0.05). The IgM content in the group with the hyperplastic type of inflammatory process in the endometrium exceeded that of women with intact mucosa (p <0.05), as well as with the hypoplastic type (p<0.05).

The distinctive features of the humoral immunity of women with the hyperplastic CE type were the presence of high immunoglobulin indices in case of the uterine mucosa contamination – more than in the intact (p<0.05). In the group with the hypoplastic CE variant the IgA content (p<0.05) dominated at the microbial contamination of the uterine mucosa. IgM (p<0.05) and IgG (p<0.05) were low compared to the "sterile" uterine mucosa.

The content of immunoglobulins among women with CE and the intact uterine mucosa differed from healthy women by in slightly increased values, IgM and IgA – in the hyperplastic one.

The revealed violations of the mucosal architectonics (macro- and microstigmas) in the groups with reproductive losses on the EGD background (CP and anemia) indicated high CE frequency – as a predictor of the mucosal instability in both CE variants.

The role of CE being one of the leading causes of early pregnancy termination is confirmed by studies of both domestic and foreign authors [2,4,10].

The nature of local damage and the functional activity of the reserve of immunocompetent cells (humoral immunity factors, population and subpopulation structure of blood lymphocytes) in the presence of high microbial contamination of the urogenital tract loci justifies the reasonability of a comprehensive rehabilitation therapy [7, 8].

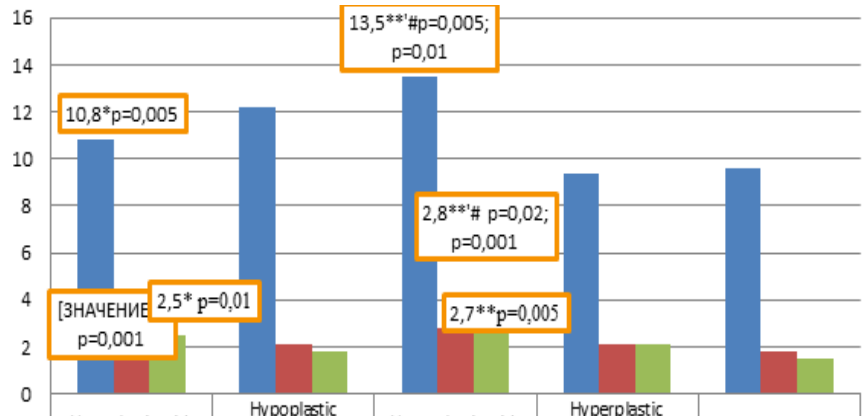
It is obvious that the traditional CE treatment among women with chronic EGD (CP and anemia), being an additional factor of immune imbalance, does not contribute to the restoration of cell-humoral systems to the state of "resource", especially for the elimination of the existing infection. The presence of endometrial contamination indicated productive inflammation and the need for elimination antibiotic therapy, taking into account the sensitivity of infections detected in various urogenital loci in diagnostically significant titers – vaginally and in the cervix, often in combination with urinary tract infection (in CP presence) and subsequent delayed treatment of chronic inflammatory diseases of the pelvic organs.

Analysis of the state of cell and humoral markers in various CE types – hypo- and hyperplastic – depending on the presence of mucosal infection will allow adequate rehabilitation of women after pregnancy termination on the EGD background, which is adequate to the identified changes in immunoreactivity.

Conclusion. The role of CE in the genesis of reproductive losses confirms the formation of abnormal embryo-placental relationship on the background of defective cytotrophoblast invasion into an inflammatory modified endometrium.

We consider it appropriate to organize a step-by-step examination of women with anemia and CP in order to identify causes of abortion, verification of chronic inflammation of the mucosa, with determining a certain CE type – hypoplastic or hyperplastic – during hysteroscopy.

Significant microbial contamination



	Hypoplastic with contamination	Hypoplastic without contamination	Hyperplastic with contamination	Hyperplastic without contamination	Healthy
Ig G	10,8	12,2	13,5	9,4	9,6
Ig M	1,4	2,1	2,8	2,1	1,8
Ig A	2,5	1,8	2,7	2,1	1,5

Fig. 3. Reactivity of humoral factors depending on the presence of the uterine mucosa contamination

of the lower parts of the genital tract among women with abortion on the anemia and CP background was revealed: normocenosis only in 6.6%, BV (bacterial vaginosis) predominance with a hypoplastic CE type – 73.4%, one and a half times, vaginitis –with a hyperplastic type – 32.5%, three times.

The frequency of the cervical canal infection among women with CE was higher than the endometrium infection, regardless of the type of inflammation. E. coli was detected among a third of all women with CE, enterococcus – among a third with a hypoplastic CE type. Endometrial persistence was found with a hypoplastic CE type, E. coli – twice as often as in the cervical canal, bacteroids – four times as often (11.0%).

The presence of productive inflammation in the uterine mucosa was accompanied by a decrease in the level of leukocytes, lymphocytes and neutrophils with the formation of an immunodeficiency state. Features of the immune phenotype of women with a hyperplastic CE type in the persistence of infections in the endometrium are the following: monocytic blood reaction, NK CD16+, CD4+ activity; with a hypoplastic type – the decrease of cellular factors production CD3+, CD4+, CD20+, CD16+ on the background of redundant – CD 95+.

Microbial contamination of the endometrium with a hypoplastic CE type is accompanied by a decrease in the level of immunoglobulins IgG, IgM with an increased rate of IgA in comparison with intact mucosa, with a hyperplastic type –all values of immunoglobulins are reduced.

An integrated approach for women with abortion on the anemia and CP background based on the results of microbiological and immunological studies contributes to the choice of pathogenetic therapy for various CE types. Unreasonable antibiotic therapy for autoimmune endometritis was proved (in the absence of microbial contamination of genital loci, immunodeficiency state).

Correction of identified immune changes seems to be a significant rehabilitation strategy tool for women with reproductive losses due to CP and anemia. The reduction of anti-infection protection of the organism predetermines the lack of pregravid recovery.

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EXPERIENCE EXCHANGE

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TREATMENT EXPERIENCE OF HEPATIC METASTASES FROM NEUROENDOCRINE TUMORS USING TRANSARTERIAL CHEMOEMBOLIZATION

DOI 10.25789/YMJ.2020.69.27

УДК 616-006.4

The aim of this work was to evaluate the effectiveness of treatment for liver metastases from neuroendocrine tumors by the TACE method. We analyzed 7 clinical cases of gastrointestinal NETs with inoperable liver metastases in patients treated at Rostov Research Institute of Oncology in 2016-2018. We studied the symptoms in each clinical case and analyzed the results of computed tomography using RECIST 1.1 criteria before and after the transarterial chemoembolization procedure. According to the results of the analysis of computed tomography using the RECIST 1.1 criteria in dynamics with an interval of 3 and 6 months, the following was established: in 2 patients (28.6%) with a relative stabilization of the process 3 months after TACE, disease progression was observed after 6 months; 3 patients (42.9%) had a persistent partial response to therapy 3 and 6 months after TACE; in 1 patient (14.3%), stabilization was registered according to CT data 3 and 6 months after TACE. Moreover, out of 7 observations, only 1 case was fatal. In a small number of patients, we showed that TACE helped to normalize the general condition of patients, reduce the intensity of carcinoid syndrome, reduce the size of metastatic foci, causing a positive response (partial response or stabilization) in more than half of patients (57.2%).

Keywords: transarterial chemoembolization, neuroendocrine tumor, metastasis, RECIST 1.1 criteria.

Background. Neuroendocrine tumors (NETs) are a heterogeneous group of malignant human tumors originating from special cells of the APUD system (Amine Percursor Uptake and Decarboxylation) localized throughout the body [2]. About 66% of all NETs occur in the gastrointestinal tract, while 30% account for the bronchopulmonary system [1].

The annual incidence of NETs is 1.8 cases for women and 2.6 cases for men per 100,000 population [1, 3]. An increasing number of newly reported NETs have been registered over the past 30 years, largely due to the widespread use of immunohistochemical diagnostics and the advent of molecular genetic methods that greatly simplify the diagnosis [4].

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NETs often metastasize to the liver, which is the main factor that determines the quality of life of patients, and is usually associated with a poor prognosis. Despite the fact that a localized primary NET can be easily resected surgically, metastatic foci in the liver are most often inoperable and require a different approach to their treatment [5]. Unfortunately, all possible therapeutic methods are palliative ones and aimed only at improving the quality of life of such patients. These methods include somatostatin analogue therapy, targeted therapy, systemic chemotherapy, and various other locoregional techniques [2, 3, 9]. Thus, the 5-year survival rate for patients with surgically removed localized primary tumor is 60-90%, and only 25-40% for patients with secondary liver metastases [5, 7].

The prognosis of patients with NETs also depends on the tumor stage, the location of the primary tumor and its histological characteristics. The current World Health Organization (WHO) classification from 2010 distinguishes well-differentiated NETs with a proliferation index Ki67 <2% (G1), moderately differentiated NETs with a proliferation index Ki67 = 3-20% (G2), and poorly differentiated NETs with a proliferation index Ki67> 20 -100% (G3), respectively [8].

Most NETs are well-differentiated and non-functioning, without any hormonal activity and specific clinical picture [1, 6]. This, in turn, significantly complicates the early diagnosis of NET and is the reason for the presence of secondary liver metastases and, often, signs of local prevalence in 40-90% of patients already at the initial diagnosis [2, 6]. But since this histological form nevertheless has a favorable prognosis, it becomes quite feasible to use aggressive surgical treatment tactics even in the presence of distant liver metastases, which is usually not used for other malignant tumors. However, when more than 75% of the total liver volume is affected, radical resection is not feasible, so one of locoregional treatment methods - transarterial chemical embolization (TACE) - is recommended to use as a preoperative preparation or independently [2, 6, 8].

The purpose of the study was to assess the effectiveness of treatment for liver metastases from neuroendocrine tumors by the TACE method based on the analysis of 7 clinical cases.

