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EDITORIAL

Dear clinicians, researchers, colleagues and friends!

A key role of the public health in all countries of the world is safeguarding and strengthening the health of the nation. Prevalence and high intensity of dental diseases make issues of contemporary diagnosis, high quality treatment and effective prevention extremely important. Qualified professionals are challenged with the task of rendering available and efficient dental services to the population.

Latest advances in dental care, new technologies, tools and materials, huge volume of information, which rapidly loses its novelty; all this demands regular updating the knowledge and constant training of clinicians and researches in new methods of therapeutic, orthopedic, orthodontic and surgical treatment. In the current issue of our journal under the section *Dentistry* you can find the results of new studies, which will increase your competence, broaden your understanding of modern dental technologies and encourage your creativity. Systematization, upgrading your skills will facilitate higher achievements and improvement of oral health in all age groups.

Executive Editor
Prof. Dmitry Domenyuk

https://doi.org/10.35630/2199-885X/2019/9/3.1 JEL Classification I18, D73

TRANSFORMATION OF THE MANAGEMENT SYSTEM IN DENTISTRY: EUROPEAN MODELS FOR UKRAINE

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ABSTRACT — The paper is focused on the problems of the management system transformation in the field of dental health service under the conditions of power decentralization and reforming of the healthcare industry in Ukraine. Theoretical analysis of the main management functions under the conditions of existence of a centralized (Soviet), transitional (centralized with elements of market relations) and decentralized (European, professionally self-governing) models of dental health service to the general public is accomplished. The main differences between the decentralized dental health service management model in European countries and in Ukraine are identified. It is concluded that the transition from a centralized to a decentralized management model improves the quality of dental services and brings closer the living standards of the population of Ukraine to European standards.

KEYWORDS — transformation, managerial functions, dental health service management models, European guidelines, medical self-government, Ukraine.

INTRODUCTION

Nowadays the social sphere produces the majority of socially significant services. This ensures that the social sphere is actively turning into a productive sector of economic activity, which significantly affects the economical development of a city, region and country as a whole [2, 7, 8, 11]. One of the powerful components of the social sphere is the healthcare system and its component — dental health service.

The problem of oral prophylaxis over the past few years has proved to be an extremely urgent problem for national governments, which in its scale and consequences already goes beyond a purely sectoral one, that is, medical problem [10, 13].

In Ukraine, about 43 million visits are made annually for dental health service. At the same time, every second Ukrainian needs full mouth debridement [4]. Therefore, vital scientific mission is the study of problems of the management system transformation in the field of dental health service under the conditions of power decentralization and reforming of the healthcare industry in Ukraine.

METHODOLOGY, MATERIALS AND RESEARCH METHODS

To achieve the objectives of the study, a desk research was conducted, during which information on management functions in the field of dental health service in Ukraine was analyzed. The study used methods of scientific analysis and synthesis, observation, comparison, academic and historical retrospective, content analysis, etc.

MAIN CONTENT OF THE STUDY AND ANALYSIS OF THE RESULTS

The WHO global program in the sphere of public health is inextricably connected with dental health protection and is on a par with other priorities of the healthcare industry as a binding component of national programs for the prevention of chronic diseases and health promotion [1, 13].

The cost of dental health service has always been high, but earlier the state defrayed major portion of these expenses. The experience of solving this problem in other countries shows that the greatest results can be achieved through timely implementation of targeted preventive measures organized at the state level at the expense of special-purpose financing from the central and local budgets [1, 6]. Unfortunately, during the existence of independent Ukraine, only one national program for dental disorders prevention was adopted [9].

It has been established that in the EU countries healthcare personnel for the dental service is trained mainly in state-run educational institutions (90%). Private educational institutions exist only in 9 European countries [5]. The share of private educational institutions for the training of dental specialists does not exceed 10% in the system of healthcare personnel training. Most educational institutions that educate future dentists are operated in Italy, Germany, Spain, France, Great Britain. According to the statistics of 2018, in Ukraine, training of dentists is carried out in 23 higher educational institutions [12], 4 institutions of which function as private ones (17% of the educational services market). The national indicators

specified in Table 1 confirm the fact that the adoption of nation-wide program for the prophylaxis and treatment of dental disorders provided an impetus for development of a system of private higher medical educational institutions with a view to train dentists in Ukraine [9].

Table 1. *Ratio of public and private dental educational institutions in the EU*

Name	Public institutions for training of dentists, pcs.	Private institutions for training of dentists, pcs.	Share of private educational institutions, %
Ukraine	19	4	17
EU countries	199	19	9

An example to follow for Ukraine is the advisory board of the Council of European Dentists (CED), which functions as part of the Council of Europe. The main mission of CED is to provide counselling to the Council of Europe on the problems of dentistry and to develop unified policy principles in this field [3]. In addition, this organization implements the principles of public administration in the protection of dental health, performing both general managerial functions (organization, control) and special functions (Table 2).

Table 2. *Characteristics of management models in dentistry*

Comparison criterion	Management models in the field of dental health		
	Centralized, USSR	Decentralized, Ukraine	Decentralized, EU countries
Legislative framework for dental health protection	absent	Absent (1 bill draft developed)	There is a special law governing social relations in the field of dentistry
Dental self-government body	absent	Coordination Council at the branch ministry was established	The Council of European Dentists functions as a part of the Council of Europe, in Poland the Council of Dentists functions as a part of the medical union
Managerial functions in the field of dental health	Planning, organization, motivation, control	Additionally: - advisory support (counselling); - delegation of specialists abroad for the purpose of internship work; - contracting of foreign specialists; - coordination of activities of specialized institutions and institutions of all forms of ownership; - communication;	Additionally: - advocacy – protection of the rights of patients and specialists; - evaluation of legislative projects on dental health risk; - legislative initiative of the Council of Dentists in the Council of Europe; - dental health monitoring

In the dental field, reforms in the age of power decentralization take place according to several scenarios: full integration (consolidation of dental institutions in one powerful institution — Kyiv, Poltava, Odessa), partial integration (at the level of the regional center there is a municipal joint dentistry), model of municipal noncommercial enterprises (Zaporizhia, Kharkiv) and reorganization model of a regional dental clinic into a regional social dental clinic with budget financing of services for the attached controlled contingent (Dnipro regional dental clinic, servicing of fighters and participants of anti-terrorist operation).

Among the main factors of the teeth's health service reorganization, contributing to the enlargement of dental clinics, it is possible to name such groups: economical (increase in maintenance expenditures and decrease in business solvency of dental public institutions), medical and social (inability to provide dental services at a competitive level with private institutions) and social-psychological (improving the corporate culture, the level of motivation to learn new technologies, etc.).

Under the conditions of power decentralization and reform of the healthcare industry, the municipal institution "Dnipropetrovsk Regional Dental Clinic" is a unique management entity, economical model of which is based on the principles of internal and external integration.

Special characteristics of internal integration include the principle of district servicing the attached contingent (I level of health care delivery), provision of specialized services in the direction of other medical institutions, including from rural areas of the region (II level of specialized medical care delivery) and provision of III level highly specialized medical services (dental surgeries with the use of general anesthesia of procedures).

Special characteristics of external integration and building of a new market-focused model include

functions on the provision of dental services of highly specialized and high-technology content. Among them it is important to note the implementation of the function of clinical base of higher educational healthcare institutions (support of scientific studies of specialized departments of State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" and TOV "Dnipro Medical Institute of Traditional and Non Traditional Medicine"), as well as base for work experience internship of students, medical colleges and secondary medical schools, training of internship doctors; skills enhancement of doctors and middle grade medical staff (at workplaces) of rural and urban medical and preventive treatment facilities; entrepreneurial function — provision of paid services in the manner and extent established by applicable law; function of delegating specialists abroad for the purpose of internship work and contracting foreign specialists in a health care institution with the view of dental practice, in accordance with the applicable legislation of Ukraine.

CONCLUSIONS

According to the study conducted, the dental health service management system in Ukraine has undergone significant transformations. In the age of a centralized dental health service management model, the functions were focused on the organization of the main activities of the dental public institutions within the subordinate territory, as well as planning, motivation and control were carried out. With the introduction of the principles of a decentralized teeth's health service management model, the range of managerial functions has significantly expanded, in particular, there have appeared consultative support for the industry reforming; regulatory support for the teeth's health service development through the preparation and implementation of regional dental health service programs; coordination of the activities of specialized institutions and institutions of all forms of ownership that provide dental health service to the general public; as well as monitoring, communication, evaluation, entrepreneurship, contracting of foreign specialists, delegating of specialists abroad for the purpose of internship work, function of clinical base of higher educational healthcare institutions and science platform for experience exchange and scientific studies.

The primary result of the transition from a centralized management model to a decentralized European one is an improvement in the quality of servicing the patients and the approaching of the Ukrainians' living standards to European standards.

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Contributors:

IKh designed the study and analysed and interpreted data. IKh and YeB interpreted and analysed the data. VS did the literature review, collected data and made the figures. IKh, YeB and VS prepared the manuscript for submission.

Declaration of interests

We declare no competing interests

REFERENCES

1. Analysis of medico-economic efficiency of dental care provided by health insurance program/ J. Zurnadjants, I. Kashkarova, D. Shapovalova, L. Gobejishvili// Archiv EuroMedica, 2018. 2018; Vol. 8; 1: https://doi.org/10.35630/2199-885X/2018/8/1/9
2. **Carson, M. (2009).** Paradigms in Public Policy: Theory and Practice of Paradigms Shifts in the EU. Frankfurt/Oxford/New York: Peter Lang.
3. Council of European Dentists: https://www.eudental.eu/about/board-of-directors.html
4. **Hordyenko, S. (2018).** Problems and development strategies of dental care in Ukraine: http://health-ua.com/article/37268-problemy-istrategii-razvitiya-stomatologicheskoj-pomoshi-vukraine
5. International comparative analysis of model of studies of doctors of dentists in the context of communication for Poland:: http://www.comdent.co/wordpress/wp-content/uploads/2016/07/Miedzynarodowa-analiza...-poszerzony-rozdzial-dotyczacy-Polski.pdf
6. **Khozhylo, I. (2015).** Mechanisms of state management in health reform : Polish experience for Ukraine. URL: http://www.doktoranci.uj.edu.pl/documents/1167150/5184220c-78bc-4761-8aee-50f6ced18239#page=21.
7. Organisation for Economic Co-operation and Development: URL://www.oecd.org/health/
8. **Parsons, T. (1951).** The Social System. Glencoe, IL: Free Press.
9. Dental Disease Prevention and Treatment Program for 2002-2007:URL: https://ips.ligazakon.net/document/view/u475_02?an=&ed=2002_05_21&dtm=
10. Tokiiska deklaratsiia stomatolohichnoi dopomohy ta hihiieny porozhnyny rota dlia zdorovoho dovholittia: URL: http://www.who.int/oral_health/en
11. **Tsaruk, I. (2009).** Theoretical approaches in determination the social sphere as component economy and its functions: URL: http://www.nbuv.gov.ua/ejournals/eui/2009_1/09 cimtyf.pdf
12. Higher educational institutions of Ukraine: URL: http://ru.osvita.ua/vnz/guide/search-17-0-0-282-0.html
13. World Health Organization 2003: URL: https://www.who.int/oral_health/media/en/orh_report03_en.pdf

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PREVENTION OF LYMPHATIC FILARIASIS THROUGH MASS DRUG ADMINISTRATION PROGRAM: MAJOR HINDRANCES TO ITS EFFECTIVENESS IN ENDEMIC AREAS IN THE WESTERN REGION OF GHANA

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ABSTRACT — Lymphatic Filariasis is one of the five main neglected diseases that affect poor communities in Ghana and actually the only neglected disease that is still endemic in certain areas(hotspots) in the western region of Ghana after many years. Mass drug administration with ivermectin and albendazole has been the main preventive means to eradicate the disease. This study is focused on identifying the reasons for the endemicity and more especially lapses in the mass drug administration that affect the effectiveness of the program. The Ahanta west municipal assembly was the focus of the study of which several lapses with regards to the mass drug administration were identified and recommendations made for correcting these lapses that will make the program effective thereby helping in reducing if not eradicating the disease in this area.

KEYWORDS — Mass drug administration, hotspots, Lymphatic filariasis, Ivermectin, Albendazole.

INTRODUCTION

Lymphatic filariasis is a debilitating disease caused by the filarial worm *Wuchereria bancrofti*. It is earmarked for elimination by the year 2020 through the Global Program for the Elimination of LF (Lymphatic Filariasis). Mass drug administration has been on-going since the year 2000 as a way of preventing and controlling the disease. Lymphatic Filariasis has been in existence in Ghana for many years with many projects taking place to help eradicate them but till now there are still places endemic areas in Ghana.

The major focus of this work is to find ways of making mass drug administration more effective in endemic areas in the western region. Mass Drug Administration with Ivermectin and Albendazole for treatment of LF in Ghana started in 2000 with 5 districts and gradually scaled up to include all LF endemic districts in 2004. Ninety-eight out of 216 districts in Ghana were identified as endemic for LF in 8 out of the 10 regions in the country. Significant progress has been made so far with LF treatment; a total of 83 out of 98 endemic districts would have stopped treatment by the end of 2017 leaving 15 districts expected to continue treatment in 2018.There are currently three districts in the western region endemic to lymphatic filariasis.

There are three different filarial species that can cause lymphatic filariasis in humans but in Ghana it is caused mainly by *Wuchereria bancrofti*.

The infection spreads from person to person by mosquito bites. The adult worm lives in the human lymph vessels, mates, and produces millions of microscopic worms, also known as microfilariae. Microfilariae grow and develop in the mosquito. When the mosquito bites another person, the larval worms pass from the mosquito into the human skin, and travel to the lymph vessels. They grow into adult worms, a process that takes 6 months or more. An adult worm lives for about 5–7 years. The adult worms mate and release millions of microfilariae into the blood. People with microfilariae in their blood can serve as a source of infection to others. In Ghana, the most common vector is Anopheles mosquito. Many mosquito bites over several months to years are needed to get lymphatic filariasis which is possible in areas of poor sanitation which breeds mosquitoes.

Purpose of the study

The aim of this paper is to find out the reasons behind the endemicity despite the various efforts with the use of mass drug administration in these areas of the western region of Ghana.

MATERIAL AND METHOD

Analysis of data from District health directorate (Ahanta west district) 2014–2018, Data from End Neglected tropical diseases in Africa, annual work plan October 2017–september 2018.World Health organization (annual report 2000–2017), Ministry of health Ghana annual report 1998–2017, Ghana neglected tropical diseases program (5-year strategic plan — 2013–2017).

RESULT AND DISCUSSION

Analysis index of main neglected tropical diseases in Ghana which include the following:

Agona sub district:

year	Total population	Total number treated	Total population coverage-%	Non-eligible	refused	Absent
2014	27299	21791	79.82	610	367	2646
2015	26088	20814	79.88%	324	552	2016
2016	24441	21060	86,2	1189	738	1430
2017	30209	25858	85,6	2278	622	1451

** Non eligible comprises of 1.Severely sick 2.Pregnant women 3.under height 4.Breast feeding mothers and children under 1 week.*

The total number of people who refused and absent were 3013 representing 11% of the population in 2014, if 2015 it was 2568 representing 9,8% of the population, in 2016,238 representing 4,8% of the population. In 2017 it was 6,9% of the population, that is 2073.This indicate how part of the population miss out on the mass drug administration program. The absentees were due to the timing of the administration of the program, the education before the program and the value the people place on the program. The refusal mostly is due to religious belief and myth about the drug of which the religious leaders should be educated and used to inform their people. These will ensure total coverage which will lead to prevention of these diseases and reduce the endemicity.

CONCLUSION

To ensure the effectiveness of the mass drug administration program in these endemic areas and thereby eradicating the disease, the anomalies specified above should be corrected.

REFERENCES

1. **Hotez PJ, Kamath A (2009). Cappello, Michael, ed.** Neglected Tropical Diseases in Sub-Saharan Africa.
2. World Health Organization. Geneva: WHO; 2013. Lymphatic Filariasis: Fact sheet No 10. [Google Scholar]
3. https://endinafrica.org/wp-content/uploads/2018/04/Ghana-FY18-Workplan-Final.pdf
4. Annual Report Ghana health Service 2000–2017

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EVALUATION OF SOCIAL MEDIA SURVEILLANCE FOR IMPROVED DISEASE RECOGNITION AND MONITORING IN SRI LANKA

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ABSTRACT — The aim of this research is to develop an understanding of the effectiveness and potential of new communication media such as social media and mobile technology as tools for sending and receiving health messages along with providing insights into the use of new technology in the dissemination of health messages. Methods- a questionnaire was developed as a google form to gather information from Sri Lankans under five age groups. Special attention was paid to public opinion regarding the relationship between social media and healthcare. The research team collected information from general public regarding the actual usage of social media for healthcare. Results- responses for the questionnaire were studied and presented in the form of tables. According to results, the majority of people came across health education-related messages on social media platforms. In conclusion, there is a low tendency of using popular media for healthcare purposes in several areas of Sri Lanka which can be developed in the future productively and effectively with the help of the government. Some of the latest methodologies of media usage are to be introduced in healthcare sectors for the better performance of service.

KEYWORDS — Sri Lanka, Social Media, Communication, Healthcare, Patients, Healthcare professionals, Telemedicine, Dengue, HIV/AIDS.

INTRODUCTION

Traditional media and the internet are crucial sources of health information. Media can significantly shape public opinion, knowledge, and understanding of emerging and endemic health threats. Recently, however, public health surveillance has expanded to included social media information. Many people use social media, to communicate with others about the same health concerns and share information related to their illnesses, medication use, and many other aspects. As digital communication rapidly progresses in Sri Lanka, local access and dissemination of health information contribute significantly to global disease detection and reporting. The general public sees social media as efficient and accessible, but health care has been slow to embrace this advance in communication [3]. Therefore, a pressing issue for public health institutions is to determine how to strategically get health information across to its target audience. One such important strategic decision is the choice of communication media used to send out health information [2]. In terms of benefits, social media has provided healthcare professionals with a way to overcome barriers in delivering healthcare to patients, has enhanced self-management skills among patients who can familiarize themselves with specific illnesses and also provides numerous opportunities for providers to research in their relevant fields. Some clinicians have suggested that social media is among the best ways to design, collect, and analyze data into scientific papers for academic journals [4].

METHODS

According to recent statistics, internet usage in Sri Lanka has experienced rapid growth. It signifies 6.9 million of the community, among them 6 million are active social media users (Digital Sri Lanka 2019). Health messaging is an area that has been relatively ignored in the literature and almost no research focuses on the effectiveness of social media and other new technologies as tools for sending health messages [2]. Regarding this matter, decisions were made to carry on research on the usage of social media for healthcare communication. Several media platforms have been analyzed including social media forums and government web sites to surveillance access to health information and disease detection. The health assessment questionnaire form was created and distributed randomly among Sri Lankan citizens respectively. This questionnaire consists of four main parts: Biographic data (2 questions), Health promotion and mass communication media (5 questions), Social media (4 questions) and Health promotion (4 questions). Collected data has been thoroughly processed and presented. Sri Lanka community has been divided into four groups based on their needs to use social media regarding healthcare. They are the general public, patients,

healthcare professionals, and healthcare organizations significantly. The questionnaire was focused on gathering information about the usage of social media platforms to access health information and to evaluate the reachability of the general public to healthcare information.

RESULTS

Only Sri Lankan citizens were invited to the survey. It was found that more than half of the respondents (52.3%) are people from 15 to 25 years old and almost 82% — from 15 to 35 years old. The vast majority of respondents own a mobile phone (97.7%), a computer (56.3%) and a tablet (25.3%). Most of the respondents (88.6%), are subscribed to social networks (Facebook, Whatsapp, etc.). Among the respondents, Whatsapp uses 79.3%, Facebook — 73.6%, Instagram — 65.5%, Twitter — 10.3%. From this, it is clear that the questionnaire is available only to those Sri Lankans who use their electronic devices. 77.3% of respondents admitted that they had previously seen messages related to health education and medical information on their social networks, and 35.6% heard about telemedicine. Among the respondents, the majority (86.4%) had previously heard about health education. The leading information resources providing the population with information related to disease prevention, include television (78.2%), the Internet (59.8%) and social networks Facebook (59.8%). Unfortunately, in only a quarter of cases (25.3%) medical workers act as providers of health education (Fig. 1).

Least of all, Twitter (5.7%) provided health information. According to respondents, the most effective resources among them there are Facebook (37.5%), television (29.5%) and Internet recourses (22.7%). Youtube holds an intermediate position (4.5%). The effectiveness of leaflets, newspapers, and health workers as a source of sanitary information is rated low (1.1%, 2.3%, 2.3%, respectively).

As you can see, the main issue of health education that came upon in the population of Sri Lanka is Dengue - a disease that has taken in epidemic form and was noted by 88.6% of respondents. The top three health issues highlighted by health education also included HIV/AIDS (69.3%) and drug abuse (56.8%) (Fig. 2).

DISCUSSION

In conclusion, traditional disease surveillance systems are reliant on health data from a hospital or public health department records to detect and monitor disease across populations. Recently public health surveillance has expanded to include digital information. Digital disease surveillance involves the collection of health-related information from web-based or mobile telephone sources to better understand the distribution, incidence, or risk factors associated with a disease. The major benefits of using digital disease detection methods include the rapid acquisition and dissemination of real-time or near real-time information and the ability to significantly expand the quantity of information not easily gained through more traditional methods of disease surveillance through official records. With the increase in the availability of information, changes in the way people communicate and a general increase in concerns about one's health, new technologies are influencing and will continue to influence the healthcare sector. For this reason, further investigation needs to be conducted to assess the real impact of social media on the healthcare decisions taken by both healthcare professionals and patients in Sri Lanka.

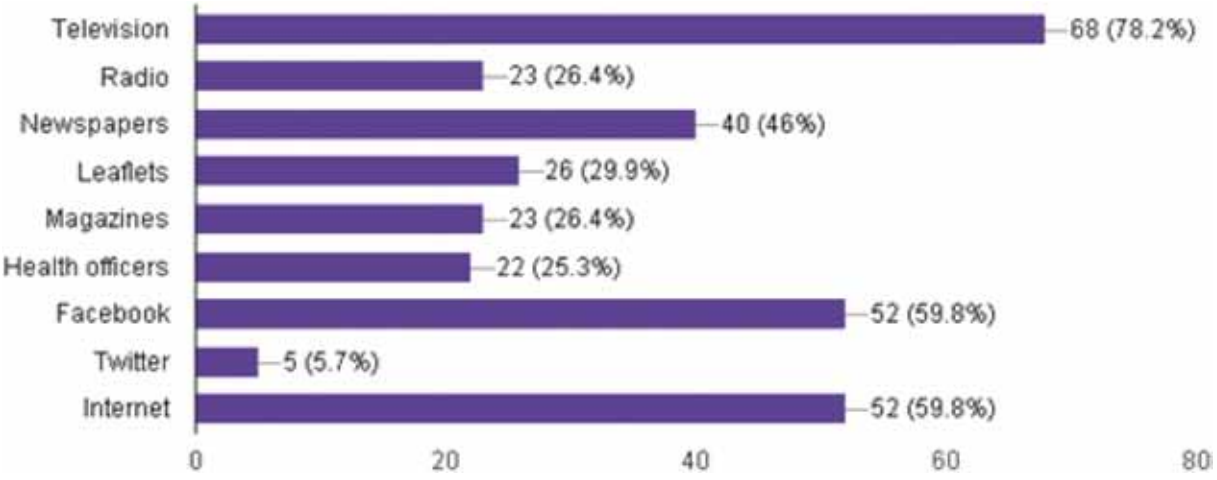

Fig. 1. *Media rating as a source of public health education in Sri Lanka*

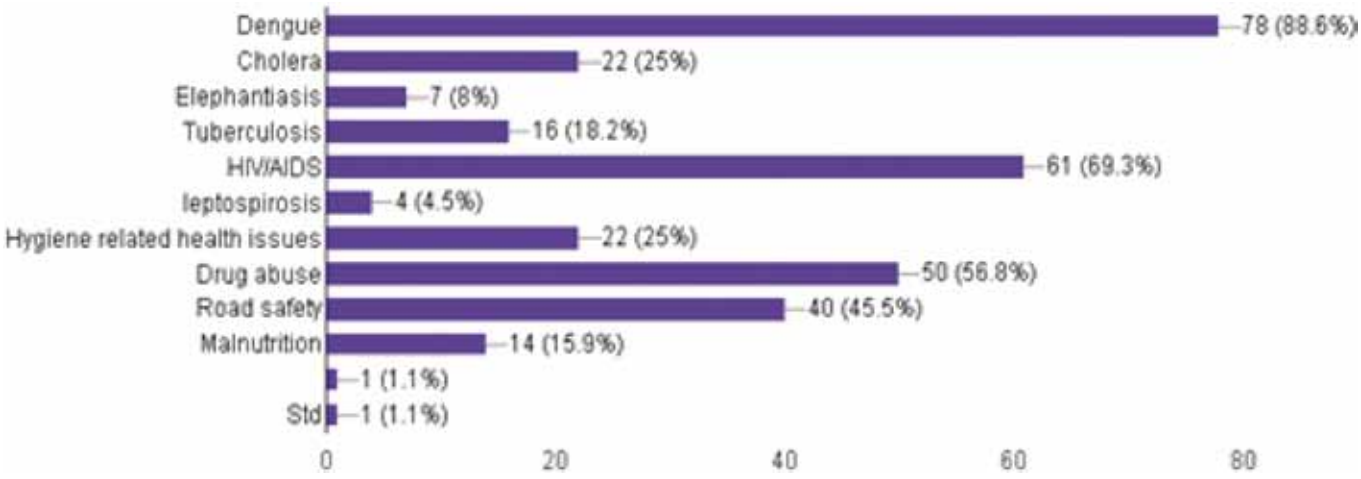

Fig. 2. *Leading health education advertisement issues for Sri Lanka*

REFERENCES

1. **Alma Pentescua, Iuliana Cetina, Gheorghe Orzanb** (2015, November 02). "Social Media's Impact on Healthcare services". Procedia Economics and Finance, 2015, 27, 646–651.
2. **Richard Bannor, Anthony Kwame Asare, Justice Nyigmah Bawole,** (2017) "Effectiveness of social media for communicating health messages in Ghana", Health Education, Vol. 117 Issue: 4, DOI: 10.1108/HE-06-2016-0024.
3. **Shashi Pratap Singh, Dr. A.K. Rai, Ankita-Wal, Dr.Gaurav Tiwari, Ruchi Tiwari, Asfa Parveen** (2016) "Effect of social media in health care: uses, risks, and barriers", World journal of pharmacy and pharmaceutical sciences. V. 5, Issue 7, 282–303.
4. **Surani, Z., Hirani, R., Elias, A., Quisenberry, L., Varon, J., Surani, S., Surani, S.** (2017, November 29). Social media usage among health care providers.
5. **Ventola, C. L.** (2014, July). Social media and health care professionals: benefits, risks, and best practices.
6. **Smailhodzic, E., Hooijsma, W., Boonstra, A., & Langley, D. J.** (2016). Social media use in healthcare: A systematic review of effects on patients and on their relationship with healthcare professionals. BMC Health Services Research, 16(442), [442].
7. **Publishing House "Scientific Survey".** (2018). The Sanitary And Hygienic Problems Caused By Quality Of Fresh Water In Sri Lanka And Available Measures Of Prophylaxis. Medicus International Medical Journal (Vol. no 1 (19). Volgograd, Russia. Retrieved from http://scimedicus.ru/d/medicus_no_1_19_january.pdf

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STRUCTURAL TRANSFORMATIONS OF PIRIFORM NEURONS IN DIFFERENT AREAS OF THE HUMAN CEREBELLAR CORTEX FROM BIRTH TO 6 YEARS

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ABSTRACT — The article is devoted to the study of age-related changes in the size of piriform neurons (Purkinje cells) of the human cerebellum. Histological material has been obtained from 36 males aged from birth to 6 years who died as a result of injuries without brain damage. The material was grouped in annual intervals. Measurements of the area of piriform neurons were made in the posterior part of the anterior quadrangular lobule (H V), posterior quadrangular lobule (H VI) and paramedian lobule (H VII B). For this purpose, we used virtual images of sagittal paraffin sections of the cerebellar cortex 10 microns thick, stained with cresyl violet on Nissl. Average value, standard error and confidence interval were calculated for measurable indicators of different age groups. It has been established that in the course of postnatal ontogenesis an intensive increase in the size of piriform neurons is observed in the period from birth to 2–3 years, as well as in the anterior lobe of the cerebellum to 5 years, in the posterior lobe of cerebellum - mainly to 6 years. Left-hand asymmetry of mean group sizes of piriform neurons is observed in children aged from 1 to 5 years, including in the lateral zone H V — during the 1st and 2nd years of life, H VI — during the 1st and 5th years of life, H VII B — during the period from 2 to 4 years.

KEYWORDS — human cerebellar cortex, piriform neurons, morphometry, postnatal ontogenesis.

INTRODUCTION

The cerebellar cortex is an important component of distributed neural networks that control the most complex forms of behavior [5]. The problem of obtaining objective data on the terms and rates of postnatal structural transformations occurring in the cerebellar cortex, as well as on the stages of growth and asymmetry of the microstructural organization of the cortex in the right and left hemispheres of cerebellum is relevant [12]. Of particular interest are data on the lobule of H V, the damage to which is associated with cerebellar motor syndrome [10], as well as H VI of the posterior lobe of cerebellum, which is related to bimanual coordination control [2], planning, and preparation of arbitrary movements [1]. In addition, the structural and functional features of H VI and H.VII B lobules are currently being actively studied in connection with data on their activation in performing cognitive tasks and implementing a wide range of non-motor functions [11].

OBJECTIVE

The aim of this work was to study age-related changes and interhemispheric asymmetry of piriform neurons (Purkinje cells) in functionally different areas of cerebellar cortex in children.

MATERIALS AND METHODS

A total of 36 male cerebellums of people aged from birth to 6 years who died from injuries unrelated to brain damage were studied. Collection of sectional material was authorized by the Ethical Commission of the Institute of Developmental Physiology of the Russian Academy of Education (Protocol No. 3 of 23.05.1996) and was carried out in the forensic mortuaries of Moscow and Moscow region. The material was grouped in annual intervals. Pieces of cerebellar cortex were taken for histological research from the posterior part of anterior quadrangular lobule (H V), posterior quadrangular lobule (H VI) and paramedian lobule (H VII B), recorded in 10% neutral formalin, dehydrated in ascending alcohols and poured into paraffin. On sagittal slices of 10 microns thick, painted with cresyl violet (Nissl`s staining), by computer morphometry using Image Tools technology (National Institutes of Health, USA) and the ImageExpert™ Gauge (NEXSYS, Russia) geometric measurement programs measured the area of piriform neurons' profile fields (APN) in the histological cut plane at the apex and lateral wall of the folium of cerebellum. The sample size for each section was not less than 10, for each histological preparation — not less than 40, for each age — not less than 120 measurements. For indicators of different age groups, the mean value, the error of the mean and confidence intervals [9] with the level of significance P=95% ($p<0.05$) were calculated.

