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

The articles are given in the authors' translation

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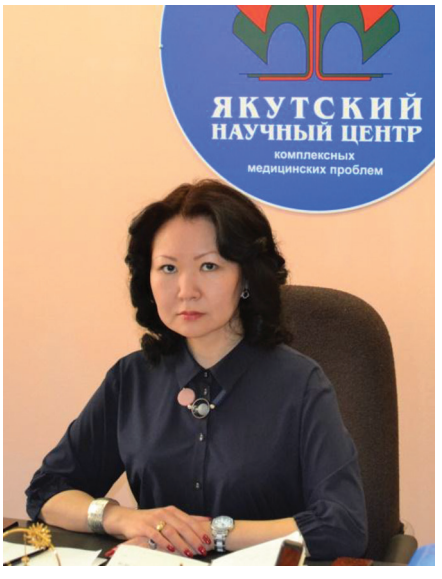
EDITOR'S COLUMN

TO THE ANNIVERSARY OF REVO ALEKSEEV



Dear readers!

Here is the 62nd issue of the Yakut Medical Journal, in which, besides the articles of the current issue, materials of the Interregional Scientific-Practical Conference with International Participation "Effect of cold on the human body", dedicated to the 80th anniversary of MD, Professor RevoZakharovich Alekseev are presented. The conference was held on May 17, 2018 in the assembly hall of the Motherhood and Childhood Protection Center of the Republic hospital No1-the National Center of Medicine.The Yakut Science Center of Complex Medical Problems and the Ministry of Health of the Republic of Sakha (Yakutia) were organizers of scientific-practical conference. 115 participants, the leading scientists and experts in the field of medicine and biology have taken part in conference work.Reports were made by researchers from the Yakut Science Center of Complex Medical Problems, the Medical institute of the North-Eastern Federal University in Yakutsk, theInstitute for Biological Problems of Cryolithozoneof the Siberian Branch of the Russian Academy of Science and from the other institutes.Also online reports of John Odland, Professor of Public Health Department of the Arctic University of Norway (Tromsø, Norway), Saverio Cinti, Professor of Human Anatomy, Department of Experimental and Clinical Medicine, AziendaOspedaliRiuniti-University of Ancona (Politecnicadelle Marche) (Ancona, Italy), Tseluyko S.S., MD, Professor, Vice-rector for Science and Innovation of the Amur State Medical Academy of the Ministry of Health of the Russian Federation (Blagoveshchensk, Russia), Prakhin E.I., MD, Professor of the Krasnoyarsk State Medical University n. a. Prof. V.F. Voyno-Yasenetsky (Krasnoyarsk, Russia) were presented.During the conference the questions of cold effect on the human and animals; features of brown adipose tissue in conditions of cold; pathogenesis of man overall cooling; characteristics of freezing in humans at temperature of -40°C and below; clinic and treatment of frostbite tissues with glaciation; principles of nutrition in conditions of low temperatureswere discussed.

In Russia, the issue of cold injury has always been relevant, since most of the country's territory is located in cold or temperate zones. Living conditions in the Republic of Sakha (Yakutia)in many ways are extreme for people, cause the development of adaptive reactions complex directed to maintenance of homeostasis. Almost all organs and systems take part in these reactions. In people arriving to the Far North from the Central regions of Russia and other countries (temperate latitudes), there is a violation of adaptive mechanisms (cold adaptation), characterized by a decrease in the adaptive capacity of the body and the development of pathological conditions (cold injury).The complexity of treatment, long-term disability, high level of disability and mortality at cold injury are striking proof of the unresolved on this problem. The features of death from the general cooling under conditions of extremely low temperatures (below -40°C) and the possibility of resuscitation of the victims are not sufficiently studied. In this regard, the issue to develop and introduction of the regional standards of specialized medical care at frostbites and general cooling is relevant.

The Yakut Science Center of Complex Medical Problems has been studying the effect of cold on the human body for many years. Our colleagues studied the regional features of biochemical and immunological, molecular-genetic parameters in order to prevent and early diagnosis of socially significant diseases and identification of risk groups. Patents were obtained: "Method of reducing the risk of limbs necrosis in cold injury" (invention to patent No.2637086), "Method of treating frostbite in pre-active period" (invention to patent No.2152806).

We express our confidence that this conference will make a real contribution to solving the problems related to the influence of cold on the human body in the Republic of Sakha (Yakutia), and will establish strong ties between people engaged in common business.

The warmest congratulations to Doctor of Medical Sciences, Professor Revo Alekseev on the Anniversary! Fidelity to the chosen way, firmness and purposefulness in overcoming professional difficulties characterize You as talented and faithful to work person.

Let your sense of purpose and efficiency, erudition and competence, the ability to find the right solution to the most difficult issues help Youto reach new heights to development and prosperity of medical science and practice! Please accept my sincere wishes of long and active years of life, strong health, good spiritand luck in all endeavors, reliable students and followers of your business, well-being to you, your family and friends!

Anna Nikolaevna Romanova, MD, Director of the YSC CMP, Yakutsk, Republic Sakha (Yakutia), Russia, e-mail: ranik@mail.ru.

MATERIALS OF SCIENTIFIC-PRACTICAL CONFERENCE WITH INTERNATIONAL PARTICIPATION «THE INFLUENCE OF COLD ON THE HUMAN ORGANISM»

I. THE INFLUENCE OF COLD ON THE HUMAN AND ANIMAL ORGANISM (BIOCHEMICAL, IMMUNOLOGICAL AND GENETIC ASPECTS)

S.K. Kononova

THE ETHICS OF CARRYING OUT RESEARCHES ON LABORATORY ANIMALS

ABSTRACT

The basic ethical principles and rules of carrying out researches on laboratory animals are presented in the article. First of all, modern ethics of the humane treatment of animals should be based on correctly thoughtful design of an experiment to receive qualitative results. The science develops in the direction of minimization of using animals in experiments if there is an opportunity to receive similar results by alternative methods.

Keywords: bioethics, laboratory animals, clinical tests.

Historically in scientific researches a person always used different types of animals for studying of fundamental laws of life: anatomy, physiology, pathology. Animals are very convenient objects for experiments for imitation of biological conditions, human diseases, for development of scientific techniques, use as a training material etc. So, according to an ultimate goal, as models of a research insects (Drosophila), nematodes (Caenorhabditiselegans), fishes (Daniorerio or zebrafish), frogs (Xenopus) and many mammals as mice, rats, rabbits, dogs, cats, pigs and monkeys are used [5].

Conditioned reflex theory, established more than 100 years ago by I.P. Pavlov, is a fundamental theory in the history of physiology and psychology up to now. Of course, many operations performed by the scientist end deplorable for an experimented animal. In the parlance of Pavlov,when he cuts and destroys a live animal, he suppresses in himself bitter rebuke that breaks the art mechanism, but reminds himself to do it only in the interests of truth and for the sake of human benefits. Making the experiments, Pavlov did all surgical interventions only under anesthetic to prevent an animal additional suffering. The monument to a dog, established by Pavlov in St. Petersburg, also tells about the scientist's attitude to his little patients [3,4]. Nowadays, an interesting example of the experiments on dogs is the imitation model of Fallot's tetrad congenital heart disease (also known as a blue baby syndrome) developed by Vivienne Thomas and Alfred Blalok. This model allowed developing a surgical method which salvages more than half a million children a year [15] these days.

Anyway, nearly 90% of the Nobel Prizes got by researchers in the opening in the field of physiology and medicine are deeply bound with the experiments on animals. Animals are peculiar victims of science, gratuitously and dumbly giving the lives on service to mankind. To the present, major bioethical discussions were held generally only about using human primates in experiments (a chimpanzee, etc.). After 2007 only the United States and Gabon continued to use a chimpanzee for researches, but in 2015 the United States made a statement that they won't finance any researches with participation of chimpanzees [5] any more. On the other hand, for example, the main problem with HIV infection is its increased tropism in human tissues complicating an animal HIV modeling. The virus isn't able to infect mice, rats, rabbits or macaques though it can be replicated in a chimpanzee. Find this way out using chimeric immunodeficient mice with the transplanted human cells and tissues. Progress in genetic technologies allows making a great number of experiments on transgene animals; there are created the whole pure line animals with prescribed properties of genes or, on the contrary, null mutant animals, so-called gene knockout animal models [9].

The fundamental ethical principles of work with laboratory animals should be considered the principles entered by Russell and Bertsch [5,6]:

a) reduction - the greatest possible decrease of number of animals put to the necessary educational or scientific purposes;

b) refinement - improvement of the experimental techniques for depression (exception) a negative (painful, high-stress, etc.) influence on an animal;

c) replacement - elimination of animals from an experiment or a study if there is an opportunity to receive similar results by alternative methods [13,16].

Primarily, modern ethics of the humane attitude towards animals have to be based on correctly thoughtful design of an experiment to produce qualitative results and to exclude undesirable deviations. It is necessary to pay an attention to acceptance criteria (exclusion and inclusion criteria), required sampling size (the necessary quantity of animals) for ensuring the reproducible results [6,10].

Scientists notice that in basic biomedical researches large financial means are put and huge quantities of different types of animals are used, but when it comes to applied researches and introducing the results in practice many of the best research ideas promising translational effects fail. Especially, this includes translational researches in the field of aspects of human behavior where it cannot show any similarities between model of an animal and a human [6, 12] yet.

The right choice of species of a model

animal is of great importance for an ethical scientific experiment, for example, promising results on studying of type 2 diabetes mellitus were obtained on mice, because glucose exchange happens generallyin myocytes and hepatocytes equally in all organisms including human [7].

Management of laboratory animals in an experimental room have a significant impact on the final results of the research. The housing conditions (temperature, humidity, light, food) is very important, an animal should have no stress. For example, in the research of studying of breast cancer on models of mice it was shown a tendency of tumor volume reduction of mice which lived in the improved conditions in contrast with mice kept in standard conditions where stress could enlarge inflammation of the mammary gland [11].

For a scientific experiment with use of animals it is ethically correct to calculate quantity of animals which should not be too little or too much. The amount of selection depends on four parameters: minimum expected difference; the calculated standard deviation; statistical significance; importance criterion. Before planning an experiment with animal models it is necessary to make meta-analysis of publications on the studied problem [6,8]. Advantages of meta-analysis over reviews of literature following: • specifies that selection is more various than it was supposed, proceeding from a variety of samples;

• generalizes several researches;

• controls a variety between researches;

• can explain a variety between data;

• enlarges statistical power;

• works in the conditions of information overload (a large number of articles is published every year);

• generalizes several researches and therefore depends on separate finds less than individual researches;

• can notice systematic errors [8].

For the first time «Cruelty to Animal Act» was adopted by the British Parliament in 1849, he determined three main issues: 1. experiments on animals have to be made when there is an absolute need for knowledge useful to conservation or prolongation of life or relief of suffering of the person; 2. an animal has to be anesthetized; 3. animals have to be killed right after the experimental procedure if they were damaged or felt pains as a result of an experiment [2,5].

in 2010, at the initiative of the international organization of the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) the management of ARRIVE (Animal Research: Reporting of In Vivo Experiments),approved by scientific magazines and the sponsor organizations,was framed. The ARRIVE contains the guides which were translated to several languages and has the check list of 20 points concerning such information as number and specific characteristics of the experimented animals (for example, types, gender, strain, genetic features), conditions of keeping, the description of experimental, statistical and analytical methods [5].

The ethical rules of work with animals applied in the Russian Federation are based on regulations of the Declaration of Helsinki and **References** in directives of the European Community (86/609 EU) [16] and also Rules of carrying out high-quality clinical tests in the Russian Federation (the order MZ USSR N 755 of 12.08.77 «About measures for further improvement of forms of work with use of «experimental animals»):

• Institutions can carry out work on animals if the following conditions are satisfied: a) having a vivarium (experimental biological clinic) equipped according to the sanitary requirements N 1045-73 from 06.04.73; b) having an experimental operation room (laboratory) with appropriate equipment; c) having staff providing care of animals.

• Housing conditions of an animal in a vivarium (clinic) have to provide a normal biological background and completely conform to the building code requirements.

• While planning studies or scientific experiments the species of the used animals, and quantity requested for obtaining reliable results have to be proved.

• All procedures on an animal which can cause severe pain or stress should be performed by adequate anesthesia (under local anesthesia or under narcosis), except the cases stipulated in the Appendix 3 to Order No. 755 of the Ministry of Health of USSR of 10.08.77.

• Use of an animal for morbid procedures more than once, except the animals used for experiment tests in a chronic series, is forbidden.

• Presence of a person responsible for acting a procedure and controlling adequacy of anesthesia and a condition of an animal is strictly necessary while carrying out the experiments and other procedures in the conditions of the increased risk for animal life or while working with animals by unexperienced persons (for example, students).

• In the postoperative period an animal should receive the qualified care and adequate anesthesia.

• Upon completion of the educational or scientific manipulations on an animal leading to physiological dysfunctions and viability, the animal has to be killed with compliance of all humanity requirements.

• Euthanasia, i.e. humane killing of laboratory animals, should be performed by the responsible person or under his direct observation.

• An optimum and universal method of laboratory animal killing is an overdose - administration of an anesthetic in a lethal dose (x3 dosage for narcosis). Different possible ways of euthanasia of small and big animals are given in the Appendix 4 to Order No. 755 of the Ministry of Health of USSR [1, 2, 16].

Conclusion

Use of different types of animals in a scientific research allowed making an impressive progress in many spheres of human activity, prolonging thereby human life by that, having cured of serious diseases, prevented risks in use of new technologies, etc. Animals will always be test objects in experiments, it can't signify a consent or disagreement therefore only the scientist can take the responsibility for an ethical component of the researches to minimize an injury, to deal towards animals extremely humanely. The need for live objects of a research will increase in parallel with development of science, but also ethical demands to protocols of a research and design of an experiment by conducting ethical examination in committees on bioethics of different level will be tightened.

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The author:

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

R.Z. Alekseev, M.I. Tomsky, N.A. Struchkov, K.R. Nifontov, A.S. Andreev, V.S. Fomina

THE STUDY OF BIOELECTRIC INDICATORS OF BRAIN FUNCTION AND CARDIOVASCULAR ACTIVITY IN ANIMALS WITH NATURAL HYPOTHERMIA UNDER THE EXPERIMENT CONDITIONS IN YAKUTIA

ABSTRACT

Some aspects of studying of bioelectric indicators of function of a brain and cardiovascular activity at a natural hypothermia of a pig organism at temperature -40 °C and below in the experimental conditions are presented in article.

Keywords: EEG, ECG, pigs, hypothermia.

Introduction

The hypothermia (frigorism) – a condition of an organism or its certain area at which its temperature is lower than is required for maintenance of a normal metabolism and functioning. On a cooling parentage source the condition of a hypothermia happens natural and artificial. Researches in the field cover the directions bound to functioning of an organism in the conditions of a life-threatening thermolysis to the environment, the general cooling of an organism in a condition of the general narcosis etc [3].

In modern conditions of development of the Arctic the problem of a frigorism and hypothermia of an organism gains fundamental and applied character from the person and animals [1]. In the republic during the winter about 200 people with a freezing injury of extremities and in a condition of a deep hypothermia come to hospitals of the Sakha (Yakutia) Republic. Studying of organism restoration after a deep hypothermia on experimental models is relevant for Yakutia. The correct well-timed delivery of health care in the region of the Far North is in many respects provided with high-quality preliminary clinical and technical researches by results of which versatile researches of an organism are conducted and their main clinical and physical properties, such as impulses of a brain and cardiovascular activity are defined [1].

In medicine the problems of hypothermia and «resuscitation» of an organism remains open. For the last 15 - 20 years in many countries researches are conducted on a large scale and the works confirming thoughts of a possibility of «resuscitation» of an organism are published. With cold physical solution with bringing body temperature to +10 °C and further gradual replacement with a blood with slow temperature increase I led the method developed by Tisherman and Peter Rhee from Arizona State University since 2000 about full replacement of a blood after a cardiac standstill to heartbeat restoration though it is sometimes artificial. At the same time no negative impact of process of introduction to an anabiosis and the subsequent resuscitation on physical and cognitive functions of animals was taped [3]. Preceding from it is possible to claim that the hypothermal state has neuroprotectiveeffect at various hypoxemic pathologies. Protective properties of a hypothermia were investigated by coryphaeuses of domestic resuscitation V.A. Negovsky, A.I. Treshchinsky and L.P. Chepky. Mechanisms of neuroprotective action of hypothermia aren't quite clear [4].

Objective of research – to studybioelectric activity of a brain and cardiovascular system of a pig at natural deep hypothermia at temperatures -40 ° C and below in the conditions of Yakutia.

We make the following tasks:

1. To set changes of brain EEG and heart ECG indicators of a pig at natural deep hypothermia.
2. To develop methods of body revitalization at a deep hypothermia.

To perform the tasks, we modeled the conditions for obtaining natural deep hypothermia of animals at temperatures of -40 ° C and lower, at which the mechanisms of introducing animals into the state of anabiosis were studied and data on the bioelectrical activity of the brain and heart were obtained.

In the present work we undertook an investigation of the brain EEG and ECG of the cardiovascular system of a pig in a state of deep hypothermia in order to detect the features of the change in the EEG power spectrum and ECG with a decrease in body temperature that could shed light on the mechanisms underlying the temperature dependence of the function of the brain and heart. It was also proposed to develop methods for restoring the function of the brain at deep hypothermia.

Materials and methods of a research

Work is performed in 2018 from January to March on the basis of faculty of veterinary medicine of Yakut State Agricultural Academy, Yakutsk.

Experiments were made on clinically healthy pigs at the age of 2-3 months with a body weight from 15 to 20 kg,received from Hatassky pig farm. For the purpose of restriction of mobility and bracing of animals at the beginning of the experiment carried out a neuroplegia (a neuroleptic – XylaVet of 0,2% 0,5ml and Droperidolum of 0,5 ml.). Further for modeling of alcohol intoxication - ethyl alcohol inside in a dose of 5-6 ml/kg of live weightwas applied. Animals were fixed and placed on the street at ambient temperature –40 °C…–43 °C.

Experimental work was carried out according to the ethical standards regulating experiments on animals according to the European convention on protection of the vertebrate animals used for experiments or in other scientific purposes No. 123 of March 18, 1986, Strasbourg and the order of the Russian Ministry of Health of 01.04.2016 No. 199n «About the approval of Rules of appropriate laboratory practice». The permission of the Local bioethical commission of the YSC CMP for the research was obtained.

For a research of bioelectric activity of a brain we used the computer complex «Neyron-Spektr — 1» which is executed on base «Neyron-Spektr-4P» and is intended for registration of an EEG, the

long-latent of the caused potentials (CP) of a brain in any unscreened room. The recording electrodes connected to the amplifier of biological potentials. Further «Neyron-Spektr- 1» was connected to the computer.All the data were registered on the hard drive. The EEG was recorded during experience to a stopping of signals and emergence of isoelectric amplitude. An ECG carried out by means of the device Poly-range 8/B.

Results of researches

During the «cooling-warming» experiment, the temperature of the pig's internal organs gradually decreases (Fig. 1).V- amplitude beta-diffuse activity is dominant. As the temperature of the body decreases, the EEG parameters of the pigs brain naturally change - the frequency of oscillations and their amplitude gradually decrease, and finally, at a body temperature of about + 18 ... + 20 ° C, the EEG becomes practically an isoelectric (flat) line (Fig. 2-3) .

We have produced selective antegrade cerebral perfusion with an artificial blood circulation apparatus with perfusion rate 8ml/min/body mass with gradual warming the perfusate to obtain bioelectric indicators. For perfusion after sternotomy, aortic cannula in the aortic root and the venous cannula in the cranial vena cavawere established. Heparinizationwas performed at a rate of 3 mg/kg. Warming the perfusate through the AIC performed by maintaining a temperature gradient of less than 5 °C. In the experiment №1 perfusion event began an hour after stopping the heartbeat, in an experiment №1 12 hours. Against the background of perfusion and gradual warming, we did not notice electric brain activity.

When the animal warms after deep hypothermia, the EEG undergoes reverse minor changes, but the appearance of reliable indicators of the recovery of electrical activity is not revealed.Based

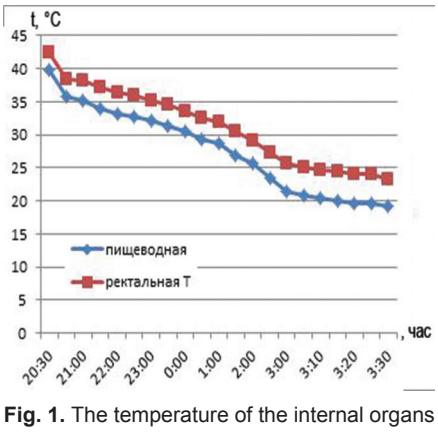

Fig. 1. The temperature of the internal organs of the pig in the period of hypothermia

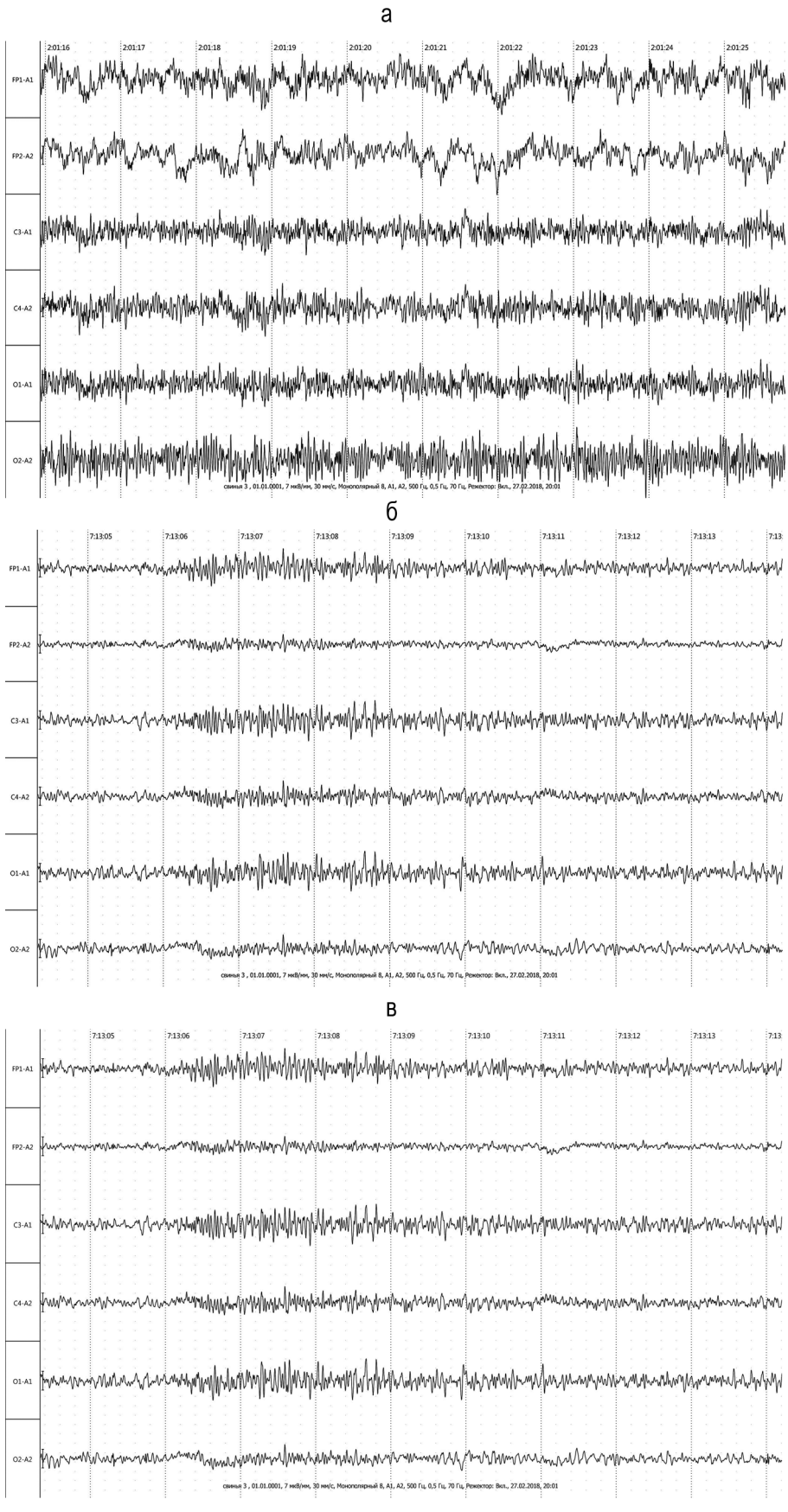

Fig.2. Changes in the EEG of the pig's brain: a - after 2 h of hypothermia (rectal T 35.2 ° C, esophageal 34 ° C); b - after 7-10 h of hypothermia (rectal T 27.3, esophageal - 23.5 ° C); c - after 7-20 h of hypothermia (rectal T 19.2 ° C, esophageal -23.3 ° C)

on the results of our experiments, it can be argued that the decrease in internal temperature depends on the ambient temperature. At the same time, according to ECG indications, gradual slowing of atrioventricular conduction and, accordingly, bradycardia followed by arrhythmia and cardiac arrest. The appearance of the isoelectric line occurred immediately after the cardiac arrest.

Experiments with animals have made it possible to establish a number of factors that make it difficult to restore the vital functions of the brain. These include long-term exposure to low temperature, the impossibility of establishing a time when you can «start» the reverse mechanism of recovery of the brain.

The experimental data presented above show that the mechanisms of the brain functioning in the case of cold trauma have not yet been clarified, and the researchers face still enormous and complex tasks of further studying this problem. We need to search for new technologies for «revitalization», and experimental research on this issue will continue.

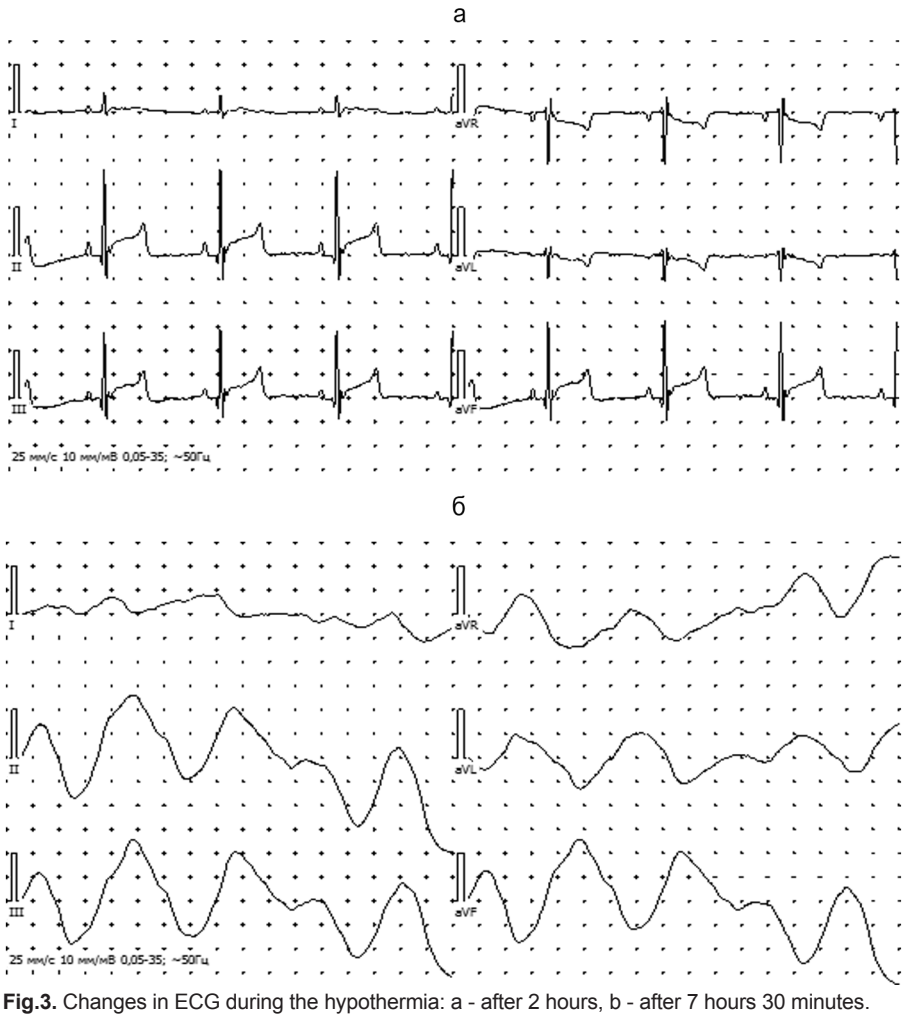

Fig.3. Changes in ECG during the hypothermia: a - after 2 hours, b - after 7 hours 30 minutes.

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The authors:

1. Alekseev R.Z., doctor of medical sciences, Professor, Senior Researcher of the Department for Studying Adaptation Mechanisms, Federal State Budgetary Scientific Institution «Yakutsk Scientific Center of Complex Medical Problems», arzrevo@mail.ru

2. Tomsky M.I., doctor of medical sciences, Professor, chief physician of State Budgetary Institution Republican Children's Tubercular Sanatorium of T.P. Dmitriyeva, ogus@list.ru

3. Struchkov N.A., candidate of veterinary sciences, associate professor of the Department of Internal Non-communicable Diseases, Pharmacology and Obstetrics named after. Professor G.P. Serdtseva Federal state educational institution of higher professional education «Yakut State Agricultural Academy»,struchkovnik@mail.ru

4. Nifontov K.R., candidate of veterinary sciences, associate professor of the Department of Internal Non-communicable Diseases, Pharmacology and Obstetrics named after. Professor G.P. Serdtseva Federal state educational institution of higher professional education «Yakut State Agricultural Academy», kosnif@yandex.ru

5. Andreev A.S., post-graduate student of the Institute of Physical and Technical Problems of the North, Siberian Branch of the Russian Academy of Sciences. V.P. Larionova, leading engineer of the department of heat and mass transfer processes, asandreev92@mail.ru

6. Fomina V.S., anesthesiologist-resuscitator of the Department of Cardiovascular Surgery of the Pediatric Center of the State autonomous institution of the Republic of Sakha (Yakutia) «Republican Hospital No.1 - National Center of Medicine» fomina.valeria.89@mail.ru.

L.I. Arzhakova, D.K. Garmaeva, T.I. Dmitrieva, A.I. Fyodorova, D.S. Belolubksaya, O.G. Afanaseva, A.I. Egorova

INDICATORS OF PERIPHERAL BLOOD AT EXPERIMENTAL COLD EXPOSURE

ABSTRACT

The article presents the results of an experimental study, the purpose of which was to study changes in the cellular composition of the blood of rats depend of their exposure time to cold. The obtained results indicate that the cold affects the activity of cells that provide nonspecific and specific immune responses.

It is shown that the exposure of rats in our experiment for 7 to 30 days had a fairly long-term effect, as it led to suppression of the activity of monocytes and neutrophils. However, we observed an increase in the number of leukocytes on day 14, which may be due to a short-term stimulation of leukocytopoiesis. The number of lymphocytes in our study remained elevated throughout the experiment, maximally increasing by 7 and 30 days. We were also able to demonstrate a decrease in the number of platelets, which was an appropriate reaction of the body in response to cold exposure, as platelets take a direct part in the repair processes observed when the tissue is damaged by cold, and also improve the migration of leukocytes to the focus of inflammation. An increase in hematocrit was also established, which is one of the signs of a reaction to cold stress.

Thus, the present study revealed patterns of changes in the cellular composition of peripheral blood during cold stress in the experiment, which were expressed in the features of the reaction from erythrocytes, platelets and leukocytes.

Keywords: cold stress, cellular blood composition, specific and nonspecific immune response, experiment.

Introduction. In connection with the increased rates of development of the Far North, the question of adapting the human organism to life in northern latitudes, where it is exposed to low natural temperatures, is again becoming relevant [7, 12].

It is known that the human body to the negative impact of various environmental factors corresponds to a violation of the state of regulatory systems, accompanied by a change in the cellular composition of blood [1, 5, 13, 14]. It is shown that leukocytes play an important role in the implementation of the protective reaction of the body. The phagocytic activity of leukocytes is a nonspecific cellular immunity of the body and depends on the effect of any stress factors [10, 13, 14]. Further, this is accompanied by changes in immunological reactivity, a decrease in the adaptive capacity of the organism, the development of transient or persistent forms of secondary immune deficiency [12].

Imbalance of the immune system affects the formation, nature of the course and outcomes of many pathological processes. The highest incidence rates fall on diseases of the respiratory, nervous and sensory organs, and the circulatory system [4, 9, 15].

Thus, the study of the mechanisms of cellular adaptation of the blood system, as well as the response of immune organs, the search for ways to increase the body's resistance, prevention and treatment of immune response disorders in low-temperature conditions is extremely urgent in the Sakha (Yakutia) Republic.

This study is part of a comprehensive work related to the study of the mechanisms of disadaptation in the Arctic and the Subarctic. This work is carried out taking into account the priority areas of the scientific platform "Immunology" of the state program "Strategy for the Development of Medical Science in the Russian Federation 2025".

The aim of the study is to study changes in the cellular composition of blood in rats in the experiment, depending on cold exposure time.

Materials & Methods.

Work has been completed at the Department of Normal and Pathological Anatomy, Operative Surgery with Topographic Anatomy and Forensic Medicine at the M.K. Ammosov North-Eastern Federal University's Medical Institute. 25 male mongrel rats weighing 200-250 g were used as experimental animals, aged 5-6 months. The animals were divided into 4 groups: 1 group as control, which were kept in standard vivarium conditions; groups 2, 3, 4, 5 were animals that were exposed to cold. The cooling was carried out in the climatic chamber "Vestfrost" (Denmark) at -10 ± 20C [2, 7, 8] for 1 hour daily for 7, 14, 21, and 30 days.

The protocol of the experimental part of the studies, used at the stages of animal maintenance, modeling pathological processes and removing them from experience, was consistent with the principles of biological ethics set out in the International Recommendations for Biomedical Research with Animals (1985); The European Convention for the Protection of Vertebrates used for experiments or other scientific purposes (Strasbourg, 1986); Order of the Ministry of Health of the USSR No. 755 of 12.08.1977 "On Measures to Further Improve Organizational Forms of Work Involving Experimental Animals"; Order of the Ministry of Health of the Russian Federation No. 267 of 19.06.2003 "On Rules of Laboratory Practice".

The rats were decapitated in accordance with the requirements of humanity in accordance with Appendix No. 4 "On the Procedure for Euthanasia (Killing) of an Animal" to the Rules for carrying out work using experimental animals (annex to the Order of the Ministry of Health of the USSR No. 755 of 12.08.1977). Blood samples and serum were obtained during decapitation of animal. Blood sampling was carried out in glass tubes with anticoagulant heparin in an amount of 5 ml from the abdominal cavity on 7, 14, 21, 30 days. Hematologic examinations were carried out immediately after obtaining samples on the automated hematological analyzer Abacus Junior 30, biochemical studies were made on the Mindray BA-88A biochemical analyzer with ready-made solutions of High Technology. The study of blood and blood serum was performed in the scientific and research clinical diagnostic laboratory for agricultural and domestic animals at the Yakut State Agricultural Academy.

Results & Discussion. As a result of the experiment, it was established that the blood cell counts in the control group of animals kept under optimal temperature conditions were not accompanied by deviations from the physiological norm. While when assessing the condition of the experimental groups of rats, changes in the number of formed elements (from 0.5 to 1.3%) were detected, including a decrease in the level of hemoglobin,

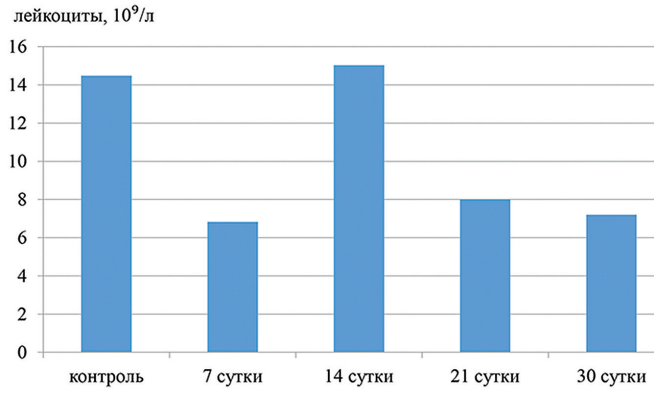

Fig.1. Changes in the total number of leukocytes in experimental animals in comparison with the control group

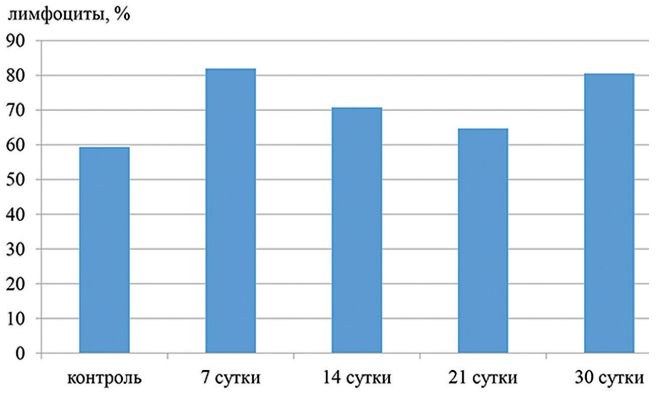

Fig.2. Changes in the relative amount of lymphocytes in the experiment in comparison with the control group

granulocytes, MCHC, an increase in the number of hematocrit and MCV.

The results of the study indicate that cold exposure affects the activity of cells that provide responses to a nonspecific and specific immune response. Thus, the total number of blood leukocytes decreases on days 7, 21 and 30 at 52.9; 44.8; 50.4%, respectively, despite the fact that on the 14th day there was a slight increase (by 3.7%) (Fig. 1).

At the same time, the number of lymphocytes remains elevated thr oughout the experiment, maximally increasing by 7 and 30 days (by 22.6% and 21.2%, respectively) (Fig. 2).

MID – the indicator reflecting the content of a mixture of monocytes, eosinophils, basophils and immature cells is reduced by 7.1% on day 7; on the 21st day by 45.6%; and 30 days by 62.1%; and on the 14th day there was a slight increase of 2.1%. The number of granulocytes (eosinophils, neutrophils and basophils) also decreases on the 7th, 14th, 30th day of the experiment, and on the 21st day it corresponds to the indicator in the control group (Fig. 3).

A significant decrease in the total number of leukocytes on days 7 and 21 and 30 indicates that cold exposure is indeed a stress factor for warm-blooded animals. This correlates with the studies of E.G. Kostolomova, where it is shown that populations of isolated COCs react differently to the duration of cold exposure [6]. Short-term cooling is a factor that activates the functional activity of monocytes and neutrophils, and prolonged cooling is a depressant. In the studies of V.M. Nikolaev. It was also noted that when adapting rats to hypothermia, the indices of nonspecific cellular immunity associated with phagocytic activity of leukocytes change [7]. Statistically significant decrease in the average number of absorbed particles by leukocytes in both the first and second groups of experimental animals testifies to the suppression of nonspecific cellular immunity under the influence of negative temperatures. We will assume that the exposure of rats in our experiment for 7 to 30 days, which results in the suppression of leukocyte activity, was quite long. However, the increase in the number of leukocytes on day 14 (by 3.7% to control and 59.6% compared to the index on day 7) is associated with a short-term stimulation of leukocytopoiesis. In the experiments of T.V. Abarashova et al., It was also shown that male Wistar rats subjected to combined (cold) swimming in water at a temperature of + 70C showed an increase in the number of leukocytes, mainly due to a sharp increase in granulocytes. The authors claim that as a result of the action of the cold factor, a specific immune response is stimulated, and reactions of the nonspecific response mediated by leukocytes are suppressed [11].

There was also a significant decrease in the number of platelets after exposure to cold on the body. The observed changes in the hematological status of these animals are consistent with the literature data, which describes the decrease in the number of platelets, as a reaction to stress [17]. The decrease in the number of platelets seems to be an appropriate reaction of the organism in response to cold exposure, as platelets take a direct part in the repair processes that occur when the tissue is damaged by cold, and also improve the migration of leukocytes to the focus of inflammation. Being a highly active metabolite of arachidonic acid, it is a potent inhibitor of aggregation of the latter. Also, The authors indicate a decrease in the enzymatic and mediator potential of blood cells, as a result of which their ability to form aggregates decreases [16].

The increase in hematocrit and erythrocytes is one of the quantitative characteristics of the physiological "adaptation" of the organism to the new conditions of life. Increased hematocrit and simultaneous enhancement of the synthesis of erythropoietin, stimulating the maturation of red blood cells, may be one of the signs of a reaction to stress, in our case, cold [3].

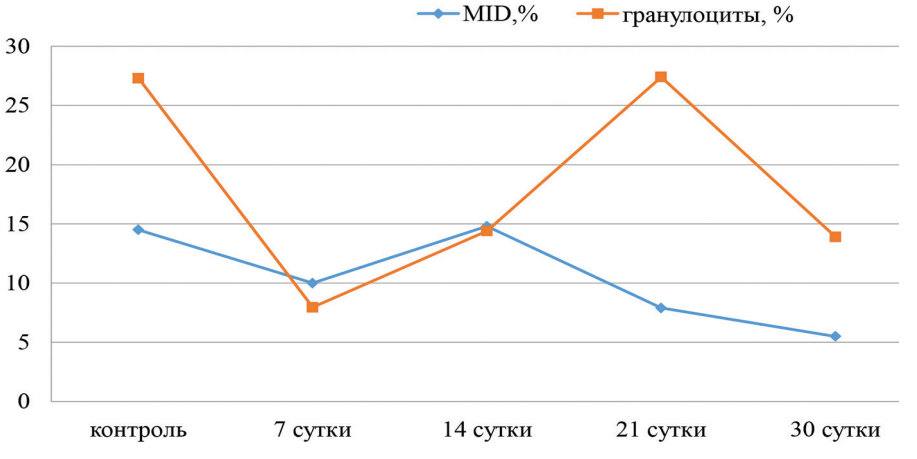

Fig.3. Changes in MID and granulocyte counts during the experiment

Conclusion

Thus, cold exposure is a stress, expressed in the reaction from the whole cellular composition of the blood. As a result of the action of the cold factor, a specific immune response is stimulated, as indicated by an increase in the amount of lymphocytes in the blood, and reactions of the nonspecific response mediated by other types of leukocytes are suppressed. Reducing the number of platelets is also represented as an appropriate response of the body in response to cold exposure, as platelets take a direct part in the repair processes that occur when the tissue is damaged by cold. Increased hematocrit indicates an increase in the proportion of blood cells relative to plasma, and is a reliable criterion for responding to stress.

Further research will concern the study of the processes of proliferation and differentiation of immunocompetent cells of organs and tissues of the lymphoid complex (spleen, thymus, lymph nodes, MALT of hollow organs) under exposure to cold.

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The authors:

Yakutsk, Republic Sakha (Yakutia), Russia:

1. Arzhakova Lena Ignatevna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79644150606, e-mail lenaarzhakova@mail.ru

2. Garmaeva Darima Kyshektovna, Doctor of Medical Sciences, Professor, M.K. Ammosov NEFU Medical Institute Docent, +79142349680, e-mail dari66@mail.ru

3. Dmitrieva Tuyara Ivanovna, Candidate, Federal State Budget Educational Institution "Yakut State Agricultural Academy", +79644298776, e-mail dark_dell@mail.ru

4. Fedorova Aida Ivanovna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79241696871, e-mail fed.aida@rambler.ru

5. Belolyubskaya Dariya Stepanovna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79142976118, e-mail b_d_st@mail.ru

6. Afanasyeva Oksana Gavrilovna, Candidate of Medical Sciences, доцент M.K. Ammosov NEFU Medical Institute Docent, +79142671992, e-mail kafanatomiya@mail.ru

7. Egorova Angelina Innokentievna, Candidate of Biological Sciences, Junior Research Associate, M.K. Ammosov NEFU Medical Institute Docent, +79148220249, e-mail egorovaanil@mail.ru.

E.A. Malyuk, S.S.Tseluyko, N.P. Krasavina

MORPHOFUNCTIONAL CHARACTERISTICS OF SKINS OF RATS OF VARIOUS AGE GROUPS AT LOCAL COOLING

ABSTRACT

In this article, modern ideas about the structure of skin integuments of animals of different age groups are revealed. The features of the structure of the epidermis in sexually mature and immature animals are described. It is shown that the age-related changes in the dermis are associated with a decrease in the number of fibroblasts, a decrease in the amount of collagen and a change in its structure.

Keywords: the epidermis, keratinocytes, melanocytes, Langerhans cells, dermis fibers, the effect of low temperature on the skin.

The epidermis is a constantly renewing system of cells (with a predominance of keratinocytes), in which proliferation, differentiation and apoptosis processes simultaneously support dynamic equilibrium and play an important role in preserving the integrity of the epithelial layer [6].

Physiological regeneration of the integumentary epithelium during the life of the organism occurs continuously, by proliferation of the cells of the basal layer and their transfer to the upper layers to replace the sloughing layers of horny scales [1, 2]. The epidermis regenerates by cellular type. In different groups of animals in different parts of the body, the rate of renewal of the epidermis is different. Thus, the cover epithelium of the ear of the rat is renewed for 34 days, in the mouse for 24 days, for the abdominal region of the rat for 18 days, for the sole of the mouse for 6 days [10]. The duration of the cell cycle in the cells of the basal layer of the epithelium ranges from 20 to 100 hours [3].

Temperature is the most important factor of the environment affecting the human body and animals. The effect of low temperatures on biological objects depends on the degree of phylogenetic maturity of the organism and is realized through various mechanisms in in vitro and in vivo conditions [14].It is known that with deep cooling, there is a significant decrease in Langerhans cells (CL) and the appearance of pronounced degenerative processes in them [9]. At the same time, the form of CR in the epidermis of cells significantly changed: they lost characteristic process, decreased in size, ATPase activity decreased in them. In the terminal sections of the sebaceous glands, Sudanophilia decreased as it increased in the excretory ducts. After a brief cold exposure to the skin in rats, two- and multi-nucleus cells appeared in the basal layer of the epidermis. Their number reached large values (up to 100), and these cells appeared repeatedly, after and after the cessation of the effect of low temperatures [10].

In young rats, the thickness of the skin is approximately 1.2 mm, i.e. it is 1.5-3 times thinner than the skin in adults, 1.5-2 times less than the total surface of the skin. The thickness of the epidermis in the four-month-old rat is small and is about 0.15-0.25 mm, consists of only two or three layers of cornified epithelium and contains more water than in adult rats, which gives the impression of a large thickness of this layer [4,5]. Keratin is absent in the cells of the granular layer.On top of the horny layer of the epithelium, it is also thin. At the age of 7 months the thickness of the epidermis is from 0.25 to 0.35 mm [7]. In the epidermis of 4-month-old rats, the number of Langerhans cells is increased, the number of melanocytes, on the contrary, is reduced. The basal membrane in the epidermis is poorly developed, the number of fixing fibrils is much less, as a result of which the epidermis-dermis connection is less strong [8,9].

Actually, the skin of rats consists of two layers: papillary and reticular. The papillae of the dermis and the intergrowth of the epidermis are poorly developed. The composition of the skin itself includes collagen, elastic and argyrophilic fibers, creating the density of this layer [11]. In the dermis there are connective tissue cells: histiocytes, fibroblasts, monocytes, mast cells, reticulocytes [13]. Fibers and cells are united by an intermediate amorphous substance, which has a great physiological significance. If the young rats in the dermis are dominated by fibers, then with age, there is an abundance of cellular elements and much more amorphous substance [12]. Actually, the skin of rats consists of two layers: papillary and reticular. The papillae of the dermis and the intergrowth of the epidermis are poorly developed. The composition of the skin itself includes collagen, elastic and argyrophilic fibers, creating the density of this layer [11]. In the dermis there are connective tissue cells: histiocytes, fibroblasts, monocytes, mast cells, reticulocytes [13]. Fibers and cells are united by an intermediate amorphous substance, which has a great physiological significance. If the young rats in the dermis are dominated by fibers, then with age, there is an abundance of cellular elements and much more amorphous substance [12].Collagen, elastic and argyrophilic fibers in 4 months thin, delicate, have fuzzy contours, which indicates their unfinished formation. Cellular elements are located between the fibers and along the course of blood vessels. Among the cells there are many more undifferentiated connective tissue cells [16].

The main component of the dermis is collagen, the structure of which is represented in the form of massive bundles of fibrils in the dense fibrous tissue of the mesh layer [14]. About 15% of the collagen in the skin of a young adult rat is included in the «soluble» fractions. With age, there is an increase in the size of dermal fibroblasts, an increase in the content and compaction of the components of their cytoskeleton: even with light microscopy, actin fibrils remain close to each other; the specific content of microtubules and their organizational centers increases. With age, the amount of hyaluronic acid decreases in the basic substance, and the age-related rearrangements in the skin of rats are associated with changes in the quantitative ratios of various glycosaminoglycans [15]. It is known that the total content of glycosaminoglycans at the age of 1 month was 1700 - 2170 μg / g, with aging this value is reduced to 550-800 μg / g [12].

Local cooling is one of the most common environmental impacts that a person experiences in the Far East. Under the action of low temperatures, free radicals, accumulation, in cells in the form of oxygen, singlets to toxic compounds, lead to secondary damage to cellular structures, in particular, signs of an inflammatory reaction. Destructive processes also develop after the termination of the action of low temperature [3].

Skin is a kind of connective tissue,

which has a high metabolic activity. Collagen dermis throughout the life of the animal undergoes intensive renewal. Even more active in the skin is the metabolism of glycosaminoglycans [13]. The half-life of hyaluronic acid in the skin of rats is only 2.5-4 days. While in the skin of immature rats the process of biosynthesis of hyaluronic acid is slower [14].

Thus, in white rats during the reproductive period changes in the thickness of the epidermis and dermis are noted. These differences are most pronounced between animals of 5 and 18 months of age. In animals of 4 months compared with rats 7 months, the thickness of the epidermis is 10.4% higher, and the thickness of the dermis increases by 11.5%. With age, decreased mitotic activity of the epithelium and an increase in the apoptotic index of the structural elements of the skin. In animals 4 months the level of apoptosis and mitosis is higher than in animals of older age.

Conclusion: age affects the morphological features of all structures of the epidermis and dermis, which is especially pronounced with the onset of the period of puberty of animals. With the action of cold on the skin, there are pronounced degenerative processes in all structures of the epidermis and dermis, especially in young immature animals.

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The authors:

MALYUK Ekaterina Alekseevna - Post-graduate student of the Department of Histology and Biology, Amur State Medical Academy,Blagoveshensk, Russia, tel. 8-909-815-42-72, e-mail: nikishina@mail.ru; TSELUYKO Sergey Semenovich - Dr. med. Sci., Professor, Vice-Rector for Scientific Work of the Amur State Medical Academy,Blagoveshensk,Russiatel. 8-(4162) -31-90-20, e-mail: agma.agma@yandex.ru; KRASAVINA Nadezhda Pavlovna - Dr. med. Sci., Professor of the Department of Histology and Biology of the Amur State Medical Academy, Blagoveshensk,Russia.

A.K.Akhremenko, Y.A.Akhremenko, E.V. Pshennikova

CONCEPT OF HYPOBIOTIC STATES OF ANIMALS OF COLD CLIMATE

ABSTRACT

Large animals that inhabit in regions with a cold climate tend to flow into hypobiotic states. These states are distinguished by reduced level of metabolism, that along with high thermal insulation of the body allow them to save energy resources and reduce feed intake in winter. In general, the dynamics (from summer to winter) of a number of physiological and biochemical indicators is largely similar to the dynamics of these indicators in hibernators. For the first time, it was found that the fraction 1-10 kD from the brain of a yakut horse, a yakut cow, a northern reindeer, an elk and a brown bear has hypometabolic, hypothermic, cardiotropic and central effects similar to those of similar fractions from the tissues of hibernators. The most promising sources for isolating and studying the structure of peptides responsible for the organization of hypobiotic states are the brain tissues of yakut horse and brown bear.Analyzing the influence low negative temperatures in annual vital function of hibernators and big mammals, authors come to **Conclusion** that extraordinary stability of animals it is not only developed ability of creating high heat insulation but against that background also of starting peptides regulation, which take part in decreasing of metabolism, and consequently of powers inquiry.

Keywords: hypobiosis, metabolism, temperature of body, motive activity, hibernators, brown bear, yakut horse, northern reindeer, elk, yakut cow, peptides.

Introduction

In the classification of hypometabolic states, proposed by N.N. Timofeev [1], the basis is the degree of inhibition of metabolism. To the «superficial»hypobiosisconcern the state of natural sleep and the winter sleep of the bears. Hypobiosis of the «average» depth is manifested by hibernators, falling into winter and summer hibernation with a pronounced decrease of metabolism and body temperature. In the «deep»hypobiosis, arbitrary movements and contractive thermogenesis are suppressed, but the basic vital functions are not violated. Such a state is reached in hibernators inhabiting the extracontinental climate. These are representatives of squirrel: the yakut long-tailed and arctic gophers, whose temperature in the abdominal cavity and the periphery of the body can drop below zero degrees, and the metabolic rate can drop in two orders of magnitude.

It seems that the last two directions of adaptation to low temperatures are a series of states physiologically similar to some extent. That is to say, they can be attributed to the states of reduced and limited ability to live.

Results and discussion

From the position of the hierarchical system approach it is distinguished the following main nodes that characterize the hypobiotic states: immobility is clearly manifested in hibernators (bats, chipmunks, gophers, groundhogs, bears).Transition to passive behaviorrequires special observations (raccoon dog, badger, yakut hare, voles etc.). An obligatory feature of the hypobiotic condition is a refusal of food or a decrease of the level of its consumption with varying degrees of utilization of endogenous reserves. The main component of hypobiosis is a decrease of the level of metabolism, and there is no strict dependence between metabolism and body temperature. Animals came out from these conditionsindependently.

At the tissue and cellular levelshypobiotic state is characterized by a reduction of the functional activity of the cardiovascular system, thyroid etc. Lipolytic activity of adipose tissue cells, the cells ability to maintain a high activity of ionic calcium pumps, and deeper, the preservation of mitochondrial membrane functions increase.

How often do these moments of hypobioticstates occur in non-gibernants? First of all, it is a marked reduction of motor activity in winter, which is noted in a number of species of deer, elk, bison, musk-ox, yakut horse, yakutcow and yak.

For the listed species, it is known examples of a decrease of metabolism in winter [9, 14, 15, 16, 17, 18, 19]. Thus, the yakut horse (mare) has a 40% lower level of metabolism in winter than in summer. In the yakut cow, metabolism declines by more than half - 55.8%,in she-deers of reindeer - from 26 to 59%, in yak (female) - 20% and in elk-cow with calf - 60%.

Moreover, in free-living species (musk-ox, deers, yakut horse, saiga antelope, roe deer, etc.) such metabolic alterations are combined with the phenomenon of winter hypophagy [8, 10, 11, 12, 20]. And with apparent saturation and changing gross consumption of food there is a starvation developing against the background of decrease of the protein content in plants from autumn to the end of winter.

An important sign of a tendency to fall into hypobioticstates could be the body temperature, but such data are not available. There are only measurements of the temperature of the peripheral parts of the body, more often it is rectal and subcutaneous temperature. Some decrease of that temperature in animals in winter indicates,first of all, the increase in the heat-insulating properties of the skin and deposits of subcutaneous fat.

Just as in the hibernators, deposition of fat in large animals occurs in autumn, and the deposition of protein and fat stores is divided in time. For example, in the yakut horse, the daily weight gain in August is 2-2.5, and in September is only 0.5 kg.

The tissues of northern animals contain high concentrations of polyunsaturated fatty acids and, according to this index, they are similar to those of hibernators. According to our data, in the blood plasma of yakut horse the content of polyunsaturated fatty acids in winter exceeds 50%. The yakut and kazakh horses that spend the winter under the open sky at a stern feed have the most fusible fat among domestic large mammals, comparable in this respect to wild large mammals.

The iodine number of fat in the yakut cow is significantly higher than in other breeds of cattle [18].

It is known that unsaturated fatty acids serve as the main substratum of free radical oxidation, whose products outside the norm can disrupt many processes and cell structures. The system of protection against endoperoxides is determined by various factors, including reduced glutathione (tripeptide containing sulfhydryl group - SH2). Reduced glutathione is a cofactor of enzymes destroying peroxide fatty acids.

It is established that the change of the glutathione content in the yakut horse has a pronounced seasonal character. Its high content is determined in winter and its low content is determined in summer. Along with this, it was shown that the highest antioxidant activity of lipids is high in winter, which is also due to the low level of products of lipid peroxidation.

The same is observed in hibernators.

In general, a number of agricultural animals of Yakutia are characterized by high indicators of the oxidation and reduction system of glutathione.

Both in hibernators and in large animals the albumin content, the main transporter of fatty acids and peptides (regulators of many functions in the body) increases in the blood in winter.

Seasonal changes in the activity of the thyroid gland are significant in a number of hibernators. The activity of the gland is minimal in hibernation. And the maximum activity is detected in spring after exiting it [27]. Analogy can be made with the northern reindeer, in the blood serum of which contains 30, 0 nmol / L of thyroxin and 0.3 nmol / L of triiodothyronine in winter, and in summer - 100.0 and 2.0, respectively.

Unidirectional represent shifts to winter in the structure of cell membranes in both the hibernator (gopher) and the yakut horse. This can be judged by the increase of erythrocyte resistance in the bloodstream.

It is also interesting that in such different species as the red-cheeked gopher (Novosibirsk region), the red vole and the yakut horse, the populations of mitochondria of hepatocytes become polymorphic in winter. The development of the lysosomal apparatus increases in these species in winter. All of it confirms the state of chronic starvation [30].

Thus, the animals of cold climate have the ability to fall into hypobiotic states characterized by a decrease of the metabolic level, which along with high thermal insulation of the body leads to a significant saving of energy reserves and allows surviving the winter with a lack of food and nutrients.

From a review of the seasonal dynamics of metabolic, tissue and subcellular reconstructions, although obtained in different species but, chiefly, in their natural habitat, it follows that many unique adaptations of animals living in a cold climate should be provided with reserve capacity of regulatory systems.

The abiotic factors, that vary abruptly, can lead to an intensification of a number of evolutionary ancient regulations, in particular peptide regulation. In other words, the amplification of the function occurs when the corresponding function is insufficient. And here we see the analogy between winter hibernation and adaptation of large animals to the cold. In support of this, an attempt was made to compare the biological activity of peptide fractions from the tissues of large animals and hibernators, believing that such an approach would facilitate the search of a link between the ability to fall in winter hibernation and the transition of non-hibernators to hypobiosis.

The search of regulators responsible for the organization of hibernation dates back to the 1930s. The first experiments on this direction were carried out by Kroll [citation]. The essence of these experiments was that from various tissues of hamsters, hedgehogs and bats that were in hibernation, he received extracts that were introduced to cats and dogs. These extracts caused dreamlike conditions in animals. In parallel, experiments were carried out with extracts from tissues of gophers and marmots. These extracts were introduced to white rats, after a short period of anxietythey have apathy and lethargy. Basic exchange decreased by 20 - 30%. In rabbits was noted a 28% decrease of blood pressureand a 20%decrease of the heart rate. In the 1950s, along with German researchers, work began in Canada and in the USA. In the USSR similar studies were initiated by S. Kolaeva in the Institute of Biophysics of the Academy of Sciences of USSR [33].

In the Institute of Biological Problems of the Cryolithozone, it began the work on the search and isolation of peptides responsible for the organization of hypometabolic states. They started with horses as the most accessible donors for obtaining active material. Later the circle of objects expanded [34, 35, 36, 37].

Even the first experiments on mice have shown that the material is quite active. Intraperitoneal injections of a peptide fraction weighing from 1 to 10 kD from the brain of horses seized in the winter at a dose of 1 mg / g caused a decrease of body temperature by 8-9 degrees, and a depression of metabolism by more than 60%.

Determination of the activity of the material obtained from summer and winter horses showed that in the first case its activity is weaker.

On isolated heart preparations (frog, cat), peptide fractions from the brain and small intestine of hibernatorgophers and from thebrain of yakut horse at a concentration of 2-10-4 g / l caused complete cessation of the heart. Comparison of the activity of fractions from these twospecies revealed that they have a similar cardiotropic effect and show activity in the same range of concentrations, namely from 2-10-6 to 9-10-5g / l. The introduction of fractions has a dose-dependent inhibition of heart rate and a decrease of the amplitude of mechanical activity [38].

The introduction of the fraction from the horse's brain inhibits the total protein synthesis in the liver and heart tissues of mice. After 30 minutes, the inclusion of amino acids in proteins decreases by 30-40%.

The investigation of the effect of different concentrations of the fraction on the rate of passive and active transport of Ca2+ to the vesicles of sarcolemma of cardiomyocytes has shown that the effect on calcium transport is the same as that of hibernator gophers, and in the same concentration range, from 10-7 to 3 x 10-5.

This same fraction also suppresses the conduction of the slow type of calcium channel of perforated cardiomyocytes of rats.

The successive separation of the fraction of 1 to 10 kD of the horse's brain led to the excretion of the octadecapeptide [39] having a pronounced hypothermic effect withintroduction to mice. When animals leave hypothermia, achieved with a lack of air, the introduction of the peptide inhibits the buildup of body temperature. In the experiment on isolated perforated cardiomyocytes, the octadecapeptide blocked calcium current at a concentration of 5 μM - by 35.5%, and in a concentration of 25 μM - by 59.1%.

From other species of animals, brown bear, northern reindeer, snow sheep, elk and yakut cow were examined for the content of hypometabolic factors. The peptide fraction was isolated in winter. It was found that the fraction from the elk's brain, introduced to the cold-adapted mice (the animals were kept at an air temperature of 5-10 °C) at a dose of 1 mg / g, lowered the metabolic rate from the initial one by 40%, and the northern reindeer'sfraction lowered the metabolic rate by 36%. Body temperature decreased by 2.6°. The same decrease in body temperature in mice was also caused by a fraction from the yakut cow. The introduction of a fraction from the snow sheep'sbrain reduced the temperature by 7.5°. A deeper effect was exerted by the fraction from the brain of the brown bear. The body temperature of mice was reduced by 9°, and the metabolism was reduced by 70% from the original level. Both intraperitoneal and intranasal introduction of the fraction prolonged mice the yield from the hypothermic state. And the time to get out of this state was 4 - 5 times higher than the time for heating the animals after introducing a fraction from the horse's brain.

Intraventricular introduction of the fractionin rats showed the following. They have a significant decrease of the number of behavioral reactions. Animals adopt a pose characteristic of sleep. They closed their eyes and fell into a dreamlike state. The electric activity of the brain, that was judged by an electroencephalogram (EEG), was also reconstructed. Initially, the EEG was characterized by a wide spectrum of frequencies in the delta, kappa alpha beta ranges. After the fraction introduction, the slow components (delta and kappa) were amplified and high-

frequency components (alpha and beta) were suppressed. The fraction from the brain of gophers causes a reorganization of the behavior and the EEG that is similar in many respects to what was observed in experiments with a similar fraction of the bear's brain. In the experiments with the fraction from the bear's brain it was found that the proportion of paradoxical sleep persists. In gophers, as they dive into hibernation, episodes of paradoxical sleep become rare and disappear.

It was shown that some subfractionsreleased from the fraction 1-10 kD significantly inhibit the calcium current in perforated cardiomyocytes, some of them by 60%, the activity of fractions released from the tissues of hibernators is removed by naloxone (an opiate receptor blocker), while this is not observed in bears and in yakut horse, or this effect is masked.

Conclusions

Thus, large animals inhabiting regions with a cold climate tend to flow into hypobiotic states, which are distinguished by a reduced level of metabolism, that along with high thermal insulation of the body allows them to save energy resources and reduce feed intake in winter. In general, the dynamics (from summer to winter) of a number of physiological and biochemical indicators is largely similar to the dynamics of these indicators in hibernators. For the first time, it was found that the fraction 1-10 kD from the brain of yakut horse, yakut cow, northern reindeer, elk and brown bear has hypometabolic, hypothermic, cardiotropic and central effects similar to those of similar fractions from the tissues of hibernators. The most promising sources for isolating and studying the structure of peptides responsible for the organization of hypobiotic states are the brain tissues of the yakut horse and the brown bear.

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The authors

1. Akhremenko Aleksandr Kuzmich - Candidate of Biological Sciences, Senior Researcher in Institute of Biological Problems of Cryolithozone

2. E-mail: yanalex2007@yandex.ru моб. тел. 89241753177

3. AKHREMENKO Yana Aleksandrovna - Candidate of Medical Sciences, Docent, Associate Professor of the Department of Histology and Microbiology of Medical Institute, the North-Eastern Federal University named after M.K. Ammosov, Yakutsk, Russia;

4. PSHENNIKOVA Elena Vissarionovna – Candidate of Biological Sciences, Docent, Head of the Department of Histology and Microbiology of Medical Institute, the North- Eastern Federal University named after M.K. Ammosov, Yakutsk, Russia. E-mail: el_viss@mail.ru.

E. V. Slobodenyuk,E.A.Litovchenko, N.V.Korshunova, M.A.Shtarberg

USE OF PHYTOADAPTOGENS FOR THE CORRECTION OF COLD STRESS ON THE BODY

ABSTRACT

The purpose of this research was to study the possibility of using a mixture of phytoadaptogens for the correction of the body's compensatory responses to the conditions of low temperatures.Experiments have been conducted on experimental animals (50 white mongrel rats-males weighing 180-200 g) in accordance with generally accepted methodological approaches. Research of cold adaptation reactions of experimental animals have been conducted by using the model of a long cold action with appropriate climatic chamber.It was established experimentally that in doses of 150-300 mg/kg daily of the studied mixture has a strong antioxidant effect in the conditions of cold stress on warm-blooded organism. The research allowsusing a mixture of phytoadaptogens as a regulator of adaptive reactions of the organism when exposed to low temperatures.

Keywords:cold effect,resistance of organism,phytoadaptogens.

Introduction

One of the most important problems of studying environmental impacts on humans and animals is considered to be the stress effect of cold. Currently, the most significant national priorities which represent the basis of innovative development of the country are rapid socio-economic development of the Arctic territory andconstruction and operation of the first Russian civil cosmodrome «Vostochny» in the cold winter of the Amur region[1].

These tactical and strategic directions are realized in cold climatic conditions of environment that causes relevance of a problem of adaptation of the population of the Russian Federation to temperature stress. In this regard, it is interest to study the mechanisms of adaptation reactions of the warm-blooded organism to low temperatures, because the depletion of reserves of organs and systems is possible until the adaptation is achieved [2-4].

The development of the state of disadaptation in cold stress is possible to prevent by system of hygienic measures, correction of diets of the population with the use of adaptogenic products from animal or plant origin [4].

A promising component for the production of a mixture of substances used in the nutrition of the warm-blooded organism during exposure to low temperatures an important role can be assigned to Hypericumperforatum (HP) and Rhodiolarosea (RR).