Material and methods. We retrospectively analyzed 7 clinical cases of gastrointestinal NETs with inoperable liver metastases in patients treated at Rostov Research Institute of Oncology in 2016-2018. We studied the symptoms in each clinical case and analyzed the results of computed tomography using RECIST 1.1 criteria taking into account all types of treatment that patients received immediately before TACE (including therapy with somatostatin analogues). The patients included 6 women and 1 man aged between 34 and 68 years before the treatment. Primary tumors were in the rectum (n=1), pancreas (n=1), stomach (n=1), small intestine (n = 2), sacrum (n = 1); in one case, primary tumor focus was not detected. 4 patients (57.1%) had undergone prior surgical removal of the primary tumor (resection of the ileum,

resection of the rectum, resection of the tail of the pancreas). Metastases were morphologically verified in 7 cases (100%) with needle biopsy and subsequent histological analysis. G1 – well-differentiated cancer (Ki67 <2%) was found in 28.6% of patients, G2 - moderately differentiated cancer (Ki67 = 3-20%) in 0%, G3 - low-differentiated cancer (Ki67 = 20-100%) in 71.4%, respectively. 85.7% of patients received TACE for the first time, and 14.3% of patients underwent several TACE courses for the entire treatment period. 71.43% of patients received polychemotherapy courses prior to TACE, 28.57% of patients did not (Table 1).

Table 1

Characteristics of patients before TACE

Criterium	Assessment (n=7)
Mean age	55 years
Gender	6/7 (85.7%) women. 1/7 (14.3%) men
Sizes (cm) of metastatic foci	From 4 to 11 cm
Prior removal of the primary tumor	4/7. 57.1%
Extrahepatic metastases	3/7. 42.9%
Tumor grade, Ki67, %	G1 (Ki67<2%) – 28.6% (2/7) G2 (Ki67=3-20%) – 0% (0/7) G3 (Ki67=20-100%) – 71.4% (3/7)
Clinical picture	General symptoms (weight loss. loss of appetite. weakness. abdominal pain) 7/7. 100% Symptoms associated with hormonal activity: carcinoid syndrome 5/7. 71.4%; insulinoma/ hypoglycemia 1/7. 14.3%; gastrinoma 1/7. 14.3%

The procedure of transarterial chemoembolization involves the following steps. The standard puncture of the right brachial artery is performed under aseptic X-ray conditions (angiographic 18 G needle), with the following Seldinger arterial catheterization (5F introducer 11 cm). CB1 catheter is sequentially inserted through the catheter guide .035" 150 cm into the right axillary and subclavian artery, brachiocephalic trunk, descending aorta. Catheter guide is removed, aortography is performed. Using P1 5F catheter with a hydrophilic guide .035" 180 cm, the right and then the left hepatic arteries are selectively sequentially catheterized. Using a microcatheter 2.6F 150cm on a .014 "300cm micro-guide, segmental arteries supplying the tumor site are superselectively catheterized. An emulsion containing chemotherapeutic agents is prepared, and parenchymal chemoembolization of the liver is performed. Arterial embolization is performed with a Spongostan gelfoam slurry. During control angiography, a pronounced slowdown in contrast is determined by the segmental branches of the right hepatic artery supplying the tumor focus. The signs of nontarget embolization are detected. The catheter is inserted into the aorta. The tools are subsequently removed.

The hepatic artery is the best choice for selective chemoembolization because it supplies up to 95% of the liver tumor tissue [7]. Chemoembolization agents enter both the tumor and healthy liver tissue. Due to the muscle layer, the arterial bed of the unaffected parenchyma ensures the distribution and rapid elimination of the drug. Pathological tumor vessels do not have a muscle layer, which leads to the chemoembolization agent retention in the tumor [1, 3, 5].

Table 2

Comparative analysis of CT data and assessment of tumor response using RECIST 1.1 criteria

№	CT data before TACE	CT data 3 months after TACE	CT data 6 months after TACE and later	Assessment of results
1	A solitary lesion of 4x3.7 cm in S7 of the right lobe	A solitary lesion of 5x4.3 cm in S7 of the right lobe	A solitary lesion of 4.8x5.2 cm in S7 of the right lobe	Increase by 25% (stabilization)
2	Metastatic foci up to 6.2 cm in both lobes	Metastatic foci up to 5 cm in both lobes	Metastatic foci up to 3 cm in both lobes	Decrease by 50% (partial response)
3	CT image of multiple liver metastases. Coalesced metastatic foci up to 5 cm.	CT image of relative stabilization. процесса. Coalesced metastatic foci up to 4.5 cm.	CT image of multiple liver metastases with signs of progression. Coalesced metastatic foci up to 8 cm.	Increase by 60% (progression)
4	Coalesced metastatic foci up to 11 cm.	N/A	N/A	N/A
5	A solitary lesion of 6.7x7.0 cm in S8 of the right lobe	A solitary lesion of 5x5.2 cm in S8 of the right lobe	A solitary lesion of 4x4.3 cm in S8 of the right lobe	Decrease by 43% (partial response)
6	A metastatic focus 2.4x2 cm in S1 of the right lobe is closely adjacent to the inferior vena cava, deforming it. A metastatic focus 4.6x4 cm in S7	A metastatic focus 2.2x1.8 cm in S1 of the right lobe. A metastatic focus 3.2x3.5 cm in S7	A metastatic focus 1x1.2 cm in S1 of the right lobe. A metastatic focus 2.2x2 cm in S7	Decrease by 50% (partial response)
7	CT image of multiple liver metastases without changes in the number of metastases since December 19, 2017. An increase in the size of one of the lesions in the right lobe of the liver.	CT image of a relative stabilization. Multiple liver metastases without changes in the number of metastases. No increase in foci size.	Negative dynamics, the appearance of new small foci, an increase in the liver volume.	Progression

In our opinion, the indications for TACE in NETs were: inoperable liver metastases; sufficient functional reserves of the liver (bilirubin <70 μmol/l); hemoglobin >80 g/l; no extrahepatic tumor spread. Contraindications were: active systemic infection; ongoing bleeding; Child-Pugh C class; leukopenia (white blood cells <1000/ml); prothrombin time less than 40%; heart failure (left ventricular ejection fraction less than 50%); unmanageable sensitivity to the contrast; ECOG functional status >3; damage to more than 50% of the liver; extrahepatic metastases; tumor invasion into the inferior vena cava and the right atrium; ascites; severe thrombocytopenia; history of portocaval anastomosis; high total bilirubin> 60 μmol/l; LDH> 425 U/L; transaminases> 100 IU/L.

According to clinical recommendations, in the pre- and post-procedural period, patients received infusion therapy, octreotide (in case of pronounced hormonal activity), non-steroidal anti-inflammatory drugs, glucocorticoids (dexamethasone 4 mg, 2-3 times a day, per os, to manage postembolic syndrome and symptoms such as nausea, vomiting, fever, abdominal pain, decreased appetite), antibacterial drugs (a day before TACE to prevent complications such as liver abscess, cholangitis, sepsis), antifungal preparations.

Results and discussion. In all cases, we evaluated the response to therapy using CT data (Table 2) obtained 3-6 months after TACE, using RECIST 1.1 criteria (2009). 1 out of 7 patients died, 6 others report an objective improvement in their general condition. All 6 patients complain of periodic fatigue. 2 of them have severe abdominal pains with no relief after NSAIDs administration. Tumors were hormonally active in all 7 patients, in 5 of them there was a pronounced carcinoid syndrome (facial redness, stool up to 7-9 times a day, changes in blood pressure). After TACE, the intensity of carcinoid manifestations decreased (stool frequency up to 3-4 times a day). All 6 patients in the postoperative period receive polychemotherapy courses and therapy with somatostatin analogues.

Assessing the results of CT scans in dynamics with an interval of 3 and 6 months (Table 3), according to the RECIST 1.1 criteria, the following was established: in 2 patients (28.6%) with a relative stabilization 3 months after TACE, disease progression was observed after 6 months; in 3 patients (42.9%) - a persistent partial response to therapy 3 and 6 months after TACE; in 1 patient (14.3%) - stabilization based on CT data after 3 and 6 months after TACE.

Conclusions. In a small number of patients, we showed that TACE helped to normalize the general condition of patients, reduce the intensity of carcinoid syndrome, reduce the size of metastatic foci, causing a positive response (partial response or stabilization) in more than half of patients (57.2%). There was no clear correlation between the tumor stage, grade and the TACE effectiveness. Table 2 demonstrates the need for cyclic TACE every 2-3 months. Thus, the effectiveness of this technique, a clear tumor response, minimal toxicity, no damage to a healthy liver parenchyma, and minimal invasiveness make TACE a valuable "tool" in treatment of patients with NETs.

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OPTIMIZATION OF REMOVAL OF X-RAY VISUALIZED FOREIGN BODIES OF SOFT TISSUES

DOI 10.25789/YMJ.2020.69.28

УДК 616-003.6-073.75-089

Aim. To improve the results of removal of x-ray visualized foreign bodies of soft tissues.

Material and methods. The data of treatment of 135 patients with x-ray visualized foreign bodies of soft tissues in the department of purulent surgery of the 301 military clinical hospital of Khabarovsk from 1987 to 2013 was analyzed.

Results. The use of a set of measures to remove x-ray visualized foreign bodies, including the use of copper mesh and marking with an indelible marker on the skin of the projection of the foreign body and the direction of the incision proves statistically significant ($p<0.05$) diminishment the frequency of repeated operations to remove foreign bodies from 29.3% to 0%, the time of surgical intervention during the first operation from 45.8±0.8 minutes in patients of the control group – up to 20.6±0.3 minutes in patients of the main group, as well as the frequency of suppuration of the surgical wound from 7.3% to 0%, respectively.