RESULTS

In newborns, APN was 63.8±2.2 μm² in the anterior quadrangular lobule on the right (H VR) on average, and 40.1±0.7 μm² in the same lobule on the left (H.VL). By the time of birth, significant differences in the individual mean group sizes of piriform neurons in the anterior lobe of the cerebellum on our material were observed in 75% of cases. At the same time, the size of piriform neurons on the right was 1.5–1.7 times larger on average than on the left. APN in the anterior quadrangular lobule of both right and left increased by the end of the first year of life, by 2 and 5 years (Fig. 1). In the H VR area, the size of piriform neurons was 1.8 times larger at 1 year, 2.1 times larger at 2 years and 3.0 times larger at 5 years compared to newborns. The growth rate of piriform neurons in the H VL area from birth to 6 years was higher than that of H VR. In the H VL region, the area of piriform neurons on the slice was 3.5 times larger et 1 year, 4.0 times larger at 2 years and 4.6 times larger at 5 years compared to newborns. Right-sided APN asymmetry, which was observed in the anterior lobe of neonatal cerebellum, was replaced by marked left-sided asymmetry in children aged 1-2 years. At this age range, the piriform neurons on the left were 1.2 larger than on the right. After 2 years, no asymmetry was observed in the anterior quadrangular lobule of piriform neurons in terms of both mean group and individual dimensional parameters. By the age of 6 years, the area of piriform neurons in the anterior quadrangular lobule of the cerebellum was 182.2±6.1 μm² on the average on the right, and 175.3±4.7 μm² on the left.

In the posterior quadrangular lobule of newborns, APN was 59.8±0.5 μm² on the average right (H VIR) and 39.8±1.0 μm² on the left (H VIL).As in the anterior cerebellar lobe, 75% of newborns had piriform neurons in the posterior quadrangular lobule of the right cerebellar hemisphere, on average, 1.5 times larger than in the left hemisphere. The area of piriform neurons in the posterior quadrangular lobule on the right increased to 1, 2 and 6 years, and on the left — to 1, 2 and 5 years (Fig. 2). In the area of H VIR, the size of piriform neurons was 1.9 times larger at 1 year, 2.6 times larger at 2 years and 3.1 times larger at 6 years compared to newborns. In the region of H VIL, the area of piriform neurons was 3.4 times larger by 1 year, 4.0 times larger by 2 years and 4.6 times larger by 5 years than that of newborns. During the first and fifth years of life, left-sided asymmetry of mean group and individual piriform neuronal dimensions in the posterior quadrangular lobule was observed: APN on the left was 1.2 times greater than on the right. By 6 years of age, no interhemispheric differences in the dimensions of piriform neurons in the posterior quadrangular lobule were observed. APN was on average 185.4±5.4 μm² in the H VIR region and 186.1±4.6 μm² in H VIL.

In the paramedian lobule in newborns, APN was 41.3±1.5 μm² on the right side average (H VII BR) and 40.5±0.9 μm² on the left side (H VII BL). APN in the paramedian lobule on the right increased to 1, 2 and 6 years, on the left to 1, 2, 3 and 6 years (Fig. 3). In the H VII BR region, piriform neurons were 2.7 times larger than newborns by 1 year, 3.3 times larger than newborns by 2 years and 4.6 times larger than newborns by 6 years. In the H VII BL region, APN was 3.1 times bigger by the end of 1 year, 3.9 times bigger by the end of 2 years, 4.3 times bigger by the end of 3 years, and 4.6 times bigger by the end of 6 years compared to newborns. At the age of 2 to 4 years in the paramedian lobule cortex, the piriform neurons on the left were 1.2 larger than on the right. After 4 years, no asymmetry was observed in the paramedian lobule of piriform neurons in terms of both mean group and individual dimensional parameters. By 6 years of age, APN in the paramedian lobule cortex of children was 189.9±3.9 μm² on the average on the right and 188.1±4.2 μm² on the left.

DISCUSSION

The conducted research allowed to establish that during postnatal ontogenesis intensive growth of piriform neurons in the cerebellar cortex of children is observed in the period from birth to 2–3 years, as well as in the anterior lobe of the cerebellum to 5 years, in the posterior lobe - mainly to 6 years. Newborns have lateral right-sided asymmetry in the middle group and individual dimensional parameters of piriform neurons in the anterior and posterior quadrangular lobules of the cerebellum. Later, left-handed APN asymmetry is observed in children aged 1–5 years, including in the anterior quadrangular lobule - during the 1st and 2nd years of life, in the posterior quadrangular lobule — during the 1st and 5th years of life, in the paramedian lobule — during the period from 2 to 4 years. It is interesting that the data on left-hand asymmetry of morphometric parameters of piriform neurons in H VI are consistent with the data on the functional dominance of this lobule in both men and women obtained during the study of neural networks with the participation of the cerebellum [8]. In our opinion, the interhemispheric asymmetry of piriform neuronal parameters of the cerebellum is a consequence of uneven rates of their development. The heterochronic and heterodynamic character of growth and development of effector neurons of the cerebellar cortex is to a certain extent genetically programmed, and is also conditioned by a complex of direct and indirect interactions with other nerve centers, primarily with the

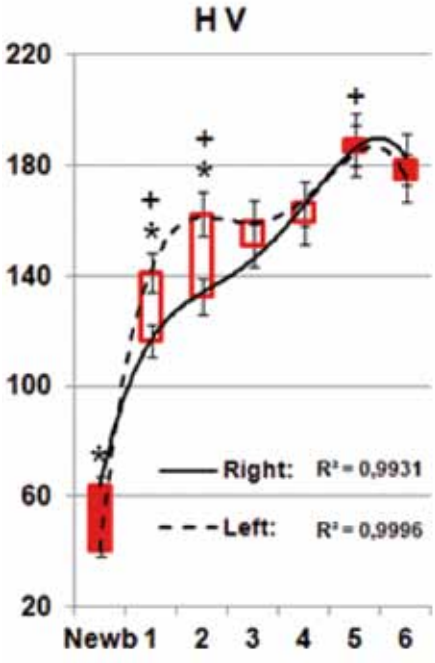

Fig. 1. Changes in the area of piriform neurons in the posterior part of anterior quadrangular lobule (H V) of the cerebellum in children from birth to 6 years of age

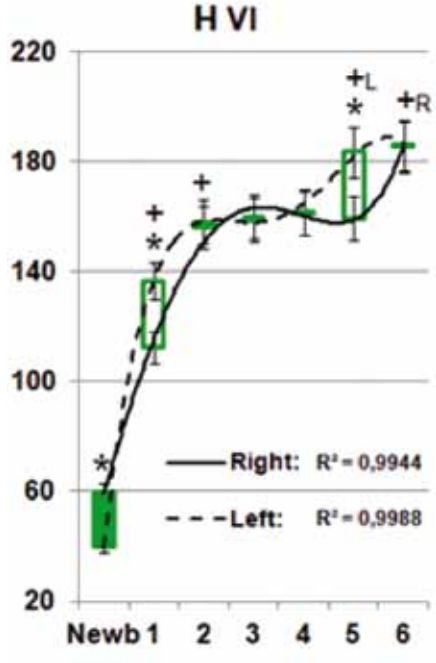

Fig. 2. Changes in the area of piriform neurons in the posterior quadrangular lobule (H VI) of the cerebellum in children from birth to 6 years of age

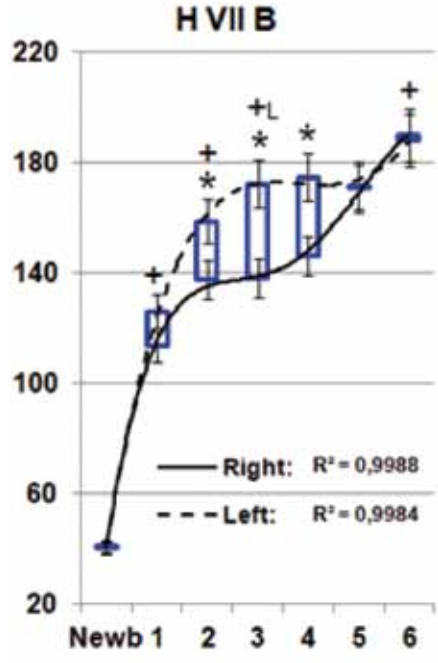

Fig. 3. Changes in the area of piriform neurons in the paramedian lobule (H VII B) of the cerebellum in children from birth to 6 years of age

Here and on Fig. 2 and 3: *on the x-axis — age in years, newb — newborns; on the y-axis — piriform neuron area in μm². The lines of approximation of average values are presented: right — right hemisphere, left — left hemisphere. R^2 indicates the level of significance of approximation. Light bars — increase of parameters on the left, dark bars — on the right. The vertical segments represent the error of the mean. * — significant interhemispheric differences, + — significant difference from the previous significant age indicator.*

Here and on Fig. 3: *+L — significant difference from the previous significant age indicator of the left hemisphere, +R — the same for the right hemisphere.*

cortex of large hemispheres, reticular nuclei of pons, basal nuclei, and subtalamic nuclei [3, 4, 6, 7]. The data we have obtained also suggest that ascending ontogenesis increases the role of H VI and H VII B cerebellar lobules in functional neural networks associated with cognitive activity and emotional control when planning complex motor tasks and behavior in general.

CONCLUSION

The results of the study suggest that postnatal growth of piriform neurons is heterochronous in functionally different areas of the cerebellar cortex. The analysis of the revealed age dynamics of dimensional parameters also allows to assume that at the early stages of postnatal development the growth and differentiation of piriform neurons in the left hemispheric lateral areas of lobules H.V, H VI and H VII B of the cerebellar cortex has a leading character in comparison with their counterlateral right hemispheric zones.

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REFERENCES

1. **BELKHIRIA C., MSSEDI E., HABAS C., DRISS T., DE MARCO G.** Collaboration of Cerebello-Rubral and Cerebello-Striatal Loops in a Motor Preparation Task. Cerebellum. 2018. doi: 10.1007/s12311-018-0980-z.
2. **BOISGONTIER M.P., CHEVAL B., VAN RUITENBEEK P., CUYPERS K., LEUNISSEN I., SUNAERT S., MEESEN R., ADAB H.Z., RENAUD O., SWINNEN S.P.** Cerebellar grey matter explains bimanual coordination performance in children and older adults. Neurobiology of Aging. 2018, pp.1-53. doi: 10.1016/j.neurobiolaging.2018.01.016.
3. **BOSTAN A.C., DUM R.P., STRICK P.L.** Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci. 2013. Vol. 17, N 5, pp. 241–254. doi:10.1016/j.tics.2013.03.003.
4. **CALIGIORE D., PEZZULO G., BALDASSARRE G., BOSTAN A.C., STRICK P.L., DOYA K., HELMICH R.C., DIRKX M., HOUK J., JÖRNTELL H., LAGO-RODRIGUEZ A., GALEA J.M.,**

MIALL R.C., POPA T., KISHORE A., VERSCHURE P.F., ZUCCA R., HERREROS I. Consensus Paper: Towards a Systems-Level View of Cerebellar Function: the Interplay Between Cerebellum, Basal Ganglia, and Cortex. Cerebellum. 2017. Vol. 16, pp. 203–229. DOI 10.1007/s12311-016-0763-3.

5. **KOZIOL L.F., BUDDING D., ANDREASEN N., D'ARRIGO S., BULGHERONI S., IMAMIZU H., ITO M., MANTO M., MARVEL C., PARKER K., PEZZULO G., RAMNANI N., RIVA D., SCHMAHMANN J., VANDERVERT L., YAMAZAKI T.** Consensus paper: the cerebellum's role in movement and cognition. Cerebellum. 2014. Vol. 13, N 1, pp. 151-177.
6. **PALESI F., TOURNIER J.D., CALAMANTE F., MUHLERT N., CASTELLAZZI G., CHARD D., D'ANGELO E., WHEELER-KINGSHOTT C.A.M.** Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. Brain Struct Funct. 2015. Vol. 220, pp. 3369–3384.
7. **PELZER E.A., HINTZEN A., GOLDAU M., VON CRAMON D.Y., TIMMERMANN L., TITTGEMEYER M.** Cerebellar networks with basal ganglia: feasibility for tracking cerebello-pallidal and subthalamo-cerebellar projections in the human brain. Eur J Neurosci. 2013. Vol. 38, N 8, pp. 3106–3114. doi: 10.1111/ejn.12314.
8. **PEZOULAS V.C., MICHALOPOULOS K., KLADOS M., MICHELOYANNIS S., BOURBAKIS N., ZERVAKIS M.** Functional connectivity analysis of cerebellum using spatially constrained spectral clustering. IEEE J Biomed Health Inform. 2018. doi: 10.1109/JBHI.2018.2868918.
9. **STEFANOV S.B., KUHARENKO N.S.** Uskorennye sposoby kolichestvennogo sravneniya morfologicheskih priznakov i system. [Accelerated methods of quantitative comparison of morphological features and systems]. Blagoveshchensk, VSKHI, 1989. 65 p. (In Russ.)
10. **STOODLEY C.J., SCHMAHMANN J.D.** Functional topography of the human cerebellum. In: M. Manto, T.A.G.M. Huisman (Eds.), Handbook of Clinical Neurology. Vol. 154 (3rd series). The Cerebellum: From Embryology to Diagnostic Investigations. Elsevier; 2018: 59–70. doi:10.1016/b978-0-444-63956-1.00004-7.
11. **STRICK P.L., DUM R.P., FIEZ J.A.** Cerebellum and nonmotor function. Annu Rev Neurosci. 2009. Vol. 32, pp. 413–434. doi:10.1146/annurev.neuro.31.060407.125606.
12. **TSEKHMISTRENKO T.A., KLOCHKOVA S.V., MAZLOEV A.B., NIKITYUK D.B., OBUKHOV D.K.** Changes in thickness of cortex and its layers in the posterior lobe of the cerebellum in postnatal ontogenesis. Journal of Anatomy and Histopathology. 2018. Vol. 7(4), pp. 88–93 (In Russ.). doi: 10.18499/2225-73572018-7-4-88-93.

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LYMPHOID ORGANS IN EXPERIMENTAL PROSTATE CARCINOGENESIS

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ABSTRACT — Histological methods were used to study structural changes in the thymus and pelvic lymph nodes of SVA mice on day 18 after transplantation of ascitic Ehrlich tumor into the prostate gland. On day 18 of the experiment, a complete replacement of normal tissue with atypical cells, disorganization of the thymus structure – an increase in the volume of cortical matter, the number of epithelial reticular cells, a decrease in the number of immunoblasts in the cortical and cerebral matter was found. In the lymph nodes, on day 18, metastases were determined, follicular reaction was detected, increased transport function, against the background of an increase in the number of lymph vessels in the prostate.

KEYWORDS — thymus, pelvic lymph nodes, prostate tumor.

INTRODUCTION

Carcinogenesis disrupts the stages of the immune response and its consistency. The thymus undergoes involution, t-cell immunodeficiency is formed. Generalization of carcinogenesis-metastasis of tumor cells into lymph nodes. The state of pelvic lymph nodes in prostate cancer is a significant factor in the prognosis of disease [1], and the detection of micrometastases in lymph nodes is the most important task in the stage of prostate cancer [2]. The study of the Central and peripheral organs of the lymphoid system during transplantation induction of carcinogenesis, reveals changes in their structure depending on the stage of carcinogenesis, the dynamics of metastasis in the lymphatic system, which will assess the effect of known and new anti-tumor drugs.

PURPOSE

Identification of structural transformations of the thymus and regional lymph nodes in various experimental prostate tumors.

MATERIALS AND METHODS

We used 60 Mature male SVA mice weighing up to 30 g (Institute of Cytology and genetics SB RAS, Novosibirsk). The experiment was performed according to "Rules of works using experimental animals", approved by order of Ministry of health of the USSR №577 of 12.08.1977, principles of humanity set out in European community Directive (86/609/EC).An experimental model of a malignant prostate tumor was created (under ether anesthesia) by inoculation of a diluted cell strain of ascitic Ehrlich carcinoma into the organ parenchyma: 0.2 ml of ascitic fluid containing $500–550 \cdot 10^3$ cells was injected. A tumor node was formed in the prostate from polymorphic atypical cells [3]. Experimental groups: 1) intact; 2) animals on the 18th day of experimental prostate tumor growth. Animals were removed from the experiment by dislocation of cervical vertebrae under ether anesthesia. For histological examination, the prostate, thymus, pelvic lymph nodes were taken, with fixation in Tellesnitsky's solution. From the material in paraffin, longitudinal slices (5 and 7 microns) were made, stained with hematoxylin-eosin according to Mayer and AzurII-EOSIN according to Nocht-Maksimov. At magnification of 16, 32, 200 and 1000 times the method of point counting was used to perform morphometry of sections and counting of cell elements of the above described organs according to International histological terminology. The results were processed by methods of variational statistics, determined the reliability of differences using the student's criterion. $P < 0.05$ was considered reliable.

RESULTS AND DISCUSSION

On the 18th day of tumor growth, complete replacement of prostate tissue with atypical polymorphic cells (tumor parenchyma — 82.3±0.6%, tumor stroma — 17.7±0.4%) of oval, elongated or polygonal shape with hyperchromic nuclei was revealed. Nuclear cytoplasmic cell index 1.66±0.08. In the thymus, cortical matter increased by 8%, the area of connective tissue structures — by 29%, glandular epithelial formations — by 2.8 times. Areas of brain matter decreased by 16% compared to the same value in the group of intact animals. The number of Gassal bodies and the size of glandular epithelial formations increased in comparison with the control values. In all areas of the thymus decreased the number of small lymphocytes, cells at the stage of mitosis, macrophages, immunoblasts, against the background of growth of epithelial reticular cells and medium lymphocytes, in comparison

with the control group. The exception was the corticomedullary zone, in which the number of immunoblasts increased (Table 1).

son with the control values, as well as the number of epithelial reticular cells. According to the literature, glandular epithelial formations of the thymus are

Tab. 1. *Relative sizes of structural and functional zones of the thymus in normal and experimental tumor growth in the prostate (M±m) (%)*

Structural and functional zones	Intact animals	18th day of experimental prostate tumor growth
Cortical substance	58,45±1,65	63,12±0,79*
Brain substance	34,76±1,37	29,15±0,41*
Cortical-brain index	1,68±0,05	2,16±0,03*
Connecting-woven elements	6,75±0,17	7,61±0,2*
Area of glandular formations	0,04±0,02	0,11±0,05
Parenchymal/stromal ratio	13,8±0,4	12,1±0,16*

** These differences are significant in comparison with control animals at P < 0.05.*

By the 18th day-in the marginal and cerebral sinuses of the pelvic lymph nodes, tumor metastases were detected — atypical large cells with pronounced polymorphism (stage II). In comparison with the control group, the area of the paracortical zone increased by 20%. The size of the brain cords decreased by 3%, the B-dependent zone — by 7%. The area of the brain sinuses-decreased by 9%. In germinative centers of lymphoid nodules, in comparison with those in the control group, the number of immunoblasts (from 7.68±0.36 to 11.65±0.54) increased by 35%, the number of macrophages increased by 28.5% (from 4.29±0.25 to 6.0±0.37). In the brain strands-there was an increase in average lymphocytes (from 6.55±0.27 to 21.18±0.79) by 3–4 times and a decrease in the number of Mature plasmocytes by 34% (from 44.17±0.81 to 28.26±0.91). The number of macrophages increased by 30% — from 3.46±0.21 to 4.89±0.32 (Table 2).

CONCLUSIONS

Malignant tumors produce substances that reduce or block the antitumor immune response [8]. By suppressing the local immune response, the tumor suppresses immune organs that reduce the production of immunocompetent cells or produce defective cytotoxic lymphocytes, which serve as a source of immunosuppressive T-reg cells [9, 10]. Thymus involution and disturbance of peripheral t-lymphocyte replenishment underlie the development of T-cell immunodeficiency in carcinogenesis [11]. Prostate tissue is completely replaced by atypical cells (18 days), with a decrease in blood vessels in the stroma of the tumor. In these terms of carcinogenesis in the thymus — the 2nd phase of accidental involution [13]. The relative area of glandular epithelial formations increases in comparifunctional structures that enhance the secretion of its hormones under extreme effects on the body [12]. The experimental data duplicate the data of other authors — the growth and formation of a malignant tumor leads to accidental involution of the thymus and is a consequence of antigenic stimulation [3], and immunosuppressive action of vascular endothelial growth factor (VEGF) [14]. When metastases appear in the marginal and cerebral sinuses of lymph nodes, the structural organization changes and their transport function is disturbed. In the cortical substance of lymph nodes, structural signs of inferiority of the local immune response were revealed — a decrease in the area of the paracortical (T-dependent) zone, an increase in the size of the B-dependent zone, a nodular reaction. In the brain substance of lymph nodes there is a reaction to metastasis — a reduction in the size of the brain sinuses, which is characteristic of the late stages of carcinogenesis.

REFERENCES

1. **Berezhnaya N.M., Chekhun V.F.** Immunology of malignant growth. /Kyiv: Naukova Dumka, - 2005.- 790 p.
2. **Alekseev B. Ya, Rusakov I. G, Frank G. A. et al.** determination of watchdog lymph nodes in patients with prostate cancer // Ross. onkol. Journ.- 2006. - No. 5. - P. 16-22.
3. **Harisinghani M.G., Barentsz J., Hahn P. F. et al.** Noninvasive detection of clinically occult lymph-node metastases in prostate cancer // New Engl. J. Med. – 2003. – Vol. 348. – №25. – P. 2491–2499. DOI: 10.1056/NEJMoa022749
4. **Astashov V. V., Lomshakov A. A., Larionov P. M., et al.** Lymph nodes and vessels in experimental tumors of the prostate // Vestnik NSU; ser. Biol. - 2011, – Vol. 9, – №2. – P. 118–125.

Tab. 2. *Structural components of pelvic lymph nodes of mice in normal and experimental prostate tumor (day 18) (M±m) (%)*

Structural components	Intact animals	18th day of experimental prostate tumor growth
Secondary lymphoid nodules	4,39±0,16	4,3±0,09
Germinative center	1,62±0,21	1,2±0,09
Mantle zone	2,77±0,17	3,1±0,16
Primary lymphoid nodules	3,6±0,2	1,82±0,15*
Interstitial zone	2,63±0,21	1,82±0,15*
Paracortical zone	19,5±0,47	27,23±1,55*
Brain cords	46,0±0,86	44,64±1,67
Brain sinuses	18,54±1,2	15,21±0,92
Edge sine	2,29±0,21	1,91±0,2
Capsule	2,87±0,21	2,45±0,18
Trabeculas	0,19±0,09	0,6±0,12
Cortical substance	30,1±0,83	35,18±0,8*
Brain substance	64,54±1,58	59,85±1,25
B-dependent zone	56,6±0,53	52,59±1,24
Cortical \ brain index	0,47±0,01	0,59±0,02

** These differences are significant in comparison with control animals at P < 0.05.*

5. **Lilly R.** Pathological technique and practical histochemistry. M.: World, 1969. – 646 p.
6. **Sarkisov D. S., Perov Yu. L.** Microscopic technique – 544 p.
7. **Lapach S. N., Chubenko, L. V., Babich P. N.** Statistical methods in biomedical studies using Excel. Kiev: MORION, 2001. – 408 p.
8. **Whiteside T.L.** The role of immune cells the tumor microenvironment // Cancer Treatm. Res. – 2006. – Vol. 130. – P. 103–124. DOI: 10.1007/0-387-26283-0_5
9. **Mailloux A.W., Young M.R.** Regulatory T-cell trafficking: from thymic development to tumor-induced immune suppression // Crit. Rev. Immunol. – 2010. – Vol. 30. – №5. – P. 435–447. PMID: 21083525
10. **Stewart T. J., Smyth M.J.** Improving cancer immunotherapy by targeting tumor-induced immune suppression // Cancer Metastasis Rev. – 2011. – Vol. 30. – №1. – P. 125–140. DOI:10.1007/s10555-011-9280-5
11. **Kiseleva E. P.** Mechanisms of thymus involution in tumor growth. // Uspekhi sovr. Biology. – 2004. – Vol. 124. – P. 589–601.
12. **Bodey B., Siegel S. E., Kaise H.E.** Immunological Aspects of Neoplasia – The Role of Thymus. /Dordrecht: Boston: Kluwer Acad. Publ., – 2004 – 207 p. DOI :10.1007/1-4020-2185-2
13. **Ivanovskaya T.E, Zaretians O. V., Leonova L. V., Voloshchuk I. N.** Pathology of the thymus in children. / SPb. SOTIS, – 1996 – 270 p.
14. **Ohm J.E., Gabrilovich D.I., Sempowski G.D. et al.** VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression // Blood. – 2003. – Vol. 101. – P. 4878–4886. DOI: 10.1182/blood-2002-07-1956
15. **Datta K., Muders M., Zhang H., Tindall D.J.** Mechanism of limph node metastasis in prostate cancer // Future Oncology. – 2010. – Vol. 6, – №5. – P. 823–836 DOI:10.2217/fon.10.33.

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ANTIHYPOXIC ACTIVITY OF PYRIMIDINE DERIVATIVE PIR-9 IN HYPOBARIC HYPOXIA IN MICE

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ABSTRACT — A study was conducted to assess the effect of a new pyrimidine derivative (PIR-9 50 mg/kg) on the resistance of mice to acute hypobaric hypoxia. It was confirmed that the studied compound PIR-9 contributes to an increase in the life time at the test site by 2,07 times ($p<0.05$) compared to the control group of animals and exceeds the strength of the effect of the reference drug Mexidol by 15,38% ($p<0,05$).

KEYWORDS — cerebral circulation, hypobaric hypoxia, pyrimidine derivatives, Mexidol.

INTRODUCTION

In the pathogenesis of almost all types of cerebrovascular disorders, hypoxia and its induced processes are an integral part of pathobiochemical reactions in conditions of oxygen deficiency [1]. The effectiveness of cerebroprotective agents is significantly affected by their ability to neutralize the consequences or mitigate the course of hypoxia [2]. Previously, the potential cerebroprotective activity of pyrimidine derivatives has been proved [3], and therefore it is interesting to study the antihypoxic effect of these derivatives as one of the possible mechanisms of anti-ischemic action.

Objective

To study the antihypoxic activity of pyrimidine derivative PIR-9 in hypobaric hypoxia in mice.

MATERIALS AND METHODS

The experiment was performed in accordance with the " Guidelines for preclinical studies of drugs, ed. A. N. Mironov (2012 Ed.) [4]. The study was conducted on 30 mongrel white mice (m=20–24 g). The animals were divided into 3 groups (n=10). The animals were kept in controlled vivarium conditions with natural light-dark regime change with free access to water and food. The first group — the control group, received a suspension of purified water with tween-80, the second group was administered the compound PIR-9 (50mg/kg) [5], the third — the comparison drug Mexidol (50 mg/kg) [6, 7]. All objects were injected intraperitoneal for an hour before the experiment. Acute hypobaric hypoxia was modeled by "lifting" mice in a hyperbaric chamber (h =11000 m, υ=100 m/s) [8, 9]. All findings were processed by means of variation statistics methods using the STATISTICA 6.0 software. The normality of distribution was assessed by the Shapiro-Wilk test. In the case of a normal distribution of the data, a parametric t-test was applied. In the case of abnormal distribution of the data, the statistical processing was performed using the Mann-Whitney U-test. The difference was considered significant at the significance level of more than 95% ($p<0,05$).

RESULTS

Testing for resistance of mice to acute hypobaric hypoxia showed that the average life expectancy of animals treated with intraperitoneal experimental substance PIR-9 was 104,3±2,61 seconds, which was 2,07 times ($p<0,05$) was statistically significantly higher than that of the control group (50,3±2,69 seconds). The life time at the "death site" in mice, which were administered the comparison drug Mexidol, was 90,4±3,22 seconds and 1,79 ($p<0.05$) times higher than the control group. At the same time, the life expectancy of PIR-9 animals exceeded the value of Mexidol group by 15,38% ($p<0,05$), which was statistically significant.

CONCLUSION

The use of a new pyrimidine derivative under laboratory code the PIR-9 (50 mg/kg) significantly increased the life expectancy of mice by 2,07 times compared to the control group and by 1,79 times compared to mice treated with Mexidol, which may indicate the antihypoxic effect of this compound, exceeding the comparison drug Mexidol at a dose of 50 mg/kg. Since the antihypoxic effect can be one of the mechanisms of cerebroprotective activity, this pyrimidine derivative is a promising object for further study and correction of ischemic brain damage.

REFERENCES:

1. **Evseeva M. A., Evseev, A.V., Pravdivtsev, V. A., Shabanov, P. D.** Mechanisms of acute hypoxia and

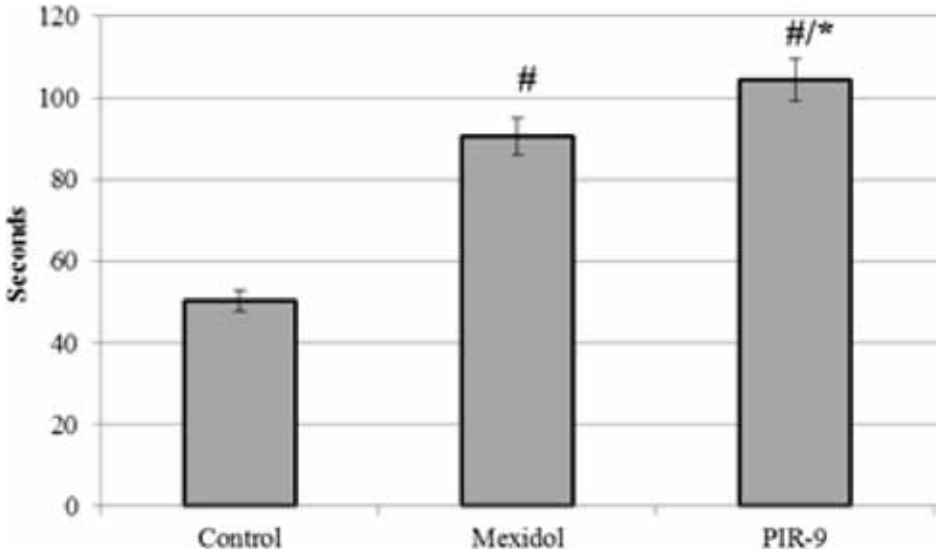

Fig. 1. *Assessment of the effect of PIR-9 compound and Mexidol on the lifespan of mice in hypobaric hypoxia*

Note: *Control — control group of mice, Mexidol — group of mice treated with Mexidol; PIR-9 — group of mice treated with PIR-9; # — statistically significant relative to the control group of mice (p<0,05); * — statistically significant relative to the group of mice treated with Mexidol (p<0,05).*

ways of its pharmacological correction / / Reviews of clinical pharmacology and drug therapy. – 2008. – Vol. 6. – №. 1 (In Russ.)

2. **Kurkin D. V., Volotova E. V., Litvinov A. A., Bakulin D. A., Ozerov, A. A.** Investigation of cerebroprotective and antihypoxic activity of γ-hydroxy and γ-aminobutyric acid derivatives //Siberian medical journal (Irkutsk). – 2012. – Vol. 111. – №. 4. – P. 107–109. (In Russ.)
3. **Voronkov A.V., Shabanova N.B., Kodonidi I.P., Shatalov I.S.** Cerebroprotective activity of new derivatives of pirimidine-4-(1H)-one PIR-9 and PIR-10 in irreversible occlusion of the common carotid artery. Pharmacy & Pharmacology. 2018;6(2):167–181. (In Russ.) DOI: 10.19163/2307-9266-2018-6-2-167-181
4. **Mironov A.N.** The guidelines for preclinical studies of pharmaceuticals. Part one. – M.: Grif and K, 2012. – 944 p. (In Russ.)
5. **Voronkov A.V., Shabanova N.B., Voronkova M.P., Lysenko T.A.** Study of cerebrotropic dose-dependent effect of pyrimidine derivative under pir-9 code against the background of experimental cerebral ischemia in rats.Pharmacy & Pharmacology. 2018;6(6):548–567. (In Russ.) DOI: 10.19163/2307-9266-2018-6-6-548-567
6. **Katunin, N. P., Gneushev I. M., Parfenov E. A.** Experimental study of the antihypoxic activity of new physiologically compatible antioxidants under the code πqна model of acute hypoxia with hypercapnia // Bulletin of Bryansk state University. – 2012. №. 4 (2). – P. 142–145. (In Russ.)
7. **Inchina, V. I., Korshunova, A. B., Prosvirkina, I. A., Semenov, A.V., Ulanova, T. V., Chairkin, I. N.** Comparative evaluation of some effects of z-hydroxypyridine and pyrimidine derivatives in experiment //Bulletin of new medical technologies. – 2010. – Vol. 17, - №. 3. – P. 158–160. (In Russ.)
8. **Pogorelov E. V., Makarova, L. M., Novikova, N. A., & Skacelova, S. Y.** the Study of the effectiveness of a derivative of taurine in experimental a hypobarium //pharmacy and pharmacology. – 2015. – Vol. 3. – №. 5s. – P. 82–83. (In Russ.)
9. **Odrinsky P. N.** Influence of Allim-2 on the life expectancy of mice in acute hypobaric hypoxia / / Nauka i sovremennost. – 2010. – №. 5–2. – P. 310–313. (In Russ.)

https://doi.org/10.35630/2199-885X/2019/9/3.7

PREMATURE AGING AND STRUCTURAL ORGANIZATION OF THE MESENTERIC LYMPH NODE

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ABSTRACT — The aim of the study was to estimate the structural organization of a mesenteric lymph node in comparative analysis at young rats of OXYS and Wistar. We used a morphological method of a research. The age-induced changes of lymphoid tissue are various at Wistar and OXYS rats. The structural answer of a lymph node is optimum to three-months age of rats of Wistar. At the same time, we noted reduction of structures of cortical substance, especially lymphoid follicles and a paracortex, against the background of increase of medullary substance at OXYS rats. Observed changes of structure of lymph nodes are a morphological equivalent of premature aging and confirms early decrease of drainage and immune functions at OXYS rats.