The aim of the present work was to investigate the possibility of using the mixture of HP and RR for the correction of compensatory reactions of the organism to low temperatures.

Materials and methods

The work was performed under standard conditions of vivarium of Amur State Medical Academy. Experiments were carried out observing the rulesof the "European Convention for theprotection of vertebrate animals usedfor experimental and other scientificpurposes" (Strasburg, 1986) and theorder of the RF Health Ministry №267concerning the GLP rules (19.06.2003). Experiments on the study of cold adaptive reactions of laboratory animals with the introduction of a mixture of HP and RR using a model of long-term cold exposure were performed on 50 white rats-males with body mass 180-200 g for 10 individuals in the group.

The study of cold adaptation reactions of animals was carried out on the model of long-term cold exposure for 28 days with the introduction of a mixture of HP and RR [2].The animals were divided into 5 groups: 1st- intact rats were kept in standard vivarium conditions; 2nd – control group, animals were subjected to cooling; 3rd, 4th, 5thgroups – the experimental groups, before placing the rats in climatic chamber in a small amount of feed added a mixture of HP and RR in powder form in the dose of 30 mg/kg; 150 mg/kg; 300 mg/kg respectively. The study of biochemical parameters was carried out on the 7th, 14th, 21st, 28th days of cold exposure.

After the experiment, the animals were decapitated under ether narcosis. The study was approved by the Ethics Committee of the Amur State Medical Academy. The statistical processing was carried out by the standard method with the use of the Student's t-criterion.

Results and discussion

The effect of cold affects the increase in lipid peroxidation products (LPP) in the blood of rats.The results of experimental studies have shown that the prolonged action of cold on the warm-blooded organism observed an increase in the content of all products of peroxide reactions on the 7th, 14th, 21st and 28th days.It was found that the introduction of a mixture of HP and RR in doses of 150 mg/kg and 300 mg/kg significantly reduced the content of the LPP in all research periods.Significant changes in the content of the LPP under the introduction of phytoadaptogenic mixture at a dose of 30 mg / kg have not been registered.

Most of all, the content of hydroperoxides of lipids during cold exposure decreased on the 14th day under the introduction of a mixture of HP and RR at a dose of 300 mg / kg and amounted to 19,93±0,92nmol/ml;the concentration of diene conjugates is maximally reduced on the 28th day under the introduction of the mixture at a dose of 150 and 300 mg / kg; the content of malonicdialdehyde decreased in all days of research, especially on the 21st day of the experiment(table).

Thus, feeding an experimental animals the mixture of HP and RR during prolonged cold stress leaded to decrease in the formation of LPP in the blood of rats, that's why an increase in the level of adaptive reactions were leads.

Conclusion

We have first experimentally confirmed and substantiated the effectiveness of phytoadaptogens mixture of HP and RR with the purpose of correction of oxidative stress under conditions of cold stress on warm-blooded organism.The experiments allow recommending the studied mixture as a regulator of adaptive reactions of the organism under the influence of low temperatures.

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The concentration of products of lipid peroxidation in blood of rats during prolonged cold stress and using the phytoadaptogens mixture (M±m, n =10)

Indicators, nmol / ml	The period of the experiment, day	Intactgroup	Controlgroup	The experimental group: cold+30 mg/kg of the mixture	The experimental group: cold+150 mg/kg of the mixture	The experimental group: cold+300 mg/kg of the mixture
Hydroperoxideoflipids	7th	17,63±0,46	31,13±0,81*	30,26±0,63	27,82±0,91**	23,83±1,5**
	14th	18,09±0,39	29,15±1,0*	28,5±1,3	28,85±2,5**	19,93±0,92**
	21st	17,03±0,51	30,25±0,9*	30,10±1,02	26,12±2,2**	22,97±0,41**
	28th	17,9±0,56	28,6±2,6*	28,4±2,3	25,3±3,2**	20,71±0,67**
Dieneconjugates	7th	91,77±1,6	112,77±2,3*	113,12±5,3	106,71±6,5**	89,16±2,39**
	14th	90,52±1,0	124,63±1,6*	120,46±2,5	116,52±3,5**	99,42±2,6**
	21st	86,6±0,5	119,56±1,4*	119,45±2,6	109,22±1,7**	95,42±2,1**
	28th	89,11±1,2	120,9±3,3*	119,16±5,3	106,41±2,1**	94,1±3,8**
Malonicdialdehyde	7th	0,7±0,9	2,72±0,18*	2,43±0,05	1,8±0,1**	1,0±0,07**
	14th	0,97±0,15	3,15±0,31*	3,08±0,13	2,47±0,3**	1,49±0,08**
	21st	1,13±0,1	4,57±0,12*	3,8±0,52	3,3±0,3**	1,74±0,01**
	28th	1,17±0,2	3,25±0,31*	3,25±0,52	2,61±0,35**	1,13±0,33**

* - differences between intact and control groups (p<0,05); ** - differences between control and experimental groups (p<0,05).

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The authors

1. Elena V. Slobodenyuk, Dean of the faculty of pharmacy, Doctor of Biological Sciences, Associate Professor, Head of the Department of Pharmacology and Clinical Pharmacology, Far Eastern State Medical University, Khabarovsk, Russian Federation;

2. Ekaterina A. Litovchenko, MD, Postgraduate student of Department of General Hygiene, Amur State Medical Academy, 95 Gor'kogo Str., Blagoveshchensk, 675000, Russian Federation. E-mail: ekaterinalitovchenko-89@mail.ru;

3. Natalia V. Korshunova, MD, PhD, DSc, Professor, Head of Department of General Hygiene of Amur State Medical Academy, 95 Gor'kogo Str., Blagoveshchensk, 675000, Russian Federation, mob. 89246729557.

4. Mikhail A. Shtarberg, candidate of medical Sciences, senior researcher of the Amur State Medical Academy, 95 Gor'kogo Str., Blagoveshchensk, 675000, Russian Federation.

E.I. Semenova, Z.N. Krivoshapkina, L.D. Olesova, G.E. Mironova, L.I. Konstantinova, A.V. Efremova, A.I. Yakovleva, S.I. Sofronova

EVALUTION OF THE INDICES OF HEMODYNAMICS IN THE ARCTIC ZONE RESIDENTS FROM THE POSITION OF «GOLDEN RATIO»

ABSTRACT

The data of arterial pressure of 91 residents of the Arctic zone of the Republic of Sakha (Yakutia) from the position of «golden ratio» was investigated. It was revealed that the most harmonious blood pressure is found in the Chukchi and Yukagirs, and it is confirmed by the highest percentage of those with a diagnosis «healthy».

Keywords:arterial blood pressure, arterial hypertension, golden ratio.

Introduction. Currently arterial hypertension (AH) remains to be one of the most significant medical and social problems, as it is an important risk factor of cardiovascular diseases, mainly determining high mortality rates in our country and around the world in general.

The blood circulatory system in Russia accounts for more than a half of deaths and 46% of disabilities in Russia. According to the results of 2016, cardiovascular diseases occupied the second ranked place in the structure of general morbidity of the adult population, meaning that it got 14.5% (3172 per 100000 of the total population), and the hypertensive heart disease got 674,6 per 100000 of the total population [5,8].

Based on the results of the conducted representative survey of the population of SakhaRepublicin 2003, the prevalence rate of arterial hypertension (AH) averaged 0.3 ± 0.8%.Among the indigenous population of Yakutia, the incidence of AH is slightly less than in the non-indigenous population (22.9 and 27.7% respectively). However, the prevalence rate of AH suddenly increases to 29.3% and more in the indigenous population starting from the 6th decade of life [9].

Unfortunately, in recent years, despite all the health care efforts, the sickness

statistic of AH has been increasing, so for 2016-2017 the morbidity of AH in the Republic of Sakha (Yakutia) was 43.7% and 44.82% respectively [10].

It is known that the body functions in a state of dynamic equilibrium and the exits beyond its limits as the result of various kinds of influences or diseases of organs and systems are considered as violations of hierarchical interactions.These violations are either quickly compensated for, or they lead to the pathological process development, and individual links to the functional circulatory system with its full compensation are in a certain relationship. An assumption has been made that this relationship between individual elements obeys the rule of «golden ratio» [6].

The concept of the «golden ratio» (GR) has been used for a long time and is described by proportions – it is a division of the segment into two parts so that the length of the bigger part refers to the length of the smaller part in the same way as the length of the whole segment refers to the length of the larger part. The golden ratio and the golden proportion (which is the same thing), or harmonious division, is obtained if the whole segment refers to the one part as 1: 0.618, and the bigger part refers to the smaller as 0.618: 0.382.

It is revealed now that the golden proportion is the criterion of optimality in choosing the parameters of many physiological functions for the human body – blood levels, respiration, central nervous function. The structure of the heart and the relationship between the main indicators of its activity (systolic, diastolic, pulse arterial blood pressure, heart rate) also refer to each other in the proportion of GR. It is assumed that for healthy individuals deviations from ideal (1.618 or 0.618) are not more than 5 - 8%, even with significant (1.5 - 2 times) changes in hemodynamic parameters [1].

In 1998 the clinical value of the ratio of DBP to SBP was studied by V.V. Shkarin. The term «structural point of BP» (SPBP) was assigned to this ratio. It is known by now that SPBP is closer to the value of the Golden Ratio (GR) proportion – 0,618 [3].

Deviations from the golden proportion of the ratios of hemodynamic indices mentioned above are treated either as a process of structural and functional rearrangement of physiological systems, or as a state of dysregulation, decompensation of these systems, especially if it is recorded in a state of rest (sleep, rest, etc.).

Thus, even if the parameters of hemodynamics do not fit into the range of normal values, but their relationships are subject to the principle of GR, it is a sign of optimality, compensation, consistency and harmony of the processes occurring in the human body [1].

The purpose of this study is to evaluate and analyze the indices of arterial blood pressure of residents of Andryushkino village, using the principle of «golden ratio».

Material and methods of research. The data of arterial pressure of 91 residents of Andryushkino village (NIzhnekolymsky District, Republic of Sakha (Yakutia)) have been researched. The average age was 43.47+5.51 years old.

The values >25 and <30 kg/m2 were considered overweight. The obesity was recorded with a body mass index (BMI)> 30 kg/m2 (according to European recommendations III revision, 2003).

At the classification of arterial blood pressure (BP) levels mm Hg, the data from the National Clinical Guidelines (2009) [2] was used, so the optimal was <120 and <80 mm Hg, normal - 120-129 and / or 80-84 mm Hg, high normal - 130-139 and / or 85-89 mm Hg. Arterial hypertension (AH) of the 1st degree corresponded to 140-159 and / or 90-99 mm Hg, AH of the 2nd degree - 160-179 and / or 100-109 mm Hg, AH of the 3rd degree - ≥ 180 and / or ≥110 mm Hg.

The «structural point of BP» (SPBP) and the ratio of DBP / SBP were used for the evaluation of blood pressure indicators. By now, it is known that SPBP approaches the value of the golden proportion (GP) - 0.618 (harmonious ratio). The values of BP with SPBP in the range from 0.564 to 0.673 for healthy subjects were considered stable. For patients with arterial hypertension (AH), «disharmony» ranged from 0.549 to 0.687 (deviation of GP from 8% to 11%). The biggest differences from the proportion of the GR and «imbalance» (12% and higher) are characteristic for unstable states: borderline AH, severe forms of hypertension and, possibly, the crises form of hypertension [3].

Statistical processing of the obtained results was carried out using the SPSS software package (version 17). The data is presented in the form of M ± m, where M is the mean value and m is the standard error of the mean value.

Results and discussion.

According to the results of anthropometric data from the residents of Andryushkino village, the following average growth rates were received: Chukchi - 153.28 ± 3.74 cm, Evens-154.93 ± 3.0 cm, Yukagirs - 155.43 ± 4.06 cm, Yakuts - 156.13 ± 3.02 cm. Body weight: Chukchi - 63,17 ± 7,04 kg, Evens - 69,07 ± 7,39 kg, Yukagirs - 68,43 ± 9,35 kg, Yakuts 72,53 ± 6,40 kg. The body mass index (BMI), regardless of ethnicity, was at the level of excess body weight. Thus, for Chukchi - 26.69 ± 2.19, Evens - 28.88 ± 3.22, Yukagirs - 28.39 ± 4.01, Yakuts - 29.86 ± 2.73 (table 1)

During the study of hemodynamics, it was found that, depending on ethnicity, the average values of blood pressure are within the permissible normal values. The average values of the ratio / of DBP SBP (SPBP) and SBP / DBP were in the range of recommended norms, and the closest correlation of blood pressure to the «golden proportion» was found in Evens and Yakuts (Table 2). Harmonious blood pressure and SPBP (close to 0.618) were detected in 16.67% of the Chukchi and Yukagirs, 13.8% of the Evenes, and 6.67% of the Yakuts. Disharmony was found in 77.77% of the Chukchi, 75.86% of the Evenes, 78.57% of the Yukagirs, and 76.67% of the Yakuts. BP imbalance was detected in 5% of Chukchi, in 10.34% of Evens, and in 16.66% of Yakuts, but in Yukaghirs it was not detected.

The analysis of hemodynamics from the position of the «golden proportion» on the established diagnoses showed that the average BP indices for all ethnicities diagnosed with «AH 2 risk 2» are within the permissible norm. Arterial pressure of Evens and Yakuts with diagnoses of «AH 3 risk 2» varied at the level of «moderate hypertension» (hypertension of the 1st degree, soft SBP - 140-149 mmHg and DBP - 90-99 mmHg). At the same time, within the diagnosis of «healthy» regardless of ethnicity, blood pressure was at the level of the «optimal pressure» category (SBP - 100-119 mmHg, DBP - 60-79 mmHg) according to the Russian clinical recommendations (2009) (Table 3).

It is generally believed that the damage to the body is caused by fluctuations in the upper pressure, however, according to Professor Katsudzo Nishi (2006), who lived at the beginning of the 20th century,

Table 1

Anthropometric data and indicators of hemodynamics depending on ethnicity

Indicator	Chukchis n=18	Evens n=29	Yukagirs n=14	Yakuts n=30
Height, cm	153,28±3,74	154,93±3,0	155,43±4,06	156,13±3,02
Body mass, kg	63,17±7,04	69,07±7,39	68,43±9,35	72,53±6,40
Body mass index	26,69±2,19	28,88±3,22	28,39±4,01	29,86±2,73
SBPmmHg	118,33±3,81	125,17±8,81	115,71±5,63	129,67±8,65
DBPmmHg	77,22±2,24	77,24±3,62	74,28±3,34	80,33±2,86
DBP/SBP	0,653±0,01	0,623±0,02	0,643±0,001	0,627±0,02

mmHg

the relationship between upper and lower pressure is considered particularly dangerous, and vice versa. He considered the «golden ratio» of pressure, which is 7/11 (or close enough to it in the range of 6/11 - 8/11) to be a health indicator. At this ratio, upper and lower pressure numbers pose absolutely no danger to a person, even 274/174 mm Hg (0.635). But if this «golden ratio» is violated, for example, at a blood pressure level of 127/95 mm Hg. (0.748), there is a significant danger to health. And, of course, the greater the difference between the upper / lower pressure ratio and the «golden ratio» is, the higher the risk of developing cardiovascular diseases gets. It should be noted that this formula is applicable only towards the people over twenty years old [7].

In 2010, M.A. Karpenko, et al. (2010) examined the clinical significance of the quantitative analysis of ECG and arterial blood pressure using the «golden ratio» method. They found that when the ECG and BP values deviate from the optimal values by more than 15%, the probability of finding coronary heart disease (CHD) in the examined patients is 85% [5].

The closest to the GP harmonious ratio of DBP / SBP (SPBP) with the diagnosis of «AH2 risk 2» was found in Evens – 0.617 ± 0.01 (SBP - 130 ± 11.54, DBP - 80 ± 5.77 mm Hg), with the diagnosis of «AH3, risk 2» in the Yukagirs - 0.615 ± 0.01 (SBP -130.0 ± 0.0 DBP - 80.0 ± 0.00 mmHg). In all ethnic groups SPBP with the diagnosis of «healthy» was on the range of stable disharmony and amounted to 0.656 ± 0.01 in the Chukchi, 0.651 ± 0.01 in the Evens, 0.646 ± 0.02 in the Yukagirs and 0.651 ± 0.01 in the Yakuts. But at the same time, the occurrence of «healthy» diagnosis was higher for the Chukchi (72.22%) and for theYukaghir (64.29%).

It is interesting that according to a large-scale study HOT (Hypertension Optimal Treatment), which included the study of 18.790 patients with AH, with the optimal blood pressure in terms of the lowest risk of death due to cardiovascular causes, the optimal blood pressure is considered to be 138.8 / 86.5 mm Hg. Calculation of SPBP from these data gives us a number of 0.6231, which is absolutely identical to the average value of SPBP, which was obtained from the study of a group of healthy individuals. The lowest risk of developing cardiovascular complications was established with blood pressure = 138.5 / 82.6 mm Hg. Wherein the SPBP is 0.5942, which is also within the range of SPBP ± 1s [3].

Therefore, the assessment of indices of hemodynamics from the position of the «golden proportion» in examined residents of the Arctic zone revealed that the most harmonious arterial blood pressure occurs in Chukchi and Yukaghirs, and this is confirmed by the highest percentage of people with the diagnosis of «healthy». According to the obtained results among the patients of Andryushkino village with AH, stable blood pressure with the least risk of developing cardiovascular complications among patients is in the range of 130.0 ± 0.0 / 80.0 ± 0.00 mm Hg. (0,615). **In conclusion**, it can be noted that the stable the values of the «golden proportion» for blood pressure are maintained, the more effective the coronary circulation and the more stable state of the body's regulatory systems is.

Table 2

The ratio of DBP / SBP(SPBP)and percentage deviation from the number of «golden proportion»

Ethnoses	DBP / SBP(SPBP)	Deviation from the "golden proportion" in%	SBP/DBP	Deviation from the "golden proportion" in%
Chukchis, n=18	0,653±0,01	5,66	1,533±0,02	5,25
Evens, n=29	0,623±0,02	0,8	1,614±0,05	0,25
Yukagirs, n=14	0,642±0,01	3,88	1,557±0,03	3,77
Yakuts, n=30	0,627±0,02	1,46	1,609±0,07	0,55

Table 3

Hemodynamics indicators on diagnoses depending on ethnicity

					Healthy	
	AH 2, risk 2		AH 3, risk 2			
Ethnoses	SBPmm. m.c.	DBPmm. m.c.	SBPmm. m.c.	DBPmm. m.c	SBPmm. m.c.	DBPmm. m.c
Chukchis	124±3,66	80,0±0,00	-	-	116,15±4,04	76,15±2,67
Evens	130±11,54	80,0±5,77	141,81±10,07	82,56±2,72	110,71±5,53	72,14±4,14
Yukagirs	123,33±4,38	80,0±0,00	130,0±0,0	80,0±0,00	110,0±5,0	71,11±3,47
Yakuts	125,0±7,82	80,0±0,00	148,0±13,72	85,0±4,78	118,57±3,43	77,14±2,42

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The authors:

1. Semenova Evgenia Ivanovna - PhD, Senior Scientist, E-mail: kunsuntar@mail.ru;
2. Krivoshapkina Zoya Nikolaevna - Ph.D., senior researcher. Laboratory of Biochemical Research, OIMA FGBNU «Yakut Scientific Center of Complex Medical Problems».
3. Olesova Lybov' Dygynovna - PhD, Senior Scientist, Head of Laboratory of biochemical studies FGBNU 'Yakut Scientific center of complex medical problems. «
4. Mironova Galina Egorovna, Ph.D., professor of FGAOU M.K. Ammosov «North-Eastern Federal University», mirogalin@mail.ru.
5. Konstantinova Lena Ivanovna, - researcher, Laboratory of Biochemical Research, OIMA FGBNU «Yakutsk Scientific Center of Complex Medical Problems».
6. Efremova Agrafena Vladimirovna - Ph.D. Laboratory of Biochemical Research, OIMA FGBNU «Yakutsk Scientific Center of Complex Medical Problems».
7. Yakovleva Alexandra Ivanovna – researcher, Laboratory of Biochemical Research of the Department of Mechanisms of Adaptation of the OIMA of the FBBNU «Yakutsk Scientific Center fof Complex Medical Problems».
8. Sofronova Sargylana Ivanovna, - Ph.D., leading researcher, head of the department FGBNU «Yakut Scientific center of complex medical problems.»

A.V. Efremova, M.I. Tomsky, S. Cinti, E.A. Isakov, V.A. Alekseev, A.A.Grigorieva, L.I. Konstantinova, E.D. Okhlopkova, A.I. Yakovleva, L.D.Olesova, E.I. Semenova, Z.N. Krivoshapkina

METABOLIC INDICES OF BLOOD IN CONDITIONS OF COLD EXPOSURE

ABSTRACT

We investigated 200 employees of the diamond mining company who worked in cold condition from 2 to 8 hours a day. Reliable correlations have been revealed to prove the effect of cold on weight, body mass index, waist volume and hip volume. Cold exposure increased expression of genes markers of browning. These results provide evidence pointing to PMBCs as an easily obtainable material.

Keywords: cold exposure, brown adipose tissue, lipid metabolism, obesity.

Introduction

The discovery of brown adipose tissue caused great interest in studying the origin of this thermogenetic tissue underlying the fight against obesity and complications associated with it.

Cold exposure is one of the strongest stimulators of brown adipose tissue (BAT) activation. The process of activation of brown adipose tissue is manifested in the growth of beige adipocytes in the depot of white adipose tissue, this process is called browning.

It is known that mammals have two types of adipose tissue, white and brown. White adipose tissue mainly consists of white adipocytes, which are a storehouse of the excess fat, designed to store energy, in the form of a large lipid drop. BAT consists of multi-compartment adipocytes that specialize in fat oxidation, producing heat during thermogenesis, in response to cold stimulation or consumption of a high-calorie diet during stimulation with B-adrenergic receptors.

The thermogenetic activity of BAT is associated with the presence of the mitochondrial protein UCP1 and represents an important part in the energy expenditure of the critical and total energy balance. The main thermogenetic stimulus in cold exposure is the stimulation of the sympathetic nervous system by cold and the control of B-adrenergic antagonists caused by the oxidation of fatty acids in adipose tissue and thermogenesis in BAT by the mediocre growth of the size of the BAT tissue, mitochondriogenesis, and expression of the UCP-1 protein and the activity of proteins to maintain body temperature [3, 5, 7, 15-17]. In addition, stimulation of B-adrenergic receptors by cold promotes such a process as browning, in which brown-like adipocytes (brite) form in the depot of typical white adipose tissue [1,4,5,6,7,10,25]. These adipocytes are called brite (brownish, beige, intermediate form between brown and white fat tissue), which prove specific gene expression and have some features characteristic of classical brown adipocytes, such as expression of UCP-1 protein in mRNA [1, 2, 9, 18, 19, 21, 22]. In the case of rodent studies, it is known that the Browning process can increase energy consumption and help maintain body weight [2,8,20]. Interest in the research of BAT appeared when the cases of active BAT in adults were proved [12]. At the moment, the main issue discussed by the world community is the possibility to activate or increase the mass of BAT in adults, since active BAT can play a significant role in controlling energy homeostasis and promote the development of drugs for the treatment of obesity.

Objective: to establish the usefulness of the use of peripheral blood mononuclear cells as a method for carrying out a study related to the activation of brown adipose tissue and the transition of white adipose tissue to brown tissue by analyzing the key markers of Browning in response to the main thermogenetic stimulus-the cold exposure.

Materials and methods

In 2016, biomaterial (blood) was collected for genetic and biochemical analyzes of 200 workers of the diamond mining company, mainly sinkers, who openly mined the diamond-bearing soil in the winter season. Workers spent on extraction from 4 to 9 hours a day depending on their professional duties.

The first group consisted of 76 workers, who conducted at low temperatures from 2 to 4 hours. The second group included 110 sinkers, the time of cold exposure was from 6 to 8 hours per day.

All subjects were examined for anthropometric measurements with determination of growth, body mass index (BMI), waist circumference (WC), hip circumference (HC), WC/HC ratio. The body mass index was calculated as the ratio of the body weight (kg) to the height (m). When evaluating the body mass index, the criteria of the World Health Organization (WHO) were used. The waist circumference was measured in a standing position midway from the lower edge of the costal arch to the crest of the abdominal bone. The hip circumference was measured in the standing position at the level of the greater trochanteres of the femurs.

Glucose, total cholesterol, high-density lipoprotein (HDL), triglycerides (TG) were determined by the enzymatic method on an automated Labio 200 analyzer using Biocon kits (Germany).

Total RNA was isolated from the

peripheral blood with the use of the Trizol reagent. The quality of the obtained RNA samples was evaluated on the IMPLEN P-300 nanophotometer. After determining the quality, RNA samples were stored at -80°C.

Gene expression in PBMC was determined on CFX96 qPCR thermal cycler. The reverse transcription was carried out using the iScript cDNA synthesis kit (Bio-Rad), on T-100 Thermal Cycler (Bio-Rad). The reaction conditions were as follows: 5 minutes at 25°C, 30 minutes at 42°C, and 5 minutes at 85°C. Each PCR sample consisted of diluted cDNA sample (1:5), forward and reverse primer (1μM), SYBR Green PCR Master Mix (Bio-Rad) and DEPC water, total volume was 20 μl.

PCR reaction conditions: 15 minutes at 95°C, 1 minute at 60°C and 15 seconds at 95°C. The primers used in this study are shown in Table 1.

All studies were carried out with informed consent of the subjects in accordance with the ethical norms of the Helsinki Declaration (2000).

Statistical analysis of the study materials was carried out using the SPSS program (version 19). A check on the normality of the distribution of the quantitative indices studied was carried out according to the Kolmogorov-Smirnov test. The reliability of the differences between the mean values was estimated using Student's t-test for independent samples, the probability of a fair hypothesis was taken at $p \leq 0.05$. Correlation analysis was carried out according to Pearson. The data in the tables are presented in the form M±m, where M is the arithmetic mean, m is the error of the mean.

Results and discussion

In the statistical analysis of anthropometric data, we showed that workers with prolonged exposure in the cold (up to 9 hours a day) showed a significant decrease in weight ($r = 0.359$, $p = 0.01$) and, respectively, BMI ($r = 0.435$, $p = 0.00$) (Table 2).

Also, with a prolonged cold exposure (up to 9 hours a day), significantly decreases RT ($r = 0.263$, $p = 0.01$) and OB ($r = 0.171$, $p = 0.026$). The results of our work confirm the study by Saito M. et al (2009), in which the relationship between the presence of active BAT and the thinness of the examined individuals is proved. According to the literature, the average mass of BAT in the body of a healthy adult is about 50 grams. Despite the small amount in the body, BAT can have a disproportionately large metabolic effect.

According to the International Diabetes Federation, 10.9 million patients in Russia suffer from diabetes mellitus, 11.9 people have impaired glucose tolerance and impaired fasting glucose. Obesity, usually preceded by diabetes, occurs as a result of changes in blood glucose. Indeed, adipocytes regulate insulin resistance, where half of the lipids from white adipose tissue are depot and regulate insulin signals. Also, the relationship between the presence of BAT with depletion [17] and euglycemia [13] has been proved. These researchers suggest that adipocytes of brown adipose tissue can affect metabolic processes, such as obesity and diabetes. A unique feature of BAT is the expected effects of obesity and the control of excess glucose in the mitochondria, which contain the splitting protein 1 (UCP-1). UCP-1 cleaves oxidative phosphorylation by exclusion protons when entering the mitochondrial matrix, independent of the synthesis of ATP, which produces heat instead of chemical energy [3]. The study of rodents showed that after stimulation BAT consumes glucose and free fatty acids for thermogenesis (heat production), which proves the regulatory role of BAT in glucose homeostasis and insulin resistance.

At present, the physiological role of BJT in the activation of metabolic indicators in humans has not been adequately studied. Researchers Orava J. et al [14] and Ouellet V. et al [13] found that with a cold exposure, a 12-fold increase in the glucose concentration in the adipocytes of BAT is observed, but not in other tissues. This suggests that after activation, BAT promotes the consumption of glucose in the blood plasma. But despite this, these researchers did not show differences in the content of free-circulating glucose between the groups with the presence of BAT and the absence of BAT, which raises the question of the ability of adipocytes of BAT to influence glucose metabolism. When comparing two groups with different exposure times, we did not find any significant differences, the blood glucose in the subjects was within the normal range (Table 3).

The study of BAT in humans requires invasive techniques, such as adipose tissue biopsy or the use of positron emission tomography, which involves the use of radioactive isotopes. Therefore, it is necessary to use a safe and accessible source of biomarkers. Peripheral blood mononuclear cells (PBMCs) are readily available biological materials that can be used to study brown fatty tissue with minimal invasion. PBMCs constitute a fraction of the blood, consisting mainly of lymphocytes and monocytes. These cells circulate in the body and are responsible for internal and external signals expressing a large number of genes that include tissue-specific transcription and reflect metabolic adaptation. PBMCs are capable of producing about 80% of the entire genome, including tissue-specific transcripts. Although these cells can not express the main key thermogenetic gene of UCP1, these cells have the ability to produce other brown / beige markers such as Cidea, Hoxc9, Prdm16 and Slc27a1. Our study is the first on the effect of cold exposure on the expression of genes in PBMC in humans. We have found that a prolonged cold exposure increases the expression of the Browning markers Slc27a ($r = 0.421$, $p = 0.01$), Hoxc9 ($r = 0.164$, $p = 0.032$), Cpt1a ($r = 0.270$, $p = 0.00$) and Cidea $r = 0.187$, $p = 0.014$). The data obtained show that PBMCs can reflect changes in the expression of genes in response to cold and prove the usefulness of PBMC as a method for performing a study related to activation of brown adipose tissue in humans.

Conclusions

1. A significant negative correlation was found between weight, waist volume and hip volume, depending on the duration of exposure in the cold.

Table 1

Sequences of primers used for real-time PCR

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
Cidea	ATCGGCTCCTTAACGTGAA	AACCGCAGCAGACTCCTCA
Cpt1a	TCCACGATTCCACTCTGCTC	CAGCAACCCCGTGGCC
Hoxc9	CAGCAACCCCGTGGCC	CCGAGGTCCCTGGTTAAA
Prdm16	CCCAACAAGTACAGCCTGGA	GCGGATGAGGTTGGACTTCC
Slc27a1	GCGATATACCAGGAGCTGCA	TCTTGAAGGTGCCTGTGGTG
GAPDH (reference gene)	GTCGGAGTCAACGGATTTGGT	AGTGATGGCATGGACTGTGG

Cidea, cell death-inducing DNA fragmentation factor-α-like effector A; Cpt1a, carnitine palmitoyl transferase 1a; Hoxc9, homeo box C9; Prdm16, PR domain containing protein-16; Slc27a1, solute carrier family 27.

Table 2

Anthropometric characteristics of studied groups

	I group N=77	II group n=107
	Cold exposure (h)	
	2 – 4	5 –8
Age (years)	32,16±1,41	31,29±0,66
Height (cm)	170,72±0,67	171,81±0,56
Weight (kg)	75,66±1,34	71,32±1,24
BMI (kg/m2)	25,97±0,42	23,96±0,36
WC (cm)	89,11±1,74	83,15±1,41
HC (cm)	96,15±1,50	93,62±1,37
WC/HC	0,91±0,01	0,83±0,02

Table 3

Biochemical indicators depending on the duration of exposure in the cold

Indice	I group n=76	II group n=110
	M±m	
Glucose, (mmol/L)	5,41±0,14	5,18±0,98
TG (mmol/L)	1,32±0,09	1,15±0,05
Cholesterol (mmol/L)	4,63±0,75	4,64±0,07
Cholesterol HDL (mmol/L)	1,19±0,28	1,39±0,03
Cholesterol LDL (mmol/L)	2,80±0,08	2,69±0,08
Cholesterol VLDL (mmol/L)	0,59±0,04	0,53±0,02
Atherogenic coefficient	3,13±0,14	2,55±0,11

2. The weight, waist and thigh size of the subjects were reduced with prolonged exposure in the cold.

3. At the analysis of biochemical parameters it is not revealed essential changes. We show reliable correlation links between the markers of the Browning process and the exposure in the cold.

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The authors

1. Efremova Agrafena Vladimirovna - Candidate of Biological Sciences, Senior Researcher, DAMS YSC CMP, Yakutsk, Russia, PhD student at Università Politecnica delle Marche;

2. Tomskiy Mikhail Innokentievich - Doctor of Medical Sciences, Professor, Yakutsk, Russia;

3. Saverio Cinti - MD, professor at Università Politecnica delle Marche, Director, Biology of Obesity-Diagnostic Electron Microscopy United Hospitals of Ancona Director Obesity Center University of Ancona;

4. Isakov Yevgeny Andreevich - junior researcher, DAMS YSC CMP, pathologist at NCM-RH1, Yakutsk, Russia;

5. Alekseev Vladislav Amirovich - junior researcher, DAMS YSC CMP, Yakutsk, Russia;

6. Grigoryeva Anastasiya Anatolievna - junior researcher, DAMS YSC CMP, Yakutsk, Russia;

7. Konstantinova Lena Ivanovna – researcher, DAMS YSC CMP, Yakutsk, Russia;

8. Okhlopkova Elena Dmitrievna - Candidate of Biological Sciences, Leading Researcher, DAMS YSC CMP, Yakutsk, Russia;

9. Yakovleva Alexandra Ivanovna - junior researcher, DAMS YSC CMP, Yakutsk, Russia;

10. Olesova Lyubov Dygynovna - Candidate of Biological Sciences, Leading Researcher, DAMS YSC CMP, Yakutsk, Russia;

11. Semenova Evgenia Ivanovna - Candidate of Biological Sciences, Senior Researcher, DAMS YSC CMP, Yakutsk, Russia;

12. Krivoshapkina Zoya Nikolaevna - Candidate of Biological Sciences, Senior Researcher, DAMS YSC CMP, Yakutsk, Russia.

Z.N.Krivoshapkina, G.E.Mironova, E.I.Semenova, L.D.Olesova, A.I.Yakovleva

LIPID METABOLISM IN THE NON-INDIGENOUS POPULATION OF YAKUTIA DEPENDING ON LENGTH OF STAY IN THE NORTH

ABSTRACT

Changes in lipid metabolism, depending on the length of residence in the North, in the winter season in the non-indigenous population of Yakutia, aged 18 to 62 years, were examined. It was revealed that the adaptation of the organism to the North conditions is accompanied by changes in lipid metabolism. In the first year of residence in the North in the blood serum high cholesterol is compensated by increasing the content of HDL cholesterol and APO A-I. This is indicated by the coefficient of atherogenicity, which varies within the limits of normal values. At residence in the North from 2 to 5 years lipid metabolism indicators correspond to normal values; after 5 years - there is an increase in the level of cholesterol and atherogenicity coefficient due to an increase in LDL cholesterol.

Keywords: adaptation, indicators of lipid metabolism, the North.

Introduction

Adaptive changes in the human body to the conditions of the North have a number of common physiological signs: the stage of the process, the absence of a definite period for each stage, the passage of several phases in adaptive rearrangements. All these adaptive changes correspond to the formula proposed by G. Selye (1977): anxiety, stress, exhaustion [8].

In high-latitude conditions, adaptation is carried out by enhancing lipid metabolism, which is beneficial to the body, since the oxidation of fats produces more energy than glucose oxidation.

The goal of the study was to study the changes in lipid metabolism parameters depending on the time of residence in the North.

Material and methods. Studies were conducted in the winter season. A total of 318 newly arrived residents of Yakutia aged 21 to 67 years were surveyed, the average age was 46.91 ± 2.72 years.

Exclusion criteria from the study were exacerbations of chronic diseases, the presence of oncological, infectious and viral diseases. Were also excluded individuals with coronary artery disease, past heart attack and stroke in anamnesis To assess the objective state, a survey was conducted on the questionnaire developed at the Yakutsk Scientific Center of Complex Medical Problems of the Siberian Branch of the Russian Academy of Medical Sciences; received informed consent of respondents to conduct research, taking blood.

Blood for biochemical research was taken from the ulnar vein in the morning hours on an empty stomach 12 hours after meals.

Determination of total cholesterol (CH), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol) was performed by the enzymatic method.

Low-density lipoprotein cholesterol (LDL cholesterol) and very low-density lipoprotein cholesterol (VLDL cholesterol) were calculated by the formula Friedewald et al. (1972) [9]. The coefficient of atherogenicity was calculated according to the formula proposed by A. Klimov. (1977) [5].

Apoproteins apo A-I and apo B were determined by immunoturbidimetric method using La Roche reagents. The method is based on measuring the fine suspension, formed as a result of the immunological reaction of anti-apoproteins with antibodies. By the degree of development of turbidity, the concentration of apoproteins is judged.

Behind hypercholesterolemia taken a cholesterol level ≥ 5.0 mmol/l, increased level of LDL cholesterol is ≥ 3.0 mmol/l, reduced levels of HDL cholesterol – ≤ 1.0 mmol/l in men and 1.2 ≤ in women. Hypertriglyceridemia attributed levels of TG ≥ 1.7 mmol / l.

All biochemical studies were performed on an automatic biochemical analyzer Cobas Mira Plus by La Roche (Switzerland) using Biocon reagents (Germany).

The statistical processing of the data was carried out using the SPSS Statistics 17.0 application statistical software package. Standard methods of variational statistics were used: calculation of mean values, standard errors, 95% confidence interval. The data in the tables are presented in the form M ± m, where M is the mean, m is the mean error. The reliability of the differences between the averages was estimated using the t Student-Kolmogorov-Smirnov test. Probability of the validity of the null hypothesis was assumed for $p < 0.05$. Correlation analysis was performed using the Pearson and Spearman method.

Indicators of lipid metabolism depending on the period of residence in the North (mmol /L)

Indicators of lipid metabolism	1 year (n=17)	From 2 to 5 years (n=25)	5-9 years (n=18)	10-19 years (n=43)	More than 20 years (n=215)
TG	0,99±0,11	1,16±0,43	1,45±0,20	1,11±0,08	1,18±0,04
Cholesterol	6,36±0,37	4,96±0,51	6,16±0,27	6,24±0,21*	6,19±0,08*
HDL cholesterol	2,0±0,12	1,40±0,09	1,58±0,13	1,66±0,07	1,54±0,03
LDL cholesterol	3,49±0,32	3,02±0,40	3,95±0,26	4,02±0,19	4,13±0,07
VLDL cholesterol	0,31±0,05	0,53±0,20	0,66±0,09	0,54±0,06	0,54±0,02
Atherogenic coefficient	2,93±0,51	2,62±0,54	3,29±0,41	2,94±0,23	3,19±0,09

*Note: * compared with the group with experience up to 5 years $p < 0.05$.

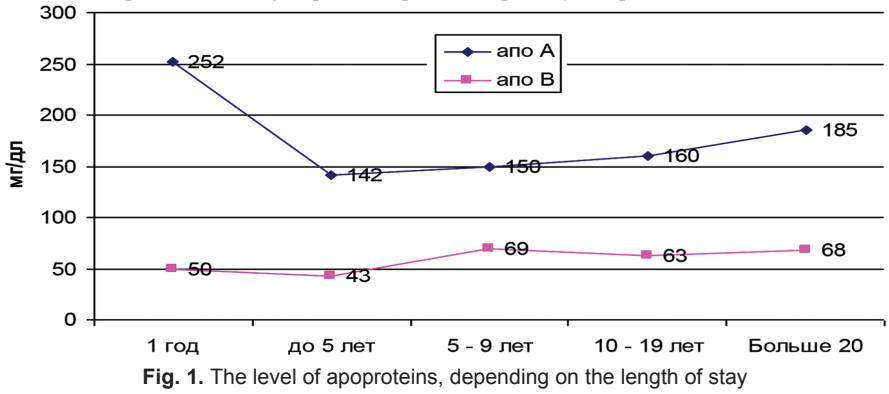

Fig. 1. The level of apoproteins, depending on the length of stay

Results and discussion. The energy supply of adaptation reactions is a very complex biochemical process. It should be borne in mind that adaptation to the severe natural and climatic conditions of the North requires an increase in the energy metabolism of the organism and the transition from the carbohydrate type of metabolism to fat, as the role of lipids in the energy supply of adaptive reactions increases [4].

Analysis of the dependence of the state of lipid metabolism on the time of residence showed that the alien population had the highest value of total cholesterol in the first year of residence in the North. The increase in the level of HDL cholesterol in the blood 1,2 - 1,4 times in this period in comparison with other groups indicates the adequate mobilization of body reserves, as a result of which there are no atherogenic changes in blood (Table 1).

In the studies of Novosibirsk scientists it was shown that adaptive changes in the body lead to significant changes in the lipid metabolism. We received a high level of HDL cholesterol in newly arrived people to the North also does not contradict the literary data [7].All these shifts in lipid metabolism indicators reflect the mobilization of energy resources for the adequate functioning of tissue metabolic pathways in response to the combined effects of natural climatic stimuli and social factors [2].

At the periods of residence from 2 to 5 years, there is «stabilization and synchronization of regulatory and homeostatic processes» [3], which is expressed in the normalization of lipid metabolism. In our studies, signs of destabilization in the newly arrived residents began after 5 years of residence in the North. In this group of visitors, dyslipidemia was characterized by expressed hypertriglyceridemia, increased levels of total cholesterol and LDL cholesterol. In groups with «northern experience» of more than 10 years, dyslipidemia was caused by an increase in the blood of total cholesterol and LDL cholesterol. In these groups, the TG level was relatively low in comparison with the group of persons with an experience of 5-9 years.

The increase in blood levels of antiatherogenic and atherogenic fractions of cholesterol, associated with the duration of residence in the North, indicates an adaptive character of the lipid spectrum change, although the increase in HDL is not fully compensated for dyslipidemia, as confirmed by the high atherogenicity coefficient.

Our data on the increase in the level of HDL cholesterol associated with the duration of residence in the North are consistent with the literature data, but in these studies, unlike our studies, the coefficient of atherogenicity corresponded to normal values [1,6].

The content in the blood of apoproteins also had some differences, depending on the length of residence in the North. So, in the first year of arrival, the level of apo A-I, the main transport protein of HDL, was 1.4-1.8 times higher than in individuals with a longer residence time in the North. Subsequent decrease in the content of apo A-I (experience up to 5 years) was associated with normalization of lipid metabolism. The relative increase in blood apo A-I in the studied groups was associated with an increase in the blood of HDL cholesterol (Figure 1).

The level of apo B, which is a protein that carries all the triglyceride-rich atherogenic lipoproteins - VLDL, LDL, did not differ significantly in these groups, depending on the northern experience, although it tended to increase with increasing «northern experience».

Thus, the adaptation of the human body to the conditions of the North is accompanied by changes in lipid metabolism. In the first year of life in the north in the serum, high cholesterol is compensated by an increase in cholesterol-lowering cholesterol and apo A-I. This is indicated by the coefficient of atherogenicity, which varies within the limits of normal values. From 2 to 5 years, the values of lipid metabolism correspond to normal values; after 5 years of life, there is an increase in the level of cholesterol and the coefficient of atherogenicity due to the increase in LDL cholesterol.

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The authors

1. Krivoshapkina Zoja Nikolaevna, Candidate of Biological Sciences, the senior researcher of Laboratory of Biochemical Research of the Department for Studying Adaptation Mechanisms FSBSI «Yakutsk Scientific Center for Complex Medical Problems», zoyakriv@mail.ru.

2. Mironova Galina Egorovna, Doctor of Biological Sciences, professor of the Department of Natural Sciences Institute FSAEI HVE «North-Eastern Federal University» named after M.K.Ammosov, mirogalin@mail.ru.

3. Semjonova Evgenija Ivanovna, Candidate of Biological Sciences, the senior researcher of Laboratory of Biochemical Research of the Department for Studying Adaptation Mechanisms FSBSI «Yakutsk Scientific Center for Complex Medical Problems», kunsuntar@mail.ru.

4. Olesova Ljubov' Dygynovna, Candidate of Biological Sciences, leading researcher of Laboratory of Biochemical Research of the Department for Studying Adaptation Mechanisms FSBSI «Yakutsk Scientific Center for Complex Medical Problems», oles59@mail.ru.

6. Yakovleva Alexandra Ivanovna, junior researcher of Laboratory of Biochemical Research of the Department for Studying Adaptation Mechanisms FSBSI «Yakutsk Scientific Center for Complex Medical Problems», sashyak@mail.ru.

L.D. Olesova, G.E. Mironova, Z.N. Krivoshapkina, E.I. Semenova, S.I. Sofronova, A.I. Yakovleva, A.V. Efremova, L.I. Konstantinova, E.D. Okhlopkova

COMPARATIVE ASSESSMENT OF THE FREQUENCY OF DYSLIPIDEMIA AMONG THE INDIGENOUS POPULATION OF THE ARCTIC ZONE OF YAKUTIA

ABSTRACT

One-stage population studies of biochemical markers of the lipid transport function of the indigenous population in the Arctic, Central and Southern zones of Yakutia have been carried out. An increase in the content of triglycerides and cholesterol and atherogenic fractions of lipids in the population from the north to the south was noted. Atherogenic changes in lipid metabolism are more pronounced in the arctic Yakuts, than in Dolgans, living in the same zone, and Evens of the Southern zone, which indicates a lower susceptibility to a disadaptive change in lipid metabolism in the Dolgans and the Evens.

Keywords: dyslipidemia, indigenous population, Arctic.

Introduction

Cold is one of the factors limiting activity of a human body. The most northern inhabited territory is the Arctic where living conditions differ in the maximum extremeness. The Arctic zone of the Russian Federation includes 2/5 of the Sakha (Yakutia) Republic territory. According to bioclimatic zoning by the magnitude of the complex cooling effect and the coefficient of discomfort, this area belongs to the extreme-severe zone, which is characterized by prolonged exposure to cold, strong winds, powerful heliomagnetic disturbances, specific photoperiodicity and permafrost.

It is known that under the influence of external high-latitude factors in the indigenous population in the process of long-term adaptation, certain metabolic and morphofunctional features were formed, aimed at maintaining homeostasis. A characteristic feature of the northern metabolism, a «polar metabolic type» (E.L. Panin, 1978) is an increase in the role of lipids for the intensification of energy processes and an increased content of unsaturated fatty acids in tissues and blood that are faster incorporated into catabolism and compensated by diet as the most important manifestation of human adaptation in the North [1, 4, 8]. The protein - lipid type of nutrition can be considered a prevention of the development of alimentary - dependent diseases, since the metabolism of indigenous lipids is characterized by a lower content of total cholesterol, triglycerides and a higher level of antiatherogenic fraction of lipoproteins [1, 7, 9].

A healthy, educated, able-bodied population is the key to the development of the economy, and, consequently, the quality of life. The implementation of national interests in the Arctic, noted in the development strategy of the Arctic zone of the Russian Federation and ensuring security for the period until 2020, requires the improvement of demographic processes [12]. The worsening of the demographic indicators of the population of the Arctic zone in recent decades indicates the manifestation of disadaptive processes. Depopulation in the Arctic regions of Yakutia is associated, mainly, with high mortality of the population from diseases of the circulatory system (345.7 per 100.000 people) [3, 13].

Disruption of adaptation, which is caused by biochemical disruption of the functioning of regulatory and protective systems of the body, underlies the development of various pathologies. Timely detection of persons with signs of disadaptation, in particular lipid imbalance and the restoration of body reserves, is the main task of preventive measures to preserve public health and to justify the need for investment in the development of public health in general and Arctic medicine in particular.

Purpose of the study: comparative assessment of lipid metabolism in a population sample of indigenous residents of the Arctic zone of Yakutia.

Materials and methods of research

The material was collected in winter time at one-stage population random sample research of an indigenous population in the Arctic zone (Anabary and Srednekolymsky districts).The comparison groups comprised samples of the indigenous population of the Central (Megino-Kangalassky, Gorny districts) and Southern (Lensky, Ust-Maysky districts) zones of the Sakha Republic (Yakutia). In total 678 people aged 18 to 68 years were examined - 406 women and 272 men. The average age in the groups was 45 years. All participants in the study were representatives of indigenous populations: the Yakuts, Dolgans, Evens.

To assess the objective state, a survey was conducted on the questionnaire developed at the FSBSI «Yakut scientific center of complex medical problems». We received informed consent from respondents for research and blood donation. Blood for biochemical research was taken from the ulnar vein in the morning on an empty stomach, 12 hours after eating.

Biochemical parameters were determined by the enzymatic method using standardized sets on a biochemical analyzer: the level of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol). The concentration of low-density lipoprotein cholesterol (LDL cholesterol) and very low-density lipoprotein cholesterol (VLDL cholesterol) was calculated by the formula of Friedewald et al. [17]. Assessment of lipid and lipoprotein content of blood plasma was carried out in accordance with the criteria of NCEP ATP III (2001) [16]. To assess atherogenic disorders of blood lipid profile, the following markers of atherogenicity were used: the ratio of total cholesterol to high-density lipoprotein cholesterol (Chol / HDL - C) (more than 5), low density lipoprotein cholesterol to high (LDL-C / HDL-C) (more than 3.3), atherogenicity coefficient (Ca) (more than 3). (Ca) was calculated by A.V. Klimov formula (1990): Ca = TC - HDL - C / HDL - C. The indicator Ca more> 3.1 is used as a marker of the risk of atherosclerosis development [6].

Statistical processing of the results was carried out using the SPSS 11.5 for Windows software package. At performing the statistical analysis, the normality test for the distribution of the quantitative indicators studied was

carried out according to the Kolmogorov-Smirnov test. The data of the descriptive analysis are presented in the form of M ± m and median, where M is the mean value, m - is the standard error of the mean value. At comparing the quantitative indices of the groups, the significance of the differences was assessed using the Student's t-test and ANOVA using the Bonferroni method for independent samples with normal distribution and the Mann-Whitney test for an abnormal distribution. The threshold level of statistical significance was taken at the value of the criterion p <0.05.

Results and discussion

The examined population within the zones was divided into 3 groups according to the level of total cholesterol. One group included individuals with a «normal» level of total cholesterol, equal to or below 5.2 mmol / l, the other - those with a «borderline high» level of total cholesterol, equal to 5.21-6.19 mmol / l and the third - individuals with a «high» level of total cholesterol, equal to and above 6.2 mmol / l.

In a percentage ratio, the occurrence of «normal» cholesterol levels in the blood is higher among the Arctic population, a «borderline high» level of total cholesterol falls on the Central zone population. A lower percentage of the frequency of occurrence of the «high» level of TC is found among the population of the Arctic zone (8.2%), which is 8.8% lower than in the Central, and 13.5% - than in the Southern zone (Fig. 1).

Summing of the percentages of the occurrence of «borderline high» and «high» total cholesterol levels in the zones showed that in the surveyed population of the Arctic zone the incidence of high cholesterol is lower (34.5%) than in the Central and Southern zone by 16.9% and 7.1 % respectively.

Comparison of the percentages of the occurrence of «normal» and «borderline high» total cholesterol content with respect to the «high» total cholesterol content in each zone showed a more favorable picture in the Arctic zone. The proportion of people with "normal" cholesterol among the arctic population is 2 times higher than in the inhabitants of the central and southern zone (Fig. 2).

However, the evaluation of the values of markers of atherogenicity among groups with «normal», «borderline high» and «high» levels of total cholesterol within the zones revealed a rather high incidence of atherogenic disorders, even among groups with normal cholesterol level (Table 1).

Thus, in the group with "a normal" level of cholesterol of the Arctic zone, the mean percentage of occurrence of atherogenic disorders was 24.8%, in the Central zone group - 38.7%, in the Southern zone group - 25.2%. In groups with a «borderline high» level of cholesterol, the percentage of occurrence of atherogenic disorders in the Arctic zone averaged 36%, in the Central zone 24.7%, in the Southern zone 45.9%. In groups with a «high» level of cholesterol, the occurrence of atherogenic disorders is lower in the Central zone (29%), in the Arctic zone an average of 45.7% and the highest in the Southern zone - 56.7%.

As follows from Table 2, the total cholesterol content exceeded the norm for residents of the Southern zone. The content of triglycerides, lipoprotein cholesterol does not go beyond the limits of normal values.

Determination of the significance of differences in the non-parametric Mann-Whitney method showed significant differences between the mean values of the Arctic and Southern zones in the content of triglycerides, high-density lipoprotein cholesterol and very low density lipoprotein cholesterol. An increase in the level of TG, total cholesterol and VLDL cholesterol is observed in the direction from north to south. The content of the HDL-C anti-atherogenic fraction was lower in the Southern zone and higher in the Central zone.

Analysis of mean values of markers of atherogenicity by zones showed that the coefficient of atherogenicity (Ca) in all zones exceeded the norm, which indicates a chronic tension of the organism. The indicators of TC / HDL-C and LDL - C / HDL-C, unlike Ca, did not go beyond normal values, lower values of three markers of atherogenicity were found in the inhabitants of the Central zone (Table 3).

Comparative analysis of average lipogram data by sex and ethnicity did not reveal significant differences. An analysis of the frequency of occurrence of atherogenic disorders, depending on ethnic factors and the zone of residence, showed that the occurrence of dyslipidemia in all ethnic groups is quite high. In the Arctic zone, in percentage terms, atherogenic changes are more common in the Yakuts than in Dolgans. In the Southern zone the same tendency is observed: in the Yakuts the occurrence of atherogenic disorders is greater than in the Evens (Table 4). This indicates a process of changing the gene phenotypically conditioned adaptation mechanisms of indigenous people in the cold climate of the North, based on the traditional way of life i.e. high physical exertion with prolonged cold exposure and asian protein-lipid type of nutrition. In the opinion of V.V. Tsukanov. et al. [14] the leading cause of stable metabolism of lipids and low frequency of so-called «metabolic» diseases in a number of ethnic groups of Mongoloids of Siberia is the ability of the liver to active cholesterol esterification, intensive synthesis of bile acids and efficient transportation of sterols to bile.

L.I. Kolesnikov et al. [5] believe that on the scale of evolution a fairly rapid change in the nature of nutrition in favor of the prevalence of the carbohydrate part of the diet occurs, in the north aborigines an intensive transformation of the protein-lipid type of metabolism

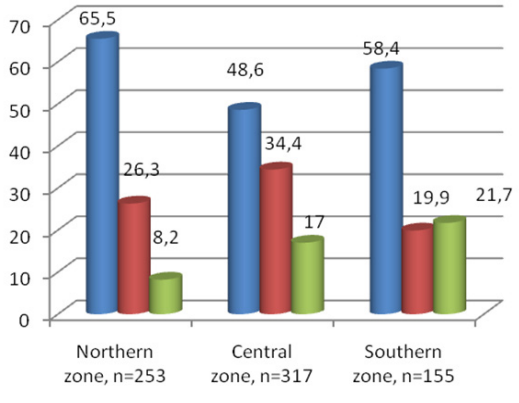
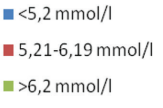


Fig.1. Distribution of the researched people by the level of total cholesterol in the zones of Yakutia (%)



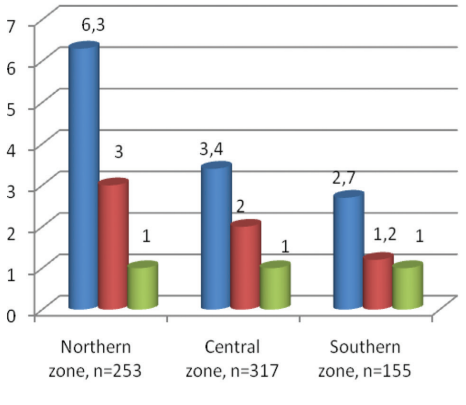


Fig.2. Ratio of the proportion of «normal», « «borderline high» and «high» level of total cholesterol within the zones of Yakutia

into protein-carbohydrate continues. The formation of the type of metabolism of the population is slower than the nature of nutrition changes, and this fact can be the cause of the development of metabolic disadaption or alimentary dependent diseases [5].

If we compare the percentage indices of the atherogenic coefficient among the Yakuts by zones (Table 4), then we can say that the frequency of dyslipidemia is the greatest in the northern Yakuts. The share of atherogenic changes in the zones does not differ sharply, which indicates the signs of a violation of the mechanisms of population adaptation to the changing external factors of the environment, not only climatic, but also to whole complexes of socioeconomic, technogenic and other factors that led to a drop in the quality of life. The main negative factors are a drop in the level of medical care for remote settlements, a complicated transport scheme, low income, unemployment, depression, alcoholism, problems of northern delivery, problems of development of traditional sectors of the arctic economy, increasing pollution of the environment, violation of vulnerable ecosystems in conditions of modern nature management [11, 13, 15]. Medical and social studies conducted in Yakutia have shown that a high level of personal anxiety among rural residents is primarily associated with a low standard of living [10]. A state of prolonged emotional stress is one of the reasons for the disruption of adaptive reactions of the organism [2].

Conclusions

1. Percentage ratio of the frequency of occurrence of the «normal» level of total cholesterol by zones in Yakutia shows that in the population of the Arctic zone the proportion of people with normal cholesterol is greater than in other zones.

2. The detected atherogenic shifts in the lipogram in individuals with a «normal» cholesterol level indicate the onset of changes in the lipid transport system. A greater imbalance in lipid metabolism was found in the inhabitants of the Central zone.

3. Reliable dependence of mean values of triglycerides, HDL-C, VLDL - C and markers of atherogenicity from the zone of residence is expressed in an increase in the level of TG, CHOL, LDL-C, LDLP-C from the north to the south. The content of the anti-atherogenic cholesterol fraction is lower in the Southern zone and higher in the Central zone.

4. According to the frequency of atherogenic shifts of the lipogram depending on ethnic factors, the disadaptive change in the body's lipid transport system is more pronounced in the northern Yakuts than in the Dolgans of the Arctic zone and Evens of the Southern zone.

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Table 1

The frequency of atherogenic disorders, depending on the level of cholesterol in the zones of Yakutia (%)

The level of total cholesterol, mmol/l	Zone of Yakutia	Ca		CHOL/ HDL-C		LDL-C / HDL-C	
		<3,0	>3,0	<5	>5	<3.2	>3,2
=or<5,2	Arctic	62,9	37,1	85,4	14,6	77,2	22,8
	Central	55,2	44,8	55,2	44,8	73,4	26,6
	South	65,5	34,5	80,5	19,5	78,2	21,8
5,21-6,19	Arctic	61,2	38,8	66,6	33,4	64,2	35,8
	Central	65,1	34,9	81,7	18,3	78,9	21,1
	South	43,3	56,7	65,5	34,5	53,3	46,7
=or>6,2	Arctic	71,4	28,6	45,5	54,5	45,5	54,5
	Central	59,3	40,7	77,8	22,2	75,9	24,1
	South	27	73	54,1	45,9	48,6	51,4

Table 2

The content of triglycerides and cholesterol depending on the zone of residence, mmol / l

Zone	Statistics	TG	CHOL	HDL-C	LDL-C	VLDLP-C
Arctic	Mean	0,95±0,02	5,05±0,05	1,24±0,02	3,40±0,04	0,44±0,01
	Median	0,83	4,95	1,18	3,33	0,39
Central	Mean	0,96±0,02	5,20±0,06	1,34±0,02	3,42±0,05	0,45±0,01
	Median	0,88	5,18	1,32	3,39	0,40
South	Mean	1,07±0,02	5,72±0,06	1,31±0,02	3,61±0,10	0,51±0,01
	Median	0,97	5,62	1,15	3,45	0,44
Significance of differences		$P_{1,3}$<0,007		$P_{1,2}$<0,000		$P_{1,3}$<0,006
		$P_{2,3}$<0,002		$P_{2,3}$<0,032		$P_{2,3}$<0,005

Note: In the Tables 2-3 the significance of the differences is determined by the Mann-Whitney t- criterion.

Table 3

Mean value of markers of atherogenicity by zones of Yakutia

Zone	Статистика	Ca	CHOL/ HDL cholesterol	LDL cholesterol /HDL cholesterol
Arctic	Mean	3,29±0,07	4,28±0,07	2,89±0,06
	Median	3,2	4,19	2,81
Central	Mean	3,09±0,08	4,08±0,07	2,72±0,06
	Median	2,90	3,91	2,56
South	Mean	3,33±0,10	4,30±0,07	2,86±0,08
	Median	3,0	4,02	2,66
Significance of differences		$P_{1,2}$<0,019 $P_{1,3}$<0,050	$P_{1,2}$<0,020	$P_{1,2}$<0,022

Table 4

Frequency of occurrence of dyslipidemia by nationality and zones of Yakutia,%

Zone	National.	Ca		CHOL/ HDL-C		LDL -C /HDL-C	
		<3,0	>3,0	<5	>5	<3,2	>3,2
Arctic	Yakuts N=107	42(39)	65 (61)	76 (71)	31(29)	63(59)	44(41)
	Dolgans N=147	76(52)	71(48)	116(79)	31(21)	98(67)	49(33)
Mean	N=254	118(46,4)	136(53,6)	192(76)	62(24,4)	161(63)	93(37)
	Yakuts N=271	161(59)	111(41)	215(79)	59(22)	196(72)	76(28)
South	Yakuts N=70	34(48,5)	36(51,5)	47(67)	23(33)	44(63)	26(37)
	Evens N=83	57(68)	26(32)	62(74)	21(28)	59(71)	24(29)
Mean	N=153	91(60)	62(40)	109(71)	44(29)	103(67)	50(33)

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The authors:

1. Olesova Ljubov' Dygynovna, PhD (Biology), head of Laboratory of Biochemical Research of the FSBSI «Yakut Scientific Center of Complex Medical Problems», 677010, Yakutsk, Sergelyakhskoye shosse, 4, oles59@mail.ru:

2. Krivoshapkina Zoya Nikolaevna, PhD (Biology), Senior Researcher, Department for studying adaptation mechanisms of FSBSI «Yakut Scientific Center of Complex Medical Problems», 677010, Yakutsk, Sergelyakhskoye shosse, 4; zoyakriv@mail.ru;

3. Semenova Evgenija Ivanovna, PhD (Biology), Senior Researcher, Department of the study of adaptation mechanisms of the FSBSI «Yakut Scientific Center of Complex Medical Problems», 677010, Yakutsk, Sergelyakhskoye shosse, 4, kunsuntar@mail.ru;

4. Sofronova Sargylana Ivanovna, PhD (Medicine), head of Scientific-organizational and information publishing Department, 677010, Yakutsk, Sergelyakhskoye shosse, 4, sara2208@mail.ru;

5. Yakovleva Alexandra Ivanovna, Senior Researcher, Department of the study of adaptation mechanisms of the FSBSI «Yakut Scientific Center of Complex Medical Problems», 677010, Yakutsk, Sergelyakhskoye shosse, 4; sashyak@mail.ru;

6. Efremova Agrafena Vladimirovna, PhD (Biology), Department for studying adaptation mechanisms of the FSBSI «Yakut Scientific Center of Complex Medical Problems»677010, Yakutsk, Sergelyakhskoye shosse, 4; a.efremova01@mail.ru;

7. Konstantinova Lena Ivanovna, Researcher, Department for studying adaptation mechanisms of the FSBSI «Yakut Scientific Center of Complex Medical Problems» 677010, Yakutsk, Sergelyakhskoye shosse, 4, konstanta.l@mail.ru;

8. Okhlopkova Elena Dmitrievna - PhD (Biology), Leading researcher-head of the laboratory of immunological studies, Department for studying adaptation mechanisms of the FSBSI «Yakut Scientific Center of Complex Medical Problems», 677010, Yakutsk, Sergelyakhskoye shosse, 4, elena_ohlopkova@mail.ru;

9. Mironova Galina Egorovna, Doctor of Biological Sciences, Professor of Biological Branch of Institute of Natural Sciences, North-Eastern Federal University. M.K. Ammosov, Yakutsk, Belinskogo, 58, mirogalin@mail.ru.

Nikolaev V.M., Alekseev R.Z., Fedorova S.A.

INTENSITY OF LIPID PEROXIDATION IN PATIENTS WITH COLD INJURY

ABSTRACT

The authors report their study on the intensity of lipid peroxidation processes and the state of antioxidant protection in patients with cold trauma of varying severity. It was established that in the organism of patients with frostbite of extremities, the intensity of free radical oxidation and the level of antioxidant defense depended on the degree of frostbite.

Clinical and biochemical studies were conducted in 151 people, 81 of whom were patients with a cold trauma of varying severity, who entered the burn department of the Republican Hospital №2. The control group included 70 practically healthy people. The material of the study was fasting venous blood samples, drawn from the ulnar vein.

The parameters of the intensity of free radical lipid oxidation (malonicdialdehyde, diene conjugates) and antioxidant protection (low-molecular antioxidants, activity of superoxide dismutase, catalase, glutathione peroxidase, glutathionereductase) were determined by spectrophotometric methods. Clinical and biochemical parameters in blood serum were determined on the biochemical automatic analyzer CobasMiraPlus (Roche).

In the body of patients with frostbite of the extremities of the first and second groups, a significant increase in the parameters of lipid peroxidation - MDA and DC - is observed. In patients of the second group, the intensity of lipid peroxidation processes was higher than in patients of the first group.

The state of the body's antioxidant defense depends on the severity of the injury. In patients of the first group, the activity of SOD is increased by 8 times, CAT by 1.3 times, HP by 1.7 times, and GR activity decreased by 1.9 times in comparison with the control. The concentration of LMWA increases 2.1 times, and the content of ascorbic acid decreases by 1.2 times. In patients of the second group with respect to control, the activity of SOD increases 12.6 times, catalase 1.1 times, HP 1.5 times, and GH activity decreased 2.8 times. The content of LMAO increases 1.5 times, and the level of ascorbic acid in the blood decreases 2.4 times.

The shift in the prooxidant-antioxidant equilibrium toward the intensification of free radical reactions is also indicated by an increase in the coefficients: KSOD / CAT, KSOD / HP. The values of the coefficients (KSOD / CAT, KSOD / GP) depend on the severity of the cold trauma.

Keywords: lipid peroxidation, antioxidant protection, cold trauma, catatoxic and syntoxic adaptation programs.

Introduction

The cold in the Far North potentiates the development of not only adaptive rearrangements (cold adaptation), but the emergence of pathologies too (cold trauma). Under the cold trauma, most authors mean the effect of negative temperatures, leading to frostbite [5]. Cold trauma is one of the most common types of thermal trauma, which comprises almost 10% of all surgical diseases [20] and has a well-defined seasonal character. In Yakutia, where winter lasts 6-7 months in a year and the temperature drops to -60°C, these figures are much higher [14]. Despite some successes achieved in the treatment of cold trauma, some pathogenesis issues remain poorly understood. When using the traditional methods of treatment of cold trauma, 30-60% of the patients become severely disabled. This extremely high level of disability is a clear confirmation of the unresolved problem [1].