Conclusions. Surgical intervention to remove x-ray visualized foreign bodies from soft tissues should be carried out taking into account the indications and contraindications to the operation, use optimal anesthesia depending on the specific situation after the mandatory x-ray and ultrasound examination, with the mandatory use of copper mesh and marking with an indelible marker on the skin of the projection of the foreign body and the direction of the incision.

Key words: x-ray visualized foreign bodies, soft tissues, treatment.

Introduction. The choice of treatment strategy of patients with foreign bodies of soft tissues is a very difficult problem due to the wide incidence of this pathology [3, 5, 12]. For example, in 12-38% of patients traumatic injuries are complicated by various foreign bodies entering the wound. [2,11]. Some patients consciously introduce various foreign bodies into the soft tissue [1,15,13].

Removal of small and deep-located foreign bodies of soft tissues is particularly difficult and unsuccessful attempts are observed in 12.5–30% of cases [5,12]. In order to clarify the localization of foreign bodies such methods as ultrasound and computer tomography are used. Meanwhile, despite of preoperative examination, the search of a foreign bodies of soft tissue during surgery often takes a lot of time, leads to extensive tissue damage and also increases the risk of complications [12,14].

The **aim** of this work is to optimize the methods of diagnosis and removal of x-ray contrast foreign bodies of soft tissues.

Research Material and Methods. The analysis of treatment of 135 patients with x-ray contrast foreign bodies of soft tissues and had been hospitalized to the department of purulent surgery of the 301 Military clinical hospital of Khabarovsk from 1987 to 2013 was carried out.

Among these patients 29 (22%) have introduced various foreign bodies into the soft tissue consciously.

The traditional method of diagnosis of x-ray contrast foreign bodies of soft tissues was used from 1985 to 2001 in 82 (60,7%) patients of the control group.

For the period from 2002 to 2018 the diagnosis of x-ray contrast foreign bodies of soft tissues was based on the application in addition to x-ray examination such methods as ultrasound and use of copper mesh with subsequent marking of projection of a foreign body and operative access on skin [7].

The age of patients ranged from 16 to 55 years, average age was 25,9±3,2 years in the main group and 23,7±2,6 years in the control group. In both groups there were 132 men (97,8%) and 3 women (2,2%).

According to the terms of finding foreign bodies in soft tissues at the time of hospitalization, patients were distributed as follows: The 77(57%) patients were hospitalized within the first 7 days after injury, 22(16.3%) patients – from 7 days to 1 month after injury, 15(11.1%) patients – from 1 month to 6 months after injury, 9(6.7%) patients – from 6 months to a year after injury, 12(8.9%) patients – a year or more from the date of injury.

The main and control groups were the same in sex and age of patients, duration of the disease, which allowed to compare the results (Table 1-3).

Results. The number of operations, which were performed in order to remove foreign bodies, are presented in Table 4.

In 5 (6.1%) patients of the control group, foreign bodies, despite repeated operations, were not removed.

The duration of the first operation in patients of the main group averaged 20.6 ± 0.3 minutes, in patients of the control group - 45.8 ± 0.8 minutes, the difference in performance was statistically significant ($p <0.05$).).

In 6 (7.3%) patients in the control group were diagnosed with postoperative wound suppuration, which is connected, in our opinion, with the duration of the operation and tissue trauma, while in the main group of patients there was no such complication.

Discussion. There are known methods for removing X-ray contrast

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Table 1

The types of x-ray contrast foreign bodies, (n=135)

Вид инородного тела	Foreign body (abs., %)	
	unintentionally inserted	deliberately inserted
Sewing needle	18 (17)	28 (96.6)
Needle for injection	3 (2.8)	0
Surgical needle	3 (2.8)	0
Metal splinters	35 (33)	0
Metal shards	5 (4.7)	0
Metal bullet	22 (20.8)	0
Fragments of metal structures	6 (5.7)	0
Glass	5 (4.7)	0
Wire	9 (8.5)	1 (3.4)
Total	106	29

Table 2

Localization of foreign bodies of soft tissues in patients (n=135)

Localization of foreign body	Foreign body (abs., %)	
	Unintentionally inserted	Deliberately inserted
Hand	29 (27.4)	-
Gluteal region	10 (9.4)	-
Thigh	16 (15.1)	1(3.4)
Shin	4 (3.8)	28 (96.6)
Foot	40 (37.7)	-
Other areas	7 (6.6)	-
Total	106 (100)	29 (100)

Table 3

The nature of the inflammatory process in the area of localization of foreign bodies of soft tissues in patients (n=135)

The nature of the inflammatory process	Foreign body (abs., %)	
	Unintentionally inserted	Deliberately e inserted (abs., %)
No clinically significant inflammation	72 (67.9)	9 (31)
Inflammatory infiltrate	26 (24.5)	8 (27.6)
Abscess	6 (5.7)	4 (13.8)
Phlegmon	2 (1.9)	8 (27.6)
Total	106 (100)	29 (100)

Table 4

The distribution of patients depending on the number of operations performed when removing foreign bodies of soft tissues

The number of operations performed per patient	Patient group (abs., %)	
	Main group	Control group
1	53 (100)	58 (70.8)
2	0	17 (20.7)
3-5	0	6 (7.3)
More than 5 operations	0	1 (1.2)

foreign bodies from soft tissues, involving the use of various search probes using magnets for the intraoperative search and removal of a foreign body [4, 6, 8, 9, 10]. These devices have the following disadvantages. First, the real magnetic environment of the operating room, created by metallic surgical instruments and equipment, reduces the possibilities of using these devices, reducing their sensitivity, and contributing to the appearance of false signals. Secondly, they have low sensitivity in relation to small foreign bodies. Thirdly, when the various search probes proposed by the authors work, the light and sound alarms can only determine the approximate location of the foreign body, which is usually clear after the preoperative examination. Finally, free capture of a small foreign body in the depth of tissues, for example, using the tool proposed by the authors [10], is impossible in the case of an encapsulated foreign body, since its separation from the capsule formed around it is required. There is also a danger of fragmentation and leaving a part of the foreign body in the wound.

A known method of removing a foreign body of human soft tissues [3], which consists in determining the X-ray projection of a foreign body on the skin using a metal grid, followed by performing an incision in the intended square. However, this method of removing a foreign body has several disadvantages that reduce its effectiveness. First, after a preoperative examination using a metal grid, the projection of a foreign body and the line of operative access with an indelible marker are not applied to the skin. Secondly, the implementation of surgical intervention begins with a fixed mesh, which does not allow for adequate access, as the mesh itself interferes with the manipulation of the wound.

In addition, in order to improve the efficiency of removal of foreign bodies of soft tissues, it is necessary to take into account the indications and contraindications for the operation, use the entire arsenal to improve the determination of the exact localization of foreign bodies, and also choose the best method of anesthesia.

The main indications for the removal of radiopaque foreign bodies are, in our opinion, dysfunction of the limb caused by a foreign body, chronic pain syndrome due to the presence of a foreign body in soft tissues, inflammatory changes in soft tissues or fistulas supported by a foreign body.

In addition to well-known contraindications to any surgery associated with high surgical and anesthetic risks, we consider that such contraindications as localization of foreign bodies in the immediate vicinity of major vessels, nerves and vital organs with a high risk of intraoperative injury, significant depth of the location of foreign bodies with small sizes and the absence

of clinical manifestations, as well as the surgeon's lack of sufficient experience for these operations are also considerable.

In order to more accurately localize radiopaque foreign bodies of soft tissues, it is necessary to use all possible methods, including X-ray and ultrasound examination, the use of a copper mesh and the projection of the foreign body itself on the skin and the most rational prompt access directions.

The choice of type of anesthesia is carried out taking into account the size, location, depth of the foreign body, as well as the age of the patient. In the absence of well-known contraindications to local anesthesia, this type of anesthesia can be used for superficial localization of foreign bodies (no deeper than 3-4 cm from the skin surface within the subcutaneous tissue or directly under the fascia) or if the foreign bodies are large, palpable, and no technical difficulties are foreseen in their removal. It is advisable to use general anesthesia for deep localization (more than 4 cm from the skin surface) of small foreign bodies adjacent to anatomically important formations. Before performing anesthesia, it is desirable to temporarily reduce blood flow in the operated limb segment by applying an arterial cord, which facilitates the search for a foreign body.

A common mistake, often leading to an unsuccessful attempt to remove a foreign body, should be considered a refusal to involve a second surgeon in the assistance, who provides a complete visualization of the surgical wound during the operation.

The search for foreign bodies of soft tissues in the overwhelming majority of cases, even after preliminary marking, is associated with significant difficulties. In this regard, while searching for foreign bodies it is recommended to use a number of the following techniques. Thus, during the revision of the wound, one should pay attention to the state of the tissues in the intended zone of foreign body localization. Approximate topical diagnostics of a foreign body in soft tissues is often carried out by black-brown staining of tissues, which indicates a close localization of the desired object. Initially, accurate probing of tissues with a closed Billroth-type hemostatic clamp is used with continuous visual inspection until a feeling of "scratching" appears. However, while removing foreign bodies from areas with multiple connective tissue webs, for example, palms or soles, the described sensations can be difficult to differentiate. A delicate examination of the wound with a finger, during which it is possible to palpate a foreign body, can be of great help in the search. However, the surgeon should be extremely careful in the presence of a piercing or cutting foreign body in soft tissues.

When a foreign body is detected, the main task is to remove it entirely, without leaving fragments. Anatomical tweezers are used for removal, which, unlike a clamp, allows precise gripping and avoiding foreign body fragmentation.

After successful removal of a foreign body and provided there are no signs of surgical infection of the soft tissues, the wound is stitched. The decision on the need for wound drainage and antibiotic therapy is taken individually.

In the postoperative period, control radiography is performed to eliminate accidentally left foreign body fragments.

Conclusions

1. Diagnostics of radiopaque foreign bodies of soft tissues should be based on the mandatory use of a complex of non-invasive methods, including X-ray and ultrasound examination, the use of a copper mesh and marking with a permanent marker on the skin of the projection of the foreign body itself and the direction of the incision.