KEYWORDS — lymph node, premature aging, OXYS rats.

INTRODUCTION

The problem of aging has great interest from many experts of science and medicine. Until now there is no aging explanation, as well as is absent the universal theory of aging. The existing theories of lymphoid [1] and humoral [2] ageings need representation of morphological equivalents from lymphoid tissue including lymph nodes [3, 4, 5]. Age disturbances of structure and functions of peripheral lymphoid bodies lead to disturbance of an endoecological homeostasis against the background of decrease of a lymph flow and development of immune insufficiency [6].

The immune deficit is considered as aging manifestation. It was logical to assume that the premature (accelerated) aging at OXYS rats can be connected with morphology of regional lymph nodes. There is an urgent need of a morph of functional assessment of lymph nodes. Lymph nodes are an integral part of the general protective system of an organism in the lymphatic region [5, 6, 7]. Reactive changes of a design of lymph nodes not always find the explanation, especially, in presenilation.

The aim of the study is simultaneous assessment of the structural organization of a mesenteric lymph node of young rats of OXYS and Wistar.

MATERIALS AND METHODS

Rats of the Wistar and OXYS lines are received from Center of collective use "Gene pools of laboratory animals" of Institute of cytology and genetics of the SB RAS. N.G. Kolosova is a holder of the license for OXYS rats. These rats have genetically caused defect of metabolism with great content of oxygen radicals (oxidative stress), it is considered as an accelerated aging syndrome [8]. OXYS rats differ in low lifetime, early involute and pathological changes of internals, frequent developing of tumors in comparison with Wistar rats [8, 9, 10].

The experiment was executed on young white rats of three-months age with a morphological research of mesenteric lymph nodes of caudal group. Lymph nodes fixed in 10% neutral formalin. After fixing we adhered to the classical scheme of washing, dehydration, imbibition with a xylol, paraffin and preparation histologic sections on the microtome. Histologic sections of lymph nodes painted hematoxylin and eosine, azure-II-eosine, trichromatic paint on Masson.

The morphometric analysis of structures of a lymph node was carried out by means of a morphometric grid and the Image-Pro Plus 4.1 program. Statistical data processing was performed with licensed statistical software package StatPlus Pro 2009, AnalystSoft Inc. Data were expressed as average arithmetic with definition of a standard (mean square) error. Belonging to normal distribution was defined when calculating criterion of Kolmogorov–Smirnov and the accompanying indicators. A P-value < 0.05 was considered statistically significant.

RESULTS

The morphological analysis of results revealed certain differences of the structural organization of

peripheral lymphoid organs of Wistar and OXYS rats in an experiment (Table 1, Fig. 1). Lymphoid tissue of rats of Wistar reaches optimum development to three-months age [6]. Degree of a maturity of a parenchyma of lymph nodes is connected with their topographical localization and belonging to the lymphatic region [5, 7]. Lymph nodes of young animals of Wistar have an intermediate morphotype when cortical and medullary substances are developed equally, proceeding from the value of cortical and medullary index (1.33±0.14). It reflects rather high immune and drainage potential of lymph nodes in the "hepatoenteric" region (Table 1).

Table 1. *Morphometric parameters of mesenteric lymph node structure of young Wistar and OXYS rats (three-months age), %*

Structures and indices of the mesenteric lymph node	WISTAR	OXYS
Capsule	5.47±0.57	5.54±0.62
Subcapsular lymphatic sinus	3.50±0.30	2.65±0.26
Cortical plateau	7.63±0.45	4.34±0.36*
Lymphoid follicles without germinative center	3.30±0.26	2.44±0.15
Lymphoid follicles with germinative center	5.06±0.25	1.52±0.08*
Paracortex	16.14±1.26	5.66±0.31*
Medullary cords	10.74±0.96	15.75±0.93*
Medullary lymphatic sinus	7.00±0.48	4.69±0.65
Total cross-sectional area	58.83±2.55	42.59±1.34*

Note: **P < 0,05 — statistical significance level between Wistar and OXYS rats.*

We saw other morphological picture in mesenteric lymph nodes at young rats of OXYS in three-month age. First of all, the total area of cross-section of a mesenteric lymph node decreased in 1.4 times. It leads to change of the size of the majority of structural and functional zones of a lymph node in comparison with Wistar rats (table 1, fig. 1). So, the cortical plateau (in 1.7 times), lymphoid follicles with the germinative center (in 3.3 times), a paracortex (in 2.9 times) are reduced. Reduction of the area of cortical substance structures happens at increase of medullary substance in a mesenteric lymph node of rats of OXYS. The character dynamic change of structure is indicated also by the size of a cortical and medullary ratio, reaching 0.81±0.05 (Table 1). Noted changes of structure of a lymph node demonstrate decrease of drainage and immune function at rats of OXYS in three monthly age.

DISCUSSION

The intestinal lymphatic region is a part of the general protective system of an organism and includes a tissue microregion with lymphoid follicles, vessels and lymph nodes [5]. It is in close contact with external environment that causes intake of antigenic material from an intestines gleam, and lymphoid tissue serves as a barrier on the way of this stream of antigens. Localization of a lymph node defines forming of morphological variant of structure according to the principle of a regional determinant [6, 7].

The age-induced changes of lymphoid tissue were various at rats of the Wistar and OXYS. Structural and functional zones of a lymph node reach the greatest development in rats of Wistar. The genetic defect at rats of OXYS led to lag of development of lymph nodes that is characterized by reduction of cortical substance structures against the background of increase in medullary substance. Barrier function of lymph nodes suffers. It is known that early involution of a thymus gland with decrease of the activity of the T-cellular link of the immune system is observed at OXYS rats [10, 11]. A morphological equivalent is reduction of paracortical area in a lymph node.

At the same time also the area of lymphoid follicles with the germinative center decreases. Lymphoid follicles together with paracortical area participate in forming of the immune response. Regional lymph nodes actively react to any changes of drained areas, but the created structure of lymph nodes of OXYS rats does not provide adequate drainage and immune functions in the lymphatic region. Observed manifestations of the accelerated aging of peripheral lymphoid organs supplement the lymphoid and humoral theory of aging [1, 2].

CONCLUSION

Results of researches allow to draw a conclusion that the structural disorganization of peripheral lymphoid tissue developing at OXYS rats occurs earlier and characterizes premature aging and possible risk of developing of pathology. It is expressed in minimization of cortical substance structures and increase of medullary substance of lymph nodes. These changes are caused with features of the intestinal lymphatic region. The found morphology of lymph nodes allow to consider OXYS rats as universal model of immune insufficiency. It needs to be considered at a research of pathogenesis and creation of correction methods at premature aging.

REFERENCES

1. **Dontsov V.I., Krutko V.N.** Aging: system approach // Collection of articles. Reports of MOIP.

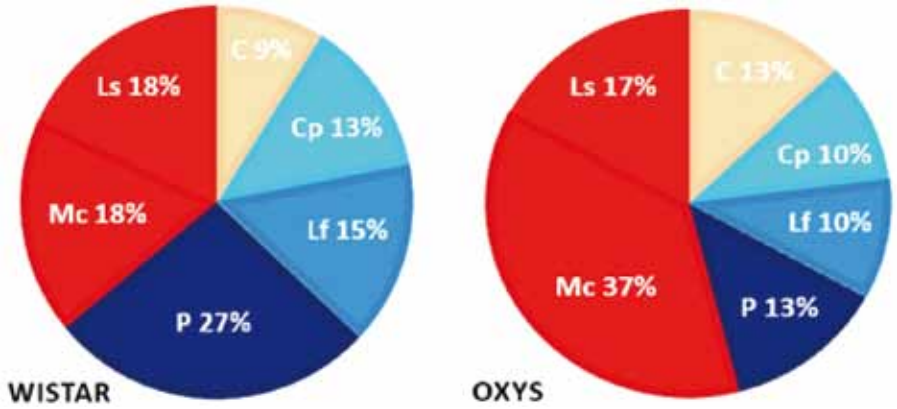

Fig. 1. *The share of structures from the area of mesenteric lymph node taken as 100% in Wistar and OXYS rats. C — capsule, Cp — cortical plateau, Lf — lymphoid follicles, P — paracortex, Mc — medullary cords, Ls — lymphatic sinus*

Gerontology section. – M.: Tsifrovichek, 2015. – Vol. 59. – P.22–37. [In Rus.]

2. **Toporova S.G.** Features of a system of pericellular humoral transport when aging: overview of literature // Almanac "Gerontology and Geriatric". – M, 2003. – Issue 2. – P.90–94. [In Rus.]
3. **Passos J., Zglinicki T., Kirkwood T.B.** Mitochondria and ageing: winning and losing in the numbers game // Bioassays. – 2007. – Sep. – V. 29 (9). – P. 908–917.
4. **Chernilevsky V.E., Kudashov A.A.** The main methodical mistakes, myths and stamps in the general analysis of a problem of aging // the Collection of articles. Reports of MOIP. Gerontology section. – M.: Tsifrovichek, 2015. – Vol. 59. – P. 3–11. [In Rus.]
5. **Borodin Yu.I., Gorchakova O.V., Gorchakov V.N.** Peripheral lymphoid structures: formation and function // Morphology. – 2016. – Vol. 150. Issue 4. – P. 90–96. [In Rus.]
6. **Gorchakova O.V., Gorchakov V.N.** Increase in drainage and immune functions of a lymph node as a factor of endoecological wellbeing at advanced and senile age // ADVANCES IN GERONTOLOGY. – 2015. – Vol. 28. – No. 3. – P. 521–526.
7. **Borodin Ju.I., Gorchakova O.V., Suhovershin A.V., Gorchakov V.N., Fartukov A.V., Kolmogorov Ju.P., Demchenko G.A.** The concept of lymphatic region in preventive lymphology. LAP LAMBERT Academic Publishing. 2018. – 74 p.
8. **Kolosova N.G., Aydagulova S.V., Nepomnjashchih G.I.** Dynamics of structural and functional changes of mitochondrions of hepatocytes of prematurely aging rats of the OXYS line // Bulletin exper. biol. – 2001. – Vol. 132. – No. 8. – P. 235–240. [In Rus.]
9. **Kolosova N.G., Stefanova N.A., Korbolina E.E., Fursova A.Zh. and Kozhevnikova O.S.** Senescence-Accelerated OXYS Rats: A Genetic Model of Premature Aging and Age-Related Diseases // ADVANCES IN GERONTOLOGY. – 2014. – Vol. 27. – No. 2. – P. 336–340.
10. **Obukhova L.A., Skulachev V.P., Kolosova N.G.** Mitochondria-targeted antioxidant SkQ1 inhibits age-dependent involution of the thymus in normal and senescence-prone rats // AGING. – 2009. – V. 1(4). – P.389–401.
11. **Markova E.V., Obukhova L.A., Kolosova N.G.** Indicators of activity of a cellular link of the immune response of rats of the Wistar and OXYS lines and feature of their behavior in the test of "open field" // Bulletin exper. biol. – 2003. – Vol. 136. – No. 10. – P.427–429. [In Rus.]

https://doi.org/10.35630/2199-885X/2019/9/3.8

INFLUENCE OF SELANK, PRO-GLY-PRO AND PRO-GLY-PRO-LEU ON THE INTENSITY OF REDOX REACTIONS IN IMMUNOCOMPETENT ORGANS UNDER CONDITIONS OF "SOCIAL" STRESS

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ABSTRACT — The experiment investigated the effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on the intensity of redox reactions in immunocompetent organs (thymus and spleen) on the model of "social" stress. The intensity of redox processes was assessed by determining the intensity of lipid peroxidation (LPO) in immunocompetent organs (thymus and spleen) and catalase activity. "Social" stress, formed in the experiment, is accompanied by an increase in the peroxidation processes in immunocompetent organs, which contributes to the development of stress-induced functional disorders of the immune system. Under the influence of "social" stress, the activity of the investigated antioxidant enzyme in the thymus and spleen increased in comparison with the corresponding indicators in intact rats. Against the background of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu administration under "social" stress, its pronounced corrective effect on lipid peroxidation rates is observed, as evidenced by a decrease in spleen and thymus tissue homogenates of male rats in the baseline level of TBA-reactive products, speed of spontaneous and ascorbate-dependent lipid peroxidation, and catalase activity.

INTRODUCTION

In the age of scientific and technological progress in modern society, the relevance of stress is caused by the continuous growth of social, economic, technological, environmental and other changes in our lives. In recent years, special attention of scientists has been given to the study of social stress, which is characterized as a mass adaptation syndrome, which reflects the degree of physiological and psychosocial stress, psychophysiological and socio-psychological adaptation and maladaptation in extreme situations [1]. One of the non-specific reactions to stressful effects of various nature is the development of oxidative imbalance, leading to a change in the functional activity of various systems at the cellular, tissue and organ levels [2, 3, 4]. Long stress loads lead to the accumulation of products of lipid peroxidation processes, which serves as a signal for mobilization of the neurohumoral and immune regulation system and as a result activation of the antioxidant defense of the body [5]. Considering the above, the question arises sharply about the search for means of correction of the data of the violated protective functions of the body as a result of stressful exposure. From the standpoint of modern medical science, the most promising in this direction are neuropeptides [6, 7, 8], which include the registered drug Selank, as well as new synthetic compounds Pro-Gly-Pro and Pro-Gly-Pro-Leu.

The aim of research

study the effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on the intensity of redox reactions in the thymus and spleen under the conditions of "social" stress.

MATERIAL AND METHODS

White non-linear rats (males, 6–8 months old) were used as experimental animals. In order to create a "social" stress in the experiment a model of intermale confrontations was chosen. Animals were placed in pairs in experimental cells separated by a septum which prevents physical contact but has openings that provide sensory contact. Every day the partition was removed for 10 minutes which overwhelmingly led to agonistic collisions (confrontations) [9]. Groups of animals with alternative types of behavior were formed: aggressive type — in case of repeated victories experience (winner, aggressor) and submissive type - in case of defeats (victim). Laboratory animals were divided into 5 groups (n = 10): a group of intact males; a group of animals that were exposed to stress for 20 days (sensory contact); a group of individuals treated intraperitoneally with Selank at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days;a group of individuals treated intraperitoneally with Pro-Gly-Pro at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days;a group of

individuals treated intraperitoneally with Pro-Gly-Pro-Leu at a dose of 100 μg/kg/day under conditions of 20-day stress exposure (sensory contact) in a course of 20 days. The intensity of redox processes was assessed by determining the intensity of lipid peroxidation in immunocompetent organs (thymus and spleen) and catalase activity [10].

The experiment results were statistically processed using the following programs: Microsoft Office Excel 2007 (Microsoft, USA), BIOSTAT 2008 Professional 5.1.3.1. To process the obtained results, a parametric method was used with the Student t-test with the Bonferroni correction. Statistically significant differences were considered at $p<0.05$.

RESULTS AND DISCUSSION

Under conditions of "social" stress, an increase in the initial, spontaneous, as well as ascorbate-dependent levels of lipid peroxidation in the spleen was observed. The initial level of TBA-reactive products increased among aggressors by 57% ($p<0.01$), among victims — by 38% ($p<0.05$). The level of spontaneous lipid peroxidation in rats with an aggressive type of behavior was statistically significantly increased by 35%, in individuals with a submissive - by 31% compared with the control group of animals ($p<0.05$). "Social" stress led to an increase in the rate of ascorbate-dependent lipid peroxidation by almost 60% ($p<0.001$) in aggressors and 49% ($p<0.01$) in victims. In addition, the level of catalase activity in spleen tissue in animals with aggressive behavior increased by 63% ($p<0.01$), and in rats with submissive - by 28% ($p<0.05$) (Table 1).

With the introduction of Selank, the initial level of TBA-reactive products in the spleen decreased by 26% ($p<0.05$) in individuals with aggressive behavior and in animals with submissive — by 25% ($p> 0.05$) relative to the stress group. This drug statistically significantly adjusted the indicators of both spontaneous lipid peroxidation in aggressors by 27% ($p<0.05$) and in victims by 36% ($p<0.05$), and ascorbate-dependent lipid peroxidation in 48% ($p<0.001$) in aggressors and 34% ($p<0.05$) in victims compared with stressed animals. In addition, the catalase level in the spleen decreased statistically significantly under the influence of Selank in stressed rats with aggressive behavior by 31% ($p<0.05$) and in individuals with submissive - by 29% ($p<0.05$). The effects of the neuropeptides Pro-Gly-Pro and Pro-Gly-Pro-Leu under experimental stress conditions showed the following results. So, with the introduction of Pro-Gly-Pro, the level of TBA-reactive products in the spleen decreased in aggressor rats by 22% ($p> 0.05$) and in animal victims by 36% ($p<0.05$), and spontaneous Sex of aggressors by 36% ($p<0.01$) and 42% ($p<0.01$) in victims and ascorbate-dependent sex on average by 28% ($p<0.05$) in rats with aggressive and submissive behaviors in relation to to stressed animals. The level of catalase in the tissue of the spleen against the background of "social" stress under the influence of Pro-Gly-Pro decreased in the aggressors by 44% ($p<0.01$) and 36% ($p<0.01$) in the victims. The use of Pro-Gly-Pro-Leu under stress conditions showed a decrease in the initial level of TBA-reactive products in the spleen of stressed individuals with aggressive behavior by 27% ($p<0.05$) and in animals with submissive — by 31% ($p<0 , 05$) relative to the stress group. The level of spontaneous LP under the influence of Pro-Gly-Pro-Leu decreased by 40% ($p<0.01$) in aggressors and by 47% ($p<0.001$) in victims; as well as the level of ascorbate-dependent LPO among aggressors — by 37% ($p<0.01$) and among victims — by 19% ($p> 0.05$). Catalase activity in the spleen homogenate under stress Pro-Gly-Pro-Leu decreased in aggressor rats by 35% ($p<0.05$) and in individuals of victims — by 38% ($p<0.01$) compared with the stress group ". In the thymus homogenate against the background of "social" stress, an increase in the level of TBA-reactive products was noted by 37% ($p<0.05$) among aggressors and by 57% ($p<0.01$) in victims relative to the control group. "Social" stress also led to an increase in the thymus rate of spontaneous lipid peroxidation in animals with aggressive by almost 40% ($p<0.01$) and submissive — by 52% ($p<0.01$) types of behavior. The rate of ascorbate-dependent lipid peroxidation under experimental stress was statistically significantly increased by 29% ($p<0.05$) in aggressors and by 45% in victims ($p<0.05$) in relation to control animals. Catalase activity against the background of "social" stress increased in male rats of aggressors by 57% ($p<0.01$), in animal victims — by 32% ($p<0.05$) compared with the "control". The use of Selank under stress was accompanied by a decrease in the initial level of TBA products in the thymus tissue by more than 30% in aggressors ($p<0.01$) and in victims by 26% ($p<0.05$) relative to the stress group. Under conditions of "social" stress, Selank reduced both the rate of spontaneous lipid peroxidation in aggressor rats by 34% ($p<0.01$) and in individuals of victims by almost 20% ($p<0.05$), and ascorbate-dependent LP in an average of 30% in aggressors ($p<0.01$) and victims ($p<0.05$) relative to animals exposed to stress. The catalase level with the introduction of Selank decreased by more than 30% ($p<0.01$) among aggressors and by 28% ($p<0.05$). Under the influence of Pro-Gly-Pro, animals with an aggressive type of behavior showed a decrease in the initial level of TBA products by 16% ($p> 0.05$) and in individuals submissive by 22% ($p<0.05$).

In addition, Pro-Gly-Pro contributed to the suppression of both spontaneous lipid peroxidation

Table 1. *The effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on lipid peroxidation and catalase activity in the spleen of male rats under the conditions of "social" stress*

Experimental groups (n = 10)	Lipid peroxidation indicators			Catalase activity, %
	The initial level of MDA, M ± m, nmol/g tissue	The rate of spontaneous lipid peroxidation, M ± m, nmol/g · h	The rate of ascorbate-dependent lipid peroxidation, M ± m, nmol/g · h	
Animals with an aggressive type of behavior				
Control	1,75 ± 0,19	2,12 ± 0,23	3,07 ± 0,23	40,56 ± 3,66
"Social" stress	2,76 ± 0,26**	2,88 ± 0,27*	4,90 ± 0,39***	66,33 ± 6,24**
"Social" stress + Selank (100 mcg /kg/day)	2,03 ± 0,15#	2,10 ± 0,24#	2,57 ± 0,33###	45,27 ± 5,15#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	2,15 ± 0,20	1,83 ± 0,21##	3,48 ± 0,37#	36,89 ± 4,31##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,00 ± 0,18#	1,70 ± 0,24##	3,09 ± 0,30##	42,83 ± 4,94#
Animals with a submissive type of behavior				
Control	1,75 ± 0,19	2,12 ± 0,23	3,07 ± 0,23	40,56 ± 3,66
"Social" stress	2,43 ± 0,27*	2,79 ± 0,24*	4,57 ± 0,32**	51,78 ± 4,19*
"Social" stress + Selank (100 mcg /kg/day)	1,81 ± 0,32	1,78 ± 0,28#	3,01 ± 0,48#	36,67 ± 3,72#
"Social" stress + Pro-Gly-Pro (100 mcg/kg/day)	1,54 ± 0,23#	1,61 ± 0,26##	3,30 ± 0,44#	33,11 ± 3,23##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	1,67 ± 0,21#	1,47 ± 0,20###	3,68 ± 0,45	31,84 ± 3,03##

Note: ** — p<0,05; ** — p<0,01;*** — p<0,001 — comparing with control; # — p<0,05; ## — p<0,01; ### — p<0,001 — comparing with stress (Student's t-test with Bonferroni amendment for multiple comparisons)*

in animals with aggressive behavior by 39% (p <0.01) and in rats with submissive — by 41% (p <0.01), and ascorbate-dependent lipid peroxidation an average of 21% (p <0.05) among aggressors and victims relative to the stress group. The activity of the catalase enzyme against stress during the use of Pro-Gly-Pro decreased by 36% (p <0.01) in aggressors and by 33% in victims. Under the influence of Pro-Gly-Pro-Leu, stressful animals with aggressive behavior showed a decrease in the initial level of TBA products by 20% (p <0.05) and in male rats with submissive — by almost 30% (p <0, 05). It should also be noted that under the influence of Pro-Gly-Pro-Leu under conditions of "social" stress, spontaneous lipid peroxidation was suppressed by aggressors by 29% (p <0.01) and by 43% in victims (p <0.001), and as well as ascorbate-dependent lipid peroxidation by 24% (p <0.05) in rats with aggressive behavior and in individuals with submissive — by 9% (p> 0.05) relative to animals subjected to stress. In addition, this neuropeptide reduced the level of catalase in the thymus in aggressors by 27% (p <0.05) and in victims by 38% (p <0.01) compared with the stress group.

CONCLUSION

Thus, experimental "social" stress, modeled by 20-day inter-male confrontations, is accompanied by an increase in free radical processes in immunocompetent organs (spleen and thymus), which indicates the immunosuppressive effect of this type of stress exposure. Under the influence of the Selank preparation and new representatives of neuropeptides Pro-Gly-Pro and Pro-Gly-Pro-Leu, its pronounced corrective effect on lipid peroxidation is noted, which is confirmed by a decrease in the tissues of the spleen and thymus of laboratory animals of the initial, spontaneous and ascorbate-dependent levels of lipid peroxidation, as well as a decrease in the activity of the antioxidant enzyme — catalase in conditions of "social" stress.

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REFERENCES

1. **Bali A., Jaggi A.S.** Preclinical experimental stress studies: protocols, assessment and comparison //

Table 2. *The effect of Selank, Pro-Gly-Pro and Pro-Gly-Pro-Leu on lipid peroxidation and catalase activity in the thymus of male rats under the conditions of "social" stress*

Experimental groups (n = 10)	Lipid peroxidation indicators			Catalase activity, %
	The initial level of MDA, M ± m, nmol / g tissue	The rate of spontaneous lipid peroxidation, M ± m, nmol / g · h	The rate of ascorbate-dependent lipid peroxidation, M ± m, nmol / g · h	
Animals with an aggressive type of behavior				
Control	2,70 ± 0,30	3,01 ± 0,20	2,41 ± 0,20	36,48 ± 2,54
"Social" stress	3,72 ± 0,30*	4,21 ± 0,30**	3,11 ± 0,20*	57,42 ± 5,67**
"Social" stress + Selank (100 mcg /kg/day)	2,56 ± 0,20##	2,77 ± 0,31##	2,18 ± 0,20##	40,09 ± 3,10#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	3,11 ± 0,20	2,55 ± 0,29##	2,48 ± 0,22#	36,50 ± 3,06##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,97 ± 0,21#	2,98 ± 0,27##	2,36 ± 0,20#	41,77 ± 3,19#
Animals with a submissive type of behavior				
Control	2,70 ± 0,30	3,01± 0,20	2,41 ± 0,20	36,48 ± 2,54
"Social" stress	4,24 ± 0,40**	4,60 ± 0,30**	3,50 ± 0,32*	48,40± 3,23*
"Social" stress + Selank (100 mcg /kg/day)	3,13 ± 0,32#	3,71 ± 0,28#	2,43 ± 0,22#	34,67 ± 3,68#
"Social" stress + Pro-Gly-Pro (100 mcg /kg/day)	3,31 ± 0,23#	2,70 ± 0,32##	2,72 ± 0,17#	32,40 ± 3,25##
"Social" stress + Pro-Gly-Pro-Leu (100 mcg/kg/day)	2,98 ± 0,28#	2,63 ±0,25###	3,19 ± 0,25	29,78 ± 3,15##

Note: ** — p<0,05; ** — p<0,01;*** — p<0,001 — comparing with control; # — p<0,05; ## — p<0,01; ### — p<0,001 — comparing with stress (Student's t-test with Bonferroni amendment for multiple comparisons)*

Eur J Pharmacol. 2015. Vol. 746. P. 282–292. DOI: 10.1016/j.ejphar.2014.10.017

2. **Garcia Y.J., Rodríguez-Malaver A.J., Peñaloza N.** Lipid peroxidation measurement by thiobarbituric acid assay in rat cerebellar slices// J Neurosci Methods. 2005.Vol.144,No.1. P. 127–135. DOI: 10.1016/j.jneumeth.2004.10.018
3. **Jurczuk M, Brzóska M.M, Moniuszko-Jakoniuk J, Gałazyn-Sidorczuk M, Kulikowska-Karpińska E.** Antioxidant enzymes activity and lipid peroxidation in liver and kidney of rats exposed to cadmium and ethanol // Food ChemToxicol. 2004. Vol.42No.3.P.429–438. DOI: 10.1016/j.fct.2003.10.005
4. **Tsikas D.** Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges// Anal Biochem. 2017. № 524. P. 13–30. DOI: 10.1016/j.ab.2016.10.021
5. **Teply D.L, Gorden M.V.** The influence of emotional-painful stress on lipid peroxidation and the relative mass of reproductive and immunocompetent organs in young and old rats // Advances in gerontology. 2004. Vol. 14, № 14. P. 044–047. (in Russ.)
6. **Ashmarin I.P., Koroleva S.V.** Regularities of interaction and functional continuum of neuropeptides (on the way to a unified concept): Overview // Bulletin of the Russian Academy of Medical Sciences. 2002. No. 6. P. 40–48. (in Russ.)
7. **Levitskaya N.G., Glazova N.Yu., Sebentsova E.A., Manchenko D.M., Vilensky D.A., Andreeva L.A., Kamensky A.A., Myasoedov N.F.** Study of Spectrum of Physiological Effects of ACTH 4-10 Analog Heptapeptide Semax. Neyrokhimiya.2008; Vol. 25, No. 1. P. 111–118. (in Russ.)
8. **Hill J.W., Faulkner L.D.** The Role of the Melanocortin System in Metabolic Disease: New Developments and Advances // Neuroendocrinology. 2017. Vol. 104, No. 4. P. 330–346. DOI: 10.1159/000450649
9. **Kudryavtseva N. N., Smagin D. A, Kovalenko I. L, Galyamina A. G., Vishnivetskaya G.B., Babenko V. N., Orlov Y. L.** Serotonergic genes in the development of anxiety/depression-like state and pathology of aggressive behavior in male mice: RNA-seq data // Molecular biology. 2017. Vol. 51, No. 2. P. 288–300. (in Russ.) DOI: 10.7868/S0026898417020136
10. **Mironov A.N.** A guide to preclinical drug research. Part One / Ed. A.N. Mironov. – Moscow: Grief and K, 2013. – 944 p.(in Russ.)

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THE INFLUENCE OF PRO-GLY-PRO-LEU ON THE LEVEL OF CYTOKINES UNDER THE CONDITIONS OF "SOCIAL" STRESS

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ABSTRACT — The experiment investigated the effect of Pro-Gly-Pro-Leu on the level of cytokines under the conditions of "social" stress. The level of cytokines under study was determined by enzyme-linked immunosorbent assay. The stress-induced changes observed in the experiment consist in increasing the production of IL-1β, IL-6, TNF-α and TGF-β, which allows us to consider stress exposure as an inducer of the production of pro-inflammatory interleukins and various growth factors. It was found that the introduction of Pro-Gly-Pro-Leu is accompanied by the restoration of increased values of the studied cytokines in stressed animals almost to the level of indicators of the control group. The obtained results indicate the pronounced stress-protective properties of this compound, which are manifested in the restoration of the level of the studied cytokines to the level of control values.

KEYWORDS — "social" stress, peptide, glyprolins, cytokines, interleukin-1β, interleukin-4, interleukin-6, tumor necrosis factor-α, transforming growth factor β1.

INTRODUCTION

Currently, special attention is paid to the creation of drugs with stress-protective activity, which is directly related to modern human conditions, constantly accompanied by various stressful factors, which often entail the development of a complex of reactions, both compensatory and pathological, and, ultimately, they can lead to disruption of the immune mechanisms of homeostasis [1, 2, 3, 4, 5].

Modern studies indicate that in the development of immune disorders caused by stress exposure, the leading place is occupied by the production of cytokines, such as interleukins, neurotransmitters, hormones, neuropeptides, etc., whose main role is to regulate intercellular and intersystem interactions and to act functions of stress-limiting and immune systems of the body [6, 7, 8, 9, 10].

Of particular interest today are drugs from the group of peptide analogues with proven regulatory function relative to homeostasis and the ability to participate in the formation of adaptive changes under the influence of stress factors [11]. It was established that peptide compounds related to glyprolins, along with the above properties, have neuroprotective, neurotrophic, anxiolytic and other types of activity, however, information on the immunotropic effect of these substances is insufficient [12, 13].