The few data, available in the literature, indicate that the effect of low temperatures on human and experimental animals is accompanied by the activation of free radical processes [9, 10]. Moderate activation of lipoperoxidation processes in response to the effect of an unfavorable factor is one of the variants of adaptation mechanisms and is aimed at increasing the permeability of the cell membrane and facilitating the work of membrane proteins. However, beyond certain limits, these shifts can become a pathogenetic factor by themselves, which are manifested by denaturation and inactivation of proteins, delipidization of membranes, disruption of cell division and growth [4]. Thus, the intensity of the processes of lipid peroxidation and the state of its main regulator - the antioxidant system - under the influence of cold on the human body as a stressful environmental factor, requires further study.

The objective of the study was to estimate the intensity of lipid peroxidation processes and the state antioxidant defense in the body of patients with cold trauma of varying severity.

Materials and methods

Clinical and biochemical studies were conducted on 151 people, 81 of whom were patients with a cold trauma of varying severity, who were admitted to the burn trauma department of the Republican Hospital No. 2 in Yakutsk. Among the injured were 74 men and 7 women. Patients were hospitalized in 1-5 days after receiving a cold injury, i.e. in the reactive period. Depending on the degree of frostbite, the patients were divided into two groups: the first group consisted of 35 patients with first and seconddegree frostbites, the second - 46 patients with the third and fourthdegree frostbites. The manifestation of frostbite in both groups was characterized by changes depending on the severity of the injury. The control group included 70 healthy people. The material of the study was fasting venous blood samples, drawn from the ulnar vein.

The study was approved by the local Committee on Biomedical Ethics at the Yakutsk Scientific Center of Complex Medical Problems (Yakutsk, Protocol 8, October 10, 2007). Patients and healthy subjects received informed consent for taking biological samples (venous blood) and participation in this study.

The intensity of lipid peroxidation was determined by the accumulation of malonicdialdehyde (MDA) [18] and diene conjugates (DC) [7] using spectrophotometric methods. The antioxidant defense system parameters of the organism were determined by the total content of low-molecular weight antioxidants (LMWA) [16] and the activity of superoxide dismutase (SOD) [22], catalase (CAT) [12], glutathione peroxidase (GPx) [7] and glutathione reductase (GR) [7]. Clinical and biochemical parameters: the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total protein, glucose, triacylglyceride (TAG) and urea in blood weretested on the automatic biochemical analyzer "COBAS MIRA Plus" (Roche).

Statistical processing of the data was carried out on a package of applied statistical programs SPSS Statistics 17. Standard methods of variational statistics

were used: calculation of average values, standard errors, 95% confidence interval. The reliability of the differences between the averages was estimated using the Student's t-test for independent samples. The data in the tables are presented in the form "M±m", where M is the mean, m is the mean error. Probability of the validity of the null hypothesis was assumed for p<0.05.

Results and discussion

According to our data, the rate of free radical reactions in the body caused by cold trauma depended on the degree of frostbite (Table 1). In patients of the first group, the MDA content was 1.8 times higher than the control, while in the second group the MDA level exceeded the control value by a factor of 2. The concentration of DC in the first group of patients was 1.9 times higher than control, and in the second group - 2.5 times.

Activation of lipid peroxidation in both groups of patients with cold trauma can be explained as an adaptive response of the organism to stress effects, since free radicals are a link in the development of urgent and long-term adaptation. At the stage of urgent adaptation, a deficit of macroerges arises in the cell, which leads to a «respiratory explosion» and excessive generation of reactive oxygen species, initiators of lipid peroxidation. Thus, the formation of a structural trace in the body under the influence of a stressing factor, including low temperatures, is accompanied by an acceleration of free-radical processes.

The development of inflammatory processes in the body is accompanied by a change in microcirculation, an increase in the permeability of blood vessels and the influx and activation of leukocytes in the affected tissues [17]. The chemotaxis factors of leukocytes are cytokines, leukotrienes, thromboxanes, prostaglandins, a substrate for the biosynthesis of which are polyunsaturated fatty acids with conjugated bonds. Therefore, the change in the ratio of the final and the initial products of lipid peroxidation towards the increase in the concentration in the blood of DC in patients with the third and fourth degree of frostbite is probably a consequence of the activation of membrane phospholipases and the release of polyunsaturated fatty acids, the oxidation of which increases the level of eicosanoids - mediators inflammation [11].

Peroxidation products have the ability to directly increase the ion permeability of the lipid bilayer by modifying proteins. The appearance of defects in the lipid layer of cell membranes and mitochondria is associated with the oxidation of thiol groups of membrane proteins, primarily Ca2+-ATPase [2, 3]. Inactivation of this enzyme leads to a delay in the evacuation of calcium ions from the cells and an increase in the intracellular concentration of calcium ions. Sodium ions enter the cell through the pores formed due to the difference in electrical potentials on the membranes, while potassium ions enter the mitochondria. As a result, the osmotic pressure within cells and mitochondria increases which leads to swelling. This further leads to inability of mitochondria to synthesize ATP, which induces energy hunger in the cell. A decrease in the stability of the lipid bilayer of the mitochondria can lead to an electrical breakdown of the membrane by its own membrane potential and electron leakage, which results in an increase in the concentration of superoxide radicals in the cell.

The increase in the products of lipid peroxidation reduces the rate of anabolic processes, which is manifested in slowing down the processes of tissue regeneration and wound healing. Our results are confirmed by the literature data [8, 19].

Accumulation of products of lipid peroxidation stimulates the antioxidant defense of the body. Assessment of the state of the enzymatic link of antioxidant protection in the blood of patients with cold trauma showed that the enzyme activity also depended on the degree of cold trauma (Table 2).

The activity of SOD - an enzyme that reduces and re-oxidizes the superoxide radical of oxygen to hydrogen peroxide, was increased in the first group of patients by a factor of 8.0, and in the second group – by a factor of 12.6.

The catalase activity in both groups of patients with frostbites was also increased. In the first group of patients catalase activity was 1.3 times higher than control, and in the second group – 1.1 times.

Antioxidant enzymes SOD and CAT work together, promptly inactivate ROS, superoxide anion-radical and hydrogen peroxide, which are formed during the normal metabolism of cells, as well as during significant intensification of the processes of lipid peroxidation. However, these enzymes have little activity with respect to lipid peroxides formed during

Table 1

Concentration of MDA (µmol/L) and DC (µmol/L) in the blood of the control group and patients with cold trauma

Group	MDA	DC
Control	1.98±0.05	1.25±0.05
First	3.73±0.12**	2.40±0.10*
Second	4.05±0.26*	3.19±0.15**

Note: In Table 1-4 * p <0.05 compared with the control group, ** p <0.01 compared with the control group.

chain reactions of lipid peroxidation. The destruction of these products is carried out with the participation of the enzyme system of glutathione.

GPx is able to efficiently decompose hydroperoxide lipids and hydrogen peroxide. Its affinity to hydrogen peroxide is higher than that of catalase, therefore GPx effectively works at low peroxide concentrations [23, 24], however catalase plays a key role in protecting cells from oxidative stress caused by high concentrations of hydrogen peroxide.

Activity of GPx in the first group of patients was 1.7 times greater than control, in the second group - 1.5 times. GR activity decreased in blood of patients of the first group - in 1.9, and in the second group of x - in 2.8 times.

The concentration of the total content of LMWA in erythrocytes of patients with cold trauma also depended on the severity of the injury.

In the first group of patients, the LMWA content was 2.1 times higher than the control value, in the second group - 1.5 times. The concentration of one of the most important antioxidants - ascorbic acid in the blood of patients in the first and second groups was below the control value of 0.8 and 0.4 times, respectively (Table 3).

Probably, the decrease in the concentration of ascorbic acid, depending on the severity of the cold trauma, is related to the mechanism of action of this vitamin, since the utilization of ascorbic acid in the body has a close relationship with the exchange of catecholamines and steroid hormones of the adrenals. Thus, it has been established that under various stress effects on the human body (cooling, burn, blood loss, etc.), a sharp decrease in the concentration of ascorbic

Table 2

Activity of SOD, CAT, GPx and GR in the blood of patients with cold trauma of varying severity

Group	SOD, µmol/min*ml	CAT, µCat/L	GPx, IU/gHb	GR, µmolNADPH/min*gHb
Control	0.03± 0.01	0.60±0.01	0.04±0.01	0.86±0.03
First	0.24±0.02**	0.79±0.03*	0.07±0.01*	0.44±0.02*
Second	0.38±0.01**	0.69±0.02	0.06±0.01	0.31±0.01**

acid in the adrenal glands is observed. On the other hand, the introduction of vitamin C into the body increases resistance to various unfavorable environmental factors [25].

The data obtained by us testify that the state of antioxidant defense system of the organism of patients with cold trauma depends on the degree of frostbite of tissues. In both groups of patients there was an increase in the concentration of LMWA in the blood serum. Decrease in the content of LMWA in the second group of patients in comparison with the patients of the first group can probably be explained not only by its depletion during slaking of free radical and oxidative reactions, but also by a decrease in the activity of the GR -enzyme that reduces oxidized glutathione. The increase in SOD activity in the blood of patients of both groups is probably a consequence of an increase in the superoxide anion radical concentration. The change in catalase activity, depending on the degree of frostbite, is similar to the change in activity of GPx, probably because they have the same substrate.

Antioxidant enzymes form a single metabolic chain, in which the product of the first reaction is the substrate of the subsequent. In this regard, in order to sustain normal functioning of the whole enzyme antioxidant system, it is important to maintain certain ratios in the activity of individual enzymes in the chain. First of all, this concerns SOD-GPx and SOD-catalase, since unbalanced increase in the activity of SOD may lead to elevation of steady-state concentration of peroxides, which are toxic to the cell. Therefore, we carried out an analysis of the changes in the coefficients reflecting the state of the antioxidant system of the body, the KSOD/CAT, KSOD/GPx.

According to above data, in severe frostbite, the system of antioxidant defense of the organism is disturbed as a result of their imbalance (Table 4). The increase in the valuesof KSOD/CAT and KSOD/GPx in cold trauma of thirdand fourth degree is due to a sharp increase in SOD activity (6.5 times in the first and 10.4 in the second group) and comparatively a slight increase in the activity of GPx and catalase, enzymes that inactivate the product of the superoxide radical oxidation, which leads to an increase in the concentration of hydrogen peroxide and, as a result, the appearance of new forms of active oxygen (OH*, HClO) and intensification of lipid peroxidation.

Reflection of inflammatory-destructive processes in the body is an increase in the blood of patients with activity of enzymes: ALT, AST, GGP and ALP. According to our data, in patients with cold trauma the level of enzymes (IU) in the blood in the first and second groups corresponded to: ALT 31.17±1.69 IU and 77.20±2.05 IU, AST 47.43±2, 29 IU and 109.00±4.48IU, GGT 34.29±1.17IU and 64.09±2.49IU, ALP 150.55±6.43IU and 154.38±6.14IU, respectively. In the control group, the activity values of the enzymes ALT, AST, GGT and ALP were 21.11±0.50; 27.90±0.39; 24.12±1.35 and 116.20±5.45IU, respectively. The increase in the level of these enzymes in the blood of patients was in direct proportion to the severity of the injury.

Table 3

The concentration of ascorbic acid (mg / dL) and the total content of low molecular weight antioxidants (mgEq / ml * erythrocytes) in the blood of patients with cold trauma of varying severity

Group	LWMA	Ascorbic acid
Control	0,044±0,001	0,57±0,02
First	0,094±0,004**	0,48±0,01*
Second	0,066±0,003*	0,24±0,01**

Note: * p <0.05 compared with the control group, ** p <0.01 compared with the control group.

Table 4

Values of KSOD/CAT and KSOD/GPx

Coefficients (K)	Group		
	Control	First	Second
KSOD/CAT	0.06±0.002	0.30±0.017*	0.55±0.02*
KSOD/GPx	0.97±0.035	3.57±0.14*	6.21±0.24*

The concentration of MDA and total cholesterol in the blood in patients with frostbite of 3-4 degrees were in a directly proportional relationship. In the first group, a 8% decrease in MDA compared with the second group was associated with a 13.6% decrease in cholesterol (5.07±0.27 mmol/L); in the second group, the increase in MDA concentration was combined with high cholesterol (6.08±0.24 mmol/L). The cholesterol level in the control group was 5.85±0.30 mmol/L. This is probably due to the ability of lipid peroxidation products to inhibit the activity of the key enzyme of cholesterol catabolism - 7-ά-hydroxylase, which leads to the sustenance of its stably high level with the intensification of processes of free radical oxidation in the body [21]. The data obtained by us on the increase in cholesterol in the blood of patients with cold trauma confirm this position.

We found a relative decrease in the total protein in comparison with the control value (73.57±1.69 g/L): in the first group the concentration of the total protein was 59.08±1.05 g/L, and in the second group - 59.53±2.97 g/L. Probably, the decrease in blood plasma proteins is associated with the activation of catabolism, as evidenced by the tendency to increase the urea concentration depending on the degree of severity of the cold trauma. The concentration of urea in the first group was 3.72±0.10 mmol/L, in the second - 4.15±0.12mmol/L, in the control group was 3.59±0.06 mmol/L.

The level of TAG in the blood of patients also depended on the degree of frostbite, in the first group of patients its concentration was 1.14±0.03 mmol/L, in the second - 1.28±0.01mmol/L, in the control group - 0.81±0.02 mmol/L.

According to V.N. Morozov, A.A. Khadartsev [13], depending on the depth and area of the lesion, the organism chooses the adaptation mechanism: synthoxic or katatoxic, which will determine the course of the disease in the future. The area of tissue damage in the ourpatients was insignificant and amounted to approximately 1 to 3% of the entire surface of the body. Therefore, katatoxic adaptation programs developed in patients of both groups [6,15].

Conclusion

The development of cold trauma is associated with the intensification of lipid peroxidation. In the organism of patients with frostbite of the extremities of the first and second groups, a significant increase in the parameters of lipid peroxidation – MDA and DC – is observed. In patients of the second group, the intensity of lipid peroxidation processes was higher than in patients of the first group.

Accumulation of products of lipid peroxidation stimulates the antioxidant defense of the body. The state of the body's antioxidant defense depends on the severity of the injury. In patients of the first group, the activity of SOD increased 8-fold, CAT in 1.3-fold, GPx in 1.7-fold, and GR activity decreased 1.9-fold compared with the control. The concentration of LMWA increases 2.1 times, and the content of ascorbic acid decreases by 1.2 times. In patients of the second group with respect to control, the activity of SOD increases 12.6 times, catalase in 1.1, GPx in 1.5, and the activity of GR decreased 2.8 times. The content of LMWA is increased 1.5 times, and the level of ascorbic acid in the blood is reduced 2.4 times.

The shift in the prooxidant-antioxidant equilibrium toward the intensification of free radical reactions is also indicated by an increase in the coefficients: KSOD/CAT, KSOD/GPx. The valuesof these coefficients depend on the severity of the resulting cold injury.

Cold trauma is characterized by the development of inflammatory-destructive processes, manifested in the increase in the activity of enzymes in the blood: ALT, AST, γ-GT, ALP. In addition, patients with cold trauma experienced an increase in cholesterol, and its concentration in the blood increases in direct proportion to the degree of tissue damage and the level of inflammation.

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The authors:

1. Nikolaev Vyacheslav Mikhailovich - PhD, head of the department for studying adaptation mechanisms, Yakutsk Scientific Center of Complex Medical Problems, 677010, Yakutsk, ul. Sereylyakhskoyeshosse 4, phone: (4112) 32-19-81, e-mail: Nikolaev1126@mail.ru;

2. Alekseev Revo Zakharovich - MD, Professor of the M.K. Ammosov North-Eastern Federal University, Senior Researcher, Yakutsk Scientific Center of Complex Medical Problems, 677010, Yakutsk, ul. Sergelyakhskoyeshosse 4, phone: (4112) 32-19-81, e-mail: ynckmp@yandex.ru;

3. Fedorova Sardana Arkadevna - Doctor of Biological Sciences, Head of the Research Laboratory of Molecular Biology, M.K. AmmosovNorth-Eastern Federal University, 677000, Yakutsk, ul. Kulakovsky, 46, k.504, phone: (4112) 49-68-42, e-mail: sa.fedorova@s-vfu.ru.

A.I. Yakovleva,E.D.Okhlopkova,Z.N. Krivoshapkina,A.V. Efremova,L.I. Konstantinova, G.E. Mironova, L.D. Olesova, E.I. Semenova

THE STATE OF ANTIOXIDANT PROTECTION OF THE BODY IN PATIENTS WITH CORONARY HEART DISEASEIN THE NORTH, DEPENDING ON ETHNICITY

ABSTRACT

The state of antioxidant protection of the body in patients with coronary heart disease, depending on ethnicity in the North, was under study.

It was revealed that dyslipidemia in patients with coronary heart disease is characterized by an increase in the level of triglycerides in blood. Dysadaptation to the northern conditions occurs due to the activation of lipid peroxidation processes, which is caused by the accumulation of malonicdialdehyde and is accompanied by inhibition of the antioxidant potential of the organism.

Keywords:coronary heart disease, lipid peroxidation, antioxidant protection of the organism, North.

Introduction. In the course of a long evolution under the influence of environmental factors, certain morphofunctional (including metabolic) features of northern populations were formed. These features, combined into «adaptive types» [7] represent the norm of biological responses to a complex of environmental factors that ensure the viability of the population in northern conditions.

One of the general patterns changes of metabolism in the population of these regions, with indigenous and alien residents, is an increase in the content of fats in blood and tissues, predominantly unsaturated fatty acids, and an increase in their consumption with food [1, 3, 6]. It was found that the low prevalence of dyslipidemia among the indigenous inhabitants of the northern regions depends on the nature of nutrition, namely, the consumption of fish with a high content of ω3-polyunsaturated fatty acids [2,12]. In general, we can talk about the «polar metabolic» type [7, 8], as one of the most important manifestations of human and animal adaptation in the Far North.

With acclimatization in the Far North, a person is exposed to a number of environmental factors: cold, severe aerodynamic conditions, changes in photoperiodism [4] and phenomena of an electromagnetic nature [6].

Coronary heart disease is characterized by high rates of morbidity, high degree of disability, mortality and currently has a tendency to rejuvenate [5, 9]. In patients with atherosclerosis, the rate of generation of lipid peroxides increases. The measurement of hydroperoxides correlates with angiographic changes in the walls of the coronary vessels [5, 13].

In the newcomer population of the Far North, there has been an increase in the incidence of myocardial infarction and cardiovascular mortality (CVD). In the indigenous inhabitants of the Far North, leading the traditional way of life, myocardial infarction is relatively rare, the prevalence of IHD was lower than in middle latitudes [5, 11, 13, 14].

Normally, the levels of free radical and antioxidant processes are in dynamic balance. The imbalance between these two systems, which develops against the background of a violation of the blood supply to the myocardium, is important for the pathogenesis of IHD. It is one of the causes of metabolic and myocardial dysfunction, takes part in the genesis of pain syndrome, rhythm disturbances, leads to a decrease in contractility of the myocardium [2].

Purpose of the study. Assessment of the state of antioxidant protection of the body in patients with IHD, depending on ethnicity in the conditions of North.

Material and methods of research. The study was performed with the participation of 92 patients with coronary heart disease, aged 35 to 75 years who were hospitalized in the department of cardiology of the Republic of Belarus No. 1 NCM. The patients were divided into 2 groups according to ethnicity: I group - Yakut (indigenous) - 52 men, II group Russian (outsiders) - 40 men. The second group consisted of patients who came from different cities of Russia (Cherkassk, Moscow, Voronezh, Baku, etc.), but lived at the time of research in the North.

Blood for biochemical studies was taken from the ulnar vein in the morning hours on an empty stomach, 12 hours after eating. Whole blood was used to study antioxidant indices and products of free radical oxidation.

To determine the intensity of LPO and antioxidant parameters, standard analysis techniques were used. Biochemical analyzes were performed on a biochemical analyzer «Cobas Mira Plus» (Switzerland), using «Biocon» reagents (Germany). The content of products of LPO and AOP of the organism was determined on a spectrophotometer «Specord-40».

Statistical analysis of the data was carried with using the program Statistica 19. Standard methods of variational statistics were used: calculation of mean values, standard errors, 95% confidence interval. The data in the tables are presented in the form M ± m, where M is the mean, m is the mean error. To assess the statistically significant differences in the obtained data, nonparametric methods, the Student's criterion, the Spearman correlation analysis were used. Probability of the validity of the null hypothesis was assumed for $p < 0,05$.

Results and discussion. Biochemical parameters of blood serum on average varied within the limits of normal values. At the same time, there were relative differences depending on ethnicity. According to the data obtained, the activity of the enzymes participating in the glucose-alanine shunt was high in the native population. Thus, the high activity of gamma-glutamyltransferase (GGT) was statistically significant and exceeded by 1,79fold in Yakut people than in russians. The activity of alkaline phosphatase (ALP) varied at the upper limit of the norm in the indigenous populations. The activity of GGT and ALP in indigenous people was combined with a higher level of total protein in them than in the case of new residents.

Perhaps this is due to the activation of membrane mechanisms of amino acid

transport and indicates the intensive borrowing of amino acids from tissues [10]. A statistically significant correlation between the indices of GGT and ALP activity (r = 0,386, p = 0,001) indicates an increased requirement of the cell in adenosine triphosphate (Table).

The relatively low level of total protein, which is at the lower limit of the norm, in unmarried men compared with indigenous men was combined with a low level of urea. A significant correlation was found (r = 0,342 p = 0,044) between the urea content and the total protein level.

The coefficient of deity, the index of adaptive reactions of the organism, was lower than the norm for foreigners. Given the statistically significant correlation of the urea level with the coefficient of deity(r = 0,615, p = 0,002).

Thus, the low level of both total protein and urea, significantly correlated with a low level of coefficient of deityin foreigners residents, indicates signs of depletion of the body's functional reserve.

The parameters of lipid metabolism of total cholesterol, LDLP cholesterol, and VLDLP cholesterol in patients with IHD corresponded to the generally accepted norms, although the level of total cholesterol was at the upper limit of the norm in foreignersmen. The level of triglycerides, regardless of ethnicity, exceeded normal values. Differences in lipid metabolism in the surveyed, depending on ethnicity, were statistically significant. Due to the violation of the ratios of atherogenic and antiatherogenic cholesterol fractions in IHD patients, the atherogenicity coefficient was high. At the same time, the coefficient of atherogenicity in native and alien ethnics exceeded permissible values of 1,85indigenousand 2,39fold in Russians.

The study of antioxidants in the blood revealed that the content of vitamin C in both groups was low. At the same time, this indicator was 1,64 fold higher in Yakuts than in Russians, but it did not correspond to the normal content of the norm, so in the Yakuts the content of vitamin C was 3,5 fold lower than normal, while for Russians it was 5,7 fold (the norm 0,7-1,4 mcg).

The level of superoxide dismutase was also 1,52fold lower in foreigners than in the Yakut. The content of low-molecular antioxidants in native was 20,9fold higher than in the case of new residents (Fig.).

The level of lipid peroxidation product of MDA in Yakut people was 3,50 ± 0,49 mM/l, in Russians 4,89 ± 0,66 mM/l, this fact indicated intensification and intensification of LPO processes.

Analysis of the state of antioxidant protection of the body and lipid peroxidation was determined by the AOD/POL. As indicators of antioxidant protection of the body were used: the content of the vitamin C, superoxide dismutase and low-molecular antioxidants, and peroxide oxidation of lipids - the accumulation of malonicdialdehyde. At the same time, a statistically significant increase (p <0,05) of KAOD/POLwas observed in persons of the indigenous population in 1,98 fold than in foreigners.

Conclusion

Proceeding from the foregoing, it can be assumed that in the foreigners the disadaptation processes are most pronounced. According to the calculated KAOD/POL, it can be argued that the prevalence of antioxidant processes over peroxidases in patients with indigenous people with coronary heart disease is higher than that of Russians almost 2fold.

The persons of the foreigners are noted to activate the processes of lipoperoxidation, expressed in the accumulation of malonicdialdehyde, which may be associated with the disadaptation of the organism to the extreme conditions of the North, namely, to the cold. The predominance of prooxidant factors over antioxidants, indicates the occurrence of oxidative stress. The trigger mechanism for adaptation to stress of any origin is the activation of peroxidation processes. The physiological meaning of the stress reaction is the emergency mobilization of the energy and structural resources of the organism and the creation of a positive background for the implementation of reactions aimed at maintaining homeostasis in extreme conditions of living [6, 7, 10].

According to our research, in representatives of russian nationality, dyslipidemia is most pronounced in comparison with the Yakuts. This is due to the increase in triglyceride levels and the coefficient of atherogenicity from normal values in the Yakuts by 15% and 46%; for Russians by 27% and 58%, respectively.

To fully understand the nature of peroxide processes in the structure of peroxide damage in the body, as well as in the selection of a rational antioxidant correction, a comprehensive examination including evaluation of LPO products, as well as the level of factors providing protection against possible damages of the cell membrane apparatus by lipid peroxidation intermediates.

In other words, the nature of disadaptation of the alien population in patients with coronary heart disease to the extreme conditions of the North proceeds more intensively than in the indigenous population.

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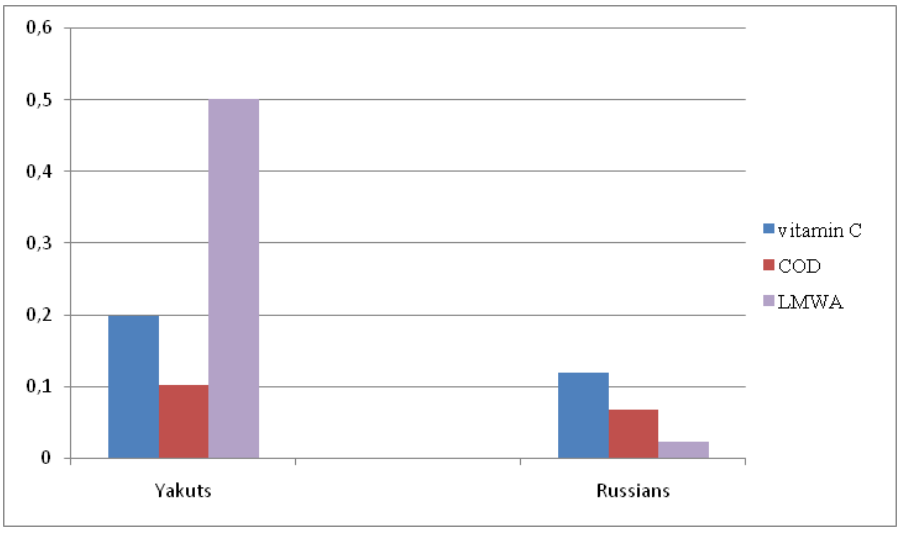
Biochemical parameters of blood serum in patients with coronary heart disease

Biochemical index	Nationality	
	Yakuts (n=29)	Russians(n=26)
GGT, U/l	54,51±9,29*	30,47±5,26
ALP, U/l	150,86±10,58	141,23±11,34
Coefficient of deity	1,34±0,22	1,12±0,21
Urea, mmol/l	5,28±0,56	5,06±0,48
TP, g/l	71,90±0,91	64,34±4,83
Glucose, mmol/l	4,90 ±0,32	4,68±0,29
Chol, mmol/l	6,08±0,36	6,52±0,47*
Triglycerides, mmol/l	2,01±0,20	2,33±0,32*
HDLP, mmol/l	1,09±0,08*	0,84±0,10
LDLP, mmol/l	3,99±0,34	4,27±0,44*
VLDLP, mmol/l	0,99±0,11	1,05±0,14*
Ca	5,56±0,61	7,18±0,91*

* - reliabilityofdifferences p <0.05.



Antioxidant components in patients with IHD, depending on ethnicity

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The authors

Yakutsk, Republic Sakha (Yakutia), Russia:

1. Yakovleva Alexandra Ivanovna – researcher of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems", e-mail: sashyak@mail.ru.
2. Okhlopkova Elena Dmitrievna – c.b.s., leading specialist of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems".
3. Krivoshapkina Zoya Nikolaevna - c.b.s., senior researcher of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems".
4. Efremova Agrafena Vladimirovna c.b.s., senior researcher of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems".
5. Mironova Galina Egorovna – d.b.s., prof., biological branch of the INC FSAEI HE "Northeastern Federal University". M. K. Ammosov.
6. Olesova Lyubov Dygynovna - c.b.s., leading researcher of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems".
7. Semenova Eugenia Ivanovna - c.b.s., senior researcher of the FSBSU "Yakutsk Scientific Center of Complex Medical Problems".

A.A. Nikanorova, N.A. Barashkov, E.E. Diakonov, S.S. Nakhodkin, V.G. Pshennikova, A.V. Solovyev, S.S. Kuzmina, M.I. Tomsky, T.E. Burtseva, S.A. Fedorova

ANALYSIS OF THE POLYMORPHISM OF SNP-MARKERS OF NON-SHIVERING THERMOGENESIS GENES *UCP1* (RS1800592), *UCP2* (RS659366) AND *UCP3* (RS2075577) IN THE YAKUTS AND CHUKCHI'S

ABSTRACT

For the first time an analysis of the frequencies of alleles polymorphismof the gene *UCP1*-rs1800592, *UCP2*-rs659366 and*UCP3*-rs2075577were studiedthe Yakuts (n=281) and the Chukchi's (n=39) populations, living in the extreme climate of Eastern Siberia.The Yakut population was divided into three groups: northern (N.YAK), viluysk (V.YAK) and central Yakuts groups (C.YAK).From project of «1000 Genomes», information was received on the frequencies of the studied polymorphisms for Chinese – CHB (n=103), CHS (n=108), CDX (n=99), Japanese – JPT (n=104), Vietnamese populations– KHV (n=101).In general, the frequencies of the studied polymorphisms were analyzed in nine populations of Asia (n=835), living in different climatic zones. Populations living in the subarctic (CHU, N.YAK) and on the border of the temperate and subarctic climate (V.YAK, C.YAK) were merged into the group «Northern Asia». Populations living in the temperate (CHB), subtropical (JPT; CHS; CDX) and subequatorial climate (KHV) were joined into the «Southern Asia» group. Comparative analysis showed that the frequency of the allele A rs1800592 (*UCP1*) in the group «Northern Asia» (61.8%, CI: 56.8-66.7%), did not statistically differ (p>0.01) from the «Southern Asia» group (53.4%, CI: 49.4-57.4%). The frequencies of allele T rs659366 (*UCP2*) in the group «Northern Asia» (49.5%, CI: 44.5-54.6%), as compared with the group «Southern Asia» (41.5%, CI: 37.7-45.5%), also statistically differences not found (p>0.01). It was found that the frequency of allele A rs2075577 (*UCP3*) in the group «Northern Asia» (66.7%, CI: 61.8-71.4%) was much higher in comparison with the group «Southern Asia» (42.3%, CI: 38.4-46.3%) (p<0.01). The increased frequency of allele A rs2075577 of the *UCP3* gene in populations of Yakuts and Chukchi's living in low temperature conditions, in comparison with other populations of Asia, can be associated with random population effects, or indicate the presence of adaptation mechanisms associated with thermoregulation.

Keywords: brown adipose tissue, nonshivering thermogenesis, uncoupling proteins, *UCP1* gene, *UCP2* gene, *UCP3* gene, adaptation, cold climate, Yakut population, Chukchi population.

Introduction

Recently, in 2015, the first case of finding brown adipose tissue(BAT) in samples from the paraaortic, perirenal, subclavian and perityroid areasof the postmortal body of the adult resident of Yakutia (54 years), who spent most of his time outside and was exposed to cold [1]. It is considered that BAT is one of two types of fatty tissue at the person and mammals which is well developed only at newborns and at the animals falling into hibernation[8]. The main function of the tissue is to participate in the mechanism of thermoregulation, by means of incontinent thermogenesis and the release of energy in the form of heat [16]. Unlike white adipocytes (cells of white adipose tissue) having one large fat drop, in adipocytes of BAT there are several small fat drops and a lot of mitochondria containing more iron (in cytochromes), which causes a brown color of the tissue [9]. It is believed that BAT has evolved in mammals during evolution to protect the body from hypothermia [16] and is optional, that is, it is activated only with prolonged cold exposure [6, 7, 10].

A characteristic of BAT is the high expression of the *UCP1* gene (uncoupling protein1), which encodes a protein of thermogenin, which in turn reduces the proton gradient in oxidative phosphorylation and weakens the work of mitochondrial ATP synthase, thereby stimulating nonshivering thermogenesis [2]. In 1997, the homologues of the uncoupling protein 1 — *UCP2* and *UCP3* [19, 20]. The *UCP2* gene is widely expressed in adipocytes of white adipose tissue and in pancreatic beta-cell, whereas the *UCP3* gene is expressed mainly in skeletal muscles and, to a lesser extent, in BAT [21]. It is now known that the uncoupling proteins *UCP2* and *UCP3* are involved in the regulation of the metabolism of the adipocytes of BAT [17] and transport fatty acids through the mitochondrial membrane during nonshivering thermogenesis [5, 12, 15]. Thus, it is believed that one of the most likely candidate genes associated with adaptation to a cold climate is the genes involved in nonshivering thermogenesis, such as the genes *UCP1*, *UCP2* and *UCP3* [13]. In turn, adaptation to various environmental factors can occur both due to the emergence and spread of novel mutations, and by changing the frequencies of the alleles of genes that were present in the gene pool of the population [11]. It is possible that in populations living in a cold climate, the frequency distribution of gene alleles potentially associated with nonshivering thermogenesis will differ from populations living in a warmer climate.

Thereby, the purpose of this work is to analyze the polymorphism of genes*UCP1*, *UCP2* and *UCP3*,involved in nonshivering thermogenesis,in populations of the Yakuts and Chukchi, living in low temperatures in comparison with southern populations of Asia.

Materials and methods

The sample of Yakuts(YAK) was 281 people, women (n=186) and men (n=95), the average age of which was 19.84±1.97 years. The sample of the Yakuts was divided into three groups according to ethno-territorial affiliation: northern (N.YAK, n=16), vilyuysk (V.YAK, n=67) and central Yakuts (C.YAK, n=198). The sample of Chukchi's (CHU) was 39 people, women (n=18) and men (n=21), the average age of which was – 14.23±2.62 years. From the open sources of the project «1000 Genomes» [18], information was received on the frequencies of the polymorphisms studied for Chinese populations – CHB (n=103), CHS (n=108), CDX (n=99), Japanese - JPT (n=104), Vietnamese – KHV (n=101). Thus, the final sample was 835 people.Populations living in the subarctic (CHU; N.YAK) and on the border of the temperate and subarctic climate (V.YAK; C.YAK) were grouped into the group «Northern Asia». Populations living in the

temperate (CHB), subtropical (JPT, CHS, CDX) and subequatorial (KHV) climates were combined into the group «Southern Asia» (Fig.1).

This work was approved by the local ethics committee on biomedical ethics at the YSC CMP. Blood samples were taken with informed written consent of the examined individuals or their parents (Yakutsk, protocol #16 of December 13, 2014).

Genotyping was performed by PCR-RFLP analysis. The original oligonucleotide primers were selected using the FastPCR program (http://primerdigital.com/) (Table 1). For the polymorphisms rs1800592 (*UCP1*) and rs659366 (*UCP2*) for the restriction endonuclease Ksp22I and BspFNI, respectively, natural restriction sites were used (Fig.2-A,B). For the polymorphism rs2075577 (*UCP3*), an artificial restriction site created for the RsaNIendonuclease was used with a mismatch reverse primer differing from the template sequence by one nucleotide, where guanine (G) is replaced by cytosine (C) (Fig.2-C).

The detection was carried out using standard PCR, followed by hydrolysis of the amplification products with restriction endonucleases and electrophoresis in a 3% agarosegel at a voltage of 120V (Fig.3-A, B, C).

Statistical analysis of the frequencies of identified major alleles of the polymorphisms rs1800592 of the *UCP1* gene, rs659366 of the *UCP2*gene and rs2075577 of the *UCP3* gene was performed using the Sampling program, kindly provided by M. Macaulay and M. Metspalu (Tartu, Estonia). Differences at the 99% significance level were considered statistically significant.

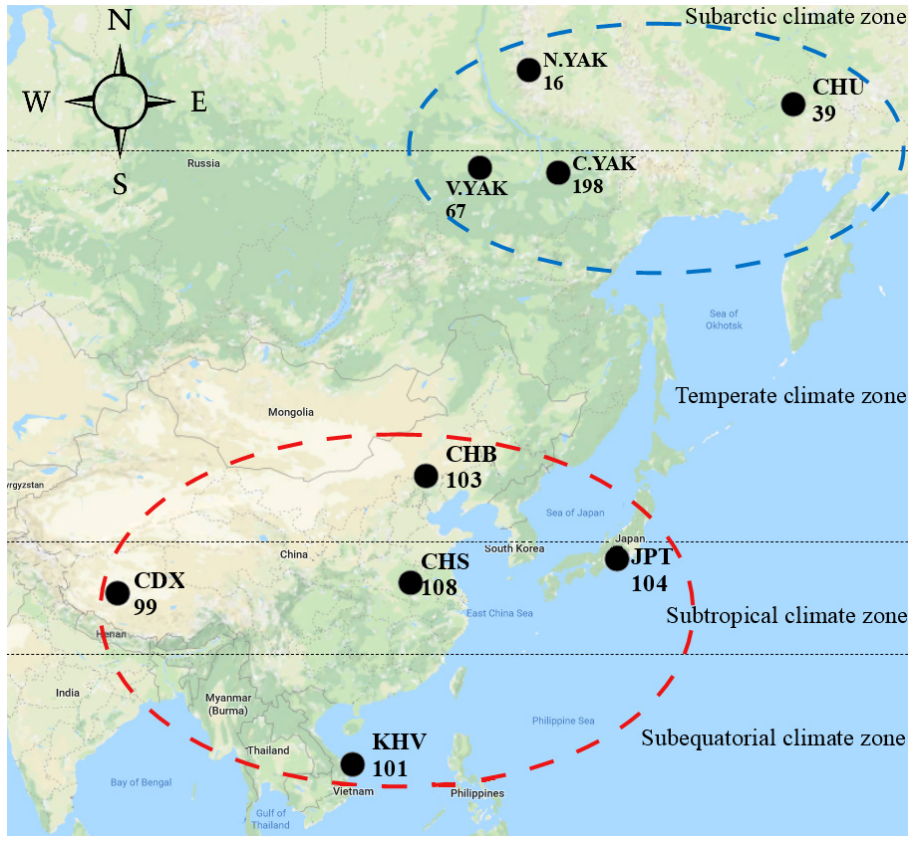

Fig. 1. Regions of residence of the studied populations «North Asia»: N.YAK – the northern Yakuts, V.YAK –vilyuyskYakuts, C.YAK –centralYakuts; CHU – Chukchi's; «South Asia»: CHB, CHS, CDX – Chinese; JPT – Japanese; KHV – Vietnamese

Results

At the first stapes of the study, the frequencies of the polymorphisms rs1800592 of the *UCP1* gene, rs659366 of the *UCP2* gene and rs2075577 of the *UCP3* gene in the Yakuts and Chukchi'spopulations were determined using the detection method developed by

Table 1

Oligonucleotide primers and detection methods for rs1800592 of the gene *UCP1*, rs659366 of the *UCP2* gene and rs2075577 of the *UCP3* gene

Gene	SNP	Majorallele	Minorallele	The primer sequence from the 5'®3' end	The size of the fragment to be amplified	Restrictionenzymes	Results of electrophoretic separation
UCP1	rs1800592	A	G	F: 5'–ACATTTTGTGC AGCGATTTCTG-3' R: 5'–TTCACCACTT CTGACAGGCT–3'		*Ksp22I*/ T↑GATCA	Normally, one restriction site, fragment sizes of 36 bp and 265 bp.If there is a mutation, the restriction site is absent, the fragment size is 301 bp.
UCP2	rs659366	T	C	F: 5'–AGCGTGACCT CACGCTCCTA–3' R: 5'–GACTGAACGT CTTTGGGACTCCGT–3'	299 п.н.	*BspFNI*/ CG↑CG	Normally, one restriction site, fragment sizes 178 bp and 121 bp.If there is a mutation, the restriction site is absent, the fragment size is 299 bp.
UCP3	rs2075577	A	G	F: 5'-GGGACTGGAA CCCAAGTCT-3' R: 5'-ACGACATCCT CAAGGAGAAGCTGCTGGAGTA-3'	249 п.н.	*RsaNI*/ G↑TAC(G)	Normally, one restriction site, fragment sizes of 218 bp and 32 bp.If there is a mutation, the restriction site is absent, the fragment size is 249 bp.

us. The frequencies of the major alleles of the SNP-markers we studied in the northern, vilyuysk, central Yakuts and Chukchi's, as well as the frequencies of the polymorphisms studied for the populations of the Chinese – CHB (n=103), CHS (n=108), CDX (n=99), Japanese – JPT (n=104), Vietnamese – KHV (n=101) are presented in Table 2.

Next, we conducted a comparative analysis of polymorphisms'frequenciesin studied by us nine populations of Asia, living in different climatic (subarctic and temperate to subtropical and subequatorial).

Comparative analysis showed: that the frequency of the allele A rs1800592 of the *UCP1* gene in the group «Northern Asia» (61.8%, CI: 56.8-66.7%) was not statistically different from the group «Southern Asia» (53.4%, CI: 49.4-57.4%) (p >0.01) (Fig. 4, A); the frequency of the allele T rs659366 of the *UCP2* gene in the group «Northern Asia» (49.5%, CI: 44.5-54.6%), as compared with the «Southern Asia» group (41.5%, CI: 37.7-45.5%), also statistically did not differ (p>0.01) (Fig. 4, B);the frequency of the allele A rs2075577 of the *UCP3* gene in the «Northern Asia» group (66.7%, CI: 61.8-71.4%) was significantly higher than the «South Asia» group (42.3%, CI: 38.4-46.3%) (p<0.01) (Fig. 4, C).

Discussion

In the present work, for the first time, the frequencies alleles of the polymorphism of the genes *UCP1* (rs1800592), *UCP2* (rs659366) and *UCP3* (rs2075577) in the Yakuts and Chukchi'spopulations living in the extreme climatic conditions of Eastern Siberia were detected, where the lowest temperatures of air were recorded (-71°C). For the detection of adaptation to cold signals, an analysis was made of allele frequencies between populations living in a relatively cold climate (subarctic and temperate climatic zone), compared to populations living in a relatively warm climate (subtropical and subequatorial climatic zone). Populations living in the subarctic (CHU; N.YAK) and on the border of the temperate and subarctic climate (V.YAK; C.YAK) were merged into the «Northern Asia» group. Populations living in the temperate (CHB), subtropical (JPT; CHS; CDX) and subequatorial (KHV) climates were combined into the «Southern Asia» group (Fig. 3). As a result of the comparative analysis, statistically significant increased frequencies were found for the A allele of polymorphism rs2075577 of the *UCP3* gene in the group «Northern Asia» compared to the «Southern Asia» group. The obtained results on the increased frequency of the allele A polymorphism rs2075577 of the *UCP3* gene in the population of the

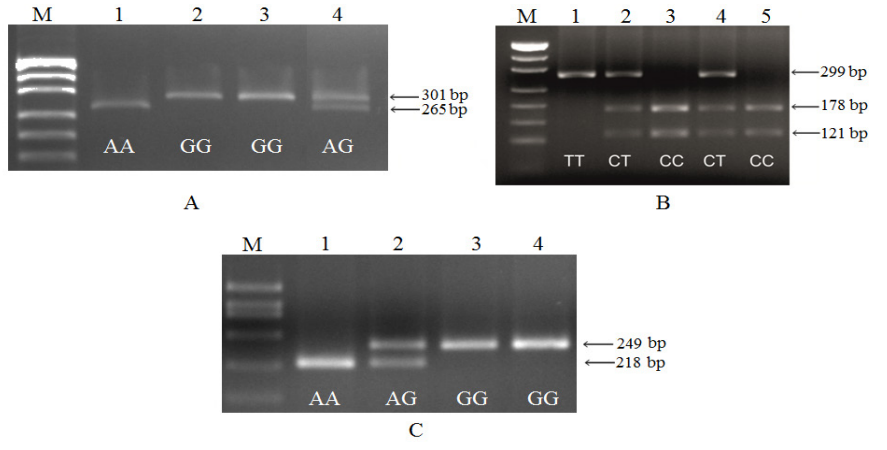

Fig.2. Design of PCR-RFLP analysis of rs1800592 gene of UCP1 (A), rs659366 of UCP2 gene (B) and rs2075577 of UCP3 gene (C)

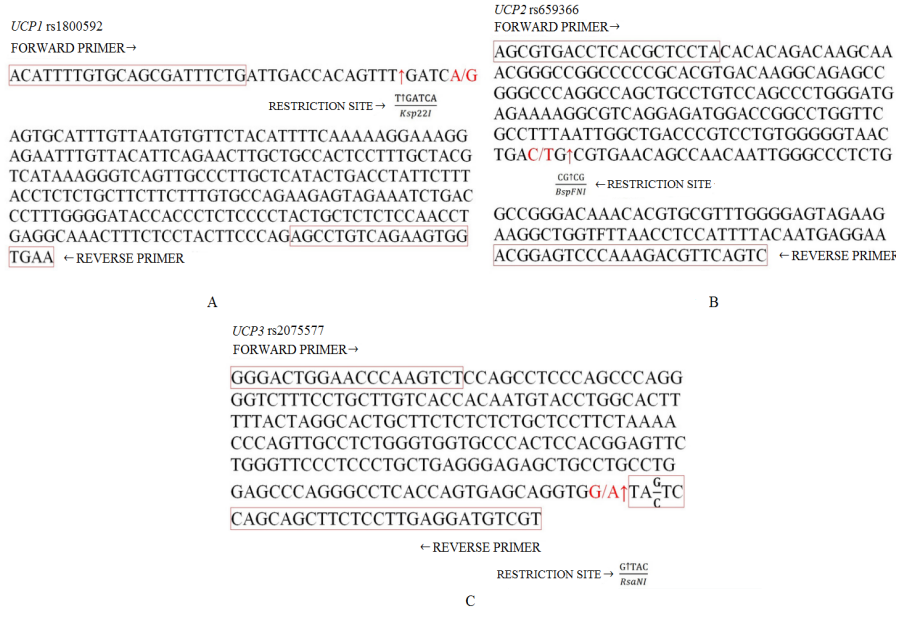

Fig.3. Detection of polymorphismrs1800592 gene of UCP1 (A), rs659366 of UCP2 gene (B) and rs2075577 of UCP3 gene (C)

Yakuts and Chukchi's living in conditions of low temperatures in comparison with other populations of Asia can be associated with random population effects (for the Yakut population, the pronounced founder effect on the paternal lines of the Y-chromosome) [4], or may indicate the existence of adaptation mechanisms aimed at increasing cold resistance. In general, the data obtained by us agree with the previously obtained results on the involvement of the genes *UCP1* (rs1800592), *UCP2* (rs659366) and *UCP3* (rs1800849, rs2075577) to nonshivering thermogenesis in human populations [3; 14].

Thus, a group of Russians researchers investigated the frequencies of alleles of 28 genes potentially associated with adaptation to cold climate (to low temperatures) in populations of Northern Eurasia, including Yakuts (n=102) and Chukchi's (n=95). As a result of these studies, a significant relationship was established between the polymorphisms rs1800592 of the gene *UCP1* and rs1800849 of the *UCP3* gene with climatic (temperature) and with geographical (latitude and longitude) variables. However, during the additional FDIST-test, The authors did not record directional selection signals for the polymorphisms rs1800592 of the *UCP1* gene and rs1800849 of the *UCP3* gene [3]. Another research team from the University of Chicago, using an evolutionary approach, tested the hypothesis that high expression of the genes of uncoupling proteins (*UCP1*-rs1800592, *UCP2*-rs659366 and *UCP3*-rs1800849) may indicate adaptation to a cold climate [14]. To do this, they calculated the correlation of allele frequencies with the winter climate variables for these polymorphisms with genotyping of 52 world populations.

Table 2

The frequency of polymorphisms of the genes *UCP1, UCP2* and *UCP3* in nine populations of Asia living in different climatic zones

	Populations	n	Climaticzones	*UCP1* rs1800592 AlleleA	*UCP2* rs659366 Allele T	*UCP3* rs2075577 Allele A
«North Asia»	Chukchi (CHU)	39	subarctic	0,62	0,52	0,71
	NorthernYakuts(N.YAK)	16	subarctic	0,62	0,46	0,62
	VilyuyskYakuts(V.YAK)	67	temperate	0,60	0,50	0,69
	CentralYakuts(C.YAK)	198	temperate	0,62	0,51	0,65
«South Asia»	Chinese(CHB)	103	temperate	0,49	0,47	0,47
	Japanese(JPT)	104	subtropical	0,53	0,53	0,54
	Chinese (CHS)	108	subtropical	0,56	0,35	0,36
	Chinese (CDX)	99	subtropical	0,53	0,38	0,37
	Vietnamese (KHV)	101	subequatorial	0,54	0,34	0,35
	Total	n=835				

Notes:A: M – molecular weight marker pUC19/MspI, line 1 – DNA sample with AA genotype (265 bp), lines 2, 3 – DNA samples with genotypes of GG (301 bp), line 4 – DNA sample with genotype AG (301 and 265 bp); B: M – molecular weight marker pUC19/MspI, line 1 – DNA sample with genotype TT (299 bp), lines 2, 4 –DNA samples with genotypes of CT (299, 178 and 121 bp), lines 3, 5 – DNA samples with CC genotypes (178 and 121 bp); C: M - molecular weight marker pUC19/MspI, line 1 - DNA sample with AA genotype (218 bp), line 2 – DNA sample with genotype AG (249 and 218 bp), line 2 – DNA samples with genotypes of GG (249 bp).

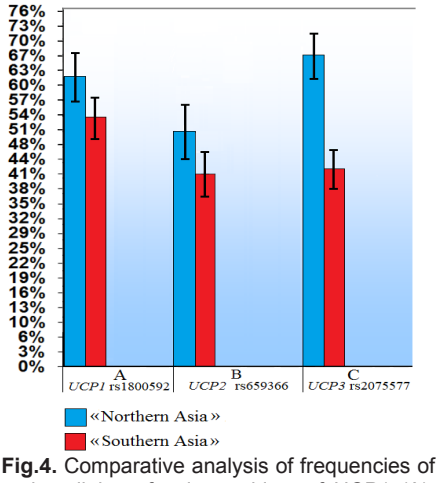

Fig.4. Comparative analysis of frequencies of major alleles of polymorphism of UCP1 (A), UCP2 (B), UCP3 (C) genes by populations of «Northern Asia» in comparison with «Southern Asia» populations

It was found that the high frequency of allele A rs1800592 of the *UCP1* gene is found in populations living in high geographical latitudes, where the least amount of solar radiation is observed. It was also found that the frequencies of the major alleles of several polymorphisms (rs1800849, rs2075577) of the *UCP3* gene have strong correlations with temperature, are associated with cold resistance and, apparently, represent several independent signals of directional selection. However, for polymorphism rs2075577 of the *UCP3* gene, allele frequencies presented in the HapMap project were available only for eleven human populations [14].

In general, further studies are needed to study the mechanisms of nonshiveringthermogenesis associated with BAT in humans, especially the need to clarify the role of the genes of uncoupling proteins *UCP1*, *UCP2*, *UCP3*, as the most promising candidate genes involved in the mechanisms of thermogenesis and human adaptation to cold climates.

Conclusion

Thus, the obtained results on the increased frequency of the allele A polymorphism rs2075577 of the *UCP3* gene in the population of the Yakuts and Chukchi's living at low temperatures, compared with other more southern populations of Asia, may be associated with random population effects, or evidence of the existence of adaptive mechanisms, associated with the genes of nonshivering thermogenesis, and aimed at increasing cold resistance.

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The authors:
Yakutsk, Republic Sakha (Yakutia), Russia:
1. Nikanorova Alena Afanasyevna – junior researcher of the Yakut Scientific Center of Complex Medical Problems, the Master's Student, Institute of Natural Science, NEFU M.K. Ammosov. E-mail: nikanorova.alena@mail.ru, 89244611585;
2. Barashkov Nikolay Alekseyevich – Candidate of Biological Sciences, Leading Researcher - the Head of Laboratory of the Yakut Scientific Center of Complex Medical Problems. E-mail: barashkov2004@mail.ru;
3. Diakonov Egor Egorovich – student, Institute of Natural Sciences NEFU. M.K. Ammosov. E-mail: diakonov2007@mail.ru;
4. Pshennikova Vera Gennadiyevna – Candidate of Biological Sciences, Research Associate of the Yakut Scientific Center of Complex Medical Problems. E-mail: pshennikovavera@mail.ru;
5. Nakhodkin Sergey Sergeyevich – Engineer-researcher of the Laboratory of Molecular Biology, The Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sergnahod@mail.ru
6. Solovyev Aisen Vasilyevich – Postgraduate Student, Institute of Natural Science, NEFU M.K. Ammosov. E-mail: nelloann@mail.ru;
7. Kuzmina Sargylana Semenovna – Candidate of Biological Sciences, Associate Professor, Department of Biology, The Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sskuzmina@bk.ru;
8. Tomsky Mikhail Innokentyevich – Doctor of Medical Sciences, Acting as Director of the Yakut Scientific Center of Complex Medical Problems. E-mail: ogus@list.ru;
9. Burtseva Tatiana Egorovna – Doctor of Medical Sciences, Professor of the Medical Institute of NEFU M.K. Ammosov. E-mail: bourtsevat@rambler.ru;
10. Fedorova Sardana Arkadyevna – Doctor of Biological Sciences, Head of the Laboratory of Molecular Biology, Institute of Natural Sciences NEFU M.K. Ammosov. E-mail: sardaanafedorova@mail.ru.

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

POLYMORPHISM RS738409 OF THE ADIPONUTRIN GENE (*PNPLA3*) AMONG THE INDIGENOUS RESIDENTS OF THE NORTH

ABSTRACT
In this paper, we analyzed the polymorphism rs738409 of the adiponuclein gene *(PNPLA3)* among the indigenous inhabitants of the North of the Republic of Sakha (Yakutia). Under the constant influence of low temperatures, the human body needs a high level of energy metabolism, which in turn is accompanied by a significant consumption of lipids. Epidemiological data indicate the frequent combination of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) characterized by accumulation of lipids both in the hepatocytes themselves and in the intercellular space. Recently, great importance is attached to the genetic conditionality of NAFLD.
Keywords: diabetes mellitus type 2, insulin resistance, adiponutrin gene, polymorphism.

Introduction

The problem of adaptation to the conditions of the North is being actively studied in the world. The achievements of Russian science are related to the identification of physiological, mental, biochemical features of the organism, the fundamental differences in the state of the organism of the northerners and inhabitants of the middle latitudes. By the present time it is an established fact that when a person adapts to the extreme natural conditions of the North, all kinds of metabolism of proteins, fats, carbohydrates, vitamins, macro- and microelements are restructured. Under the constant influence of low temperatures, the human body needs a high level of energy metabolism, which in turn is accompanied by a significant consumption of lipids.

Metabolism of the organism passes to a qualitatively new level of homeostasis, characterized by greater use of fats and proteins for energy needs and less use of carbohydrates.

High-calorie nutrition, excessive intake of (saturated) fats correlate with increased body weight and obesity, and recently their relationship with NAFLD has been revealed. Non-alcoholic fatty liver disease (NAFLD) is usually associated with obesity, metabolic syndrome and type 2 diabetes mellitus (DM 2), is one of the most common chronic liver diseases [1]. Epidemiological data indicate a fre-

quent combination of type 2 diabetes and NAFLD characterized by accumulation of lipids both in the hepatocytes themselves and in the intercellular space [1].

Patients with type 2 diabetes mellitus are insulin resistant, often obese, have dyslipidemia and increased activity of liver enzymes, they tend to accumulate fat in the liver regardless of BMI, thereby they have a higher risk of developing severe liver disease compared to patients without diabetes [3]. Recently, great importance is attached to the genetic conditionality of NAFLD. The value of the PNPLA3 gene, which codes for the synthesis of the protein-enzyme adiponase, is isolated.

The full-genomic search for associations (GWAS) has shown that SNP in the PNPLA3 gene affects the levels of liver enzymes in the plasma. The allele G of the polymorphism rs738409 of the PNPLA3 gene is strongly associated with NAFLD, as well as with the increase in ACT and ALT, ferritin level, and fibrosis stage in patients with NAFLD [4]. With the objectiveto clarify the genetic background of NAFLD in the Yakut population of patients with type 2 diabetes, the present study analyzes the polymorphism of rs738409 of the PNPLA3 gene.

PNPLA3 is mainly expressed in the liver and has lipase activity of triacylglycerol. The mutation I148M is associated with a decreased activity of triglyceride lipase, as shown in studies with the recombinant PNPLA3 protein. This leads to the accumulation of triglycerides in the liver cells, but reduces the release of very low density lipoproteins (VLDL) into the circulation. Reduced lipid concentrations in the blood can reduce the deposition of lipids in the wall of blood vessels. There is a natural reaction of the body to the cold, the so-called «peripheral vasoconstriction», which is to maintain the internal temperature of the body by narrowing the blood vessels.

Materials and methods of research

The experimental part of the genotyping of polymorphism rs 738409 of the PNPLA3 gene was performed in the laboratory of hereditary pathology of the department of molecular genetics of the Yakut Scientific Center of Complex Medical Problems (YSC CMP). DNA samples from the collection of the YMC biomaterial (UNU «Genome of Yakutia», reg. No.USU_507512) were used for the study. The indigenous residents of North, living in the territory of the RS (Ya) participated in the study. The study was conducted with the written consent of the participants. 153 DNA samples of patients with a diagnosis of type 2 diabetes were tested, 105 of which belonged to women, 48 to men. The comparison group was a sample of 84 healthy volunteers, men (n = 26) and women (n = 58).

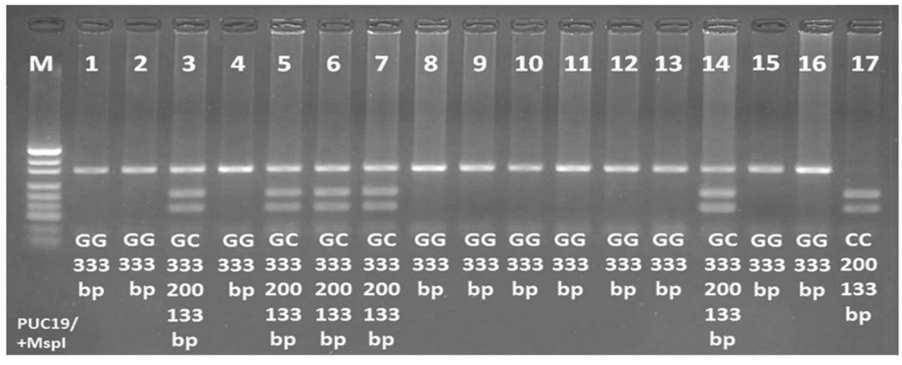

Fig. 1. Electrophoregram of the amplification product of the *PNPLA3* gene site in a 4% agarose gel. 17 - genotype CC, 3, 5, 6, 7, 14 - genotype GC, 1, 2, 4, 8, 9, 10, 11, 12, 13, 15, 16 - genotype of GG. M - marker PUC19 / + Msp I. bp - base pairs.

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

The isolation of DNA from peripheral blood lymphocytes was carried out by a standard phenol-chloroform extraction method. The single nucleotide polymorphism (SNP) of I148M (rs738409) was determined by a PCR-RFLP method.

Amplification of the region of the gene containing the polymorph variant was carried out by standard primer pairs (forward primer: 5'-TGGGCCTGAAGTCCGAGGGT-3 'and reverse primer: 5'-CCGACACCAGTGCCCTGCAG-3') (Biotech Industry Ltd., Moscow) for polymorphism rs738409. The composition of the reaction mixture for PCR (total volume of the reaction mixture was 25 μl): 13 μl of ddH2O, 2.5 μl of 10x PCR buffer, 2.5 μl of 25 mMMgCl2, 2.5 μl of 2.5 mMdNTPMix, 1.5 μl (10 pkmol / μl) of each oligonucleotide primer, 0.3 units. (1.5 units) of the «hotstart» Taq polymerase and 3 μl of DNA. PCR was performed by the MJMiniGradientThermalCycler (BioRad).

The temperature conditions of the PCR were as follows: 95 ° C for 5 minutes, then 37 cycles at 94 ° C for 30 seconds, 66 ° C for 30 seconds, and 72 ° for 40 seconds, and the final elongation at 72 ° C for 5 minutes. The PCR products were then cut with BstF5 I restriction enzyme (SibEnzyme LLC, Novosibirsk) for 16 hours at 65 ° C. PCR-cut products were subjected to horizontal electrophoresis in 1.5% agarose gels stained with ethidium bromide in 1 x TBE buffer at 120 V for 1 hour and visualized using a gel-documenting system(VilberLourmat, France).

The detection of RFLP products was carried out by horizontal electrophoresis in a plate of 4% agarose gel stained with ethidium bromide using a standard tris-acetate buffer at 120 volts for 1 hour. Visualization of restriction products was carried out in UV-rays using a gel-documenting system (VilberLourmat, France) (Figure 2).

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

Statistical analysis of the results of the study was carried out using the program: OfficeMicrosoftExcel 2010, Statistica 8.0. The distribution of genotypes by the investigated polymorphisms was checked for compliance with the Hardy-Weinberg equilibrium using the exact Fisher test. To compare the frequencies of the alleles between different groups, we used the χ2 criterion with the Yates correction for continuity. The expected heterozygosity was calculated by Nei. The results were considered significant, with a value of p <0.05 (p <0.05).

Results and discussion

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

The revealed high frequency of the allele G polymorphism rs738409 of the PNPLA3 gene associated with fat accumulation in the liver in the samples studied is probably related to the adaptive qualities of the organism to the extreme natural conditions of the North. Since it is known that fatty acids entering the bloodstream

Table 1

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

	n		Genotype, %			Allele		χ^2	p
			CC	CG	GG	C	G		
	Patientswithdiabetes 2								
Women	105	H	8,57	30,48	60,95	0,238	0,762	2,688	0,101
		O	5,67	36,28	58,05				
Men	48	H	16,67	25,00	58,33	0,292	0,708	7,488	0,006
		O	8,51	41,32	50,17				
	Healthy								
Women	58	H	6,90	36,21	56,90	0,250	0,750	0,069	0,793
		O	6,25	37,50	56,25				
Men	26	H	23,08	15,38	61,54	0,308	0,692	10,613	0,001
		O	9,47	42,60	47,93				

enter the liver and muscles, where glycogen is the main source of energy. By acting on the process of the decomposition of glycogen, they act as a dissociation factor for oxidation and phosphorylation, causing a smaller terminal yield of ATP and a larger final heat yield. According to the «1000 genomes» project in Asia, the high frequency of G allele is found in Japanese (42.3%). In their studies of the Japanese population of patients with type 2 diabetes, M. Ueyama, N. Nishida (2015) and KanH. with co-authors [5], note the high frequency of the G allele (48-48.8%).The low frequency of G allele is noted in the African American population (19%),in patients with type 2 diabetes - 13.7% [7].

At comparing the mean values of biochemical blood indices in carriers of different genotypes of the PNPLA3 gene (rs738409) in the group of patients with type 2 diabetes, an increased level of triglycerides, fasting glucose and glycated (glycosylated) hemoglobin was observed, the remaining parameters were within the norm (Table 2).

The highest content of triglycerides in the bloodof the investigated sample of diabetes patients was revealed in the GG genotype carriers in comparison with the carriers of the CC and CG genotypes, that is consistent with the findings of research Jean-MichelPetit et al. [7], who found the association of the polymorphism PNPLA3 rs738409 with the fat content in the liver independent of general and visceral obesity and insulin resistance. They believe that adiponutrincan be an important key to understanding the mechanisms associated with the difference between fatty liver and fatty liver without metabolic effects, so the accumulation of fat in the liver can be metabolically benign [7].

Conclusion

As a result of the investigation of the PNPLA3 gene in the Yakuts with type 2 diabetes, it was established that the frequency distribution of the alleles and genotypes of the PNPLA3 gene (rs738409) is in accordance with the Hardy-Weinberg law. In patients with type 2 diabetes, a high incidence of allele G (69.5-74.7%) was found with a predominance of the GG genotype (55.8-58.2%).

Thus, it has been established that the frequency of the mutant allele of functional polymorphism of the gene rs738409 PNPLA3 is higher than in other known world populations. The normally functioning protein of the PNPLA3 gene regulates the activity of triglyceride hydrolase and acetyltransferaselisophosphatidic acid. Therefore, it can be assumed that the high frequency of the mutant allele G of the I148M polymorphism of the PNPLA3 gene in Yakuts with type 2 diabetes may be adaptation of the organism to low temperatures. The study of the adiponutrin gene can be an important key to understanding the mechanisms of adaptation to low temperatures and metabolic processes in the indigenous population of the North.

Table 2

The average clinical indices of patients with type 2 diabetes, depending on the genotype

Indicators	CC (n=16)	CG (n=40)	GG (n=78)	Norm
Cholesterol, mmol / l	5,38±0,37	4,96±0,73	5,04±0,52	within3,2-5,6
Triglycerides, mmol / l	2,04±0,31	1,71±0,59	2,32±0,11	within 0,41-1,8
HDL, mmol / l	1,17±0,08	1,32±0,45	1,33±0,40	0,78-1,81
LDL, mmol / L	2,89±0,32	3,02±0,87	2,86±0,59	1,71-3,5
AST, U / L	18,82±1,83	21,53±0,48	19,70±0,39	Women -31 Men – 37
ALT, U / l	20,38±3,42	22,69±0,57	22,86±0,32	Women – 34 Men- 45
AST / ALT	1,11±0,15	1,04±0,39	0,97±0,53	0,91-1,75
Hb. A 1c, %	8,48±0,56	8,34±0,59	8,71±0,55	4-6,2 %
Totalbilirubin, μmol / l	9,47±1,09	9,41±0,62	10,15±0,26	3,4-17,1
Glucose on an empty stomach, mmol / l	8,51±0,96	8,84±0,76	9,19±0,53	3,89 - 5,83

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The authours

FGBIU "Yakut Scientific Center of Complex Medical Problems", 677010, Republic of Sakha (Yakutia), Yakutsk, Sergelyakhskoye shosse d.4, Russian Federation:

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

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

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

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

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

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

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

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

II. ISSUES OF THE MANIFESTATIONS AND TREATMENT OF COLD TRAUMA

S.S.Tseluyko, T.V.Zabolotskikh, S.A.Dudarikov, N.P.Krasavina, L.S.Korneeva

ACTION OF COLD ON THE ORGANISM. CRYOPROTECTORS AND MEANS OF ANTI-ISCHEMIC TISSUE PROTECTION

ABSTRACT

Temperature is the most important environmental factor affecting humans and animals. The effect of low temperatures on biological objects depends on the degree of phylogenetic maturity of the organism and is realized through various mechanisms including in vitro and in vivo conditions. The report discusses the mechanisms of cold and ischemic damage to biological objects, examines the mechanisms of damage to tissues and organs after heating, and cryoprotection products of biological objects. Particular attention is paid to preparations of pharmacological protection of tissues with antioxidant properties from cold ischemia.