2. X-ray contrast foreign bodies of soft tissues are accompanied by clinically significant inflammatory processes in 40% of cases.

3. Radiopaque foreign bodies which are deliberately inserted into soft tissues are usually sewing needles and are usually localized deep in the tissues of the posterior surface of the left tibia.

4. In our practice the usage of a set of measures to improve the localization of radiopaque foreign bodies of soft tissues and the usage of the above described features of their removal allowed statistically significantly ($p < 0.05$) reduce the frequency of repeated operations to remove foreign bodies from 29.3% to 0%, the time of surgical intervention for conducting the first operation from 45.8 ± 0.8 minutes in patients of the control group up to 20.6 ± 0.3 minutes in patients of the main group, as well as the incidence of suppuration of the surgical wound from 7.3% to 0%, respectively.

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BIOETHICAL RULES FOR DNA TESTING OF AUTOSOMAL RECESSIVE DEAFNESS 1A IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.69.29

УДК 612.858.77(571.56)

As a result of studying the bioethical aspects of DNA testing of autosomal recessive deafness-1A (DFNB1A), the main range of bioethical problems that may arise during the mass introduction of DNA testing for hereditary hearing impairment, which in the future will require moral, ethical and legal understanding of the results of the introduction of DNA testing in medical practice was identified. Ethical rules for DFNB1A DNA testing have been developed.

Keywords: autosomal recessive type 1A deafness, DNA diagnostics, bioethics.

Since 2005, the Republic of Sakha (Yakutia) has been conducting a molecular-genetic study of hereditary non-syndromic sensorineural deafness. For the first time in the Yakut population, the molecular-genetic cause of the hereditary congenital form of deafness was identified, which is caused by a mutation in the donor site of the splicing c.-23+1G>A of the GJB2 gene (Cx26) and is classified as an allelic variant of autosomal recessive deafness-1A (DFNB1A) in accordance with the international OMIM catalog (Online Mendelian Inheritance in Man). The prevalence of DFNB1A is 16.2 per 100,000 of the Yakut population, and the frequency of heterozygous carriage of the c.-23+1G>A mutation varies from 3.8% to 11.7% among the indigenous population of Yakutia (Evens, Evenks, Dolgans, Yakuts). The results of the study of the mutation of the GJB2 (Cx26) gene splicing site indicate the existence of the world's largest "endemic focus" of c.-23+1G>A accumulation in Eastern Siberia [1]. We studied the bioethical problems of DFNB1A DNA testing, previously described in an article by Kononova et al. (2018) [2]. As a result of our research, the ethical rules for genetic counseling in the molecular genetic diagnosis of DFNB1A were adopted and approved at a meeting of the local committee on biomedical ethics at the YSC CMP, presented in Table.

Conclusion. As a result of studying the bioethical aspects of DNA testing of autosomal recessive deafness-1A, the main range of bioethical problems that may arise during the mass introduction of DNA testing for hereditary hearing impairment, which in the future will require moral, ethical and legal understanding of the results of the introduction of DNA testing in medical practice, was identified.

The work was performed with the financial support of the RFBR "Study of bioethical aspects of DNA testing of hereditary hearing disorders" grant (18-013-00738 A).

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Bioethical rules for DNA testing of autosomal recessive deafness 1A in the RS (Ya)

Bioethical rules	Comments
1. The relationship between the geneticist and the tested individual in genetic counseling is built on mutual trust and is nondirective;	Directivity - a deliberate attempt by a consultant (through deception, threat or coercion) to violate a person's autonomy and push them to a particular decision [4]

2. Every individual who wants to undergo testing has the right to receive complete information about the disease, its development and consequences, the nature of testing, possible results;	To find out the causes of deafness / hearing loss in a family burdened by DFNB1A, patients with different genetic and phenotypic status can apply for genetic counseling: individuals with a normal genotype without hearing impairment ([wt];[wt]), heterozygous carriers with “normal hearing” (c.[mu];[wt]), homozygotes by mutation with severe hearing loss (c.[mut];[mut]). Accordingly, approaches to genetic counseling and obtaining informed consent for DNA testing of these groups of patients should also be different [2].
3. The decision to undergo DNA testing must be voluntary;	Counseling and DNA testing aims to improve psychological well-being and adapt the patient to a genetic condition or risk [4].
4. The presence of a sign language interpreter when consulting patients is mandatory	Information should be communicated to the patient in the most complete and accessible form [4]
5. The necessary condition for conducting DNA testing is informed consent, which means that a capable individual is fully acquainted with the information presented to him, understands it adequately and makes a decision on examination independently	It is necessary to create special conditions for counseling and obtaining informed consent from the deaf. Informed consent to DNA testing of DFNB1A must be in writing and be as accessible as possible. Avoid complex genetic terms and use simple words and sentences [2].
6. DFNB1A DNA testing is acceptable for underage children	Upon receiving informed consent from hearing parents for DFNB1A DNA testing, it can be explained that the child inherits the damaged gene from each parent and, perhaps, some parents will see this as an even distribution of responsibility for the disease. On the other hand, a burdened family history (the presence of deaf relatives in the family) greatly facilitates counseling and obtaining consent for DNA testing, since patients are psychologically ready to accept such hereditary burden in the family. DNA testing of children under 14 years of age for carriage of DFNB1A should be carried out with the informed consent of parents or guardians, and it is very important to inform parents in detail about the genetic status of their child and provide adequate psychological support when reporting the results of DNA testing [2]
7. The patient is given time to think about the decision to undergo DNA testing	Generally, patients are more satisfied if they are adequately informed and actively involved in decision-making. Therefore, it is necessary to respect the patient's choice of consent / rejection of DNA testing [2,4]
8. Information about the results of DNA testing is strictly confidential. Reporting results by mail and phone is not allowed.	Reporting the result of DNA testing about the risk of DFNB1A can carry a significant moral and psychological burden for a person. First, the test taker learns about the risk of having a deaf child in a family. In this case, when heterozygous carriage of DFNB1A is identified in an individual, it is necessary to recommend him prospective medical and genetic counseling or preconception prophylaxis. Secondly, a heterozygous carrier must be provided with information on a rather high risk of hearing loss in old age. The statement of this fact can be supplemented by recommendations for maintaining an appropriate lifestyle and work that would reduce the burden on the organs of hearing (avoid work associated with noise, etc.) [2]
9. The use of DNA diagnostics on DFNB1A for patients with deafness in the Republic of Sakha (Yakutia) can be recommended for prenatal DNA testing procedures, as well as for in vitro fertilization procedures, with the exception of genome editing technology.	The scope of genome editing technology is currently one of the most controversial, as it raises many legal and ethical issues, due to the technical imperfection of genome editing technology:insufficient accuracy and efficiency, mosaicism of the obtained embryos, etc. The absence of long-term observations of the consequences of genome editing technology does not allow us to say with certainty that the modification of the genome will not lead to the development of genomic anomalies in the long term and will not affect the health of offspring in an unpredictable way [3,5].

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COMPLICATIONS AND REPEATED SURGICAL INTERVENTIONS AFTER SURGICAL TREATMENT OF CHILDREN WITH ACUTE SCROTUM SYNDROME

DOI 10.25789/YMJ.2020.69.30

УДК 616-089-06

Objective. Identify the causes of complications and repeated surgical interventions in the surgical treatment of patients with "acute scrotum syndrome" in the early and late postoperative period.

Materials and methods. The results of treatment of 3315 patients aged 0 to 18 years with acute scrotum syndrome are analyzed. 43 complications of a tactical and technical nature were stated, and surgical intervention was required in 32 cases.

Results and discussion. The most frequent complication is the incorrect determination of the vitality of the gonad when it is torsion. This is due to the fact that surgery is often accompanied by surgery. However, decision making requires no objective data to save gonad, which requires subjective character and in all cases leads to the lost gonad and need for repeated surgical intervention and does not require objective arguments. Disorders of surgical hemostasis are most often caused by defects in the surgical technique; insufficient consideration of background inflammatory changes in the scrotum organs is enhanced. Purulent complications are most often associated with acute epididymitis and are caused by the presence of an inflammatory lesion in the scrotum. Performing a broad revision of the scrotum in hydatid pathology is not justified, since the frequency of non-emergence of the second hydatid - a rare complication, the invasiveness of the intervention increases. Other complications are casuistic.

Conclusion. Surgical complications in acute scrotal diseases are different. Typical errors can be both tactical and technical. Complications are more common in the acute period (88.4%). Purulent complications are directly dependent on the duration of the disease and are aggravated by secondary changes in the scrotum organs. The low frequency of undetecting hydatid with its combination of torsions (0.03%) is not a reason for a complete revision of the scrotum, since the overall invasiveness of the operation will increase significantly. The frequency of their occurrence is reduced.

Keywords: acute scrotum syndrome, children, complications, repeated operations.

Acute scrotum diseases are a common nosological group in childhood. Operations with nosological forms, united in this syndrome, make up the second place after appendectomy in childhood [1]. A significant number of operations are performed not only by a pediatric urologist, but also by a pediatric surgeon and an urologist of an adult medical department involved in emergency care [3].

Technically, these surgical interventions are quite simple, do not require significant surgical skills, and do not pose significant difficulties for the practitioner. The tactical component in some cases is more complicated and is discussed in the literature, first of all, this concerns the assessment of viability and tactics in testicular inversion in a state of severe ischemia [2,6].

Nevertheless, in some cases, the surgical interventions discussed lead to the development of complications, both technical and tactical in nature, and often require repeated surgical interventions [7]. A number of complications arise when performing operations for acute scrotum syndrome in the long term - with gonad fixation, prosthetics, etc. this question finds extremely poor consecration in the literature and the almost complete absence of an analysis of complications [4,9,10]. To a large extent, the small number of publications on complications is due to the high frequency of legal conflicts associated with various complications, and the corresponding social tension caused by them [5.8]. This leads to limited publications on this issue. All of the above allows us to consider such a study relevant.