The aim of research:
study the effect of Pro-Gly-Pro-Leu on the level of cytokines (IL-1β, IL-4, IL-6, TNF-α and TGF-β1) under the conditions of "social" stress.

MATERIAL AND METHODS

White non-linear rats (males, 6–8 months old) were used as experimental animals. The effect of the peptide compound Pro-Gly-Pro-Leu on the plasma concentration of cytokines was carried out on the model of social stress — "sensory contact". Laboratory animals were divided into 3 groups (n = 10): a group of intact males; a group of animals that were subjected to stress for 20 days (sensory contact); a group of animals that received intraperitoneally Pro-Gly-Pro-Leu at a dose of 100 mcg / kg / day under conditions of 20-day stress (sensory contact) course of 20 days.

In order to create a "social" stress in the experiment a model of inter-male confrontations was chosen. Animals were placed in pairs in experimental cells separated by a septum which prevents physical contact but has openings that provide sensory contact. Every day the partition was removed for 10 minutes which overwhelmingly led to agonistic collisions (confrontations) [14, 15]. Then groups of animals with an aggressive and submissive type of behavior were formed.

The study of the cytokine level under the influence of Pro-Gly-Pro-Leu on the model of "social" stress was carried out by the method of enzyme-linked immunosorbent assay (ELISA) using test systems based on monoclonal antibodies manufactured by BenderMedSystems (Austria) according to the guidelines attached to the sets.

The experiment results were statistically processed using the following programs: Microsoft Office Excel 2007 (Microsoft, USA), BIOSTAT 2008 Professional 5.1.3.1. To process the obtained results, a parametric method was used with the Student t-test with the Bon-

ferroni correction. Statistically significant differences were considered at $p<0.05$.

RESULTS

The results of the determination of serum cytokines IL-1β, IL-4 and IL-6 are presented in Table 1.

of stressed animals however, compared with the control group, the changes did not have statistical significance; the level of IL-6 decreased by 1.2 times ($p>0.05$) and almost reached the level of the group of intact animals. In the group of animals with a submissive type of behavior, a decrease in the levels of IL-1β and IL-6 was

Table 1. *The concentration of interleukins under the influence of Pro-Gly-Pro-Leu in conditions of «social» stress*

Experimental groups (n=8)	IL-1β, M±m, pg / ml	IL-4, M±m, pg / ml	IL-6, M±m, pg / ml
Control	107,80 ± 10,76	3,97±0,18	79,60 ±5,40
Animals with an aggressive type of behavior			
«Social» Stress	152,80 ± 15,36 *	3,38 ± 0,27	100,60 ±8,20*
«Social» stress + Pro-Gly-Pro-Leu (100 mg / kg / day)	95,60 ± 11,26##	3,96 ±0,12	82,20 ± 5,40
Animals with a submissive type of behavior			
«Social» Stress	171,60 ± 12,94**	3,48 ± 0,22	104,00 ± 7,20*
«Social» stress + Pro-Gly-Pro-Leu (100 mg / kg / day)	97,80 ± 14,46##	3,84 ± 0,11	82,20 ± 8,3

Note: ** — p<0,05; ** — p<0,01;*** — p<0,001 — comparing with control; # — p<0,05; ## — p<0,01; ### — p<0,001 — comparing with stress (Student's t-test)*

Compared with the control group of animals, an increase in the concentration of IL-1β and IL-6 was observed in animals with experimental "social" stress and aggressive behavior by 42% ($p<0.05$) and 26% ($p<0.05$), respectively. whereas in animals with submissive behavior, 60% ($p<0.01$) and 30% ($p<0.05$), respectively; a decrease in the level of IL-4 was also observed in groups of animals with simulated stress, however, these changes were not significant.

When the peptide compound was intraperitoneally administered under the code Pro-Gly-Pro-Leu at a dose of 100 mg / kg, a 1.6-fold decrease in the concentration of IL-1β was observed in animals with aggressive behavior ($p<0.05$) compared with the group observed in comparison with the stressed group by 1.8 ($p<0.01$) and 1.3 ($p>0.05$) times, respectively. In relation to the intact control, the concentration of IL-1β decreased by 1.1 ($p>0.05$). Against the background of the introduction of the peptide compound, an increase in the concentration of IL-4 in blood serum was noted as in both groups of animals, however, these changes were not significant.

The results of the determination of TNF-α and TGF-β1 in blood serum are presented in Table 2. A statistically significant increase in the level of TGF-β1 by more than 2 times ($p<0.001$) was found in the social stress group in animals with an aggressive type of behavior, and in the group with a submissive type

Table 2. *The concentration of TNF-α and TGF-β1 under the influence of Pro-Gly-Pro-Leu in conditions of «social» stress*

Experimental groups (n=8)	TGF-β1, M±m, pg / ml	TNF-α, M±m, pg / ml
Control	138,8±17,6	81,8±7,8
Animals with an aggressive type of behavior		
«Social» stress	292,4±25,8***	93,4±5,8
«Social» stress + Pro-Gly-Pro-Leu (100 mg / kg / day)	207,8 ± 16,2#	82,2 ±6,2
Animals with a submissive type of behavior		
«Social» stress	230,0±24,6**	91,4±7,8
«Social» stress + Pro-Gly-Pro-Leu (100 mg / kg / day)	165,8 ± 18,4#	78,8 ± 7,2

Note: ** — p<0,05; ** — p<0,01;*** — p<0,001 — comparing with control; # — p<0,05; ## — p<0,01; ### — p<0,001 — comparing with stress (Student's t-test)*

of behavior — 1.7 times ($p < 0.05$) in comparison with the control group; under the same conditions, there was a statistically significant decrease in TGF-β1 in 1.4 ($p < 0.05$) in two groups compared with stressed animals. When assessing the level of TNF-α in conditions of "social" stress in animals with various types of behavior, there was a tendency to increase this indicator; with the introduction of Pro-Gly-Pro-Leu, the level of the studied cytokine almost reached the control values, but these changes were not statistically significant.

Thus, when studying the effect of the peptide compound of the glyproline group Pro-Gly-Pro-Leu on the level of cytokines under conditions of "social" stress, it was found that this peptide is able to reduce the concentrations of IL-1β, IL-6 and TNF-α and TGF-α β1 almost to the level of control values.

DISCUSSION

Currently, one of the priority areas is a more detailed study of the mechanisms of cytokine regulation, as one of the leading links that determine the intercellular interaction both in normal and in pathological conditions. It is proved that the level of cytokines changes in any pathological process, including with stress-mediated etiopathogenetic cause. In this study, "social" stress was accompanied by an increase in the concentration of IL-1β, IL-6, TNF-α, and TGF-β1 in the blood serum, confirming the fact that the stressful effect on the body leads to the induction of the synthesis of pro-inflammatory cytokines and growth factors that have a significant effect on the body as a whole, which provokes a change in the functional activity of the stress-limiting and immune systems of the body. The results obtained when studying the effect of the peptide compound of the glyproline group Pro-Gly-Pro-Leu on the level of cytokines under conditions of "social" stress indicate the presence of stress-protective activity of the peptide compound of the glyproline series under the code Pro-Gly-Pro-Leu.

CONCLUSION

Thus, the results of a study of the effect of a peptide compound of glyprolin nature Pro-Gly-Pro-Leu on the plasma concentration of cytokines such as IL-1β, IL-4, IL-6, TNF-α, and TGF-β1, under conditions "social" stress indicates the need for a detailed analysis of the role of cytokine and growth factors in the development of stress-induced changes in order to find optimal correction tools.

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REFERENCES

1. **Sarapultsev P.A., Sarapultsev A.P.** Stress and the immune system. Cytokines and inflammation. 2014; 13 (4): 5–10. (in Russ.)
2. **Glaser R, Kiecolt-Glaser JK.** Stress-induced immune dysfunction: implications for health. Nature Reviews Immunology. 2005; 5(3): 243–51. doi: 10.1038/nri1571.
3. **Samotrueva MA, Sergalieva M.U., Yasenyavskaya A.L., Mazhitova M.V., Teplyy D.L., Kantemirova B.I.** Information stress: causes, experimental models, effects on the body. Astrakhan medical journal. 2015; 10 (4): 25–30. (in Russ.)
4. **Romero-Martínez Á, Moya-Albiol L.** Stress-Induced Endocrine and Immune Dysfunctions in Caregivers of People with Eating Disorders. International Journal of Environmental Research and Public Health. 2017; 14(12). doi: 10.3390/ijerph14121560.
5. **Samotrueva M.A., Yasenyavskaya A.L., Tsibizova A.A., Bashkina O.A., Galimzyanov H.M., Tyurenkov I.N.** Neuroimmunoendocrinology: current understanding of molecular mechanisms. Immunology. 2017; 38 (1): 49-59. (in Russ.)
6. **Ménard C, Pfau ML, Hodes GE, Russo SJ.** Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. Neuropsychopharmacology. 2017 J; 42(1): 62-80. doi: 10.1038/npp.2016.90.
7. **Tyurenkov I.N., Samotrueva M.A., Tsibizova A.A., Yasenyavskaya A.L.** Phenotropil as a modulator of the level of cytokines in experimental immunopathology. Experimental and clinical pharmacology. 2015; 78 (12): 15–17. (in Russ.)
8. **Rose-John S.** Interleukin-6 Family Cytokines. Impact Factor of Cold Spring Harbor Perspectives in Biology. 2018; 10(2). doi: 10.1101/cshperspect.a028415.
9. **Tanaka T, Narazaki M, Masuda K, Kishimoto T.** Regulation of IL-6 in Immunity and Diseases. Advances in Experimental Medicine and Biology. 2016; 941: 79–88.
10. **Dinarello CA.** IL-1: discoveries, controversies and future directions. European Journal of Immunology. 2010; 40(3): 599-606. doi: 10.1002/eji.201040319.
11. **Kasian A, Kolomin T, Andreeva L, Bondarenko E, Myasoedov N, Slominsky P, Shadrina M.** Peptide Selank Enhances the Effect of Diazepam in Reducing Anxiety in Unpredictable Chronic Mild Stress Conditions in Rats. Behavioural Neurology. 2017. doi: 10.1155/2017/5091027.
12. **Volkova A, Shadrina M, Kolomin T, Andreeva L, Limborska S, Myasoedov N, Slominsky P.** Selank Administration Affects the Expression of Some Genes Involved in GABAergic Neurotransmission. Frontiers in Pharmacology. 2016; 18(7): 31. doi: 10.3389/fphar.2016.00031 (in Russ.)
13. **Andreeva LA, Mezentseva MV, Nagaev IY, Shapoval IM, Shcherbenko VE, Potapova LA, Russu LI, Narovlyansky AN, Ershov FI, Myasoedov NF.** Ex vivo screening of prospective peptide

drugs: new approaches. Doklady Biological Sciences. 2010; doi: 10.1134/S0012496610050029. (in Russ.)

14. **Kudryavtseva N.N.** Serotonergic control of aggressive behavior: new approaches - new interpretations (review). Journal of Higher Nervous Activity. I.P. Pavlova. 2015; 65 (5): 546. (in Russ.)

15. **Kudryavtseva N.N.** The sensory contact model for the study of aggressive and submissive behaviors in male mice. Aggressive Behavior. 1991; 17 (5): 285–291. (in Russ.)

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ANTHRACYCLINE CARDIOMYOPATHY IN ANESTHESIOLOGY

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ABSTRACT — The review covers the formation of clinical forms and manifestations of the mutual influence of carcinogenesis, chemotherapy and concomitant cardiovascular diseases, mechanisms of heart failure development and ways of its medical correction.

KEYWORDS — cardiotoxicity, carcinogenesis, anthracyclines, endothelial dysfunction, cytoprotection.

As a result of a targeted cancer therapy which has led to an increase in the number of patients who have survived, the frequency of use and intensity of chemotherapy, there are conditions for the formation of chemotherapy complications, the most important of which is the myocardial damage. [1, 2]. Patients began to "live" until the development of such delayed complications as cardiomyopathy and congestive heart failure (CHF).

An anesthesiologist at a general surgery clinic sees an increasing number of patients who have previously undergone chemotherapy treatment. In our opinion, the chemotherapeutic history does not receive proper attention. However, these data may be critical for the assessment of the functional operability and prevention of cardiovascular complications during the perioperative period in this category of patients..

The objective of the review is to describe the mechanisms of the cardiotoxicity development in combination with the pathogenesis of the oncological process, chemotherapy and concomitant cardiovascular diseases as well as to find ways to reduce cardiac risks in general surgical practice.

The most commonly used drugs in chemotherapy are anthracycline antibiotics. Anthracycline-induced cardiomyopathy (AC-CMP) is a malignant form of heart disease with a mortality rate of up to 50% during the first 2 years after chemotherapy [3]. The therapeutic efficiency of anthracyclines is high and dose-dependent. The dose-dependency is traced not only in the therapeutic effect of the drug, but also in its toxic effects [4].

The predictors of the cardiotoxicity are the cumulative dose, age and concomitant cardiovascular pathology, as well as the duration of treatment [5]. The developing heart is particularly vulnerable; children who receive anthracyclines are at an extremely high risk of developing an anthracycline-induced cardiotoxicity. A study by Cardinale et al, involving 2,625 patients (the mean follow-up time of 5.2 years), found cardiotoxicity in 9% of cases after an anthracycline treatment, with 98% of cases occurring during the first year and being asymptomatic. A 15-fold increase in the risk of developing heart failure was found in those who had undergone cancer treatment in childhood [6].

Cardiologists distinguish between the following forms of cardiotoxicity: symptomatic cardiotoxicity is found in 2–4% and asymptomatic reduction of LVEF in 9–11% of patients. However, the increase of cardiac biomarkers in patients who have undergone chemotherapy was noted in 30–35% of patients. [5].

The spectrum of complications in the cardiovascular system as a result of an anticancer therapy is not limited to cardiac pathology. Arterial hypertension, thromboembolic complications, peripheral vascular diseases, strokes, pericarditis are additional probable components of risk conditions in this category of patients [7].

The pathophysiological picture in cancer patients is not a simple sum of the changes in the systems, but rather a complex superposition of tumor development, antitumor treatment and related conditions. The cancer process has a multidimensional effect on the body, including mechanical compression of surrounding structures by the tumor, invasion of the pathological agent into the surrounding tissues and a polysystemic effect on the body. On the other hand, chemotherapy is not only aggressive towards tumor cells, but also towards all cellular systems. When these processes are imposed on the concomitant states and their medication, not only the differences in pathogenetic mechanisms, but also their coincidences are determined. The scope of the review includes the effects on the most vulnerable system, the cardiovascular system.

The main antitumor mechanism of the antracycline action is implemented through the blockade of

the topoisomerase (Top) system, the enzyme system responsible for the cell division. Top2α is the main molecular target of the antitumor activity of anthracycline. Top 2β is subjected to exposure while it is in cardiomyocytes [8, 9].

The realisation of the direct cardiotoxic influence of anthracyclines through topoisomerase is combined with the indirect influence. Cardiomyocyte apoptosis is mediated by the release of reactive oxygen species (ROS) and oxidative stress [2], mitochondrial and endothelial dysfunction. The calcium overload is also involved in the formation of the ROS pool [5] and in the blockade of the mitochondrial pore [10]. The mitochondrial pore is a channel that plays a significant role in the calcium metabolism between the mitochondria and the medium and can initiate the process of cellular degradation. Nitrogen oxide may act as a modulator of the mitochondrial pore opening (here, the intersection with the endothelial dysfunction process). When the apoptosis activators leave the mitochondria, the cell destruction is triggered.

Doxorubicin-iron complexes are the second pathway of the formation of toxic radicals leading to an increase in nitrosative stress and mitochondrial dysfunction [8].

A consensus of oncologists discusses the mechanisms of cardiomyopathy development after chemotherapy [6]. The most important pathophysiological mechanisms are: suppression of vascular endothelium growth factor ejection, nitrogen oxide synthesis, vascular rarefaction (reduction), oxidative stress, renal thrombotic microangiopathy, hypercoagulation, direct endothelial damage. Coronary spasms and arterial thrombosis form ischemic syndromes: arrhythmia, ACS, sudden death. Endothelium (E) is one of the cellular systems most sensitive to the influences. During the AC-CMP formation, a depression of the nitrogen oxide formation leads to a decrease in the vascular dilation reserve, β-adrenergic inotropic and chronotropic cardiomyocyte responses [11].

Thus, direct and delayed destructive cardiotoxic effects of chemotherapy form the risk of cardiovascular complications. Direct effects on cardiomyocytes are supplemented by indirect pathogenic processes caused not only by the chemotherapy medication, but also by the oncological process itself.

MECHANISMS OF CARDIOTOXICITY OF CARCINOGENESIS

The cancerous process, even in the absence of mechanical compression of tissue due to the extra volume, causes severe body disorders in the form of tumour intoxication. Toxic manifestations can be characterized by various syndrome complexes: anorexia-kahexia, asthenisation, tumour decomposition syndromes, hemolytic-uremic syndrome, paraneoplastic syndrome, etc. [12]. Common for the cancer process of any localisation is a combination of anemia, energy deficiency, hemostasis disorders...

Anemia is an independent negative prognostic factor of the tumor growth. A 1% decrease in oxygen content stimulates the development of transcription factors for responsible genes. Tumor cell adaptation to anemia stimulates angiogenesis, blocks apoptosis and promotes tumor growth, invasion and metastasis. A low oxygen content in the cell is a factor of chemo- and radio-resistance of the tumor [12].

Anemia is responsible not only for the degree of malignancy of the tumor cell, but also for its energy deficiency. Nutritional disturbances, as an element of the cancerous intoxication, occur after restructuring the metabolism of tumor cells in combination with anemia, and cause deficiency of many substrates (amino acids, vitamins, trace elements) [13].

In terms of the postoperative prognosis, special attention is paid to the influence of tumor cells on the hemostasis system. The pathogenesis of thrombotic complications consists of a combination of disorders caused by the tumor and the treatment. Blood coagulation activation mechanisms include: isolation of a highly active tissue factor and procoagulant by tumor cells, increase of procoagulant activity of monocytes, platelets and endothelial cells in response to the tumor growth [14].

In practice, it is not the thromboembolic complications (TECs) that are more frequently dealt with, but rather their risks. Risk factors for TECs in both surgical patients and patients receiving antitumor therapy do not differ much from the common ones: clinical (age over 40, infection, TEC in the patient's history, varicosity, heart and vascular diseases, kidney diseasse, obesity, etc.), hypercoagulation and thrombocytosis, leukocytosis, anemia, erythropoietin use [15].

The tumor process itself, being an arrhythmogenic process, increases the likelihood of the TEC onset [16].

The influence of factors related to the endothelium on the malignancy of the tumor has been proven. The lowest levels of the angiogenic inhibitor, endostatin, have been reported in patients with ovarian cancer. The vascular endothelial growth factor (VEGF), an angiogenesis activator, was three times higher in the malignant process than in the benign process and six times higher in comparison with the control group. In other words, it is necessary to consider the endostatin and the VEGF levels as malignancy factors in ovarian cancer [17].

On the one hand, there is the activation of neoangiogenesis, hemostatic balance stress, anemia and

energy deficiency. On the other hand, there is a critical increase in the pool of aggressive compounds and radicals, mitochondrial insufficiency and disturbance of nitrogen oxide homeostasis. These are the main components of the pathogenesis of the tumor process, which is subject to chemotherapy. An endothelial dysfunction is common for the above mentioned processes of complex mutual influences of tumor growth and chemotherapy. A tumor process, combined with a therapeutic effect, leads to tension, hyperfunction and exhaustion of the endothelium system.

Cardiovascular pathology associated with an oncological process, being both the cause and result of the endothelial dysfunction, [18] complements the pathogenetic picture.

Thus, the conditions of the endothelial dysfunction formation in the considered category of patients is an integral factor of mutual influence of the processes of tumor growth, chemotherapy and concomitant pathology.

CARDIAL RISKS, THEIR PREVENTION AND WAYS OF REDUCTION IN AC-CMP

When examined by an anesthesiologist in general surgery, patients in this group are often either denied surgical care as "hopeless" or do not receive a proper assessment of the cardiovascular system with a risk of postoperative fatal events. The assessment of cardiovascular risk factors and the prevention and reduction of these risks are of particular importance.

Cardiac risk factors (over 65 years of age, cardiovascular pathology) in the development of AC-CMP are supplemented by a previous radiation exposure of the mediastinal area in the course of chemotherapy, cumulative dose of chemotherapy medication, as well as the total dose administered per day or per course of chemotherapy, the rate of drug administration, the female sex and electrolyte imbalance [19]. In the long run, the cardiovascular risk factors become cardiac in nature. The main information which draws the attention of an anesthesiologist when working with this group of patients is cardiac anamnesis. Thus, the main argument in the correction of risks is the adherence and sequence of the cardiac therapy.

Currently, there is no consensus in regard to the control of antacycline-induced cardiotoxicity [9]. The lack of highly effective specific treatment of the anthracycline-induced heart failure sends us back to the standard treatment of the congestive heart failure with ACE inhibitors, beta-blockers, and looped diuretics [20].

The traditional cardiac strategy is complemented by the cytoprotectors reamberin [21], carvedilol [22], and ivabradine [23].

In terms of the correction of the endothelial dysfunction, statins are of particular interest in the treatment of AC-CMP. In cases with melanoma, colorectal and lung carcinoma, lovastatin demonstrated not only a decrease in the risk of doxorubicin-induced cardiotoxicity, but also an increase in the antitumor effect of the chemotherapy medication [24]. Preclinical experimental models of breast cancer showed antineoplastic activity in statins [25]. Antitumor effects of statins are associated with their ability to slow down tumor cell growth, induce apoptosis, reduce its metastatic potential, and inhibit angiogenesis [26]. The known hypolipidemic and pleiotropic effects of statins determine the possible potential in the prevention and treatment of myocardial injuries during the treatment with antitumor drugs, without affecting the dynamics of the carcinogenesis [27].

The use of Dexrazoxane (Cardioxane) is questionable, given the common target with antitumor drugs. However, to some extent, its effect can be regarded as a specific cardioprotective one. In the Cochrane meta-analysis of adult cancer patients receiving anthracyclines, Dexrazoxane significantly reduced the risk of the heart failure development without significant differences from the control group in terms of efficacy and survival [6].

Therefore, the preparation for chemotherapy should include examination of the cardiovascular system before and during the treatment, and chemotherapy should be accompanied by a continuous cardiac treatment.

CONCLUSIONS

The anesthesiologist may see patients months and years after their chemotherapy. During this time, heart failure of varying degrees of severity is formed. A large risk group of patients with maximum cardiotoxicity and severe general surgery prognosis are those who received a prolonged chemotherapy treatment in childhood. The mechanisms of the myocardiocytes damage are difficult to correct, which urgently requires the inclusion of cardioprotective drugs in the chemotherapy treatment and in the follow-up period. The targets and methods of chemotherapy contradict the development of cardiovascular complications: the majority of authors confirm the dependence of cardiovascular complications formation frequency on the total dose of the chemotherapy drugs. The effectiveness of therapy also depends on the cumulation. Contradictions can be resolved by using endothelial protection drugs and statins.

When prescribing treatment for cancer patients, the interaction of a cardiologist and an oncologist is crucial. It is important to study the subject of the car-

diovascular therapy as a component of the antitumor treatment.

REFERENCES

1. Minimum clinical recommendations of the European Society of Medical Oncology (ESMO). Editors of the Russian translation: Prof. S.A. Tyulyandin, Candidate of Medical Sciences D.A. Nosov; Prof. N.I. Translatorova. M.: The Blokhin Russian Academy of Medical Sciences Publishing Group, 2010, 436 pages;
2. Anthracycline Chemotherapy and Cardiotoxicity. John V McGowan, Robin Chung, Angshuman Maulik, Izabela Piotrowska, J. MalcolmWalker, Derek M. Yellon// Cardiovasc. Drugs Ther (2017) 31:63–75. DOI 10.1007/s10557-016-6711-0;
3. **Rickard J., Kumbhani D.J., Baranowski B., Martin D.O., Tang W.H., Wilkoff B.L.:** Usefulness of cardiac resynchronization therapy in patients with Adriamycin-induced cardiomyopathy, Am J Cardiol; 2010, feb. 15, 105 (4): 522–526;
4. **L.V. Bolotina, A.G. Ovchinnikova:** Problems of cardiovascular complications induced by chemotherapy and targeted drugs // Studies and practice in medicine. 2015, vol. 2, No. 4, pp. 106–114;
5. Cardiovascular prophylaxis 2017. Russian national recommendations // Russian Journal of Cardiology. 2018; 23(6): 7–122. http://doi.org/10.15829/1560-4071-2018-6-7-122
6. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines // Russian Journal of Cardiology, 2017, №3 (143): pp. 105–139. http://doi.org/10.15829/1560-4071-2017-3-105-139
7. **R.A. Yandieva, E.K. Saribekyan, M.N. Mammadov:** Cardiotoxicity in the treatment of cancer // Journal of Heart and Vascular Diseases. Vol. 6, No. 17, 2018, pp. 3–11;
8. **G. E. Gendlin, E. I. Emelina, I. G. Nikitin, Y. A. Vasyuk:** Modern view on cardiotoxicity of chemotherapy of oncological diseases, including anthracycline antibiotics. // Russian Journal of Cardiology. 2017, 3 (143): pp. 145–154;
9. **Henriksen P.A.** Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart, 2018; 104: pp. 971–977;
10. **E. V. Pozhilova, O. S. Levchenkova , V. E. Novikov:** The regulatory role of the mitochondrial pore and the possibilities of its pharmacological modulation // Reviews on clinical pharmacology and drug therapy. Volume 12. 2014. Vol. 3, pp. 13–19;
11. **A.T. Teplyakov, S.N.Shilov, A.A. Popova, E.V. Gracova, et al:** State of the cardiovascular system in patients with anthracycline-induced cardiomyopathy // Bulletin of Siberian medicine. 2017; 16 (3): pp. 127–136;
12. **A.V. Novik:** Anemia and metabolic disorders in cancer patients // Practical oncology. 10. №3. 2009. pp. 131–140;
13. **Dzhugashvili M., Pokrovsky V. S., Snegovoy A. V.** Novel approaches for the correction of micronutrient deficiency in patients with malignant tumors. Malignant Tumours. 2016; 2: 55–65. http://DOI:10.18027/2224–5057–2016–2–55–65
14. **Falanga A., Marchetti M.** Hemostatic biomarkers in cancer progression. Thrombosis Research, 2018, V. 164 (Suppl. 1): pp. 54–61;
15. Practical recommendations for the prevention and treatment of thromboembolic complications in cancer patients // Practical recommendations of RUSSCO. - Version 2013. – pp. 372–376;
16. **Kilickap S, Barista I, Akgul E, Aytemir K, Aksoy S, Tekuzman G.** Early and late arrhythmogenic effects of doxorubicin. South Med J. 2007; 100: pp. 262–265. http://doi:10.1097/01.smj.0000257382.89910.fe [PubMed]
17. **D.N. Kushlinskiy, I.V. Tereshkina, V.G. Degtyar et al:** Vascular endothelium growth factor and its receptors in ovarian cancer//Molecular medicine. 2013, pp. 3–11;
18. **Lezhnev A., Paramonov V, Solontsov O, Davidov D, Novikov D, Davidov A, Bikbaev R.** Endotelial disfunction in The Anaesthesiologists practice//Archiv Euromedica. 2018. Vol.8. №1, pp. 93–96;
19. **I. B. Podubna, N.F. Orel:** Manual for chemotherapy of tumor diseases. Editor: N. I. Translatorova. M. 2011: pp. 435–436;
20. **Volkova M, Russell R.** Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment //Curr Cardiol Rev. 2011 Nov; 7(4): pp. 214–220;
21. **E.A. Gaisina, O.V. Nekrasova, V.I. Pavlova:** Influence of the preparation of rheamberine on the cardiotoxic effect of anthracyclines in the treatment of locally spread breast cancer // Tyumen Medical Journal. № 3-4. 2010, pp. 41–42;
22. Carvedilol Administration Can Prevent Doxorubicin-Induced Cardiotoxicity: A Double-Blind Randomized Trial Tashakori Beheshti A. Mostafavi Toroghi H. Hosseini G. Zarifian A. Homaei Shandiz F. Fazlinezhad A. Cardiology. 2016; 134: 47-53. https://doi.org/10.1159/000442722
23. **Y.A. Vasyuk, E.L. Shkolnik, V.V. Nesvetov et al.,** Anthracycline cardiotoxicity: prospects of using Ivabradine "Consilium Medicum. Cardiosomatics". 2012. V 3. №4, pp. 65–69;
24. **Riad A., Bien S., Westermann D. et al.** Pretreatment with statin attenuates the cardiotoxicity of doxorubicin in mice // Cancer Res. 2009. Vol. 69 (2), pp. 695–699;
25. **Zakikhani M., Dowling R., Fantus I.G. et al.** Metformin is an AMPkinase-dependent growth inhibitor for breast cancer cells // Cancer Res. 2006. Vol. 66. P. 10269–10273;
26. **Hindler K., Cleeland C. S., Rivera E., Collarda.** The Role of Statins in Cancer Therapy//The Oncologist. 2006. Vol. 11, pp. 306–315;
27. **Bonovas S., Filioussi K., Tsavaris N. et al.** Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials // J. Clinic. Oncol. 2006. Vol. 21 (30), pp. 4808–4817;

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TWO-STAGE OPERATIVE MANAGEMENT OF EARLY ONSET SCOLIOSIS

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KEYWORDS — early onset scoliosis; growth-friendly implant; conversion surgery; transpedicular screw fixation; 2-stage management.

INTRODUCTION

Early-onset scoliosis (EOS) remains challenging for spinal surgeons all over the world. The cornerstone of EOS treatment is a decision making. Deformity correction with dorsal instrumentation using transpedicular screw fixation (TSF) implant is a golden standard of adolescent idiopathic scoliosis treatment providing excellent results with relatively low complication rates[9]. Comparing with AIS, in EOS surgeon has to deal with growing spine, posing a child at risk of developing crankshaft phenomenon, correction loss and need for revision surgery in case of choosing TSF. However, the question about which spinal implant is the best for growing spine still remains controversial. Nowadays there are a plenty of growth friendly constructs but data referred to complications, reoperation rate and a risk of correction loss differs from study to study[6, 8, 10, 11].

The main issue is whether to perform an early operation using growth friendly implant or wait unless growth spurt finishing and perform TSF construct implantation. It's well-known that bracing alone can't be an effective way to prevent scoliosis progression to surgery[3]. Otherwise, traditional growing rods (TGR) being the most popular implant for EOS surgery, can lead to a different complications rate mainly associated with open implant distractions. Unlike TGR new implants such as MAGEC and Shilla don't require additional operation for distraction procedures, although there isn't any reliable evidence for one of these implants being superior to another[10].

Despite all mentioned issues there is an option for EOS management utilizing 2 stages of surgical treatment. First one is early deformity correction followed by implantation of growth-friendly non-distractable device with further reoperation changing growth-friendly implant to TSF construct ("implant conversion"). We present here a case for this tactical decision.

CASE PRESENTATION

10-year-old child have been referred to Filatov Children's City Hospital for operative treatment of EOS. He had his pectus excavatum been corrected earlier at the age of 4. The child has genetically proven Marfan syndrome. He received full list of conservative treatment regimens including bracing (TLSO), physical therapy and underwent treatment in our special scoliosis rehabilitation facility. Spinal deformity was presented as S-shaped scoliosis curve consisted of 2 curves. Curve magnitudes were 81o for thoracic and 80o for lumbar respectively. Side-bending X-rays revealed both thoracic and lumbar curves were structural. Curve type was defined as Lenke 3CN, King type 1 (fig. 1). Th4-Th12 kyphosis was 19o and Risser test 0. For the first operation growth-friendly hook-type non-distractableLSZ-3 implant was used which application is approved by the ministry of health of Russian Federation.The mechanism of distraction is presented with hooks at distal 2 levels of fixation freely attached to plate-like rods. This type of construct allows plate-type rods moving freely through distal hooks allowing the spine to grow caudally. Three-dimensional stability in this case is provided by rectangular plate-like shape of rods allowing them to move only axially at the distal level of fixation. We got excellent correction rate both for thoracic curve (84%) and for lumbar curve (82,5%) (fig. 2). Child's standing and sitting height increased to 147 cm and 73,5 cm with 6 cm increment. First 3 postoperative years underwent without any complications with stable curves but the X-Ray made on 4th postoperative year revealed increased curve magnitude for both curves. This trend remained unchanged till his child's next referral to our department (fig. 3).