Keywords: mechanisms of cold action on the body, preparations preventing cryo-damage of biological objects.

1.1 Mechanisms of cryo-damage of biological objects

During action of a low temperature on biological objects, including the organism as a whole, there are two main mechanisms of the damaging effect of cold [1, 22, 25, 28, 28, 29, 30].The first, most obvious mechanism, is a direct cryo-damage. Cold impact is crucial when a low temperature leads to frostbite or is used to conserve cells, cell suspensions and tissues.

Damage to biological objects develops both during cooling and during heating. Even before the transformation of water into a solid phase, the rate of metabolic processes slows down, and the cells undergo deep changes in the activity of enzymes. In the development of cryo-damages, the formation of ice is of great importance, which occurs in different ways depending on the freezing rate [12]. In the case of slow cooling, crystallization of water first occurs in extracellular fluids, since they have a higher freezing point than protoplasm and the nucleus. This process leads to an increase in the concentration of salts and other substances in the extracellular space and the disturbance of osmotic equilibrium. The release of water from the cells begins, the mass of ice outside the cells gradually grows, and cells lose water and undergo osmotic compression. This process up to a certain limit contributes to the preservation of cells' life, as the loss of water, in turn, increases the concentration of salts and colloids in the protoplasm, preventing its freezing.However, the continuation of the process leads to an «osmotic shock», disrupting the permeability of the membranes. After reaching the temperature of tissues -21.2 ° C, salts begin to crystallize, membranes break and the death of cells occurs.

In conditions of rapid cooling, the dehydration processes do not have time to develop, small crystals are formed both inside and outside the cells. Microscopic examination reveals minimal changes, however, the protoplasm of cellular elements is already in a state of severe disorganization, leading to cell death, mainly due to damage to membrane structures.

Thus, generalizing the factors that cause cell damage in the direct effect of cold (freezing), we can distinguish the following:

1) cell compression by extracellular ice;

2) increase in the concentration of extra- and intracellular electrolytes;

3) disturbanceof membrane permeability as a result of changes in cell lipoproteins (phase transition and separation of lipids and proteins in the plane of the membrane);

4) rupture of membranes due to rapid loss of water;

5) abnormal pH shifts;

6) mechanical rupture of membrane structures by intracellular ice;

7) thermal shock upon warming.

The second, the most probable mechanism is when at the same low temperature action on the body as a whole, only at a temperature 30 ° Cbelow zero, frostbites may appear on exposed parts of the body, which are caused by the damaging effect of the cold directly on the tissue [18]. In most cases, frostbite develops when the level of local hypothermia of tissues is clearly insufficient to immediately cause their death. It occurs as a result of disturbances in metabolic processes developing against the background of progressive circulatory disorders.

Speaking about the mechanisms of peripheral blood flow disorder during frostbite, a number of authors consider the start-up moment to be a persistent and prolonged spasm of peripheral vasculature, which occurs under the influence of the stimulating action of the sympathetic nervous system that activates under cold stress [18, 26]. At a temperature of +12 to +8 ° C, the dissociation of oxyhemoglobin ceases and the blood does not give oxygen to the tissues. Further decrease in temperature leads to a complete disruption of blood circulation. Erythrocytes are glued together in «coin pillars» and occlude capillaries, a progressive occlusion of the microcirculatory system occurs [6,7]. In this case, the fact that the cold is a specific activator of the internal mechanism of hemocoagulation plays its role, which leads to intense intravascular thrombosis [20].

Thus, local cold trauma should be considered as acute ischemia (complete or incomplete) followed by the development of early and late postischemic disorders [11].

1.2 Mechanisms of ischemic damage to biological objects

Normally, the cells of functioning organs receive energy by oxidizing substrata brought by the blood (glucose, fatty and amino acids, and ketones). In the case of liver cells and muscle cells, energy can also be obtained by cleavage of endogenous glycogen. Within the cells, energy is stored in the form of cyclic phosphates: ATP, creatine-phosphate and other nucleotides. The constancy of the composition of the cellular environment is supported by numerous chemical reactions catalyzed by enzymes, the consistency of which is ensured by the humoral mechanisms of regulation.

Ischemia leads to a cessation or a significant restriction of the influx of nutrients and oxygen into the cell. Metabolism becomes anaerobic; glycolysis is not a method to maintain a normal level of high-energy phosphates in the cell. The decomposition of ATP causes an increaseof adenosine, inosine and hypoxanthine in the cellular levels. The exhaustion of cellular energy reserves inactivates K-Na-dependent ATP, an enzyme that feeds the membrane K-Na pump. Sodium and chloride, freely hydrated ions, normally actively excluded from the cell, begin to penetrate the membrane through a concentration gradient. Since the osmotic power of the non-hydratable cellular proteins and anions is no longer balanced by the displacement of sodium, water penetrates the cell, enlarging it more and more. Mitochondrial oxidation is impossible and calcium penetrates into the cytosol and mitochondria. Experimental reproduction of cytosol overload by calcium ions showed that damage to biomembranes developing in this case is accompanied by dissociation of oxidation and phosphorylation processes, however, the penetration of calcium into the cell is not the only mechanism of influence of cold ischemia on the functions of mitochondria [32].

Anaerobic metabolism temporarily uses glucose reserves for the production of ATP, but lactic acid also forms, which leads to progressive intracellular acidosis, and subsequently to the activation of lysosomal enzymes and cell death.

Most cells and organs are able to withstand acute ischemic hypoxia within 30-60 minutes without irreversible damage [10,11], but the sensitivity of different tissues to ischemia is not the same.

Endothelial vascular cells are more sensitive to hypoxia, and microcirculation disorders that result from the damage to these cells lead to aggravation of ischemic disorders. Normally, blood cells, due to their ability to deform, freely pass through capillaries, the size of which can be less than the diameter of erythrocytes and especially leukocytes, and transcapillary exchange is normal. This is due to the functioning of the system of autoregulation of microcirculation, including, among others, the normal function of the endothelium, in particular the production of prostacyclin and nitric oxide (NO). NO is continuously synthesized from L-arginine with the participation of the NO synthetase enzyme. The main target for NO is the smooth muscle cells of arteries and arterioles: by stimulating guanylate cyclase, NO increases the concentration of cyclic guanosine monophosphate in cells, which leads to relaxation of contractile elements and vasodilation. Like prostacyclin, NO inhibits adhesion and aggregation of platelets. In physiological conditions, the endothelium carries out active transport of metabolites between the blood and perivascular tissues. It synthesizes and destroys metabolites, which regulate the interaction of blood components with the vessel wall [24].

With the fall of tissue temperature, the ability of erythrocytes to deformation decreases and their aggregation capacity increases [41]).

In the conditions of ischemia, the regulatory function of a number of vasoactive substances, primarily prostaglandins, which under normal conditions have an anti-thrombotic action and stimulate the function of leukocytes and endothelium, isdisrupted. As a result, the microcirculation protection system begins to be activated, which is designed to ensure adequate interaction of platelets, leukocytes and endothelium. Activation of blood cells under conditions of ischemia is accompanied by the release of a number of vasoactive substances (cytokines) consisting of small polypeptides. Leukocytes produce the following cytokines: tumor necrosis factor (TNF), interleukins (1L-1, IL-6, IL-8, IL-12, IL-15), platelet activating factor (PAF), proteolytic enzymes, oxygen radicals. Platelets produce serotonin, thromboxane A2, plasminogen activator inhibitor, PAF. The listed products of cytokine activity in turn activate granulocytes, platelets, endothelial cells, fibroblasts, etc.

The damaged endothelium releases the von Willebrand factor and inhibitors of the plasminogen activator. In the endothelium, as well as in platelets and leukocytes, adhesion receptors are formed. Neutrophils induced by IL-1 and TNF secrete lysosomal proteases - elastase, collagenase, toxic metabolites of oxygen, which damage the microcirculatory bed, causing increased vascular permeability, hemorrhage and microthrombosis. The action of hydrolases is realized in the development of endothelial necrosis, destruction of the basal membrane, facilitating the emigration of granulocytes. Along with interleukins, the above-mentioned PAF, which is secreted by various cells of the body, plays an important role in the pathogenesis of tissue damage. Sources of its origin are the phospholipids of cell membranes. Hyperproduction of PAF affects mainly the development of microcirculatory disorders due to activation and hyperaggregation of platelets [24].

These processes are accompanied by local hypoxia and metabolic acidosis, the

development of endothelial and tissue edema, the formation of platelet and leukocyte «plugs» in microvessels, leading to capillary obstruction and post-capillary adhesion of blood cells [20], which leads to increased ischemic disorders.

The principal difference between cold ischemia and ischemia of cardiovascular genesis is that the processes of cellular degradation in the first case are slowed down by cooling, but they do not cease altogether; therefore, ischemic disorders in the freezing of limbs are reversible only to some extent [10,11]. The simple cooling from + 37 ° C to 0 ° C increases the tolerance of most organs to ischemia from 1-2 to 12 hours [20].

The experience of cold preservation of the liver indicates that the degree of damage to the cellular organ membranes significantly increases with the duration of the cold ischemia period [18]. Similar data were obtained when studying the effect of the duration of cold ischemia on the preservation of endothelial cells of arterial vessels [23]. This circumstance, according to The authors, is a prerequisite for the occurrence of post-ischemic disorders after warming.

1.3 Mechanisms of damage to tissues and organs after warming

Not less, but no more destructive processes develop after the restoration of tissue temperature. At the cellular level during the period of cold ischemia, toxic end products of anaerobic metabolism are accumulated; after the restoration of adequate blood flow, they enter the blood, causing the development of a reperfusion syndrome.

Free radicals accumulating in cells in the form of oxygen singlets to toxic concentrations lead to secondary damage to cell membrane structures. Lipid peroxidation (LPO) of cell membranes is one of the types of normal metabolic process and proceeds continuously with low efficiency in all tissues of the body. Enzyme systems (dysmutaz, catalase, glutathione system), which under normal conditions inactivate free radicals that are formed, are mostly damaged by low temperature; endogenous cellular antioxidants (non-enzymatic part of the antioxidant system), including vitamin E, ascorbic acid, selenium salts, are rapidly depleted during cold ischemia [12].

Damage of biomembranes, primarily the walls of the endothelial vessels by free radicals , leads to increased aggregation of platelets and erythrocytes, thrombus formation with the beginning of the restoration of blood flow, increased permeability of the vascular wall, accompanied by a thickening of blood. Thus, the restoration of tissue temperature after a short period of the resumption of blood flow leads to the progression of ischemia with the only difference that in this case the processes of cellular autolysis are no longer suppressed. Cellular elements perish, in the surrounding necrosis of tissues the inflammatory process begins [23].

1.4 Mechanisms of cryoprotection of biological objects

To protect cells from the direct damaging effects of cold (usually in order to preserve them), various liquid media and chemical compounds, cryo-protectors, are used. The study of Polge C.et al. was fundamental in this regard [38,39], which showed that with deep cooling the spermatozoa can be protected from damage with the help of glycerin, which actually became the first known cryo-protectors.

In addition to the glycerol mentioned, conventional materials include such widely known substances as dimethylsulfoxide (DMSO, dimexide), polyvinylpyrrolidone, polyethylene glycol with various molecular weights.

Some of these cryoprotectants (glycerol, DMSO, polyethylene glycol) penetrate well into the cells during their freezing and balance the osmotic gradient during warming and modify the ice crystals in such a way that they become loose and do not cause large damage to the cell.

Experience in the use of polyethylene glycol with a molecular weight of 20,000 daltons (PEG-20) in the conservation of organs taken for transplantation shows that it reduces the degree of inflammatory response in the donor after the transplantation performed [34]. The authors believe that this effect is explained by the ability of PEG-20 to reduce the degree of ischemic and reperfusion injury of tissues. The disadvantage of this group of compounds is that solutions of a sufficiently high concentration (for example a 5% solution of dimethylsulfoxide (DMSO) in Ringer's solution) should be used for effective cryoprotection of biological objects, which causes their cytotoxic effect. Dimexide is also able to enhance the activity and toxicity of most drugs [2].Another group of cryoprotectants (polyvinylpyrrolidone, polyethylene oxide, dextran, oxyethylated starch) penetrates into the cell not enough. These substances are fixed mainly on the outer membrane of cells, stabilizing it both in the process of freezing and heating. These substances are low-toxic, but their effectiveness in terms of cryoprotection is still lower than that of penetrating cells [12].

On the basis of simple cryoprotectants, complex preservative solutions are created. The main requirement for a solution intended for cold preservation is the inclusion of compounds possessing osmotic activity in its composition, which makes it possible to perform effective prevention of cellular edema. Such substances include large anions of the lactate type (molecular weight 358 Da), as well as non-electrolytes for example, polysaccharides (molecular weight 505 Da) or citrate magnesium chelates (molecular weight - 1000 Da). Glucose (molecular weight - 180 Da) for these purposes is unsuitable, because it is able to penetrate slowly into cells, stimulating the production of lactic acid and hydrogen cations by anaerobic glycolysis. Therefore, glucose in complex canned solutions should be replaced with sucrose.

Another important requirement for a complex preservative solution is an effective buffer (phosphate or citrate) for arresting cellular acidosis. The importance of the two above-mentioned cryoprotection mechanisms can be illustrated by the fact that a two-component solution consisting only of sucrose and phosphate buffer has been successfully used for cold preservation of the kidney and is comparable in effectiveness to a much more complex «solution of the University of Wisconsin» [40].

The electrolyte composition of complex preservative solutions can be quite variable. The chloride-anion freely circulating through the membrane is usually replaced with lactate, gluconate or chelate citrate complex. Preservative solutions usually have a high concentration of potassium (130 mmol / L) and a low concentration of sodium (30 mmol / l). Since such a high concentration of potassium is capable of causing bradycardia, solutions of this composition can not be used for early systemic intravenous infusion. A high concentration of potassium in solutions also has a vasospastic effect, which significantly reduces the resistance of tissues to cold ischemia. In connection with the foregoing, the most effective in practice are preserving solutions with a Na / K ratio of 130/30 mmol / l, provided that buffer systems, osmoactive substances and a low concentration of chlorides are present in them.

Many preservative solutions contain magnesium ions, since they participate in the formation of chelates with citrate, making the cell membrane impenetrable to the latter. On the contrary, the content of calcium in most solutions is very low,

or this ion is excluded altogether, since cell damage in the process of cold ischemia is associated with the penetration of calcium inside it.

Among the complex solutions used for the cold preservation of organs and tissues, the most well-known solution was developed by Southard et al. [41] as a result of an analysis of a variety of factors affecting the efficiency of conservation. This solution was called «a solution of the University of Wisconsin» (UW-solution). It contains osmoactive substances (D-lactate, raffinose), phosphate buffer, free radical oxidation inhibitors, glutathione, allopurinol, precursors of energy metabolites (adenosine), vasoactive agents, hormones (steroids, insulin), and colloid (hydroxyethyl starch). This solution has proven to be clinically effective in storing entire organs used in transplantation [32,41], since in addition to cryoprotectants it includes pharmacological preparations that protect the tissues of the canned organ from cold ischemia, as it will be discussed below.

Prospects for improving the cold storage conditions of biological objects are associated with the introduction of such anti-ischemic tissue protection agents as calcium channel blockers (verapamil, diltiazem, trifluoperazine) into complex preservative solutions, as well as stable prostacyclin analogues.

1.5 Mechanisms of pharmacological protection of tissues from cold ischemia

Studies of recent decades in the field of molecular biology have shown that the pathological processes in acute ischemia of cold and cardiovascular genesis are developed according to the same laws. It was established that under these conditions there is an activation of free radical and peroxide oxidation of lipids, mediators of inflammation, adhesion molecules, etc., which take an active part in the damage of cellular and subcellular structures with the development of microthrombosis at the microcirculatory level [22, 25, 28, 28, 29, 30] .

In this connection, it is expedient to single out a special group of pharmacological preparations used to protect tissues from cold ischemia. Since the changes developing in tissues under the influence of cold ischemia are the basis for the development of postischemic disorders, the same drugs can also be considered as a means of preventing reperfusion syndrome that occurs after tissue temperature recovery and adequate blood flow.

Cold is a specific activator of the initial mechanisms of hemocoagulation [36]. However, the use of anticoagulants for the prevention and treatment of arterial thrombosis is ineffective (as opposed to venous thrombosis). This is due to the fact that there is a great difference in the mechanisms of blood clots in arteries and veins, which is largely due to the different blood flow velocity, which determines the structural features and composition of thrombi. The arterial thrombus consists mainly of platelets with a small amount of fibrinogen, since a large part of the procoagulant material is removed from the thrombotic focus by rapid blood flow even before the activation of the coagulation mechanism has occurred. In the venous thrombus, primarily fibrin is accumulated, platelets are retained in places of turbulent blood flow, in the area of valves [24]. Therefore, the most effective for the prevention of arterial thrombosis, which develops in cold ischaemia, are platelet function inhibitors, which include [4]:

1) inhibitors of cyclooxygenase (nonsteroidal anti-inflammatory drugs, acetylsalicylic acid);

2) inhibitors of phosphodiesterase and adenylatecyclase (dipyridamole, ticlopidine, pentoxifylline);

3) selective thromboxantinesynthetase inhibitors (imidazole derivatives);

4) stimulators of prostacyclin synthesis (pyrazoline derivatives, pentoxifylline, coumarin and nicotinic acid derivatives);

5) antagonists of calcium ions;

6) Prostanoids;

7) inhibitors of the release of platelet components (suloktidil, piracetam).

Thus, the main target of the action of platelet antiaggregantsare cyclooxygenase, thromboxane and prostacyclinsynthetases of platelets and vascular walls.

Among these drugs, the most popular and affordable is acetylsalicylic acid. Under its influence, on the one hand, blockade of the cyclooxygenase of platelets leading to inhibition of their aggregation occurs, on the other hand, a reduction in the synthesis of the prostacyclin of the vascular wall, a powerful antiaggregational and antithrombotic factor. The degree of oppression of prostacyclin synthesis depends on the dose of acetylsalicylic acid: small doses (3.5 mg / kg) inhibit platelet cyclooxygenase and platelet aggregation with a slight inhibition of prostacyclin synthesis, with an increase in dose (5-10 mg / kg), the antiaggregation effect of the drug rises slightly , but there is a complete loss of antiadhesive properties of the vascular endothelium [3].

For the prevention of arterial and venous thrombosis, agents that have less pronounced effects on the synthesis of prostacyclin, in particular ticlopidine or ticlid, which is the most effective antiaggregant agent, are used [5]. The drug inhibits ADP-induced platelet aggregation and aggregation, caused by collagen, reduces the adhesion of platelets to the vascular wall, normalizes erythrocyte deformability. The drug in a dose of 250 mg 2 times a day is used. However, a pronounced antiplatelet effect occurs from the 10th day of treatment, in contrast to acetylsalicylic acid, which significantly decreases the activity of platelets from the first days of application. Therefore, ticlid can be used only as a means of preventing ischemic damage in case of an expected cold exposure.

As it was noted, platelet antiaggregants are many medicinal agents of different mechanism of action, some of them have a more multiprofile effect and will be described below.

With the purpose of prevention and treatment of post-ischemic disorders, in particular, thrombo-formation, patients should use anticoagulants, the most common of which is heparin. In particular, in patients with limb frostbites, heparin is administered at a dose of up to 60,000 - 80,000 units per day for 7-10 days [7,8].

In recent years, low-molecular heparins (Fraxiparin), which have a pronounced antithrombotic activity and have a rapid and prolonged effect, have been actively used in anthological practice.

The most effective from the point of view of anti-ischemic protection of tissues are the so-called vasoactive drugs of complex action. Among the preparations of this group, pentoxifylpin (trental) is often used, which, in addition to the expressed influence on platelet hemostasis, helps to reduce aggregation of thrombocytes and increase their plastic properties, increases the content of c-AMP in tissues, and also possesses prostacyclin-stimulating action [19]. It inhibits the anti-inflammatory effect of various cytokines (IL-1 and TNF), as well as their superoxide production [24]. Pentoxifylline is most effective when applied at a dose of 1200 mg per day.

The most «old» vasoactive drug is nicotinic acid and its derivatives. It plays an essential role in the life of the organism, participating in oxidation-reduction processes, improves carbohydrate metabolism. Nicotinic acid is used in the composition of intravenous infusats for the prevention and treatment of microcirculation disorders as a 1% solution [21].

Long enough as a vasoactive agent

of complex action for the prevention and treatment of ischemic disorders curantil, which reduces the aggregation of platelets due to its ability to block phosphodiesterase is used [24, 37]. It also has a pronounced vasodilating effect, although a decrease in systemic blood pressure when it is taken, as a rule, does not occur. It is possible to use the drug in large doses (75-150 mg 3 times a day), but only in case of oral administration, since intravenous injection develops the syndrome of «intercoronary stealing».

Among non-steroidal anti-inflammatory drugs, which have anti-aggregation properties, mefenamic acid has been used in the treatment of cold ischemia and post-ischemic disorders. The drug is a derivative of anthranilic acid, which has elements of structural similarity with salicylic acid and its derivatives. According to the mechanism of action, mefenamic acid is close to other non-steroidal anti-inflammatory drugs, the ability to inhibit the synthesis of prostaglandins occupies an intermediate position between butadion and indomethacin. The anti-inflammatory effect is associated with a normalizing effect on increased permeability of capillaries and improvement of microcirculation processes; a decrease in the activity of enzymes involved in the synthesis of «mediators of inflammation» (histamine, bradykinin, serotonin, etc.); decrease in the formation of ATP and a decrease in the energy supply of biochemical processes; presence of fibrinolytic activity. For the prevention and treatment of frostbites, mefenamic acid is administered orally at a dosage of 50 mg / kg [1].

Antagonists of calcium ions (verapamil, diltiazem, corinfar) reduce the total peripheral resistance, blocking the pathologically increasing the transmembrane current of calcium ions into the cells of the smooth muscles of the vessels in ischemia. Calcium channel blockers also increase myocardial perfusion and improve its contractile function [26]. These drugs can prevent the development of distant postischemic disorders, inhibiting the proliferation of smooth muscle cells in blood vessels.

Taking into account the peculiarities of the pathogenesis of cold ischemia, drugs that have antioxidant activity play an important role in the treatment of its consequences. Among the antioxidants that have found wide application in medical practice in our country is emoxipine, a water-soluble compound from the class of 3-hydroxypyridines. Participation in various molecular reactions and influence on a number of enzyme systems of the organism cause a wide range of pharmacological activity of emoxipin [13, 14].

As an antioxidant, emoxipin inhibits the formation of hydroperoxides of phospholipids - the precursors of prostaglandins and leukotrienes. The latter can cause hemodynamic disorders that develop with cold trauma, and in addition, the inflammatory reaction caused by leukotrienes is one of the causes of microcirculatory disorders in the reactive period of acute cold trauma [40].

The effect of emoxipin on the blood coagulation systemis not associated with its antioxidant properties. At a dose of 20 mg / kg, the drug causes an increase in clotting time. This effect depends on the ability of emoxipin to form a complex with heparin, and is also the result of inhibition of fibrin polymerization [13,14]. The decrease under the influence of emoxipin both spontaneous and induced platelet aggregation is, on the contrary, due to the nonspecific antioxidant action of the drug, which inhibits the activity of platelet phosphodiesterase [17].

But the main property of emoxipin is the ability to inhibit lipid peroxidation when exposed to low temperatures, proven by the in vivo experiment, increasing the activity of the components of the antioxidant system to a greater extent than tocopherol acetate under similar conditions, which allows emoxipine to go to the number of cryoprotectants .

Among the promising antioxidant drugs used to prevent the harmful effects of cold on the body isotiorbamine (TB-6) has proved to bewell-established. It was synthesized at the OdessaStateUniversity by Candidate of Chemical Sciences S.G. Soboleva, under the leadership of Academician A.V. Bogotsky, with the participation of the Doctor of Chemical Sciences L.A. Litvinova. Isothirobamine is a pyrimidine derivative with pronounced antihypoxic properties and is a white powder with a weak specific odor, highly soluble in water and 95% ethyl alcohol [43,44].

In the course of a comprehensive study of the effect of the drug, it was found that due to its membrane-stabilizing action under conditions of general body cooling, isothiobamine prevents damage to ultrastructural elements of cardio-myocytes, reducing the cost of adaptation to cooling and thus preventing hemodynamic disturbances. In addition, changes in the morphology of the nervous system of the lungs under the influence of cold stress with simultaneous administration of TB-6 were less expressed [17].

It was established that the introduction of TB-6 in the experiment reliably prevents the development of hypercoagulability as a result of cold stress in experimental animals [17]. The obtained results indicate that TB-6 inhibits the blood coagulation, causes hypofibrinogenemia, activates the fibrinolysis system, increases the anti-coagulant activity of the blood. In the study of platelets under the influence of TB-6, antiadherent, antiaggregational and disaggregating effects of the drug were revealed. In some cases, in comparison with heparin, TB-6 causes less coarse changes in the coagulation system. Another advantage of the anticoagulant effect of TB-6 is a longer duration of action (6-fold) and the possibility of using different ways of administration. An increase in the dose from 10 to 50 mg / kg does not lead to an increase in hypocoagulation [13,14].

In addition, the use of TB-6 as a means of preventing cold stress increases the level of regenerative processes in bone tissue, reduces the risk of development of periosteal reactions with cold bone damage in the experiment [9, 15, 16].

Very promising means of anti-ischemic tissue protection are prostaglandin preparations, such as vasaprostan and iloprost [24]. Iloprost has already proved itself to be quite well in the treatment of freezing [32, 42].

The most promising means are bioflavonoid compounds. AmetisOOO (Blagoveshchensk, the Amur Region) receives dihydroquercetin (taxifolin) from Amur larch. The abbreviation is DQU. This compound according to the world literature has a powerful antioxidant effect. For the first time, information on the preparation of dihydroquercetin dates back to 1948, when Pew J.C. [60] published data that from the bark of trees belonging to the hardwood, it is possible to obtain compounds called flavonoids (dihydroquercetins). In Russia, Professor N.A. Tyukavkina in the 60's in the Irkutsk Institute of Chemistry namedafter A.E.Favorsky SB AS received dihydroquercetin (DQU) from Daurian larch.

In addition to the powerful antioxidant effect, dihydroquercetin has a rather pronounced effect in the inactivation of cytotoxic substances. [43, 44].

I would like to emphasize the report on the increase in the effect of antitoxic action of DQU in relation to acetaldehyde (the first product in the chain of processing the ethyl alcohol) by the body [31].

In addition to these effects, dihydroquercetins have an antidiabetic effect - they reduce the sugar content in the blood. [31].

Dihydroquercetins according to the literature have the ability to reduce the content of low density lipoproteins (forerunners of the atherosclerotic process) in the blood plasma and in the liver. [43].

It was noted that DQU have antitumor effect [33,34].

Flavonoid dihydroquercetin obtained from Daurian larch has anti-radiation, antiviral and immunoregulatory effects.

As it can be seen from the literature data, the application points of dihydroquercetins (DQU) are diverse. This information allows to use DQU as a basis for the creation of food additives (FA), as a material for the production of pharmaceuticals with a wide range of preventive and curative properties.

Preliminary experimental studies at the Department of Histology and Biology of the AmurMedicalAcademy have shown that dihydroquercetin obtained from Amur larch really has powerful antioxidant activity (AOA) in cold damage [28-49].

Taking into account the literature data, including the works carried out to determine AOA of DQU it is necessary to conduct research on further studying the properties of DQU received from Amur larch.

From the experimental directions it would be desirable to evaluate the effect of DQU on coagulation and aggregation hemostasis, on the thrombocytopoietic activity of the bone marrow under various models of induction of lipid peroxidation.

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The authors:

1. Tseluyko Sergey Semenovich, Head of the Department of Histology and Biology, FSBEI HE Amur State Medical Academy of the Ministry of Health of the Russian Federation, Doc. Med. Sc., professor, 675000, Blagoveshchensk, str. Gorky 95, AGMA, Tel. 8 (4162) 319-020.,T. 89145553554, E-mail: agma.agma@ya.ru

2. Zabolotskikh Tatyana Vladimirovna, Rector of the Amur SMA

3. KrasavinaNadezhdaPavlovna, professor, Doc. Med. Sc., Department of Histology.

4. Dudarikov Sergey Alexandrovich, Director of the microsurgical center of the Amur regional children's Clinical Hospital Doctor,Traumatologist - orthopedist, Candidate of Medical Sciences.

5. Korneeva LarisaSergeevna, Candidate of Medical Sciences, Department of Dermatolgy.

A.I. Fedorova, D.K. Garmaeva, L.I. Arzhakova, D.S. Belolubskaya, O.G. Afanaseva, A.I. Egorova, T.I. Dmitrieva, I.P. Semyonov, A.P. Arzhakova

IMMUNE STRUCTURES – COLD – NATURAL ADAPTOGENES

ABSTRACT

The article presents an analysis of literature data on the effect of cold on human health, the structure of the immune system, and the properties and effects of natural adaptogens.

In general, the general cryogenic climatic parameters of the Far North create uncomfortable conditions for human existence and affect people's health. In extreme conditions, protective mechanisms and adaptive alteration of the body can lead to disruption – maladaptation. A whole series of pathological phenomena develops.

In modern conditions, the development of adaptogens from local raw materials for enhancing the body's resistance, prevention and treatment of immune response disorders in low temperature conditions of the Sakha (Yakutia) Republic is a priority area.

Keywords: cold, maladaptation, immune system, lymphoid tissue, lymph nodes, natural adaptogens, the Sakha (Yakutia) Republic.

The territory of the Sakha (Yakutia) Republic is located in the zone of extreme natural and climatic factors (permafrost with a large annual temperature range from +35°C in summer to -67°C in winter, anticyclonic regime and low oxygen partial pressure in winter, etc.) and is the coldest inhabited region in the northern hemisphere of the Earth, which is due to the considerable remoteness and isolation of mountain massifs affected by moist and warm air masses from the Atlantic and Pacific Oceans and proximity to the cold seas of the Arctic Ocean [11, 17, 42].

Despite the success of mankind in creating technical means of protection against unfavorable factors of the external environment, a person is still vulnerable to the harsh power of the Arctic. For Yakutia, the extra continental climate against the background of a constantly operating cooling screen from the surface of the earth is the main external factor that negatively affects the health of the northerner. The results of numerous studies have identified two important aspects of this problem: 1) the change in the structure of northern populations by constitutions, psychological makeup, adaptive types is the result of natural selection of people most effectively adapting to the North, i.e. having good prerequisites for adaptation in these conditions (preadaptation); 2) cost of adaptation is manifested in a decrease in functional reserves and efficiency at the organismic level and in life expectancy at the population level [21].

In general, these general cryogenic climatic parameters of the Far North create uncomfortable conditions for human existence and affect people's health [1, 9, 37]. In extreme conditions, protective mechanisms and adaptive alteration of the body can lead to disruption – maladaptation. A whole series of pathological phenomena develops [7, 31].

It is known that the human body to the negative impact of various environmental factors corresponds to a violation of the immune system, especially local immunity. Damaged morphologically and functionally the organs of the immune system are not able to protect the human body from foreign influences, external or internal [32]. A consequence of the disturbance of the normal functioning of the immune system in the regions of the Far North is the widespread occurrence among residents of acute and chronic infectious and inflammatory diseases of the respiratory tract, allergic and autoimmune processes, and malignant neoplasms of certain localization [18]. The most common diseases characterized by sensitivity to climatic factors include respiratory diseases. The prevalence of respiratory diseases among children in the northern regions of the country is 1.5 to 2 times higher than the average for the Russian Federation [31].

A number of studies have shown that people arriving to the Far North from central regions of Russia and other countries (temperate latitudes) have a violation of adaptive mechanisms, characterized by a decrease in the adaptive capabilities of the body and the development of pathological conditions. In this regard, for the regions of the Far North, it remains relevant to study the mechanisms of adaptation, as well as the regulation of adaptive responses. [26]. In the studies of L.K. Dobrodeev, E.M. Dyuzhikova, L.V. Schegoleva et al. [36] showed that residents of the polar regions (Nenets Autonomous Okrug) have low rates of phagocytic activity. In the inhabitants of the North, the switching of macrophages to other functions (the exchange of blood lipoproteins) reduces their role in the formation of an immune response. For example, in the North, this leads to a "breakthrough" of the antigens of the intestinal microflora in the body's lymphoid system, followed by an increase in the immune response.

The extreme stage of the effect of cold on the human body is frostbite, which is aggravated by factors such as: alcohol, exhaustion, inactivity. In Russia, more than 1.5 thousand people die from frostbites annually. They are mostly men over 20, which is clearly associated with the consumption of alcohol [31].

The immune system is one of the most complex systems of the body, about the work of which scientists still do not have a comprehensive understanding.

It is a unique, natural defense mechanism. Thanks to the coherence of the entire functional system of immunity, the body is able to withstand many factors that have a negative impact. The uniqueness of the immune system lies in the fact that it contains such regulatory functions that allow, in the presence of each specific antigen being the starting point, to bring a huge machine called the immune system into action and react with a specific immune response in accordance with its individual characteristics [29]. Only two types of biological systems – nervous and immune – have the capacity for "intelligent" information processing, including memory, learning, recognition and decision-making in previously unknown situations. A new interdisciplinary approach to the study of the immune system will require additional information describing the interaction of its components, which should be presented in quantitative terms. In this form it will

be available not only to immunologists, but also to specialists from other fields of science - mathematicians, physicists, engineers and other researchers [4]. The computational capabilities of the immune system have only recently been evaluated as a new promising direction, called immunocomputing (IC) [43]. In this case, each cell of the body is subject to control of its own immune system (IMC) – an information security system that for each cell solves the problems of integrity, confidentiality and accessibility of information [4].

In recent years, interest in the immune system, its structure and functions has increased significantly. The cellular and subcellular levels of studying the organs of the immune system, in particular lymphoid tissue, are of particular importance in the development of the problems of immunomorphology. Structures of the immune system are present in virtually all organs and tissues. Some structures are located on the pathways of possible introduction into the body of foreign substances, others on the way of following them in the body. Located at the surface of the respiratory tract, lymphoid tissue serves as the first specific barrier to the penetration of foreign antigens. They are the first "target" on the way of penetration of cold air into the respiratory system [19, 31]. In connection with this, the resistance of the organism to the action of low temperatures, the formation of adaptive processes in it, depends on the functional activity of immune structures [12, 31].

Lymphoid tissue, being the main polygon of development of specific immunological reactions, contains the basic cellular populations (lymphocytes, macrophages, plasmatic, fat, reticular cells) involved in ensuring genetic consistency of the internal environment of the body. Carrying out a lifelong monitoring of the maintenance of antigen homeostasis, the immune system is in strict interaction with other functional systems (nervous, endocrine, etc.) involved in the processes of adaptation of the organism to the changing factors of the external and internal environment. The immune system protects the body from the effects of various damaging factors of exogenous and endogenous origin, provides protection against pathogens, viruses and fungi, performs antitumor protection, and participates in processes of elimination of tissue structures that have become due to mutation or alienation processes. The adequacy of the body's response to genetically alien agents and the likelihood of developing allergic, infectious, autoimmune and oncological diseases depend on the state of the immune system, its adaptive capabilities [32, 34, 38].

Lymph nodes are the most numerous peripheral organs of the immune system that serve as biological filters. Lymph nodes are located on the path of lymph flow (tissue fluid) from organs and tissues. Alien substances enter the sinuses of the lymph node, where they are recognized by lymphocytes and destroyed with the help of macrophages. Through the lymph nodes, which together with the lymphatic capillaries, vessels and trunks form the lymphatic system, the tissue fluid is filtered and again returns to the bloodstream from all regions of the body. Therefore, the importance of lymph nodes and lymphatic system in general in the performance of protective functions in the body is great. The lymphatic system is considered as the most important component of the immune system [3, 6, 23, 28, 41].

As a result of exposure to the human body of various unfavorable factors of the external environment, the body's defenses are weakened. Damaged morphologically and functionally the organs of the immune system are not able to protect the human body from foreign influences, external or internal. Depending on the degree of damage, disruption of the structure and function of the immune system, a person is more often and heavier sick [32].

Currently, the study of various organs of animals and humans subjected to cold exposure draws the attention of researchers. Influence of low natural temperatures in Sakha (Yakutia) Republic causes depletion of diffuse lymphoid tissue of the laryngeal mucosa, which is expressed by a decrease in the number of cells of the lymphoid series, in particular T-lymphocytes, B-lymphocytes, plasma cells, and a significant increase in the number of destructively altered cells, and as a consequence, macrophages [5]. Changes in diffuse lymphoid tissue in the mucous membrane of the larynx under the influence of low natural temperatures are characterized by a significant decrease in lymphopoietic processes, which is expressed in a decrease in the percentage of lymphoblastic cells and cells in mitosis [5, 8].

Complex morphological changes in the trachea of rats with cooling according to O.N. Lee et al. [25] showed changes characteristic for the stage of adaptive stress, at which destructive changes of ciliate cells, goblet cells, and expressed migration of mast cells occur. Under the action of low temperatures in the lungs of experimental animals, foci of fibrosis and edema, dilatation of blood vessels, increased migration of mast cells and eosinophils to the bronchial epithelium appear [13]. The results of the studies N.P. Krasavin, V.A. Dorovskikh, S.S. Celuyko [20] showed that unfavorable factors of the air environment quite often have a negative effect on the airways, especially when the body stays in a low temperature for a long time. When the cold factor influences the organism, protective and compensatory processes at the subcellular and cellular levels are first mobilized [35].

According to the results of research L.A. Obukhova [27], O.V. Matkina [24], structural transformations in the thymus, revealed during experimental cooling, can be characterized as a pronounced accidental involution of the thymus in the stage of hypotrophy, the main manifestations of which are a decrease in the mass and volume of the organ, a decrease in the size of the cortical substance; oppression of the lymphopoietic function and an increase in the death of lymphocytes by the type of apoptosis, leading ultimately to a decrease in the number of lymphoid populations in the thymus. From the side of the lymph nodes during extreme cooling, changes characterized by activation of B-dependent zones with the formation of new ones and stimulation of pre-existing germinal centers, hypertrophy of the brain strands, development of plasmacytic, eosinophilic and mast cell responses were noted.

O.T. Devonayev [15] studied lymphoid structures of the urinary organs of rats susceptible to cold stress and high altitude conditions. With the action of cold for 7 days, the author observed a decrease in the length, width and area of lymphoid nodules, the number of lymphoid cells in the ureter and bladder, and the size of the glands of the bladder. The decrease in the amount of lymphoid tissue, the increase in degenerative processes in it, and the decrease in lymphocytopoiesis were maximal on day 14 of the experiment, after which gradual quantitative and qualitative normalization were observed.

Hypothermia has a depressing effect on the severity of the cellular and humoral immune response [10, 14, 16, 39]. The research of V.M. Nikolaev showed a change in the phagocytic activity of leukocytes when exposed to low temperatures. Reduction of the number of absorbed particles by leukocytes testifies to the suppression of nonspecific cellular immunity in hypothermia [26].

At the same time, structural changes in various organs and systems of the

organism in the extreme conditions of the North have not yet been studied. In this regard, in modern conditions, increasing unfavorable environmental and professional impacts, morphological studies of the immune system organs remain adaptable and promising, and maladaptation of the organism to the action of extreme factors. The data obtained will provide the basis for establishing the state of protective, adaptive capabilities of organs, taking into account the temperature regime of Yakutia.

The tasks of today are to find ways to preserve the health of workers in the Arctic region by modern means of medical and biological science. The search for solutions is seen in the prevention of psychoemotional stress, sleep and desynchronosis disorders, physical stress (cold, hypoxia, etc.) [21]. One of the most effective ways of healing is the use of natural stimulants for the functions of organs and systems of the human body [40]. In these conditions, the task of restoring the working capacity of the human body systems responsible for adaptation to unfavorable environmental factors is urgent. One of the ways of healing is the use of natural stimulants of the functions and systems of the human body. There are two approaches to solving the problem of adaptation (adaptation) of a person to a new environment. The first is strict environmental protection and at least the preservation of its condition. The second is to increase the stability of the human body itself to harmful environmental factors. In connection with the second approach, substances that stimulate the body's resistance are of great interest, capable of mobilizing its unused reserve mechanisms under normal conditions. These compounds include stimulants and adaptogens (from the Latin "adaptation" – adaptation), differing in the mechanism of their impact. When adaptogens are used, all human protective forces are harmoniously mobilized, because these substances directly affect tissue metabolism, increase mental and physical performance, and also prevent disorders caused by emotional stress and other extreme effects [2].

Adaptogens have a specific immunostimulating and anabolic effect on the condition of the central nervous system, hemopoietic organs and hormones, causing a humoral response by sensitizing B-lymphocytes (immunoglobulin synthesis) and T-lymphocytes (thymus-dependent cells), the result of which is the cellular response [3, 22]. In conditions of general body cooling, timely and targeted correction can help reduce the effect of cytotoxic factors. Addition to the main treatment application of adaptogen will prevent the development of chronic inflammation and optimize the quality of therapy for patients with respiratory diseases [13]. In the climatic conditions of the Far North, chronic lung diseases are characterized by a protracted course, and often accompanied by exacerbations, in connection with which the need for individualization of treatment and the selection of means of prevention becomes apparent. Therefore, one of the leading places is the use of drugs of natural origin, allowing to reduce the level of negative influence of low temperatures on the body [8, 29, 30].

Immunotropic or immunomodulating drugs are used to correct immunity. In the work of L.A. Obukhova [27] it was shown that when polyphenol compounds were introduced from the overground part of the cuff ordinary under conditions of physiological norm, tendencies were revealed in the structural transformations of lymphoid organs, indicating an increase in their functional activity and an increase in structural reserves. In the thymus – increased proliferation of lymphoid and epithelial cells, accompanied by an increase in the number of lymphocytes in the organ and the formation of additional endocrine structures (glandular formations); the formation of additional elements of the microcirculatory bed; activation of the mast cell population carrying out local regulatory functions; Enrichment of epithelial cells with subcellular structures responsible for protein synthesis and energy supply. In lymph nodes – an increase in the size of B-dependent zones and increased proliferation of cells of different specializations. Prophylactic and early pathogenetic correction by polyphenolic compounds from the overground part of the cuff of the ordinary leads to a decrease in the loss of body weight and lethality of animals during the period of extreme cooling, a decrease in the manifestation of involutive changes in the thymus, a decrease in the reactivity of the lymph nodes, not associated with the development of destructive processes in them, and full restoration lymphoid organs during the period of readaptation.

According to domestic and foreign studies, currently up to 30% of patients suffering from various diseases need the appointment of immunomodulatory therapy. The syndrome of secondary immune deficiency, accompanied, as a rule, by reversible disturbances in the functioning of the immune system, its adaptive mechanisms and other functions, significantly complicates the course of any diseases. Violation of the normal functioning of the immune system not only determines the more severe, prolonged course of any illnesses, but also contributes to the generalization of inflammatory processes, the development of complications, to a decrease or lack of clinical effect from basic therapy, to an increase in lethality [33].

Thus, in modern conditions, the development of adaptogens from local raw materials for enhancing the body's resistance, prevention and treatment of immune response disorders in low temperature conditions of Sakha (Yakutia) Republic is a priority area.

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Credits:

1. Fedorova Aida Ivanovna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79241696871, e-mail fed.aida@rambler.ru

2. Garmaeva Darima Kyshektovna, Doctor of Medical Sciences, Professor, M.K. Ammosov NEFU Medical Institute Docent, +79142349680, e-mail dari66@mail.ru

3. Arzhakova Lena Ignatevna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79644150606, e-mail lenaarzhakova@mail.ru

4. Belolyubskaya Dariya Stepanovna, Candidate of Medical Sciences, M.K. Ammosov NEFU Medical Institute Docent, +79142976118, e-mail b_d_st@mail.ru

5. Afanasyeva Oksana Gavrilovna, Candidate of Medical Sciences, доцент M.K. Ammosov NEFU Medical Institute Docent, +79142671992, e-mail kafanatomiya@mail.ru

6. Egorova Angelina Innokentievna, Candidate of Biological Sciences, Junior Research Associate, M.K. Ammosov NEFU Medical Institute Docent, +79148220249, e-mail egorovaanil@mail.ru

7. Dmitrieva Tuyara Ivanovna, Candidate, Federal State Budget Educational Institution "Yakut State Agricultural Academy", +79644298776, e-mail dark_dell@mail.ru

8. Semenov Ilya Petrovich, 2nd year student of "General Medicine" at M.K. Ammosov NEFU Medical Institute, +79246647537, e-mail Ilyamedik@icloud.com

9. Arzhakova Aleksandra Petrovna, Аржакова Александра Петровна, Candidate of Sociological Sciences., Senior Associate. RAS SB Institute of Biological Problems of Cryolithozone, e-mail sasha.a7.t9@mail.ru.

E.D. Oкhlopkova, L.I. Konstantinova, L.D. Olesova, G.E. Mironova, E.I. Semenova, A.I. Yakovleva, A.V. Efremova, Z.N. Krivoshapkina, V.A.Alekseev, V.M. Nikolaev, S.D. Efremova

THE CORRECTION OF PEROXIDATION DURINGPHYSICAL ACTIVITYBY EXOGENOUS FACTORS IN THE CONDITIONS OF COLD CLIMATE OF YAKUTIA

ABCTRACT

The effect of the vitamin-mineral complex and one-day koumiss on the imbalance of the LP-AOS organism of athletes of Yakutia was studied. It is established that in winter during the period of intense physical activity the intake of the vitamin and mineral complex helps to reduce the intensity of lipid peroxidation and has a supporting effect of the body's antioxidant defense during the 20-day period. The antioxidant effectiveness of koumiss in summer is manifested by an increase in the activity of the enzymatic link already on the 10th day of administration and is an effective means for accelerating the body's recovery processes

Keywords: lipid peroxidation, antioxidant system, physical activity, cold, Yakutia.

Introduction

In the Far North, where winter lasts for more than 6 months, cold is one of the main factors affecting metabolic changes in a human body. It is known, that one of the adaptive reactions of the organism to the cold climate is an acceleration of metabolic processes, including theoxidation of free radicals[1,5,11]. At the same time, intense physical loads contribute to the intensification of peroxidation processes and formation of free radicals [9].

In modern sports, with an increased level of physical activity at all stages of training process, the prevention of fatigue, the acceleration of recovery processes and the increase in general and physical performance through various exogenous additives is becoming increasingly popular [9]. In the conditions of Yakutia, the recovery processes can be accelerated with the help of bio-additives from local raw materials of plant and animal origin [2]. Products with antioxidant effect can stimulate the body's defenses, increase overall stability and vitality, physical and mental performance. Therefore, study of properties of biological additives that reduce negative impact of negative environmental factors, has special role in prevention of development of pathological conditions associated with intense physical exertion not only among athletes, but also in population engaged in physical labor in extreme cold conditions of Yakutia.

The aim of the study was to evaluate the effectiveness of the vitamin and mineral complex and koumiss in maintaininglipid peroxidation (LP) and antioxidative defense (AOD) systems ofathletes under intensive physical exertion in Yakutia.

Materials and methods

The study involved 79 volunteers (freestyle wrestlers) of Yakut nationality, which were divided into four separate groups. The first and the second group consisted of 39 highly qualified athletes from the School of Higher Sportsmanship in Yakutsk and students of the Institute of Physical Training and Sports of Northeastern Federal University, at the age of 21 to 24. The first group consisted of 21 sportsmen who took «Valtek-SP Active» drink prepared from a dry mixture supplemented with vitamins and minerals once a day after evening workout during 20 days. The second group consisted of 18 sportsmen who took similar drink that did not contain vitamin and mineral additives made by ValetekProdimpexas a placebo. Biochemical studies in these groups were performed three times (before the drink administration, after 10 days and after 20 days of administration). The study was carried out in the beginning of the competition period, during the winter period (November-December).

The third and the fourth group consisted of 40 athletes from the School of Olympic Reserve aged 13-16 years. The study was conducted during the beginning of the recovery period in the summer sport camp «Rodnik».

The third group included 20 athletes who took 250 ml of kumis drink everyday 4 times a day (3 times 20-30 minutes before meals and once before the bedtime) during 10 days; the fourth group consisted of 20 sportsmen who did not take kumis during the recovery period. The study was performed twice, before the start of kumis administration and on the 11th day after the end of kumis administration.

The vitamin-mineral supplemented drink was prepared by dissolving 10 g of the dry mixture in 250 ml of bottled water at room temperature. The drink contained following vitamins and minerals: A (0.39 mg), E (7.5 mg), D3 (5.35 μg), C (64.0 mg), B1 (0.95 mg), B2 (1.1 mg) , B6 (1.2 mg), B12 (1.6 μg), PP (9.65 mg), K1 (48.5 μg), pantothenic acid (2.9 mg), folic acid (0.38 mg) , biotin (16.0 μg), calcium (140 mg), magnesium (100 mg), succinic acid (50 mg), carbohydrates (6.7 g). Certificate of Conformity of the Russian Federation No. C-RU.AE84.V.06712 TR 0497019 and «Dry mixture with vitamins and minerals «Valetek-SP Active»(cherry and orange) in the form of a drink (certificate of state registration RU.77.99. 11.003.E.045369.11.11 issued 03.11.2011) produced by ZAO ValetekProdimpeks. Kumis was manufactured byOAO Sakhaplemobedineniyefrom mare's milkwith the use of standard technology TU 9222-001-55673105-2009.

The research material was heparinized blood and serum. Blood sampling was performed in the morning on an empty stomach from the ulnar vein. The study protocol was approved by the local committee on biomedical ethics at the Yakutsk Scientific Center of Complex Medical Problems (Minutes

No. 24 of June 29, 2010). The samples were collected after voluntary informed agreement of the participants.Studies of the lipid peroxidation rate and the state of antioxidative system were carried out on erythrocyte suspension using spectrophotometric method on Specord 40 spectrophotometer. Lipid peroxidation was determined by the accumulation of thiobarbiturate-active substances(TBAS) [12].

Antioxidative protection was measured by superoxide dismutase (SOD)[10] and catalase [4] activities, as well as by the total content of low molecular weight antioxidants (LMWA) [7]. The content of ascorbic acid in blood serum was measured using titrimetric method. The statistical analysis was done using statistics software Statistica 6.0 and SPSS 19.0 for Windows. The normality of independent variables was confirmed by nonparametric Kolmogorov-Smirnov test.

The reliability of the mean differences between the groups with an abnormal distribution was determined by the Mann–Whitney t-test. Probability of the validity of the null hypothesis was assumed for $p < 0.05$.

Results and discussion

The results of our study demonstrated that the intensity of lipid peroxidation and the state of antioxidative system in the first, third, second and fourth groups before taking the vitamin-mineral drink and kumis on the first day of the study were significantly different. The concentration of TBAS in the first and second groups was reduced by 45 and 41%, compared to the third and fourth groups, respectively (Fig. 1-2). The initial values of the total LMWA content of the athletes of the first and the second group were higher by 75 and 69%, SOD by 71%, and catalase activity in both groups was reduced by 33 and 43%, compared to the third and fourth groups, respectively. The level of vitamin C in all groups of athletes was normal, but was lower in the third group (Table 1-2).

Changes in indicators were associated with different levels of load during training periods and with the time of the year during the study and were consistent with previously published data [6,8]. On the 10th day, the following changes were recorded in the study groups: the concentration of TBAS in the first, second, and the fourth group did not change, and in the third group it was significantly decreased by 35% ($p<0.05$) compared to the first day of the study 1-2). The total content of LMWA during this period increased in all four groups, but the nature of the increase had some differences. In the first and the third group LMWA levels were significantly increased - by 44 and 41%, respectively, which was due to the positive effect of the synthetic vitamin-mineral complex and kumis drink. In the second and the fourth group, the increase was insignificant - by 6 and 19% respectively, compared to the first day. The activity of antioxidative defense enzymes varied in different ways. A decrease in catalase activity in all groups was observed. The greatest decrease was by 11 and 19% in the first and the third group respectively, which is probably due to a parallel increase in SOD activity, and in the second and the fourth group the decrease was by 8 and 11% respectively. The activity of SOD in the first group did not change, and in the third group it was increased by 80%, in the second group the enzyme activity remained at the initial level, and in the fourth group it increased by 24% compared to the first day of the study. Nutritional factors that reduce catalase activity include lack of vitamin B, folic acid, biotin, vitamin A. The reduction of catalase levels in the third group was more pronounced, similar to the effect of excess of methionine, tyrosine, cystine, copper and zinc, which are contained in kumis. Catalase prevents the accumulation of hydrogen peroxide in the cell, which is formed during aerobic oxidation of reconstituted flavoproteins and also from oxygen. The decomposition of peroxide requires very small amount of enzyme, the reaction

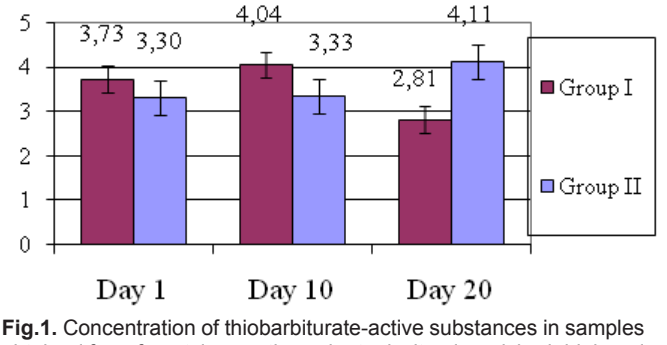

Fig.1. Concentration of thiobarbiturate-active substances in samples obtained from freestyle wrestlers who took vitaminenriched drink and a placebo for 20 days (nmol/L).

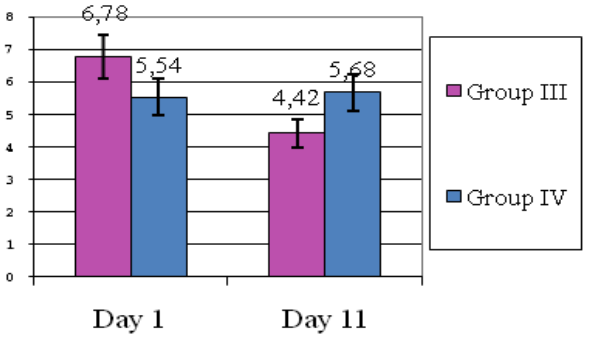

Fig.2. Concentration of thiobarbiturate-active substances in samples obtained from freestyle wrestlers who drank kumis for 10 days and did not drink kumis (nmol/L).

Table 1

The indicators of the antioxidative system of freestyle wrestlers before and after administration of the vitamin-mineral drink

	GroupI (People who were administered the drink) (n=21)			GroupII (People who were administered placebo) (n=18)		
	Day 1	Day 10	Day 20	Day 1	Day 10	Day 20
LMWA,mg×equvalent /ml erythrocyte	0,065±0,00	0,098±0,00**	0,130±0,01***	0,068±0,00	0,072±0,00	0,087±0,00
SOD, μM/min×ml	0,061±0,00	0,060±0,05	0,061±0,00	0,061±0,01	0,062±0,00	0,061±0,00
CAT cat/L	0,700±0,03++	0,625±0,05*	0,592±0,05**++	0,509±0,05	0,467±0,04	0,251±0,03
Vitamin C, 0.7-1.5 mg/dL	1,01±0,09	1,51±0,07	1,76±0,06*+	1,01±0,12	1,24±0,17	1,04±0,20

*) $p<0,5$; **)$p<0,001$; ***)$p<0,0001$ in the first group compared to the first day of study; +) $p<0,5$; ++) $p<0,001$; +++)$p<0,0001$ compared to the second group that was administered a placebo.

Table 2

The indicators of the antioxidative system of freestyle wrestlers who were and were not administered kumis

	Group III (people who drank kumis) (n=20)		Group IV (people who did not drank kumis) (n=20)	
	Day 1	Day 10	Day 1	Day 10
LMWA, mg×equvalent /ml erythrocyte	0,016±0,00	0,027±0,00*	0,021±0,00	0,026±0,01
SOD, μM/min×ml	0,018±0,00	0,090±0,05**	0,019±0,01	0,022±0,00
CAT cat/L	0,915±0,04++	0,750±0,05*	0,899±0,01	0,804±0,05
Vitamin C, 0.7-1.5 mg/dL	0,87±0,08	1,38±0,09*	1,03±0,10	0,95±0,08

*) p <0.5; **) p <0.001; in the first group, in comparison with the first day of the study.

speed is determined by diffusion and does not require energy for its activation [3]. It should be noted that catalase is the second link of antioxidative defense system, therefore, the reduced activity of the enzyme in athletes of the 3rd and 4th groups can be related to more efficient work of the first link of the antioxidative defense system, in particular, SOD and non-enzymatic antioxidants. On the 20th day of the study in the 1st group of athletes who were taking the vitamin drink, the concentration of TBAS decreased by 24%, which indicates a decrease in the intensity of lipid peroxidation in this group. In contrast, in the second group of athletes who were administered a placebo, the concentration of TBAS, increased by 20%, compared to the first day, which is an unfavorable sign and shows the tension of adaptation processes during the period of competition (Fig. 1). The total content of LMWA increased in both groups of athletes: in the first group by 50 (p <0.0001) and in the second group by 22%. Catalase activity in both groups decreased in comparison with the first day of the study, but in the first group of athletes the decrease in activity was insignificant - 15% (p <0.001), while in the second group, 51% (p <0.001). The SOD level remained unchanged throughout the study period. The content of vitamin C in the first group increased by 57%, while in the second group it remained at the same initial level (Table 1). Consequently, «Valtek-SP Active» vitamin-mineral complex had a significant antioxidative effect on the 20th day of the study. To determine the efficacy of vitamin-mineral drink and kumis, a comparative analysis of pro- and antioxidant equilibrium was performed in all groups, which was calculated with the formula:

CAOD / LP = LMWA + SOD + CAT / TBAS.

At the beginning of the study, the coefficient of pro- and antioxidant balance in the athletes of the first group was 30% higher than in the third group (Fig. 3), which can be explained by the relatively low level of TBAS (Fig. 1). Thus, the lower intensity of lipid peroxidation and the best state of antioxidative system (increased level of SOD activity, content of LMWA and ascorbic acid (Table 1)), was common for the beginning of the competition period. In the third group, a decrease in CAOD/LP value was attributed to a high level of TBAS and a decreased antioxidativedefence, as the athletes were fatigued and overtrained at the initial stage of the recovery period. On the 10th day of the study, the three groups showed a decrease in CAOD/LP index: in the first group, by 10, in the second group by 6 and the fourth group by 12%. The third group, demonstrated a significant 30% increase in CAOD/LP (Fig. 3), which is a favorable sign in the recovery period and is associated with a decrease in TBAS levels (Figure 2). The increase in LMWA, SOD and vitamin C levels (Table 2) indicate ongoing regenerative processes in the body and adaptation of the organism. On the 20th day in the first group there was 20% increase in CAOD/LP value compared to the first day and 36% on the 10th day (Fig. 3), which was caused by statistically significant decrease in TBAS by 24%, an increase in the content of LMWA by 15, vitamin C by 57% and with the supportive action on the enzymatic link. Catalase activity associated with increasing competition loads decreased by only 15%, and SOD activity did not change (Table 2). In the second group CAOD/LP value decreased by 50 and 53%, respectively, compared to the first and the tenth day, indicating a decrease in antioxidativedefense levels (nonenzymatic and enzymatic part) and the prevalence of prooxidative processes.

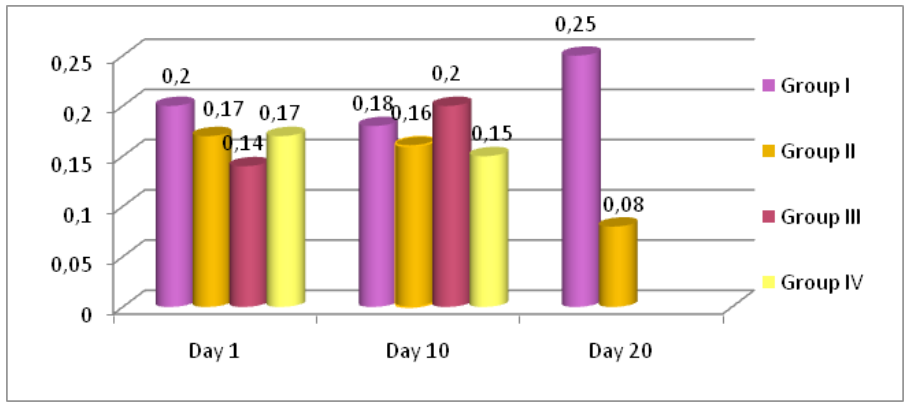

Fig. 3. The level of antioxidant balance before and after administration of the vitamin-mineral complex and kumis

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The authors

1. Yakutsk Scientific Center for Complex Medical Problems, 677010, Yakutsk, Sergelyakhskoye Highway, 4 km.

2. North-East Federal University. M.K. Ammosova, 677000, the city of Yakutsk, ul. Belinsky, 58.

3. Okhlopkova Elena Dmitrievna - Candidate of Biological Sciences, Leading Researcher - Head of Immunology Laboratory, FGBICU «YANC KMP», elena_ohlopkova@mail.ru

4. Konstantinova Lena Ivanovna - Researcher at the Laboratory of Biochemistry, FGBICU «YANC KMP», konstanta.l@mail.ru

5. Olesova Lyubov Dygynovna - Candidate of Biological Sciences, leading researcher - head of the laboratory. Biochemistry, FGBNU «YaNC KMP», oles@mail.ru

6. Mironova Galina Egorovna - Doctor of Biological Sciences, Professor of Biological Branch of the IAN FGAOU VOFU. M.K. Ammosov, mirogalin@mail.ru

7. Semenova Evgenia Ivanovna - Ph.D., Senior Researcher of the laboratory. biochemistry, FGBNU «YAC CMP», kunsuntar@mail.ru

8. Yakovleva Alexandra Ivanovna - a research fellow at the laboratory. biochemistry, FGBNU «YAC CMP», sashyak@mail.ru

9. Efremova Agrafena Vladimirovna - Ph.D., Senior Researcher of the laboratory. biochemistry, FGBNU «YaNC KMP», a.efremova01@mail.ru

10. Krivoshapkina Zoya Nikolaevna - Ph.D., senior research fellow of the laboratory. Biochemistry, FGBNU «YaNC KMP», zoyakriv@mail.ru

11. Alekseev Vladislav Amirovich - junior research fellow of the laboratory. Immunology, FGBNU «YaNC KMP», vldsvalekseev@gmail.com

12. Nikolaev Vyacheslav Mikhailovich - Ph.D., Chief Researcher - Head of the Department for the Study of Adaptation Mechanisms, FGBICU «YANC KMP», Nikolaev1126@mail.ru

13. Efremova Svetlana Dmitrievna - junior research fellow of the laboratory. immunology, FGBNU «YaNC KMP», esd64@mail.ru

A.G. Egorova, N.S. Arkhipova

DYNAMICS OF MORTALITY FROM HYPOTHERMIA IN SAKHA (YAKUTIA) REPUBLIC FOR PERIOD OF 2006-2015

ABSTRACT

The article presents an analysis of mortality from total body hypothermia in the Sakha (Yakutia) Republic for the period from 2006 to 2015. Dynamics shows persistent trends of reducing deaths from the defined causes, the frequency of which depends on the place of residence (territorial zone), the season of the year, the age and length of stay.

Keywords: mortality, general hypothermia, cold trauma, Yakutia.

The Republic of Sakha (Yakutia), due to its geographical location, is the coldest region in the world. More than 40% of the territory of the Republic is located to the north of the Arctic Circle. That is, half of Yakutia has the same weather properties as the Subarctic. It has extreme climatic and geographic conditions, where cold is one of the main environmental factors adversely affecting the human body [1]. It is here that the pole of the cold of the Northern Hemisphere – Oymyakon is situated. The study of the effect of low temperatures on the human body represents both theoretical and practical relevance in fundamental and medical science. In the Far North, more than 11,000 cases of medical care to victims of acute cold trauma, general body hypothermia or frostbite are recorded annually. The most frequently effects of low temperatures with adverse effects on the human body among the population of Yakutia are recorded [4].

We analyzed the data from all deaths (2009) from total body hypothermia in the Sakha (Yakutia) Republic for 2006-2015 of the Yakut Republican Medical Information and Analytical Center database. It should be noted that the term «mortality from general hypothermia» is a collective term in which we included the following disease codes for ICD-10: the effects of excessively low natural temperature (X31), frostbite (T33-T35), hypothermia (T68) and other effects of low temperature (T69).

In the structure of all causes of death from injuries, poisonings (class XIX) and external causes (class XX), the proportion of deaths from fatal hypothermia is, on average, 10%, i.e. 200 of the Republic's people die from hypothermia every year (Table 1).

In the dynamics of observation in the period of 2006 to 2015, there is a persistent tendency to reduce deaths from total hypothermia in a group of men. The analysis of the comparison of groups by sex showed gender differences in the frequency of detection of death from fatal hypothermia. Men in comparison with women are much more often exposed to low temperatures with fatal outcome. In women, there is no decrease in deaths from total hypothermia. In the structure of all causes of death from trauma, poisoning and external causes among the deceased from general hypothermia, women account for the largest share. In 2009, in comparison with other years, we recorded the greatest number of deaths from fatal hypothermia with an increase in the group of men and women (Fig. 1).

Mortality from general hypothermia in the uluses (territories), depending on the socio-territorial zones, proposed by M.A. Tyrylgin [3] showed that the Arctic zone is the first place in terms of death rate, followed by rural and mixed ones. The lowest mortality rate is observed in the industrial zone and in Yakutsk. The peak of mortality from hypothermia in the Arctic zone falls at 2009-2010, with a decrease by 2011 with a subsequent rise to 2013, followed by a decline in mortality from this pathology until 2015. In general, for the period from 2009 to 2010 is characterized by an increased mortality from total hypothermia in three main areas of residence: Arctic, rural, and mixed (Table 2, Fig. 2). There are speculations that the risk of pathological hypothermia is higher in places of residence with extreme climatic conditions and not densely populated areas [8, 9].