Purpose: To establish the causes of complications and repeated surgical interventions in the surgical treatment of patients with acute scrotum syndrome in the early and long-term postoperative periods.

Materials and methods. We have analyzed the experience of treating children with acute scrotum syndrome over a period of 25 years. During the period under discussion, the department treated 3315 patients aged from birth to 18 years, including with testicular torsion - 299, acute epididymitis - 267, scrotal organ injury - 47, hydatid torsion - 2673, and other diseases - 29. Surgical interventions were performed in 3106 (93.7%) patients, among whom, during testicular torsion, emergency operations were performed 269, delayed and planned 218, including on the contralateral testicle, with acute epididymitis 155, with torsion of hydatides - 2431, with scrotal organ injury - 22, for other diseases Organ Precursor Cells scrotum - 11.

Complications were noted in 43 (1.38%) patients. The existing complications are divided by us conditionally into two groups - technical (n = 23) and tactical (n = 20).

Tactical complications:

1. Incorrect determination of the viability of the gonad during testicular torsion (n = 19)
2. Secondary orchoepididymitis (n = 1)

Technical complications:

1. Disorders of surgical hemostasis (n = 12)
2. Suppuration and partial failure of the wound in the postoperative period (n = 5)

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3. Failure to detect twisted hydatide due to incomplete revision of the scrotum organs (n = 1)

4. Complications of orchiectomy - ligature fistula of the scrotum (n = 1)

5. Complications of testicular prosthetics (n = 2)

6. Complications of testicular fixation during torsion (n = 2)

Selected study design does not allow statistical analysis

Results and discussion. The frequency of complications and reoperations in the conditions under discussion was analyzed, the largest number of complications, both tactical and technical, are noted in testicular torsion, acute epididymitis and scrotal organ injury, less often in hydatid torsion. The results of the analysis are shown in table 1.

The recurrence rate usually correlates with the incidence of complications. Most complications relate to the acute period of the disease. Repeated operations for complications were performed in 32 (74.4%) patients.

The most common complication is an incorrect determination of gonad viability during testicular torsion (n = 19). This error was found in patients with critical ischemia, when, against the background of detorsion, it was difficult to assess the viability of the gonad with available clinical and radiation methods. The testicle was left to assess its perfusion over time. In all cases, a follow-up audit was performed after 1-2 days, in which the gonad, erroneously defined as viable, was removed in 16 (84.2%) cases, in three (15.8%) the testis was regarded as viable and preserved, however, with an assessment after a year noted atrophy with a loss of 65-92% of the volume and performed secondary orchiectomy. This position may be controversial from the point of view of interpreting it as a complication, the chosen tactics are often dictated by the surgeon's desire to leave the organ-bearing operation, in some cases, the decision to perform an orchectomy is made against the background of errors in the prehospital phase, exacerbates social stress and entails potentially judicial collisions. Note that such a decision is made without objective data for the possibility of maintaining the gonad, is exclusively subjective. Such tactics in all cases leads to loss of gonad during repeated revision or delayed against testicular atrophy, causes the need for repeated surgical intervention and cannot be justified. The above allows us to regard it as a tactical error that has no clinical background

Disorders of surgical hemostasis are the second most common group of complications (n = 12). The reason for the development of complications of this group is due directly to defects in surgical technique, as well as insufficient consideration of background inflammatory changes in the scrotum, leading to impaired hemostasis. So, out of 12 complications, 9 developed with a disease duration of more than 3 days against the background of pronounced inflammatory changes in the soft tissues of the scrotum.

In 9 cases, the source of bleeding was the vessels of the membranes of the scrotum. The reason was insufficient hemostasis of the membranes against the background of their secondary inflammatory changes. These complications were noted in all forms of acute scrotum syndrome - testicular inversion (n = 4), torsion of hydatides (n = 2), scrotal organ injury (n = 1), orchoepididymitis (n = 2). The volume of hematomas ranged from 12 to 250 ml (35.8 ± 11.9 ml). Their evacuation and drainage were performed in five patients, the volume was estimated as 57.2 ± 8.1 ml, with a smaller volume of hematoma, patients received conservative therapy and was accompanied by a gradual lysis followed by puncture.

One patient had scrotum hematoma due to bleeding from the hydatid pedicle during coagulation. A complication arose against the background of secondary orchoepididymitis, the operation was performed on the 6th day of the disease. The accumulation of the hematoma was detected 2 hours after the operation, with a repeated audit performed urgently, its volume was 40 ml, and the coagulation of the hydatid pedicle was repeated

In one case, insolvency of the ligature was noted during ligation of the spermatic cord in a patient with testicular torsion. The latter was carried out in a single side without separation of the elements and their flashing. A scrotum hematoma with a volume of 300 ml was ascertained, which required repeated revision, flashing of elements and drainage. Subsequently, all orchectomies were performed only with stitching of the elements and, with severe edema, with separate dressing, which avoided such complications.

In one case, the scrotum hematoma was caused by incisions on the testicle's white membrane, an assessment to assess its viability during inversion. A small volume of hematoma (20 ml according to ultrasound) allowed for conservative treatment. In the described observation, the gonad was saved in an acute situation; when assessed after 1 year, atrophy was found with a loss of 85% of the volume.

Prevention of this complication is considered to be the most careful observance of hemostasis during wound closure, mandatory control of the hydatid pedicle and double suturing of spermatic cord elements during orchiectomy. Subject to the above precautions, only two cases of bleeding from the scrotum membranes have been noted over the past 10 years.

Purulent complications were noted in five patients - 1.15% of the total number of operations performed. Their relative rarity is due to the good vascularization of the organs of the scrotum and its membranes. It is characteristic that three of them were noted in acute epididymitis and are probably associated with an inflammatory focus in the scrotum cavity. A partial discrepancy of sutures of the postoperative wound, which required local treatment, was noted. In all cases, the intervention was carried

The frequency of complications and reoperations depending on the form "Acute scrotum syndrome."

Form of acute scrotum syndrome and surgery	Number of operated patients	Number of complications	% complications	Number of operations for complications	% operations for complications
Testicular inversion (detorsion, orchiectomy, prosthetics, fixation)	487	27	5.54	26	96.29
Acute epididymitis	155	5	3.22	2	40
Hydatide torsion	2431	4	0.16	3	75
Scrotal organ injury	22	2	9.09	1	50

out against the background of secondary inflammatory changes in the membranes of the scrotum and its organs. Prevention is the appointment of antibiotic therapy for signs of inflammatory changes in the scrotum.

Secondary epididymitis was detected in one patient with scrotal organ trauma (2.12%). A patient with a 20 ml intravaginal hematoma who arrived 12 hours after the injury was given conservative treatment. Perforated hematoma with almost complete emptying. Against the background of therapy, by the third day of treatment, acute orchioepididymitis with impaired perfusion in the lesion zone was detected. The patient was operated on, a rupture of the albuminous membrane was found without significant damage to the parenchyma in the lower pole of the testis, scrotum sanitation and drainage were performed. Suturing of the protein coat is considered impractical due to inflammation and compression of the parenchyma. By the 9th day, the subsidence of the inflammatory process was ascertained.

Non-detection of twisted hydatide due to incomplete revision of the scrotum organs occurred in one observation for 2431 surgical interventions (0.04%) - during an emergency operation by access from mini-access, the inflamed hydatide was detected at the upper pole of the testis and removed. A complete audit of the scrotum was not carried out in connection with the discovery of the source of the disease. In the postoperative period, persistent pronounced edema of the scrotum and hyperemia was noted, with repeated ultrasound in order to identify possible complications on the 3rd day after the operation, an altered hydatide was detected with ultrasound. In an emergency reoperation, the diagnosis is confirmed, an altered hydatide with torsion of the pedicle below the first is detected (Fig. 1). Hydatide removed. In this case, it was possible that there was a torsion of a previously unchanged hydatide after surgery, and a primary torsion of both hydatides, not detected during the primary operation. Performing a wide audit of the scrotum is not considered appropriate, because the frequency of such a complication is very small, and the invasiveness of the intervention is substantially obtained. It should be noted that the detected unchanged hydatides during any operations on the scrotum organs are considered necessary to be removed simultaneously.

Complications of orchiectomy are quite rare. We noted such a complication

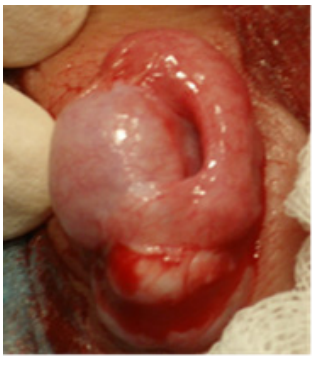


Fig. 1. The second hydatide, which was not removed during the initial audit, went unnoticed.

in one case, performing 96 orchectomies (1.04%). A ligature fistula of the scrotum was noted 6 months after performing an orchectomy (Fig. 2). We consider the reason for the complication to bandage the elements without separation by coarse silk thread. Subsequently, the removal of this ligature through the fistula was required, because its presence and infection prevented prosthetics.

Complications of testicular prosthetics are also not frequent - two cases were noted in 98 operations of implant implantation (2.04%). In one case, a bedsore of the scrotum membranes was associated with a relative discrepancy between the size of the implant and the volume of the scrotum cavity. This discrepancy is due to the desire to install an implant of the appropriate age and size of the testicle in the cavity, which subsided after an orchectomy performed three years before the intervention (Fig. 3). The second case is represented by the migration of the implant to the scrotum root and its wrinkling and is due to both the mismatch of the volume of the cavity and the implant, and probably the structural characteristics of the material of the implant (Fig. 4). Prevention of these complications is considered an adequate selection of the implant size with prosthetics without significant tension of the scrotum tissue and the use of modern synthetic implants.