Further history of curve magnitude shift presented in the Table 1.

The second operation was performed at the age of 16. After performing posterior longitudinal incision and achieving approach to pedicles we noticed unequally distributed bone formation on both side of vertebrae in lumbar region as well as completely bone cover in thoracic region (fig. 4). It was defined as a

Table 1. *Curve magnitude (Cobb angle) and correction rate (in brackets) for two curves (thoracic and lumbar) changing from pre-operative X-rays, during postoperative period, right after implant changing (conversion*) and 6-years post second surgery**.*

	Pre-op	Post-op	1 year	2 years	3 years	4 years	5 years	6 years	Conv*	6 mon**
Thoracic	80°	13° (84%)	14° (82,5%)	14° (84%)	14° (84%)	22° (72,5%)	22° (72,5%)	22° (72,5%)	19° (76%)	19° (76%)
Lumbar	81°	14° (82,5%)	12° (85%)	12° (85%)	12° (85%)	28° (65%)	29° (64%)	29° (64%)	23° (72%)	23° (72%)

Fig. 1

Fig. 2

Fig. 3

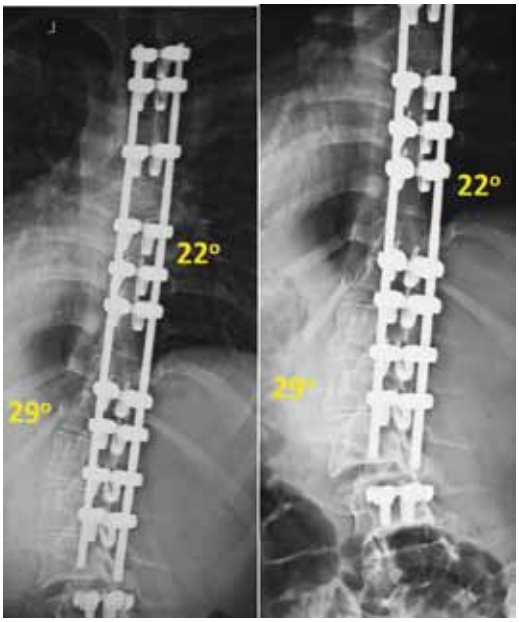

Fig. 4

partial spontaneous fusion. Standard TSF was applied using free-hand technique for screw placement and X-Ray for screw position confirmation. Immediate postoperative correction rate was 76% for thoracic and 71% for lumbar curve respectively which hasn't been changed till 6 months postop (fig. 5). SRS-24 used as patient-reported outcome measurement tool with overall median value of 4,23 representing overall excellent result especially addressing to appearance (fig. 6).

We conducted fully morphometric assessment of the spine using special parameters showed in fig. 7. The assessment of these parameters revealed general wedging index increase due to a disc-vertebral index on concave side decrease (fig. 8). This phenomenon occured during period of child's growth spurt starting at the age of 13 years and stabilizing at approximately 14 years. Patient's standing height increased to 178 cm (+31 cm), while sitting height increased to 83,5 cm (+10 cm). Both curves were involved in this process similarly.

DISCUSSION

Detailed morphometric analysis supported out theory about the cause of curve magnitude rising. According to previous studies male adolescents usually have their growth spurt during a period from the age of 13 till 15 years old [2]. We made a suggestion that this patient developed partial spontaneous fusionbefore growth spurt appeared. That could result in unequal growth distribution between 2 parts of vertebral end plates and served as trigger to activation of Heuter-Volkmann's law, which could lead to further curve progression. Another factor contributed to curve progression was so called crankshaft phenomenon which can develop in skeletally immature children after spinal fusion as a result of continued spinal growth with increased axial rotation of fixed spine[5].

Despite the evidence stating that TSF implants have higher correction rates and lower complication rates compared with hook-type constructs[4], our case is an example of an excellent correction rate of 82,5% and 84% for thoracic and lumbar curves respectively. As LSZ-3 implant is similar to Luque-trolley construct, it's well known that there are potential limitations for gaining spinal growth after surgery mainly caused by limited length of rods' free distal parts [7].

Despite loss of correction in some degree we achieved overall correction rate after conversion surgery 76% for thoracic and 71% for lumbar curve respectively with 2 surgeries, while traditional growing rods surgery requires usually up to 6 repetitive operations to perform lengthening which poses a child at risk of developing various complications [1]. We didn't observe any medical or implant-associated complications during 6 years before conversion surgery.

Fig. 5

Fig. 6

MAGEC implant was developed with the aim for achieving lower risk of reoperations and opportunity of distant lengthening at outpatient hospital, but there are still plenty of studies reporting relatively high rates of either implant-related and medical complications

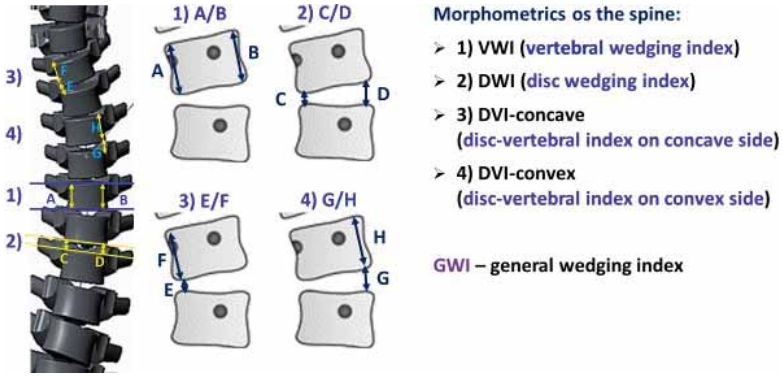

Fig. 7

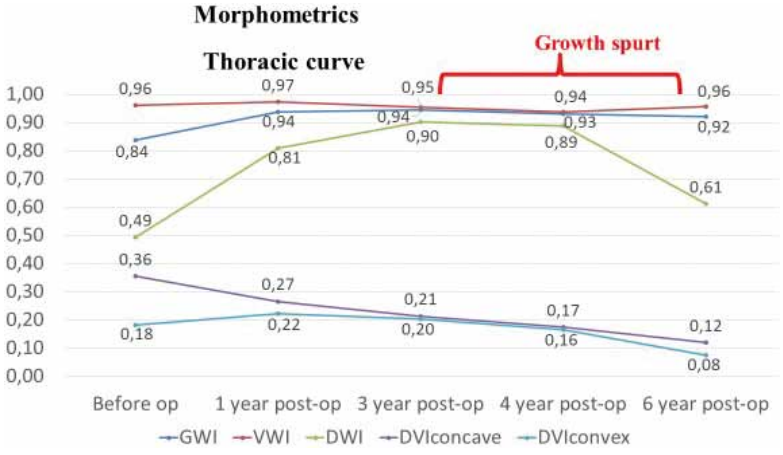

Fig. 8

[8].One of the key points of our clinical case is getting high increments of standing and sitting growth with values of 34 cm and 10 cm respectively.

CONCLUSIONS

Early EOS treatment allows to avoid many of complications and reoperations. Growth-friendly LSZ-3 implant can provide primary stabilization and maintain correction till growth spurt appear. Further TSF implant implementation can reliably stabilize the spine. However, it's still not defined which period of time is best fit for conversion surgery considering a risk that crankshaft phenomenon may occur. Further studies are necessary to define the best option for EOS correction.

REFERENCES

1. **Andras L.M. [et al.].** Growing Rods Versus Shilla Growth Guidance: Better Cobb Angle Correction and T1–S1 Length Increase But More Surgeries // Spine Deformity. 2015. № 3 (3). C. 246–252.
2. **Charles Y.P., Canavese F., Diméglio A.** Curve progression risk in a mixed series of braced and nonbraced patients with idiopathic scoliosis related to skeletal maturity assessment on the olecranon // Journal of Pediatric Orthopaedics Part B. 2017.
3. **Hung A.L.H. [et al.].** Thumb Ossification Composite Index (TOCI) for Predicting Peripubertal Skeletal Maturity and Peak Height Velocity in Idiopathic Scoliosis: A Validation Study of Premenarchal Girls with Adolescent Idiopathic Scoliosis Followed Longitudinally Until Skeletal // The Journal of bone and joint surgery. American volume. 2017. № 17 (99). C. 1438–1446.
4. **Kim Y.J. [et al.].** Comparative analysis of pedicle screw versus hook instrumentation in posterior spinal fusion of adolescent idiopathic scoliosis. // Spine. 2004. № 18 (29). C. 2040–8.
5. **Murphy R.F., Mooney J.F.** The Crankshaft Phenomenon // Journal of the American Academy of Orthopaedic Surgeons. 2017.
6. **Ouellet J.A. [et al.].** Evaluation of the Modern Luque Trolley Construct for the Treatment of Early-onset Scoliosis Using a Gliding Implant in an Immature Animal Model // Clinical Spine Surgery. 2017. № 4 (30). C. E460–E465.
7. **Pratt R.K. [et al.].** Luque trolley and convex epiphysiodesis in the management of infantile and juvenile idiopathic scoliosis. // Spine. 1999. № 15 (24). C. 1538–47.
8. **Rushton P.R.P. [et al.].** Magnetically controlled growing rods in the treatment of early-onset scoliosis // The Bone & Joint Journal. 2017. № 6 (99-B). C. 708–713.
9. **Tambe A.D. [et al.].** Current concepts in the surgical management of adolescent idiopathic scoliosis // Bone and Joint Journal. 2018. № 4 (100B).
10. **Thakar C. [et al.].** Systematic review of the complications associated with magnetically controlled growing rods for the treatment of early onset scoliosis // European Spine Journal. 2018.
11. **Yang S. [et al.].** Early-Onset Scoliosis: A Review of History, Current Treatment, and Future Directions // Pediatrics. 2016. № 1 (137). C. e20150709.

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CHOICE OF OSTEOSYNTHESIS IN FRACTURES OF THE PROXIMAL FEMUR IN CHILDREN

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INTRODUCTION

Fractures of the femur are some of the serious injuries that occur in childhood. Due to the increasing number of types of extreme sports, the development of infrastructure, an increase in the number of road traffic accidents, these types of fractures are no longer rare and, according to various authors, make up to 16% of all fractures. Fractures of the proximal femur deserve special attention, which is associated with the peculiarities of the anatomical location. If surgical treatment of such fractures is necessary, the question arises of choosing a method for fixation of fragments. [2, 4, 6].

MATERIALS AND METHODS

In the period from 2000 to 2019 in the Unit of Traumatology N.F. Filatov Children's Hospital were treated 725 patients with fractures of the lower extremities. Of them, 332 children — with fractures of the femur, of which 46 children — with fractures of the proximal femur. The largest number were intraarticular fractures (osteoepiphysiolysis of the femoral head) — more than 50%, femoral neck fractures and intertrochanteric fractures — 12%, fractures of the upper third of the femoral diaphysis — 30%. The choice of fixators was determined by the anatomical peculiarity of the damaged segment, the plane of the fracture and its proximity to the growth plate, the patient's age and the presence of concomitant pathology. The main criterion for choosing surgical access and implant was bone anatomy and the presence of active growth zones. [2, 4, 6]. It is known that at the age of about 4 to 6 years, ossification of the greater trochanter of the femur occurs, almost complete ossification of the femoral head (except its medial surface) and the ossification of the femoral neck ends. The medial part of the femoral head, the small trochanter, the apex of the greater trochanter, the metaepiphyseal growth plate of the femur in this age interval still have a cartilaginous structure. Starting from 7 years old and pumping in at approximately 10 years of age, the ossification of the femoral head, major and minor trochanters takes place. The proximal metaepiphyseal growth plate, as well as the growth plate of the greater and lesser trochanters, have a cartilaginous structure. At the age of 10 to 14 years, the ossification of the apophyses occurs, and at the age of 15 to 17 years, the final synostosis of the metaepiphyseal sprout of the femur and sprout zones of the greater and lesser trochanters takes place. [5]. Based on the age-related features of bone anatomy, the selection of the fixator was individual and proceeded from the fact that when the implant was placed, the growth plate remained intact. [4, 5]. The general requirement for choosing the optimal fixation method was minimally invasive and maximum stability with the possibility of early rehabilitation of the patient. According to the AO classification, we dealt mainly with fractures: 31-E / 1.1, 31-M / 2.1, 31-M / 3.1, 31-M / 3.2. [7, 8]. Surgical treatment was carried out during the first 48 hours after admission to the hospital.

Clinical example 1. A 10-year-old child, a boy engaged in the football sports section, fell on his right lower limb during training. A few days after the fall, in connection with severe pain, the parents delivered the child to the clinic. From the moment of injury to the moment of seeking medical help, the child noted an increase in pain in the area of the right hip joint and further impossibility of resting on the right leg. Radiography revealed epiphysiolysis of the head of the right femur with a shift. Minimally invasive osteosynthesis with cannulated screws was performed. The child is upright and discharged from the hospital during the first week. Fixators removed after 15 months (Fig. 1, 2). [3]. Clinical example 2. A boy aged 17 was admitted to the hospital after an injury sustained when falling from a bicycle onto his left lower limb. As a result of the injury, a fracture of the neck of the left femur occurred (Fig. 3). Osteosynthesis was performed by cannulated screws. The result of treatment after 6 months is presented in Fig. 4. [3]. Clinical example 3. A 13-year-old child with a combined injury from a car accident and having a closed overtrochanteric fracture of the right femur with a displacement was selected

Fig. 1

Fig. 2

Fig. 3

Fig. 4

by the method of osteosynthesis using the Pediatric Hip Plate (PHP) 130° 5.0 (Fig.5, 6). To a younger age, with subtrochanteric fractures of the femur located closer to the diaphyseal section of the bone, minimally invasive intramedullary TEN osteosynthesis was performed. Radiographs of a child 5 years old before and 4,5 months after treatment are presented in Fig. 7, 8. [1]. At the oldest ages, children received intramedullary pin fixation. Figure 9, 10 shows the radiographs of one of the clinical cases, a 16-year-old girl who had a pathological fracture of the proximal left femur against a benign aneurysm cyst (the diagnosis was made histologically). Metal osteosynthesis using PFNA and bone grafting supplemented with biocomposite material was performed (Fig. 9, 10).

RESULTS AND DISCUSSION

Of the variety of fixatives, cannulated screws were used: for osteoepiphysiolysis of the femoral head, lockable plates (PHP) and intramedullary fixators (TEN, PFNA) for intertrochanteric fractures and fractures of the upper third of the femur. Stable-functional osteosynthesis allowed early start activation of patients. Removal of fixatives was carried out after complete consolidation of the fracture — on average after 6–12 months, depending on age.

CONCLUSIONS

The use of various types of fixatives for fractures of the proximal femur in children should be strictly individual and create the least trauma to the surrounding anatomical structures when performing osteosynthesis, and subsequent removal of the fixative, without affecting the development and growth of bone. A rational approach when choosing a metal fixator allows for sufficient stability in the fracture area, contributing to the early functional rehabilitation of the injured limb and the prevention of immobilization complications.

REFERENCES

1. **Alberghina F, Andreacchio A, Cravino M, Paonessa M, Canavese F.** Extra-articular proximal femur fractures in children and adolescents treated by elastic stable intramedullary nailing. Int Orthop. 2019 Dec;43(12):2849-2856. doi: 10.1007/s00264-019-04379-x. Epub 2019 Jul 27.
2. **Management of Pediatric Femoral Neck Fracture. Patterson JT, Tangtiphaiboontana J, Pandya NK.** From the Department of Orthopaedic Surgery, University of California, San Francisco, CA. J Am Acad Orthop Surg. 2018 Jun 15;26(12):411-419. doi: 10.5435/JAAOS-D-16-00362.
3. **Palocaren T.** Department of Orthopaedics, Christian Medical College, Vellore, Tamil Nadu, India. Femoral Neck Fractures in Children: A Review. Indian J Orthop. 2018 Sep-Oct;52(5):501-506. doi: 10.4103/ortho.IJOrtho_404_17.
4. **Rockwood and Wilkins** Fractures in Children.1252 pages. LWW; Eighth edition (October

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

Fig. 10

1, 2014) ISBN-10: 1451143931 ISBN-13: 978-1451143935.

5. **Sadofieva VI.** Normal X-ray anatomy of the osteoarticular system of children. LENINGRAD "MEDICINE" Leningrad branch 1990.
6. **Sankar WN, Mehlman CT.** The Community Orthopaedic Surgeon Taking Trauma Call: Pediatric Femoral Neck Fracture Pearls and Pitfalls. J Orthop Trauma. 2019 Aug;33 Suppl 8:S22-S26. doi: 10.1097/BOT.0000000000001541.
7. https://www2.aofoundation.org/wps/portal/surgery.
8. https://radiopaedia.org/articles/proximal-femoral-fractures.

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SURVIVAL AFTER SURGICAL TREATMENT OF SYNCHRONOUS METASTATIC LESION OF THE ADRENAL TUMORS

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ABSTRACT — This article presents an assessment of the survival rate of 68 patients after surgical treatment of synchronous metastatic lesion of the adrenal tumors in the in the Department of oncourology of the P.A. Hertsen Moscow Oncology Research Center — branch of FSBI NMRRC of the Ministry of Health of Russia, Moscow, Russian Federation. Almost all patients (86.8%) underwent open access adrenalectomy, the rest — laparoscopic access. The duration of follow-up for all patients was on average 14.0 months. The morphological type of tumor affects the survival of patients with synchronous metastatic adrenal lesions. We recorded significantly greater survival in patients with renal cell carcinoma compared to non-small cell lung cancer, melanoma and urothelial cancer (p=0.001).
FINDINGS: in patients with synchronous adrenal metastatic lesions after surgical treatment, the one — year survival rate is 53.5±6.5%, three-year survival rate is 29.8±6.8%, and five-year survival rate is 14.9±1.1%

KEYWORDS — Metastatic adrenal tumors, surgical treatment, laparoscopic adrenalectomy, open adrenalectomy, survival.

INTRODUCTION

Currently, adrenal tumors are detected with greater frequency due to the better quality of radiation diagnosis [1, 2]. Adrenal tumors, including metastatic tumors, are detected in about 3.4% of cases with computed tomography [3].

Because of the rich vascularization, the adrenal glands are the organ of metastasis lesions [4]. The adrenal glands (NP) hold the fourth place in the frequency of localization of metastatic tumors [5]. In the presence of cancer history, the probability of having metastatic lesions is about 50% [6]. Currently, the main method of treatment of synchronous metastatic lesions of the adrenal is surgical: open, laparoscopic, robot-assisted adrenalectomy. Therefore, the survival of patients with synchronous metastatic of the adrenal tumors lesions after surgical treatment is of particular interest to doctors.

Aim

Assessment of survival after surgical treatment of synchronous metastatic lesion of the adrenal tumors.

METHODS

The study included 68 patients who were treated in the P.A. Hertsen Moscow Oncology Research Center — branch of FSBI NMRRC of the Ministry of Health of Russia in the period from 1991 to 2019. All patients have agreed to the processing of personal data. All patients had synchronous adrenal metastatic lesion and underwent simultaneous surgery in the form of removal of the primary tumor and adrenalectomy. For all patients, we evaluated overall survival-time from adrenalectomy to the date of last contact or death of the patient, and progression-free survival — calculated from the date of adrenalectomy to disease progression. We did not include patients with metachronous metastatic adrenal lesions in the study.

Statistical processing of the results obtained during the study was carried out using the program SPSS Statistics 23 (IBM, USA). Survival in groups of patients in a certain period of time was carried out using the Kaplan-Meyer method.

RESULTS

All patients were around 52–64 years old. The number of men prevailed over the number of women: 51(75%) and 17(25%). The most common localization of the primary tumor was renal cell carcinoma (RCC) - 58(85.3%). There were 5(7.4%) people with non-small cell lung cancer (NSCLC). The diameter of the adrenal tumor was on average 44 mm (4.0–170.0 mm). The grouping of patients based on the side of the adrenal lesion is shown in fig. 1.

The majority of patients underwent open access adrenalectomy — 59 (86.8%), the remaining 7(10.3%) — laparoscopic access. There were 2 (2.9%) conversions. A small number of patients to whom adrenalectomy was performed by laparoscopic access is related to the presence of infiltrative tumor growth, tumor thrombus of the renal or inferior Vena cava, the presence of previous surgical interventions on the abdominal organs, the tumor size (more than 5 cm).

The median follow-up time was 14.0 months. In patients with synchronous adrenal metastatic lesions, one-year, 3-year, and 5-year survival rates were— 53,5±6,5%, 29,8±6,8% and 14.9±1.1%. Median progression-free survival in patients with synchronous adrenal metastatic lesions was 9 months (1-140).

One-year, three- and five-year progression-free survival in patients with synchronous adrenal metastatic lesions was 40,3±6,2%, 19,2±5,6%, 8,5±4,9% accordingly.

There was no statistically significant difference in survival of patients with primary tumor localization in lung and metastatic adrenal lesions in the studied group of patients (p=0.911; Log Rank).

In Cox regression analysis, survival in patients with synchronous adrenal lesions was influenced by the morphological type of tumor (with a favorable prognosis for PCR compared to NSCLC, melanoma and urothelial cancer), p=0.001.

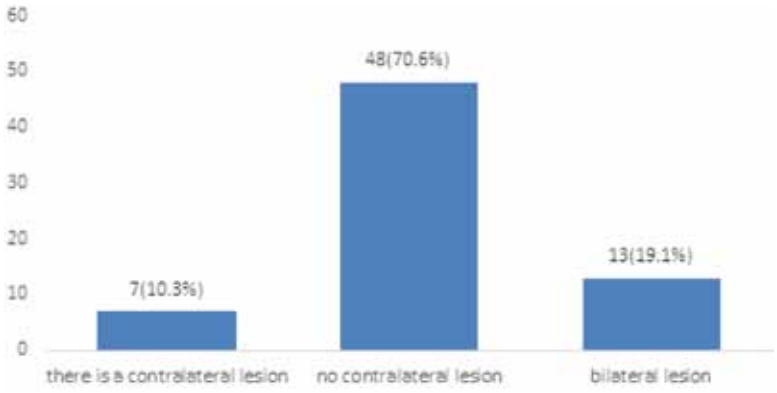

Fig. 1. *Number of patients based on the side of the adrenal tumors lesion*

DISCUSSION

Analysis of literature data shows that adrenal metastases occur in 40–50% of patients with liver cancer or PCR, in 25% of patients with melanoma or NSCLC, breast cancer — 35% [7]. In our study, most of the metastases came from the kidney (PCR) – 85.3%. According to Frilling A. et al., 89% of patients with adrenal metastatic lesions had a history of PCR [8].

According to Lin C. T. et al. the size of the adrenal tumor has a prognostic value [4]. Thus, 25% of adrenal lesions less than 3 cm were metastatic, but 86% of adrenal metastatic lesions were greater than 6 cm [4].

The size of the adrenal tumor also plays a role in the planning of surgical treatment tactics. Thus, laparoscopic adrenalectomy is effective in patients with tumor size up to 5 cm [9]. With a larger tumor size (≥ 5 cm), there may be an increased risk of postoperative complications and a decrease in the efficacy of treatment after laparoscopic adrenalectomy [9].

The stage of malignancy of the primary tumor also has a prognostic value in the prognosis of metastatic lesions of the adrenal tumors [4]. Thus, only 25% of patients (6 out of 24) in the clinical stage of T1 or T2 had metastatic adrenal malignancies. And, in the clinical stage of T3 or T4, up to 56% of patients (14 out of 25) had metastatic adrenal lesions [4].

The overall survival prognosis for patients with metastatic adrenal cancer leaves much to be desired. After adrenalectomy, about 25% of patients with isolated adrenal metastasis achieve 5-year relapse-free survival [10]. In another study, the overall 5-year survival rate was 33% (calculated using the Kaplan-Meier method) [11]. The Russian study showed a total five-year survival rate of 46.8+11.7% in patients with secondary adrenal tumors after adrenalectomy (calculated by the Kaplan-Meier method) [12]. Our study showed a lower overall five-year survival rate in the studied patients — 14.9% (Kaplan-Meier calculation), perhaps due to the morphological type of tumors and their differentiation (with a tendency to low- and undifferentiated).

CONCLUSIONS

The most common primary tumor localization was the renal cell carcinoma (85.3%). In the prognosis of survival in synchronous metastatic lesions of the adrenal tumors, it is necessary to take into account the morphological type of tumor. In patients with synchronous metastatic adrenal tumors lesions after surgical treatment, one-year survival occurs in every second case, three-year survival occurs in every third case, five-year survival happens in every seventh case.

REFERENCES

1. **Boland GW, Blake MA, Hahn PF, Mayo-Smith WW.** Incidental adrenal lesions: principles, techniques, and algorithms for imaging characterization. Radiology 2008;249(3):756–775. doi: 710.1148/radiol.2493070976.
2. **Kostin A.A., Tolkachyov A.O., Kul'chenko N.G., Muradyan A.G.** Morphological analysis of the results of surgical treatment of patients with adrenal tumors. Morphology. 2017; 151(3): 78–78a.
3. **Nieman LK.** Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab. 2010; 95(9): 4106–4113. doi: 4110.1210/jc.2010-0457
4. **Lin CT, Shao IH, Chuang CK, Pang ST, Chang YH.** Isolated Synchronous Adrenal Lesions in Patients with Newly Diagnosed Extra-Adrenal Malignancies. International surgery. 2018; 103(3–4): 207-213. DOI: 10.9738/INTSURG-D-18-00019.1

5. **Bartlett E.K., Simmons K.D., Wachtel H., Roses R. E., Fraker D.L., Kelz R. R., Karakousis G.C.** The rise in metastasectomy across cancer types over the past decade. Cancer. 2015; 121(5): 747–757. doi:10.1002/cncr.29134

6. **Fassnacht M., Arlt W., Bancos I., Dralle H., Newell-Price J., Sahdev A., Dekkers O. M.** Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. European Journal of Endocrinology. 2016; 175(2): G1–G34. doi:10.1530/EJE-16-0467

7. **Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR.** The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 2004; 25(2):309–340.

8. **Frilling A, Tecklenborg K, Weber F, Kuhl H, Muller S, Stamatis G.** Importance of adrenal incidentaloma in patients with a history of malignancy. Surgery 2004; 136(6):1289–1296.

9. **Gryn A, Peyronnet B, Manunta A, Beauval JB, Bounasr E, Nouhaud FX, Rioux-Leclercq N, Caron P, Thoulouzan M, Verhoest G.** Patient selection for laparoscopic excision of adrenal metastases: A multicenter cohort study. International journal of surgery. 2015; 24: 75–80. DOI: 10.1016/j.ijsu.2015.10.038

10. **Duh QY.** Resecting isolated adrenal metastasis: why and how? Ann Surg Oncol. 2003; 10(10):1138–1139.

11. **Sebag F., Calzolari F., Harding J.** Isolated adrenal metastasis: the role of laparoscopic surgery. World J. Surg.2006; 30(5): 888–892.

12. **Koloskov V.V.** Metastatic adrenal tumors: Retrospective data review of a 10-year observation. Annals of surgery. 2007; 6: 35–37.

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DIAGNOSIS PARTICULARITIES OF TRAUMATIC DIAPHRAGMATIC RUPTURES

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KEYWORDS — trauma, rupture of the diaphragm, diagnosis, treatment, traumatic diaphragmatic hernia.

INTRODUCTION

Diaphragm rupture is one of the relatively rare and poorly studied type of injury, that causes complications and occurs in patients with blunt combined trauma of the chest and abdomen [1, 2]. Rupture of the diaphragm is characterized by the severity of the clinical course, the difficulty of timely diagnosis, the complexity of treatment and high mortality [1, 2]. The intense increase of trauma over the past decades makes the problem more relevant due to a noticeable tendency to increase the frequency of diaphragm rupture [3, 4]. According to the literature sources, the number of ruptures of the diaphragm varies from 0,5 to 6,8% in the overall structure of blunt combined and multiple injuries of the chest and abdomen [1, 5].

Recognition of diaphragm rupture in the early stages after a trauma is difficult [1, 6]. Some authors consider the diagnosis of victims to be untimely in more than 50% of cases, which determines an unfavorable prognosis [3, 4, 6]. It is also alarming that even during surgery for abdominal injuries diagnostic errors are made and the rupture of the diaphragm is detected during repeated surgery or autopsy [1].

Therefore, the aim of the work was to identify the features of clinical manifestations and modern concepts for diagnosing injuries of the diaphragm and its traumatic hernias.

MATERIAL AND METHODS

The analysis of the features of the clinical picture and diagnostic algorithms in 91 patients with diaphragm injury and 68 with traumatic diaphragmatic hernias was carried out. All patients were treated at the clinical bases of the Department of Oncology, Surgery and Palliative Medicine of Tver State Medical University since 1964. In most cases (83, 5%) among the victims were men. The median age was 37.2±1,7 years.

RESULTS AND DISCUSSION

The mechanisms of injury were the following: in 66 car accident trauma (61.5%), catatrauma (20.9%), a blow to the abdomen (7.7%), compression of the body between objects (5.5%), penetrating injuries (4.4%). The condition of most of the victims was of medium severity, due to the development of acute and massive blood loss, traumatic brain injury and the presence of bone fractures. Furthermore, the presence of alcohol intoxication significantly complicated the diagnosis of diaphragm injury.

During the physical examination of the chest in cases with large diaphragmatic hernias there were determined the lesion of the upper half of the chest on the side of the injury, weakening of the voice tremor, shortening of the percussion sound and in some patients the displacement of the mediastinum in the opposite direction. Weakened vesicular respiration was heard during auscultation. Peristaltic intestinal noises in the pleural cavity were detected in 42 patients.

X-ray and ultrasound diagnostic methods were used. However in some cases the use of ultrasound was impossible due to large amount of subcutaneous fat or the presence of subcutaneous emphysema due to multiple rib fractures, which is often found in diaphragm lesions.

The overview x-ray of the thoracic cavity in the left pulmonary field reveals an additional thin-walled formation which contains gas and liquid. It is also necessary to pay attention to the condition of the diaphragm domes, their location and mobility. The presence of liquid in the colon is better detected on a lateral x-ray. Usually the abdominal organs stationed in the chest cavity cause compression hypoventilation of the lung, which is manifested by a decrease in its volume and the convergence of pulmonary vessels. Indirect symptoms also include displacement of the mediastinum, trachea and main bronchi to the opposite side. The appearance of several horizontal levels of fluid of small size on the background of pulmonary tissue indicates a movement of the intestine into the pleural cavity.

Clinical experience shows that the diagnosis of suspected traumatic diaphragmatic hernias is not difficult, especially under conditions of a specialized clinic.

The analysis showed that the main causes of diagnostic errors were: rarity of this pathology; underestimation of anamnesis, which indicates injury of the chest or abdomen; refusal to use the radiological methods of diagnostics; insufficient knowledge of the clinical course of traumatic diaphragmatic hernias by doctors; incomplete examination of the thoracic and abdominal cavities.

Confirmation of the above can be the fact that the diagnosis was established correctly only in 2 of the 21 patients with strangulated traumatic diaphragmatic hernias.

CONCLUSIONS

To date, the problem of surgical treatment of diaphragm injury and its consequences remains extremely relevant. Early use of the x-ray method of diagnosis and ultrasound will reduce the multifaceted complications of diaphragm injury.