Analysis of mortality from low temperatures on the human body by age group indicates a high mortality rate in the group of people of working age, from 40 years and above. For the period from 2006-2015, a consistently high

Table 1

Proportion of deaths from total hypothermia in the structure of all causes of death from injuries, poisoning and external causes in the Sakha (Yakutia) Republic 2006 - 2015

Year	All deaths from injuries, poisoning and external causes			Cases of death from hypothermia					
				abs.			Proportion in %		
	total	male	female	total	male	female	total	male	female
2006	2061	1654	407	204	162	42	9	9	10
2007	2010	1648	362	184	140	44	9	8	12
2008	2036	1668	368	211	171	40	10	10	11
2009	2364	1877	487	306	226	80	13	12	16
2010	2009	1604	405	246	186	60	12	12	15
2011	1863	1506	357	200	156	44	11	10	12
2012	1683	1365	318	181	144	37	11	11	12
2013	1540	1237	303	170	113	57	11	9	19
2014	1484	1212	272	162	123	39	11	10	14
2015	1407	1147	260	145	104	41	10	9	16

death rate is observed in the age group of 45-49, 50-54. The highest mortality rate was registered in 2009 for almost all age groups, beginning under 20 and up to 55-59 years (Table 3). Only in 2011 the highest indicator was found in the group of persons from 40 to 44 years. The lowest mortality rate for each year of observation falls on the age of up to 20 years. In 25-29 yrs group we also trace decreasing trend of people dying from general hypothermia. It should be noted that in only one age group – over 60, in dynamics the mortality rate decreases every year. The older a person, the more quickly the body loses heat. In comparison with the young, they are more prone to hypothermia in view of the accumulation of chronic diseases with age and the intake of medications [5, 7].

The greatest frequency of occurrence of cases from total hypothermia is in the winter months of the year (Table 4). As of March, the most frequent cases of mortality were in 2009 and 2012. In these years, the highest percentage of deaths from hypothermia was observed in December, January and March. Frequency of deaths was almost identical in January and March, 2009 and slightly higher in March, than in January, 2012. However, 2015 is different from all previous years, the fact that exactly then the high frequency of cases of exposure to cold was recorded not only in December and January, but also in April and May. In that year's spring months there were more cases of hypothermia than in January. Thus, based on statistics, the most frequent seasonal causes of mortality from total hypothermia are the winter and spring periods of the year, as shown more clearly in Fig. 3. According to other studies, The authors argue that death from general hypothermia is seasonal. From their sources it follows that about 16% of death from hypothermia occurs in the autumn-winter months, and more than 19% in spring [2, 6].

The analysis of the investigated deaths from total hypothermia by nationality revealed that the highest mortality rate is observed in people of ethnic groups that do not belong either to the indigenous (Yakuts, small indigenous peoples of the North), nor to non-indigenous people (Russians). The second place in the group of frequent deaths from cold is given to the small peoples of the North. From 2008 - 2010 there is a positive trend in a significant decrease in mortality in the group of the small people of the North

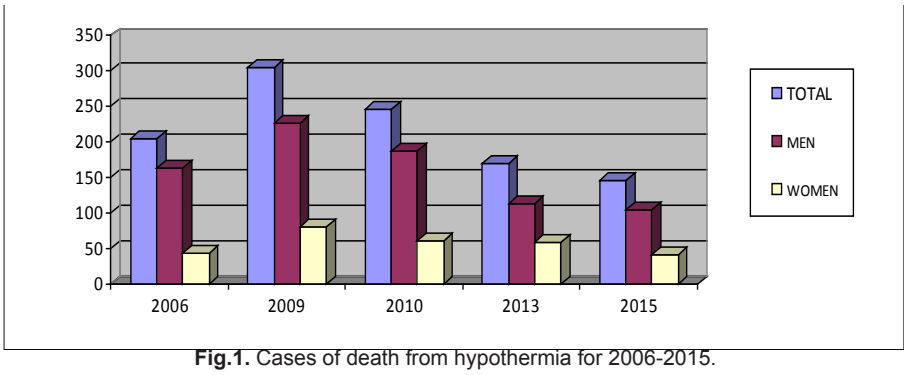

Fig.1. Cases of death from hypothermia for 2006-2015.

Table 2

Mortality Rate from Hypothermia by Socio-territorial Zones from 2006 - 2015 per 1000 People

area	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yakutsk	0,20	0,10	0,15	0,23	0,19	0,15	0,16	0,18	0,11	0,09
Arctic	0,31	0,45	0,49	0,59	0,59	0,39	0,29	0,49	0,26	0,23
Industrial	0,20	0,11	0,17	0,19	0,16	0,12	0,08	0,08	0,09	0,11
Rural	0,18	0,29	0,27	0,52	0,28	0,30	0,28	0,23	0,26	0,23
Mixed	0,31	0,29	0,29	0,32	0,43	0,30	0,27	0,16	0,28	0,21
Sakha Republic	0,21	0,193	0,222	0,32	0,26	0,209	0,189	0,177	0,169	0,151

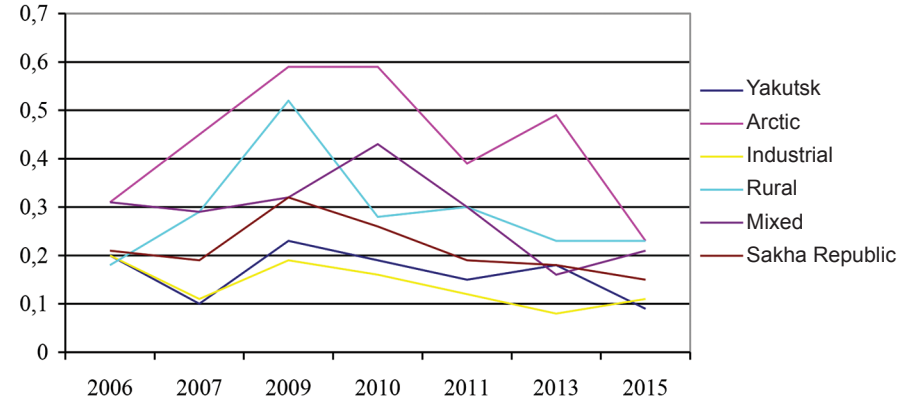

Fig.2. Death Rate from Hypothermia by Socio-territorial Zones from 2006 - 2015 per 1000 People.

Table 3

Death Rate from Hypothermia by Age Groups for 2006-2015 (per 1000 Persons of Corresponding Age Groups)

Age group	year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
<20	0,019	0,010	0,020	0,031	0,025	0,021	0,014	0,011	0,011	0,007
20-24	0,128	0,157	0,109	0,109	0,077	0,088	0,115	0,122	0,053	0,056
25-29	0,106	0,209	0,165	0,198	0,165	0,165	0,161	0,045	0,090	0,068
30-34	0,182	0,111	0,209	0,556	0,289	0,261	0,150	0,159	0,272	0,126
35-39	0,182	0,319	0,346	0,404	0,281	0,177	0,250	0,281	0,177	0,190
40-44	0,235	0,374	0,423	0,546	0,443	0,413	0,304	0,238	0,222	0,298
45-49	0,431	0,378	0,344	0,579	0,315	0,388	0,353	0,449	0,385	0,381
50-54	0,503	0,361	0,524	0,726	0,584	0,337	0,454	0,377	0,385	0,355
55-59	0,423	0,373	0,273	0,646	0,574	0,312	0,305	0,298	0,227	0,254
>60	0,464	0,271	0,336	0,351	0,477	0,307	0,273	0,241	0,239	0,218
total	0,214	0,193	0,222	0,322	0,257	0,209	0,189	0,177	0,169	0,151

Table 4

Seasonal frequency of mortality from fatal hypothermia in Sakha (Yakutia) Republic for 2006-2015

month	year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
January	14,71	14,13	16,11	18,30	15,04	14,21	16,57	12,35	16,67	12,41
February	10,78	10,33	8,06	11,76	14,23	10,53	9,94	15,88	10,49	10,34
March	9,80	9,24	9,48	17,97	10,16	10,53	17,13	17,06	10,49	11,03
April	9,80	10,87	7,58	11,11	7,72	7,37	7,18	8,24	10,49	13,10
May	6,37	6,52	9,48	7,19	6,10	6,32	8,29	7,65	8,02	14,48
June	0,49	1,09	2,37	1,31	0,41	0,53	4,42	0,59	2,47	6,21
July	0,49	1,63	0,47	1,63	0,41	1,05	1,10	1,18	0,62	0,69
August	1,96	0,00	1,42	0,33	0,81	0,00	1,10	1,18	0,00	0,00
September	6,37	4,35	6,16	3,92	8,54	10,53	2,76	4,71	2,47	2,76
OCTOBER	13,73	11,41	9,48	6,54	7,72	9,47	7,18	6,47	9,88	2,76
NOVEMBER	8,82	13,59	15,64	7,19	8,54	12,63	9,94	6,47	10,49	6,90
DECEMBER	16,67	16,85	13,74	12,75	20,33	16,84	14,36	18,24	17,90	19,31
TOTAL	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0

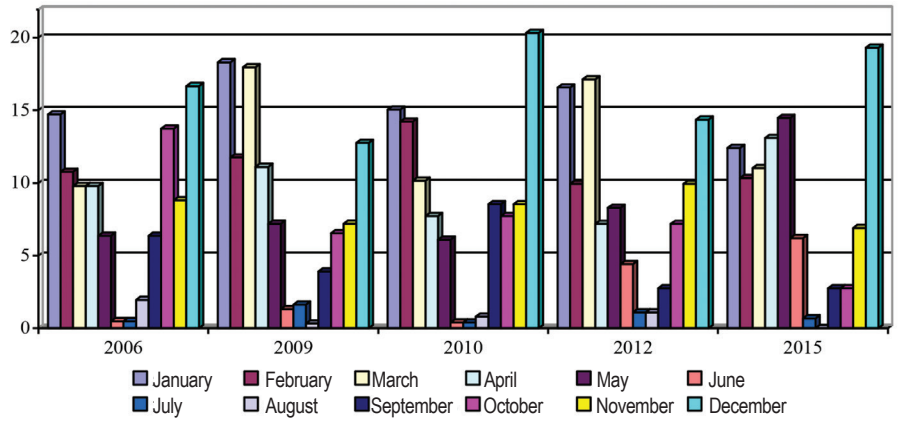

Fig.3. seasonal frequency of hypothermia in sakha republic for 2006-2015.

Table 5

Structure of Mortality from Hypothermia by Ethnic Groups for 2006-2015 (per 1000 Persons of Corresponding Ethnic Groups)

Ethnic group	year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yakuts	0,199	0,250	0,229	0,368	0,103	0,066	0,064	0,028	0,051	0,047
SIPN	0,434	0,403	0,713	0,651	0,351	0,376	0,200	0,376	0,175	0,125
Russians	0,205	0,102	0,131	0,146	0,136	0,088	0,085	0,037	0,068	0,062
Others	0,280	0,268	0,443	0,804	0,939	0,885	0,737	0,845	0,617	0,684
total	0,214	0,193	0,222	0,322	0,257	0,209	0,189	0,177	0,169	0,151

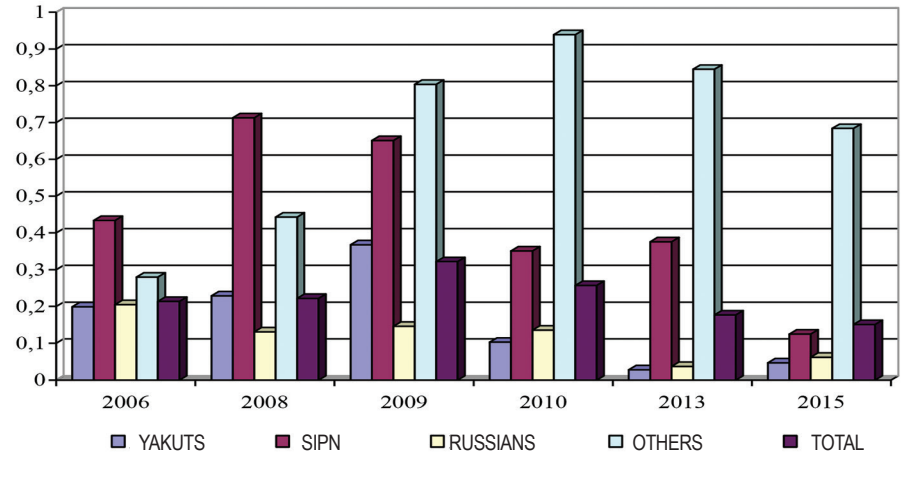

Fig.4. structure of mortality from hypothermia by ethnic groups for 2006-2015 (per 1000 persons of corresponding ethnic groups).

- the tendency to reduce the susceptibility to hypothermia of people of other ethnic groups. The death rate of Yakuts and Russians in the structure of mortality from hypothermia is the smallest in comparison with other ethnic groups and has not increased since 2009 (Table 5, Fig. 4).

People, who have been born or lived for a long time in a warm climate and adapted to it, are exposed to cooling more often than the native population in view of the increased sensitivity to it [2].

In a study done in Sweden from 1992 to 2008, the northern regions of Sweden were analyzed for fatal causes of hypothermia, the following **Conclusion**s were drawn:

- causes for fatalities were heart disease, strokes, dementia, mental illness, alcoholism, as well as recent trauma;
- 72% of deaths occurred in rural areas and 93% in out-of-the-premises areas;
- more than 75% of deaths occur in the cold season of the year from October to March months [6].

Synthesis of the results of the analysis of hypothermia mortality in Sakha (Yakutia) Republic for 2006-2015 suggests that the frequency of deaths from hypothermia depends on the place of residence (territorial zone), the season of the year, the age and the length of stay. Considering these risk factors, it is necessary to develop a set of measures aimed at developing preventive, socio-economic, production and technical directions to increase the effectiveness of measures to reduce the risk of death from general hypothermia.

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The authors:

Yakut Science Centre of Complex Medical Problems, 677010 Yakutsk, 4 Sergelyakhskoe Shosse, Yakutsk, Russia:

1. Egorova Aitalina Grigorievna - Candidate of Medical Sciences, Chief Scientific Officer, Head of Department, aitalina@mail.ru;

2. Arkhipova Natalia Spartakovna - Candidate of Medical Sciences, senior researcher, cardiologist, nati8692@mail.ru.

N.S. Arkhipova, E.K. Popova, Z.N. Krivoshapkina, A.G. Egorova, N.P. Makarova, Z.N. Alekseeva

CLINICAL MANIFESTATIONS OF ATHEROSCLEROSIS AMONG THE GROUP OF PATIENTS OVER 60 YEARS OF AGE WITH CHD LIVING IN CONDITIONS OF THE FAR NORTH

ABSTRACT

The clinical manifestations of atherosclerosis in the indigenous and non-indigenous population in a group of patients with CHD older than 60 years, living in the Far North, were studied. The highest frequency of myocardial infarction has been identified (at the time of the survey) among the group of patients of senile age (75 years). The frequency of myocardial infarction and angina pectoris decreases as the age increases. The gender disparities have been observed on clinical manifestations of angina pectoris that can be clearly monitored in the indigenous group. The analysis of five-year survival observation revealed the senile age, myocardial infarction and higher class of angina pectoris to be the most relevant factors of mortality in the group of people over 60 years of age.

Keywords: coronary heart disease, myocardial infarction, non-indigenous, indigenous (Yakut) population, elderly, senile age, long-livers.

Introduction. The death from the diseases of the circulatory system has been rated the major cause in Russia and mostly due to CHD [8]. In Russia more than 50% of mortality accounts for cardiovascular diseases compared toin West countries.Furthermore, more than 80 per cent of fatal cases are related to the CHD and cerebral stroke [5,7,10]. From the studies it can be seen that CHD is still one of the major health-related issues and more common among the older and senior aged population rather than young [6,12]. Myocardial infarction (MI) is one of the serious forms of CHD for people aged over 60.According to studies, the compared analysis of the mortality rate due to MI taken from 2006 to 2015 years revealed the significant increase of the death rate in the group of long-livers and its stability in the group of patients aged 80 years and older [3].Most patients with cardiovascular diseases living in the Far North have demonstrated the significant change in the threshold of the physiological reaction to the climatic factors that in turn lead to the decrease of body adaptation to the external environment. Severe climatic factors of Sakha Republic are proved to play the negative role in the formation and prognosis of the different diseases, particularly the atherosclerosis and myocardial infarction [11, 13].

Purpose. To study the clinical manifestations of atherosclerosis in the group of patients with CHD aged over 60 years living in the Far North.

Materials and methods. We analyzed 354 patients aged 60 years and older with a verified diagnosis of CHD who had passed the examination and treatment at Cardiologic department of Geriatric Center, Yakutsk city.The studied population were divided into two groups as following: native – Yakut people (100%) (n=205, average age 77,6±0,6) and non-native – Russians (91,3%),Ukrainians, Tatars and Germans (8,7%) (n=149, average age 75,5±0,7). We divided all the surveyed patients based on gender – men (n=187)and women(n=167), on age – elderly (from 60 to 74 years, n=154), senile (from 75 to 89 years, n=149)and long-livers (aged 90 years and over, n=51) (WHO, 1963). By the time of the study, the period of residence of non-native patients in Yakutia was more than 30 years.

The diagnosis of CHD was verified based on complaints, medical history, laboratory research, data taken with instrumental methods – electrocardiographs (ECG with the use of Minnesota code) for the estimation of ECG [Rose G.A. et al.,1982]), echocardiography, Holter monitoring of ECG and careful study of patients' medical records taken from repository of medical authority.

The local committee on biomedical ethics at Science Centre of Complex Medical Problems approved the study.

Parametric and non-parametric statistical methods were used to conduct the statistical processing of the received results. Student's T-test was applied to estimate the cross-group differences in evidence having continuous distribution, while Pearson Chi-square testand Fisher's method were usedfor comparison of frequency values. Other used methods were Kruskal-Wallis H test, one-, two- and three-factor analysis

of variance (ANOVA). The comparison of paired samples was implemented using the paired Td test (Student's). The analysis of dependency between the indicators was conducted with the use of the following criteria: Pearson product-moment correlation coefficient (Pearson's r), Spearman Rank-order Coefficient (rs) endχ^2-Pearson criterion. Used also the linear discriminant analysis method. The statistical processing of the material was conducted withStatistica for Windows (v. 6.0). The figure 0.05 was taken as the critical level of credibility of nil statistical hypothesis (the absence of significant distinctions or factor influences).

Results.The frequency of MI was 56,2% (199 patients out of 354). MI was found in 53% of cases among non-native representatives (n=79), native – 58,5% of cases (n=120) (χ^2=0,85; p>0,10).

The study revealed MI to be more common with pathological Q-wave (27,4%), less frequently with non-Q wave (16,1%) and MI established based on medical history.

No statistical differences were received (p>0,10) on the MI's frequency between the non-native and native patients.

Yakut people with MI have a more often tendency(change the word) to the damaged anterior wall of left ventricular non-Q (χ2=3,64; p=0,056) and significantly more often - across the whole anterior wall (χ2=4,44; p=0,035).

Non-native patients demonstrate the changes in scarring of the anterior and posterior wall of the left ventricle - 16,8 and 12,8 respectively, native patients - 12,2 and 9,8% of cases. MI non-Q is more often observed among native people (χ2=3,76; p=0,050).

Macrofocal and microfocal MI were identified in the group of men and women with roughly the equal frequency, while MI by medical history was seen more often among men. The more detailed picture demonstrated the tendency of the increased scarring frequency of posterior wall (χ2=2,91; p=0,088) as well as anterolateral wall non-Q wave (χ2=3,45; p=0,063) among men.

The same frequency of MI with pathologic Q-wave was detected in the groups of elderly, senile age and long-livers (p>0,10).

It was found that at senile age (149 patients) there were more cases of non-Q wave MI (22,8% cases, 34 patients) in comparison with other age groups (χ2=13,39; p<0,001). Furthermore, patients of senile age tend to have myocardial infarction of the anterior-partition with Q (χ2=7,56; p=0,023) and myocardial infarction established anamnestic (16,1% cases, 24 patients) (χ2=6,87; p=0,032) moreoftencompared tootheragegroups.

The group of long-livers demonstrated the approximately similar frequency of MI both with pathologic Q wave (23,6%) andnon-Q (21,6%); much less likely MIestablished based on medical history (2,0% of patients).

Correlation analysis was used to determine the MI depending on age among the group of patients with CHD. Thus, the frequency of MI established based on medical history and non-Q decreases with age (r= –0,13; p=0,048 и r= –0,14; p=0,030 respectively).

The decrease with age can be noticed in frequency of MI with localization of posterior wall in the group of non-native patients (r= –0,17; p=0,038; rs= –0,16; p=0,046) as well as in the circular MI (r= –0,16; p=0,059; rs= –0,14; p=0,099). The previous stated tendency was not observed in the native group of patients.

The use of regression analysis revealed the downward trend in the proportion of Yakut patients after non-Q wave MI and also the lower number of people with MIanamnestic. The relative number of patients after non-Q wave MI decreases by 0,05% as the age of patients increases by 1 year. The similar picture is observed in the group with MIestablished anamnestic, the only difference is in slightly higher mortality rate – 0,06% (table 1).

As can be seen from the picture, the frequency of MI established based on medical history non-Q wave is complex (parabolic) function depending on the age of examined people. The mean value (for the whole range of age groups) of frequency Q neg is 19,0% (red horizontal line).

The frequency of non-Q wave MI established based on medical history does not depend on the age and accounts for 11,4% (blue horizontal line) for non-native population, which is far less than in the native group (χ^2=3,76; p=0,050).

The highest frequency of non-Q wave MI and defined on medical history is found at age of 75 in the general group of patients. In the non-native group of patients, the highest frequency of MI of posterior wall with pathological Q wave and circular MI is found at age of 60 and 70 respectively. As for the native group, the highest frequency of non-Q MI and defined on medical history is found at age of 73 and 77 respectively.

Gender differences in clinical manifestations of angina can be traced in the group of native patients. Angina of III functional class (χ^2=4,22; p=0,040) is more often identified among men. There is also the tendency of more frequent identification of unstable angina (χ^2=2,71; p=0,099).

Native people tend to have different classes of angina depending on the age: the older the patients are, the less is the angina class (r= -0,16; p=0,021), which is not observed in the non-native group (r=0,14; p=0,095).

The frequency of angina detection decreases with age in the total group of patients: Functional Class (FC) II (r= –0,17; p<0,001), FC III (r= –0,16; p=0,003) and FC I (r= –0,12; p=0,021).

222 people out of 354 were included to the catamnestic follow up group. The share of the age groups was distributed as following: 40% (n=80) – older people, 49,5 (n=101) – people of senile age and 51,2% (n=41) – long-livers. According to the analysis of survivability (n=222), the patients with Q-negative MI and angina of FC II, III, IV were more common demonstrating 73,2% (41 people out of 56) (χ^2=3,14; p=0,073) and 63,2% (134 people out of 212) (χ^2=12,23; p=0,032) respectively. The main disease, which determined the high mortality rate in this group of patients, was CHD with the proportion of 51,5% (n=53) in the structure of CVD. MI of the anterior wall (Q-positive) was recorded in anamnesis of 33 patients out of 222, 22 of them died within five years (66,7%). That was higher compared to the mortal cases due to other clinical form of CIHD (n=81, or 42,9%) (χ^2=6,40; p=0,011).

High mortality rate was observed in the group of patients with the acute form of CHD. Most clearly it can be seen while studying the causes of death of elderly patients. The angina of II, III, IV were identified in 116 patients (52,3%) and 209 (94,0%) had I, II, III. It was found that the higher angina, the higher was the risk of mortality in the group of patients CHD of older age groups (Table 2).

Discussion. The absence of significant ethnic diversities in the frequency of MI was not surprising as the frequency of CHD tends to increase with age [9]. The transferred large-focal MI was equally traced in all three age cohorts.

The analysis of MI depending on gender revealed that the men more often suffer from MI than the women. The latest can be confirmed by the results of studies conducted in Yakutsk during 2004-2006 years where MI was the cause of death 3 times more often in men than in women, due to the earlier progression of atherosclerosis [1].

The high frequency of MI (at the time of survey) was found at the age of 75 years in the general group, between 60 and 70 years in the non-native group of patients and 75-80 years in the native group. Judging by the incidence of MI in people of different ages, it can be assumed that atherosclerotic lesion of coronary

Table 1

The frequency of non-Q wave MI and MI anamnestic among the Yakut depending on the age (results based on regression analysis, n=205)

Indicator	Statistical parameters		
	b (coefficient of regression)	t	p
Non-Q wave MI	-0,00048	1,75	=0,081
MI anamnestic	-0,00059	2,38	=0,018

vessels in non-native patients occurs approximately 10 years earlier than in Yakut. The dependence of the vascular lesion by the atherosclerotic process on the national identity and adaptation of a person to the extreme conditions of the Far North can be traced in the number of works [1, 2, 9, 13].

The analysis of the data received on the frequency of angina showed no significant differences in relation to ethnicity, gender, and age. Our research determined the clear evidence of links between angina and age: the older is the patient, the less is the frequency of angina in every FC, particularly in II and III. The decrease with age in the number of patients after MI and high FC of angina are not related to the better prognosis for atherosclerosis over the years, but to the death of people who have previously been recorded with these diseases before they reach a more advanced age. This is also confirmed by the analysis of a 5-year follow-up observation. Mortality was statistically higher in the group with MI and high class of angina pectoris. Other literature sources indicate that the presence of CHD indisputably increases the risk of death in the elderly group of CVD and all other causes [4].

Considering the unfavorable prognosis of atherosclerosis with age and the impact of the length of stay in the Far North on its progression, it is necessary to conduct early preventive measures with the concern of the climatic features of the region.

Conclusions

1. The highest frequency of MI occurs at senile age (75 years) aligning them into the group with high cardiovascular risk.
2. Dependency analysis revealed the decrease in MI and stroke with age (clearly seen in the group of the native population, and tendency to the decrease in the group of the non-native population).
3. Clinical manifestations of angina pectoris can be clearly traced in the group of Yakut patients depending on the gender: FC III angina is detected more often in men as well as the tendency to the more frequent display of unstable angina.
4. Based on the results of a 5-year follow-up observation, it was noted that the most significant mortality factors in the group of people over 60 years of age are the senile age, MI and high class of angina pectoris.

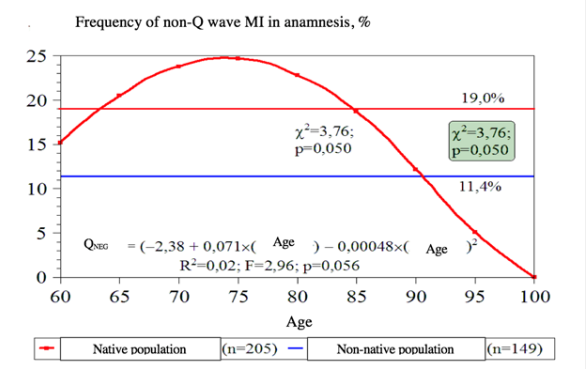

Fig.Dependence of the non-Q wave MI frequency on the age among the non-native and native patients with CHD aged 60 year and over

Table 2

Frequency of the mortality depending on the Functional class of Angina Pectoris (n=116)

Angina Pectoris	n	Patients				χ^2	p
		alive		dead			
		abs.	rel., %	abs.	rel., %		
ФК II	59	41	69,5	18	30,5	12,42	<0,001
ФК III	44	18	40,9	26	59,1	3,16	=0,076
ФК IV	13	2	15,4	11	84,6	6,53	=0,011
Всего	116	61	52,3	55	47,7	–	–

Note. χ^2=16,38; p<0,001.

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The authors:
Yakutsk, Republic Sakha (Yakutia), Russia:
1. Natalya Arkhipova – Candidate of Medical Science, Senior Researcher of Laboratory of Clinical-Population and Medico-Social Research in the YSC of the Complex Medical Problems (CMP), cardiologist, nati8692@mail.ru;
2. Elena Popova – Candidate of Medical Science, Associate Professor of the Department of Propaedeutics and Endocrinology Faculty Therapy and Physiotherapy Faculty at the Medical Institute of the Federal Autonomous Educational Institution of Higher Education North Eastern Federal University M.K. Ammosov, a cardiologist.
3. Zoya Krivoshapkina - Candidate of Biological Science, senior researcher of the Laboratory of Biochemical Research in the YSC of the CMP;
4. Aitalina Egorova - Candidate of Medical Science, Chief Researcher of the Department of Epidemiology of Chronic Noncommunicable Diseases in the YSC of the CMP;
5. Nadezhda Makarova - junior research assistant of the Laboratory of Clinical-Population and Medico-Social Research in the YSC of the CMP, cardiologist of the State Budgetary Institution in Republic of Sakha (Yakutia) Republican Hospital No. 3, in-patient care No. 2;
6. Zinaida Alekseeva - junior research assistant of the Laboratory of Clinical Population and Medico-Social Research in the YSC of the CMP, a psychologist.

K.M. Stepanov, U.M. Lebedeva

BASES OF RATIONAL NUTRITION UNDER THE INFLUENCE OF LOW TEMPERATURES

ABSTRACT
In the article, based on the study of local food raw materials and traditional food, the necessity of optimizing the structure of the population's nutrition and improving the quality of food products under low-temperature conditions is substantiated. The set of factors influencing the increase of interest of food industry enterprises in the output of national specialized products is considered.
Production of northern house and trade animals, gifts of the nature differs a high nutrition value as contains a large amount of proteins, fats, mineral substances, vitamins and the biologically active agents (BAA). Therefore, meat and milk of the Yakut cattle, the Yakut horse, a reindeer, meat of trade animals and fishes, wild berries and wild-growing food plants of Yakutia are the most valuable national wealth on which rational use the special attention has to be paid.
Keywords:nutrition in the north, actual nutrition, food products, traditional food, local food raw material, national dishes.

According to domestic and foreign scientists, low ambient temperatures in themselves already violate the balance between energy expenditure and its formation in the body. On their impact, it responds with a kind of protective reaction - increased heat production. This reaction to the cold is called the German hygienist RM. Rubner «chemical heat regulation.» Soviet physiologist A.D. Slonim, for example, believes that in the conditions of prolonged exposure to low temperatures, the maintenance of body temperature at a constant level does not occur due to the processes of chemical thermoregulation, but mainly due to the regulation of heat transfer [2].

Under the influence of low temperatures, the northerners developed a specific so-called «polar», protein-lipid type of metabolism. This means that in the North, nutrition should be built with a slightly larger inclusion of proteins and fats at a lower relative energy significance of carbohydrates [3, 4].

In actual nutrition of the inhabitants of the republic, there was a replacement of the traditional for the peoples of the North protein-lipid ration for carbohydrate, characteristic for residents of European countries. The change in the historically formed structure of food causes the prevalence of alimentary-dependent pathology, especially of the hemopoiesis (anemia), the endocrine system (obesity), the circulatory system, the musculoskeletal system (osteoporosis). In the diet, the ratio of proteins of animal and vegetable origin, half-saturated fatty acids is violated, a low content of water-soluble vitamins is revealed [3, 10].

Identified by researchers the signs of nutritional deficiency in Yakutia, in particular, a deficiency of proteins, fats in the body is considered a factor that increases the risk of developing immunodeficient conditions leading to chronic non-infectious diseases. On the other hand, with a deficiency of proteins, fats and vitamin C, the propensity of development of hypochromic anemia in the inhabitants of the North is associated. In addition, with a deficiency of calcium, phosphorus is associated with a risk of osteoporosis. However, the combination of a lack of these minerals with a pronounced potassium deficiency, magnesium in the body predisposes to a breakdown of neuromuscular conduction. At the same time, the combination of established forms of mineral deficiencies is a risk factor for cardiac rhythm disturbances. Against this background,

the excess sodium in the diet of the examined can lead to the development of hypertension.

Studies have shown that the winter diet of Yakut people is represented by low-calorie food with a low content of not only basic macronutrients (proteins, fats, carbohydrates), but also with a lack of vitally important micronutrients such as Ca, K, Mg and P, as well as vitamins: A, group B and C both in the city and in the villages [10].

Correction of the revealed disturbances in the diet of Yakutia residents during the winter season requires the addition of products rich not only with proteins, fats, vitamins, but also vitally important minerals like calcium, potassium, magnesium and phosphorus and vitamins, the deficiencies of which have been established.

In this regard, the meat of the Yakut horses occupies a significant share in the diet of man in the conditions of the North. The best in taste and dietary qualities meat products are obtained by slaughtering young horses, grown with year-round pasture content. The meat is high in calories, has a pleasant appearance and is evenly permeated with fatty interlayers. Young horse meatis much easier to digest and assimilate than beef and is inferior only to venison [4].

Young horse meat is a high-quality meat product, the fat of which contains a huge amount of linolenic acid - 24% of the total mass. The foal meat contains a significant amount of vitamin A - up to 20 mg%, vitamin C - 0.8 mg%, vitamin E - 0.82 mg%. Of the other vitamins, it contains: thiamine 0.16 mg%, riboflavin 0.26 mg%, niacin 3.5 mg%. In comparison with this, in beef the content of these vitamins corresponds to 0.006; 0.15 and 4.7 mg%. Thus, the foalmeat for the content of the main water-soluble vitamins significantly exceeds the beef. In the foalmeat, more than in beef, potassium, calcium, copper, almost 4 times more iron, zinc, cobalt.

The fat of the Yakut horse contains the highest amount of unsaturated fatty acids (59%), including a large amount (up to 24.3%) of essential alpha-linolenic acid.

Reindeer meat has a delicate taste, high content of nutrients, and its low calorie content is ideal for those who aspire to a healthy lifestyle, as well as children, the elderly, sportsmen, representatives of «heavy» professions.

In the deer meat - 16 kinds of amino acids, vitamins B, vitamin E, as well as potassium, magnesium, sodium and iron, selenium and manganese, copper, zinc and phosphorus. A unique combination of substances in the meat of reindeer does not allow fat to accumulate in the human body.

Reindeer meat includes protein by 6.7% more than the best varieties of beef meat. Fat in the amount of deer meat is small enough, so venison enjoys high consumer demand. In addition, reindeer are reared in ecologically clean areas, and they also feed exclusively on mosses and lichens, which favors the formation of llenolic acids in wild reindeer, which protect the human body from atherosclerosis and carcinogen [4].

Traditionally, fish should be used in the diet. The caloric content of local fish is as follows: nelma - 200, omul - 164, crucian - 146, burbot - 73, pike - 83, muxun - 88 kcal / 100 g.

Fish have high nutritional value not only due to the protein, but also due to the high content of fish in fatty sorts of omega-3 and omega-6 fatty acids. These polyunsaturated fatty acids, which have high physiological activity, are extremely important for intercellular processes, have an anti-inflammatory effect, reduce the amount of lipids in the blood (thereby reducing the risk of cardiovascular diseases), to some extent contribute to weight reduction.

According to the results of studies of the biochemical composition of commercial fish, it is found that they are rich in calcium, potassium, magnesium, phosphorus, trace elements, especially iodine, fluorine, contains a sufficient number of limiting amino acids (leucine, lysine, methionine, tyrosine, cystine), rich in polyunsaturated fatty acids and vitamins [4].

The study of the chemical composition and collagen content in bone collagen-containing waste from the cutting of commercial fish showed that the skeleton of various species of commercial fish has a similar chemical composition and contains 17.0 to 18.3% protein.

Proteins of bone tissue are represented by ossein, by amino acid composition and properties close to collagen. The chemical bond between ossein and the mineral composition of the fish bone is less strong than in the bone tissue of animals and birds.

Yakut crucian is a special subspecies of goldfish and officially named as the Yakut crucian of Kirillov (CarassiusGacuticusKirillov) named after the first scientist who described the Yakut crucian carp, the doctor of biological sciences F.N. Kirillov.

A distinctive feature of the Yakut carp in comparison with the European ones is high fat content (up to 10% vs. 2.5%), high content of polyunsaturated fatty acids, macro-microelements, vitamins. Therefore, they have high energy value.

The use of carp is due to the protein content, which is easily and quickly absorbed in the body. In addition, it contains unique amino acids that are irreplaceable for humans. The composition of carrots includes a large amount of calcium, which is necessary for bone tissue, and it improves the condition of teeth and nails.

The composition of the crucian includes vitamin A, which is necessary for vision, as well as vitamin E, which has a favorable effect on the skin condition. A large amount of potassium is found in fish, which is necessary for the cardiovascular system, and it also normalizes the pressure. There is in it phosphorus, involved in the restoration of bone tissue [4].

The peoples of the Republic of Sakha (Yakutia) have developed centuries-old ethnoecological traditions in the rational use of natural resources. However, with the development of industry, especially mining, the negative impact not only on the environment, but also on the health of the population. Therefore, the problem of providing the population with high-grade food products in the extreme conditions of Yakutia is becoming a top priority. In solving this problem, traditional food products from local raw materials (dairy products, natural food plants) should occupy an important place [9].

A special place among them in human nutrition in the North is occupied by the Yakut national dairy products.

National dairy products of the Yakuts are traditional food products that provide the population with a need for nutrients in the harsh conditions of Yakutia. So, Yakuts due to dairy products provided more than 50% of the demand for food. Therefore, in the old days each family tried to use milk without losses, preparing butter, cottage cheese, various sour-milk products from milk in the summer months, and in the autumn processed milk for chokhon, hayah, tar, which they consumed in the winter. This method of processing and storing dairy products has become a kind of waste-free technology that, while improving technological processes, can currently contribute to the production of high-quality national natural dairy products of a new generation [8, 9].

In Yakutia, as in the southeast regions of the CIS and in some countries of Asia, a sour-milk drink of spirit and milk fermentation is distributed - kumis. It is produced from mare's milk using leaven of thermophilic lactobacilli and yeast.

Kumis is a sour milk drink made from

mare's milk of lactic acid and alcoholic fermentation. As a result of lactic acid and alcohol fermentation, the mare's milk is enriched with lactic acid, alcohol and carbon dioxide, nitrogenous substances in koumiss contain albumin, peptones, and amino acids. Casein is in the form of small, imperceptible flakes.

For medical purposes, it is used for pulmonary tuberculosis. It improves digestion, hematopoiesis, metabolic processes in the body, suppresses putrefactive processes in the intestine, increases the reserves of all vitamins in the body, thereby increasing the body's resistance to diseases [4, 9].

A koumiss drink from cow's milk is a fermented sour foaming carbonated drink, produced by ripening milk with pure cultures of lactic acid rods and milk yeast with the addition of sugar.

Sorat is a Yakut national product, produced from whole or reconstituted milk by fermenting with direct starter cultures containing Bulgarian rods, acidophilus rod of non-slippery race, thermophilic lactate streptococci, kefir fungi, bioculture.

Igegegei is a cottage cheese. In skim milk add acid sour cream or sorate and boil on low heat. To get a soft curd, remove from heat, once the milk is well curdled. Cool, filter, mix with sugar, dry in the oven. Untreated curd is used for baking flat cakes.

Sumeyh is cheese. The finished thick sorat is placed in a special bowl of birch bark with a pointed bottom and expanding from the top. Cover and hang at room temperature for several hours, a thick mass squeeze, dry.

A drizzle. Milk boiled, put in a warm place, after a few hours it thickens, chills, add sugar, cranberries, currants or jam.

Byyrpah is a Yakut national sour-milk drink, produced from pasteurized or skimmed milk with the addition of sugar and fruit and berry fillers, by fermenting with direct starter cultures containing acidophilic rods, thermophilic lactic streptococci, lyophilized yeast culture, fermenting lactose.

Tar - the Yakut national fermented milk product, which is produced by fermenting milk or cream with pure cultures of lactic acid bacteria. The nutritional value of tare is explained by the presence of lactic bacteria in it. Getting into the intestines, they create conditions that prevent the development of putrefactive microbes. Tar contains fat-soluble vitamins AD, E, easily assimilated amino acids, calcium, magnesium, phosphorus salts.

The production of therapeutic and prophylactic dairy products is given great attention. The nature of the therapeutic effect of traditional products on the human body has been revealed. Despite a rather large assortment of described sour-milk drinks, the set of products with directed therapeutic effect is very limited. The creation of new products with more pronounced therapeutic properties will make it possible to vary widely their use depending on the nature of the diseases.

Most of the Yakut national dairy products are low-fat, produced using recycled materials, with the full use of milk nutrients and conform to the technology of combined dairy products.

The problem of dysbiosis is becoming more urgent in Yakutia in connection with a decrease in immunological reactivity, which arises in people mainly due to environmental changes. Therefore, to maintain and restore the microflora of the digestive tract, it is necessary to use the Yakut national dairy products. containing natural natural additives from the unique Yakut raw material. It should also be emphasized that such biologically active additives as products of processing of forest berries, wild-growing food plants, etc., should take the proper place in the composition of the combined dairy products, ensuring that they reach the widest masses of the population, increasing the biological value of food without any or an increase in its caloric value, which is especially important for the prevention of violations of fat metabolism and cardiovascular diseases [8].

Products with natural food plants of Yakutia are characterized by a high content of protein substances, carbohydrates, macro-microelements and biologically active compounds, so their use for human nutrition in the North will make the diet of the local population more complete and adequate due to a significant expansion of sources of food raw materials from natural resources, the use of which has been forgotten in recent years.

After all, in the diet of the Yakuts before the development of grain growing, that is, until the 80-90s. XIX century, a very large place after dairy and meat products was occupied by products of plant origin - stems and roots of wild plants, berries and wood sapwood [6, 7].

Edible wild plants, used by the Yakuts, can be divided into two groups: edible roots and edible stems and leaves.

The most commonly used of them are: Susak (Butomusumbellatus) - Unnuula. By definition, E.K. Pekarsky in the Dictionary of the Yakut language (1925), Unnuula is: a shrimp, a breadbasket, a genus of water grass, a finely ground powder of dried dried apricots, which goes to food instead of flour (actually to thicken milk) [5, 9].

Some plants have vegetative organs for food. The most important among them is Artemisia vulgaris L., Artemisia Vulgaris L., Artemisia Vulgaris L. For consumption in food, young leaves were collected before flowering, dried. Then boiled, squeezed, shredded leaves of wormwood wormwood were introduced into buttermilk or suorat. The resulting fermented milk product was called «From үөрīte». Wormwood Chernobylnik is a high-protein plant containing up to 18% protein in dry mass. Sorrel is acidic or pyramidal (rumexacetosa L., rumexthyrsiflorus F.). Sorrel was also used, as well as wormwood, the Chernobyl. Fresh or boiled leaves of sorrel (along with the decoction) were added to the buttermilk, some flour was added for thickening. People drank it cooled, sometimes added to improve the taste of sour cream. Onions (Allium dauricum F., splendens W.) - chuchunah, onion, fast, Rezun (Allium schoenoprasum L.) and onion linear (Allium lineare L.) - HonuLuug. These plants with a high vitamin content were eaten as seasoning in fresh form and conserved for the future salted [16, 9].

Consequently, the development of combined and functional products of the new generation, enriched with biologically active compounds and using new technologies, is very promising. They not only allow making nutrition in low temperatures full and balanced, but also significantly expand the sources of food raw materials, which previously were practically not used in the diet.

Thus, when feeding in low-temperature conditions, it is necessary to take into account the national peculiarities of nutrition. This primarily affects the local population. It is necessary to widely recommend all traditionally used in food groups of products, including milk and dairy products, meat of various animals, fish, fruits and berries, growing in these climatic zones. The basis of public health in extreme conditions is the preservation of ethnic nutrition.

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The authors

Yakutsk, Republic Sakha (Yakutia), Russia:

1. STEPANOV Konstantin Maksimovich - deputy director for science, the Doctor on agricultural sciences,Yakut Science Centre of complex medical problems,Stenko07@mail.ru,;

2. LEBEDEVA Uliana Mikhaelovna – head of the Center of medical and preventive nutrition, candidate of medical sciences, Research Institute of Health, FSAI HPE «Northeast federal university of M. K. Ammosov», ulev@bk.ru.

A.G. Egorova

A LOOK AT THE PROBLEM OF DEATH FROM HYPOTHERMIA on the example of cases of hypothermia-related resuscitations

ABSTRACT

In the Far North, one of the main environmental risk factors is the cold, which lasts for 8 months. The problem of the effect of cold on the human body has always been and remains relevant. Annually, about 3,000 people around the world are frozen to death, of which about 200 cases take place in Yakutia.

The article describes a unique case of resuscitation of a frozen patient, which gives grounds to revise algorhythm of actions in relation to frozen patients, both from medical and legal points of view.

Keywords: general hypothermia, frozen person, death from hypothermia, case of resuscitation.

In the Far North, one of the main environmental risk factors is the cold, which lasts for 8 months. The problem of the effect of cold on the human body has always been and remains relevant. Annually, about 3.000 people around the world are frozen to death, of which about 200 - in Yakutia.

Despite the harsh climate, indigenous peoples of the Far North are able to feel relatively comfortable here, because of innate resistance. However, under the influence of socio-economic factors (long distances between settlements, alcohol intoxications, prolonged staying outside without suitable clothes, traumas that do not allow them to move and keep warm), both the indigenous and the foreign populations die from the cold. Death from the effects of cold is usually the result of an accident. Suicide by hypothermia is extremely rare [1].

Men of working age die more often from the effects of cold. Less often people die sober from hypothermia, among others – exhausted during a blizzard or lost in the forest. According to statistics in Yakutia every year (on average) 200 people die from general hypothermia. In the Republic, cases of resuscitation of "firmly" frozen people in recorded medicine are extremely rare. Thus, according to Professor R.Z. Alekseev, engaged in cold trauma, in his 50 yrs practice there were only 2 cases when a frozen man and child came back to life after thawing in morgue.

At the same time, there are many examples in scientific literature where people who had seemed dead from hypothermia revived and were brought back to life. In all these cases, they were healthy and fairly young people who froze; this was the main factor that contributed to the resuscitation from the frozen state. However, until now there are no scientifically sound methods for revitalizing frozen people globally.

According to some Internet sources, the most effective way to revitalize frozen people is to warm the body using living

person's heat. During World War II, the command of the German naval forces instructed military doctors to find the most effective way of resuscitation of people affected by hypothermia. A lot of medicinal and other ways of reviving on war prisoners were tried out. The best way was recognized to be... street prostitutes, who with their naked bodies resuscitated frozen men much faster than all other means. They brought back to life those who could not be reanimated by any other means [3].

A unique case of the revitalization of a "firmly" frozen man occurred in 1996 in a village in Verkhnevilyuisky Ulus, which was noted in the newspaper "Uehee Buluu" dated November 19th, 1996. Patient A., 37, on the evening of March 25th, 1996 after drinking alcoholic drinks with friends in the evening went home by motorcycle. The next morning at 6 am he was found by fellow villagers outside the village in the snow. According to eyewitnesses, when he was found, he was without clothes glaciated in a pose of "man, warming himself by the fire," with arms and legs extended and without any signs of life. The outer temperature was 37o below zero. In this form, he was immediately taken to the district hospital, where, fortunately, at that time, Nadezhda Vasilievna Mikhaylova (Brusenina), a doctor from Yakutsk, had her shift at the hospital. According to the description of N.V. Mikhailova, the frozen man was unconscious, the skin had marble-white colors, the eyes were open, but the tip of the tongue protruded from the corner of the mouth, the pulse could not be felt, the arms and legs seemed "wooden", stretched out in the posture above described. The victim had frozen traces of urination on his back, traces of violence on the body were not found. The doctor was shocked by the picture she saw, but did not lose her head, and began to resuscitate the patient. For almost 12 hours – from 7 am to 7 pm, N.V. Mikhailova was warming the frozen body with her own hands, warming them over the flame of a candle. Simultaneously, she orally gave a teaspoonful of vodka during the day, and also rubbed the victim's body. All this time, the victim was lying on the floor, where the temperature was just below room temperature (presumably +18°C). After the body has softened, arms and legs have relaxed, he was laid on a bed and covered with blankets. After some time, the patient suffered a severe shivering fit. At midnight patient A. came back to sense without resuscitation and could answer questions. The first portion of his urine was bloody. After taking hot tea and broth, after a few hours, urine recovered and acquired a normal color. The next morning, the "resuscitated" patient A. went home. N.V. Mikhailova managed to save not only all the fingers and toes, but miraculously restore all internal organs. Saved from certain death, patient A. still lives and works in his home village in Verkhnevilyuisky Ulus.

According to some observations, when the temperature of the body drops by just one degree, coordination and motor skills deteriorate and a certain muscle tone appears that precedes jitters. The receptors send a signal to the center of thermoregulation about reduction of all surface capillaries. Hands and feet begin to ache from the cold. When the body temperature reaches 35o C, the state of mild hypothermia develops, the person feels a strong tremor, in which the muscles quickly contract to produce additional heat. And when the body temperature drops to 31.1o C, it refuses to try to warm itself up by trembling, the body ceases to produce heat. The blood thickens like motor oil in a cooled engine. Consumption of oxygen decreases by more than a quarter. However, the kidneys work in a strengthened mode to cope with the hypervolemia that arose at the time when the blood vessels of the limbs contracted and pushed the fluid toward the center of the body. In this case, a person feels a powerful urge to urinate. At a temperature of 30°C, the heart begins to beat arrhythmically and can only distil two-thirds of the normal blood volume. Lack of oxygen and a decrease in the rate of brain metabolism, meanwhile, lead to visual and auditory hallucinations. At a temperature of 29.4°C, freezing people begin to rip off their clothes in a strange agonizing bout. Scientists have not yet agreed on phenomenon causes, the most logical explanation for it may be that shortly before complete loss of consciousness, the narrowed blood vessels located near the surface of the skin suddenly expand, which causes a feeling of intense heat on the skin. At 20°C, the heart stops. At air temperature of 35°C below zero the body temperature drops by an average of one degree every 30-40 minutes [3].

In the presented case, patient A. was on the street at an air temperature of 37°C below zero not less than 9 hours in a state of alcohol intoxication. Thus, the temperature of his body could have reached about 23°C, as evidenced by involuntary urination and tearing off his clothes during a hallucination. And the presence of alcohol in the body exacerbated the situation. With alcohol intoxication in cold conditions, metabolic processes are slowed down and the reflex of muscular tremor is blocked, which leads to a decrease in heat production, due to a slowdown in the oxidation of fat and carbohydrate stores. Heat transfer is faster (even despite active oxidation of ethanol as heat energy) than heat formation, which leads to a negative balance of the overall body temperature and its rapid decrease. People die in the cold under the influence of alcohol, without realizing and taking measures to save themselves even with rapid sobering [2, 5].

In experiments on mice, injected with alcohol, after it they were placed in a box with thawed snow, it was found that they died 5 times faster than mice without alcohol. It was also found that the higher the dose of alcohol administered, the faster the death [1].

In fact, according to Professor R.Z. Alekseyev, many victims of hypothermia die more often at the very moment when they are being resuscitated. Traditional ways of saving hands and feet with severe cold damage - intense massage, flexion-extension, and abrupt placement of the patient in a warm or hot bath - do not help, but on the contrary, do harm. At a sudden warming, the narrowed capillaries expand all at once, which leads to a sharp drop in pressure. The slightest movement can provoke strong spasms of the heart muscle of the victim. At extremely low temperatures, the human body is doing its best to preserve itself, greatly slowing down internal processes. Many people found with hypothermia seem dead only at first glance. The body can survive in this state for hours, and resuscitation process must be gradual, precise, and very careful.

However, those who are familiar with frost effects know that, although the cold deprives organisms of their vital energy, it can also grant chance for life's preservation. Heat is a presence – intense vibration of molecules. Cold is an absence – a slowing down of vibrations. At absolute zero, the motion of the molecules completely ceases. It is this retardation that allows gases to turn into liquid, and liquids into solids. It slows the growth rate of bacteria and chemical reactions. In the human body, the cold stops metabolism. The lungs receive less oxygen; the heart pumps less blood.

At normal temperature, this can cause irreversible brain damage. But a frozen brain, whose metabolism also slows down, needs much less oxygenated blood and under certain circumstances can remain intact.

The slowing down of all processes that accompanies freezing is in ways so useful that sometimes it is even artificially reproduced. Nowadays, cardiologists often use severe hypothermia to slow the metabolism of their patient in preparation for surgical operations on the brain or heart. In this state, the patient's blood flows very slowly, and the heart does not beat very much, and with CPB – stops beating completely. With states like those, death seems to be inevitable. However, under close supervision, the patient may be in a state of hypothermia without harming one's health.

American researcher Mark B. Roth from the Fred Hutchinson Cancer Research Center in Seattle, Washington, studied the effect of cold on garden worm embryos as they turned into full-fledged young worms. The researcher noticed that when exposed only to freezing temperatures, embryos of worms died and after warming did not restore cell division. But after first depriving them of oxygen and later freezing, the embryo still stopped cell division due to lack of oxygen, there is a sudden stop of chemical reactions in the body. After 2.5 hours later the oxygen supply was restored and the cell division resumed unchanged. Thus, Mark Roth noted the connection between low temperature and low oxygen content, which can lead to a method of prolonging preservation time of human organs for transplantation [6].

In conclusion one can say that this unique case of resuscitation of a frozen person gives grounds to review many questions in the actions towards hypothermia cases, both from medical and legal points of view. In the USA, frozen people are declared dead only after unsuccessful attempts to warm them up and provide aid. Meanwhile in Russia frozen people are delivered straight to the morgue, where, they, naturally, do not receive help. In this case, patient A. was lucky that doctor N.V. Mikhailova was at the right place at the right time, who did not hesitate and thawed the frozen body, thereby successfully bringing the patient back to life.

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The author

Egorova Aitalina Grigor'evna – PhD, Yakut Science Centre of Complex Medical Problems, 677010, 4 Sergelyakhskoe Shosse, Yakutsk, Russia, e-mail: aitalina@mail.ru.

MATERIALS OF THE «YAKUT MEDICAL JOURNAL» NEXT ISSUE

ORIGINAL RESEARCHES

S.A. Kashchenko, A.A. Zakharov

CHANGES IN THE STRUCTURE OF SEMINAL VESICLES OF REPRODUCTIVE PERIOD RATS AT THE CONDITIONS OF CYCLOPHOSPHAMIDE-INDUCED IMMUNOSUPPRESSION

ABSTRACT

Objective: to establish the morphometric changes in the seminal vesicles of rats of the reproductive period at the conditions of prolonged systemic immunosuppression.

Material and methods. The study was carried out on 60 white rats of the reproductive period, obtained from the vivarium of laboratory animals of the SI LPR «ST. Luke Lugansk State Medical University». The immunosuppressive state was modeled by administration of cyclophosphamide at a dosage of 1.5 mg/kg body weight intramuscularly tenfold. The rats were taken out from the experiment by decapitation under ether anesthesia on 1, 7, 15, 30 and 60 days after the end of the drugs administration. The organs were weighed, the relative mass was calculated, the length, width and thickness were determined by means of a caliper. The volume of the organ was established by the method of water displacement in a graduated cylinder containing distilled water. At the microscopic level, examined the height and width of epithelial cells, their volume, and also the larger and smaller diameters and the volume of the cell nuclei. Volumetric values were calculated from the formula for the volume of an elongated ellipsoid of revolution.

Results of the study. Statistically significant decrease in all studied organometric parameters occurred both at the early (7, 15 days) and late observation periods (30 days). Micromorphometric parameters after cyclophosphamide administration also decreased with respect to the control group at similar times. The size of the nuclei and their volume decreased on 7, 15 and 30 days: the larger and smaller diameters significantly decreased by 3.99%, 4.98%, 8.38% and 3.22%, 6.56%, 8, 06% respectively. The parameters of the volume of the nuclei of the epithelial cells of the seminal vesicles of the animals of the control groups significantly exceeded the data of the experimental rats at the same time by 7.07%, 11.02% and 15.77%. At 1 and 60 days, statistically significant differences between the parameters studied were not established.

Conclusions. Statistically significant changes in organometric parameters of the organ are noted both at the early (7, 15 days) and late observation periods, which indicates the direct influence of cyclophosphamide on the biosynthetic processes in the organ. Micromorphometric changes, as well as the results of cyto- and karyometry, confirm the organometric data and indicate the development of local disturbances in the morphogenesis of seminal vesicles caused by disregulation of the endocrine-immune homeostasis of the organ.

Keywords: seminal vesicles, cyclophosphamide, immunosuppression, rats.

Introduction

In recent years, the efforts of scientists are aimed at revealing the structural and functional foundations of human interaction and the environment, based on a comprehensive analysis of the influence of external factors on the organism, the structure of anthropological connections, the characteristics of individual manifestations [1]. The first to change the environment are the regulatory systems of the body - immune, endocrine, nervous. It has been proved that unfavorable exogenous effects, including the use of various pharmacological agents, cause pronounced systemic immunosuppression in the body [5]. Violations in the structure and functioning of regulatory bodies naturally stimulate a complex reaction from other structures, including those performing reproductive function. Being in constant functional tension during puberty, these organs are especially sensitive to changes in homeostasis, which is reflected in a number of clinical experiments. However, against the backdrop of a variety of laboratory-instrumental research methods, a fundamental morphological study of the organs of the male reproductive system in immunosuppression, according to available literature, has so far not been carried out.

Objective- to establish morphometric changes in the seminal vesicles of rats of the reproductive period at the conditions of prolonged systemic immunosuppression.

Material and methods. The study was carried out on 60 white rats of the reproductive period, obtained from the vivarium of laboratory animals of the SI LPR «St. Luke Lugansk State Medical University». The immunosuppressive state was modeled by administration of cyclophosphamide at a dosage of 1.5 mg/kg body weight intramuscularly tenfold. Animals belonging to the control group received similar volumes of 0.9% NaCl solution in the same way. The rats were taken out from the experiment by decapitation under ether anesthesia on days 1, 7, 15, 30 and 60 days after the end of the drugs administration. When working with animals, they were guided by the Directive 2010/63/ EU of the European Parliament and the Council of the European Union for the protection of animals used for scientific purposes [4]. The organs were weighed on a torsion balance, the relative mass was calculated, the length, width and thickness were determined by means of a caliper. The volume of the organ was established by the method of displacement of water in a graduated cylinder containing distilled water. The organ underwent classical histological wiring, the resulting sections 4-6 μm thick were stained with hematoxylin-eosin and photographed using the «Olympus CX-41» morphometric complex.

Micromorphometric measurements of objects were carried out by uploading the obtained digital images to the computer program ASCON «Compass-3D 17.0» with calibration by means of photos of the object-micrometer in similar modes of shooting. At the microscopic level, the organs examined the height and width of epithelial cells, their volume, and the larger and smaller diameters and the volume of the cell nuclei. The volume indices were calculated from the formula for the volume of an elongated ellipsoid of revolution:

V = ,

where V is the nucleus volume, A is the larger diameter, and B is the smaller diameter [2].

The obtained data was processed using the specialized program «StatSoft Statistica v6.0». The methods of parametric statistics were used, since the use of the Shapiro-Wilk criterion allowed the establishment of a normal distribution of indicators in the sample. The reliability of the differences between the values of the parameters of the experimental and control groups was determined with the help of the Student-Fisher criterion with an error probability $p<0.05$ permissible for biomedical research.

Results of the study. Seminal vesicles are paired organs, which necessitates their two-sided study. However, the obtained data indicate that in the control and experimental groups there were no significant differences between the analogous parameters of the right and left seminal vesicle, so the results of the right organ research will be presented in the following.

Seminal vesicles have the appearance of sacciform formations located above the prostate gland, and are covered with a connective tissue capsule. The clearance of each vesicle is irregular in shape; the mucosa is characterized by a specific architecture, giving it the appearance of honeycomb cells (Fig. 1). The epithelium consists of columnar secretory and rounded basal cells.

The parameters of the seminal vesicles of the animals of the control groups underwent regular changes in connection with the peculiarities of their morphogenesis (Table 1).

Macromorphometric parameters of seminal vesicles after administration of cyclophosphamide were also subjected to significant dynamics. A statistically significant decrease in all the studied parameters occurred both at the early (7, 15 days) and late observation periods (30 days). The deviation of the length of the organ from the control group

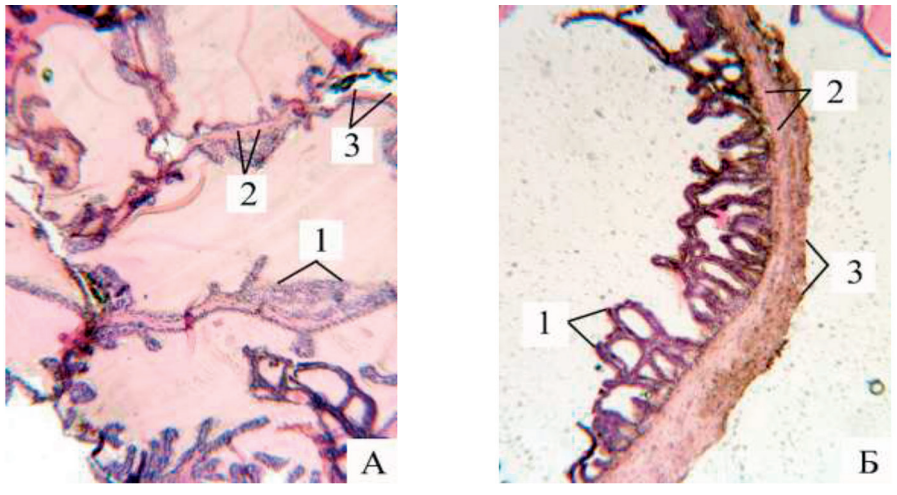

Fig. 1. Seminal vesicles of animals of the reproductive period: A - 7 days after application of cyclophosphamide; B - 7 days after application of 0.9% solution of NaCl. 1 - mucous, 2 - muscle layer, 3 - adventitia. Coloring with hematoxylin-eosin. Zoom: approximation: Zoom 18,5. Objective: PlanC N 10x/0.25 ∞/-/FN22.

of the rats was 13.55%, 16.05% and 14.62%, respectively, of the above-mentioned days. Similarly, the width and thickness of seminal vesicles decreased with immunosuppression: the changes were 5.62%, 4.77%, 3.16% and 10.78%, 12.25%, 4.82% at the same time. A statistically significant decrease in body volume was observed on days 7, 15 and 30, and were 27.16%, 29.86% and 21.30%, respectively. The micromorphometric parameters of the epithelial cells of the seminal vesicles of the reproductive period in the control groups underwent a regular age dynamics (Table 2).

After the administration of cyclophosphamide, the decrease in the height and width of the epithelium was 4.61, 5.02, 7.09 and 4.87, 6.64, 7.91%,

Table 1

Organometric indices of the seminal vesicles of rats in the reproductive period of the control groups (M±m, n=30)

Parameters	Dates of observation, days				
	1	7	15	30	60
Absolute mass, mg	395,80±17,45	420,52±6,57	455,00±10,28	498,34±6,25	525,71±16,65
Relative mass, mg/g	1,91±0,12	1,93±0,08	1,91±0,04	2,21±0,09	2,27±0,11
Length, mm	21,53±1,08	24,32±1,12	26,28±0,66	28,87±1,24	30,15±1,53
Width, mm	8,88±0,31	9,20±0,17	9,95±0,12	10,97±0,11	11,43±0,19
Thickness, mm	6,40±0,32	6,65±0,12	6,80±0,15	7,60±0,14	9,30±0,10
Volume, mm^3	640,75±45,64	779,04±29,87	930,99±21,24	1260,24±28,74	1678,04±109,56

Table 2

Micromorphometric indices of the seminal vesicles of rats in the reproductive period of the control groups (M±m, n=30)

Parameters	Dates of observation, days				
	1	7	15	30	60
Height of epitheliocyte, μm	17,14±0,12	17,66±0,11	18,53±0,29	19,66±0,18	20,24±0,34
Width of the epitheliocyte, μm	11,97¬±0,24	12,65±0,19	13,25±0,17	13,95±0,19	15,62±0,32
Volume of epitheliocyte, μm3	1285,83±27,35	1479,65±20,31	1703,31±34,56	2003,17±35,63	2585,58±69,21
Larger nucleus diameter, μm	11,20±0,12	11,45±0,05	11,86±0,05	12,69±0,12	12,39±0,28
Smaller nucleus diameter, μm	7,65±0,07	7,98±0,07	8,23±0,06	8,64±0,08	8,79±0,14
Nucleus volume, μm^3	89,68±1,76	95,63±1,15	102,16±0,96	114,76±0,94	113,99±5,17

respectively, on 7, 15 and 30 days of follow-up. The size of the nuclei and their volume decreased at the same time: the larger and smaller core diameters significantly decreased by 3.99%, 4.98%, 8.38% and 3.22%, 6.56%, 8.06%. The parameters of the volume of the nucleus of the epithelial cells of the seminal vesicles of the animals of the control groups significantly exceeded the data of the experimental rats at the same time by 7.07, 11.02 and 15.77%.

At 1 and 60 days statistically significant differences between the parameters studied were not established.

The established changes in the parameters of the seminal vesicles indicate an intensive reaction from the organ in response to the immunosuppressive effect. It is known that the use of cyclophosphamide according to this scheme induces the development of the systemic immunosuppression state [6]. Under these conditions, changes in the organ indicators can be explained by the direct cytotoxic effect of the drug on actively dividing cells, including secretory epitheliocytes. S.S. Ostrovskaya et al. (2014) observed the active reaction of the organs of the male reproductive system in the experiment after exposure to salts of heavy metals [7]. Changes in micromorphometric indicators, indicative of the degree of functional activity of seminal vesicles, may explain the disregulatory effect of cyclophosphamide on local endocrine and immune homeostasis. Thus, Yu.S. Khramtsova et al. proved the fact of spermatogenesis disturbances under conditions of changes in the cooperation of the endocrine apparatus of the testes with the local complex of immunocompetent cells [3].

Conclusions.

1. In conditions of prolonged immunosuppression, an active response is observed on the part of the seminal vesicles of animals of the reproductive period.

2. Statistically significant changes in the organ's organ indicators are observed both at the early (7, 15 days) and late observation periods, which indicates the direct influence of cyclophosphamide on the biosynthetic processes in the organ.

3. Micromorphometric changes, as well as the results of cyto- and karyometry, confirm the organometric data and indicate the development of local disturbances in the morphogenesis of seminal vesicles caused by the dysregulation of the endocrine-immune homeostasis of the organ.

4. The results obtained give rise to interest in the study of the structure of seminal vesicles in acute age-related immunosuppression.

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Information about authors

1. Full name: Kashchenko Svetlana Arkad'evna;

Academic degree, academic status: Doctor of Science (Medicine), Professor;

Position: Head of the Department of Histology, Cytology and Embryology, State Establishment «St. Luke Lugansk State Medical University», Lugansk;

Contact Information: 91045, Ukraine, Lugansk, bl. 50th Anniversary of the Defense of Lugansk, 1g. Tel.: +380509678705. E-mail: masterhist@mail.ru.

2. Full name: Zakharov Alexey Alexandrovich;

Academic degree, academic status: PhD, associate professor;

Position: Associate Professor of the Department of Histology, Cytology and Embryology, State Establishment «St. Luke Lugansk State Medical University», Lugansk;

Contact Information: 91045, Ukraine, Lugansk, bl. 50th Anniversary of the Defense of Lugansk, 1g. Tel.: +380509678705. E-mail: masterhist@mail.ru.

METHODS OF DIAGNOSIS AND TREATMENT

S.K. Kononova, N.A. Barashkov, V.G. Pshennikova, A.A. Nikanorova,A.V. Solovyev, A.M. Cherdonova, G.P. Romanov, S.A. Fedorova, F.M. Teryutin,E.K. Khusnutdinova

SOME BIOETHICAL ISSUES OF MOLECULAR GENETIC DIAGNOSTICS OF AUTOSOMAL RECESSIVE DEAFNESS 1A IN THE YAKUT POPULATION

ABSTRACT

Autosomal recessive deafness 1A is one of the most frequent hereditary diseases in the Republic Sakha (Yakutia). The diagnosed features of spectrum and frequency of pathogenic variants in the GJB2 gene by the patients with congenital hearing loss allow applying routine DNA diagnostics in medical practice. In the article some bioethical issues of DNA testing of autosomal recessive deafness-1A are discussed.