Complications of the fixation of ischemic and contralateral gonad after testicular torsion were noted in two patients with 218 operations performed - only 0.92%. In one case, a ligature fistula was detected in the fixation zone associated with the reaction of tissues to suture material. In another observation, 1 year after the operation, an asymptomatic granuloma was detected at the lower pole of the testis, probably caused by the same reaction to the surgical thread. Both complications

Fig 2. Ligature fistula of the scrotum. 6 months after performing an orchectomy.

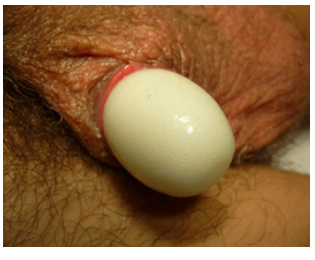
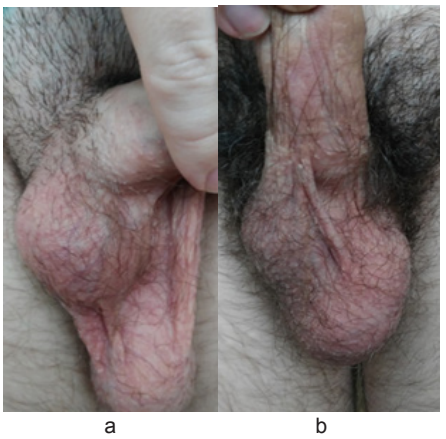


Fig. 3. Pressure ulcer of the scrotum. 7th day after prosthetics.

were noted until 2010 among the first 98 operations. In both cases, silk 3/0 was used as a suture material. Subsequently, in connection with the transition from 2010 to the PDS 6/0 thread on an atraumatic needle when performing testicular fixation in 120 patients, no complications were noted.

Conclusion. The complications of surgical treatment of acute scrotal organ diseases are diverse. The nature of the errors can be either tactical - most often the complexity of assessing the viability of the gonad during inversion, and technical - primarily defects in surgical hemostasis. Complications are noted more often in the acute period (88.4%), less often with staged treatment in the



a b

Fig. 4. Migration of the implant to the scrotum root and its wrinkling. A. - 1 month after surgery, B - 1 year after surgery.

long-term period (11.6%). Purulent complications in most cases are directly dependent on the duration of the disease before surgery and are aggravated by secondary inflammatory changes in the membranes and organs of the scrotum. The low frequency of not detecting hydatide with its combined torsion (0.03%) is not, in our opinion, a reason for a complete revision of the scrotum with this pathology, because significantly increases the overall invasiveness of the operation. In most cases, subject to a number of measures, it is possible to significantly reduce the frequency of complications.

Rational tactics of patient management, compliance with preventive measures of a technical nature will help to avoid most of the possible complications, or minimize their number.

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CLINICAL CASE

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CASES OF SYNDROME OF CONGENITAL CENTRAL HYPOVENTILATION (VTSG, CCHS, UNDIN SYNDROME) IN YAKUTIA

DOI 10.25789/YMJ.2020.69.31

УДК 616-053.3 (571.56)

Congenital central hypoventilation syndrome (CCHS, OMIM: 209880; CHS, ICD Q99, or "Ondine's curse syndrome") is a rare form of central sleep apnea, characterized by a loss of automatic and voluntary control of ventilation that causes apnea at sleep. The frequency of occurrence of the syndrome 1: 50000 - 200000 newborns [2]. This article presents 2 clinical cases of CCHS in children in the Republic of Sakha (Yakutia).

The first case of a child born in 2016, the diagnosis was confirmed at the age of 7 months. The second case is a child born in 2018, the diagnosis is confirmed up to 1 month of life. Both children were examined and treated in the perinatal center of "Republican Hospital No. 1 - National Medical Center" ("RH №1 – NCM"). The diagnosed congenital central hypoventilation syndrome was later confirmed by genetic studies in central clinics in Moscow and St. Petersburg. In clinical practice, hypodiagnosis of a given disease often occurs, which explains the rarity of its definition. Taking into account the clinical manifestations and depending on the degree of their intensity, early diagnosis prevents the undesirable effects of episodes of hypoxia and hypercapnia, ensures proper control of episodes of asphyxia and determines the prognosis of the disease. Since CCHS usually manifests itself in the neonatal period and mimics a variety of diseases, differential diagnosis requires the exclusion of various conditions involving alveolar hypoventilation, including congenital myasthenia, a number of myopathies, diaphragm dysfunction, and various lung and heart malformations.

Keywords: congenital central hypoventilation syndrome, Ondine's curse syndrome, hypoventilation, respiratory failure, PHOX2B gene.

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Introduction. Congenital central hypoventilation syndrome (CCHS, OMIM: 209880; CHS, ICD Q99, or "Ondine's curse syndrome") is a rare form of central sleep apnea, characterized by a loss of automatic and arbitrary control of ventilation, which causes apnea when falling asleep. This pathology was first described in 1962 by J. Severinghaus and R. Mitchell [6]. People with this disease are not able to breathe on their own during sleep. Along with apnea, the symptoms of this pathology include persistent cyanosis and emerging pulmonary hypertension.

The frequency of occurrence of the syndrome 1: 50000 - 200000 newborns [7]. Around 1,000 cases of CCHS have been described worldwide. In Russia there are registered 21 cases of this disease.

In the Republic Sakha (Yakutia) with a population of 964,330 people, 2 cases of CCHS were identified. The article presents these clinical cases. Congenital central hypoventilation syndrome is a genetic disease most often associated with the PHOX2B mutation in the 4p12 locus (in 93-100% of patients). Very rarely, the molecular genetic cause of the disease can be mutations in the *RET, GDNF, EDN3, BDNF* and *ASCL1* genes.

The classic CCHS syndrome is characterized by hypoventilation with normal respiratory rate and shallow breathing during sleep or during wakefulness and sleep, impaired autonomic nervous system, decreased sensitivity to hypoxia and hypercapnia, and the presence of neurocristopathy in some patients. After giving birth to a child with CCHS, this leads to the need for artificial ventilation. With age, there is a need to connect to the device during sleep. Genetic testing is required to confirm the diagnosis. Specialists from the Paris Hospital "Hospital des Enfants Malades" found that a special gene, called *Phox2B*, is associated with respiratory arrest. The analysis of the genes of 43 people with the syndrome of "the curse of Ondine" in comparison with 250 healthy people. At the same time, their parents did not have this defect, that is, the mutation was not inherited, but originated in the genetic set of germ cells.

The existence of an isolated dysfunction of autonomic centers, in the brainstem and hypothalamus, expressed by a decrease in the activity of adrenergic neurons, is shown in the structure of apnea. At the biochemical level, a decrease in the activity of adrenaline-synthesizing enzyme - phenylethanolamine-N-methyltransferase in different parts of the medulla oblongata, but most significant in the dorsal-median C2 field, which includes the nucleus gelatinosus, belonging to the nucleus tractus solitarius, and the posterior vagal nucleus was found. The cause of hypoventilation lies in the disorder of information integration at the level of the brain stem and is manifested in a violation of the transmission of impulses from the brain, setting in motion the respiratory muscles (diaphragm and muscles of the chest) [5]. Patients CCHS do not respond

to changes in the concentration of oxygen and carbon dioxide in the blood. This is due to the fact that the receptors in the blood vessels of the neck and brain do not send the correct impulses to the brain stem. The brainstem does not respond with increased respiratory stimulation when necessary. Patient CCHS does not feel, both consciously and unknowingly, that his breathing is insufficient, so that the breaths he makes remain superficial and the breathing rate is low. As a result, the supply of oxygen and the release of carbon dioxide are not sufficient. Clinical manifestations of CCHS are already in the neonatal period.

In foreign and domestic literature, polysomnography using specialized computer complexes is considered the "gold standard" for diagnosing sleep disorders [3]. Standard polysomnography allows you to reliably establish the type, type, severity, zone of localization of respiratory disorder.

Pending the results of testing *PHOX2B* genes, other causes of hypoventilation should be excluded. For differential diagnosis, an examination is necessary, including: chest X-rays; diaphragmatic fluoroscopy; electrocardiography and echocardiography; magnetic resonance imaging and / or computed tomography of the brain and brainstem; tests for metabolic disorders; comprehensive neurological assessment; polysomnography to establish the presence of hypoventilation and sleep-related breathing disorders.

The purpose of this study is to present a clinical case of CCHS syndrome, to examine the problem of diagnosing and treating patients with this very rare disease.

Materials and research methods. A pro- and retrospective analysis of the medical records of children with CCHS examined on the basis of the GAU RS (Ya) RH №1 - NCM was carried out.

Results and discussion.

Description of the first CCHS case. We happened to observe for a long time a boy who was born from a second pregnancy from a mother of 29 years old, somatically healthy, and a father of 28 years old, somatically healthy. It is known that the child's own and cousin's fathers died in infancy for an unclear reason.