Optimal preoperative and intraoperative diagnosis of diaphragm injuries and dynamic monitoring of the patient in the postoperative period to identify the cause of rupture or formation of traumatic hernia of the diaphragm are the basis for the full treatment of the considered cohort of victims.

REFERENCES

1. **Aliev SA, Bayramov NIu, Aliev ES.** Osobennosti diagnostiki I taktiki khirurgicheskogo lecheniia razryvov diafragmy pri zakrytoi sochetannoi travme grudi i zhivota. Vestnik khirurgii im. I.I. Grekova. 2014. T. 173, № 4. P. 66–72.
2. **Ercan M, Aziret M, Karaman K, Bostancab B, Akoaylu M.** Dual mesh repair for a large diaphragmatic hernia defect: An unusual case report. Int J Surg Case Rep 2016; 28: 266-269. DOI: 10.1016/j.ijscr.2016.10.015
3. **Plekhanov A.N.** Travmaticheskaia diafragmalnaia gryzha. Vestnik khirurgii im. I.I. Grekova. 2012. T. 171, № 5. P. 107–110.
4. **Toidze VV, Vasyukova EL, Kaschenko VA, Akimov vp, Volkov AM.** Lecheniie gigantskoi diafragmalnoi gryzhi. Vestnik khirurgii im. I.I. Grekova. 2013. V. 172, № 6. P. 21–25.
5. **Lim BL, Teo LT, Chiu MT, Asinas-Tan ML, Seow E.** Traumatic diaphragmatic injuries: a retrospective review of the 12-year experience at a tertiary trauma centre. Singapore Med J 2016; 1–16. DOI: 10.11622/smedj.2016185
6. **Thiam O, Konate I, Gueye ML, Toure AO, Seck M, Cisse M.** Traumatic diaphragmatic injuries: epidemiological, diagnostic and therapeutic aspects. Springer Plus 2016; 5: 1614. DOI: 10.1186/s40064-016-3291-1

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SURGICAL APPROACH FOR TRAUMATIC RUPTURES OF THE DIAPHRAGM

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ABSTRACT — Traumatic ruptures of the diaphragm are characterized by the severity of the clinical course, the complexity of timely diagnosis, the compilation of treatment and high mortality [1, 2, 3]. The intensive growth of trauma over the past decades makes the problem more relevant due to the noticeable increase of the frequency of this pathology [4, 5]. According to the literature, the number of diaphragm ruptures varies from 0,5 to 6,8% in the overall structure of blunt combined and multiple trauma of the chest and abdomen [1, 6].
During surgery for abdominal injuries tactical errors are made and the rupture of the diaphragm is detected during repeated surgery or autopsy [1, 3].

KEYWORDS — trauma, ruptures of the diaphragm, treatment, traumatic diaphragmatic hernias.

OBJECTIVE

The aim of the work is to determine the optimal algorithms of surgical approach in the treatment of diaphragm trauma and traumatic hernias.

MATERIAL AND METHODS

The analysis of the features of the clinical picture and diagnostic algorithms in 91 patients with diaphragm injury and 68 with traumatic diaphragmatic hernias was carried out. All patients were treated at the clinical bases of the Department of Oncology, Surgery and Palliative Medicine of Tver State Medical University since 1964. In most cases (83,5%) among the victims were men. The median age was 37.2±1,7 years.

RESULTS AND DISCUSSION

The mechanisms of trauma were the following: car accident trauma (61.5%), catatrauma (20.9%), a blow to the abdomen (7.7%), compression of the body between objects (5.5%), penetrating injuries (4.4%). The condition of most of the victims was of medium severity.

All patients were operated under endotracheal intubation anesthesia not later than 7 hours from the moment of admission to the clinic. Laparotomy was the operative access in 78% of cases. In 22% of cases a thoracotomy was used when a thoracic or thoracoabdominal injury was suspected.

During the revision of the abdominal and thoracic cavities, a combined lesion of the diaphragm was noted. Hollow organs, liver and spleen were the most frequently affected. In some cases (31.9%), the most difficult situations were determined by the formation of massive hematomas of the retroperitoneal space due to damage of the vascular wall of a large vessel. In such situations the doctor had to restore the vascular wall and then continue the operation.

In 83.5% of cases during the revision of the diaphragm surface the lesion was localized on the left side, which can be associated with right-sided localization of the liver. Bilateral lesion was recorded less frequently, which was associated with severe mechanisms of injury of the abdomen, such as car accident trauma, catatrauma and abdominothoracic gunshot wounds. The size of the diaphragm ruptures varied in shape and length and ranged from 2 to 40 cm.

In 3.3% of cases, due to the vastness of the prolapse, it was necessary to proceed the diaphragm plastic intervention using a pericardial flap. In other cases, the diaphragm rupture was possible to be sutured with synthetic thread without tension by a two-row seam. The operation was completed by drainage of the paradiaphragmatic spaces by setting tubular drains to the site of injury. Despite this, in 12% of cases, the development of purulent complications was noted, which caused in 8.7% of cases the suture failure with the formation of traumatic diaphragmatic hernias.

Regardless of the nature of the hernia, the treatment of traumatic diaphragmatic hernia is only surgical. Scheduled surgery is indicated after a detailed x-ray examination of the patient. Only 42 of the 47 patients with diaphragmatic hernias were operated on. Five patients refused surgery for various reasons.

When choosing surgical access, the time taken from the moment of trauma, the type and location of the hernia were taken into account. Abdominal access, in our opinion, has very limited indications. It can be used in the acute period of trauma before the development of cicatricial changes (adhesions) between the hollow organs and the diaphragm. In the late diagnosis of traumatic diaphragmatic hernias we used thoracotomy access through 6-7 intercostal space due to

the presence of adhesions between the ectopic organs and the pleura, which cannot be separated through the laparotomy access. Thoracotomy is also indicated in case of injury of the right parts of the diaphragm.

The second important point of surgical intervention is the allocation of organs that have fallen into the thoracic cavity from dense adhesions. Careless manipulations can lead to damage and bleeding due to spleen trauma (in 60 patients).

The third stage of the operation is the return of the fallen organs to the abdominal cavity, which in some cases presents significant difficulties, especially in multiple dislocation. The forced displacement to the abdominal cavity of the stomach and intestine loops leads to the development of paresis in the near postoperative period.

Suturing the hernia gate in the diaphragm is usually not particularly difficult. For these cases, we used thick silk (No. 6), drawing together the edges of the diaphragm. Only in 3 cases it was necessary to apply an additional plastic procedure on the prolapse of the diaphragm using synthetic tissue.

Mortality among patients with strangulated hernias was comparatively high. Eleven people out of 21 patients died (52.4%). The main causes of death in this group of patients were the necrosis of the colon and stomach wall, purulent pleurisy and peritonitis. It should be noted that in 3 patients with strangulated traumatic diaphragmatic hernia the operation was started with a laparotomy, during which the parietal strangulation of the colon was not established.

CONCLUSIONS

To this day, the problem of surgical treatment of diaphragm lesions and its complications remains extremely relevant.

If there is a suspicion of the formation of a traumatic hernia in the postoperative period, it is necessary to give preference to the surgical method of treatment. In our opinion, compliance with these positions will help to improve the medical assistance to patients with various injuries of the diaphragm and traumatic diaphragmatic hernias.

REFERENCES:

1. **Aliev SA, Bayramov NIu, Aliev ES.** Osobennosti diagnostiki I taktiki khirurgicheskogo lecheniia razryvov diafragmy pri zakrytoi sochetannoi travme grudi i zhivota. Vestnik khirurgii im. I.I. Grekova. 2014. V. 173, № 4. P. 66-72.
2. **Plekhanov A.N.** Travmaticheskaia diafragmalnaia gryzha. Vestnik khirurgii im. I.I. Grekova. 2012. V. 171, № 5. P. 107-110.
3. **Falidas E., Gourgiotis S., Vlachos K., Villias C. (2015).** Delayed presentation of diaphragmatic rupture with stomach herniation and strangulation. Am J Emerg Med, 33 (9), 1329. e1–3.
4. **Toidze VV, Vasyukova EL, Kaschenko VA, Akimov vp, Volkov AM.** Lecheniie gigantskoi diafragmalnoi gryzhi. Vestnik khirurgii im. I.I. Grekova. 2013. V. 172, № 6. P. 21–25.
5. **Lim BL, Teo LT, Chiu MT, Asinas-Tan ML, Seow E.** Traumatic diaphragmatic injuries: a retrospective review of the 12-year experience at a tertiary trauma centre. Singapore Med J 2016; 1–16. DOI: 10.11622/smedj.2016185
6. **Thiam O, Konate I, Gueye ML, Toure AO, Seck M, Cisse M.** Traumatic diaphragmatic injuries: epidemiological, diagnostic and therapeutic aspects. Springer Plus 2016; 5: 1614. DOI: 10.1186/s40064-016-3291-1

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ANTIBIOTIC PROPHYLAXIS FOR PREVENTION OF SURGICAL SITE INFECTION IN EMERGENCY ONCOLOGY

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ABSTRACT — A prospective randomized controlled study was performed in 268 patients with complicated forms of colon cancer. The main group included 139 patients operated with doxycycline threads, and 129 patients operated with traditional sutures. The number of patients with complicated postoperative course in the main group (32.4%) was significantly lower than in the control (62.0%) ($p < 0.05$). The number of local complications in the main group (32.4%) was significantly lower ($p < 0.05$) than in the control (62.0%). Local complications caused lethal outcomes in 17.3% patients in the main group and in 31.8% of the control group ($p < 0.05$). The rate of surgical site infection in the main group (28.8%) was significant ($p < 0.05$) less than in the control (55.0%).

KEYWORDS — surgical site infection, antibiotic prophylaxis, doxycycline threads.

INTRODUCTION

To prevent a surgical site infections the implantation antibiotic prophylaxis is recently used [1, 2]. The use of this type of infections prevention in colon surgery appears to be promising [3] because such operations are accompanied with a high risk of operative wound contamination by intestinal microflora [4, 5] and high degree of biological leakage of anastomoses and intestinal sutures [6].

The purpose of the research was to study the efficacy of suture material with doxycycline in surgical operations for complicated forms of colon cancer.

MATERIALS AND METHODS

A prospective randomized controlled study was performed in 268 patients with complicated forms of colon cancer. In 120 patients the tumor was localized in the sigmoid colon, in 51 - in the cecum, in 26 - in the spleen bend of colon, in 29 - in the hepatic bend, in 42 - in other sections of the colon. Most often, the tumor process was complicated by obturative colon obstruction (184 patients - 68.7%), less by inflammatory infiltration or abscess in the region of tumor (45 patients - 16.8%) and tumor perforation with peritonitis (28 patients — 10.4%). Tumor bleeding was in 11 (4.1%) patients. There were 116 men and 152 women. The patients' age ranged from 30 to 92. Most of them (194 — 72.4%) were over 60.

All patients were urgently operated on. Radical operations (right-sided hemicolectomy, left-sided hemicolectomy, sigmoid and other colon resections) were carried out in 176 (65.7%) patients. Palliative operations like colostomies and bypass anastomoses — in 71 (26.5%) patients. 21 (7.8%) patients had just diagnostic laparotomies. All patients were divided into two groups which were comparable by sex, age and performed operations. The main group included 139 patients operated with doxycycline threads, and 129 patients were operated with traditional sutures.

In postoperative period we observed over the patients' condition and abdominal symptoms. The postoperative wounds were monitored. The general and local postoperative complications, as well as fatal outcomes were recorded, and its association to local complications was determined.

RESULTS

The number of patients with complicated postoperative period in the main group (32.4%) was significantly lower than in the control (62.0%) ($p < 0.05$). The postoperative fatality in the main group was 23.7%, but in the control group — 40.3%. The difference is not reliable ($p > 0.05$). The frequency of systemic postoperative complications was 24.5% in main group and 34.9% in control ($p > 0.05$). The fatal outcomes cause of general postoperative complications in the main group (6.5%) was not significantly different from the control (8.5%) ($p > 0.05$).

The frequency of local complications (anastomosis and sutures leakage complicated with peritonitis, as well as continued peritonitis, wound suppuration, phlegmon of abdominal wall, intestinal stenosis and etc.) in the main group (32.4%) was revealed to be significantly lower ($p < 0.05$) than in the control (62.0%). The same data were obtained from the analysis of fatal outcomes due to local postoperative complications. It caused the death in 17.3% patients in the main group and 31.8% in the control ($p < 0.05$).

The further analysis revealed that the frequency of surgical site infections in the main group (28.8%) was significantly lower ($p < 0.05$) than in the control (55.0%). The difference in the number of non-purulent

complications (like bleeding from the suture line, stenosis of intestinal stomas) in the main (3.6%) and control (7.0%) groups was statistically unreliable ($p > 0.05$). The above data allow to link the improvement of operation results in the main group with reduction of surgical site infections due to application of surgical suture material with antibiotic.

CONCLUSION

This variant of implantation antibiotic prophylaxis of surgical site infection (use of antimicrobial suture material with doxycycline) in abdominal operations for complicated forms of colon cancer is effective and appropriate for introduction into a wide clinical practice.

REFERENCES

1. **Obermeier A., Schneider J., Föhr P., Wehner S., Kühn K.D., Stemberger A., Schieker M., Burgkart R.** In vitro evaluation of novel antimicrobial coatings for surgical sutures using octenidine // BMC Microbiol. – 2015. – Vol. 15 (1). – P. 186.
2. **Mokhov E.M., Homullo G.V., Sergeev A.N., Alexandrov I.V.** Experimental development of new surgical suturing materials with complex biological activities //Bulletin of Experimental Biology and Medicine. – 2012. – T. 153. – № 3. – P. 409–413.
3. **Goi T., Ueda Y., Nakazawa T., Sawai K., Morikawa M., Yamaguchi A.** Measures for preventing wound infections during elective open surgery for colorectal cancer: scrubbing with gauze // Int Surg. – 2014. – Vol. 99 (1). – P. 35–39.
4. **Saito Y., Kobayashi H., Uetera Y., Yasuhara Y., Kajiura T., Okubo T.** Microbial contamination of surgical instruments used for laparotomy // Am J Infect Control. – 2014. – Vol. 42 (1). – P. 43–47
5. **Zebala L.P., Chuntarapas T., Kelly M.P., Talcott M., Greco S., Riew K.D.** Intrawound vancomycin powder eradicates surgical wound contamination: an in vivo rabbit study // J Bone Joint Surg Am. – 2014. – Vol. 96 (1). – P. 46–51.
6. **Arikanoglu Z., Cetinkaya Z., Akbulut S., Ilhan Y.S., Aygen E., Basbug M., Ayten R., Girgin M., Ilhan N., Dagli F.** The effect of different suture materials on the safety of colon anastomosis in an experimental peritonitis model // Eur Rev Med Pharmacol Sci. – 2013. – Vol. 17 (19). – P. 2587–2593.

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THE USE OF THERMOGRAPHY FOR DIAGNOSIS OF ACUTE APPENDICITIS

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ABSTRACT — A prospective controlled study was performed in 37 patients to check the capability of medical thermography. The method allows to capture infrared radiation and convert it into an image that records the heat distribution on the body surface. The method is not invasive and can be easily used in examining patients for the differential diagnosis of acute appendicitis in difficult cases.

KEYWORDS — medical thermography, acute appendicitis, diagnosis.

INTRODUCTION

Up to 50% of patients are hospitalized with suspected acute appendicitis [1]. About 40% of all urgent surgeries are appendectomies. 4 to 35.5% of it are made wrongly [1, 2] and can lead to a high level of surgical site infections [3]. The main difficulty in the diagnosis of acute appendicitis is the absence of pathognomonic symptoms. One of the promising method for pre-operative examination is thermography. In some diseases thermography is characterized by a high reliability of diagnostics approaching [4, 5].

The purpose of the research was to study the possibilities of thermography in the diagnosis of acute appendicitis.

MATERIALS AND METHODS

A prospective controlled study was performed. 37 patients with Acute appendicitis were examined. The male sex was the criterion for inclusion into the study group to exclude any diseases associated with the female reproductive system, as well as the absence of various chronic inflammatory processes in patients. All patients were diagnosed on the basis of a typical clinic of acute appendicitis and leukocytosis.

Patients were thermographed using a medical infrared imager "PERGAMED 640" with record and preservation of the results on an electronic carrier. The examination was carried out after preliminary preparation of the patient, which consisted of striping to the waist, after which the patient was forbidden touch the area of examination (anterior abdominal wall) for 10 minutes, the room temperature wile examination remained 20–22° C. The results of thermography were evaluated retrospectively after intraoperative diagnosis.

All the examined patients after diagnosis were divided into 3 groups: the 1st group included patients with intraoperatively diagnosed "Acute appendicitis"; the 2nd group — patients with intraoperatively diagnosis of "Acute mezadenitis"; and the 3rd group — patients with "Intestinal colic" (the diagnosis was put by exclusion after complete relief of the symptoms due to conservative measures).

RESULTS AND DISCUSSIONS

Based on the correlation between clinical diagnosis and thermography data, it is the following: the thermograms obtained in the first observation group indicated evident changes in the right ileal region. In this region, there was a local temperature increase, clearly manifested in the form of a color patch, contrasting with intact tissues. All the thermograms determined a local increase in skin temperature in the right ileal region on average by 1–1.5° C. The average temperature of this thermographic phenomenon was 0.6° C in patients with catarrhal appendicitis, 1.58° C with phlegmonous appendicitis and 2.2° C in patients with gangrenous appendicitis respectively. The diagnosis of acute appendicitis was confirmed intraoperatively and morphologically in all patients in this group. Slight differences in the temperature characteristics of patients with different forms of acute appendicitis do not allow verifying these forms at the preoperative stage. For perhaps clearer visualization of the results, additional color palettes were used.

There are no characteristic changes in the thermographic pattern were detected during analyzing the thermograms obtained in the second and third groups (patients without appendicitis). The average temperature in all areas of the abdominal wall did not have any characteristic changes and was 34.5° C in patients with "Acute mezadenitis", 34.2° C in patients with "Intestinal Colic" accordingly. All things considered, thermography allows you to differentiate the acute inflammatory process in the appendix from the not appendicular ones. For possibly clearer visualization of the results, additional color palettes were used.

The diagnosis of acute appendicitis is mainly based on clinical symptoms at present time. Thermog-

raphy as an objective method of clinical imaging can be complement the diagnostic process, especially in unclear clinical cases, relieving the patient of invasive diagnostic methods.The use of thermography for diagnosis of acute abdominal pathologyis not widely used. Therefore, the further extensive research for possibilities of thermography in emergency surgery is needed.

CONCLUSION

Medical thermography can be used as an additional method for acute appendicitis diagnosing, which makes it possible to diagnose correctly in complex cases. Pointing to the presence of inflammatory changes in the location of the appendix, thermography does not allow us to determine the shape of acute appendicitis. The use of medical thermography can significantly facilitate the differential diagnosis of acute appendicitis and other diseases of abdominal cavity.

REFERENCES:

1. **Dubrovsky A.V., Kovalev A.I., Petrov D.Yu., Smirnov A.V.** Sovremennye aspekty lecheniya ostrogo appendicita [Modern aspects of acute appendicitis treatment] // Vestnik eksperimental'noy i klinicheskoy hirurgii [Bulletin of Experimental and Clinical Surgery]. – 2013. – Volume 6. – No. 3. – p. 375–384. (in Russian)
2. **Soroka A.K.** Laparoskopiya v provedenii klinicheskih i morfologicheskih paralleley appendektomiy [Laparoscopy in conducting clinical and morphological parallels of appendectomy] // Endoskopicheskaya hirurgiya [Endoscopic surgery]. – 2013. – No. 1. – p. 12–15. (in Russian)
3. **Mokhov E.M., Sergeev A.N.** Implantacionnaya antimikrobnaya prophilaktika infekcii oblasti khirurgicheskogo vmeshatel'stva [Implantation antimicrobial prevention of infection in the surgery intervention area] // Sibirskoe medicinskoye obozrenie [Siberian Medical Review]. – 2017. – No. 3 (105). p. 75–81. (in Russian)
4. **Bichinho G.L., Gariba M.A., Sanches I.J., Gamba H.R., Cruz F.P.F., Nohama P.** A computer tool for the fusion and visualization of thermal and magnetic resonance images // J. Digit. Imaging. – 2009. – Vol. 22. – № 5. – P. 527–534.
5. **Ring E.F.** The historical development of thermometry and thermal imaging in medicine // J. Med. Eng. Technol. – 2006. – Vol. 30. – № 4. – P. 192–198.

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TENSOMETRIC CHARACTERISTICS OF DE-EPITHELIZED SKIN GRAFT AND POLYPROPYLENE MESH IMPLANT USED IN HERNIOPLASTY

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ABSTRACT — The purpose of the research work was to study the mechanical properties of a de-epithelized skin graft and polypropylene mesh prosthesis used in herniology. Tensometric studies included: tensile strength and bursting strength of suture material. The average value of tensile load of the skin graft is 51,2±4,1 N/cm^2, of a synthetic implant – 19,9±3,4 N/cm^2. It was noted, however, that the compliance of the skin graft is higher than that of the mesh implant. The average value of the bursting strength of the skin graft by suture material is 20,1±2,7 N/cm^2. The skin graft, while maintaining anisotropy during tensometric studies, showed the ability of compliance and tensile strength more than 2 times higher, and the bursting strength 1,4 times higher than the polypropylene implant.

KEYWORDS — ventral hernia; mesh implant; autodermal transplant; tensometry.

RELEVANCE

Restoring the anatomical structures of the anterior abdominal wall with ventral hernias is a common surgical procedure. Over the past twenty years, the standard way of the reconstruction of defects of the anterior abdominal wall is the use of artificial mesh alloprostheses [1, 2, 3]. However, with their use, complications are noted (seroma, hematoma, suppuration, fistula formation, rejection, prosthesis migration, etc.). This encourages researchers to use the biological tissue. The available literature of recent years vigorously reflects studies of the tensometric properties of allografts. However, studies on the mechanical properties of biological implants are highly insufficient. Therefore, the study of the mechanical properties of the biological and synthetic implants is relevant [4, 5]. The purpose of this research work was to study the mechanical properties of a de-epithelized banked skin graft and polypropylene mesh prosthesis used in hernia surgery.

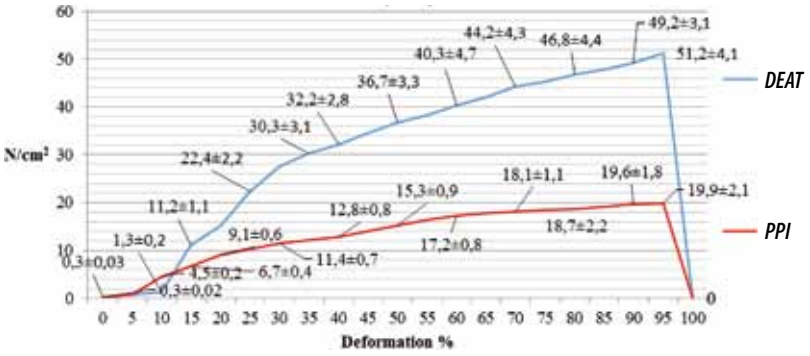
MATERIALS AND METHODS.

Tensometric tests to study such parameters as tensile strength and bursting strength of suture material were carried out in a certified laboratory for materials study. For this research we used a test laboratory kit with a software for the strength of materials from PASCO AR-8214 (USA). As a polypropylene mesh implant, a prosthesis was used with thread thickness of 0,60–0,68 mm and a density of 65 g/m^2. A de-epithelized banked human skin flap was used as a bioimplant. Skin samples were taken from patients during operations at the site of excised "old" postoperative scar. Further, the skin flap was prepared according to our own original technology including its de-epithelialization with a dermatome, preservation in a special solution containing an antibiotic and an oxygenated preparation in a certain ratio (Patent for the invention No. 2011132679/14, dated 03.08.2011). 10 samples were compared. The width of the samples was 10 mm. The result of the study was shown by a graph of the deformation curve (tensile diagram) in the coordinates: ordinate — tension (N/cm2), abscissa — relative elongation (%). The breaking load (N/cm^2) was calculated as a result of multiplying the maximum tension by the thickness of the sample. Statistical analysis of the obtained data was carried out using Data Studio software, STATISTICA 6.0 application software package.

RESULTS

The mesh and skin flaps of the implants showed linear elongation. Tensometry of both types of samples at the beginning of the study revealed a relatively uniform distribution of the load without resistance. At the same time, it was noted that the compliance of the de-epithelized banked skin graft is 1,5–2 times higher than that of the mesh implant and depends on the thickness of the sample, i.e. it represents a flatter curve than that of a polypropylene implant. The average values of the tensile load under uniaxial stretching of a free de-epithelized banked skin graft at 100% deformation amounted to 51,2 ± 4,1 N/cm^2. The average values of the tensile load of a polypropylene mesh implant under uniaxial tension along the base was 19,9 ± 3,4 N/cm^2 ($p < 0,05$) (see Fig. 1). The maximum average value of the bursting of the de-epithelized

Fig. 1. The average values of the tensile load of a de-epithelized autodermal transplant (DEAT) and a polypropylene implant PPI under uniaxial stretching (along the base) (M±m)



banked skin graft by suture material at its 100% deformation was 28,1 ± 3,7 N/cm². At the same time, the maximum average value of the bursting of a polypropylene mesh implant by suture material, with its 100% deformation was 20,1 ± 2,7 N/cm² (p <0,05) (see Fig. 2). When studying the mechanical properties of a de-epithelized skin graft and a polypropylene mesh implant, a certain mathematical dependence was revealed expressed by the formulas: for a polypropylene mesh graft $y=2x$; for a de-epithelized banked free skin graft $y=(3,5\div4,0)x$. Where x is the abscissa axis (deformation %), and y is the ordinate axis (breaking load N/cm²).

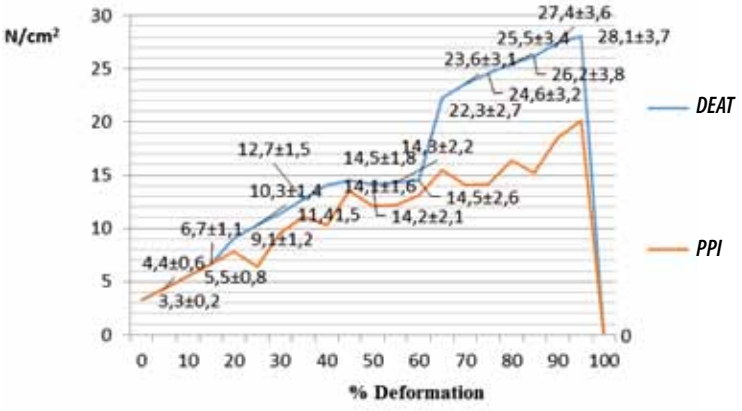


Fig. 2. The average values of the bursting strength of a de-epithelized autodermal transplant (DEAT) and a polypropylene implant PPI by suture material (M±m)

DISCUSSION

Studies of the mechanical properties of the skin graft made it possible to acknowledge its greater strength, as expressed in the tensile load parameters, which amounted to 51,2 ± 4,1 N/cm². A similar trend was reflected in the indicators of research on the bursting strength of suture material. The results on the bursting strength test of the suture material were higher than those of the mesh implant and amounted to 28,1 ± 3,7 N/cm². The compliance of the de-epithelialized skin graft was 1,5 times higher than that of the mesh implant. At the same time, it should be noted that a skin flap is characterized by flexibility, fluidity, compliance. The bioimplant exhibits this property at high loads of 15 N/cm² with its 50% deformation. This quality was absent in the synthetic mesh prosthesis, where under similar loads the deformation curve had the form of a sinusoid, which is associated with the gradual rupture of the threads of the polypropylene prosthesis. This quality of the skin graft, in our opinion, is valuable and brings it closer to the anisotropic mechanical properties of the anterior abdominal wall.

CONCLUSION

The results obtained in an experimental test of a skin transplant prepared by the proprietary methodology showed the ability of compliance, fluidity and strength, which is typical for biological tissues that include both collagen and elastin fibers. All this is confirmed in terms of tensile load indicators and indicators of the bursting strength of suture material. The results indicate the eligibility of skin graft in hernia surgery.

REFERENCES

1. **Annor AH, Tang ME, Pui CL, Ebersole GC, Frisella MM, Matthews BD, Deeken CR.** Effect of enzymatic degradation on the mechanical properties of biological scaffold materials. Surg Endosc. 2012;26:2767–2778. DOI: 10.1007/s00464-012-2277-5.
2. **Binnebösel M., Rosch R., Junge K., Flanagan T.C., Schwab R., Schumpelick V., Klinge U.** Biomechanical analyses of overlap and mesh dislocation in an incisional hernia model in vitro. Surgery. 2007;142(3):365–371. DOI:10.1016 / j.surg.2007.04.024.

3. **Lintin L.A., Kingsnorth A.N.** Mechanical failure of a lightweight polypropylene mesh. Hernia. 2014;18(1):131–133. DOI:10.1007/s10029-012-0959-5.

4. **V.P. Akimov, D.Y. Krikunov, D.S. Parshin, V.Y. Mikhaylichenko, V.V. Toidze, M.Z. Churgulia.** Possibilities of using the adhesive method of fixation of the mesh implant in laparoscopic treatment of inguinal hernias. Taurian Medical and Biological Bulletin. 2018;21(1):7–14. Available on: https://elibrary.ru/download/elibrary_35297386_91810738.pdf.

5. **V.A. Samartsev, V.E. Wildeman, S.V. Slovikov, V.A. Gavrilov, A.A. Parshakov, M.P. Kuznetsova, A.Y. Sidorenko.** Assessment of the biomechanical properties of modern surgical mesh implants: an experimental study. Russian Journal of Biomechanics. 2017;21(4):442–448. DOI: 10.15593/RZhBiomeh/2017.4.11.

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COMPARATIVE ANALYSIS OF THE DYNAMICS OF THE HYPOTENSIVE EFFICIENCY OF SINUS-TRABECULECTOMY WITH AUTOSCLERAL DRAINAGE AND STANDARD SINUS-TRABECULECTOMY IN THE TREATMENT OF PRIMARY OPEN-ANGLE GLAUCOMA

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ABSTRACT — Background. The method of modified sinus-trabeculectomy with autoscleral drainage of the anterior chamber and suprachoroidal space was developed at the Department of Ophthalmology in the Peoples' Friendship University of Russia. To assess the antihypertensive efficacy, a comparative analysis of the results with the method of standard sinus-trabeculectomy was carried out.
Aim. To compare the dynamics of the results of hypotensive efficiency of the method of modified sinus-trabeculectomy with autoscleral drainage and standard sinus-trabeculectomy in the surgical treatment of Primary open-angle glaucoma (POAG).
Material and methods. The results of surgical treatment in 75 patients (75 eyes) with primary open-angle glaucoma were studied. Patients were divided into two groups: the first group of 37 patients who were operated by modified sinus-trabeculectomy with autoscleral drainage of the anterior chamber and suprachoroidal space of autosclerosis, the second group (control) of 38 patients who underwent standard sinus-trabeculectomy. The follow-up period was 18 months.
Findings. In the remote postoperative period (after 18 months.) in the first group, 36 patients had normalization and stabilization of ophthalmo-tonus (IOP P (0) averaged 14.6±1.4 mm Hg in one(1) case, there was a moderate increase in the level of IOP, for which hypotensive therapy (beta-blockers) was prescribed. In the second group, IOP P (0) averaged 18.1±1.1 mmHg, the normalization of IOP was observed in 35 patients, in three (3) cases there was an increase in the level of IOP, for which hypotensive therapy (beta-blockers) was also prescribed.
Conclusion. The highest and persistent hypotensive effect and fewer failures were achieved after the modified sinus-trabeculectomy technique using autoscleral drainage.

KEYWORDS — glaucoma, sinus-trabeculectomy, drainage surgery of glaucoma.