Keywords: bioethical problems, autosomal recessive deafness 1A, DNA diagnostics, the Republic Sakha (Yakutia).

Introduction

Congenital deafness – one of the most frequent pathologies in the world(1 to 650-1000 of newborns), about 50-60% of all cases of congenital deafness have the hereditary reasons [14].

The general prevalence of the forms of hereditary hearing loss is 13.0:100000 in the Russian Federation. There are regions with higher frequency, for example, in the Chuvash Republic – 32.5:100000, in Rostov Oblast – 36.6:100000 [4,9]. The conducted epidemiological researches of hearing loss in the Republic of Sakha (Yakutia) note sufficiently high frequency of sensorineural hearing loss among children up to 14 years; its prevalence exceeds this figure across The Central Federal District of the Russian Federation by 1.85 times. Among pupils of hard-of-hearing schools the inherited causes of the disease are traced over 43%, and pupils of deaf schools - 31% [11].

Molecular genetic research of hereditary non-syndromic sensorineural hearing loss is carried out in the Republic Sakha (Yakutia) since 2005 [3]. For the first time in the Yakut population there is identified the molecular genetic cause of the hereditary congenital hearing loss form. It is revealed as splice donor site mutation c.-23+1G>A of the GJB2 gene (Cx26) and it is classified as the allelic variant of autosomal recessive deafness 1A (DFNB1A) according to the international OMIM catalog (Online Mendelian Inheritance in Men).

The prevalence of DFNB1A is 16.2 to 100000 of the Yakut population, and the frequency of the heterozygous carriage of mutation c.-23+1G>A varies from 3,8 to 11,7% among indigenous people of Yakutia (Evens, Evenks, Dolgana, Yakuts). The research results of splice donor site mutation of the GJB2 gene (Cx26) demonstrate existence some of the largest worldwide «endemic focus» of accumulation c.-23+1G>A in Eastern Siberia [3].

Whatever the reasons of hearing loss: congenital, hereditary or acquired, deafness is a socially significant disease. As the leading speech pathologist L. Vygotsky (1983) noted: «Deaf-muteness is an immeasurably great tragedy because it isolates a person from any communication with people. Deaf-muteness is a social deficiency mainly. It breaks social communications of person stronger than blindness» [2]. Communication of deaf people with the hearing ones can be different: from the need of help to restore the lack of auditory information to the avoiding communication with people around because of the fear of being misunderstood. Therefore people with the hearing disorder quite often prefer to be in the company with people of the same disorder [10]. Deaf persons have much more medical and psychological problems than hearing ones. Proceeding from this, a number of researches shows a marked decline of quality of life in various spheres of activity in society [15,16].

Care delivery for special group of people with hearing loss is a particular problem for a doctor since there is a set of questions, for example, how to hold medical consultation successfully taking into account tongue and cultural specifics of a patient, his associated diseases, psychosocial problems etc. [19,20]. In the research among various organizations 100 deaf were interviewed. It was shown that there is inequality in access to health care service. For example, deaf women faced insufficient awareness of medical personnel on how to communicate with them. The research confirmed these problems are of great importance for most of deaf women that results in inequality when they are compared to the hearing people [21].

Among people with hearing loss there are distinguished deaf, hard-of-hearing, deafened and implanted. We should talk about deafness when it is found a persistent bilateral (on both ears) substantial impairment of hearing, and the coherence in speech perception is impossible. Based on time of occurrence it is accepted to distinguish early onset deafness (aged up to 3 years) and late onset deafness (occurred after the speech developing). Deafness, congenital or acquired, without special training, deprives a child of an opportunity to learn speech. If speech already began to form, then early deafness leads to its breaking. However, it is necessary to know that for such or other cases of hearing disorder to use the term «deaf-mute» is unethical [10].

Deafened (late-deafened) – the people who lost hearing but kept the ability to speak. Condition of their speech depends on the time deafness onset and means for its development. Children, who became deaf aged from 3 up to 5 years and didn't receive the special help by the time of starting school, most often keep a small vocabulary and usually pronounce it in a wrong way. Children, who became deaf in later age, almost completely keep a word-stock (especially the children who already learned to read and write). Special pedagogical influence to the ability to speak can fully save it within early-onset hearing loss [5].

The implanted children and adults are the people who underwent a cochlear implantation procedure (lat. cochlea – a snail), i.e. an implantation of electrode systems in an inner ear (a cochlea), with the subsequent electrical stimulation of acoustical nerve that allows to send the signals causing acoustic sensation to a brain [5].

The purpose of the article is to

discuss the main bioethical issues of DNA diagnostics of autosomal recessive deafness 1A for the development of bioethical rules of using routine DNA testing of DFNB1A in medical practice. The bioethical rules developed with regional features are applied to the most widespread monogenic diseases in Yakutia, such as spinocerebellar ataxia type 1 (SCA1) and myotonic dystrophy.

Materials and methods of research

We considered a group of the most common form of deafness, so-called non-syndromic autosomal recessive deafness 1A. For identification of forms of deafness corresponding to clinical aspect of DFNB1A clinical genealogical analysis was carried out. At questionnaire we analyzed the answers of the hearing respondents which have children with the confirmed genetic etiology of hearing loss caused by GJB2 gene mutations. The respondents who aren't biological parents or having relatives of the remote degree of relationship (grandmothers, grandfathers, uncles and aunts) weren't included to the research. 91 hearing parents of 70 deaf of the children unrelated to each other and meeting the main clinical criteria of non-syndromic autosomal recessive sensorineural hearing loss were included in the research group. All 70 deaf patients had mutations in the GJB2 gene (in homozygous or compound heterozygous state) [6,7].

Clinical research of patients

Clinical research of patients was carried out with the organized visits of medical brigades of specialized departments to boarding schools. During medical inspection of each participant of the research it was completed the individual formalized map of inspection containing the code number, age at the time of the research and sample of a biological material, given about ethnic origin, the hereditary history, results of physical, laboratory and instrumental methods of diagnosis, the conclusion and references of the experts. Venous blood sample was taken from the median cubital vein of all participants of the research for release of DNA samples. The researches were carried out under the written informed consent of the parents. The work is approved by Local Committee on Biomedical Ethics FGBU "Yakut Science Centre of Complex Medical Problems" of the Russian Academy of Medical Science, Yakutsk, the protocol No. 16 of April 16, 2009.

Molecular genetic research

For molecular genetic research genomic DNA samples extracted from peripheral blood lymphocytes were used. DNA amplification was carried out by means of polymerase chain reaction (PCR) with use of the oligonucleotide primer sequences [13]. Determination of primary nucleotide sequence of the first and second exons of the GJB2 gene in the studied samplings was carried out by means of automated sequencing.

Results and discussion

For causation of deafness / bradyacusia in the family burdened by DFNB1A, patients can attend a genetic consultation with different genophenotypical status: individuals with a normal genotype without hearing disorder ([wt]; [wt]), heterozygous carriers with «normal hearing» (c.[-23+1G>A];[wt]), homozygous mutation with a serious degree of bradyacuasia (c.[-23+1G>A]; c.[-23+1G>A] [6]. Consequently, the approaches of genetic consultation and receiving of DNA testing informed consent for these groups of patients also must be different.

In most cases while genetic testing there can be contradictions between family members because of incorrect ideas of laws of heredity. The hearing parents consider themselves healthy people, so hearing disorder of their child - an accident. So, for example, the analysis of parents opinion about the possible reasons of their child hearing loss showed that most of the hearing respondents in Yakutia (86,1%), Tyva (73,8%) and Bashkortostan (76,2%) doesn't consider the hereditary is hearing loss of the child, and caused either environmental factors or unknown reason. It is some kind of psychoemotional protection from «unwillingness to be guilty of deafness of the child» [1]. When receiving the informed consent from the hearing parents for DNA testing of DFNB1A, it is possible to explain that the child inherits the damaged gene from each parent and, perhaps, some parents will see in it a balanced responsibility for illness. The familial clustering (presence of deaf relatives in family) considerably facilitates consultation and receiving consent to DNA testing as patients are psychologically ready to accept hereditaryburdeness in family. This fact was confirmed by our researches, it turned out that in the absence of deaf relatives parents denied hereditary character of a hearing loss at their child authentically more often ($p<0,05$), and in families where there was a hereditaryburdeness - reliable differences wasn't diagnosed [17].

DNA testing of DFNB1A can define a heterozygous carriage of the GJB2 gene mutation of the hearing patient (c.[-23+1G>A];[wt]). According to the researches of F. Teryutina (2016) it was established that the heterozygous carriage of DFNB1A mutation is associated with age-related hearing loss (presbycusis) with a conventional border of onset age ~ 40 years [6]. The results notification of DNA testing can deal a serious psychoemotional stress for the person. First of all, a tested patient is informed about risk of a child to be born deaf in family. In this case, under identification of DFNB1A heterozygous carriage of an individual it is necessary to recommend prospective genetic consultation or preconception care. Secondly, the heterozygous carrier needs to provide information about rather high risk of decreased hearing in older age. The statement of the fact can be complemented with references to maintain the corresponding way of life and work which would reduce a load by organs of hearing (to avoid the works with noise, etc).

DNA testing of people hard-of-hearing / deaf is connected with a set of organizational and ethical problems. In communication with deaf people it must be kept in mind that they are members of socially isolated community of «deaf world» with their own language, culture and habits [18]. The quantity of assortative marriages among deaf grows; sometimes spouses can express an intention to have a deaf child regardless of injustice of such decision in relation to the child.

Anyway, comparing itself to the hearing people, the most part of deaf considers itself defective and socially deprived [20]. Use of DNA testing for mutations detection responsible for development of deafness can be dangerous because of psychological tension and aggravation and exacerbate sense of inferiority of the person. Therefore, it is necessary to create special conditions for consultation and receiving the informed consent for deaf. The informed consent for DNA testing of DFNB1A should be issued in a writing form and be the most available to understand. It is necessary to avoid difficult genetic terms and to use simple words and offers. Perhaps, it would be the correct decision to except the word «mutation» in the text of the informed consent for DNA testing, so that a tested patient can't decide himself that he is «mutant» in addition to the fact that he is deaf.

In oral communication with a deaf patient it is necessary to use a direct word order, enunciate a theme consistently, point by point; if communication conducts through an interpreter, it is needed to address a person you are talking to but not the interpreter.

DNA testing of DFNB1A carriage for children up to 14 years has to be carried out with the informed consent of parents or legal guardians. What is more, it is very important to inform parents well and in details about the genetic status of their

child and to give adequate psychological support with reporting results of DNA testing.

Conclusion

Detection of the whole range of the mutations which are the reasons of a hereditary bradyacuasia / deafness of a person is happened relatively recently, the results of these researches aren't introduced to public consciousness yet, and molecular genetic diagnostics of hearing loss isn't applied widely in medical practice [13]. In 2014 the DNA diagnostics algorithm of DFNB1A of the patients with congenital hearing loss in the Republic of Sakha (Yakutia) was developed for the first time [8]. It became possible to offer DNA testing of autosomal recessive deafness 1A for applied medicine as the routine analysis for diagnosis, differential diagnostics, identification of a heterozygous carriage, and, in the future, it is possible for population screening. The primary focus of DNA testing consists not only in identification of a mutation, but also in the differentiated approaches to genetic consultation of patients depending on their features: educational, cultural, age, etc. Development of ethical references and application rules of genetic technologies in medical practice is the most priority in modern medical genetics, because public consciousness often isn't in time behind the accelerating genetic technologies. Necessary increase of the levels of ethical standards gives to society security guarantees in the achievements of modern science.

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The authors:
1. Kononova Sardana Kononova - senior researcher of the laboratory of molecular genetics, Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; konsard@rambler.ru;
2. Barashkov Nikolay Alekseevich -head of the laboratory of molecular genetics , Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; barashkov2004@mail.ru;
3. Pshennikova Vera Gennadevna - researcher of the laboratory of molecular genetics , Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; psennikovavera@mail.ru;
4. Nikanorova Alena Aphanasevna - researcher of the laboratory of molecular genetics , Yakut Scientific Centre of Complex Medical Problems, Yakutsk, Russian Federation; nikanorova.alena@mail.ru;
5. Solovyev Aysen Vasilevich - researcher of the laboratory of molecular biology, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; nelloann@mail.ru;
6. Cherdonova Alexandra Matveevna – student of the M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; cherdonovasasha96@gmail.com ;
7. Romanov Georgy Prokopevich - researcher of the laboratory of molecular biology, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; gpromanov@gmail.com;
8. Fedorova Sardana Arkadyevna- doctor of biological sciences, head of the laboratory of molecular biology, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; sardaanafedorova@mail.ru;
9. Teryutin Fedor Michaylovich- senior researcher of the laboratory of molecular biology, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russian Federation; rest26@mail.ru.
10. Khusnutdinova Elsa Kamilevna- doctor of biological sciences , professor, academician of the Academy of Sciences of the Republic of Bashkortostan, Director of the Institute of biochemistry and genetics, Ufa Federal Research Center, Ufa, Russian Federation; elzakh@rambler.ru.

T.M. Tjaptirgjanova, A.V.Tobohov, A.D.Makarov, Z.A.Yakovleva

CHOLELITHIASIS AS A CAUSE OF ACUTE BILIARY PANCREATITIS

ABSTRACT
We studied the specific weight of biliary pancreatitis in the structure of patients with cholelithiasis. Based on the results of the studies, the cause of the occurrence of biliary pancreatitis -cholelithiasis and its diagnostic signs in the form of rapidly increasing hyperbilirubinemia and an increase in the level of ALT with a history for more than 20 years is proved.
Keywords:cholelithiasis, biliary pancreatitis, laparoscopic cholecystectomy,octreotide.

Introduction

Over the past 30 years, the incidence of acute and chronic pancreatitis has more than doubled worldwide. In Russia, there was a more intensive increase in the incidence of CP. Thus, the prevalence of pancreas diseases among adults over the past 10 years has increased 3 times, and among adolescents – more than 4 times [4].

Biliary pathology is the most frequent cause of acute and exacerbation of chronic pancreatitis. One of the reasons for the formation of biliary pancreatitis is gallstone disease (GD). The incidence of pancreatitis in patients with gastrointestinal tract, according to various estimates, is 25-90% or more [1, 3]. Every year, more than 1 million surgical interventions are performed in the world for gastrointestinal disorders, and cholecystectomy is the most common abdominal operation in General surgical practice. According to various authors, the incidence of biliary pancreatitis after surgery on the abdominal cavity reaches 20-25%, and after interventions on the biliary tract — 30 - 55% [2, 5]. According to the reporting data of the Republican hospital №2 – Emergency medical care center, cholelithiasis for 2014 amounted to 5.8% (118 patients) of all surgical pathologies. The problem of prevention of postoperative pancreatitis remains very relevant [6].

Research material and methods. The case histories of 20 patients admitted to the surgical Department of the Republican hospital №2 -Emergency medical care centerof Yakutsk with acute calculouscholecystitis, complicated in some cases by biliary pancreatitis, in the winter period from November to December 2014 were analyzed. Under the age of 35 years it was 4(25%) patients; under 50 years – 6 (37.5%) patients; over 50 years – 6 (37.5%) patients. The average age of patients was 45.5 years.

The proportion of patients with cholelithiasis: indigenous -16(80%), non-indigenous-4 (20%) (Fig.1).Duration of the disease: from 1 up to 20 years -3 (60%), 20-40 years -17 (40%).

Results and discussion

The number of patients with biliary pancreatitis among 20 patients with gastrointestinal tract is – 7(35%) patients, of them 4 (20%) – women, 3 (15%) – men, while indigenous-5(71.4%), non-indigenous-2 patients (28.6%). The last

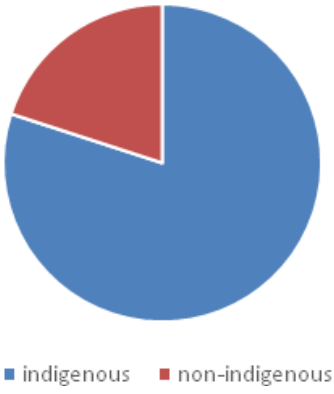

Fig.1. Structure of patients with cholelithiasis

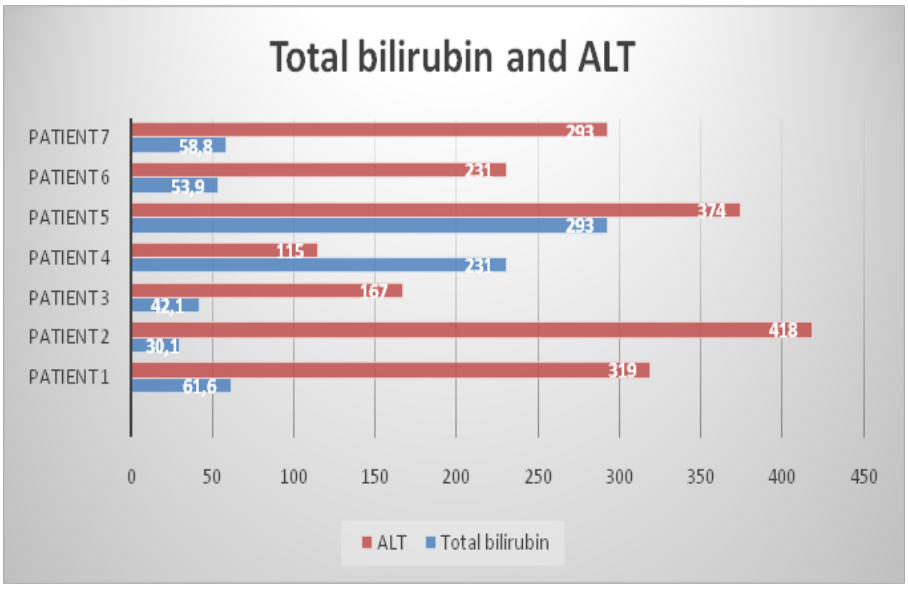

Fig. 2. Indicators of total bilirubin and ALT in patients with biliary pancreatitis

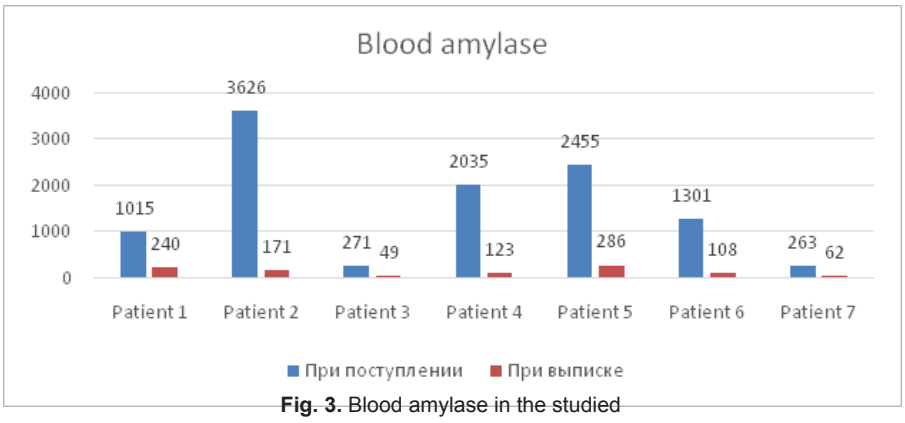

Fig. 3. Blood amylase in the studied

exacerbation was observed 2-3 days ago. Admission: consumption of excessively fatty food is present in all patients (100%) of the cases. Clinical picture: pain in the epigastric region manifested in (80%) cases in the epigastric and right upper quadrant (20%). Dyspepsia: vomiting (20%) patients, nausea (60%), without symptoms of dyspepsia (20%) of the cases. Diagnostic signs of pancreatitis biliary origin are rapidly increasing hyperbilirubinemia, with an increase in ALT (Fig.3).

Laboratory data of the studied group at admission: cholesterol within 6.8 mm / l-in (20%) patients, increase in the level of total bilirubin (from 31 μmol/l to 293) in (40%) cases, glucose to 8.3 V(100%), AST to 392 - (40%), ALT to 418 u (80%), amylase to 3626 - (20%) patients. The increase in biochemical parameters is typical for patients with more than 20 years of experience in gastrointestinal tract.

A high level of amylase in 4-28raz above the norm in the range from 569 to3626 u/l (at a rate of 15 — 130 units/ liter) was determined in biochemical blood analysis in 7(35%) patients (Fig.2).

Increased Alt activity above 34 U / l to 167 U / l was observed in 2 patients (28.5%). In 6 times the increase in Alt (up to 418 u/l) was observed in 5 patients (71%), the experience of the disease more than 20 years. An increase in total bilirubin above 21 μmol/L. to 58.8 was present in 5 patients (71%), an increase from 231 μmol/L. to 293(ie, 14raz) in 2(28.5%) patients, the experience of GIT disease more than 20 years. .

On ultrasound of the abdominal cavity -the presence of multiple nodules in (60%) cases, moderate hepatomegaly- in (20%), in the future, when ultrasound, signs of edema of the LV are determined: the heterogeneity of its structure, the irregularity of the contours in (80%) cases. Esophagogastroduodenoscopy of all 7 patients with acute biliary pancreatitis revealed gastritis (Fig.4): superficial –in 4 (57.1%) patients, erosive – 2 (28,6%), atrophic – 1 (14.3%) cases.

Endoscopic signs of superficial gastritis: mucosa expressed the brilliance (lots of mucus). The mucosa is moderately edematous, hyperemic from moderately red to cherry color. Hyperemia can be a drain and focal. Laparoscopic cholecystectomy was performed in patients with gastrointestinal tract complicated by biliary pancreatitis. To suppress immune inflammation, hormone therapy is prescribed. One of the most effective drugs in this category is octreotide. Its effect is to relieve inflammation, reduce enzymatic activity, as well as reduced secretion of the stomach and pancreas. After use, already on the third day there is a significant decrease in the activity of blood amylase. The effectiveness of the drug is reflected in Fig .2.

We present a clinical case.Patient S., 32 years old.Nationality: Sakha.

Clinical diagnosis: Acute biliary pancreatitis. Edematous form.GSD. Chronic calculous cholecystitis.Stenosis of terminal part of common bile duct. Migration of concrements.

Complication: Mechanical jaundice. State after ERCPG.EPST.Revision byDormiabasket.

Clinic. Complaints of bursting pain in the epigastrium with irradiation in the right hypochondrium, expressed general weakness, dry mouth, nausea, vomiting, weight loss of 8 kg.

Medical history: he has been ill since

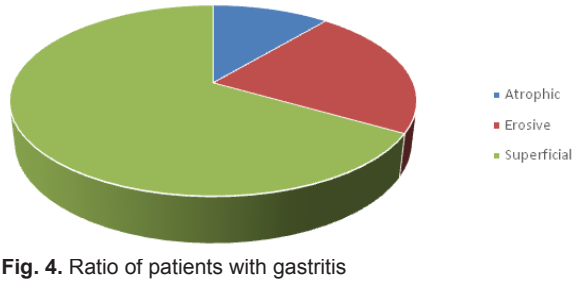

Fig. 4. Ratio of patients with gastritis

December 2015, when there was pain in the epigastrium of burning nature; he took gastric pills, a few days later the pain passed. In January 2016 suffered a rotavirus infection (sick) with fever up to 40C, epigastric pain bothered 2 days, and then remained weak, dieted, hunger. The re-deterioration after ingestion of spicy food in a small amount 07.03.16 again epigastric pain, then took tensile in nature radiating to both upper quadrant. Comply with the diet, the pain subsided. Deterioration since the 20th of March. 29.03.16 in the morning he ate a sandwich with butter, boiled sausage. In the afternoon, increased pain in the epigastrium, right hypochondrium, at night 2 times vomiting. Addressed to the receiving Department, after ultrasound of abdominal cavity, taking tests he was hospitalized in emergency department on the severity of the condition.

Survey data:

30.03.16 CBC: leukocytosis (11,7 10^9/L), lymphopenia (8%), acceleration of ESR (18 mm/h).

30.03.16 Biochemical blood test: hyperproteinemia (92.59 g/l), hyperbilirubinemia (total-86.39 mmol/l, direct-73.78 mmol/l), hyperamylasemia (4746.6 U/l), increased ALT (319 U/l) and AST (271ed.l).

30.03.16 Urine test: hyperstenuria (1030), proteinuria (1 g/l), leukocyturia=1-2-2. Appointed infusion therapy, octreotide. Preoperative preparation included: introduction of Ringer solution 500 ml once a day intravenously drip;cerukal 2 ml 3 times a day i/m; no-spa 2 ml 3 RVD V/ m; mixtures (MgSO4 25% 5 ml, insulin Actrapid NM 12 IU, glucose 10% 500 ml, KCl4% 30 ml); Aprotex 10 ml 3 RVS V / drip; Cefotaxime 1gr 2 times a dayi / m – 16 (100%); -0.01% 1 ml of 3 times a dayi/v . The patient underwent surgery. The postoperative course was without complications. Discharged with improvement on 17 day.

Summary

1. The most common is cholelithiasis in indigenous residents of Yakutsk, they accounted for 80% of patients.

2. Patients with acute biliary pancreatitis make up 35% (7) of all patients urgently hospitalized due to cholelithiasis (20 patients) for a short winter period (November-December). More common in women-4 (20%) than in men – 3 (15%).

3. There is a high rate of total bilirubin and ALT in 71% of patients with biliary pancreatitis with long-term cholelithiasis (more than 20 years).

4. Octreotide has a pronounced effect in patients with biliary pancreatitis, reducing the level of activity of amylase.

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The authors

MI M.K. Ammosov NEFU, Yakutsk, Republic Sakha (Yakutia), Russia:

1. Tjaptirgjanova Tat'jana Matveevna - MD, prof.tmt50@mail.ru;
2. Tobokhov Aleksandr Vasil'evich - MD, prof.,zav.kafedroj,avtobohov@mail.ru;
3. Makarov Al'bert Dmitrievich – docent, makarov_albert@mail.ru;
4. Yakovleva Zoja Afanas'evna - postgraduate, doctor RHN№2.

A.V. Khabarova, Ya.A. Sotskaya

DYNAMICS OF FUNCTIONAL AND MORPHOLOGICAL PARAMETERS OF MICROCIRCULATION IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS DUE TO AN INFECTIOUS MONONUCLEOSIS

ABSTRACT

The aim of our work was to assess the effectiveness using of the combination of a hepatoprotector phosfogliv and immunomodulator cycloferon on the state of functional and morphological parameters of microcirculation in patients with non-alcoholic steatohepatitis (NASH) after infectious mononucleosis (IM).

We examined 78 patients with a diagnosis of fatty liver disease after infection mononucleosis in age from 19 to 46 years, divided into two groups. The main group included 40 patients who received as therapy combination of drugs phosphogliv and cycloferon. The comparison group consisted of patients (n=38) who received conventional NASH treatment. To examine the state of microhemodynamics we used the slit lamp universal ml-2M, morphometry of capillaries of the nail bed capillaroscope carried the M-60 A.

For MCR morphological study we calculated indices of vascular, intravascular, extravascular disorders and General (integrated) conjunctival index using the formula KI. = KI1+KI2+KI3. In the result, it was found that patients with fatty liver disease was due to infectious mononucleosis there are significant violations on the part of all departments of the MCR. Standard treatment for patients with this comorbid pathology improves morphological and functional parameters of microcirculation, but not effectively and rapidly than the combination of phosphoglyceride and cycloferon. So, using the combination of hepatoprotector phosphogliv and immunomodulator cycloferon in patients with fatty liver disease after infectious mononucleosis authentically significantly contributes the elimination of the phenomena of stasis and sludge syndrome in the arterioles and capillaries, and accelerate blood circulation.

Keywords: non-alcoholic steatohepatitis, infectious mononucleosis, indicators of microcirculation.

Introduction. Knowing about modern literature information, chronic diseases of liver, in particular non – alcoholic steatohepatitis (NASH), are becoming increasingly common and relevant. For the residents of ecologically unfavorable, large industrial region of Donbass, the situation is complicated by the fact that in conditions of high level of environmental pollution by xenobiotics, the functional state of liver parenchyma is significantly disturbed due to the negative influence of toxic compounds, which contributes to the increase in the incidence of chronic diffuse liver diseases, including NASG [4, 12]. Moreover, in the conditions of ecologically unfavorable regions the probability of secondary immunodeficiency states [9, 10], which becomes the cause of infectious mononucleosis (IM) in Donbas. There are assumptions that immune disorders, which are characteristic of NASH and IM, correlate with shifts in microhemodynamics, reducing the amount of perfusion with arterial blood of the liver, and thus play a significant role in the progression of chronic lesions of its parenchyma [6, 11, 12].

There is no consensus according to the NASH therapy, is it nessesary to use some hepatoprotector's. Several sources indicate that hepatoprotective funds are first-line drugs, others do not give them so much importance [5, 8]. Hepatoprotector phosphogliv contains two active substances: phosphatidylcholine () and glitzirrizinova acid (GLA). This successful combination has allowed as a highly effective hepatoprotector [1]. We believe that the scope of phosphogliv can be expanded. So, we thought it promising to analyze the influence of hepatoprotector phosphogliv in combination with the inductor of endogenous interferon cycloferon, often used to treat infectious mononucleosis at the state of the microcirculation (MC) in patients with fatty liver disease was due to infectious mononucleosis.

The aim – to study the efficacy using the combination of medicines of phosphogliv and cycloferon on the functional and morphological characteristics of microcirculation in patients with NASG as a result after IM.

Materials and methods of research. Under our supervision there were 78 patients with diagnosis of NASH as a result of IM. The age of the examined patients ranged from 19 to 46 years, including 36 men (46.2%) and 42 women (53.8%). All patients were divided into two groups: basic, consisting of 40 people and a comparison group, consisting of 38 people. Both groups were randomized by age, sex, duration of course and frequency of NASH exacerbations.

The diagnosis of NASH was confirmed on the basis of anamnesis morbi et vitae, clinical, laboratory and instrumental methods of research. The generally accepted routine laboratory methods of the study included the clinical analysis of blood and urine, the study of the content of glucose in the blood. To assess the functional state of the liver, biochemical parameters in the blood were studied: the level of total bilirubin and its fractions (direct and indirect), the activity of serum aminotransferase – Alat and ASAT; the content of cholesterol and albumin, the activity of excretory enzymes – alkaline phosphatase (AF) and gamaglutamiltranspeptidase (GGTP), the thymol sample indicator. Ultrasound examination of the liver was performed using a digital diagnostic system SonoScape SSI 8000 (sensors-C362 2-6 MHz; L743 5-15 MHz; 6V3 3-11 MHz; 2P1 1-4.4 MHz), at the same time we noted diffuse hyperechogenicity of liver parenchyma, heterogeneity of its structure and fuzzy vascular pattern [4]. To exclude viral infection of the liver, a study was conducted of serum for markers of viral hepatitis (VH) − HBV, HCV and HDV using ELISA method. Persons who, according to the medical history, abused alcoholic beverages and were registered with a narcologist, or had experience in the introduction of narcotic substances, were also excluded from the work.

The diagnosis of IM was made taking into account epidemiological data and clinical picture. Laboratory confirmation of the disease was lymphomonocytosis and the content of atypical mononuclears over 10%, the detection of specific antibodies of IgM class to the capsid antigen VCA, to the early antigen (EA) and to the nuclear antigen (NA-1) in the acute period of the disease in the serum of ELISA method, as well as the identification by polymerase chain reaction (PCR) DNA virus [7]. At the time of the study, patients were predominantly in the reconvalescence stage, which was confirmed by an

increased content of IgG antibodies to virus antigens. Mandatory conditions were the exclusion of HIV infection, other forms of replicating herpesvirus infections: HSVS, BB3, CMV, HSV 6.

All the examined patients received conventional treatment. The therapy included diet food-table № 5, enriched with lipotropic ingredients with limited animal fats and cholesterol, and common treatment, which included detoxification therapy, herbal hepatoprotectors, enterosorbents, antioxidants and vitamins. In General, the treatment of the examined patients was carried out in accordance with the methodological recommendations «Diagnosis and treatment of non-alcoholic fatty liver disease» [5]. Patients of the main group received additional hepatoprotector phosphogliv 2 capsules 3 times a day for the first 2 weeks, and then 1 capsule 3 times a day for 30-40 days, and cycloferon 12.5% 2 ml/m 1 time a day for 5 days, then 2 ml/m a day (total for the course of treatment 10-12 injections), if necessary, patients were transferred to the tablet forms. Patients of comparison group received only conventional treatment as hepatoprotectors of plant used (karsil or silibor).

As the main method of studying the state of microcirculation in the examined patients, we used a universal lamp designed for visual biomicroscopy of bulbar conjunctiva (BBC), and we performed morphometry of capillaries of the nail bed using a capillaroscope M-60 a [2]. We analyzed the course and caliber of microvessels, the presence of vascular aneurysms and glomeruli, the speed and nature of blood flow in the microcirculatory bed, the number of functioning capillaries and the state of the extravascular zones. For the quantitative analysis of the expression of morphological change, we calculated the vascular index (KI1), intravascular (KI2), extravascular (perivascular) (KI3) violations [2, 12], and the total (integral) conjunctival index (KI.) according to the formula: KI. = KI1+KI2+KI3. The obtained results were statistically processed with the calculation of mean values (M±m) using the Student's reliability criterion (statistically reliable results were considered at the value P≤0.05, and highly reliable at P≤0.01). The results of the study were processed using the Microsoft Excel and PAST software.

Results and discussion. Most of the examined patients (73 people, 93,6%) with non-alcoholic steatohepatitis as a result of infectious mononucleosis before treatment had complaints of periodic general weakness, fatigue, which often did not disappear after rest. Characteristic (pattern 79,5%) for them was also a decrease in appetite, periodically arising a sense of «gravity» in the right hypochondrium (69,2%), bitterness or metallic taste in the mouth (78,2%). 18 patients (23,1%) had low-grade fever often occurs, mostly in the evening. At objective examination we observed a slight subicteric sclera in 43 patients (55,1%), while 69 people (88,4%) - presence of blue sclera (a sign of Vysokovich), in 36 patients (46.2 per cent) increase in size of the liver, which has performed at 2-3 cm from under the rib cage, the seal, the sensitivity of the liver edge palpation. In general, this clinical picture corresponded to the exacerbation of steatohepatitis due to infectious mononucleosis.

Biochemical examination found that in some patients (34 people, 58.6 %) there was an increase in the content of total bilirubin in serum, which averaged 29.5-36.5 mmol / l; at the same time, the activity of Alat in all patients was increased within 0.9-1.6 mmol/ g•l, ASAT was also increased and amounted to 0.7 – 1.55 mmol/ g•l. The activity of GGTP and SCF corresponded to the values of the norm, which indicated the absence of a cholesterol component in the examined patients. However, we have seen an increase in thymol samples in the range of 5.6 to 7.9 units. In general, according to clinical and biochemical studies, we noted a moderate exacerbation or unstable remission of NASH in all patients. Ultrasound of the liver in the majority of patients (92,3%) revealed diffuse enlargement of the «brightness» of the hepatic parenchyma with the presence of small amounts of fine-grained inclusions, the uniformity of its contours, blurring of vascular pattern, the distal attenuation of the echo signal, which is a characteristic sonographic picture of NASH. Noninvasive diagnosis was performed on the FibroScan device, where in most cases a moderate stage of fibrosis was detected from F1 (54 people, 69.2%) to F2 (24 people, 30.8%).

Analysis of the obtained data on the morphological and functional parameters of MCR showed that before the start of therapeutic measures in patients we found the same type of microcirculation disorders. All departments of MCR – vascular, intravascular and paravasal-were involved in the pathological process. We have established a generalized spasm of arterioles, dilation of venules with unevenness of their caliber, a significant reduction in the total number of functioning capillaries with the formation of sufficiently large avascular zones. There were also clearly expressed intravascular disorders, namely, slowing blood flow in the veins, sometimes up to the development of the stasis, against the background of sludge syndrome of II-III degree. In a number of patients, we were able to detect more pronounced disorders of microhemodynamics - sludge syndrome of III-IV degree not only in venules, but also in capillaries and arterioles. Extravascular disorders manifested perivascular edema, and the presence of microhemorrhage and pigmentation (dark-brown to yellow-brown), indicating long-existing disorders. When the morphometry of capillaries of the nail bed in patients, we noted the pallor and the haze of the background, the lack of visibility of the capillary loops due to edema pericapillary. A number of capillaries had a different shape due to deformation: twisty, comma, dots or eights. Therefore, the use of both methods – BBC and morphometry of capillaries of the nail bed confirmed the presence of expressed violations of microhemodynamics.

In the study of conjunctival indices, we found that the studied KI were significantly higher than normal (table.1). It can be seen from the table that before the start of therapeutic measures the index KI1 in the examined patients of the basic group significantly exceeded the norm, on average - 3.4 times (P<0.05). At the same time, KI2 was significantly increased by an average of 2.6 times (P<0.05), which indicates intravascular disorders. Coefficient KI3 before treatment was significantly increased-8.5 times (P<0.05) relative to the norm. After all, the integral index is KI, was above the norm before the start of therapeutic measures 3.4 times (P<0.05). In comparison group group: index KI1 exceeded normal values 3.3-fold (P<0.05); KI2 – similar to almost 2.6 times (P<0.05); the coefficient KI3 – 9.5 times (P<0.05). Integral index – KI. in patients of comparison group were also above normal by 3.4 times (P<0.05). The obtained data indicate the presence of pronounced disorders in the MCR system of both morphological and functional character.

After completion of the course of treatment, a repeated study of the state of MCR allowed to establish that in patients of the basic group there was almost complete normalization of vascular, intravascular and extravascular indices, and as a consequence – normalization of the conjunctival index, while in patients of the comparison group receiving conventional treatment, there was only a tendency to improve the studied parameters, with their data significantly different from those of the norm and the basic group. So (table.2), KI1 in the examined patients of the basic group were 1.08 times higher than normal (P<0.05), KI2 only 1.2 times higher than normal (P<0.05), figure KI3 on average 2 times higher than normal (P<0.05). Finally,

the integral index KI after the course of treatment exceeded an average of 1.2 times the corresponding rate (P<0.05). So, the indicators of MCR after treatment in patients of the comparison group, they are significantly higher than the norm and similar indicators of the basic group, were as follows: KI1 was 1.6 times higher than the norm, KI2 - 1.8 times ki3 – almost 5 times, and finally, the integral index KI. in patients of this group exceeded the average of 1.85 times the corresponding index norm (P<0.05).

In addition, when conducting a BBC it was found that the treatment of basic group patients receiving the combination of drugs phosphogliv and cycloferon, had disappeared avascular zones and stasis of blood, accelerate blood circulation, elimination of sludge syndrome in the arterioles and capillaries. A similar trend was found in capillary morphometry: in patients of the basic group pallor and background turbidity disappeared, the number of functioning capillary loops increased, the shape of capillaries and their caliber normalized, blood flow accelerated. Morphometry of capillaries in patients of the comparison group showed that the murky and pale capillaroscopic background was noticeably preserved, the number of non-functioning capillaries remained, their poor visibility due to the presence of pericapillary edema.

Thus, the obtained data testify to positive influence of combinations of drugs in the form of a hepatoprotector phosphogliv and inducer of endogenous interferon-cycloferon on the state of the MCR and microhemodynamics in patients with this comorbid pathology. It is proved that the use of this combination of drugs contributes to the restoration of morphological and functional parameters of MCR and improve microcirculation. On this basis, it is possible to recommend the use of a combination of drugs in the form of phosphogliv and cycloferon in the treatment of patients with non-alcoholic steatohepatitis due to infectious mononucleosis.

Summary:

1. In patients with non – alcoholic steatohepatitis as a result of infectious mononucleosis revealed distinct functional and morphological disorders of the MCR, which cover all its departments-vascular, intravascular and extravascular.
2. Prior to treatment, all patients in both groups had similar changes of conjunctival indices in the form of a significant excess of their normal values.
3. The inclusion of a combination of drugs with phosphogliv and cycloferon in the treatment of patients with non-alcoholic steatohepatitis on the background of infectious mononucleosis contributes to the almost complete normalization of the studied conjunctival indices, namely the reduction of KI1, KI2, KI3, and as a consequence - KI. In carrying out only the conventional treatment, there is also a tendency to decrease vascular, extracurricular and intravascular indices, but significantly less pronounced, so at the time of completion of the main course of treatment, most of the analyzed indicators remain elevated relative to the norm. Thus, the use of conventional therapy does not provide full normalization of microcirculation.
4. The inclusion of a combination of drugs consisting of hepatoprotector phosphoglyphiv and endogenous interferon inducer cycloferon, contributes to the elimination of morphological and functional disorders of the MCR, as well as to improve microcirculation in patients with this comorbid pathology.

Conjunctival indices in patients with non-alcoholic steatohepatitis on the background of infectious mononucleosis before and after treatment (M±m)

Conjunctival indice	Norm	Before treatment		After treatment	
		basic group (n=40)	comparison group (n=38)	basic group (n=40)	comparison group (n=38)
KI1	2,4±0,12	8,1±0,04***	7,9±0,02***	2,6±0,02***	3,8±0,04***
KI2	1,4±0,05	3,7±0,1**	3,6±0,12**	1,7±0,03**	2,6±0,02**
KI3	0,2±0,01	1,7±0,02***	1,9±0,04***	0,4±0,5***	0,98±0,3***
KI	4,0±0,2	13,5±0,2***	13,4±0,2***	4,7±0,5***	7,4±0,4***

KI. 4,0±0,2 13,5±0,2*** 13,4±0,2***

Note. Reliability of the difference relative to the norm ** p<0.01, * * p<0.001; p > 0,005 reliability of the difference between the indicators of the main group and the comparison group.

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The authors

1. Habarova Alina Valer'evna, post-graduate student of V. M. Frolov Department of infectious diseases and epidemiology, Saint Luka LSMU. Postal address: Luhansk, Lyapina str. 2; code: 91002; e-mail: khabarova9191@mail.ru; telephone: + 380994911440.

2. Sotskaya Yana Anatol'evna, Doctor of Medical Sciences, Professor, head of V. M. Frolov Department of infectious diseases and epidemiology, Saint Luka LSMU. Postal address: Luhansk, Lyapina str. 2; code: 91002; e-mail: sotckaya@mail.ru; телефон: +380509820895.

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

PRE-NOSOLOGICAL DIAGNOSIS OF PEDIATRIC PATHOLOGY WITH THE USE OF AUTOMATED DISPENSARY EXAMINATION COMPLEXES

ABSTRACT

The article discusses the results of the use of ACDE (Automated complex of dispensary examinations) in the regions of the Republic of Sakha (Yakutia). In the course of the work, the main organizational approaches were identified in the study of the health status of children, and the most advantageous use of automated complexes of dispensary examinations in the Republic of Sakha (Yakutia) was identified to improve the quality of preventive examinations.

Key words: children, ACDE, preventive examinations.

Introduction. We have analyzed the statistical data of the general morbidity of the child population of the RS (Y) over the past 10 years. It was revealed that over the past 10 years there has been an increase in the incidence of children in almost all classes of diseases.

In practical pediatrics, the early intervention strategy is much more effective. It is based on the earliest possible recognition of deviations from normal development or the onset of disease and timely correction of the environment and the conditions that caused them. Screening tests and systems targeting different types of pathology help detect children at risk of developing a disease. The best results are demonstrated by universal systems designed for multidisciplinary screening. Such systems, in particular, include the complex «ACDE», which has become widespread in the pediatric service of Russia [1]. ACDE is an automated complex of dispensary examination of children and adolescents. It was developed in 1991. Scientific Research and Design and Technological Institute of Biotechnical Systems of the Ministry of Education and Science of the Russian Federation in conjunction with specialists from the St. Petersburg State Pediatric Medical Academy. The ACDE system issues a decision about the presence of a pathology or the degree of its probability and focuses on the tactics of further monitoring and counseling of the child. Calculation of the pathology spectrum is provided in the following areas: rheumatology, cardiology, cardiology in the aspect of neurocirculatory dystonia, immunology in the aspect of immunodeficiency states, neuropathology, endocrinology, pulmonology, otolaryngology, gastroenterology, allergology, nephrology, hematology, ophthalmology, orthopedics, speech therapy, surgery, phthisiology, oncology, nutrition, psychoneurology, dermatology, dentistry, genetics, activity of the process HIV infection.

The results of the child's examination, presented in the conclusion of the ACDE, clearly demonstrate the child's health status in the form of an «expanded map» and «highlight» its most vulnerable places. For preventive work, it is extremely important that the medical worker receives a list of profiles where hardly any pathological deviations have been observed. Thus, the child enters the zone of minimal risk or border state [2].

Objective isto study the features of the ACDE system complex in the districts of the Republic of Sakha (Yakutia) and to identify the most appropriate options for ACDE work in the districts of the RS (Y) to improve the quality of preventive

Table 1

Dynamics of number and age structure of children in the Oleneksky district

Index	Year		
	2010	2011	2012
Populationintotal	4028	4113	4155
Children from 0 to 17 years old	1349	1372	1376
includingfrom 0 to 14 years	1104	1127	1142
adolescents	245	246	234
childrenunder 1 yearold	95	80	99

Table 2

The number and frequency of pathology by pathology profiles in the Oleneksky district of the RS (Y)

Name	Allchildren		
	Total	boys	girls
Totalsurveyed	166	82	84
Total healthy children	2	0	2
Total children with pathology	164	82	82
Cardiology	92,8	92,7	92,9
Endocrinology	51,2	56,1	46,4
Ophthalmology	40,4	36,6	44,0
Stomatology	36,7	36,6	36,9
Pulmonology	21,1	24,4	17,9
Neuropathology	20,5	26,8	14
Allergology	13,3	14,6	11,9
Orthopedics	12,0	18,3	6,0
Otolaryngology	11,4	13,4	9,5
Gastroenterology	7,2	7,3	7,1

examinations.

Materials and methods.The analysis of the application of the automated complex ACDE in the districts of the Republic of Sakha (Yakutia) is made taking into account the number of children living. The approximate time of the ACDE examination was calculated and the necessary number of automated complexes for the effectiveness of medical examinations in the field was determined.

Results of the study and discussion.A pilot project in the framework of the priority national project «Health» is implemented ACDE technology in 10 districts of Sakha (Yakutia): Anabar, Abyisky, Oleneksky, Bulun, Ust-JanskyAllaikhovskiy, Lower Kolyma, Mid-Kolyma, Zhigansky, Kobyayskiy.

The use of this technology in the field made it possible to identify the following problem. In the Arctic and northern regions, 1 or 2 pediatricians are actually working, who are charged with working in the AKDO system. The time of examination of 1 child on an ACDE apparatus takes 20-25 minutes on average.

To assess the possibility of using automated systems of preventive examinations (ACDE) in the regions of the Far North of Yakutia, the Olenek region was chosen as the model object.

The Olenek district is located in the northwestern part of the Republic of Sakha (Yakutia), beyond the Arctic Circle in the Arctic zone. The distance from the village of Olenek (district center) to the city of Yakutsk is 2020 km. In the area there are 4 settlements: Olenek (732 children), Haryalah (286 children), Zhilinda (207 children), Eyik (124 children). Eyik and Zhilinda - inaccessible and remote communities, communication with them is carried out in the winter on snow road in the summer - on the river, in addition, have the opportunity to take advantage of by air. The distance from the village of Olenek to the village of Zilinda by air is 195 km, by auto-zoo - 300 km, by car, the trip takes 9 hours. Distance from settlement until Olenek sat Eyik by air is 350 km, on snow road - 600 km, a car trip takes more than 24 hours.

The population of the district is 4155 people. The population of the Olenek region is presented in Table 1. The population density is 0.0012 people per km2.

Obviously, the cost of medical care residents of the district, many times higher than the cost of citizens living in close proximity to medical facilities. The consequence of this is the actual inaccessibility of specialized and highly qualified medical care for many residents of the region (see Table 1)

Treatment and prophylactic work in the area is carried out by the Olenek Central Regional Hospital, the Zhilindinsky district hospital, the Kharyalyk medical outpatient clinic, the Eiik district hospital. Only the Olenek Central District Hospital has a license for child care.

General practitioners in the Olenek district - 1. Pediatricians in the district - 2. The trainees have the status of small plots, in the district hospitals of the villages (the village of Zilinda, Kharyalakh) there are physician-therapists, in the village of Eyik there is a general practitioner.

With the use of the automated ACDE system, 166 children were examined in the Olenek district, 117 of them in Olenka, 31 in the village of Zhilinda, 16 in the Kharyalyakh village, and 2 in the village of Eyik. The results of the survey are presented in Table 2.

The most common pathology in the nosological classes: «Cardiology» (92.8%), «Endocrinology» (50.3%), «Ophthalmology» (40.4%), «Stomatology» (36.7%), «Pulmonology «and» Otolaryngology. «

As a result of the study, a high incidence of the children of the Olenek district of the RS (Ya) was revealed. Thus, the expediency of carrying out such kind of preventive examinations is obvious.

It should also be emphasized that since the dictionary describing the child's condition in terms of ACDE includes complaints and symptoms recorded at the pre-medical level, this technique can be mastered by the average medical staff. This fact is especially important for areas where there is a problem of insufficient staffing of medical personnel.

At the second stage, we calculated the approximate time that would be needed to conduct an examination on an automated complex, based on the number of children living in different areas of the RS (Ya). Also, the number of necessary devices was calculated (see Table 3-4).

Table 3

An approximate calculation of the timing of preventive examinations using ACDE technology in the districts with the number of children from 1000-4000

Specialistload	The timing of preventive examinations using ACDE technology
Number of months of ACDE examination for the first year, if they inspect 10 children per day.	6-9 months
Number of months by ACDE if they examine 30 children per day.	For 2-4 months

Table 4

An approximate calculation of the timing of preventive examinations using ACDE technology in the districts with the number of children from 4000-8000

Specialistload	The timing of preventive examinations using ACDE technology
Number of months of ACDE examination for the first year, if they inspect 10 children per day.	From 16-40 months. (on one machine)
Number of months by ACDE if they examine 30 children per day.	For 5-13 months (on 1 device ACDE)

Conclusion.In the districts of the Republic of Sakha (Yakutia), on the automated complexes of dispensary examinations, it is possible to involve the average medical staff in the field, as this will improve the efficiency of conducting medical examinations by visiting teams. There will be selection of patients for consultation by narrow specialists. Ideally, these technologies (ACDE) would be successfully used at the school level. According to our calculations, an area with a population of up to 4,000 children requires one automated facility, and areas with a population of 5,000-8,000 children will have two automated devices if an exempt specialist works on this device.

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The authors

1. Evseeva Sardana Anatolievna, junior researcher YNC CMP, electr.post: sarda79@mail.ru, contact. telephone: 89679111195
2. Savvina Maya Semenovna - Candidate of Medical Science, Senior Researcher of the YNC CMP, 89142947946, maya_savvina@mail.ru
3. Burtseva Tatyana Egorovna, MD, Professor of the Department of Pediatrics and Pediatric Surgery of the MI SVFU, Laboratory of the YNC of the CMP, e-mail: bourtsevat@yandex.ru, contact. telephone: 89142943244.
4. Munkhalova Yana Afanasyevna, MD, associate professor, head. Department of Pediatrics and Pediatric Surgery of MI SVFU, e-mail: tokmacheva@mail.ru, contact. phone: 89142707107
5. Chasnyk Vyacheslav Grigorievich, Dr Med Sci., professor, head of lectern of «The State pediatrist medical Academy of St. Petersburg», e-mail: chasnyk@gmail.com, contact. phone: 89062296831.

V.V.Saveliev, M.M.Vinokurov, V.P.Egorova, T.V.Yalynskaya

EXPERIENCE OF SYNTHETIC ANALOGUES OF SOMATOSTATINE FROM ESOPHAGEAL VARICEAL BLEEDING IN PATIENTS WITH HEPATIC CYRROSIS WITH SYNDROME OF PORTAL HYPERTENSION IN THE MULTIDISCIPLINARY SURGICAL CENTER OF REPUBLIC SAKHA (YAKUTIA)

ABSTRACT

The aim of the study was to evaluate the effectiveness of vasoactive therapy with synthetic somatostatin analogues from acute esophageal variceal bleeding in patients with hepatic cirrhosis with portal hypertension syndrome.

Material and methods. The study is based on a retrospective analysis of the results of a comprehensive treatment of 57 patients with cirrhosis and portal hypertension syndrome who were on treatment at the emergency surgical department of the Republican Hospital №2 − the Center for Emergency Medical Care of the Republic of Sakha (Yakutia) in the period from 2015 to 2017.All patients were divided into two groups. The first group consisted of 23 (40,4%) patients, who only used the Sengstaken-Blakemore probe to stop from acute esophageal variceal bleeding. The second group of the study comprised 34 (59,6%) patients who, together with the Sengstaken-Blakemore probe installation, used synthetic somatostatin analogues in complex intensive therapy.

Results. The presented clinical experience of the use of synthetic somatostatin analogues in complex therapy from acute esophageal variceal bleedingto recommend their wide use in the practice of urgent surgical clinics.

Conclusion. The introduction of complex intensive therapy from acute esophageal variceal bleeding in patients with hepatic cirrhosis with the syndrome of portal hypertension of synthetic somatostatin analogues allowed to reduce the overall lethality to 10,7%, and to reduce the risk of rebleeding by 17%.

Keywords: hepatic cirrhosis, portal hypertension, esophageal variceal bleeding, vasoactive therapy.

Introduction. It is well known that among a number of numerous causes of gastrointestinal-bleeding, esophageal varicose vein dilatation (EVVD) is at least 5-10% [12]. In most patients with hepatic cirrhosis (HC), a portal hypertension syndrome (PGS) occurs, which in more than 60-70% of cases is complicated by the development of gastrointestinal-bleeding [3]. According to [1], mortality even after the first episode of bleeding is more than 30%, and in 50-70% of cases, it'srebleeding. Treatment of complications of PGS, especially hemorrhage from EVVD, remains to this day an urgent problem of urgent gastroenterology due to high mortality and a large number of their rebleeding [1]. A key role in the development of esophageal varicose vein dilatation and bleeding is played by an increase in the portocaval pressure gradient. Risk factors are the degree of varicose enlargement, the presence of «red markers» and the severity of hepatic dysfunction [15]. The risk of developing bleeding from the EVVD in patients with HC within the first year is 10-15% and reaches 30% by the end of the second year of the disease [4]. If bleeding is stopped without the use of endoscopic or surgical methods, bleeding recurrence occurs in 50-70% of patients and in 80-90% in the case of a two-year follow-up [4,8]. Currently, combined treatment with vasoactive drugs and endoscopic methods is recommended [9].

Materials and methods. The presented work is based on a retrospective analysis of the results of complex treatment of 57 patients with HC and PGS who were on treatment in the emergency surgical department of the Republican Hospital №2 - Center for Emergency Medical Care of the Republic of Sakha (Yakutia) in the period from 2015 to 2017. The average age of the patients was 45,1 ± 6,5 years, with men being 38 (66,7%), women - 19 (33,3%). The diagnosis of HP and PGS is verified on the basis of a multilevel complex examination. All patients were taken to the clinic by an ambulance carriage with a clinical picture of bleeding from the EVVD and subsequently hospitalized in the intensive care unit (ICU). The volume of intensive care was determined in accordance with the recommendations of the international consensus Baveno VI (2015) (Italy) [2]. The main areas of intensive care were: the replenishment of circulating blood, the use of hemostatic and vasoactive drugs, antibiotics (for the treatment and prevention of spontaneous bacterial ascites-peritonitis), hepatoprotectors, anticoagulants. Synthetic somatostatin analogs were used as vasoactive agents

(Somatostatin, Octreotide).Endoscopic examination was performed with GIF Type 2 T 160 gastrofibroscope firm «Olympus» (Japan). In interpreting the endoscopic picture, they were guided by the recommendations of the Japanese scientific society on the study of portal hypertension (1991) [5]. The cumulative degree of esophageal and gastric dilatation was established according to the modified criteria of K-J Paquet (1983) [14].

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

Results and discussion. To achieve the purpose of this study, patients were divided into two groups. The first (control) group included 23 (40,4%) of the observed patients who had only the Sengstaken-Blakemore probe installed to stop bleeding from the EVVD.The second (main) group comprised 34 (59,6%) patients, who along with the installation of the Sengstaken-Blakemore probe in complex intensive therapy used synthetic somatostatin analogues(table 1).

As in [4], in order to evaluate the effect of vasoactive therapy on hemodynamic, a comparative analysis of mid arterial pressure, heart rate, cardiac output, and the main dopplerographic indices of portal blood flow at the time of admission was made and 30 and 90 minutes after the introduction of the synthetic somatostatin analogue (table 2).

BPmid, mm Hg. - mid arterial pressure, HR - heart rate, Vmid.vp.cm/s - time averaged speed over the portal vein, VFvp, ml/min - volumetric speed of the portal vein, RI - hepatic artery resistance index.

The study found that the introduction of synthetic somatostatin analogs was accompanied by a significant decrease in both linear and volume flow rate of the portal vein from 21,9 ± 5,2 to 17,6 ± 3,9 cm / s and 734,5 ± 621,7 to 621,7 ± 201,3 ml / min, respectively. This effect was observed after 90 minutes from the administration of the drug. On average, the portal blood flow speed decreased by 20,1 ± 3,7% (p <0,05), and the volume flow of blood decreased by 17,4 ± 2,8% (p <0,05). The index of resistance of the hepatic artery also decreased somewhat, but no significant differences were found in the groups (p <0,05).

It should also be noted that the introduction of synthetic somatostatin analogs was accompanied by changes in the parameters of central hemodynamics. There was a decrease in the mean arterial pressure and heart rate, a decrease in cardiac output.

Esophageal-gastric bleeding of portal genesis is the most frequent and life threatening complication of chronic diffuse liver diseases [4]. Over the past decade, due to the widespread introduction of endoscopic methods for the prevention and control of bleeding from EVVD and modern vasoactive drugs, the mortality from bleeding from EVVD has decreased from 40-60% to 10-15% [6]. However, all the same authors note that 20-30% of patients have profuse, hard to control bleeding, and early rebleeding develop in every 5 patients [11]. At present, it is generally accepted that complex pharmacotherapy contributes to the achievement of hemostasis in a significant number of patients [10]. The most justified is the prescription of drugs, whose action is aimed at reducing portal pressure and reducing blood flow to the EVVD. Studies have shown that with the development of bleeding vasoactive drugs should be introduced as early as possible, and their use is continued to prevent recurrence of bleeding within 5-7 days [7,13].

The results of the study showed that the combined use of the Sengstaken-Blakemore probe against the background

Table 1

Demographic, clinical-nosological characteristics of research groups

Testsubject	Numberofpatients					
	1 (control) group (n=23)		2 (main) group (n=34)		Total (n=57)	
	abs.	M±ε	abs.	M±ε	abs.	p
Age, years	48,1±11,8		43,2±12,7		45,1±6,5	
Men's	14	36,8±2,4	24	63,2±1,7	38	p<0,05
Women	9	47,4±2,5	10	52,6±1,8	19	p<0,05
Viralhepatitis B	4	36,4±1,3	7	63,6±1,1	11	p<0,05
ViralhepatitisC	6	31,6±2,1	13	68,4±1,5	19	p<0,05
Mixed-hepatitis B+D	2	66,7±2,7	1	33,3±2,1	3	p<0,05
Mixed- hepatitisB+C+D	1	50,0±2,6	1	50,0±1,9	2	p<0,05
AlcoholicHC	7	38,9±2,1	11	61,1±1,5	18	p<0,05
CryptogenicHC	3	75,0±2,5	1	25,0±1,8	4	p<0,05
EVVD						
IIdegree	1	33,3±1,7	2	66,7±1,2	3	p<0,05
III degree	14	41,2±1,3	20	58,8±1,1	34	p<0,05
IVdegree	8	40,0±1,6	12	60,0±1,9	20	p<0,05
Child-Pughcriteria						
ClassA	2	40,0±1,8	3	60,0±1,1	5	p<0,05
ClassB	11	36,7±2,3	19	63,3±2,1	30	p<0,05
ClassC	10	45,5±1,4	12	54,5±1,6	22	p<0,05

*Reliability of differences of the I group in relation to II p <0,05

Table 2

Parameters of central and regional portal hemodynamics

Index	1 (control) group			2 (main) group		
	At the time of admission	After 30 minutes	After 90 minutes	At the time of admission	After 30 minutes	After 90 minutes
BPmid, mm Hg.	103,4±4,5	110,2±7,6	115,8±8,9	107,2±7,1	98,1±7,1	101,4±6,5
HR	107,3±8,1	99,3±7,1	90,6±4,6	110,8±8,3	84,2±6,5	86,7±3,7
Cardiac outputl/min	8,6±4,3	7,4±3,4	7,3±4,4	9,6±5,1	8,2±3,3	8,5±3,8
Vmid.vp.cm/s	20,9±6,6	19,7±3,1	15,4±3,0	21,9±5,2	17,6±3,9	19,1±4,5
VFvp, ml/min	760,4±271,2	668,1±284,3	578,5±234,6	734,5±256,1	621,7±201,3	699,9±275,2
RI	0,82±0,18	0,74±0,15	0,65±0,12	0,86±0,22	0,62±0,11	0,76±0,17

* Reliability of differences of the I group in relation to II p <0,05
BPmid, mm Hg. - mid arterial pressure, HR - heart rate, Vmid.vp.cm/s - time averaged speed over the portal vein, VFvp, ml/min - volumetric speed of the portal vein, RI - hepatic artery resistance index.

of a 24-hour intravenous injection of synthetic somatostatin analogues for bleeding from the EVVD made it possible to achieve hemostasis in 94,3% of the observations. Early recurrence of bleeding from the EVVD in the first 5-7 days after stopping bleeding against the background of the administration of drugs was noted in only 4 (11,8%) patients, another 2 (5,9%) of our patients had repeated episodes of hemorrhage at the 10th and 14th day of inpatient treatment. In the case of patients of the control group, in the complex treatment in which only the installation of the Sengstaken-Blakemore obturator was used to stop bleeding, it was not much more than 77,6% of cases that the hemostasis was achieved. Early recurrence of bleeding in the first 5-7 days was noted in 5 (21,7%) patients and in 3 (13,0%), episodes of bleeding were fixed on the 9th and 12th day of treatment. In this case, the common mortality in the main group was 10.7%, and in the control group - 36.8%.

Thus, the following conclusions can be drawn that, in addition to the widespread introduction of endoscopic and endovascular methods of stopping bleeding from the EVVD in clinical practice, pharmacotherapy is an integral part of the treatment. Priority direction of therapy with vasoactive drugs should be considered the earliest inclusion in the intensive care complex of synthetic somatostatin analogues. The data obtained by us allow us to consider synthetic analogs of somatostatin, as the drugs of choice for bleeding from EVVD.

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The authors

FGAOU VO «North-Eastern Federal University named after M.K. Ammosov «677000, Yakutsk, ul. Belinsky, 58. Phone: 8 (4112) 35-20-90, fax: 8 (4112) 32-13-14. E-mail: rector-svfu@ysu.ru.

1. Savelyev Vyacheslav Vasilievich - MD, Professor of the Department of Faculty Surgery, Urology, Oncology and Otorhinolaryngology, Medical Institute, Federal State University «North-Eastern Federal University named after M.K. Ammosov «, 677018, Yakutsk, ul. Krupskaya 37, Apt. 58. E-mail: vvsavelievv@mail.ru;

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

3. Egorova Varvara Prokopievna - postgraduate student of the Department of Faculty Surgery, Urology, Oncology and Otorhinolaryngology, Medical Institute, Federal State University «North-Eastern Federal University named after M.K. Ammosov «, 677000, Yakutsk, st. Dzerzhinsky 41/3, apt. 114. E-mail: varchik19@mail.ru;

4. Yalynskaya Tatyana Vadimovna - clinical resident of the Department of Surgical Diseases and Dentistry of the Faculty of Postgraduate Education of Physicians of the Medical Institute of the Federal State University «North-Eastern Federal University named after M.K. Ammosov «, 677009, Yakutsk, st. Dzerzhinsky 45/2, apt. 70. E-mail: barbuzyaka@mail.ru.

HEALTHY LIFESTYLE. PREVENTION

T.S. Mostakhova

MALE OVERMORTALITY IN THE REPUBLIC OF SAKHA (YAKUTIA) AND THE WAYS OF ITS REDUCTION IN ORDER TO MAINTAIN DEMOGRAPHIC SECURITY OF THE REGION

ABSTRACT

The purpose of the study is to show the significance of high mortality of men as one of the most problematic issues in the sphere of mortality. The main characteristics of the excess mortality of males identified using the methods of demographic data analysis on the dynamics of mortality rates by individual age groups, gender breakdown, by selected causes of death. A sufficient number of problematic issues present in the sphere of mortality. This is a relatively high proportion of deaths in working age, maintaining the structure of causes of death substantial relative weight of deaths from accidents, poisonings and injuries, i.e. external causes.Although the positive dynamics in reducing the proportion of these causes of death in the total number of deaths observed, however, these causes of death consistently occupy 2nd place after diseases of the circulatory system.

Male overmortalityof men is one of the significant problems in the field of mortality and has economic consequences, e.g., loss of the working population, and social (from the point of view of family life). In recent years, the mortality rate in men was constantly higher than in women. Male overmortalityis stored in the active working ages; in the working age index of high mortality of men is much higher than a similar index in the general population. The highest rates are added to these causes of death external causes of death, suffering from consumption and chronic alcoholism. Mortality due to external causes is significant growth potential for the life expectancy as one of the integral indicators of demographic security. In this regard, the reduction of mortality from external causes should be one of the major events in the regional demographic policy in the sphere of mortality.

The complex of measures to reduce the high mortality of men should include the units on the improvement measures of a medical nature,and also the block of measures of primary prevention (the formation of self-preservation behavior, healthy lifestyles), the unit of measures for creation of safe habitat.

Keywords: mortality, male overmortality, the cause of death, life expectancy, regional population policy, Republic of Sakha (Yakutia).

Introduction. The process of mortality at the present time largely determine population reproduction in the Republic of Sakha (Yakutia) [5]. As in other Northern subjects of the Russian Federation in the Republic the situation with mortality of the population has a number of rather negative effects [8], although the dynamics of total mortality tends to decrease (by 13% by 2016 compared to 2000).