The first pregnancy of the mother ended with the birth of a healthy boy. This pregnancy proceeded pathologically (the threat of termination in the second trimester, placental insufficiency, chronic hypoxia of the fetus, polyhydramnios). The boy was born in the conditions of the central regional hospital from the second spontaneous birth at the 37th week of gestation, in the head previa, body weight 3420 g, length 46 cm, rated on a Apgar scale 3/7 points. The state of birth is extremely severe, depression of consciousness was noted, reduced motor-reflex activity, progressive apnea, primary resuscitation measures were held in the delivery room, the child was transferred to a ventilator. On the 5th day at stabilization, the child was extubated, breathing in the NCPAP mode. Respiratory failure increased in dynamics, the boy was re-intubated and reconnected to the ventilator. As a child, an absentee consultation with specialists from the Yakutsk Republican Clinical Hospital (YRCH) was held. On the eighth day of his life, the boy was transferred to the resuscitation department of the YRCH in a very serious condition, caused by hypoxic-hemorrhagic damage to the central nervous system, respiratory insufficiency (RI), 3rd degree, and depressed consciousness. According to the results of the neurosonogram (NSG), on the eighth day of life, diffuse changes in the brain parenchyma, ventricular dilatation on the right, intraventricular hemorrhage (IVH), 2-3 degrees on the right, expansion of the third ventricle were detected. In the course of 22 days, internal and external hydrocephalus, echo signs of brain atrophy, and cystic leukomalation were revealed according to the NSG data. Radiography of the chest from the first day was observed hypoventilation. Based on the clinical picture, the data of laboratory and instrumental diagnostics, a clinical diagnosis was made: perinatal damage of the central nervous system of a hypoxic-hemorrhagic genesis of a severe degree. Syndrome of motor disorders. Complications: Cystic leucomalacia of the brain. Cortical atrophy. Internal, external hydrocephalus. Related diseases: ventilation-associated pneumonia. Pulmonary hemorrhage in history (on the 20th day of life). The child is transferred to neonatal reanimation unit of Perinatal Center of "RH №1 - NCM". During their stay in reanimation unit, the respiratory insufficiency of the 2–3rd degree remained in dynamics. When attempting to translate for independent breathing, episodes of apnea and bradycardia were noted. It was noted the absence of spontaneous breathing during sleep. At the age of 2 months, the child had generalized convulsions, in connection with which he was prescribed anticonvulsant therapy (depakin). When examined in a clinical blood test without inflammatory changes, CRP is negative. According to the results of radiography of the chest in the first 2 weeks revealed hypoventilation of the lungs, then without pathology. An echocardiography determined aneurysm of the secondary part of the interatrial septum with a discharge (0.33-0.35 cm), signs of pulmonary hypertension of 1 degree, tricuspid valve regurgitation of 1 degree, slight right ventricular myocardial hypertrophy (0.36 cm), separation of pericardial leaves, dilation of the right ventricle (1.0-1.1 cm), right atrium (2.0 cm), expansion of the pulmonary artery (0.92-0.93 cm). According to the results of Holter ECG monitoring, episodes of sinus bradycardia were noted at night. According to ENMG, the syndrome of impaired conduction along the median and peroneal nerves on both sides of moderate degree according to the axonal type. Signs of primary muscle damage was not detected. On MRI of the brain (in the age of 4 months.), The traumas of hypoxic-hemorrhagic brain injury in the perinatal period, internal triventricular hydrocephalus, cerebrospinal fluid normotension, periventricular hemorrhage foci in the anterior horns of MR signs of perinatal encephalopathy, retrotserebellyarnaya arachnoid cysts. According to MRI of the brain at the age of 8 months, a moderately pronounced internal occlusive triventricular hydrocephalus caused by a supracellular arachnoid cyst, cerebrospinal hypertension was described. The effect of arachnoid cyst on the third ventricle, interventricular orifices, on the chiasm, the pituitary stalk, on the pituitary gland, and on the brain legs was revealed. Compared with the previous study, an increase in the suprasellular cyst is determined, leading to occlusive hydrocephalus. At the age of 8 months, the patient has a ventriculo-peritoneal shunt (HPS).

A blood test was conducted at the Center for Molecular Genetics, aimed at finding private mutations in the *PHOX2B* gene. As a result of DNA analysis, an increased number of copies of the GCN-repeat with localization in the *PHOX2B* gene was revealed, which made it possible to confirm the diagnosis of CCHS syndrome. The boy continued to be in the neonatal reanimation unit on a ventilator, whose parameters changed in accordance with the dynamics of his condition. After a complete examination of the child, the final clinical diagnosis is made: Congenital central hypoventilation syndrome. Perinatal CNS lesion of mixed genesis severe. Occlusive hydrocephalus. Condition after HPS. Syndrome of motor disorders of the type of tetraparesis. Bulbar syndrome. Rough delay of psychomotor development. Partial atrophy of the optic nerves in both eyes. Complication: respiratory insufficiency II-III degree. The carrier tracheostomy. Related diseases: Iron

deficiency anemia 1 degree. Symptomatic epilepsy, generalized form, with primary-generalized seizures. Congenital heart defect: atrial septal defect. Regurgitation on TC 1 degree. Pulmonary hypertension 1 degree. Gastroesophageal reflux with esophagitis.

During the period of inpatient treatment (1 year, 1 month), the child repeatedly suffered from ventilation associated pneumonia. Since the disease is based on a congenital genetic defect and the boy needed constant mechanical ventilation in the future, and his hospital stay threatened with the constant development of hospital infections, it was decided to organize respiratory support at home. For this purpose, a detailed discussion was conducted with the parents of the child about possible complications in patients who were on long-term ventilation. He explained the conditions necessary to provide respiratory support at home. The parents agreed to the proposed treatment plan. At the moment, the boy is 2 years old, while awake, he can do without mechanical ventilation.

The presented observation demonstrates a complex case of diagnosis of congenital central hypoventilation syndrome, in which the diagnosis was established at 7 months of a child's life.

Description of the second case. A child from a mother of 28 years old with words practically healthy, second pregnancy, second birth. From the anamnesis, it is known that the first pregnancy in 2013 ended in operative childbirth on time, a healthy boy was born with a weight of 3940g, and a child from his first marriage. This pregnancy proceeded in the first half without features, in the second half a woman received amoxiclav about sore throat and by the end of pregnancy, lower limb edema was noted. Childbirth was operational in time, in the head previa, in a medical institution of the first level. Heredity through the mother of the child is not burdened. There is no information about hereditary diseases on the father's side.

A girl was born weighing 3730 g, height 55 cm, head circumference 36 cm, breast circumference 35 cm, with Apgar score of 8/9 points. At 40 minutes of life, the child had a worsening condition in the form of respiratory arrest. The child needed moistened oxygen. On the second day of life, the girl was transferred to a ventilator for a long apnea, bradycardia. On the fourth day, air ambulance entered the newborns reanimation unit of Perinatal Center of the "RB № 1-NCM" with a preliminary diagnosis: Hypoxic-ischemic damage of the central nervous system of the II degree, depression syndrome. Apnea newborn. Respiratory insufficiency III degree. During the initial examination, the condition is extremely serious, due to respiratory failure, neurological symptoms. She was conscious, motor activity, unconditioned reflexes were reduced, muscle tone was dystonic. Hemorrhagic syndrome was noted in the form of a small amount of hematomesis. Hardware breathing, auscultation of wired wheezing. Heart tones are rhythmic, clear. Soft abdomen, leaning. Liver and spleen are not enlarged. Peristalsis is sluggish. Transitional chair. Diuresis is sufficient.

A day after admission, the girl had episodes of apnea, bradycardia when trying to switch to independent breathing, according to ABS analyzes - decompensated acidosis, she was transferred back to mechanical ventilation. When examined, in a clinical blood test without inflammatory changes, in the analysis of the cerebrospinal fluid without features, the CRP is negative. According to radiography of the chest in the first 2 weeks described hypoventilation, then without pathology. When performing tracheobronchoscopy, the pathology of the structure of the bronchial tree is excluded. Neurosonography showed no structural changes. On echocardiography, a functioning arterial duct of 0.2 cm was described. According to the results of ECG monitoring, episodes of pronounced sinus bradycardia were noted at night. Additionally, MRI, CT scan of the brain, which did not detect structural changes in the brain, were performed.

In the dynamics persisted respiratory insufficiency II-III degree. It was noted the absence of spontaneous breathing during sleep, while waking was able to briefly disconnect from the ventilator. The child suspected CCHS syndrome. On day 25, DNA analysis was sent to the Center for Molecular Genetics in Moscow, where an increased number of copies of a GCN repeat located in the PHOX2B gene was detected in one of the chromosomes, which allowed to confirm the diagnosis of "central congenital hypoventilation syndrome". For further examination and treatment, the child on the ventilator has been transferred to the Federal State Budgetary Institution "V.A. Almazov Science Center" in St. Petersburg.

Presented observation demonstrates the case of early diagnosis of CCHS syndrome.

Conclusion. It should be remembered about the possibility of variability of the clinical picture, which can complicate the diagnosis of CCHS. Genetic counseling is necessary if a child is born with suspected CCHS. Early diagnosis of CCHS and timely initiated respiratory support avoid chronic hypoxia, irreversible damage to the central nervous system and ensure an adequate quality of life for the patient.

The problem of treating and monitoring patients with rare diseases is the lack of standards of care. The exact prevalence of this pathology in children is also unknown, which is primarily due to hypodiagnosis. The examples of children with CCHS clearly demonstrate the possibility of a positive prognosis in the case of timely recognition of the disease. Many successfully ventilated patients today are more than 20 years old, which suggests a normal life expectancy, despite the genetic defect. Lethal outcomes in patients with CCHS are associated with the inability to provide optimal ventilation. A child requiring round-the-clock fan support needs a tracheostomy and a home ventilator system. In order to increase mobility and improve the quality of life in the future, such children need implantation of a phrenic nerve stimulator, which is currently performed thoracoscopically when they reach the age of 18 months.

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A CLINICAL CASE OF SPONTANEOUS PNEUMOTHORAX ASSOCIATED WITH BRONCHIAL ASTHMA IN A 17-YEAR OLD MALE ADOLESCENT

DOI 10.25789/YMJ.2020.69.32

УДК 616-053.3 (571.56)

Spontaneous pneumothorax most commonly occurs among able-bodied male population at the age of 20-40; thus revealing not only medical but also social significance of the problem. We have described the case of spontaneous pneumothorax of a 17-year old male adolescent, admitted to the department of pulmonology of the Pediatric center, Republic Hospital №1 – National Center of Medicine.

The significance of the case results from clinical manifestation of the spontaneous pneumothorax associated with a severe and acute attack of the bronchial asthma.

Keywords: pneumothorax, pneumonia, bronchial asthma, emphysema, pollinosis.