INTRODUCTION

On the basis of numerous studies, it has been proved that the main reason for reducing the duration of the hypotensive effect after filter surgery of glaucoma is the scarring process [1,2,3]. Since 2008 to the present day, the Russian University of peoples ' friendship conducts research in this direction [4,5]. Thus, to combat this problem and to prolong the hypotensive effect of standard sinus-trabeculectomy, in 2017 at the Department of eye diseases of the peoples ' friendship University Of Russia, it was decided to include basal iridectomy, deep sclerectomy, drainage of the anterior chamber and suprachoroidal space via autoscleral in the scope of the operation.

AIM OF THE RESEARCH

The aim is to compare the dynamics of the results of the hypotensive efficiency of the method of modified sinus-trabeculectomy with autoscleral drainage and standard sinus-trabeculectomy in the surgical treatment of POAG.

MATERIAL AND METHODS

The Protocol of the study was approved by the local ethics Committee (No. 24 of 21.09.2017) and written informed consent was obtained from each patient. 75 patients (75 eyes) with uncompensated b-c II-III-IV stages of primary open-angle glaucoma (POAG) were observed at the maximum hypotensive mode of instillation of drugs in the form of non-selective blockers-2-adrenoreceptors, analogues of prostaglandins F2a and inhibitors of carbonic anhydrase, previously unoperated for glaucoma. Of these, 41 (54.7%) are female, 34 (45.3%) are male. The age ranged from 57 to 94 years. All patients were divided into two groups: 37 patients of the main group (37 eyes) underwent modified sinus-trabeculectomy with autoscleral drainage (received Russian patent for invention No. 2674088 dated 04.12.2018), 38 patients of the control group (38 eyes) — standard sinus-trabeculectomy. The follow-up

period was 18 months. Duration of glaucoma — 4 to 15 years. Patients were examined according to generally accepted standards in the following scope: visometry, biomicroscopy, gonioscopy, ophthalmoscopy, perimetry. To calculate IOP, patients underwent electronic tonography with glautest 60 eye tonograph on the day before surgery and every 3 months thereafter, inclusive, and at the 18th month of follow-up. The mean intraocular pressure (IOP) before surgery in the main group was P0 27.2±3.8 mm Hg for example, the coefficient of ease of outflow on average C=0.06±0, 03 mm³ (min. mm Hg), in the control — 26.9±3.5 mm Hg, the coefficient of ease of outflow on average C=0.06±0.04 mm³ (min. mm Hg). The criteria for evaluating the results in both groups were: the level of IOP (P0), the coefficient of ease of outflow of IOP (C), the need for additional hypotensive therapy, the presence of early and long-term postoperative complications.

RESEARCH RESULTS

Intraoperative and early postoperative periods were without complications. In the first day after surgery, all patients were visualized filtration pad (AF), and there was a mild inflammatory reaction of the first (I) degree, according to the classification of S.N. Fedorov–E. V. Egorova (1992). In the postoperative period (Fig.1) (18 months) after electron tonography, in the first group 36 (97.3%) patients showed normalization of IOP, mean P(o) (14.6±1.4 mm Hg (0,35±0,08 mm³ (min. mm Hg), increased outflow of HGV and in one case (2.7%) there was an increase in IOP (P (0) 22 mmHg, C= 0.12 mm³ (min. mmHg. in the second group, normalization of IOP was achieved in 35 cases (92.1%), which required the addition of drug therapy (Beta 1,2 – blockers), the level of IOP was on average Po (18.1±1.1 mm Hg), C (0,21±0,05 mm³ (min. mm Hg and in 3 cases (7.9%) it was noted ophthalmic hypertension max. to (P (0) 24 mm Hg, C= 0.10 mm³ (min. mmHg)), which also required the addition of Beta 1,2-blockers in all 3 cases.

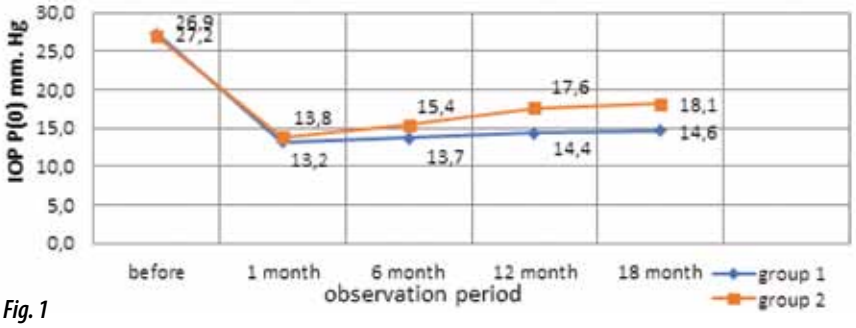

Fig. 1

CONCLUSION

The results of comparative evaluation of surgical treatment of POAG showed that the highest and persistent hypotensive effect and a more pronounced coefficient of ease of outflow as well as a lower incidence of ophthalmic hypertension were achieved after the operation of modified sinus-trabeculectomy with autoscleral drainage, the lowest effect — after the sinus-trabeculectomy by standard technique.

REFERENCE

1. **Petrov S.Y., Safonova D.M.** The modern concept of wound healing in glaucoma surgery. Ophthalmology in Russia. 2015;12(4):9–17. (In Russ.).
2. **Chen T.C., Wilensky J.T., Viana M.A.** Long-term follow-up of initially successful trabeculectomy . Ophthalmology. – 1997. Vol. 104. № 7. P.1120–1125.
3. **Watson P.G., Jakeman C., Ozturk M.** The complication of trabeculectomy (a 20-year follow-up). Eye. – 1990. – Vol. 4. – № 3. – P. 425–438.
4. **Frolov M.A., Fedorov A.A., Nazarova V.S., Gonchar P.A., Kumar Vinod, Frolov A.M.** Morphological condition of allodrenaige implanted in the case of refractory glaucoma in the long-term follow. Oftal'mologiya [Ophthalmology]. 2009; 6 (3): 11–14.
5. **Frolov M.A., Frolov A.M., Kazakova K.A.** Comparative analysis of combined treatment of glaucoma with cataract. The Journal of scientific articles "Health and Education Millennium", 2017. Vol. 19. No 3 p.13–17.

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SURGICAL TREATMENT OF GLAUCOMA BY AUTOSCLERAL DRAINING OF THE ANTERIOR CHAMBER AND SUPRACHOROIDAL SPACE

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ABSTRACT — Background. it is known from numerous studies that one of the reasons for reducing the duration of the hypotensive effect in the postoperative period in patients with glaucoma is an intensive scarring process. This was the reason for the development of a technique, which will result in persistent IOP and prolonged hypotensive effect in primary open-angle glaucoma in the postoperative period. Consequently, at the Department of Ophthalmology, RUDN a new method — a modified sinus trabeculectomy with the drainage of the sclera of the patient's anterior chamber and suprachoroidal space has been elaborated.
The aim of the work was to develop a surgical procedure for patients with sub-compensated and uncompensated open-angle glaucoma by modifying sinus trabeculectomy including basal iridectomy, deep sclerectomy and autoscleral drainage of the anterior chamber and suprachoroidal space.
Material and methods. 31 patients (31 eyes) with primary open-angle glaucoma were operated by modified sinus-trabeculectomy with basal iridectomy in combination with deep sclerectomy and autoscleral drainage of the anterior chamber and suprachoroidal space.
Findings. In the first day after surgery, the level of IOP was from 12.5 mm Hg. up to 17.5 mm Hg. In a long-term postoperative period (after 16 months.) normalization and stabilization of ophthalmo-tonus was observed in 30 patients (IOP P (0) averaged 14.6±1.7 mm Hg. In one case, there was a moderate increase in the level of IOP, for which hypotensive therapy (beta-blockers) was prescribed.
Conclusion. Modified sinus-trabeculectomy with autoscleral drainage allows the achievement of a stable hypotensive effect and does not require the use of artificial drains and donor material.

KEYWORDS — glaucoma, sinus-trabeculectomy, deep sclerectomy, basal iridectomy, suprachoroidal space, drainage surgery.

INTRODUCTION

Sinus-trabeculectomy is the most popular technique and often used by surgeons for surgical treatment of glaucoma, the results of which prove high efficiency due to persistent hypotensive effect [1, 2].

On the basis of many studies, it was determined that 10–25% of operated patients in the long-term postoperative period have scarring, which turn to block the outflow pathway of intraocular fluid via fibro-plastic process [3, 4, 5]. Such patients need additional postoperative administration, the use of various antimetabolites, control and lysis of sutures, needling, etc. In 2017, at the Department of Ophthalmology of the Peoples' Friendship University of Russia ,in order to achieve a stable hypotensive effect with the help of traditional sinus-trabeculectomy and its prolongation, it was decided to include basal iridectomy, deep sclerectomy, autoscleral drainage of the anterior chamber and suprachoroidal space in the scope of the operation. Positive properties of auto-drainage are maximum biocompatibility, minimal postoperative inflammatory response and achievement of prolonged hypotensive effect. As an auto-drainage, surgeons used the lens capsule, iris, descemet shell, sclera. In our development, we used scraps of the patient's own sclera performing a drainage function in the future. The basis and the beginning for this technique were surgical methods aimed at combating glaucoma developed at the Russian University of Peoples' Friendship by Professor Mikhail Frolov with co-authors (A.M. Frolov 2016) and others since 2008 to the present day [6, 7].

AIMS AND OBJECTIVES

The aim is to develop a surgical method for the treatment of patients with sub-compensated and uncompensated open-angle glaucoma by modifying sinus-trabeculectomy including basal iridectomy, deep sclerectomy and autoscleral drainage of the anterior chamber and suprachoroidal space.

MATERIALS AND METHODS

The study was carried out at the main base of the Department of eye diseases of the Peoples' Friendship University of Russia. V. M. Buyanova, Moscow, from September 2017 to January 2019. the Protocol of the study was approved by the local ethics Committee (No. 24 of 21.09.2017). Written informed consent was obtained from each patient. According to our method, 31 patients (31 eyes) were operated on. The selection criteria were: patients with uncompensated B-C II-III-IV stages of primary open-angle glaucoma

(POAG) on the maximum hypotensive mode of instillation of drugs in the form of non-selective blockers-2-adrenoreceptors, analogues of prostaglandins F2a and carbonic anhydrase inhibitors, previously unoperated for glaucoma. The patients were between the ages of 59 to 86 years. these, 13 were males (41.9%) and 18 were females (58.1%). Duration of glaucoma — from 4 years to 12 years. Patients were examined according to generally accepted standards in the following scope: visometry, biomicroscopy, gonioscopy, ophthalmoscopy, perimetry. To calculate IOP, patients underwent electronic tonography with the glautest 60 eye tonograph on the day before surgery and every 3 months thereafter, inclusive, and at the 16th month of follow-up. Prior to surgery, the intraocular tonographic pressure P0 averaged 28.2±3.4 mm Hg for example, the coefficient of ease of outflow on average C=0.06±0,02mm^3 (min. mm Hg). The method of sinus-trabeculectomy modified by us was carried out as follows (the patent of the Russian Federation for the invention No. 2674088 of 04.12.2018 was received). A conjunctival incision was made 8–10 mm posteriorly from the limb from 10 to 1 h. the Conjunctival flap was formed with the base to the limb. The conjunctiva and tenon sheath were separated from the sclera. With a scleral knife, a rectangular flap was cut out with the base to the limb at ⅔ thickness of the sclera, 5×5 mm in size.Then the flap was mobilized anteriorly so as to open the corneo-scleral zone. On the remaining surface ⅓ sclera produced longitudinal, parallel incisions of which formed five strips, 5 mm long and 1 mm wide . The lateral strip was cut out to a flat part of the ciliary body where, later after performing sinus-trabeculectomy, it was placed to a depth of 4.5 mm in the anterior chamber. Next, the medial strip was cut out from the limb with the base to the vault to the flat part of the ciliary body. A tunnel is prepared into the suprachoroidal space by spatula with a width of 2 mm and a length of 5 mm, where the previously separated medial strip is set to a depth of 4.5 mm. Of the five scleral strips, the middle (third) was separated completely, exposing the surface of the ciliary body in the future, where additional filtration of intraocular fluid will also occur, forming a filtration zone.The next stage was performed basal iridectomy at 12 o'clock. The rectangular flap was sutured with two nodular sutures. A continuous suture was applied to the conjunctiva. The operation was completed by administration of dexamethasone solution under the conjunctiva.

RESULT AND DISCUSSION

Intraoperative and early postoperative periods were without complications. In the first day after surgery, all patients were visualized filtration pad and there was a mild inflammatory reaction of first degree, according to the classification of S.N. Fedorov–E.V. Egorova (1992). In the study group of patients after surgery, the level of intraocular pressure was from 12.5 mm Hg up to 17.5 mm Hg. in the postoperative period (16 months) after electron tonography, 30 (96.8%) patients had normalization of IOP, Po (14.6±1.7 mm Hg) , increased outflow of IOP C (0.38±0.07 mm^3 (min. mm Hg) and in one case (3.2%) there was an increase in IOP (P (0) 22 mm.Hg, C= 0.12 mm^3 (min. mm Hg)), which required the addition of drug therapy (Beta 1,2-blockers).

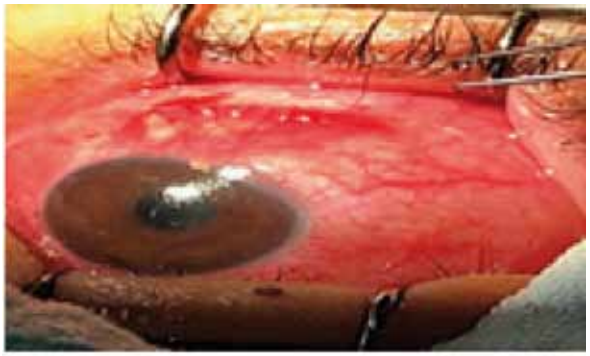

Fig.1. *Eye of the patient after completion of the steps of the operation with scleral drainage into the anterior chamber.*

Fig. 2. *Eye of the patient in the first day after surgery*

CONCLUSION

The created modified method of sinus-trabeculectomy using the patient's own sclera as a drainage component confirms its effectiveness, stabilizes the level of intraocular pressure, and also affects the duration of the positive effect of surgery. The proposed method is quite safe, contributes to the normalization of IOP level, can be applied at any degree and stage of

primary open-angle glaucoma, activates several outflow pathways of IOP, and does not require additional artificial drains, donor foreign material and various xenoplants.

REFERENCES

1. **Khaw PT, Chiang M, Shah P.** Glaucoma filtration surgery: indications, techniques, and complications.In: Albert & Jakobiec's Principles & Practice of Ophthalmology. Eds: Albert DM, Miller J, Azar DT, Blodi BA: 3rd ed., 2821–2840 (Saunders, 2008).
2. **Watson P.G., Jakeman C., Ozturk M.** The complication of trabeculectomy (a 20-year follow-up) . Eye. – 1990. – Vol. 4. – № 3. – P. 425–438.
3. **Chen T.C., Wilensky J.T., Viana M.A.** Long-term follow-up of initially successful trabeculectomy . Ophthalmology. – 1997. Vol. 104. № 7. P.1120–1125.
4. **Petrov S.Y., Safonova D.M.** The modern concept of wound healing in glaucoma surgery. Ophthalmology in Russia. 2015;12(4):9–17. (In Russ.) .
5. **Stalmans, I., Gillis, A., Lafaut, A. S. & Zeyen, T.** Safe trabeculectomy technique: long term outcome. Br J Ophthalmol90, 44–47 (2006).
6. **Frolov M.A., Fedorov A.A., Nazarova V.S., Gonchar P.A., Kumar Vinod, Frolov A.M.** Morphological condition of allodrenaige implanted in the case of refractory glaucoma in the long-term follow. Oftal'mologiya [Ophthalmology]. 2009; 6 (3): 11–14.
7. **Frolov M.A., Frolov A.M.,2, Kazakova K.A.,** Comparative analysis of combined treatment of glaucoma with cataract. The Journal of scientific articles "Health and Education Millennium", 2017. Vol. 19. No 3 p.13–17.

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ASSESSMENT OF RISK FACTORS AND ASSOCIATED CONDITIONS BY GENDER IN PATIENTS WITH III STAGE ARTERIAL HYPERTENSION

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ABSTRACT — The work investigates risk factors (RFs) and associated conditions (ACs) by gender in patients with stage III arterial hypertension (HTN). RFs and ACs were compared in men (45, average age 63.58 ± 9.12) and women (53, age 65.19 ± 10.02) with verified HTN. Age correlation of the parameters was carried out. In women, compared to men, HTN is diagnosed earlier, with longer disease duration (DD). Obesity (O), increased body mass index (BMI), left ventricular hypertrophy (LVH), decreased glomerular filtration rate (GFR) are more common. Women more often have acute cerebrovascular accidents (ACVAs) and transient ischemic attacks (TIAs), diabetes mellitus (DM). Men have a higher percentage of smokers, higher pulse pressure, damaged peripheral arteries. At the same time, ischemic heart disease (IHD) and heart failure (HF) are equally common. There is a multidirectional correlation between age and disease duration (DD), weight, lipid profile and blood glucose (BG) levels in both men and women.

Men and women have differences in the presence and severity of RFs, ACs and correlation between age and the studied parameters.

KEYWORDS — arterial hypertension, risk factors, associated conditions.

Arterial hypertension (HTN) is a multifactorial disease in which men and women share identical risk factors (RFs), but their combination may vary [1–4]. HTN is in turn a RF for the development of stroke, myocardial infarction, and renal failure [6]. Moreover, in their early sixties, the patients' organ systems undergo involutional processes with the development of comorbid pathologies. All this affects the course of HTN [5–7] and can lead to the disease progression. The risk of HTN development depends on the blood pressure (BP) values, RFs, damage to the target organs, ACs and comorbid pathologies [8, 9]. Cardiovascular risks are well studied [6], the Framingham, SCORE and PROCAM risk-assessment tools have been developed. It is noted that the presence of several RFs in a patient increases the risk of developing cardiovascular complications [10, 11, 12]. At the same time, qualitative and quantitative assessment of RFs in men and women with HTN in combination with ACs is of interest.

The aim of this study was to assess the RFs and frequency of ACs by gender in patients with stage III HTN.

MATERIAL AND METHODS

This clinical study was approved by the Ethics Committee of Tver State Medical University. The subjects selected according to the inclusion criteria were patients with stage III HTN with ACs. The exclusion criteria were cancer, acute conditions and chronic diseases in the acute stage, chronic stage III HF. The patients gave voluntary informed consent for inclusion in the study. We randomly examined 98 patients (men — 45, women — 53, average age — 64.45 years) with the verified diagnosis of stage III HTN in Tver Regional Clinical Hospital. The participants were divided into two groups according to the gender principle (men — 45, average age — 63.58±9.12; women — 53, age — 65.19±10.02). We studied their RFs: age, DD (years), smoking, burdened family history, BMI (kg/m^2), blood lipid profile (total cholesterol (TCh)), low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), triglycerides (TGs), atherogenic index of plasma (AIP)), BG (μmol/L), urea (U, μmol/L), creatinine (μmol/L) and GFR (ml/min/1.73m^2 according to the formula CKD-EPI and MDRD). The results of electrocardiography and echocardiography (US machine General Electric VIVID), ACs were analyzed. The patients were administered relevant drug therapy, their BP was at an average of 137/82 mm Hg. Statistical data processing was carried out using the program package "Microsoft Excel", "Biostat-2007". The data is presented as M±SD. Significance evaluation of the differences was carried out by the one-factor variance analysis and Fisher criterion, correlation (r) was determined using Spearman's method.

RESULTS

As can be seen from Table 1, the groups of men and women are comparable in age and number. It was found that in the women HTN was diagnosed 4 years earlier than in the men. There was difference in

the frequency of RFs between the two groups: DD (p=0.033), obesity (p=0.014), increased waist size (WS, p=0.03), incidence of DM (DM; p=0.03) and decreased GFR (p=0.01), which were more common in the women. It was revealed that in the women increased pulse pressure is detected 1.36 times less often, but twice more often there is a family history of HTN. Moreover, they are more likely to have dyslipidemia (1.5 times), increased TCh (1.2 times), LDLs (1.4 times), increased AIP (2 times) and increased BG (2 times), while impaired glucose tolerance was observed rarely and did not differ between the groups.

LVH according to ECG was more often detected in the women (1.36 times) and more often by echocardiography. Besides, a larger number of the women had significantly lower GFR (p=0.01) than the men, with GFR lower than 30 ml/min observed in one case and only in 1 man.

Each of the patients with stage III HTN had two or more ACs. The women were 2.83 times more often diagnosed with DM (p=0.03), 2.14 times more often — with cerebro-vascular diseases and 2 times more often — with TIAs. At the same time, the incidence of CAD (angina, myocardial infarction (MI), postinfarction cardiosclerosis, percutaneous intervention (PCI) and coronary artery bypass grafting (CABG)), stage I or II HF and atherosclerosis of the carotid arteries did not differ in both groups, but the women were 2.5 times less likely to have peripheral artery disease. Severe retinopathy (1 woman) and chronic renal failure (1 man) were much less common. BMI (p=0.001) was statistically significantly higher in the women compared to the men, while the lipid profile values, BG and urea parameters did not differ. The women had lower creatinine levels (p=0.03) and GFR according to the CKD-EPI formula (p=0.017) and MDRD formula (p=0.014) than the men. We noted that each of the patients with stage III HTN had two or more ACs. The women were 2.83 times more often diagnosed with DM (p=0.03), 2.14 times more often — with ACVAs and 2 times more often — with TIAs. The frequency of CHD (angina, MI, PCI and CABG), chronic stage I and II HF and atherosclerosis of carotid arteries did not differ in both groups.

The women compared to the men had statistically significantly higher BMIs (p=0.001), while the lipid profile values, BG and urea parameters did not differ. Creatinine levels in the women were lower (p=0.03), as well as the GFR according to the formula CKD-EPI (p=0.017) and the formula MDRD (p=0.014).

It was found that in the men, the age was directly correlated with the DD (r=0.41), BG level (r=0.35) and inversely correlated with weight (r=-0.30) and HDL (r=-0.35), TGs (r=-0.56), GFR according to the formula CKD-EPI (r=0.30). LDL correlated with GFR according to the formula CKD-EPI (r=-0.42) and the formula MDRD (r=-0.41). In the women, there was a direct correlation between age and weight (r=0.26), an inverse correlation with GFR according to the SKD–EPI formula (r=-35) and the diastolic pressure value (r=-0.25).

DISCUSSION

It has been established that women are earlier diagnosed with HTN and therefore they have longer DD. It can be assumed that women are better informed about HTN and its complications than men. During their initial office visit with elevated BP, they are more commonly diagnosed with stage I-II HTN, while men are diagnosed with stage II-III HTN. Comparing the RFs, it can be noted that 37.78% of men are tobacco smokers, women smoke much less often, they are better aware of their family history, which confirms their interest in their own health issues and the health of their families. Attention can be drawn to the fact that more women in relation to men are obese, have increased BMIs, dyslipidemia, increased BG levels and type II DM. All this indicates metabolic disorders associated probably with endocrine disorders due to pregnancy and childbirth, physical inactivity, cooking, eating patterns, etc. Women's BMIs correspond to Class 1 obesity, men can be classified as overweight. In women, chronic kidney disease with a moderate decrease in GFR is more common and myocardial hypertrophy is detected. It is possible that these processes are associated with hypervolemia (chronic HF), vascular wall changes, dyslipidemia, inactivity, and effects of drug therapy. Patients with stage III HTN are diagnosed with 2 or more ACs, among which CHD is detected with the same frequency in men and women, while cerebro-vascular diseases, TIAs and type 2 DM are more common in women. Stage I and II HF was detected in 96.0% of all patients and only in 4% it was compensated by systemic and pulmonary circulation.

The multidirectional correlation observed between age, DD, weight, lipid profile and BG parameters most likely reflects the influence of involutional processes on the corresponding organ systems. All this can indirectly indicate ongoing changes in the endocrine and renal systems and lipid metabolism associated with aging.

CONCLUSION

Men and women with stage III HTN demonstrate different combinations and severity of RFs, ACs and correlation between age, DD, weight, lipid profile and BG values.

Table 1. *Risk factors, target organ damage and associated conditions in men and women with stage III arterial hypertension (abs., %)*

Indicator	Patients with arterial hypertension (n=98)		
	men M (n=45)	women (n=53)	p
Risk factors			
Average age (years)	63.5±9.12	65.19±10.02	0.38
Duration of disease (years)	12.21±8.4	16.1±9.27	0.033
Tobacco smoking	19 (42.22%)	6 (11.32%)	0.001
Burdened family history	17 (37.78%)	24 (45.28%)	0.67
Obesity	15 (33.33%)	32 (60.38%)	0.015
Increased waist size	15 (33.33%)	30 (56.6%)	0.03
Pulse pressure >60	15 (33.33%)	11 (20.75%)	0.17
Dyslipidemia	24 (53.33%)	35 (66.04%)	0.22
Total cholesterol >4.9 µmol/L	37 (82.22%)	45 (84.91%)	0. 789
Low density lipoproteins >3.0 µmol/L	27 (60%)	38 (71.7%)	0.7
High density lipoproteins <1.2 µmol/L in women and <1.0 in men	0 (0%)	3 (5.66%)	0.24
Triglycerides >1.7 µmol/L	3 (6.67%)	2 (3.77%)	0.65
Atherogenic index of plasma >3	3 (6.67%)	6 (11.32%)	0.7
Glucose >5.6 µmol/L	13 (28.89%)	26 (49.06%)	0.62
Impaired glucose tolerance	1 (2.22%)	2 (3.77%)	0.9
Target organ damage			
Left ventricular hypertrophy (by ECG)	19 (42.22%)	26 (49.06%)	0.066
Left ventricular hypertrophy (by echocardiography)	38 (84.44%)	46 (86.79%)	0.2
GFR less than 60 ml/min according to either of the formulas	10 (22.22%)	25 (47.17%)	0.01
GFR less than 30 ml / min according to either of the formulas	1 (2.22%)	0	0.45
Associated Conditions			
Type 2 diabetes	6 (13.33%)	17 (32.08%)	0.03
Cerebro-vascular diseases	7 (15.56)	15 (28.30%)	0.2
Ischemic heart disease (angina/myocardial infarction/post-Infarction cardiosclerosis/percutaneous intervention / coronary artery bypass grafting)	35 (77.78%)	38 (71.7%)	0.37
Heart failure stage I, II	44 (97.78%)	50 (94.34%)	0.6
Atherosclerosis of the carotid arteries	8 (17.78%)	10 (18.87%)	0.9
Peripheral artery disease	5 (11.11%)	2 (3.77%)	0.24
Severe retinopathy	0	1 (1.89)	0.49
Chronic renal failure	1	0	-

Note: *p refers to a statistically significant difference between men and women*

REFERENCES

1. **Alekhine M. N.** The value of echocardiography in patients with arterial hypertension / M. N. Alekhine / / Cardiology. – 2018. – №. 1. – p. 90–100.
2. **Gordeev I. G.** Influence of losartan, amlodipine and their combination on elastic-elastic properties of vessels of elastic type and functional state of hemostasis system in patients with arterial hypertension. Handbook for the General practitioner. – 2016. – №. 5. p. 40–51.
3. **Gimaev R. H., Ruzov V. I., Razin V. A., Yudina E. E.** Gender-age features of electrophysiological remodeling of the heart in patients with arterial hypertension. Arterial hypertension. – 2009. – №. 1. – p. 57–66.
4. **Gilyarevsky S. R.** The role of a three-component antihypertensive drug in improving the treatment of arterial hypertension Cardiology. – 2017. – №. 2. p. 62–67.
5. **Glezer G. A., Glezer M. G.** Arterial hypertension; Meditsina-M., 2014. – 154 p.
6. European guidelines for the prevention of cardiovascular diseases in clinical practice (revision 2016). Russian journal of cardiology. – 2017 – №. 6 (146). p. 7–85.
7. **Kobalava, J. D.** Arterial hypertension. Keys to diagnosis and treatment [Text] / J. D. Kobalava, Y. V. Kotovskaya, V. S. Moiseev. – Moscow: GEOTAR-Media, 2009. – 868 p.

8. **Korichkina L. N., Borodina V. N., Poselyugina O. B.** The difference and relationship of risk factors in hypertension stage III in men and women. Kuban scientific medical Bulletin. – 2019. – №26 (3). – 55–62. https://doi.org/10.25207/1608-6228-2019-26-3-55-62

9. **Poselyugina O. B., Nilova S. A., Volkov V. S., Al–Galban N.** On clinical-functional manifestations of hypervolemia in patients with arterial hypertension. Cardiovascular therapy and prevention. – 2011. – №. 2. – p. 13–17.

10. **Khozainova N. Yu., Tsareva V. N.,** Structural-geometric remodeling and structural-functional restructuring of myocardium in patients with arterial hypertension depending on gender and age. Russian journal of cardiology. – 2005. – №. 3. – 20–25.

11. **Chesnokova A. I., Safronenko V. A., Skarzynska N. With., Safronenka A. V., Kolomak E. O.** Peculiarities of arterial hypertension in patients with comorbidities. Medical Bulletin of the South of Russia. – 2017.– №. 1. – p. 32–40.

12. Chronic kidney disease: basic principles of screening, diagnosis, prevention and treatment approaches. National recommendations. Working group of members Of the Board of the Scientific society nephrologists of Russia. http://minzdravrb.ru/minzdrav/docs/hbp.doc

https://doi.org/10.35630/2199-885X/2019/9/3.21

MATHEMATICAL MODEL OF THE DEVELOPMENT OF ATRIAL FIBRILLATION IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

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ABSTRACT — Background: Atrial fibrillation is one of the most common and heavy disorders of heart rhythm, which affects 0,4% of the general population and more than 5% among people aged 65 and older. The prevalence has increased six times in the last 25 years. AF occurs more often in men (10 times), less — in women (4 times). Therefore atrial fibrillation has lately become an issue of intensive clinical research. The challenges deal with a recurrent character of episodes, their unpredictiveness as well as a question of feasibility of attesting AF as a permanent disease. The answers to these questions may determine a choice of conservative or surgical treatment, which contributes to quality of life and life expectancy in patients.

Materials and methods: The study included 85 patients with atrial fibrillation and 30 somatically healthy individuals. All subjects underwent a comprehensive study of the protein, lipid oxidative stress and microcirculation indicators.

Findings: It was established that the formation of the clinical course of is-chemic heart disease is interconnected with the intensification of the processes of peroxidation of proteins, lipids and a change in superoxide dismutase activity. It has been proven that in patients with AF (both paroxysmal and permanent forms) in combination with a previous infarction, there is a change in peripheral microhemodynamics: a decrease in tissue perfusion and inhibition of active modulating mechanisms of tissue microcirculation.

Conclusion: According to the correlation and factor analysis, two factors have been identified that have a significant interrelation with the development of paroxysmal AF in patients with previous myocardial infarction: the level of advanced oxidation protein products and the microcirculation index. Our mathematical model for the risk of paroxysmal AF in patients with previous myocardial infarction has a level of statistical significance of 0,020, which indicates the reliability of the prediction results.

KEYWORDS — atrial fibrillation, previous myocardial infarction, oxidative stress, microcirculation index, advanced oxidation protein products.

INTRODUCTION

Atrial fibrillation (AF) is classified by the world medical community as one of the three cardiovascular «21st century epidemics» along with chronic heart failure (CHF) and diabetes mellitus [4].

It was established that AF is an independent predictor of death. Most frequently, AF occurs at various nosological units of ischemic heart disease (IHD).

Despite the large number of studies carried out in this area, the pathogenesis of the occurrence and progression of AF has not been fully explored [2].

It is now generally accepted, that there is a shortage of studies on prediction of the risk of the development of AF paroxysm in patients with IHD.

The available data are often inconsistent.