A fairly high proportion of deaths in working age is a problem in the field of mortality [3], although this indicator tends to decrease in 2000 to 46.5%, 2016 – 37,5%). Maintaining the structure of causes of death substantial relative weight of deaths from accidents, poisonings and injuries, i.e. external causes, is a significant problem in the field of mortality. «External mortality is consistently ranked the 2nd place after diseases of the circulatory system, identifying more than 17% of all population losses. For the years 1990-2015, the number of deaths fell by almost 24.2%. However, unfortunately, the mortality rate remained at the 1990 level» [6]. Positive dynamics in the reduction in the share of these causes of death in the total number of deaths observed: in 1990 the proportion of deaths from external causes amounted to 24.6%, in 2016 – an increase of 16.2%. However, the mortality rate for these causes of death consistently occupy 2nd place after diseases of the circulatory system.

The high mortality in the Northern and Arctic regions of the Republic is a significant problem in the state of mortality [2].

Materials and methods. The main method applied in the study, – demographic analysis. Data on dynamics of mortality rates by individual age groups, gender breakdown, by selected causes of death was used and analyzed. The main characteristics of the excess mortality of men is revealed. Indexes of high mortality for selected causes of death, age group the evolution over the years 2000-2016 calculated.

The results and discussion. Supermortality of men is one of the most urgent problems in the sphere of mortality, i.e. the excess mortality in men compared with similar indicators in women. In recent years, the mortality rate in men was constantly higher than in women (Fig.1), moreover, the excess mortality of men over 2000-2016 he has not changed as significantly. Supermortality of men is not an entirely new phenomenon in the demographic development of the Republic; it was noted by researchers earlier [4].

Not only higher mortality rates are typical for the male population, but a slower decline in the mortality rate.

The greatest excess mortality of the male population over the female is noted at a young age. Maximum value of the index of high mortality observed in the age groups 20-24,25-29, 30-34. Even among children under the age of 1 year mortality of boys is much higher than girls.

In total for 2000-2016 high mortality growth index was characteristic only for age groups over 60 years(table 1),while earlier ages 10-14, 15-19, 20-24, 45-49, 50-54, 55-59, 65-69 years, i.e. mainly in the young and the older working ages.

In comparison with the Russian Federation, in Yakutiasimilar indicators of 20-24, 25-29 and 30-34 yrsage groups look particularly anxious,where a significant excess over the average rates is observed. Age 5-9 years was in this group, oddly enough, where it exceeded the national index of high mortality over Russia in 2016, was the biggest - 1.5 times.

Compared with the figures for Russia and the Far Eastern Federal district the index of high mortality of menin the Republic, calculated from standardized mortality rates for men and women,is slightly lower. However, if in the Russian Federation and the Far Eastern Federal district this index for 2005-2015 has decreased, in Yakutia it was increased

(table2).

Index of high mortality of men of working age is much higher than a similar index in the general population (table 3).In the Russian Federation index of high mortality of men of working age over the 2005-2015 was decreased, but inYakutiait has not changed.

Differences in the index of high mortality of men in the context of individual causes of death are of greatest interest in terms of developing measures to reduce the high mortality of men.In connection with a significant array of data analysis of high mortality of men held on selected causes of death.They included diseases of the circulatory system, neoplasms and external causes of death.These classes of reasons account for the vast number of deaths in men and women.For example, in 2000 these causes of death in men «gave» 82% of all deaths, in 2016 – 81%.

However, a significant index value of the high mortality observed for some individual reasons, were not included in these major classes of reasons taken for analysis. In this regard, they are also included in the preliminary list of analyzed causes of death. Thiscausessuchastuber culosisandchronicalcoholism.

On these causes of death over a long period of time the highest values of the index of high mortality men observed (table 4).

Substantial changes occurred in the ranking of causes of death with the highest indexes of high mortality of men for 2000-2016. The highest index of excess mortality during 2000-2016 is maintained for such reason as suicides (5,54 in 2000 and 6,26 in 2016) (table 5).

Among all the reasons, the situation with the excess mortality of men from external causes of death, which largely determine the loss of life potential in the country, attracts the most attention. It is more typical for the rural population, which is typical for Russia as a whole [1]. Men's super-mortality rates remain almost at the same level as in 1990; moreover, this gap even increases for the urban population (in 1990 – 4.48, in 2014 – 4.81).

By some reasons this class of causes of death the largest index of high mortality of men in 2016 was typical for suicides (table 6). For this reason, there is death index growth of high mortality of men, in contrast to other causes (traffic injuries, homicide), for which there is some positive dynamics.

Conclusion.Thus, the high mortality rate of men in comparison with women is one of the most significant moments in the processes of mortality both in the Republic of Sakha (Yakutia) and in Russia as a whole. The highest rates are for causes of death, such as external causes of death, tuberculosis and chronic alcoholism. Over a long period of time the highest values of the index of high mortality of males observed on these causes of death. Unlike other causes of death with a high index of male excess mortality, this suicide rate is on the rise.

The analysis of the phenomenon of over-mortality of men leads to the conclusion that mortality due to external causes is significant growth potential for

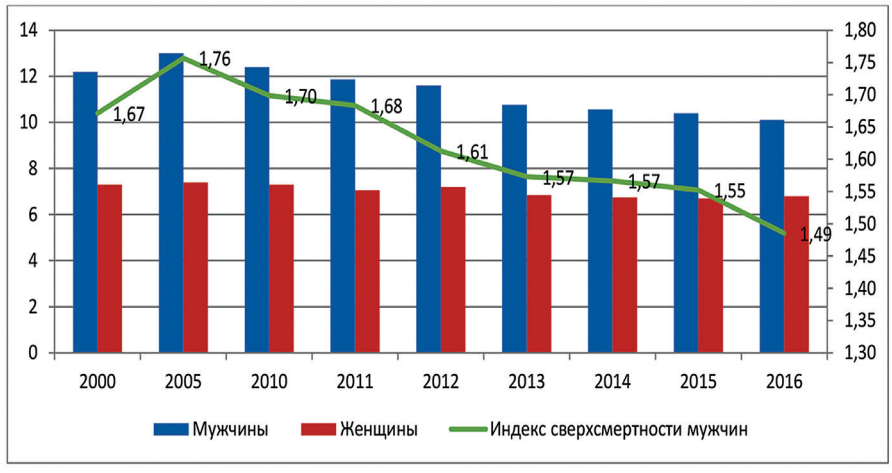

Fig.1. The overall mortality rates of men and women in the Republic of Sakha (Yakutia), 2000-2016.

Table 1

Index of high mortality of men in the Republic of Sakha (Yakutia)

Age	2000	2005	2010	2015	2016	2016/2000
0-4	1,67	1,76	1,70	1,55	1,49	0,889
5-9	1,33	1,59	1,16	1,38	1,19	0,891
10-14	2,25	1,00	1,25	1,00	1,50	0,667
15-19	2,50	2,25	1,00	1,33	1,33	0,533
20-24	2,00	2,89	3,13	3,00	1,83	0,917
25-29	4,64	5,10	3,60	3,00	4,17	0,897
30-34	4,18	3,53	3,13	4,88	3,20	0,766
35-39	4,30	4,40	5,27	3,27	3,12	0,725
40-44	3,46	4,08	3,25	3,18	2,91	0,841
45-49	3,19	3,51	3,62	3,80	3,03	0,951
50-54	2,97	3,19	2,87	2,54	2,68	0,902
55-59	2,82	2,96	2,92	2,96	2,62	0,929
60-64	2,97	3,08	2,75	2,99	2,76	0,929
65-69	2,11	2,20	2,47	2,60	2,62	1,242
70 лет и старше	1,81	2,14	2,40	2,17	2,17	1,196
total	1,26	1,33	1,40	1,32	1,31	1,040

Table 2

Index of high mortality of men for 2005-2015*

	2005	2010	2011	2012	2013	2014	2015	2015/2005
RussianFederation	2,10	2,05	2,05	2,03	2,02	2,03	2,00	0,95
The Far Eastern Federal district	2,06	2,06	2,03	2,01	1,99	1,99	1,99	0,97
The Republic Of Sakha (Yakutia)	1,92	1,99	2,00	1,95	1,91	1,98	1,95	1,01

*Calculated on standardized mortality rates for men and women.

Table 3

Index of high mortality of men of working age in 2005-2015

	2005	2010	2011	2012	2013	2014	2015	2015/ 2005
RussianFederation	3,85	3,73	3,66	3,65	3,64	3,64	3,56	0,92
The Far Eastern Federal district	3,38	3,36	3,36	3,30	3,22	3,20	3,14	0,93
The Republic Of Sakha (Yakutia)	3,75	3,66	3,47	3,77	3,76	3,62	3,75	1,00

Table 4

Index of high mortality of men in the separate classes of causes of death in 2000-2016

	2000	2005	2010	2015	2016	2016/ 2000
From all causes	1,66	1,75	1,69	1,55	1,48	0,89
From diseases of the circulatory system	1,24	1,38	1,40	1,41	1,41	1,14
From tumors	1,35	1,36	1,22	1,25	1,36	1,01
From external causes of death	4,51	4,77	4,08	4,57	4,47	0,99
From tuberculosis (allforms)	3,04	4,97	3,04	4,67	5,25	1,73
From chronic alcoholism	3,39	2,79	1,31	1,50	5,50	1,62

Table 5

The ranking of causes of death largest index of high mortality of men in 2000 and 2016

	2000	2016
Fromallcauses	1,66	1,48
Suicides	5,54	6,26
Murders	5,36	4,45
Accidentalalcoholpoisoning	4,49	3,48
Chronicalcoholism	3,39	5,50
All types of transport injuries	3,38	2,96
Tuberculosis (allforms)	3,04	5,25

Table 6

Index of high mortality of men by selected causes of class «External causes of death» for 2000-2016

	2000	2005	2010	2015	2016	2016/2000
Fromallcauses	1,66	1,75	1,69	1,55	1,48	0,89
From external causes of death	4,51	4,77	4,08	4,57	4,47	0,99
From all types of transport injuries	3,38	3,72	3,80	3,67	2,96	0,88
Fromsuicide	5,54	6,04	4,25	4,63	6,26	1,13
Frommurders	5,36	5,95	5,25	10,46	4,45	0,83

the life expectancy as one of the integral indicators of demographic security. In this regard, the reduction of mortality from external causes should be one of the main activities in the regional population policy in the field of mortality. Amongof all the measures to reduce mortality, priority should be given to measures to reduce the excess mortality of men, primarily from external causes of death, especially suicide.

The development of such measures should be based on the understanding that the risk factors for men causing high mortality are the low value of health, which is expressed in the absence of self-preservation behavior in everyday life and in the workplace, high alcohol consumption, as well as the specifics of men's employment. According to experts, neglect of one's own health, among other things, may be associated with social factors, including an incorrect understanding of the male role. Therefore, it is necessary to define as measures «education of boys in the spirit of gender equality, which, unlike the Patriarchal system, does not impose rigid roles and identities» [7].

Along with measures to improve specialized medical care preventive steps in the formation of a self-preservation behavior of the population and creating a safe environment should be mandatory directions. The formation of self-preservation behavior, increase the value of healthy life in the system of life values can be recommended such measures as informing the population about the risk factors, initiation of social advertising, TV and radio broadcasts, video clips, interviews, publications in mass media on problems of depression, psychological disadaptation and crisis in children, teenagers and adults, organization and implementation of an information campaign on the principles of prevention of crisis conditions.

Raisingthelevelofearlydetection, treatmentandcareforpeoplewithmentaldisordersandvariousaddictions, chronicpainand acuteemotionaldisorderscanbeameasuretoreducethenumberofsuicides. Improving the professional skills of doctors and medical psychologists involved in assisting patients in crisis and suicidal conditions can contribute to this.

In the spectrum of measures to counter excessive alcohol consumption, it is necessary to see such as changes in the type of alcohol consumption, as happened, for example, in the Nordic countries, which is possible when carrying out a competent anti-alcohol policy.

Measures to overcome the excess mortality of men, SC and in General policies to reduce mortality should be focused on the whole society as a whole, and on certain social groups (by sex and age, risk, etc.). Improving scientific validity and conducting scientific research should be a necessary part of the package of measures.

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The author:

Mostakhova Tatyana Semenovna, Doctor of Economy senior researcher, the Department of regional economic and social researches Yakut scientific center SB RAS, Yakutsk, Republic Sakha (Yakutia), E-mail: mostakhovats@mail.ru.

HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

G.T. Dyagilev, V.F. Chernyavsky, M.E. Ignatyeva, O.N. Sofronova, O.I. Nikiforov

EPIZOOTOLOGICAL EPIDEMIC MONITORING OF THE ANTHRAX IN THE CENTRAL AND SOUTH AREAS OF YAKUTIA

ABSTRACT

739 epizootics of anthrax were registered in 244 stationary disadvantaged settlements on the territory of the republic.

In the present work there are modern data on epizootological epidemic monitoring of anthrax in the central and southern economic zones of the Republic of Sakha (Yakutia), which significantly clarify the quantitative and qualitative aspects of the indicated problem. Thus, the maximum number of epizootics of anthrax (numerator) and disadvantaged settlements (denominator) is registered in the areas of the central economic zone (323/109), and their respective minimum values are in the areas of the south economic zone (2/2). It has been determined the intensity of death of domestic animals by species, the number of registrations at disadvantaged settlements, the prevalence and periodicity of epizootics by area of the zone.

Attention is focused on an episode associated with the possible, specific, infectious and epidemiological danger of group burials of people.

Keywords: epizootic-epidemiological monitoring, anthrax, anthrax burial sites, agricultural animals, stationary disadvantaged settlements, economic zones, incidence level.

Introduction

Anthrax, an especially dangerous saprozonotic infection, is now manifested in the form of sporadic cases, and sometimes in the form of outbreaks. The causative agent of anthrax, actively spreading in the abiotic environment, poses a potential danger to wild and farm animals, as well as humans. Despite the significant decline in economic damage from this infectious disease in recent decades as a result of preventive measures, the disease continues to be registered in many countries around the world, in various regions of Russia [1]. In Siberia and the Far East to the territories with marked epizootic-epidemiological disadvantage in the Siberian anthrax include the Altai Territory, the Omsk Region, the Republics of Buryatia and Tyva, the Novosibirsk Region and the Trans-Baikal Territory, as well as Central Yakutia [8] , on the territory of which, by the example and results of modern microbiological research, archaeological remains (Churapchinsky district) of the group burial of dead people, evidence of their specific epidemiological danger has been obtained [10].

On the territory of the Russian Federation there are over 35,000 registered stationary disadvantaged settlements, which account for about 8 thousand anthrax cattle cemeteries. More than 70,300 group and single cases of diseases of humans and animals with anthrax have been identified.

Didactic interest is represented by epizootic and epidemiological events of 2016 taking place in the tundra regions of the Yamalo-Nenetsky Autonomous District, where a large epidemic outbreak of anthrax with a number of stricken - 36 people and a case of 2,650 heads of domestic deer was recorded. The source of infection were reindeer and unaccounted anthrax burials in which B.anthracis spores persisted for a long time in the Yamal soils [2]. In the before- revolutionary Yakutia, anthrax was one of the most common and dangerous infectious diseases. The first information about the occurrence of anthrax in Yakutia dates back to 1811. In subsequent years, up to 1993-1994, i.e. for more than 100 years, almost annually diseases and death of animals from anthrax were recorded [3-5, 8]. Our monitoring studies and generalizations do not exclude the relevance of anthrax on the territory of the Republic of Sakha (Yakutia). Due to the impossibility of defining clear boundaries of stationary disadvantaged settlements (SDS), the only indicators of potential disadvantage are information on the mortality of animals from anthrax and burial related to the objects of the first class of danger. According to the study results of the characteristics of anthrax burial sites (CABS), it was established that most of the burial sites on the territory of the republic date back to 1960 [4]. For the planned organization of anti-anthrax measures, it is necessary to keep a record and constant monitoring of the status of all known stationary disadvantaged settlements, since the potential danger of occurrence of new outbreaks remains in any of these disadvantaged settlements, including «dormant» or «forgotten» [8].

The aim of the study is to conduct, evaluate and forecast epizootic-epidemiological monitoring of anthrax for various disadvantaged (primarily stationary) settlements in the Central and Southern economic zones of the Republic of Sakha (Yakutia), indicating their veterinary medical and

sanitary significance in administrative and geographical areas under implementation of megaprojects and formation of special development territories (SDT).

Materials and methods of research. In studying of the epizootic situation on the anthrax, there were used the official records of the Veterinary Department of the Yakutsk region, the annual reports, the official information of the Yakut Autonomous SSR, the Ministry of Agriculture of the Republic of Sakha (Yakutia), the Department of Veterinary Medicine of the Republic of Sakha (Yakutia) on the timing of registration of disadvantaged settlements and cases of manifestations of the disease in them, as well as materials of their own research, epizootic foci of anthrax in the Yakutsk region and the Republic of Sakha (Yakutia).

To assess the nature of epizootic and epidemiological processes of anthrax in the Central and Southern zones of the Republic of Sakha (Yakutia), there were determined the level of epizootic ill-being and the nature of prevalence, territorial confinement, duration of the process, and the frequency of recurrence of outbreaks at the level of attachment to human settlements.

Results and discussion. Based on the study of geographical, natural climatic, soil features of agroclimatic zones, the configuration of the population and the transport network, agricultural and industrial specialization of the regions, the territory of the Republic of Sakha (Yakutia) is divided into five economic zones: Arctic, North-Eastern, Western, Central and Southern [6]. In this case, we conduct an epizootic-epidemiological monitoring of anthrax in the Central and Southern economic zones of the republic.

The Central economic zone occupies the Central Yakut plain, covered with medium light-coniferous taiga. In the Leno-Amginsky interfluve there are mostly forest-steppe areas and a large number of lakes. These are the main agricultural regions of the republic [6]. It includes Amginsky, Gorny, Megino-Kangalassky, Tattinsky, Ust-Aldansky, Churapchinsky, Namsky, Khangalassky, Kobyaysky, Yakutsky districts.

The Southern economic zone includes two districts: Aldansky and Neryungrinsky. They are occupied by medium light-coniferous taiga of Dahurian larch, mountain light-coniferous, sometimes pine forests [6]. The mining industry is developed here. Agriculture and livestock farming are focal.

The territory of the Republic of Sakha (Yakutia) is divided into 4 epizootic zones according to the indices of activity of the epizootic process and the level of incidence and degree of disadvantage on the Siberian anthrax: a zone of high incidence and disadvantage (11 to 90 outbreaks), a zone with an average level of incidence and disadvantage (4-10 disease outbreaks), a zone with a low level of incidence and disadvantage (1-3 outbreaks) and an anthrax-free zone [7] (Fig. 1). Based on the results of the analysis of the epizootic situation, the frequency and degree of disadvantage, the areas of the Central economic zone; Amginsky, Gorny, Megino-Kangalassky, Tattinsky, Ust-Aldansky, Churapchinsky, Namsky, Khangalassky, Yakutsky, Kobyaisky belong to the zone with a high incidence rate and disadvantage, in which the epizootics of anthrax were recorded from 11 to 90 times during the studied period [4]. Areas of the Southern economic zone (Aldansky and Neryungrinsky) belong to the zone with a low incidence and disadvantage, since for the studied period epizootics of anthrax in the territories of these regions were recorded 2 times [4].

Fig. 1 Incidence rate and degree of disadvantage on the Siberian anthrax of the territory of the Republic of Sakha (Yakutia) for 1811-1993.

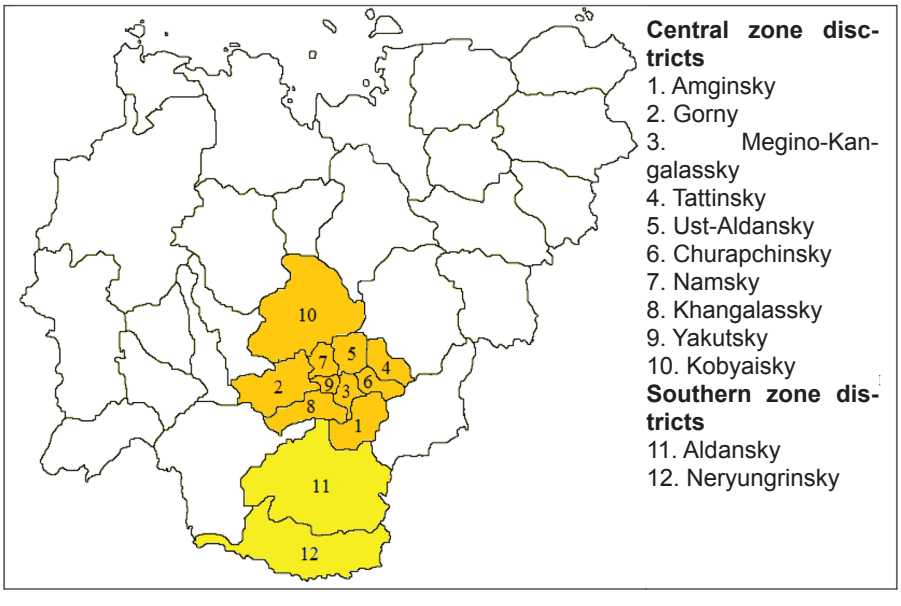
1 – a high level of incidence and disadvantage (11-90 outbreaks);

2 – an average level of incidence and disadvantage (4-10 outbreaks);

3 – a low level of incidence and disadvantage (1-3 outbreaks);

4 – an area free of anthrax.

Historically, during the 206-year observation period (1811-2017) in the Republic of Sakha (Yakutia) 739 epizootics of anthrax were registered in 244 stationary disadvantaged settlements. At the same time, the maximum number of epizootics of anthrax and stationary disadvantaged settlements was identified in the areas belonging to the Central economic zone (the number of epizootics is 323, stationary disadvantaged settlements - 109), and the minimum number of epizootics of anthrax and stationary disadvantaged settlements was noted in the areas related to the South economic zone (the number of epizootics 2, stationary disadvantaged settlements 2) (Table 1). [4]. The analysis of epizootic-epidemiological monitoring showed that 43.7% of epizootics of anthrax,as well as 38.8% of stationary disadvantaged settlements registered on the territory of the republic,were noted in the Central economic zone. During the study period, two epizootic outbreaks of anthrax (0.27%) and two stationary disadvantaged settlements (0.31%) were identified in the Southern economic zone, the cartographic situation (GIS) is still present. On the territory of the Republic of Sakha (Yakutia), 78,017 heads of domestic and wild animals fell from epizootics of anthrax (cattle – 29,480, horses – 35,995, deer - 12,517, wild animals - 25) [4].



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2 – an average level of incidence and disadvantage (4-10 outbreaks);
3 – a low level of incidence and disadvantage (1-3 outbreaks);
4 – an area free of anthrax.

In the areas of the Central economic zone of the total number of dead animals in the republic there are 26,336 heads (33.7%), including cattle 13,464 heads (51.1%), horses 12,534 heads (47.5%), deer 338 (1.28%). In the areas of the Southern economic zone, 6 heads of domestic animals fell, of which cattle 2 heads, horses 4 heads [3, 4]. During the study period, anthrax was detected in animals of nine species (cattle, domesticated and wild deer, horses, roe deer, elk, bears, wolves and dogs), the main part of which were cattle (37.7%), horses (46.1%), deer (16.1%) of the total number of cases (78,024 animals) [8, 9].

Anthrax epizootics in the areas of the Central economic zone 323 disadvantaged settlements were registered, while the frequency of epizootics of anthrax in them was expressed by the following indicators:

1 time in 100 settlements (43% of the total number);

2 times in 43 (18.5%);

3 times in 27 (11.6%);

from4 to 6 times in 38 settlements (16.4%);

from7 to 9 times in 15 settlements (6.5%);

from10 to 18 times in 9 settlements (3.9%).

18.5% of cases were recorded for 2 consecutive years in the same village, 3 consecutive years - 11.6%, 4 to 6 consecutive years – 16.4%, from 7 to 9 years in a row - 6.5%, from 10 to 18 years in a row - 3.9% of the 182 total years of activity in the Republic of Sakha (Yakutia). This is evidence that the level of repeated (in a row) diseases in the territory of the Republic was high up to the 1930s.

The analysis of epizootic and epidemiological monitoring of anthrax in the Central and Southern economic zones of the republic made it possible to identify areas and stationary disadvantaged settlements, where epizootics of anthrax and mass mortality among domestic and wild animals were active (Table).

However, the calmness of the observed pattern should be considered relative, because from soils in the zones of realized megaprojects (pipelines of the ESPO and the «Power of Siberia», Taranakh, Kankunskaya HPS and «AYAM-YaZhD» objects: locomotives, stations, bridges), we repeatedly distinguished strains of bacteria (B.cereus), closely related to the classical type - Bacillus anthracis.

Conclusion

To date, 739 outbreaks of anthrax among animals in 29 administrative districts, in 244 settlements out of 628 have been identified in the territory of the Republic of Sakha (Yakutia). 38.8% of the settlements of the republic are disadvantaged in the Siberian anthrax, with an average for the Russian Federation – 24.4%, the epizootic-epidemiological significance of which persists.

The majority of stationary disadvantaged settlements marked in the Republic of Sakha (Yakutia) are registered (47.3%) on the territory of the Central economic zone. During the study period, the number of disadvantaged settlements for the Siberian anthrax was determined, in which mass cases of diseases and mortality of agricultural animals were recorded; Amginsky (24), Gorny (21), Megino-Kangalassky (11), Tattinsky (37), Ust-Aldansky (90), Churapchinsky (21), Namsky (29),

Indicators of the epizootic process of anthrax and the mortality of animals in the Republic of Sakha (Yakutia) from 1811 to 1993

Name of economic zones and districts	Number of settlements	Number of disadvantaged settlements	% Disadvantaged settlements	Number of anthrax	Number of dead animals				
					cattle	horses	deer	Wild animals	Total
Central zone districts									
Amginsky	21	9	42,8	24	182	358	0	0	540
Gorny	16	7	43,7	21	300	671	32	0	1003
Megino-Kangalassky	36	8	22,2	11	74	47	0	0	121
Tattinsky	15	11	73,3	37	923	626	146	0	1695
Ust-Aldansky	35	24	68,5	90	6705	5244	0	0	11949
Churapchinsky	30	9	30,0	21	1355	1124	0	0	2479
Namsky	14	10	71,4	29	1454	1790	146	0	3390
Khangalassky	29	11	37,9	27	2082	2303	0	0	4385
Yakutsk (Zhatai village)	11	8	72,7	30	362	279	0	0	641
Kobyaisky	23	12	52,1	33	27	92	14	0	133
Total	230	109	47,39	323	13464	12534	338	0	26336
Western zone districts									
Mirninsky	14	6	42,8	6	3	0	97	15	115
Lensky	19	2	10,5	3	5	3	0	0	8
Olekminsky	54	21	40,5	56	763	911	160	0	1834
Suntarsky	39	12	30,7	26	964	1116	0	0	2080
Nyurbinsky	24	16	66,6	44	2085	2269	0	0	4354
Verkhnevilyuisky	29	13	44,8	47	2547	3016	299	0	5862
Vilyuisky	27	16	59,2	74	6241	5420	0	0	11661
Total	206	86	41,7	256	12608	12735	556	15	25914
Arctic zone districts									
Anabarsky	3	0	0	0	0	0	0	0	0
Allaikhovsky	7	0	0	0	0	0	0	0	0
Abyisky	7	0	0	0	0	0	0	0	0
Bulunsky	10	0	0	0	0	0	0	0	0
Zhigansky	4	3	75	5	38	18	1871	0	1927
Oleneksky	4	4	100	10	0	0	1096	10	1106
Ust-Yansky	10	0	0	0	0	0	0	0	0
Nizhnekolymsky	13	2	15,2	2	4	21	0	0	25
Verkhnekolymsky	6	2	33,3	4	34	55	0	0	89
Verkhoyansky	29	3	10,3	6	140	227	850	0	1217
Momsky	7	2	28,5	4	0	6	351	0	357
Srednekolymsky	15	11	73,3	85	2625	9617	5459	0	17701
Eveno-Bytantaisky	4	1	25,0	1	0	0	12	0	12
Total	119	28	23,5	117	2841	9944	9639	10	22434
Eastern zone districts									
Oimyakonsky	16	12	75,0	26	508	755	1109	0	2372
Tomponsky	14	4	28,5	8	1	3	882	0	886
Ust-Maisky	15	3	13,3	7	56	20	0	0	76
Total	45	19	42,2	41	565	778	1991	0	3334
Southern zone districts									
Aldansky	19	2	10,5	2	2	4	0	0	6
Neryungrinsky	9	0	0	0	0	0	0	0	0
Total	28	2	7,1	2	2	4	0	0	6
Total in the Republic of Sakha (Yakutia)	628	244	38,8	739	29480	35995	12524	25	78024

Khangalassky (27), Kobyaisky (33), Yakutsky (30) districts where it was registered 323 cases of anthrax diseases of agricultural animals in 109 stationary disadvantaged settlements. The last dates of registered epizootics of anthrax in the areas of the Central economic zone of the Republic: Amginsky - 1963, Gorny - 1976, Megino-Kangalassky - 1957, Tattinsky - 1935, Ust-Aldansky - 1394, Churapchinsky - 1929, Namsky - 1930, Khangalassky - 1932, Yakutsky - 1949, Kobyaisky - 1938.

Of the well-known - 739 (dormant, forgotten, dumb) burials associated with anthrax, only 284 were taken into account, as stationary disadvantaged settlements. It is in relation to the designated places that there are rules (code) of special measures restricting and regulating any of their use.

In addition, with large-scale excavation work, there is a high probability of a significant number of unrecorded anthrax burials, including the so-called «crippled fields», which according to archival documents, the reports of the Yakutian Autonomous Soviet Socialist Republic early in the 20th century practically cover the northern and groups of Vilyuisky territories in the Republic of Sakha (Yakutia). The presence of such sites in the designated zones is not fixed. Taking into account the epizootic situation of the Siberian anthrax in the Russian Federation in recent years, we can conclude that it is inadmissible to stop preventive measures in the regions of the republic, regardless of the period of limitation of the last manifestations of infection. One-time group burials of deceased people, as well as the circulation of closely related anthrax bacteria in the soils of Central and Southern Yakutia, are subject to special assessment. Timely sounding of risk potentials is correct and adequately to the volume and quality of preventive, medico-veterinary and preventive measures in modern conditions of anthropogenic load.

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The authors

1. Dyagilev Grigory Timofeyevich, Candidate of Veterinary Sciences, Honored veterinarian of the Republic of Sakha (Yakutia), senior researcher of the laboratory of veterinary biotechnology, FSBSI "Yakut Scientific Research Institute of Agriculture named after Safronov M.G."

Address: 677001, Republic of Sakha (Yakutia), Yakutsk, Bestuzheva-Marlinskovo, Str., 23/1.

E-mail: yniicx@mail.ru, tel/fax: 8(4112)21-45-74, 8(4112)21-45-72, mobile: 8(914)271-64-88

2. Chernyavsky Victor Fedorovich, Candidate of Medicine, Honored doctor of the Russian Federation, doctor-epidemiologist, FBHCI "Center for Hygiene and Epidemiology in the Republic of Sakha (Yakutia)"

Address: 677000, Republic of Sakha (Yakutia), Yakutsk, Oyunskovo, Str., 9, Department of natural focal and especially dangerous infections

E-mail: poiooi@fbuz14.ru, tel/fax: 8(4112)32-12-14, mobile: 8(914)223-79-14

3. Ignatyeva Margarita Egorovna, Candidate of Medicine, Honored Health Worker of the Republic of Sakha (Yakutia), Head of the Department of Rospotrebnadzor for the Republic of Sakha (Yakutia)

Address: 677000, Republic of Sakha (Yakutia), Yakutsk, Oyunskovo, Str., 9

E-mail: yakutia@14.rospotrebnadzor.ru, tel/fax: 8(4112)35-16-45

4. Nikiforov Oleg Innokentyevich, specialist in medical zoology FBHCI "Center for Hygiene and Epidemiology in the Republic of Sakha (Yakutia)"

Address: 677000, Republic of Sakha (Yakutia), Yakutsk, Oyunskovo, Str., 9, Department of natural focal and especially dangerous infections

5. Sofronova Oktyabrina Nikolaevna, Head of the department of natural focal and especially dangerous infections, bacteriologist of the highest category, Candidate of Medicine

Address: 677000, Republic of Sakha (Yakutia), Yakutsk, Oyunskovo, Str., 9, Department of natural focal and especially dangerous infections. tel/fax: 8(4112)32-12-14.

ACTUAL TOPIC

L.F. Timofeev, A.I. Gogoleva, A.L. Timofeev

STATUS OF PRIMARY DISABILITY OF ADULTS AND CHILD POPULATION IN THE REPUBLIC OF SAHA (YAKUTIA)

The data of the primary disability of the adult and children population in the Republic of Sakha (Yakutia) are presented, what is more in the context of districts / uluses over a ten-year period (2007-2016). The percentile method revealed the levels of primary disability: high, above average, medium, below average and low, which for clarity were painted in appropriate colors. The analysis revealed trends in the dynamics of indicators of primary disability (PD), as well as administrative-territorial entities, where it is better or worse PD level separately among the adult and child population. In addition, the structure of the main causes of disability and distribution to disability groups is presented.

Keywords: primary disability, primary disability of the adult population, primary disability of the child population, structure of the main causes of disability, distribution to disability groups, Republic of Sakha (Yakutia).

Introduction. At the present stage, the most unfavorable features of public health in the Russian Federation are the deterioration of public health and the growth of the disability indicator of the able-bodied population [3]. Disability of the population is a significant informative indicator of public health, accumulating the impact of social, economic, industrial, environmental and genetic factors, the level of medical care and reflecting, ultimately, the quality of the life support system [1]. By definition, Yu.P.Lisitsyn (2009), «disability is a prolonged or permanent loss of ability to work due to a significant impairment of the body's functions caused by a chronic illness or injury» [2].

Materials and methodsof research. We analyzed the primary disability of the adult and children of the Republic of Sakha (Yakutia) for 2007-2016. The number of disabled people is presented according to the data of the Regional Department of the Pension Fund of the Russian Federation for the RS (Y) (Fig. 1).

Results and discussion.Total number of disabled people in Yakutia as of 01.01.2017.57 114 people. (as of 01.01.2008 - 49,546), which is 5.9% (in 2008 - 5.2%) of the total population. Of them disabled children 6004 (6428), and this is 10.5% (13.0%) of the total number of disabled people. Over the past 7 years, the levels of primary disability of the adult population in the RS (Y) and RF are almost identical (Figure 2).

The level of primary disability of the adult and children's population has been decreasing in recent years (Tables 1 and 2, figure 3). The level of primary disability of the able-bodied population continues to decrease, from 45.4 in 2008 to 35.7 per 10,000 able-bodied population in 2016.

In terms of the level of primary disability of the adult population, our republic in 2016 occupied 43rd ranked place (in 2011 - 57th place). At the same time, the level of primary disability in the Russian Federation in 2016 was 56.7 per 10 thousand of the corresponding population (in 2011 - 72.6). In the regions of the republic, the highest levels of primary disability of the adult population were registered in 2016 in such Districts (Uluses) as Allaikhovsky, Momsky, Srednekolymsky and Even-Bytantaisky (above 89.0 per 10,000 adults).

At the same time in Nyurbinsky, Olenieksky and Even-BytantaiskyUluses, the highest increase in this indicator is registered since 2007. The level of primary disability of the adult population below 50.0 per 10 thousand of adult population in 2016 was observed in such areas as Amginsky, Verkhnevilyuisky, Lenskiy, Mirninsky and Namsky. At the same time in Anabarsky, Bulunsky, Gorny and Myrninsky Districts for all 10 years of observation there is a low level of primary disability of the adult population.

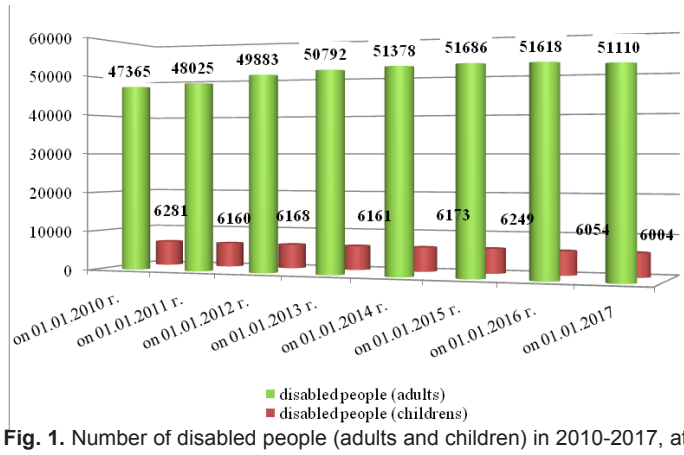

Fig. 1. Number of disabled people (adults and children) in 2010-2017, at the beginning of the year

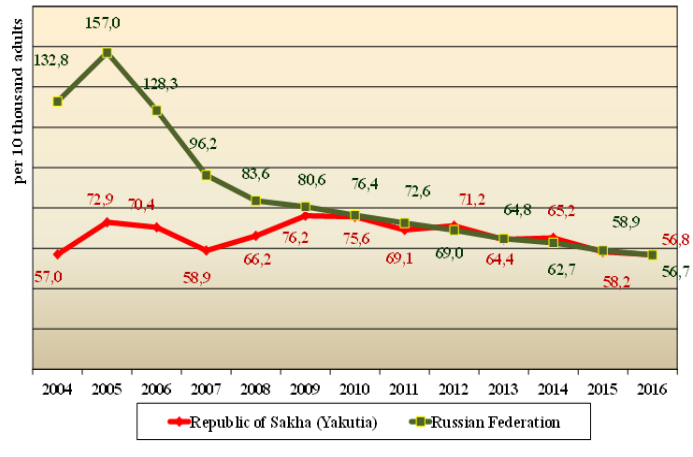

Fig. 2. The indicator of the level of primary disability of the adult population in the Republic of Sakha (Yakutia) and Russian Federation

In the structure of the primary disability of the adult population in 2016, the invalids of the third group still prevailed (Figure 4). The proportion of disabled people in the II group decreased compared to 2009-2011, while group III increased.

In 2016, the following structure of the primary disability of the adult population was formed according to classes and main subclasses of diseases.

The first ranked place was occupied by diseases of the circulatory system - 13.8 per 10 thousand of the adult population. Compared with 2009 (22.1), there was a significant decrease in the level of 1.6 times.

The second ranked place was occupied by malignant neoplasms - 13.7‰o, while their increment for the entire period under consideration attracted attention. So, in comparison with 2009 there is an increase of 28%, although in 2015 the figure was even higher and was 14.4 per 10 000 adults.

At the third ranked place - diseases of the musculoskeletal system (DMS) - 4,3‰o. There is also a decrease in the rate in recent years. And in comparison with 2009, the decline is almost twofold.

4-5th ranking places are occupied by ear and eye diseases - 3.4 per 10 thousand of the corresponding population. In comparison with 2009, there is a decrease in the level of primary disability for these classes of diseases (from 3.9‰o and 3.8‰o in 2009, respectively).

The 6th ranked place in 2016 was occupied by external causes - 2.8 ‰o.

According to the MSE General Bureau, in the beginning of 2017 there were 6004 disabled people aged 0-18, including 910 children with disabilities for the first time (2009: 869). The indicator of the newly diagnosed disability is 31.0 (2007 - 28.0). These data are higher than the average for the Russian Federation: the level of primary disability in the Russian Federation in 2016 was 25.2 per 10 thousand of the corresponding population (in 2006 - 26.0) (Figure 5). The largest group among newly diagnosed children with disabilities are children under the age of 3 (350 children, 38.5%). In the total number of disabled people, boys continue to predominate.

In terms of the level of primary disability of the child population, our republic in 2016 occupied the 9th ranked place. In the Districts of the republic, the highest levels of primary disability of the child population were registered in 2016 in such Districts as the Anabar, Verkhnekolymsky, Vilyuysky and Momsky (above 45.8 per 10,000 children's population) (Table 2). The situation is better (the indicator is lower than 14.4) in the following Uluses: Allaikhovsky, Oimyakonsky, Oleneksky and Ust-Maysky. For the period 2007-2016.a favorable situation for children's disability is observed in the Aldansky, Kobyaysky, Lensky and Neryungrynskyi Districts. And less favorable - in such Uluses as Allahovsky, Anabarsky, Nizhnekolymsky and Nyurbinsky.

Table 1

The level of primary disability of the adult population by Districts (Uluses) Republic of Sakha (Yakutia) (for 10 thousand of the corresponding population)

Ulus/District of the RS (Ya)	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Abyisky	101,6	116,9	110,1	91,2	97,9	72,9	112,2	101,6	96,7	72,7
Aldansky	56,2	65,2	85,8	72,6	59,5	67,6	66,4	68,3	69,3	60,0
Allaahovsky	64,9	119,4	108,6	124,4	87,6	103,5	45,3	141,2	58,3	96,7
Amginsky	56,4	62,4	97,3	67,5	74,3	66,7	62,8	67,9	59,5	49,9
Anabarsky	53,7	77,4	52,6	45,9	58,5	54,0	82,6	36,7	45,8	58,3
Bulunsky	38,6	46,7	61,2	69,1	53,3	41,8	32,2	61,5	44,2	52,5
Verkhnevilyuysky	50,5	65,5	57,7	71,9	65,4	74,9	66,2	51,6	44,9	47,1
Verkhnekolymsky	120,7	79,8	57,7	71,5	88,0	60,2	111,0	72,2	106,1	54,6
Verkhoyansky	53,8	67,0	79,4	60,9	40,6	61,1	79,4	53,8	59,5	65,8
Viluysky	62,8	86,3	77,6	84,3	91,8	79,2	69,7	72,0	64,2	56,9
Gorny	60,3	58,7	55,9	70,2	54,0	49,8	57,8	60,7	53,6	67,7
Zhiganskiy	66,1	91,9	94,5	41,2	58,4	50,9	79,9	81,1	95,1	63,3
Kobyaysky	70,9	68,3	65,1	81,3	94,5	69,8	103,0	76,5	48,4	63,5
Lensky	65,6	80,0	85,0	99,2	99,2	81,8	73,3	57,7	56,1	40,3
Megino-Kangalassky	76,9	78,5	89,1	88,9	81,2	88,3	69,7	84,3	78,1	71,3
Myrninsky	37,4	44,3	45,9	47,8	45,0	45,6	42,7	45,9	46,1	45,5
Momsky	63,8	98,2	61,6	87,0	69,6	106,9	100,2	149,7	95,4	91,2
Namsky	67,7	63,4	57,1	62,5	65,8	61,7	60,0	62,3	50,9	49,0
Neryungrinsky	46,5	58,9	87,6	78,4	59,3	64,4	54,5	64,4	56,7	62,0
Nizhnekolymskiy	69,9	87,0	73,7	96,0	104,0	80,8	101,6	86,9	64,6	59,1
Nyurbinsky	61,3	58,2	75,7	75,8	72,1	73,5	73,4	91,0	67,9	81,5
Oymyakonsky	64,9	51,3	95,4	79,3	79,3	81,5	75,7	69,0	45,9	66,4
Olekminsky	80,4	90,1	80,9	100,0	85,9	85,1	70,1	62,5	54,0	63,9
Oleneksky	38,5	46,3	61,8	49,3	60,7	74,2	53,1	77,8	54,5	77,2
Srednekolymsky	38,4	73,9	116,6	104,2	115,2	109,7	75,1	85,1	77,4	89,0
Suntarsky	47,6	56,6	87,4	62,4	71,9	64,2	84,5	63,1	51,7	65,3
Tattinsky	71,2	74,3	96,6	76,1	90,0	72,2	92,3	72,1	69,6	60,6
Tomponsky	54,9	96,6	72,1	72,3	77,0	61,5	53,5	62,9	78,1	50,3
Ust-Aldansky	74,6	82,7	101,9	89,2	69,9	68,2	71,2	67,4	53,0	52,7
Ust-Maysky	58,0	73,8	76,7	58,3	61,0	71,7	79,3	71,1	105,8	69,9
Ust-Yanskiy	55,7	64,7	56,0	89,1	84,5	109,7	58,4	58,7	54,1	66,2
Khangalassky	69,5	71,3	75,7	76,8	62,6	68,3	59,6	63,9	63,0	62,9
Churapchinsky	70,8	62,1	77,8	72,0	65,2	61,1	66,0	70,1	57,7	51,1
Even-Bytantaisky	37,3	69,0	105,5	119,7	72,8	82,2	63,6	75,0	58,6	128,3
Yakutsk	61,6	65,2	75,0	77,3	69,6	77,1	62,9	64,2	55,2	53,2
The RS (Y)	**58,9**	**66,2**	**76,2**	**75,6**	**69,1**	**71,2**	**64,4**	**65,2**	**58,2**	**56,8**

96,7	highlevelofdisability
77,2	below-averagelevel
49,9	above-averagelevel
40,3	lowlevelofdisability

In the structure of the causes of disability, the diseases of the nervous system are on the first place - 13.5 per 10 000 of the corresponding population, in the second place - congenital anomalies, which amounted to 4.7 ‰0, in third place - mental disorders and behavior disorders - 3.8 ‰0. In the Russian Federation, the structure is somewhat different (2016): in the first place mental disorders and behavioral disorders - 6.2 per 10 000 children's population, on the second - diseases of the nervous system - 5.0, and on the third - congenital anomalies

Table 2

Primary disability of the child population in the Republic of Sakha (Yakutia) (per 10,000 population)

№	Улусы	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
1	Abyisky	58,9	42,1	25,2	69,6	26,1	31,5	39,2	24,2	40,7	33,1
2	Aldansky	34,6	26,4	18,2	25,3	23,4	22,7	21,7	23,0	18,6	27,4
3	Allaahovsky	27,3	41,0	27,3	95,4	54,5	55,8	22,9	46,9	35,4	12,2
4	Amginsky	31,9	21,3	37,3	25,2	23,4	48,0	41,6	34,5	43,0	23,0
5	Anabarsky	15,2	37,9	45,4	62,2	85,5	15,6	32,7	16,3	49,9	58,3
6	Bulunsky	33,7	16,9	29,5	37,2	49,6	32,7	16,6	12,9	21,8	17,6
7	Verkhnevilyuysky	42,0	34,1	49,9	45,3	37,3	41,3	31,2	31,5	39,6	28,8
8	Verkhnekolymsky	45,0	54,0	36,0	55,8	18,6	28,7	19,8	50,5	20,2	70,7
9	Verkhoyansky	25,6	45,5	19,9	44,3	23,6	38,2	37,5	21,8	13,8	35,9
10	Viluysky	29,5	42,4	36,0	40,0	58,1	34,1	34,3	44,3	56,3	45,9
11	Gorny	52,5	26,3	23,6	47,4	29,0	48,8	36,9	26,0	38,0	14,8
12	Zhiganskiy	35,6	17,8	80,0	17,6	44,0	66,7	42,5	21,3	21,3	21,2
13	Kobyaysky	22,0	36,6	22,0	20,0	22,5	16,8	14,9	42,6	17,6	33,0
14	Lensky	18,0	14,0	22,0	32,7	37,8	31,2	21,0	27,4	14,9	17,1
15	Megino-Kangalassky	27,3	30,2	48,8	21,7	31,5	23,6	31,0	30,8	35,4	34,5
16	Myrninsky	27,6	32,5	29,8	24,6	29,7	26,1	24,4	27,8	21,5	17,1
17	Momsky	0,0	52,5	52,5	59,7	19,9	32,2	19,4	33,4	20,1	66,4
18	Namsky	33,7	31,1	35,0	33,8	33,8	30,6	38,7	42,2	15,4	25,5
19	Neryungrinsky	20,3	21,4	18,1	24,6	23,0	16,2	20,3	24,0	17,8	22,6
20	Nizhnekolymskiy	42,3	110,0	25,4	70,8	44,2	38,3	46,0	38,2	30,1	29,8
21	Nyurbinsky	35,5	38,1	54,6	50,3	50,3	37,6	42,7	41,7	36,6	39,0
22	Oymyakonsky	29,7	39,6	64,4	31,7	31,7	36,6	28,1	19,2	34,1	14,3
23	Olekminsky	38,4	39,8	35,7	37,9	35,1	42,1	30,5	17,7	23,7	23,8
24	Oleneksky	27,8	55,6	27,8	50,4	57,6	97,7	35,4	50,3	21,4	14,4
25	Srednekolymsky	8,5	16,9	25,4	30,4	43,4	51,6	20,0	60,4	36,6	32,2
26	Suntarsky	27,8	31,3	32,5	38,9	49,6	36,7	38,7	46,1	24,4	20,9
27	Tattinsky	44,1	33,1	42,2	29,9	31,8	53,7	24,3	24,4	24,4	45,4
28	Tomponsky	37,4	32,1	21,4	21,9	19,1	46,6	27,3	52,0	32,9	39,3
29	Ust-Aldansky	27,4	28,8	37,5	36,2	34,7	32,1	27,3	36,9	24,1	22,6
30	Ust-Maysky	46,5	41,3	31,0	27,7	27,7	30,1	15,3	15,4	10,2	10,4
31	Ust-Yanskiy	37,8	16,2	5,4	57,0	39,9	28,2	19,1	14,4	9,7	42,8
32	Khangalassky	21,8	28,1	27,0	25,7	40,7	40,3	33,2	37,8	25,7	25,6
33	Churapchinsky	28,0	23,8	32,2	43,9	38,3	33,9	27,9	36,3	37,4	25,7
34	Even-Bytantaisky	45,0	33,7	22,5	45,0	11,2	43,4	10,9	21,7	21,7	22,1
35	Yakutskandadj.terr.	28,6	27,6	39,4	37,3	40,1	39,5	36,7	38,9	31,4	39,4
	The RS (Y)	**29,4**	**29,8**	**34,0**	**34,6**	**36,0**	**35,0**	**31,0**	**34,1**	**28,2**	**31,0**

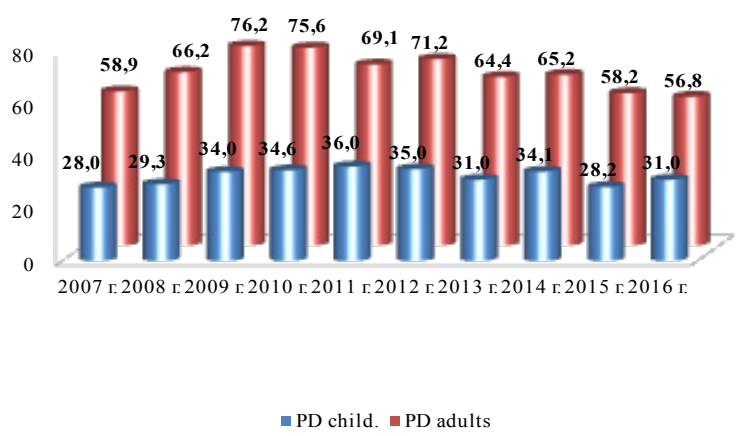

Fig. 3. The level of primary disability of the childre and adult population in the Republic of Sakha (Yakutia) by 10 thousand of the corresponding age

- 4.5 respectively.

The conclusion. Thus, the level of primary disability of the adult population has declined in recent years. In the structure of the primary disability of the adult population in 2016, the disabled of the third group prevailed. In the Districts of the republic, the highest levels of primary disability are registered in 2016 in such Districts (Uluses) as Allahovskiy, Momsky, Srednekolymsky and Even-Bytantaisky. The first ranked places in the structure of diseases that cause primary disability are steadily occupied by diseases of the circulatory system, malignant neoplasms, diseases of the musculoskeletal system.

The tendency of growth of primary disability among children from 0 to 18 years in recent years characterizes the state of health of the children of Yakutia as unsatisfactory and therefore requires the continuation of program activities to reduce their level. It can not be said that the health authorities and institutions are not doing enough work to improve the maternity and childhood protection service. This direction is today undoubtedly a priority, the leadership of the republic and the branch ministry are doing much to build and improve the material and technical base of perinatal, children's and obstetrical institutions, the training of pediatric staff.

At the same time, in order to preserve and improve the health of the younger generation, even more needs to be done, and in our view, the role of intersectoral cooperation between managers and health and social protection specialists will only increase.

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The work was carried out within the framework of the research «Multifactor study of the health status of the indigenous and newcomers of the Republic of Sakha (Yakutia) in order to optimize regional programs to improve the quality of life of the inhabitants of the republic, taking into

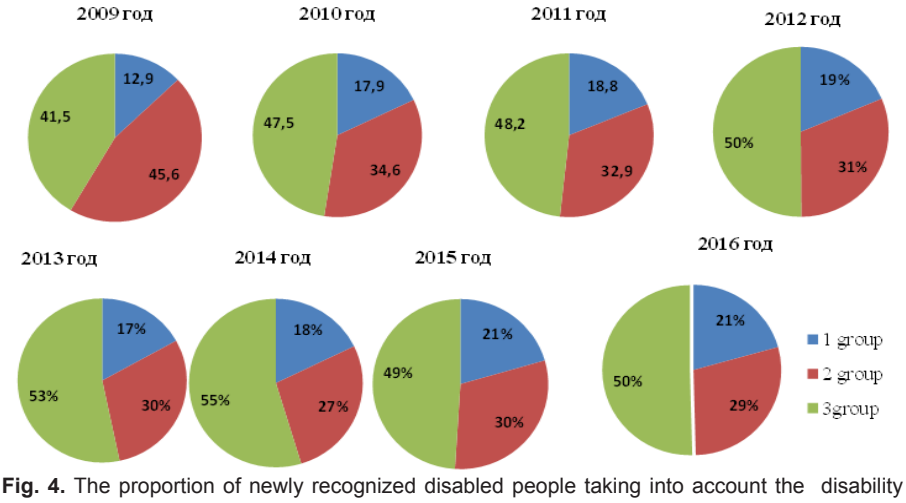

Fig. 4. The proportion of newly recognized disabled people taking into account the disability groups for the RS (Y)

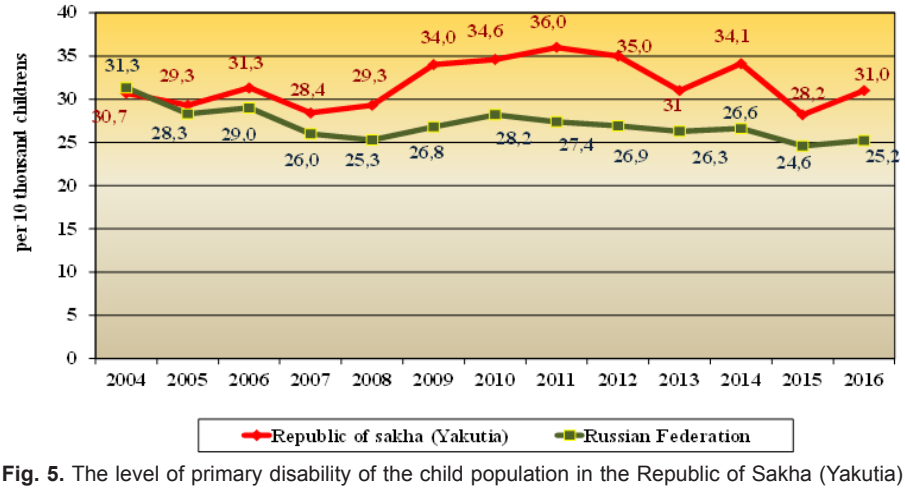

Fig. 5. The level of primary disability of the child population in the Republic of Sakha (Yakutia) and Russian Federation

account territorial, ethnic characteristics in the context of modern socioeconomic development» under the Program for Comprehensive Scientific Research in the Republic Sakha (Yakutia) for 2016-2020.

1. Timofeev Leonid Fedorovich - Doctor of Medical Sciences, Professor of the Department of Public Health and Public Health, General Hygiene and Bioethics, Medical Institute of Medicine, M.K. Ammosov NEFU. 677000 Yakutsk, ul. Oyunsky, 27. Cont. Tel. 8-914-225-88-45. E-mail: tlfnauka@mail.ru

2. Gogoleva Anastasia Ivanovna - Deputy Director for Expert Work, Medical and Social Assessment Bureau of the Sakha Republic (Yakutia), Ministry of Labor of Russia. 677018, Yakutsk, ul. Chernyshevsky 8/2. Cont. 8-924-663-18-86. E-mail: aigogoleva@mail.ru

3. Krivoshapkin Vadim Grigorievich - Doctor of Medical Sciences, Professor, Academician of the Academy of Sciences of the Republic of Sakha (Yakutia), Adviser of the Academy of Sciences of the RS (Ya). Cont. Tel. 8-914-305-46-35. E-mail: kukai1937@gmail.com

4. Timofeev Artem Leonidovich - postgraduate student of the Department of Public Health and Public Health, General Hygiene and Bioethics, Institute of Medicine, M.K. Ammosov NEFU. Address: 677000 Yakutsk, ul. Oyunsky, 27. Cont. Tel. 8-964-423-72-72. E-mail: su-yuol@mail.ru.

A.N. Argunova, A.N. Khorunov, E.A. Andreeva, R.N. Yakovleva

ANALYSIS OF DETECTABILITY OF COPD RISK FACTORS AMONG THE POPULATION OF YAKUTSK

ABSTRACT

The most common reason for the development of chronic obstructive pulmonary disease (COPD) is the damage to airways and lungs caused by tobacco smoking. About 15% of all long-time smokers develop a clinically significant obstructive pulmonary disease. In 80-90% of all cases the development of COPD is connected with smoking. Total incidence of COPD (per 1000 people) in 2008-2014 in Russia, Far Eastern Federal District and the Sakha Republic (Yakutia) in comparison is 5-5,3-6,3-6,8-8-8,6-8,2 in the Sakha Republic, 3,7-4,2-4,7-4 in the Far Eastern District and 3,7-3,9-4,1-3,7 in Russia. The number of COPD cases in the Sakha Republic over time remains high compared to the Far Eastern District and Russia, despite the low density of population.The total number of respiratory system diseases (RSD) in 2014 (preliminary data) was 74,115; pneumonia – 2,308; chronic bronchitis – 19,438; COPD – 5,740; bronchial asthma – 8,773. 2014 saw a decrease in cases of pneumonia by 334 patients as compared to 2010. The number of COPD cases increased by 1,354 patients, and the greatest increase was in the number of bronchial asthma cases – by 2,542 people. (Absolute numbers per Yakutsk Republican Medical Information and Analysis Centre data, 2014).The aim of our research was to study COPD risk factors among the citizens of Yakutsk working in dusty and polluted environments and chemical companies, as well as the people who have a bad habit of smoking.We conducted surveys and examined respiratory functions (spirometry). We examined 70 people living in the City of Yakutsk who had respiratory complaints, were subject to occupational hazards, or were long-time smokers.In order to study the COPD risk factors, we used 'A Patient's Questionnaire' developed by the Pulmonology Research Institute of Russia's Federal Medical-Biological Agency, Moscow. The questionnaire contains 22 questions to identify risk factors and respiratory symptoms. We also used a self-actualisation test to evaluate the impact of COPD on the health status of a responder. This test on chronic obstructive pulmonary disease (COPD) can be used for a simple and reliable evaluation of the health status of patients who have the disease. It is used in conjunction with other diagnostic methods and allows for a relatively simple evaluation of COPD's level of impact on health status. This test is used to evaluate the impact of COPD on the

well-being and everyday life of a patient.The most common symptoms among the COPD patients included: a cough of over 3 months – 71.4%, productive cough – 52.8%, a feeling of compressing chest pain – 32.8%, exertional dyspnoea – 75.7%, weakness – 52.8%.Common causative risk factors include smoking, i.e. those who have a history of smoking of over 10-20 years, and occupational hazards, i.e. work in chemical companies and in dusty, polluted environments.Examination of respiratory functions using spirometry showed that 40 patients (57%) had light respiratory dysfunction, 25 (36%) had moderate respiratory dysfunction, and 5 (7%) had severe respiratory dysfunction.The results of self-actualisation test show that COPD has an insignificant effect on the quality of life of 51 surveyed people (73%), has a moderate effect on the quality of life of 16 people (23%), and has a serious effect on the quality of life of 3 people (4%).All 100% of examined people have clinical aspects of COPD and respiratory dysfunction that corresponds to spirographic classification of COPD.

Keywords: COPD, risk factors, smoking, occupational hazards, bronchitis, spirometry, quality of life, shortness of breath, cough, sputum.

Introduction

The most common reason for the development of chronic obstructive pulmonary disease (COPD) is the damage to airways and lungs caused by tobacco smoking. About 15% of all long-time smokers develop a clinically significant obstructive pulmonary disease. In 80-90% of all cases the development of COPD is connected with smoking. Total incidence of COPD (per 1000 people) in 2008-2014 in Russia, Far Eastern Federal District and the Sakha Republic (Yakutia) in comparison is 5-5,3-6,3-6,8-8-8,6-8,2 in the Sakha Republic, 3,7-4,2-4,7-4 in the Far Eastern District and 3,7-3,9-4,1-3,7 in Russia. The number of COPD cases in the Sakha Republic over time remains high compared to the Far Eastern District and Russia, despite the low density of population.

The total number of respiratory system diseases (RSD) in 2014 (preliminary data) was 74,115; pneumonia – 2,308; chronic bronchitis – 19,438; COPD – 5,740; bronchial asthma – 8,773. 2014 saw a decrease in cases of pneumonia by 334 patients as compared to 2010. Thenumber of COPD cases increased by 1,354 patients, and the greatest increase was in the number of bronchial asthma cases – by 2,542 people. (Absolute numbers per Yakutsk Republican Medical Information and Analysis Centre data, 2014).

Existing data on the prevalence of COPD has significant discrepancies owing to differences in research methods, diagnostic criteria and approaches to data analysis [1]. The lowest estimations of COPD prevalence are usually obtained from patient surveys on them being diagnosed by a doctor to have COPD or equivalent disease. For example, in most countries, less than 6% of the population heard from a doctor that they have COPD [1]. This is probably due to widespread lack of understanding and under-diagnosis of COPD [2]. Despite these issues, new data allows for drawing some **Conclusion**s on the prevalence of COPD, not least because of improved quality control of results.

The aim of our research was to study COPD risk factors among the citizens of Yakutsk working in dusty and polluted environments and chemical companies, as well as the people who have a bad habit of smoking.

Materials and methods of research. We conducted surveys and examined respiratory functions (spirometry). We examined 70 people living in the City of Yakutsk who had respiratory complaints, were subject to occupational hazards, or were long-time smokers.

In order to study the COPD risk factors, we used 'A Patient's Questionnaire' developed by the Pulmonology Research Institute of Russia's Federal Medical-Biological Agency, Moscow. The questionnaire contains 22 questions to identify risk factors and respiratory symptoms. We also used a self-actualisation test to evaluate the impact of COPD on the health status of a responder. This test on chronic obstructive pulmonary disease (COPD) can be used for a simple and reliable evaluation of the health status of patients who have the disease. It is used in conjunction with other diagnostic methods and allows for a relatively simple evaluation of COPD's level of impact on health status. This test is used to evaluate the impact of COPD on the well-being and everyday life of a patient.

Results and discussion

70 people over the age of 40 (a criterion for inclusion in research) took part in the survey who had respiratory complaints, were subject to occupational hazards, or were long-time smokers. 43 of them were men (61.5%), and 27 – women (38.5%).

Most of the surveyed patients were between 40 and 50 years old. Average age of men was 47±1.2 years. Average age of women was 44±2 years (table 1).

The height of most of the surveyed patients was between 160-170 cm, representing 27 (38.5%) people. The average weight of all surveyed patients was 80-90 kg (table 2).

Most of the surveyed patients have a history of 10 to 30 and more years of smoking (table 3).

A packet/years index is calculated using the following formula: number of cigarettes smoked daily × years smoked / 20. According to our data most of the surveyed people smoke between 15 and 20 cigarettes a day.At present, of all the surveyed people, 47 are smoking(67.1%), 17 have given up smoking (24.3%), and 6 have never smoked (8.5%). Social status of the surveyed people according to questionnaire results was: employed – 56 (80%), retired pensioners – 8 (11.4%), working pensioners – 6 (8.6%) (table 4).

Analysis of occupations shows that most of the surveyed people work in an industrial company, including drivers, mechanics, chemists, operators of steam turbines, compressor units,

Table 1

Analysis by gender profile

Age	Absolute number	%
40-50	38	54,3
50-60	16	22,9
60-70	13	18,6
70-80	3	4,3

Table 2

Analysis of surveyed people's height and weight

		Absolute number	%
Height	150-160	20	28,6
	160-170	27	38,5
	170-180	22	31,4
	<180	4	5,7
Weight	50-60	10	14,3
	60-70	15	21,4
	70-80	18	25,7
	80-90	20	28,6
	90-100	7	10%
	<100	2	2,8

Table 3

Analysis of the number of years the patient smoked

Years smoking	Absolute number	%
5-10	8	11,4
10-20	21	30
20-30	19	27,1
30-40	8	11,4
40-50	8	11,4
Более 50	1	1,4

Table 4

Analysis of packet/years ratio among the surveyed people

Points	Absolute number	%
0-10	22	31,4
10-20	9	12,8
20-30	8	11,4
30-40	9	12,8
40-50	6	8,5
50-60	4	5,71
60 and over	4	5,71

Table 5

Analysisofprofessionaloccupations

Professional occupation	Абс. число	%
Working in industrial company	50	71,4
Engineering-technology	2	2,8
Scientific research work	2	2,8
Economics and law	10	14,2
Culture and arts	1	1,4
Medicine	5	7,1

Table 6

Analysisofvisits to outpatient clinic

Once a year	Absolute number	%
0-1	50	71,4
2-3	11	15,7
4-5	2	2,8
<5	2	2,8

Table 7

Analysis of concomitant diseases

Concomitant diseases	Absolute number	%
Arterial hypertension	47	67,1
Diabetes mellitus type 2	8	11,4
Coronary artery disease and angina	23	32,8
Other diseases	7	10

boilers, turbines, main control boards for pipelines, and Yakutskenergo Company boiler house coal-heaver, representing 50 people (71.4%). Among them 47 people (68.5%) work in dusty and polluted conditions or in chemical companies (table 5). To the question "How many times a year do you visit an outpatient clinic" 50 people (71.4%) answered "Once a year for any reason" (table 6).

The highest number of surveyed patients have arterial hypertension – 47 (67.1%), 23 people (32.8%) have coronary artery disease and angina, 8 people (11.4%) have diabetes mellitus type 2, 7 people (10%) have other diseases (pyelonephritis, chronic gastritis, cholelithiasis, osteoporosis, arthrosis, atopic dermatitis, hepatitis) (table 7).

The results of self-actualisation test show scores of 0-10 points among 51 surveyed people (73%), 11-20 points – 16 (23%), 21-30 points – 3 (4%).

Examination of respiratory symptoms showed that 50 people (71.4%) had cough, 37 (52.8%) – productivecough, 23 (32.8%) – a feeling of compressing chest pain, 53 (75.7%) – exertional dyspnoea, 37 (52.8%) – weakness.

Examination of respiratory functions using spirometry showed that 40 patients (57%) had light respiratory dysfunction, 25 (36%) had moderate respiratory dysfunction, and 5 (7%) had severe respiratory dysfunction. FEV1/FVC ratio of less than 70% of normal value was found in 15 (21%) of examined patients.