Introduction. A term 'spontaneous pneumothorax' (SP) was introduced by Laennec in 1803. The fact of revealing of the collapsed lung was a diagnostic victory at that time. Before the era of the X-ray any pneumothorax without any sign of the trauma was considered to be spontaneous and causeless. Spontaneous pneumothorax is a collection of air in the lung tissue not associated with trauma or iatrogenic clinical interventions. Statistically it prevails in able-bodied male population at the age of 20-40 and reveals not only medical but also social significance of the problem. There are two types of spontaneous pneumothorax as primary and secondary. Primary spontaneous pneumothorax is diagnosed among those who previously did not have clinically diagnosed lung pathology. Secondary spontaneous pneumothorax is associated with previous lung disorders. Most commonly secondary spontaneous pneumothorax complicates chronic obstructive lung disorders, bronchial asthma. Clinically pneumothorax is associated with sharp chest pain; acute shortness of breath, dry non-productive cough. That is why the choice of adequate diagnosis and therapy tactics is of great importance for pulmonologists, thoracic surgeons and phthisiatricians [1, 2, 3].

Materials and methods: We have analyzed a case history of the patient, admitted to the department of pulmonology of the Pediatric center, Republic Hospital №1 – National Center of Medicine. The patient underwent complete and profound examination according to all standards and clinical recommendations at the department of pulmonology. We have carried out clinical (complete blood count, urine test, rinocitogram), immunological (immunoglobulin level detection, antibodies to certain infections), functional methods as spirometry, X-ray examination, computed tomography of the lungs. Skin allergy testing was for standard pollen allergens (early blooming plants as birch, alder, avellane; late blooming plant as poplar; weeds as timothy, meadow, cheat, wormwood, ryegrass, dandelion and couch grass; gramineous (rye, oat, fescue grass) and food allergens. Skin sensitivity is evaluated by the indicators (+_, ++, --).

Results and discussion. The patient experienced suffocation for the first time in 9.08.2019 during the haymaking. He applied for medical assistance to his local polyclinic. He was administered intravenous aminophylline 3.0 injected very slowly, ceftriaxone 1.0 intramuscularly. Anterioposterior radiography of the chest revealed the signs of pneumothorax of the right lung and subcutaneous two-sided emphysema in 10.08.2019. The patient was referred to the department of surgery of the Pediatric center of Republic Hospital №1 – National Center of Medicine.

Past history of the patient: The fourth pregnancy child was without any gravity abnormalities, the 4th delivery, at 36th week of gestation. The weight at birth was 2800 gr, 49 cm length. He was breastfed till 2 years. He is not regularly consulted by phthisiatrician. No contact with infected people. All preventive inoculations were taken on time according to the schedule.

Past medical history: Acute respiratory diseases, respiratory infectious diseases, maxillary sinusitis, chicken pox. No traumas and surgeries were registered. The patient says he is a non-smoker.

Allergic history: The father is diagnosed with bronchial asthma, the mother has pathology of the cardiovascular system. The patient is allergic to pollen, he reacts to the smell of haymade grass associated with swollen eyelids and suffocation.

On examination the admitting physician estimated a medium severity of the condition. The height was 178 cm, weight was 65 kg, BMI was 20.515. He was in contact, active. The skin was of typical colour. The visible mucous membranes were pink. Lymphatic nodes (neck, mandibular, occipital and axillary) were not enlarged. The pharynx was not inflamed. The breathing was present in all lobes/parts, a bit weakened in the right side. The lung percussion revealed tympanic sound in the lower parts of the right lung. Bronchophony of the right lung revealed weakened sound transmission. The respiratory rate was 20 per 1 minute. Intercostal spaces of the right lung were smoothed. Cardiac tones were clear and rhythmic. Heart rate was 89 per 1 minute. The stomach was soft and painless. Urination was free. Stool, diuresis was within the norm.

Paraclinic notes: Urine analysis (12.08.2019): pale yellow colour, trans-

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parent, relative density 1013, protein was negative, leukocytes were solitary, erythrocytes were not found. Total blood count for 12.08.2019 revealed; erythrocytes $3.6x10^{12}$ /l, hemoglobin 120 gr/l, leukocytes $4.7x10^{9}$ /l, segmentated granulocytes 55, stab granulocytes 11, eosinocytes 6, monocytes 4, erythrocytes sedimentation rate 57 mm/hr.

In 12.08.2019 the patient was urgently hospitalized into the surgical department of the Republic Hospital №1 – National Center of Medicine. On admission the primary diagnosis was: J18.0 Unconfirmed pneumonia? Bronchial asthma? Right side pneumothorax. Two-sided subcutaneous emphysema.

In 12.08.2019 a second X-ray revealed subcutaneous right emphysema. X-ray showed the signs of bronchitis.

In 12.08.2019 the patient was referred to the department of pulmonology. A doctor of the department of pulmonology administered:

1. Immunoglobulins A, M, G, E circulating immune complexes
2. Immunofluorescence test for infections (mycoplasma pneumoniae, chlamydia pneumonia and herpes simplex virus)
3. Rinocitogram
4. Spirometry with testing for salbutamol
5. Alpha 1 antitrypsin test
6. Sweat test
7. C-reactive protein test in blood
8. Stool test for lamblia
9. Allergy test

The patient is recommended a special diet #4. Nebulizer therapy: 20 drops of berodual and 2 ml of saline solution to be inhaled for 10 min 2 times a day for 10 days long; pulmicort 500 mkg and 2 ml of saline solution to be inhaled for 10 min 2 times a day for 10 days long. Azythromycin 500 mkg should be taken once a day for 5 days long. Therapeutic physical training is a special complex of exercises, #5. The massage of the chest was also recommended, #5. Ultrahigh-frequency therapy (UHF-therapy) #5 of the chest was also recommended. Short-wave ultraviolet therapy of the nose and pharynx #5 was carried out.

In 15.08.2019 the computed tomography (CT-scan) revealed a focal shadow in the right lung, pneumomediastinum, subcutaneous emphysema of the right lung, and pneumothorax.

In 20.08.2019 spirometry was carried out, it did not reveal low potence of bronchial tubes. Vital capacity of the lungs was within the norm. Salbutamol test was positive.

The results of immune analyses were: IgA 2.0 gr/l, IgM 2.0 gr/l, IgG 9.6 gr/l, IgE 180 IU/ml. According to the results of the analyses IgE level was increased indicating allergic reaction.

In 12.08.2019 rinocitogram revealed high level of neutrophils 2-3 within the field of microscopy, eosinophils 5-6 within the field of microscopy.

In 12.08.2019 alpha 1 antitripsin indicator was within the norm, 0.9 g\l.

In 12.08.2019 the level of sodium chloride after the sweat test was within the norm, 10 mmol/l.

The lamblia stool analysis did not reveal any cysts of protozoa. The blood analysis for antibodies did not reveal antibodies to *Micoplasma pneumonia* IgG and *Micoplasma pneumonia* IgM, *Chlamidia pneumonia* IgG and *Micoplasma pneumonia* IgM, virus of herpes simplex 1 and 2 IgG was found out.

The allergy test revealed high reaction to timothy grass +++, cheat +++, couch grass +++, rye grass+.

According to the results of the analysis the patient was diagnosed with bronchial asthma, atopic form of medium severity; attack period (J45.0) and allergic rhinitis, pollinosis (J30.4). Complication: secondary pneumothorax. The condition was after experienced pneumothorax. Subcutaneous emphysema of the both sides was registered. Concomitant diagnosis was unconfirmed pneumonia (J18.9). Community-acquired lower lobar pneumonia of moderate severity with broncho-obstructive syndrome was diagnosed.

In 10 days the patient was discharged from the hospital in a satisfactory condition with following recommendations:

1. Regular medical check-up and examination by the local pediatrician. A daily recording of peak flow chart (in the morning and in the evening) was recommended.
2. The consultation of the pulmonologist in three months and a consultation of the allergologist in 1 year were also recommended.
3. Maintain a hypoallergenic home environment.
4. Base therapy with seredite 25/250 mkg twice a day at 8.00 a.m. and 8.00 p.m. for three weeks, flixonase (nasonex, avamys) therapy once a day for 3 months.
5. No inoculations for 1 month.

Conclusion. The treatment of spontaneous pneumothorax should be aimed at solving two problems as releasing air from the pleuroral cavity and preventing secondary pneumothorax. Not all patients with a first episode of the spontaneous pneumothorax should undergo evacuation of the air from the pleural cavity, it is necessary only in cases of extended pneumothorax and the condition experiencing the symptoms of pneumothorax. The medical literature represents different methods of treating pneumothorax as conservative treatment; pleural puncture (singular or repeated); transthoracic microdrainage; Bulau drain; drainage with active aspiration; drainage with pleurodesis; video-assisted thoracic surgery; thoracotomy. The choice of tactics is of great importance in pediatric patients. We have described the case of spontaneous pneumothorax associated with severe attack of acute bronchial asthma as a result of contact with graminoids during the haymaking. A list of authors constitute that there can be a pulmonary laceration due to high pressure in the lungs during the attack of asthma; which results in accumulation of air in the pleural cavity [2, 3]. Modern tactics of spontaneous pneumothorax treatment are conservative methods, thoracocenthesis, drainage of pleural cavity and surgical intervention [2]. An outcome of the primary spontaneous pneumothorax is favourable. It is usually possible to smooth the lung with minimum of invasion. In 20-50% the symptoms of spontaneous pneumothorax recur. The patients after spontaneous pneumothorax should regularly visit a thoracic surgeon or a pulmonologist [1, 2, 3].

Thus, timely diagnosis of spontaneous pneumothorax, adequate treatment of the developing spontaneous pneumothorax, planned base and preventive treatment of the underlying disease in a case of secondary spontaneous pneumothorax found the basis for successful treatment. In that case adequate treatment of the bronchial asthma could arrest the spontaneous pneumothorax by conservative methods and obtain stable improvement of the patient's condition.

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