Conclusions

1. The most common symptoms among the COPD patients included: a cough of over 3 months – 71.4%, productive cough – 52.8%, a feeling of compressing chest pain – 32.8%, exertional dyspnoea – 75.7%, weakness – 52.8%.
2. Common causative risk factors include smoking, i.e. those who have a history of smoking of over 10-20 years, and occupational hazards, i.e. work in chemical companies and in dusty, polluted environments.
3. Examination of respiratory functions using spirometry showed that 40 patients (57%) had light respiratory dysfunction, 25 (36%) had moderate respiratory dysfunction, and 5 (7%) had severe respiratory dysfunction.
4. The results of self-actualisation test show that COPD has an insignificant effect on the quality of life of 51 surveyed people (73%), has a moderate effect on the quality of life of 16 people (23%), and has a serious effect on the quality of life of 3 people (4%).
5. All 100% of examined people have clinical aspects of COPD and respiratory dysfunction that corresponds to spirographic classification of COPD.

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The authors:
Medical Institute of the Ammosov North-Eastern Federal University:
1. Argunova Agrafena Nikolaevna, Associate Professor, Hospital Treatment, Professional Diseases and Clinical Pharmacology Department, agrafena888@mail.ru, Yakutsk, Russia;
2. Khorunov Alexei Nikolaevich, Associate Professor, Hospital Treatment, Professional Diseases and Clinical Pharmacology Department, aleksej.xorunov.61@mail.ru, Yakutsk, Russia;
3. Yakovleva Rimma Nikolaevna, Deputy Head Doctor for Clinical Work of Yakutsk Medical Centre, Yakutsk, Russia.

SCIENTIFIC REVIEWS AND LECTURES

T.K. Sunkhalyrova, V.V. Dodokhov, N.A. Solov'eva, N.I. Pavlova, N.P.Filippova, L.M. Neustroeva, M.A. Varlamova, D'yakonovaA.T., Kh.A.Kurtanov

GENETIC FACTORS OF PREDISPOSITION TO AUTOIMMUNE THYROID DISORDERS

ABSTRACT
The article presents a review of the literature about the genetic factors of predisposition to autoimmune to thyroid disorders, the main of which are diffuse toxic goiter and autoimmune thyroiditis. Studies of recent years have made it possible to establish that genetic factors make a significant contribution to the development of the autoimmune process in autoimmune to thyroid disorders.
Keywords: endocrine system diseases, autoimmune thyroiditis, diffuse toxic goiter, genetic factors, predisposition.

Significant changes in the function of the endocrine system in the human body occur in the North, first of all, under the influence of cold. Thus, the production of thyrotropin-stimulating hormones and glucocorticoids increases, the high level of which contributes to the increase of nonspecific resistance of the organism to the cold.

Thyroid hormones increase metabolism, separate oxidation and phosphorylation processes, and also activate the biogenesis of mitochondria. It is known that the level of thyroid hormones in the blood under physiological conditions is regulated mainly by internal (thermal) and external (cold) thermoreceptors [18].

Among the various effects of thyroid hormones, the greatest attention of researchers is drawn to the effect of these compounds on energy processes and basic metabolism, the so-called «caloric effect».

The introduction of thyroid hormones to animals significantly increases the thermogenesis and oxygen consumption of the body. The stimulating effect of thyroxin on the formation of brown fat in rats is shown, which is one of the manifestations of adaptation of small animals to cold.

Thus, the thyroid gland plays an important role in the regulation of heat exchange, and, consequently, the degree of adaptation of the organism to the effect of low temperatures on the human body. Because of how correctly the thyroid gland functions, the person's working capacity, his activity and vital activity depends.

The Republic of Sakha (Yakutia) refers to territories with extreme temperature and light conditions, a pronounced seasonality of the climate, which contributes to the high prevalence of thyroid pathology both among children and adults [15].

In the structure of diseases of the thyroid gland the leading place is occupied by autoimmune diseases [3, 9, 43], the main of which are such diseases, accompanied by pathological conditions as hyperthyroidism (diffuse toxic goiter) and hypothyroidism - autoimmune thyroiditis (Hashimoto's thyroiditis).

Autoimmune thyroiditis is an activation of the immune system in the thyroid gland with the phenomena of lymphocytic infiltration (the penetration of lymphocytes into the tissue), in which specific thyroid antibodies are detected in the blood, which is evaluated as a sign of inflammation. According to different authors, the prevalence of thyroiditis in the world is from 1% to 12%, more often this pathology occurs in older persons [14].

The autoimmune thyroiditis is characterized by the appearance of antibodies to thyroperoxidase(AT - TPO), thyroglobulin (TG). When antibodies (AT) are combined with T-killers, the latter acquire cytotoxicity and destroy the thyroid follicles. In their place, connective tissue proliferates.

Variants of the course of the hypothalamus thyroiditis:

1. Depending on the size:
- hypertrophic, can be combined with nodes;
-atrophic.
2. Depending on the function of the thyroid gland, distinguish:
- normal ;
- hyperthyroidism (phase of thyrotoxicosis or Hashimoto-toxicosis);
-lowed-hypothyroidism (it is a natural outcome of the disease).

Autoimmune thyroiditis develops slowly. There is no characteristic clinical picture, as well as with iodine deficiency goiter. There are clinical manifestations associated with an increase in the thyroid gland and a violation of its function:

1. Syndrome of a lesion of a thyroid gland. Complaints in patients are associated with an increase in the organ and are not specific for the disease. With palpation more often than with endemic goiter, it is possible to find a compaction of the thyroid gland; the consistency of the gland is uneven, it is mobile, there may be a sensation of the node (s). These signs target the doctor to exclude

autoimmune thyroiditis from the patient and must necessarily be supplemented by a set of changes in the ultrasound examination of the organ and the presence of AT to TPO according to the Consensus adopted in 2002.

2. Syndrome of functional disorders: distinguish between eutireosis, hyperthyroidism and hypothyroidism. In the early stages, hyperthyroidism can be diagnosed,euthyroid status is more likely to occur, later on, turning into hypothyroidism

In the recent past, when a clinically significant titer of thyroid antibodies was obtained, the diagnosis of autoimmune thyroiditis was considered to be verified. Currently, the Consensus (2002 II Russian Thyroid Congress) on the diagnosis and treatment of autoimmune thyroiditis, according to which the presence of antibodies to thyroid tissue (antibodies to thyroid peroxidase or microsomal fraction) and primary hypothyroidism (manifest or persistent subclinical) is one of the «Large» diagnostic signs, in the presence of only one of them, the diagnosis of autoimmune thyroiditis cannot be established [7].

The term autoimmune thyroiditis, classified by Davies and Amino, published in the journal Thyroid in 1993, implies both Hashimoto's thyroiditis and Graves' disease, subdivided into types 1 and 2, which in turn are subdivided into subtypes A, B and C [23].

The well-known immunologist R. Volp (1999), only indicates that the treatment of autoimmune thyroiditis reduces to the treatment of hypothyroidism, if it has already developed, and specific methods of treatment are not yet available. In the works of Arbelle J.E. and Porath A., [20] analyzed and compared the recommendations of the American Association for Clinical Endocrinology (AASE), the American College of Physicians (ACP), the Royal College of Doctors UK (RCP) and the American Thyroid Association (ATA), diagnosed and treated autoimmune thyroiditis in phase of euthyroidismis not discussed. In foreign scientific literature, autoimmune thyroiditis as an independent clinical problem is practically not considered. Only the most important outcome of the autoimmune thyroiditis - hypothyroidism - is discussed in detail. At the same time, in the domestic literature, autoimmune thyroidism is regarded as an independent clinical problem. [11].

According to researchers, in the role of a trigger in autoimmune thyroiditis, the main role is played by environmental factors and infections, while data on infections as triggers of the autoimmune process is not enough [19]. In 2012, Zemskova E.A. with et al. using the method of mass spectrometry of microbial markers for assessing the parietal intestinal microbiota [12] suggested that the growth factor of autoimmune thyroiditis in children may be excessive growth in the parietal intestinal microflora of eubacterium (Eubacteriumlentum) [5].

For the first time in the 1960s, the term «thyroid-gastric syndrome» arose which refers to the simultaneous presence of autoantibodies to the thyroid gland in patients with pernicious anemia and atrophic gastritis [4]. It is proved that among patients with atrophic gastritis, autoimmune thyroiditis is diagnosed in 40% of cases [33].

Especially relevant diagnosis for the first time in the 60s of the twentieth century the term thyroid-gastric syndrome appeared which denotes simultaneous presence of autoantibodies to the thyroid gland in patients with pernicious anemia and atrophic gastritis [4]. It is proved that among patients with atrophic gastritis, autoimmune thyroiditis is diagnosed in 40% of cases [33].

Especially relevant is the diagnosis of autoimmune thyroiditis for people living in ecologically unfavorable zones. It is known that women (3-20 times) are sick more often than men.

As the etiological factors, we can now consider:

1. Environmental factors (radiation, chemical factors);
2. For children, an important role is chronic tonsillitis, considering the general lymphoid ring with thyroid gland;
3. Severe infectious and somatic diseases;
4. Excess iodine during therapy with drugs containing it;
5. Combination with autoimmune diseases of endocrine and non-endocrine origin;
6. The second disease on the background of iodine deficiency;
7. Medicinal preparations;
8. Stress.

A large share in the development of the autoimmune process in autoimmune thyreopathy is heredity. According to the results of the study Kandror VI In 2001, genes were detected that are involved in the development of these diseases, localized in chromosomes 2 (2q33), 6 (6p21), 8 (8q24), 12 (12q22) and 13 (13q32) [8].

It is established that autoimmune thyroiditis develops in hereditarily predisposed individuals and a connection with the HLA system is revealed. It is believed that the antigen HLA-DRW5 is involved in the mechanism of goiter, and HLA-DR3 induces the helper function of T-lymphocytes. A number of studies have shown that atrophic thyroiditis is associated with HLA-DR3, and hypertrophic - with HLA-DR5 antigens [13].

Genetic factors make their significant contribution. Under the influence of unfavorable factors, genetically caused immune cell defects (defects of T-suppressors) lead to a breakdown in natural tolerance and T-helpers are able to stimulate B-lymphocytes and simultaneously produce cytokines. All this leads to a change in the function of target cells, which express class II antigens, heat shock proteins, and intercellular adhesion molecules, and thereby enhance the immune response.

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In the works of O.Kochetova. (co-authored, 2014) showed the association of polymorphic variants of the gene DI02 (274A> G) with an increased level of antibodies to TPO and the TPO gene (2173A> C) with an increased level of free T4. The genotype GG and the allele G of the D102 gene (274A> G), the genotypes of the CT and CC of the CYP1A1 gene (-3798T> C), and the genotypes of the TD and DD of the CYPIA2 gene (-2467delT) were proposed as markers of predisposition to the development of nodular goiter associated with the development of autoimmune thyroiditis [10] .If association study of polymorphic variants of genes CYP1A1 and CYP1A2 with the development of thyroid disease in women employed in the petrochemical industry, also identified markers of predisposition to the node goiter (SSCYP1A1 allele gene) and homozygous TTCYP1A2kotory gene is associated with Hashimoto's thyroiditis in women [1].

Diffusive-toxic goiter (first described in 1825 by C. Parry, in 1835 by R. Greaves, and in 1840 by K. Bazedov), or the so-called Graves' disease, a frequently diagnosed autoimmune disease of the thyroid gland . The prevalence of diffuse toxic goiter reaches 0.5%, the frequency of detection during pregnancy is 0.05-3%. It occurs mainly at the age of 20-50 years, in women 7 times more often than in men. Toxic goiter in 90% of patients is diffuse and in 10%

The prevalence of nodular goiter in regions with iodine deficiency regions 30% and is the most common change on the part of the endocrine glands [40, 35].

The disease affects the functional work of various human organs. Especially it violates the work of the central nervous system and cardiovascular system. It is characterized by a diffuse increase in the thyroid gland and a persistent pathological increase in the production of thyroid hormones - thyrotoxicosis [16].

The reasons for the development of thyroid nodules are not fully known. Factors contributing to development include both endogenous and exogenous factors [29, 28].

Diffusive-toxic goiter is an autoimmune disease with a genetic predisposition. Violations are inherited from parents to children. A persistent pathological increase in the production of thyroid hormones is due to thyroid-stimulating antibodies, which are more active than thyroid hormones, and last longer. In fact, antibodies simulate the action of the natural thyroid hormone, they are able to enhance the synthesis and secretion of thyroid hormones. Antibodies are formed as a result of the development of the body by «incorrect» T-lymphocytes (suppressors), which instead of controlling the adequacy of the immune response, begin to destroy the thyroid gland.

These antibodies contribute to an increase in the thyroid gland, increase proliferation of thyroid cells and inhibit apoptosis. Increased thyroid volume, increased blood flow in the gland and its lymphatic infiltration leads to hypertrophy of thyroid cells and hyperplasia.

In the opinion of some authors, the diffuse-toxic goiter is autosomal recessive, in the opinion of others it is autosomal dominant. Most likely, there is a multifactorial (polygenic) type of inheritance. In the relatives of persons suffering from thyroid gland diseases (diffuse toxic goiter, idiopathic myxedema, autoimmune thyroiditis), an increase in the antibody titer to various components of the thyroid gland, as well as antibodies to other organ-specific antigens (gastric, adrenal, ovarian, etc.) compared with persons who are not suffering from thyroid disease. Genetic studies show that if one of the monozygotic twins is ill with diffuse toxic goiter, then for another, the risk of the disease is 60%; In the case of dizygotic pairs, this risk is only 9%

However, the genetic apparatus is not the determining and sole cause of the development of diffuse toxic goiter. It is believed that Graves' disease is a disease in which the genetic features of immunity are realized against the background of environmental factors such as:

- stress;
- viral infections;
- use of antiviral drugs;
- excess in the body of iodine;

Syndrome of thyrotoxicosis is the main clinical manifestation of diffuse-toxic goiter. Thyrotoxicosis is a syndrome that occurs in various pathological conditions of the human body. The frequency of thyrotoxicosis in Europe and Russia is 1.2% [17].

Syndrome of thyrotoxicosis is confirmed by the content of blood TSH (thyroid stimulating hormone) and free hormones T3 and T4 (thyroid). TSH decreases, and T3 and T4 increases with diffuse-toxic goiter. When diagnosing diffuse-toxic goiter, it is established that the level of the hormone T4 in the blood is less than T3, and the hormone T4 normalizes much faster than T3.

It was suggested that mutations of the pTTG gene [34] and Gs proteins precede the appearance of toxic adenomas of the thyroid gland [27].

Other studies have also revealed activating mutations of the TSH receptor gene in autonomous functioning thyroid nodules [36, 32, 38, 42, 22, 39, 30, 24, 2]. In iodine-deficient regions, mutations in the TSH receptor gene are more common and occur in about 57-82% of cases, making them the most frequent genetic abnormalities found in autonomic thyroid nodules [26, 37, 31, 25, 21].

A study of genetic disorders at the GNAS-1 locus that encodes the Gs protein (the replacement of Asp 619 Gly) revealed a point mutation, a subunit of the Gs protein (Asp 619 Gly), which results in a persistent receptor activation, but the mutations of this gene were detected only in a small number (2-10%) of autonomously functioning nodes [34, 37, 37]. Activating mutations of the TSH receptor are found in both safe and iodine-deficient regions [41].

A close cohesion of a number of antigens of a large histocompatibility complex (DW3, CW4, B8, WHO, B27, A3, At A28) and Graves disease (in mainland Europe it is called Basedow disease) disease was also established. In most cases, the presence of the alleles HLA-B8 BW-35 in patients with diffuse toxic goiter is described. The presence of this antigen increases the genetic risk by 2.02 times, and the haplotype A1-B8 - by 4.23 times. In persons with thyrotoxicophthalmopathy, adhesion to the haplotype HLA B8-CW3 was found. The association of the disease with HLA DR antigens is also proved. At the same time, the frequency of occurrence of HLA DW3 antigen in people with relapses of thyrotoxicosis is reported. HLA B40 antigen can serve as a prognostic sign of a severe course of the disease.

Based on the above data, domestic and foreign researchers, we can conclude that the development of autoimmune thyroiditis and diffusive-toxic goiter is

the result of a joint action of genetic and environmental factors. Yakutia belongs to territories with extreme temperature and light conditions, sharply pronounced seasonality of the climate, to the most unfavorable regions of the Russian Federation for iodine deficiency, with high prevalence of thyroid pathology both among children and adults. In Yakutia, endocrine diseases such as type 2 diabetes [6] and autoimmune thyroiditis are the most common. In this regard, the study of genetic risk factors for the development of autoimmune thyrepatitics among residents of the Republic of Sakha (Yakutia) is relevant.

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The authors:

YNC CMP, Yakutsk, Russia:

1. Sunkhalyrova Tatyana Konstantinovna - candidate of science;
2. Dodokhov Vladimir Vladimirovich - Senior Researcher, Candidate of Biological Sciences, Senior Lecturer, FGBOU Yakutsk State Agricultural Academy, dodoxv@mail.ru;
3. Solovyeva Natalia Alekseevna - Candidate of Medical Sciences, Senior Researcher, sonata608@yandex.ru;
4. Pavlova Nadezhda Ivanovna - Candidate of Biological Sciences, Leading Researcher, Head of the laboratory, solnishko_84@inbox.ru;
5. Filippova Natalia Pavlovna - candidate of biological sciences, associate professor, Researcher, inniah1970@list.ru;
6. Neustroeva Lena Mikhailovna - candidate of technical sciences, Nlm31@mail.ru;
7. Varlamova Marina Alekseevna - Researcher, varlamova.m@yandex.ru,
8. Dyakonova Alexandra Timofeevna – Junior Researcher, Dyakonovaa@bk.ru,
9. Kurtanov Khariton Alekseevich - Candidate of Medical Sciences, Chief Scientific Officer - Head of the Department of Molecular Genetics, hariton_kurtanov@mail.ru.

A.A.Sleptsov, V.A.Savvina

SURGICAL TREATMENT OF APPENDICULAR PERITONITIS IN CHILDREN

ABSTRACT

The literature review is based on the analysis of sources covering the relevance, etiology, pathogenesis, classification, and modern methods of surgical treatment of appendicular peritonitis in children. The issues for further study of this problem are considered.

In pediatric surgery at the moment there is no single point of view in the treatment of common forms of appendicular peritonitis in children. One of the reasons is the absence of a single criterion for assessing the severity of peritonitis. Each surgeon has his own opinion and measure of evaluation. We believe that assessing the severity of the peritonitis course with scoring and its use in the choice and extent of surgical intervention will reduce the postoperative complication, reduce the number of unreasonable conversions, and, if necessary, give indications for laparotomy and laparostomy. Determination of criteria for assessing the severity of peritonitis is an effective method in the choice of operational tactics for treating peritonitis, which allows to minimize the subjectivism of the surgeon, optimizes the approach to therapeutic tactics in appendicular peritonitis in children.

Keywords: appendicular peritonitis in children, literature review.

Appendicular peritonitis is one of the most common severe purulent-inflammatory diseases in children. Operations with acute appendicitis are the most frequently performed emergency operations on the abdominal organs (70%) [10,14, 17], generalized forms of peritonitis with destructive appendicitis in children occur 2.5 times more often, than local ones [14,24].

Despite of the advances in the diagnosis of [3, 10,31] acute appendicitis, the frequency of its destructive forms varies from 20 to 74% [11, 14, 20]. In connection with this, a high incidence of intra-abdominal complications remains from 4.5% to 5.1% [10, 14, 15, 24]. Local purulent-inflammatory complications in acute appendicitis occur in 15.8% of cases [11, 10,26]. Multiple surgical interventions, severe consequences of the disease and unsatisfactory quality of life: a violation of physical, psychological, social and school functioning [18,21] makepediatric surgeons consider the problem open and seek new solutions. The urgency of this problem is also due to the fact that most of the developed complications require a second operation, the danger and traumatism of which is much higher than the primary intervention.

The introduction of the endosurgical method of treatment into practice [13, 15] contributed to the reduction of postoperative complications and improvement of immediate results of treatment. The lethality according to the literature data for appendicular peritonitis in 1972 was 0.48%, in 1981 - 0.42% according to the data of V.A. Popov (1985), and at the age of 3 years it reached 1.2 % according to E.A. Stepanov (1974).

The lack of clear indications for endoscopic sanation with diffuse peritonitis in children, algorithms for conversion or program sanation dictates the need for criteria, objective indications for choosing the method of treatment, and the development of an optimal scheme of antibiotic therapy.

The operations conducted for spilled peritonitis in children are of an acute social nature and are manifested by a decrease in the fertility of girls who underwent operative treatment for peritonitis in childhood [11]. The survey of women operated in childhood showed that 68.9% had menstrual irregularities. V.V.Podkamenev (2002) emphasized that infertility in women with anamnestic appendectomy and inflammatory diseases of the abdominal cavity is 13%. The frequency of adhesions and various forms of intestinal obstruction is great. The use of laparotomy and laparostomy allows solving the main problems, both during the operation and in the postoperative period. First of all, it is an opportunity to conduct a full sanation of the abdominal cavity with revision of internal organs. A good drainage is created, which makes it possible to reduce intoxication, intra-abdominal pressure decreases and it solves the problem of respiratory failure and avoids pulmonary complications,especially in children.

In the literature, different data for the treatment of children with general peritonitisare given, where endoscopy is used for diagnostic purposes, and removal of the purulent focus is made by laparotomy. Also, various indications for switching to laparotomic access are described. There is no single index for assessing the severity of peritonitis.

In the etiology of peritonitis, the main role is played by the bacterial factor, in most cases it is the microflora of the intestine, in the overwhelming number it is a gram-negative or mixed flora. The nature and severity of the changes depend on the microbial aggression and association [6]. The nature of microflora often determines the prognosis of the disease, the risk of developing sepsis. The causative agents of peritonitis are most often microorganisms of the gastrointestinal tract. The microflora of the abdominal cavity is usually represented by associations of different Escherichia coli strains with cocco flora, Pseudomonas aeruginosa or Klebsiella, and monocultures of enterobacteria are less common [6]. In the last decade there has been an increase in the number of antibiotic-resistant strains of microorganisms and an increase in their virulence, which significantly complicates and requires correction of antibacterial therapy [5, 7,28].

Successful treatment of patients with peritonitis is possible only if the surgeonhas a deep knowledgeof the pathophysiological processes taking place in the patient's body, otherwise the highest level of operational and technical skills will not prevent the progression of severe general disorders, and the occurrence of local surgical complications [11].

Conditionally it is distinguished four aspects, which are closely interrelated: -mechanisms of the delimitation of the pathological process in the cavity of the peritoneum; -immunogenesis in peritonitis; - pathogenesis of visceral function impairment; -endotoxicosis in peritonitis. A single entry into the abdominal cavity of the infecting agent, as a rule, does not lead to the development of peritonitis, a long-acting source is needed - an uncontrolled damage of the

hollow organ or a lesion focus.

For the first time Sprengel (1906) and V.F.Voino-Yasenetsky (1943)began to classify peritonitis, they distinguished local and diffuse peritonitis. For the first time, the time factor was taken into considerationby V. Ya. Shlapobersky (1958) in his classification and he singled out the principle of staged development of the process. At the First Congress of Surgeons of the RSFSR in 1958, B.A.Petrov and A.A.Belyaev divided the course of the disease into three stages. The first stage is the stage of maximum manifestation of protective mechanisms, followed by the stage of suppression of protective mechanisms and the third, terminal stage is the depletion of protective forces.

In 1971, K.S.Simonyan (1971) proposed a classification widely known among surgeons. It is based on the principle of the prevalence of inflammation. When determining treatment tactics, assessing the prevalence of the inflammatory process is important. So, the author divides peritonitis into local and widespread. In turn, the local is divided into unlimited and limited. Local unlimited peritonitis is an inflammation of the peritoneum, in which exudate accumulates in no more than one or 2 of 9 anatomical areas of the abdominal cavity without a demarcation inflammatory barrier from the peritoneum and organs. With local limited peritonitis, there is an intraperitoneal separation of the purulent process by a biological obstruction, which is regarded as an abscess of the abdominal cavity. In diffuse peritonitis, exudate accumulates not less than 2 and not more than 5 areas of the abdominal cavity. With general peritonitis, exudate occupies more than 5 anatomical areas of the abdominal cavity. Characterizing the severity of the clinical course of peritonitis, K.S.Simonyan (1971) identifies 3 stages of the course of the disease, using the following features: 1) the reactive stage (the first 24 hours) is characterized by the manifestation of local reactions: a sharp pain syndrome, the tension of the muscles of the anterior abdominal wall, motor excitation of the patient; 2) toxic stage (24-72 hours) - the dominance of common manifestations of the disease over local reactions, which is inherent in severe intoxication; 3) terminal stage (over 72 hours) is characterized by pronounced intoxication at the boundary of reversibility. A similar picture is considered by foreign surgeons as a «septic shock».

According to scientists, participants of the All-Union Conference on Peritonitis, 1979, held at the Institute of Emergency Medicinenamed after N.V. Sklifosovsky, diffuse (general) peritonitis should be considered peritonitis, occupying more than half the areas of the abdominal cavity, i.e. 5 areas and more.

In pediatric surgery, L.M. Roshal, O.V. Karasevpromoted the division of appendicular peritonitis into: free, abscessed, combinedforms, and they separately identify total abscessed peritonitis.

In pediatric surgery the issue of operative access is connected with the hospital equipment and the certified personnel. S.Ya. Doletsky preferred laparotomic access in the right iliac region, and median laparotomy was used by authors only in 0.5% of cases of all appendectomies. To this group Doletsky included children with the prescription of the disease for more than 5 days, and with dense fibrin overlay with inter-loop abscesses. Many authors (Tretyakov A.P. and others) consider that with diffuse purulent peritonitis a medial laparotomy access is mandatory. These scientists are based on the fact that it is not always possible to perform an adequate revision of the abdominal cavity from a small incision and only the medial access gives the surgeon the opportunity to diagnose the degree of lesion, to perform a full revision and sanation of the abdominal cavity [1, 4, 8,19,20,23]. Ya. B. Yudin [27]actively recommends includinglaparotomy and laparostomyto children's surgery. When using laparostomy, the lethality decreased from 1.7% to 0.2%.

The idea of an «open abdomen» in the treatment of peritonitis belongs to N. Mikulich [30]. The first laparostomy was performed in 1949 by the Soviet surgeon N.S. Makokha [19]. Laparostomy is known in the literature under various names: «open method of treating peritonitis», «open abdomen», «fenestration of the abdominal cavity», «controlled peritoneostomy», etc. The method is based on the repeated programmed thorough sanation of the abdominal cavity [20].

The nature of pathological changes in the abdominal cavity, the lack of free space due to intestinal insufficiency and the expressed adhesion process, an increase in abnormal intra-abdominal pressure [5] do not technically allow the endoscopic operation. In such situations, only laparostomy can be effective. Its main advantage is the possibility of surgical treatment with the so-called «late» peritonitis [22], which allows to visually control the evolution of the inflammatory process, the qualitative sanation of the abdominal cavity and thereby prevents the progression of peritonitis and the formation of intra-abdominal abscesses. At the moment, many authors have proven the effectiveness of laparotomy and laparostomy in the treatment of general appendicular peritonitis in children [9,26 ,27].

Currently, many pediatric surgeons refer to the method of laparostomy very carefully because of the lack of clear indications for it. According to experts, the open abdominal cavity leads to profound disturbances in the water-electrolyte and protein balance. Frequent manipulations with the abdominal organs cause a massive adhesive process, and also lead to the formation of intestinal fistulas [12]. According to L.M.Roshal, massive washing contributes to the receipt of progressive substances in areas with increased resorption (diaphragmatic peritoneum), this increases intoxication, increases the likelihood of «penetration» of the vascular bed of toxins, contributes to the development of DIC syndrome, septic shock and multiple organ failure [16]. A comparative analysis conducted by L.M.Roshal and others showed that in clinics where lavage of the abdominal cavity was not performed during surgery, fewer postoperative complications were obtained.

The use of laparoscopic sanation of the abdominal cavity before appendectomy with peritonitis [10, 15], allows for direct, non-traumatic and complete removal of pus from the abdominal cavity, which sometimes excludes the need for traumatic laparotomy and facilitates the course of the postoperative period. R.A.Belous (2002) and others, having experience in treating children with appendicular peritonitis, indicate a low traumaticity and high effectiveness of this method [13,16].

In 1968, the All-Union Conference of Surgeons recommended draining the abdominal cavity in patients with acute appendicitis with delimited abscesses in the abdominal cavity, the inability to completely eliminate the purulent necrotic source, and the unreliable halting of bleeding [14].

Indications for drainage of the abdominal cavity and methods of drainage have their supporters and opponents. In pediatric surgery, the method of draining the pelvis by Generalov is widely used [24,30]. The method was widely used in almost all clinics and it is the method of completing the operation both after therapeutic laparoscopy and after laparotomy [1]. According to J.J. Clark

(2011), laparoscopic drainage is a safe and effective alternative to laparotomy with intra-abdominal abscesses [29].

The modern stage of the development of surgery is characterized by a significant redistribution of operational activity towards the wider use of endoscopic methods of treatment. The progress of endoscopic surgery is provided by the improvement of fiber-optical and optical techniques, endocoagulation methods, the emergence of new models of special instruments. The results of the use of endoscopic methods of treating peritonitis have shown a number of advantages over laparotomy. Based on extensive clinical experience, many authors have concluded that video laparoscopy is a low-traumatic, highly informative and highly effective method for treating peritonitis in children [25,13].

In the foreign literature of recent years, not all support the endoscopic treatment of peritonitis, but in the domestic literature almost all authors write about the benefits of endoscopy in children with peritonitis. In his doctoral work, V.I.Kotlobovsky (2002) wrote: «If the strength of the damaging active factor on the body is not great, then the body can maintain a satisfactory adaptation. In the case of a significant force and prolonged exposure to time, over-regulation of regulatory systems may occur, which ultimately leads to depletion of the body's defenses, a decrease, or even a breakdown, of its functional capabilities. The impact of considerable strength causes a universal general response of the organism in the form of a syndrome of systemic response. Severe surgical trauma caused by traditional surgical methods of treating peritonitis, in itself, can trigger systemic response mechanisms. The negative effect of surgical stress on the body occurs not only at the time of surgery, it affects the entire postoperative period, it ultimately brings a protracted course of peritonitis.» The authors attribute the advantages of laparoscopic technique to the performance of diagnostic laparoscopy, the result of which determines further tactics. The absence of an extensive surgical wound after laparoscopic appendectomy practically excludes her suppuration, divergence of seams, event, bleeding. It is possible to perform an intraoperative adequate assessment of the severity of the course, the prevalence of the inflammatory process. The minimum area of damage (puncture) practically excludes the formation of adhesions in the area of the postoperative wound and provides a good cosmetic effect. Reducing the intraoperative load on the baby's body contributes to the early recovery of physical activity of the patient and reduces the use of analgesics to a minimum, which leads to a reduction in hospitalization [2].

In the technical aspect, the implementation of endovideosurgical treatment in the widespread forms of appendicular peritonitis differs: some authors use laparoscopy as a method for diagnosing and sanation of the abdominal cavity, then perform a conversion, it occurs in 0.9-20% of cases of peritonitis in children [25]. However, N. Vettoretto (2004) and others favor this tactic, indicating conversion to laparotomy in special cases of severe peritonitis [18]. In a comparative study, L. Planka (2009) concluded that operative treatment of general appendicular peritonitis using laparoscopy does not lead to an increase in early and late postoperative complications compared to classical methods [19,28].

In pediatric surgery, currently there is no single point of view in the treatment of common forms of appendicular peritonitis in children [12,15,27]. One of the reasons is the absence of a single criterion for assessing the severity of peritonitis, as each surgeon has his own opinion and measure of evaluation. We believe that assessing the severity of the flow of peritonitis with scoring and its use in the choice and scope of surgical intervention will reduce the postoperative complication, reduce the number of unreasonable conversions, and, if necessary, give indications for laparotomy and laparostomy. Determination of criteria for assessing the severity of peritonitis is an effective method in the choice of operational tactics for treating peritonitis, which allows to minimize the subjectivism of the surgeon, optimizes the approach to therapeutic tactics in appendicular peritonitis in children.

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The authors

1. Sleptsov Alexander Alexandrovich, Head of Purulent Surgery Department of the Pediatric Center, Republican Hospital №1, National Centre of Medicine, Yakutsk, Russia, e-mail: sashaogh@mail.ru;

2. Savvina Valentina Alekseevna, Doctor of Medical Sciences, Professor of the Department of Pediatrics and Pediatric Surgery, Medical Institute, North-Eastern Federal University named after M.K. Ammosov, e-mail: SavvinaVA@mail.ru, Yakutsk, Russia.

G.A.Airapetov, A.A.Vorotnikov, E.A. Konovalov, L.V.Airapetova

THE CURRENT ISSUE OF THE INJECTABLE THERAPY OF THE KNEES INJURIES AND DISEASES

ABSTRACT

Today, there is a high significance of the consequences of injuries and diseases of the musculoskeletal system economically, medically and socially because of the high costs of treatment and rehabilitation, as well as a long period of incapability to treatment or permanent disability. There is a significant increase in the incidence of degenerative-dystrophic diseases of large joints everywhere. According to the literature, 9 to 13% of the world's population suffers from osteoarthritis. Incorrect or untimely treatment can quickly lead to aggressive surgical interventions. The article describes modern approaches to injectable therapy of the knees injuries and diseases.

Keywords:gonarthrosis, conservative treatment of osteoarthritis, hyaluronic acid, plate rich plasm

Introduction

Today, there is a high significance of injuries and diseases of large joints in the economic and medical-social terms due to high costs of treatment and rehabilitation, as well as a long period of incapacity for work or permanent disability [1].

Osteoarthritis (OA) is a chronic polyethiologic degenerative-dystrophic disease characterized by a prolonged progressive course and development of pain syndrome [7]. In this process, the synovial membrane, articular cartilage and other periarticular structures are involved.

The study of the results of 31516 arthroscopic interventions for damage and diseases of large joints showed that in 63% of cases there was pathology of cartilage of various degrees, which requires therapeutic measures, including intra-articular injections [9].

More than 50% of patients in the polyclinic of orthopedic patients are associated with injuries and diseases of large joints [2]. According to literature data, 9 to 13% of the world's population suffers from osteoarthritis [8], others speak of incidence of up to 20% [16]. According to Russian authors, the incidence of knee arthrosis in the Russian Federation is 99.6 per 10 000 population [5]. According to some reports, every third patient is affected by both joints.

According to the literature, the quality of life of patients with degenerative - degenerative diseases of large joints is much lower than in diseases of the gastrointestinal tract, cardiovascular and respiratory diseases. Osteoarthritis, like some other diseases, causes a prolonged disability, has a negative psychological and economic impact on patients. [3].

Conservative therapy OA gives a positive result at stages 1 and 2 of the disease. In some situations, conservative treatment is also used at stage 3 gonarthrosis. The main principles of conservative treatment are: relief of pain syndrome, elimination of causes contributing to the progression of the disease and restoration of lost functions [6].

Today the most popular drugs for conservative treatment of degenerative and dystrophic diseases of the knee joint are hyaluronic acid, platelet rich plasma and corticosteroids. [42]

Many modern studies report excellent results after intra-articular administration of hyaluronic acid preparations in the form of reduced pain syndrome and improvement of limb function [32, 20, 25].

Of interest is the work of Latin American colleagues who studied the effect of intra-articular administration of hyaluronic acid and the traditional conservative treatment of osteoarthritis in dogs. The study included 16 dogs and were divided into 2 groups. The authors concluded that both methods of treatment can reduce the clinical manifestations of osteoarthritis, but in the group with intra-articular administration of hyaluronic acid, the results were significantly better. [32]

Injection of highly purified hyaluronic acid, increase the viscosity of the synovial fluid and absorb the compressive forces, which is essential in the work of joints. [31].

Investigation of the chemical properties of synovial fluid after administration of the hyaluronic acid preparation showed that the positive effect persists for more than 6 months with a maximum from 5 to 13 weeks. Reduction of the pain syndrome and improvement of function in the joint are in any case comparable with the intake of NSAIDs, however, the best local effect is noted and the systemic effect is absent. [15]

In one of the large studies, various preparations of hyaluronic acid were used. The number of injections was 3 to 5 per week and a maximum of 11 for 23 weeks, the dose varied from 15 to 60 mg. The pain syndrome was assessed using the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The authors reported that hyaluronic acid preparations have a safe and effective effect in the treatment of OA. [26].

The question remains with regard to intra-articular injection of glucocorticoids. In rheumatology, this group of drugs has been used for a long time and successfully in the treatment of rheumatoid arthritis [4]. Most orthopedists say that in the treatment of gonarthrosis, glucocorticoids can only be used for osteoarthritis of 3rd stage with severe synovitis. [17, 21]

It is interesting to work in which the results of intra-articular injection of hyaluronic acid and corticosteroids were compared. The results indicate that, within 4 weeks after the injection, corticosteroids can produce better results, but hyaluronic acid preparations have a longer and safer effect. [13].

In one large study, 606 patients with gonarthrosis compared the results of intra-articular administration of hyaluronic acid, corticosteroids and placebo. Maximum efficiency was shown by the group with hyaluronic acid at 8, 12 and 24 weeks after treatment [14].

Some authors report that intra-articular administration of hyaluronic acid preparations significantly reduces the level of the inhibitor of plasminogen activation in cartilaginous and synovial cultures, which ensures a long-lasting effect of the drug [23].

The question of the influence of age on the results of OA treatment remains open. Some authors say that age does not affect the results of intraarticular administration of hyaluronic acid, but note that the long-term result remains to a greater extent in young patients (30). There is an opinion that the positive effect of corticosteroids can be prolonged by repeated administration of the drug every 3 months [28].

Our opinion is comparable with the results of large studies in which it is said about the greatest effectiveness of the administration of hyaluronic acid preparations at stage 2 of gonarthrosis, and in some cases also at stage III.

Increasingly, Plasma enriched with platelets (PRP) is used to treat diseases

and injuries of the musculoskeletal system. According to the literature, it contains growth factors that improve the regeneration of tissues. [10, 11, 12]. Osteoarthritis is the main indication for prescribing PRP. Consequently, most studies are aimed at evaluating the results of treatment of gonarthrosis [27,22,29], but there are a small number of articles on the treatment of coxarthrosis and arthrosis of the ankle. (10).

In many studies, complete safety and absence of any complications after the administration of PRP was confirmed [24,18].

In one of the large studies, the results of intraarticular administration of PRP and hyaluronic acid were compared. The authors reported that plasma allows more persistent and long lasting effect [18].

Of undoubted interest is the work carried out by DA Malanin. et al., in which 81 patients with gonarthrosis of 3 stage. In one of the groups The authors three times, intra-articularly administered PRP, in the other group the method of treatment was oral administration of NSAIDs. The authors reported on the effectiveness of intra-articular PRP administration, which reduced the pain syndrome and improved knee function in patients with stage III gonarthrosis for 9 weeks during their preparation for surgical treatment. [4]

The actual issue remains the use of hyaluronic acid and PRP in the joint. We managed to find out only one mention of the joint use of these drugs. According to The authors' data, the administration of PRP and hyaluronic acid into the joint cavity allows to summarize their positive effect [19].

We believe that intra-articular administration of drugs in the treatment of osteoarthrosis fully justifies itself at the initial stages of the disease. At the III stage gonarthrosis, when surgical treatment is contraindicated or the patient refuses surgery, hyaluronic acid or PRP preparations along with NSAIDs also have a temporary curative effect. The choice between these two groups of drugs is completely left for the doctor performing this manipulation.

It should be noted that only complex, individual treatment of patients with injuries and diseases of the knee joint can achieve positive results and delay surgical treatment.

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The authors:

Airapetov Georgii Alexandrovich – docent of the department of traumatology and orthopedics in the SSMU, candidate of the medical sciences (89624466728) (airapetovGA@yandex.ru). Stavropol. Russia.

Vorotnicov Alexandr Anatolievich – head of the department of traumatology and orthopedics in the SSMU, doctor of the medical sciences, professor, (vorotnikovaa@mail.ru). Stavropol. Russia.

Konovalov Evgeniy Alexandrovich – assistant of the department of traumatology and orthopedics in the SSMU (Konovalov_Evg@mail.ru). Stavropol. Russia.

Airapetova Lilit Viacheslavovna – resident of the department of gynecology and obstetrics in the SSMU (Airapetovalv@mail.ru). Stavropol. Russia.

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

SOCIAL - HYGIENIC AND MEDICAL-BIOLOGICAL FACTORS OF THE RISK OF CONGENITAL HEART DEFECTS DEVELOPMENTIN CHILDREN

ABSTRACT

The article presents an overview of the main socio-hygienic and medico-biological risk factors of congenital heart defects (CHD) in children. Determination of risk factors is essential in estimating and forecasting the frequency of CHDin the population.

Keywords: congenital heart defect, risk factor, children, pregnant women.

Introduction

Congenital heart defect (CHD) is a heterogeneous group of diseases, including isolated and combined anomalies of multifactorial etiology. In this regard, the study of risk factors for the development of the CHD is one of the key moments in the organization of primary prevention of this pathology. It is well known that most registers are aimed at identifying possible factors that contribute to the formation of mutational processes at both individual and population levels [2, 4]. The leading risk factors for the development of CHD in children can be conditionally divided into three groups: socio-hygienic, medical-biological and external-environmental factors. About 90% of the CHD are multifactorial, depending on the combined effect of hereditary factors and environmental factors [9].

1. Socio-hygienic risk factors for congenital heart disease.

According to a number of studies, social risk factors include: the age of the mother at the time of childbirth is more than 35 years, the birth of children out of wedlock, the presence of more than four pregnancies in the anamnesis, the level of income in the family, the nature of the mother's nutrition, the level of education of the mother and father [13, 10].

In A.R. Safiullinastudy (2012), it was shown that the diagnostic coefficient of congenital septal heart disease in relation to the «incomplete family» sign was maximum - 9 points with a threshold value of 2 or more points; more than four pregnancies - 5 points; coefficient «higher education of mother and father» - had a negative value (-3 and -5 points respectively). Given that the specialties of parents with secondary education and lower secondary education were often associated with the harmful effects of occupational factors (contact with fuels and lubricants, disinfectant solutions, building materials, etc.), the influence of the education level of parents on the increased risk of birth children with congenital anomalies of the circulatory system. In addition, it can be assumed that parents with higher education control their health more carefully, plan pregnancy more carefully and have better contact with a gynecologist monitoring pregnancy. A more important role in increasing the risk of congenital anomalies may be played by more frequent alcohol, nicotine or drug dependence in pregnant women with a low level of education. At the same time, there was no adverse effect of the living conditions of the family on the increase in the risk of congenital septal heart disease [11].

Several other significant social risk factors were found in the study conducted in PrimorskyKrai among children with congenital developmental anomalies. The authors attributed to them the increased urbanization of the territories (83%), the age of the mother under 25 (48.5%), the first pregnancy (42.4%) and

the lack of permanent work (33%) [12].

These findings are confirmed in a study of Zhu Z. (2016), which established as a risk factors for the CHD the low educational level of the mother, the age of the mother over 35, the wrong way of life. When combined, the relative risk of CHD increases to 12.25 [28]. Age of the father at the time of conception, some authors also refer to the risk factors for CHD of newborns [25].

The nature of the mother's diet can also affect the likelihood of the birth of children with CHD. For example, obesity of the mother, inadequate nutrition during pregnancy with insufficient intake of folic acid, B vitamins and iron, leading to the development of anemia, as well as proteins are recognized as risk factors for CHD in children [24]. An epidemiological study of the prevalence of developmental malformations in the China region, characterized by a deficiency of zinc and an increased copper content in food, revealed a higher incidence of heart defects in the local population than in areas with a normal content of these trace elements [17].

In the Chinese province of Shanxi, characterized by a low consumption of green vegetables, fruits, meat, containing proteins, retinol, riboflavin, vitamin E, selenium (an average of 9-77% below recommended rates), the highest birth rates of children with CHD are observed. The average value of folic acid in the serum of women who gave birth to children with CHD was 9.6 nmol / L, which was significantly lower than the level of this vitamin in the blood of women with healthy children (14.03 nmol / L) [16].

A meta-analysis of the possible association between the socioeconomic status of the mother and the development of the CHD showed a negative relationship between the level of education, family income, maternal occupational exposure and increased risk of CHD: 11% (RR = 1.11); 5% (RR = 1.05) and 51% (RR = 1.51), respectively. It is concluded that the low level of maternal social and economic status has a moderate association with an increased risk of congenital anomalies in the circulatory system [23].

2. Medical and biological risk factors for congenital heart disease

Significant risk factors for the birth of children with congenital malformations include the pathological course of pregnancy, a burdened obstetric anamnesis, the features of the current pregnancy and childbirth.

Given that pregnancy is accompanied by a rebuilding of the mother's immune and neuroendocrine systems, some authors explain the risk of developing congenital anomalies, including CHD, stimulation of cellular immunity with the production of antibodies to paternal antigens, the formation of progesterone-induced blocking factor (PIBF) inhibiting cytotoxic lymphocytes of the mother, which subsequently leads to damage to the trophoblast and an increase in the Th2-immune response. It was found that abnormalities in the ratio Th1 / Th2 lead to disturbances in the immunological relationships between the mother and fetus, intrauterine development of the fetus with the formation of congenital malformations and pathological births [19].

In some studies, the role of endotoxin of gram-negative bacteria in the intestine of the mother formed in increased amounts during hypoxia or intestinal pathology is indicated as a risk factor for intrauterine fetal development disorders and dysfunction of its organs [21].

Hypoxic conditions associated with the pathology of the circulatory system or anemic syndrome are also capable of leading to changes in the energy supply of fetal development processes, and may also exacerbate the adverse effects of other risk factors, such as smoking, infectious processes, hereditary factors [5].

In S.V. Medvedevastudy (2016), in the group of mothers who gave birth to children with CHD, the main risk factors were previous miscarriages and abortions (21.5%), infertility with appropriate treatment (4%), alcohol and smoking abuse during pregnancy (5.7% and 20.8%, respectively), stillbirths in the anamnesis (1.8%), somatic pathology, primarily anemia (48.8%), urinary tract disorders (27.7%), cardiovascular pathology (vegetative-vascular dystonia, arterial hypertension) - 17.4%, thyroid disease, obesity, diabetes (14.5%), pathology of the digestive system (7.1%), respiratory system (5.1%) . To the pathology of pregnant women, able to influence the development of CHD, chronic fetoplacental insufficiency (38%), toxicosis (22.2%), and the threat of abortion (32.6%) were attributed [8].

Numerous studies indicate a link between pregnant hypertension and congenital heart defects in their offspring. Thus, a systematic analysis with meta-analysis, including 16 clinical studies, demonstrated an increase in the relative risks of CHD in both the case of hypertension prone to treatment (RR = 2.0) and untreated hypertension (RR = 1.8). This fact can be explained by the possible teratogenic effect of antihypertensive drugs [22].

A systematic review, conducted in 2015 on the example of 12 studies, indicates that preg- nancy diabetes is a significant risk factor for CHD. At the same time, good glycemic control reduces this risk [18].

One of the reasons for the development of CHD by some authors is the presence of a persistent intracellular infection, which subsequently leads to a persistent decrease in the immune response [15]. Diagnosis of malformations in the antenatal period in this case is significantly hampered by the fact that intrauterine infection of the fetus in the vast majority of cases occurs in subclinical form or is asymptomatic [1].

Confirmation of these data is the results of N.P.Kotlukovastudy, who demonstrated that more than 97% of newborns with congenital cardiovascular pathology had a mixed viral infection, whereas in healthy newborns this indicator was 27.0% [7]. Similar results were obtained in another study, which showed that in newborns with complex CHD, class G immunoglobulins to the herpes simplex virus (HSV) and cytomegalovirus (CMV) were found in 96% and 38%, respectively [3].

A retrospective cohort study of the relationship between the presence of a viral infection (influenza, rubella, measles, chickenpox, hepatitis), as well as the use of antibiotics, tocolytics, anticonvulsants, antipyretics and analgesics, antitumor drugs, folic acid and contraceptives and the development of CHD for a period of 6 months before pregnancy and until the prenatal survey, 5381 newborns showed statistically significant differences in the cohort of children with CHD and a cohort of healthy children with regard to influenza infection, tocolytic drugs and contraceptives in the history of mothers [27].

In T.V. Osmirkostudy it was found that the relative risk of developing CHD in the presence of TORCH syndrome (toxoplasmosis in combination with other infections such as mycoplasmosis, chlamydia, listeriosis, rubella, cytomegalovirus infection, herpes) in newborn infants is 2.91 (0.64-12.26). At the same time, the overall detection rate of laboratory-confirmed cases of TORCH infections among newborns with clinical manifestations characteristic of intrauterine infection was 18.9% [6].

Proven teratogenic activity is typical for a fairly large number of drugs, which

include, in the first place, cytotoxic drugs, some antibiotics (aminoglycosides), mercury salts, some anticonvulsants, estrogens, valproic acid preparations, drugs for psoriasis.

The teratogenic effect of anticonvulsant drugs is caused by a deficiency of folic acid, necessary for the synthesis of nucleic acids in the fetus. Thus, a study by Japanese scientists showed that the intake of valproic acid during pregnancy increases the risk of developing CHD in newborns by a factor of 7 compared with other antiepileptic drugs [26]. In contrast, the intake of folic acid by pregnant women had a positive association with a decrease in the relative risk of developing CHD to 0.72 [23].

It is known that up to 75% of women suffer from candidalvulvovaginitis at least once in their life, especially during their reproductive years. Since about half of all pregnancies are unplanned, the risk of exposure to fluconazole during pregnancy is high. However, a systematic review of the relevant studies did not show a significant increase in the risk of congenital malformations as a whole when using fluconazole during the first trimester of pregnancy. The relative risk of developing CHD when taking the drug was 1.29, which requires further research in this direction [14].

In the literature, there are also data on the increased risk of CHD when using synthetic analogs of androgenic steroid hormones in the first trimester. Progesterone (medroxyprogesterone) has the same effect [20].

Thus, based on the literature data, it can be concluded that risk factors are of great importance in assessing and predicting the incidence of congenital heart disease.

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The authors

1. Nelunova Tuyara Ivanovna, doctor cardiologist Pediatric Center RH 1-NCM, post-graduate student of SPbGPMU, nelunova-ti@mail.ru, Yakutsk, Russia;
2. Burtseva Tatiana Egorovna, Dr Med.Sci., head of the laboratory of the YNC CMP, professor-researcher of the SVFU, e-mail: bourtsevat@yandex.ru, Yakutsk, Russia;
3. Chasnyk Vyacheslav Grigorievich, Dr Med Sci., professor, head of lectern of «The State pediatrist medical Academy of St. Petersburg», e-mail: chasnyk@gmail.com, St. Petersburg, Russia;
4. Evseeva Sardana Anatolievna, junior researcher YNC KMP, sarda79@mail.ru, Yakutsk, Russia.

O. N.Ivanova

COURSE «VACCINE PROPHYLAXIS IN PEDIATRICS» IN THE EDUCATIONAL PROCESS OF STUDENTS OF A MEDICAL INSTITUTE

ABSTRACT

After 2016 at the medical universities of the country training of students takes place according to new educational standards. Training of students in medical schools until 2016 did not allow senior students to participate in the provision of medical care, and graduates - to work as doctors, as in the learning process too little attention was paid to practice. For the purpose of practical teaching methods in the educational process of training of students of medical Institute was developed and implemented a new course« Vaccinal prevention in Pediatrics». It is important to emphasize that shape the students ' competencies should be focused on the semantic component of the leading types of medical activities. So, in the educational process constructed on the basis of the competence approach, a kind of dependency between knowledge and skills, subordination of the acquired knowledge and professional skills. This, in turn, contributes to the fact that education is for student personal and meaningful. We have developed a working program of discipline and teaching discipline to meet all required competencies. In accordance with the prepared and approved for publication guidelines and instructions for students. Particular attention was paid to organization of independent work of students, which is one of the most important components of the educational process and the condition for the development of competence of students. Independent work implied the use in the preparation of students to classes of situational tasks and tests designed for each lesson.

The test in the discipline included the control of acquired practical skills.

The introduction of new clinical disciplines promotes the acquisition of professional knowledge and skills.

Introduction

After 2016 at the medical universities of the country training of students takes place according to new educational standards. Training of students in medical schools until 2016 did not allow senior students to participate in the provision of medical care, and graduates - to work as doctors, as in the learning process too little attention was paid to practice. Therefore, according to the new standards in medical schools, starting from primary school, more time will be devoted to practical exercises.

The first graduation of specialists trained in the new standards is planned in 2016-2017. Thus, from 2017 there will be no need in the internship as in the transitional stage of postgraduate training (diploma of graduation and the beginning of independent professional activity). Yesterday's students immediately after graduation will be able to work independently as a district therapist, a district pediatrician in outpatient clinics. However, to get the right to work, they will have to be accredited. It will differ from the current certification system in that it will become a system of admission to specific types of medical activities [1,2,3,4,5].

For the purpose of introduction of practical methods of training in educational process of preparation of students of medical Institute the new course "Vaccinal prevention in Pediatrics" was developed and introduced. The working program of discipline and educational-methodical course of discipline taking into account performance of all necessary competences is developed.

The results of the implementation it is important to emphasize that the set of competencies formed by students should be focused on the semantic component of the leading types of medical activities. Thus, in the educational process, based

on the competence approach, a certain dependence between knowledge and skills, subordination of acquired knowledge to professional skills is established. This, in turn, contributes to the fact that education becomes personally significant for the student [1,2,3,4].

Special attention in teaching the discipline «Vaccinal prevention in pediatrics» issues of post-vaccination complications and vaccination reactions. Teachers developed lectures with a detailed presentation of the educational material. In accordance with this, methodical recommendations and instructions for students were prepared and approved for publication. Special attention was paid to the organization of independent work of students, which is one of the most important components of the educational process and a condition for the development of students ' competence. Working independently, students not only firmly and deeply assimilate the subject educational material, but also develop skills of research and professional activity, ability to work with educational and scientific literature, ability to make responsible and constructive decisions in various crisis situations.

In the course of discipline training, great attention is paid to the calendar of preventive vaccinations. At the end of the training, students should be free to navigate the timing of vaccinations.

Organization of independent work of students is carried out taking into account didactic principles that reflect the specifics of this area of pedagogical activity in high school. These include the following principles: unity of educational (classroom) and independent (extracurricular) activities of students; individualization and differentiation; professional orientation, contributing to the transfer of educational and cognitive activity of students in the professional and pedagogical; consciousness and creative activity of students; possible difficulties of tasks for independent work, taking into account the time for their implementation; systematic, sequence and continuity of the organization of independent work. Independent work involved the use of situational tasks and tests developed for each lesson in preparation of students for classes.

Offset on discipline included control of the acquired practical skills.

Conclusion:

1. Changing the educational process is a necessary condition for the formation of students ' clinical competence.

2. The introduction of new clinical disciplines contributes to their acquisition of professional knowledge and skills.

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The author:

Olga Ivanova – Doctor of medical Sciences, Professor, Department of Pediatrics and pediatric surgery of the medical Institute M. K. Ammosov North-Eastern Federal University, Oyunsky str., 27, Yakutsk, Russia, e-mail:olgadoctor@list.ru.

CLINICAL CASE

Kh.A. Kurtanov, T.N. Alexandrova, N.I. Pavlova, I.I. Mulina, I.E. Solovyeva, M.A. Varlamova, L.M. Neustroeva, A.T. Dyakonova

CLINICAL CASE OF ACUTE MYOCARDIAL INFARCTION IN THE ONSET OF CHRONIC MYELOPROLIFERATIVE DISEASE

ABSTRACT

The main clinical problem of patients with chronic myeloproliferative diseases are thrombotic complications causing death and invalidism. Possible long-term latent course of these diseases, comorbid cardiovascular pathology increases the risk of fatal complications. This article presents a clinical case of chronic myeloproliferative disease in a 57-aged man, who first manifested with acute Q-positive myocardial infarction. The patient successfully underwent recanalization, transluminal balloon angioplasty with stenting of the anterior descending coronary artery. Based on thrombocytosis and bone marrow examination he fulfill the diagnosis of essential thrombocythemia. During follow-up of three years, the progression of disease is observed with the development of secondary myelofibrosis. The diagnosis is confirmed by bone marrow histology and taking into account high risk of recurrent thrombotic complications, he administered with cytoreductive and antiplatelet therapy.

Keywords: chronic myeloproliferative diseases, thrombosis, cardiovascular complications, myocardial infarction.

Introduction

Chronic myeloproliferative diseases are clonal diseases that affect hematopoetic stem cells. The trigger mechanism of diseases is a point somatic mutation in the 14 exon of the JAK2 gene, leading to the replacement of valine by phenylalanine in codon 617 (JAK2V617F) of the polypeptide chain. As a result of this mutation, JAK2 tyrosine kinase, a key enzyme of the JAK2/STAT kinase pathway, leads to uncontrolled proliferation of myeloid precurcors [3]. Prevalence of JAK2V617F mutation among patients with polycythemia vera (PV) is 97%, essential thrombocytopenia (ET) is 55% and primary myelofibrosis (PMF) is 65% [10].

The main cause leading to disablement and a decrease in survival of patients with ET and PI is the tendency to thrombosis [4]. In case of ET, arterial thrombosis is more common than venous, which is more often seen in PV patients. ET commonly manifest with symptoms of microcirculatory disorder such as erythromelalgia and transient neurologic

disorders. Hemorrhagic complications caused by a decrease of von Willebrand factor concentration in plasma as a result of its binding with platelet glycoprotein IIb/IIIa [1].

Chronic myeloproliferative diseases affect mainly elderly people (mean age 55 years), whose somatic status is complicated by cardiovascular risk factors. Such comorbid conditions as atherosclerosis, hypertension, metabolic syndrome, and lifestyle increase the risk of cardiovascular complications in this cohort of patients [2, 8]. Often there are cases of latent course of myeloproliferative disease, when the only clinical presentation of disease is thrombosis. At the time of diagnosis, thrombosis of various localizations occur in 31,2% of patients with ET [11]. Polycythemia or thrombocytosis may be masked by an increased volume of plasma and/or hypersplenism, which makes it difficult to interpret laboratory findings and diagnose chronic myeloproliferative diseases. Delayed diagnosis of these diseases can lead to the development of fatal complications, such as myocardial infarction, strokes, thrombosis of the veins of the portal system.

Objective: to demonstrate the clinical case of myeloproliferative disease, presented with acute myocardial infarction at the onset.

Material and methods of investigation. A retrospective analysis of the medical records of patient B., followed-up by hematologists of Yakutsk since 2014, was carried out.

Clinical case

*Patient B., a man of 57 years, had become acutely ill in December 2013 when he complained of angina pectoris that are not managed with nitroglycerin. He was administered to emergency cardiology department, where a Q-positive myocardial infarction was diagnosed based on ECG, Echocardiography, dynamics of cardiospecific enzymes. Complete blood count demonstrated moderate thrombocytosis (421*109/l), mild anemia (erythrocytes 3,49*109/l, hemoglobin 107 g/l), ESR 13 mm/h, leukocytic formula is unchanged. In biochemistry hyperglycemia (blood sugar 6.1 mmol/l), dyslipidemia (total cholesterol 5.4 mmol/l, triglycerides 0,9 mmol/L, low density lipoproteins (LDL) 3,8 mmol/l, lipoproteins high density (HDL) 1,2 mmol/l) were identified. Patients denied any history of angina, he has been smoking for over 20 years for 5-7 cigarettes a day. He has a history of 3rd degree arterial hypertension without medications, varicose veins of legs which are managed by phlebectomy 2011. In hospital, selective coronary angiography (SCAG) was performed, where an occlusive thrombosis of the proximal segment of the anterior descending artery (PNA) of the left coronary artery (LCA) was detected. Recanalization, transluminal balloon angioplasty (TBCA) with PNA stenting was carried out and medical treatment – anticoagulants, antiplatelets, angiotensin converting enzyme inhibitors (ACE inhibitors), beta-blockers, statins were prescribed. During inpatient care, the platelet count increased to 864*109/l for the first time. He was discharged from hospital on the 15th day in a satisfactory condition with recommendations to continue double antiplatelet therapy (acetylsalicylic acid 125 mg + clopidogrel 75 mg), metoprolol 25 mg, ivabradine 5 mg, rosuvastatin 10 mg.*

*Patient visited hematologist in January 2014 with complaints of general weakness. In examination the skin and visible mucous membranes are of a normal color, clean. The body mass index is 26 kg/m2. Peripheral lymph nodes are not palpable. Vesicular breathing, no wheezing. Breathing rate is 16 per min. Heart rhythm sounds are muffled, heart rate is 66 min. Blood pressure is 130/80 mm/Hg. The abdomen is mild, painless, the liver and spleen are not enlarged. No signs of peripheral edema. At the examination: complete blood count – erythrocytes 4,09*109/l, leukocytes 8,5*109/l, hemoglobin 116 g/l, platelets by smear 1104.8 * 109/l, stab neutrophils 3%, segmented neutrophils 61%, eosinophils 5%, lymphocytes 24%, monocytes 7%, ESR 7 mm/h. Biochemical blood test – albumin 44,5 g/l, total protein 76,9 g/l, bilirubin total 9,9 µmol/l, direct bilirubin 2.9 µmol/l, ALT 31,7 U/l, AST 26,1 U/l, urea 7,3 mmol/l, creatinine 107,6 µmol/L, glucose 5,06 mmol/l, total cholesterol 6,06 mmol/l. Bone marrow morphology demonstrated one megakaryocyte with numerous small nuclei, platelets aggregations and giant platelets. Bases on clinical presentation, examination and laboratory findings patient was diagnosed with essential thrombocythemia and antiplatelet therapy was prescribed.*

*The patient returned to hematologist in March 2017 for routine check-up. He does not have any complaints. During examination, mild thrombocytosis 682*109/l, progression of anemia (erythrocytes 3,53, hemoglobin 85 g/l, hematocrit 29,5%), normoblastosis 2:100, hyper-segmentation of neutrophils and acceleration of ESR up to 29 mm/h were revealed. Blood biochemistry demonstated a high LDH level 822,6 U / L, hyperuricemia 511,3 µmol/l, other indices were within reference ranges. According to abdominal ultrasound there was a moderate splenomegaly (63,5 cm2). Additional studies was erformed to exclude other hematological diseases: chimeric BCR-ABL transcript - 0%, trepanobiopsy – bone marrow is hypercellular marrow (relatively to age). The erythroid lineage is represented by normoblasts. The granulocyte lineage is represented by all forms of differentiation with a predominance of maturing forms. The number of megakaryocytes is increased, with hyperchromic hypo- and hyperlobular nuclei, also present with cloud-shaped, dysmorphic, isolated nuclei in the form of reindeer antigens, located in large groups, up to 14 cells, near the bony beams. Van Gieson, Masson coloring showed collagen fibrosis proliferation in bone marrow stroma. Stroma contains of lymphocytes, eosinophils. Conclusion: The histological picture does not exclude the presence of chronic myeloproliferative disease, primary myelofibrosis. Immunohistochemical study was not conducted due to the lack of specific reagents. Histologic study is allowed to comfirm clinical diagnosis – chronic myeloproliferative disease: an essential thrombocythemia with an outcome in secondary myelofibrosis. Patient was prescribed with cytoreductive therapy – hydroxyurea is 500 mg/day and antiplatelets.*

Discussion

The clinical presentation of ET is characterized by the absence of pathognomonic symptoms and is depend on disease stage and rate of progression. Disease onset is usually asymptomatic, it proceeds slowly over a several years. Patients usually come to hospital because of microcirculation disorders – acrocyanosis, erythromelalgia, headaches, secondary Raynaud's syndrome. In a significant part of patients, blood count abnotmalities are detected during routine examination or when examined for other co-existing pathologies [1, 4]. In this clinical case disease manifested first with acute myocardial infarction. Duration of disease is unknown, since the patient has not previously visited ambulance. Probably, there was a latent course of the disease, because progression to postthrombocythemic myelofibrosis is commonly occur after long-term history of ET. The frequency of progression to secondary myelofibrosis, according to the literature, is 3-10% during the first 10

years, and 6-30% after disease duration of more than 10 years [1].

Vascular accidents at the moment of diagnosis are not rare – myocardial infarction in 10,2% of patients, strokes – in 13,0% [11]. The international prognostic risk scale for thrombosis in essential thrombocythemia (IPSET-thrombosis) includes age over 60 years, diabetes mellitus, hypertension, smoking, history of thrombosis and the presence of JAK2V617F mutation [6]. Despite the high diagnostic and prognostic significance of the determination of the mutational status of JAK2V617F, it is not always possible to perform molecular genetic studies in routine clinical practice. Additional risk factors associated with thrombogenic risk are leukocytosis and dyslipidemia [3, 9]. In this patient, the risk factors are presented by smoking, arterial hypertension and dyslipidemia.

When stratifying the risk of recurrent thrombotic complications, it should be noted that patients with history of thrombosis are at high risk and require a complex approach to the treatment of disease, as well as secondary thrombotic prevention. To correct leukocytosis and thrombocytosis in older people, hydroxyurea (Hydrea) is commonly used [5,8]. Prevention of thrombotic complications includes measures to correct lifestyle, arterial hypertension, smoking cessation and drug therapy [1]. The gold standard of long-term therapy after myocardial infarction is a double antiplatelet therapy with acetylsalicylic acid and clopidogrel. Acetylsalicylic acid is not recommended for patients taking anagrelide due to increased risk of bleeding [7].

Conclusion

Presented clinical case demonstrates the possibility of a long latent ET course that first manifested with myocardial infarction. The absence of pathognomonic symptoms makes it difficult to diagnose chronic myeloproliferative diseases. The high risk of developing fatal complications and disease progression determine the need for regular medical examinations and the introduction of molecular diagnostic methods for the detection of JAK2V617F mutation in routine clinical practice.

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The authors:

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

2. Aleksandrova Tuiara Nikonovna – junior researcher of the laboratory of heritable pathology alexandrova_tuyara@mail.ru;

3. Pavlova Nadezhda Ivanovna – PhD, temporary acting chief scientific officer - head of the laboratory of heritable pathology E-mail: solnishko_84@ inbox.ru;

4. Mulina Inna Ivanovna – Head of the Department of hematology National Centre of Medicine;

5. Solovieva Irina Eremeevna – hematologist of National Centre of Medicine;

6. Varlamova Marina Alekseevna – junior researcher of the laboratory of heritable pathology;

7. Neustroeva Lena Mikhaylovna – junior researcher of the laboratory of the Laboratory of Population Genetics;

8. D'yakonova Aleksandra Timofeevna – junior researcher of the laboratory of heritable pathology.






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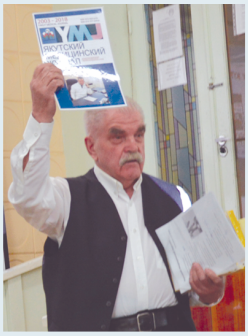


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