Early diagnosis of the factors of the development and progression of AF will improve not only the clinical status of patients, but also their prognosis [5].

The positions described above defined the purpose of our scientific research.

The purpose of the study

To create a mathematical model of atrial fibrillation paroxysm development in patients with previous myocardial infarction based on a comprehensive study of protein, lipid oxidative stress and microcirculation indicators.

MATERIALS AND METHODS

The Regional Ethics Committee (an extract of the record № 6 from 2 November 2015) approved this study.

In total 240 patients were examined, however, when criteria for exclusion were identified, patients dropped out of the study.

The main group consisted of 85 patients with AF. Of these, 39 patients had paroxysmal AF, 46 patients — a permanent form of AF. Of 39 patients with paroxysmal AF, 27 had angina pectoris, 13 had a previous myocardial infarction (MI), 12 had no angina pectoris, and 26 had no previous MI. Of 46 patients with permanent AF, 32 were diagnosed with angina pectoris, and 20 — with previous MI, 14 patients had no angina pectoris, 26 patients had no previous MI. The control group consisted of 30 somatically healthy individuals of the Astrakhan region. The average age

of the examined patients was 51.4 [40; 60] years. The average duration of the disease was 11.2 [3; 17] years. Groups of patients included in the study were comparable in age and gender parameters.

Determination of Cu/Zn — superoxide dismutase (SOD) concentrations in serum was carried out by the enzyme-linked immunosorbent assay (ELISA) using commercial test systems. Catalogue number — BMS 222. Company manufacturer — Bender Medsystems, Austria.

Determination of the advanced oxidation protein products (AOPP) in serum was carried out by the ELISA using commercial test systems. Catalogue number — K 7811w. Company manufacturer — Immundiagnostik, Germany.

Determination of the total enzymatic activity of all three types of SOD (Cu/Zn-SOD + Mn-SOD + Fe-SOD) in serum was carried out by the ELISA using commercial test systems. Catalogue number — 706002. Company manufacturer — BCM Diagnostics, USA.

To study the functional status of the vascular endothelium by means of laser Doppler flowmetry (LDF) there was used the laser analyzer of blood microcirculation «LAKK-02».

Statistical analyses were performed using STATISTICA 12.0 Stat Soft, Inc.

RESULTS

We attempted to conduct a comprehensive study of the processes of free radical oxidation as an example of AOPP and MDA, antioxidant protection, (SOD Cu/Zn with non-enzymatic activity and total SOD) and microvascular reactivity in order to identify meaningful indicators to predict such a terrible condition as a paroxysm of AF in patients with previous MI.

Correlation and factor analysis methods were used to identify factors that are related to paroxysmal AF in patients with previous MI: AOPP, microcirculation index (MI), flux, variation coefficient (Kv), alpha rhythm amplitude, vasomotion amplitude (LF), microcirculation efficiency index (index EfM), neurogenic tone (NT).

It was found that the formation of the clinical course of IHD is interrelated with the intensification of protein and lipid peroxidation and changes in the activity of SOD activity, activation of peroxidation in patients with paroxysmal and permanent AF with postinfarction cardiosclerosis.

However, in patients with a permanent form of AF, an increased activation of peroxidation processes led to the accumulation of peroxidation products in the blood serum of both protein and lipid molecules.

In patients with paroxysmal AF with the presence of previous MI an increased activation of peroxidation processes led to an increase in the total level of products of AOPP.

At the same time, the level of MDA in patients with paroxysmal AF in the group of patients with previous MI was comparable to the group of patients without previous MI, despite the fact that in comparison with the control group there was a significant difference.

Having studied the basal microcirculation (MI, flux and Kv) in patients with AF depending on the presence of previous MI, we found that in patients with both paroxysmal and permanent form of AF, in combination with a previous MI, there is a change in peripheral microhemodynamics: a decrease in tissue perfusion and inhibition of active modulating mechanisms of tissue microcirculation.

In the group of patients with paroxysmal AF and previous MI median MI was 3.54 perf.un., that was significantly lower both in comparison with the group of somatically healthy individuals ($p<0.0001$) and in comparison with the group of patients with paroxysmal AF without previous MI ($p=0.0369$).

In the group of patients with permanent AF with previous MI, the median flux was 0.11, that was significantly lower compared with the group of somatically healthy individuals ($p=0.0072$), compared with the group of patients with paroxysmal AF with previous MI ($p=0.0101$) and with the group of patients with permanent AF without previous MI ($p=0.0048$).

In the group of patients with paroxysmal AF with previous MI median Kv was 3.87%, that was significantly lower compared with the group of somatically healthy individuals ($p<0.001$) and with the group of patients with paroxysmal AF without previous MI ($p=0.0391$).

As a result of spectral decomposition of the dopplerogram into harmonic components of tissue blood flow oscillations (using mathematical Butterworth filters), we estimated the amplitudes of rhythmic components of the following frequency ranges: endothelial rhythms (Amax/M-α frequency 2–3 oscillations per minute), vasomotion (LF, frequency 4–12 oscillations per minute), respiratory rhythms of two ranges (HF1, frequency 13–30 oscillations per minute and HF2, frequency 31–49 oscillations per minute), cardiorhythms of two ranges (CF1, frequency 50–99 oscillations per minute and CF2, frequency 100–180 oscillations per minute).

As a result, we found that in patients with AF (both paroxysmal and permanent forms) there is an increase in the amplitude of cardiorhythms in patients with previous MI.

These micro hemodynamic disorders can exacerbate hypoperfusion of tissues and organs against the background of developing CHF, as well as be a risk factor for further vascular damage with the development of unstable conditions and complications.

Also, using the application program, we calculated a number of indices that allow to determine more objectify microcirculatory disorders in patients with AF: the index of microcirculation efficiency (index EfM), the neurogenic tonus of precapillary resistive microvessels (NT), the myogenic tonus of metarterioles and precapillary sphincters (MT), the shunting index (SI).

As a result, we came to the conclusion that both in the permanent form and in the paroxysmal form of AF, the presence of a previous MI was associated with a de-crease in peripheral capillary blood flow against the background of a decrease of NT, while in patients with a constant form of AF and with previous MI, microcirculatory disorders were deeper.

As a result of our scientific research on the data of correlation and factor analysis, we identified 2 factors that have a significant relationship with the development of paroxysmal AF in patients with previous MI: AOPP and MI.

Further, using binary logistic regression, we tried to create a mathematical model to predict the development of AF in patients with previous MI with the calcula-tion of the probability coefficient of AF.

p=1/1+e-z, where z=0,101*AOPP – 1,345*MI – 8,996

In this, AOPP means the total level of the advanced oxidation protein products; MI — microcirculation index in laser Doppler flowmetry.

Wald statistic was used for testing the significance of the coefficients.

The level of statistical significance of the model coefficients was 0.020, that was less than 0.05 and indicates the statistical significance of the prediction results of this model.

DISCUSSION

According to a number of researchers, AF is a common cardiac arrhythmia, leading to serious complications: heart failure, thrombosis, including stroke [1].

It is now generally accepted that over the time AF tends to progress from short and rare episodes of arrhythmia to the appearance of a stable permanent form of AF [3].

According to several researchers, the frequency of transition from a persistent form to a permanent form of AF is from 20% to 30% within 1–3 years [2].

Early diagnosis of AF progression factors, assignment of additional therapy for secondary prevention of arrhythmia and the choice of the correct treatment strategy can slow down the arrhythmia progression, which allows not only to improve the clinical status of the patient, but also his prognosis [6].

Thus, the purpose of our study is certainly relevant, and the results can open up new opportunities for specialists to predict paroxysm of AF.

In our scientific research, we decided to conduct a comprehensive study of antioxidant defence (AOD), protein and lipid peroxidation products and analysis of microcirculatory disorders in patients with AF.

We have established a significant decline of the AOD in patients with perma-nent form of AF, in this group of patients the decrease of AOD may be one of the factors modifying the clinical course of IHD with the development of painful forms.

A number of reseachers had long proved the direct relationship between AOD and peroxide oxidation.

Proteins are the most sensitive to oxidative stress, and therefore, along with MDA, we decided to investigate AOPP in the listed above groups of patients.

Intracellular accumulation of AOPP can induce apoptosis of podocytes, resulting oinproteinuria, and activation of the renin-angiotensin system in tubular cells [1].

Activation of protein and lipid peroxidation processes was revealed in patients with paroxysmal and permanent AF forms, with previous MI.

However, in patients with a permanent form of AF, increased activation of peroxidation processes led to the accumulation of peroxidation products in the blood serum of both protein and lipid molecules.

In patients with paroxysmal AF, the presence of previous MI led to the accumulation of mainly products of protein peroxidation.

We revealed a statistically significant decrease of MI and flux in groups of patients with previous MI in both paroxysmal and permanent AF, reflecting the development of peripheral hypoperfusion.

A statistically significant decrease of Kv in the groups of patients with previous MI was proved in both paroxysmal and permanent AF, reflecting a decrease in active propulsive movements of microvessels.

In patients with previous MI, correlation and factor analysis revealed a statistically significant relationship between the development of AF and MI.

Thus, the improvement of long-term prognosis of IHD depends of the level of diagnosis in the early stages of the disease, and the result of our study provides such an opportunity.

Conflicts of Interest

The authors declare no conflict of interest.

Contributors

OP and AA finally approved the manuscript for submission; EkP designed the study; ECh and EvP critically proved the work; RF and EK collected data, conducted statistical analysis; MF designed the study, interpreted the results, prepared the manuscript for submission.

REFERENCES

1. **Ciuntu A.O.** Advanced Oxidation protein products (AOPPS) in the development of glomerulonephritis in children // Международный научно-исследовательский журнал. 2017; Vol. 55(1–1), №1–1. P.178–181. (In Eng.). DOI: 10.2360/IRJ.2017.55.171
2. **Holmqvist F, Tristram D, Bahnson M.** Atrial fibrillation mapping strategies: The hunt is on // Heart Rhythm. 2018, Vol. 15, P. 1304–1305. DOI: 10.1016/j.hrthm.2018.05.007
3. **Kadyrova MV, Askerova NN, Stepanova YuA, Zhemerov NV, Malyshenko ES, Popov VA, Revishvili ASh.** Possibilities of echocardiography at the stages of surgical treatment of a patient with mitral valve posterior flap prolapse with the development of severe mitral insufficiency and atrial fibrillation (clinical observation). // Meditsinskaya vizualizatsiya. 2017; Vol. 21(2). P. 103–113. (In Russ.). DOI: 10.24835/1607-0763-2017-2-103-113
4. **Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Cas-tella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu B., Schotten U, Putte B, Vardas P.** 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. // European Heart Journal. 2016; Vol. 37: P. 2893-2962. DOI: 10.1093/eurheartj/ehw210
5. **Palagina I.A., Kudrya M.Ya., Melnikovskaya N.V., Kustova S.P., Ustenko N.V., Boyko M.A., Lalymenko O.S., Pavlenko T.A., Matveeva T.V.** Antioxidant properties of a cathiasine-based pharmaceutical composition studied on a model of the drug-induced liver impairment. // Проблемы эндокринной патологии. 2018; Vol. 3(65): P. 51–58. (In Eng.). DOI:10.21856/j-PEP.2018.3.06
6. **Podzolkov VI, Tarzimanova AI.** Changes in endothelial function in patients with paroxysmal atrial fibrillation in the treatment of propafenone. // Kardiovaskulyarnaya terapiya i profilaktika. 2018; Vol. 4: P. 40–45. (In Russ.). DOI: 10.15829/1728-8800-2018-4-40-45

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ANTIMICROBIAL THERAPY OF ACUTE UNCOMPLICATED CYSTITIS WITH NIFURATEL

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ABSTRACT — The article evaluates the effectiveness of the antimicrobial therapy of acute cystitis with nifuratel in 35 women (400 mg — 3 times a day orally). The control group of the study included 31 women who used nitrofurantoin (100 mg — 2 times a day) to treat acute uncomplicated cystitis. We examined the women on the third and seventh day of the intake. Three days after the use of nifuratel (1200 mg/day), the majority of patients (94.2%) subjectively noted the disappearance of urgency, leukocyturia disappeared in 82.8%. 22.8% of women remained uncomfortable when urinating, and we decided to extend the course of antimicrobial therapy with nifuratel up to 7 days. Three days after intake of nitrofurantoin (200 mg/day), 83.8% of women subjectively noted the disappearance of urgency, leukocyturia was stopped in 77.4%. Thus, in 12 (38.7%) cases the decision was taken to extend the course of antimicrobial therapy with nitrofurantoin up to 7 days. In the first group of patients side reactions occurred only in 3 (8.5%) cases, in the second — in 13 (41.9%). Efficiency, favorable safety profile and absence of allergic reactions make nifuratel reliable in the treatment of acute uncomplicated cystitis.

KEYWORDS — Nifuratel, acute uncomplicated cystitis (Acute uncomplicated cystitis), antimicrobial therapy.

INTRODUCTION

Acute uncomplicated cystitis remains one of the most common indications for antimicrobial drugs [1, 2]. Inappropriate treatments for urinary tract infections may lead to the spread of new strains of multidrug-resistant bacteria. It is not always possible to prescribe a patient an antimicrobial drug due to individual bacterial sensitivity [3]. Therefore, according to the guidelines of the European Association of urologists for the treatment of uncomplicated lower urinary tract infections, patients should be prescribed antimicrobials on an empiric basis. It is proved that the effectiveness of empiric treatment regimens for acute uncomplicated cystitis is possible in the absence of antimicrobial resistance in the population around 80–90% [2, 4]. Preference is given to antimicrobial agents that combine a reduced level of side effects and low resistance to the predominant causative agent of acute uncomplicated cystitis — Escherichia coli (E. coli) [2]. According to the latest recommendations, nitrofurans and phosphomycin trometamol are the first-choice drugs in the treatment of acute uncomplicated cystitis [1, 5].

Aim

To evaluate the effectiveness of antimicrobial therapy of acute uncomplicated cystitis with nifuratel.

METHODS

We examined 130 female patients with clinical signs of acute uncomplicated cystitis. The study was prospective and comparative. All women were divided into two groups on the principle of blind selection of antimicrobial drug from nitrofurans group for 3–7 days according to the guidelines of the European Association of urologists for the treatment of acute uncomplicated lower urinary tract infections. Criteria for inclusion in the study: pain during urination, frequent urination, urgency, leukocyturia, age from 18 years. Exclusion criteria: no episode of acute cystitis in the previous 3 months, no episode of acute pyelonephritis in the previous month, frequent relapses of cystitis, no pain in the lumbar region, uncomplicated gynecological history, no sexually transmitted diseases.

All patients were divided into two groups. The first group included 35 (53%) women who were prescribed nifuratel 400 mg — 3 times a day orally for the treatment of acute uncomplicated cystitis. In the second group of the study there were 31(47%) patients who were prescribed nitrofurantoin 100 mg — 2 times a day for the treatment of acute cystitis.

We examined all patients on the 3rd and 7th day of antimicrobial therapy. During the follow-up period, we evaluated the effectiveness of antimicrobial therapy, drug tolerance, risk of side effects, allergic reactions. At the same time, we focused both on the subjective feelings of patients and on the regression of laboratory parameters. Since pain during urination was the predominant complaint in all women when they came to the doctor, we evaluated the subjective disappearance of pain on a visual analog scale (VAS). Statistical processing of the material was carried out using spreadsheets "EXCEL" and the program "STATISTICA 6.0". The reliability of the differences between quantitative indicators was assessed using the Mann-

Whitney criterion. The differences were considered significant at p <0.05.

RESULTS

All patients were between the ages of 18 and 44. The median age was 28.7±8.2 years. This suggests that in our study, acute uncomplicated cystitis is more common in young women. According to the nature of complaints (frequent, painful urination), urgency of pathology, indicators of laboratory studies, both groups of patients at the beginning of the study were comparable (p>0.05). The intensity of pain in BOTH groups was 9.1±0.8 points.

In the first group of the study, three days after taking nifuratel (1200 mg/day), 33(94.2%) women subjectively noted the disappearance of urgency, the intensity of pain was 3.5±1.1 points, leukocyturia was stopped in 29 (82.8%) patients. Thus, in 8 (22.8%) cases it was decided to extend the course of antimicrobial therapy with nifuratel to 7 days.

In the second group of the study after three days of taking nitrofurantoin (200 mg/day), 26 (83.8%) women subjectively noted the disappearance of urgency, the intensity of pain according to VAS — 4.5±0.9 points, leukocyturia was stopped in 24 (77.4%) people. Thus, in 12 (38.7%) cases it was decided to extend the course of antimicrobial therapy with nitrofurantoin up to 7 days. The average course of antimicrobial therapy in both groups was 5.2±1.4 days.

After 7 days of treatment of acute uncomplicated cystitis with nifuratel, the urgency of symptoms disappeared in all patients, leukocyturia was stopped in 34 (97.1%). In the group of patients treated with nitrofurantoin urgency disappeared in all patients as well, but leukocyturia (15,3±3,1 leukocytes in the field of view) was recorded in 3 (9,6%) women. The dynamics of regression of subjective symptoms (based on the results of testing on VAS) is presented in fig. 1.

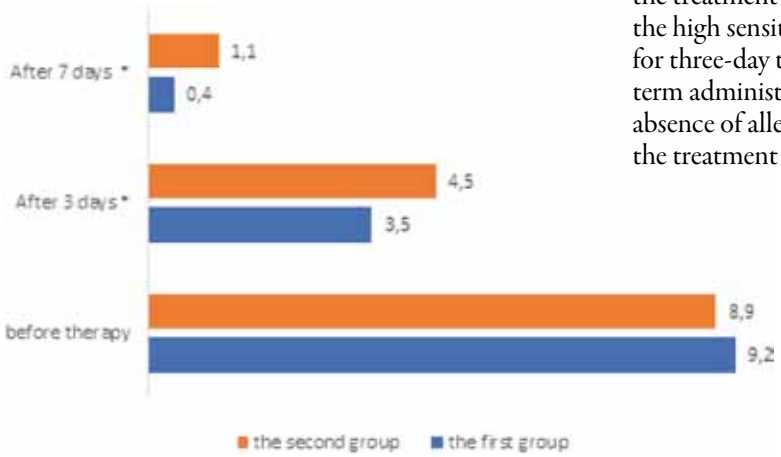

*Fig. 1. The dynamics of regression of subjective symptoms (based on the results of testing on VAS). * at p <0.05 in comparison of values between groups*

Throughout the course of antimicrobial therapy of acute uncomplicated cystitis, we evaluated side effects in both study groups (table. 1). As can be seen from table 1 side effects prevailed in the second group of patients (on the background of nitrofurantoin use) 3 times compared to the first group (treated with nifuratel). In the first group of patients, adverse reactions were observed in only 3 (8.5%) people, but they were insignificant and all women completed the full course of treatment. Against the background of taking nitrofurantoin, adverse reactions of varying severity developed in 13 (41.9%) people.

The results of this clinical study confirmed the high effectiveness of nifuratel in the treatment of uncomplicated urinary tract infections, as it was praised for its good tolerance and minimal risk of allergies and adverse effects. In this observation, we received different side effects (nausea, dizziness, allergic reaction, etc.) in the group of nitrofurantoin patients (41.9%). These results are comparable with the observations of other researchers [6, 7].

According to previous studies, it was shown that nifuratel has no effect on lactobacteria and does not cause an imbalance in the equilibrium of normal physiological flora, and resistance to it develops slowly [5]. In addition, nifuratel is approved for use during pregnancy due to its low toxicity and has vaginal dosage forms, which allow it to be used in treatment of uro-gynecological diseases [8].

Given the wide range of nifuratel and its effect not only on urinary tract infections (E. coli, Klebsiella, enterococci and others), but also on the pathogenic flora of the intestine and vagina, including candidiasis, nonspecific vulvovaginitis, bacterial vaginosis [8], this drug is of great interest for further study of its effectiveness in patients with recurrent cystitis.

CONCLUSIONS

Antimicrobial activity of nifuratel is significant in the treatment of acute uncomplicated cystitis. Due to the high sensitivity of E. coli, nifuratel is effective both for three-day therapy of acute cystitis and for longer-term administration. The favorable safety profile and absence of allergic reactions makes nifuratel reliable in the treatment of urinary tract infections.

Table 1. *Comparison of side effects in patients after treatment of uncomplicated lower urinary tract infection with nitrofurans*

Types of Side Effects	Group 1 patients (n=35) – nifuratel therapy	Group 2 patients (n=31) – nitrofurantoin therapy	p
Nausea	1(2,8%)	6(19,3%)	P<0,05
Dizziness	2(5,7%)	4(12,9%)	P<0,05
Feeling of discomfort in the epigastric region	0	2(3,2%)	P<0,05
Allergic reaction	0	1(3,2%)	P>0,05

REFERENCES:

1. **Markowitz MA, Wood LN., Raz S., Miller LG., Haake DA., Kim JH.** Lack of uniformity among United States recommendations for diagnosis and management of acute, uncomplicated cystitis. International urogynecology journal. 2019; 30(7): 1187–1194. DOI: 10.1007/s00192-018-3750-z
2. **Gupta K., Hooton T.M., Naber K.G., Wullt B., Colgan R., Miller L.G., et al.** International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis, 52 (2011), pp. e103–e120.
3. **Colgan R, Williams M.** Diagnosis and Treatment of Acute Uncomplicated Cystitis. American family physician. 2011; 84(7): 771–776.
4. **Sobke A., Makarewicz O., Baier M., Bar C.,Pfister W., Gatermann S.G., Pletz M.W., Forstner C.** Empirical treatment of lower urinary tract infections in the face of spreading multidrug resistance: in vitro study on the effectiveness of nitroxoline. International journal of antimicrobial agents. 2018; 51(2): 213–220. DOI: 10.1016/j.ijantimicag.2017.10.010
5. **Perepanova T.S.** Nitrofurans in the urological practice: are they all the same and why are we getting back to them today? Experimental and Clinical Urology. 2018; 3: 91–100.
6. **Mendling W, Mailland F.** Microbiological and pharmacotoxicological profile of nifuratel and its favourable risk/benefit ratio for the treatment of vulvo-vaginal infections – A review. Arzneimittelforschung-drug research. 2002; 52(1): 8–13.
7. **Sakaan S.A., Twilla J.D., Usery J.B., Winton J.C., Self T.H.** Nitrofurantoin-induced hepatotoxicity: a rare yet serious complication. South Med J. 2014; 107:107–113.
8. **Mendez J.L., Nadrous H.F., Hartman T.E., Ryu J.H.** Chronic nitrofurantoin-induced lung disease. Mayo ClinProc. 2005; 80: 1298–1302.

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A GIANT NODAL FORM OF BASAL CELL CANCER A CLINICAL CASE

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ABSTRACT — A clinical case of a giant nodal form of basal cell - a skin tumor developing from atypical basal cells of the epidermis and follicular epithelium-is presented. The diagnosis was confirmed by dermatoscopy and finally verified on the basis of the results of histological examination.

KEYWORDS — giant basal cell carcinoma, dermatoscopy, basal cell carcinoma, skin tumors.

DESCRIPTION

An 82-year-old woman from a former Post-Soviet country, has referred to a dermatologist for a medical examination. At the time of the examination the patient complaints of a large formation in the left eyelid, periodically bleeding, causing aesthetic inconvenience. The patient considers herself sick for 6 years, when the complaints first appeared. The patient did not seek medical assistance and practiced self-medication. She reported that she periodically lived in Moldova and was repeatedly subjected to active insolation, including episodes of sunburn. She rejected occupational hazards and exposure to ionizing radiation. Medical history excludes hereditary and skin cancer. The patient denies tuberculosis, viral hepatitis, sexually transmitted diseases. She denies injuries and surgeries in the past. Currently, the patient has not been observed by specialists and does not take drugs for concomitant diseases. The patient suffered acute cerebrovascular accident in 2010. She denies allergic reactions to drugs in the past.

LOCAL STATUS.

The pathological skin process is limited, localized on the skin of the face, in the area of the upper eyelid on the left with a partial transition to the area of the nose and brow. It is represented by a node 4.5 x 7 cm in diameter, with uneven bumpy roller-shaped edges of pink-red color, having the form of "pearls" and an extensive ulcer defect in the center with a thin serosanguineous scales-crust on the surface, when removing which erosion is detected (fig. 1). Parotid, ear, submandibular lymph nodes are not palpated.

Fig. 1. *Giant nodular basal cell carcinoma of the facial area*

Dermatoscopy (by a trainee) revealed multiple atypical tree-like vessels (fig. 2, 3).

RESULTS

Total blood count: leukocytes $11,2 \cdot 10^9$/l, erythrocytes $4,50 \cdot 10^{12}$/l, platelets $298 \cdot 10^9$/l, hemoglobin 130 g/l, ESR 25 mm/h, N 0%, With 58%, E7%, M 7,9%, L26,4%, B0,7%. Urinalysis: density 1030, protein — negative, red blood cells — negative, glucose — negative, epithelium — single in the field of view, salt — negative, leukocytes 1–3 in the field of view, ketone body — negative. Biochemical blood tests: ALT 64.8 u/l, AST 37.4 u/l, cholesterol 6.8 mmol/l, urea 6.83 mmol/l, total protein 74.3 g/l, alkaline phosphatase 247.56 u/l, total bilirubin 74.3 mmol/l, glucose 4.03 mmol/l. Microreaction of precipitation is negative.

To determine treatment tactics the patient was sent to an oncologist. Histological results: presence of typical complexes of epithelial cells with dark nuclei, the absence of intercellular bridges, palisade-like complexes on the periphery. Connective tissue stroma in the form of beams. Between parenchyma and stroma a retention gap is visualized. Histological picture corresponds to basal cell carcinoma.

The further fate of the patient: at the readmission by the dermatologist, the patient refused treatment in

Surgut and decided to undergo treatment in her home country.

Consent

Written informed consent was obtained from the patient for publication of this case report.

CONCLUSION

This clinical case is of interest to oncologists and dermatologists. Despite the fact that basal cell carcinomas are very common skin tumors, such gigantic sizes are rare and often represent neglected cases. Oncological caution for the purpose of early detection of skin tumors is relevant not only among health professionals, but also among the population.

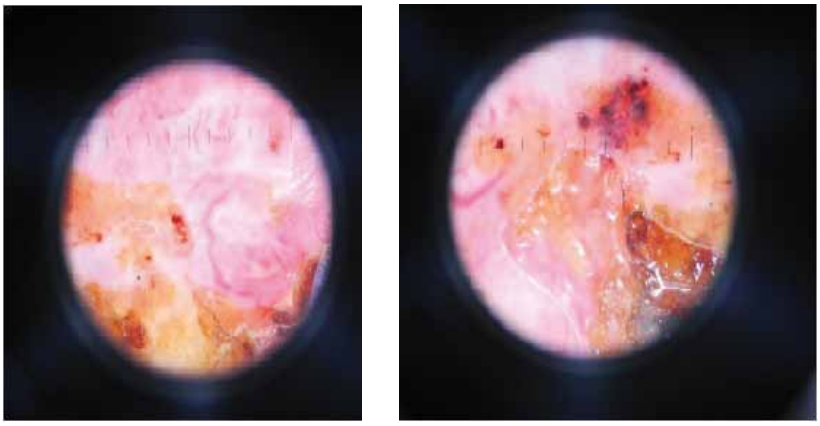

Fig. 2, 3. *Dermatoscopic pattern of basal cell carcinoma.*

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POTENTIAL USE OF CHITOZAN-BASED MULTILAYER WOUND COVERING IN DENTAL PRACTICE

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ABSTRACT — A promising area in dentistry is the development of modern biotechnological wound dressings based on chitosan, which, depending on the molecular weight and three-dimensional structure, is able to change its physico-mechanical properties from the state of a hydrogel to a dense frame structure with a different degree of swelling, and at the same time perform a depot function the drug introduced into it. Two new types of wound dressings based on chitosan with an immobilized 10% aqueous solution of iodopyrone were developed and their effectiveness was studied in an experiment on animals (rabbits) for dental practice. A comparative analysis was carried out with the well-known wound dressings *Alvostaz*, *Gelatamp* by introducing the studied samples into the well of the tooth after its extraction. The high efficiency of the proposed wound dressings based on chitosan was established.

KEYWORDS — wound coverings, porous polymer materials, biopolymer, biotechnology, surgery, stomatology, chitosan, medicine

INTRODUCTION

Despite a significant range of therapeutic measures employed to treat inflammatory diseases in the maxillofacial area, much of the effort falls short of effective suppression of the infection and proper regeneration as the outcome of the pathological process [1–6]. The development of optimal wound covering that would contribute to fast and complete recovery of the damaged structures appears an urgent issue in modern medicine. Scientific items, monographs and patents offer a wide range of materials used to create wound covering, with over 400 various types of sponges, films, combined collagen/gelatin/oxidized cellulose/starch-based implants, etc., described nowadays [7–10].

Of the well-known new-generation biodegradable synthetic and natural materials, a special place belongs to chitosan — a derivative of chitin — a natural polysaccharide obtained through its partial deacetylation, consisting of residues of D-glucosamine and N-acetyl-D-glucosamine units connected by β-1,4-glycosidic bonds. Extremely promising here is the development of biotechnological wound covering based on chitosan, which, depending on the molecular weight and a three-dimensional structure, can change its physicochemical and strength properties from the state of a hydrogel to a dense frame structure with a different degree of swelling and water absorption, as well as perform a depot function for the drug introduced into it. The potential of its use is due to a number of features which are inherent in this polymer and materials based on it, i.e. biocompatibility, a minimum number of side effects, high wound-healing activity, moisture- and air permeability, high porosity, mechanical stability along with simultaneous plasticity, controlled bioresorption time in the body, and the ability to act as biodegradable depot carriers of the drugs [11]. Gradual biodegradation of chitosan in the alteration zone, along with diffusion through the swollen walls of the hydrogel, will promote gradual release of the immobilized pharmacological agent within controlled time intervals, and replacement with native cells and tissues, which will result in a step-by-step prolonged medication therapy depending on the pathophysiological processes underway in the wound. A number of authors, too, claim high antimicrobial and hemostatic activities observed in chitosan and its derivatives [12, 13]. This means that a wound covering synthesized on its basis will feature action polyvalence.

Aim of study

to evaluate the effectiveness of chitosan-based multilayer wound covering and that of the popular wound coverings *Alvostaz* and *Gelatamp* developed for dental practice.

MATERIALS AND METHODS

The study included 12 ten-month-old male rabbits with a body weight of 2500 (±50) g. The animals were kept in a vivarium with free access to water and food, which corresponds to the standards of GOST 33044-2014 PRINCIPLES OF GOOD LABORATORY PRACTICE (approved by the Federal Agency for Technical Regulation and Metrology, order # 1700-st of November 20, 2014), entered into force on August 1, 2015.

2 popular wound coverings were selected for the control group of drugs (*Alvostaz* and *Gelatamp*).

The experimental samples taken for comparison were multilayer wound coverings based on chitosan, core-shell type (molecular mass — 600 kDa; porosity — 98%, and the following pore size: a denser core, 20–45 microns; more loose area close to the shell, 70–200 microns, different in the structure with immobilized iodopyron in the loose part of the samples; specially designed at the Kurchatov Research Institute) (Fig. 1). Porous materials were obtained through the technology of chitosan solutions freeze drying. A specific feature of the core and shell materials was the pore shape: in Sample 1c, the shell had isotropic pores, while the core was composed of longitudinal pores along the cylinder axis. In Sample 2c, the pores were initially oriented longitudinally, along the cylinder axis.

Fig. 1. *Experimental multilayer samples of chitosan-based wound coverings — Sample 1c (a), Sample 2c (b).*

Through the experiment all the studied chitosan samples revealed high biocompatibility, biodegradability, bioadhesive capacity and permeability. However, the degree of adhesion and biodegradation depended significantly on the molecular weight and the specifics of the internal orientation that pores had in the sample. The chitosan samples, while featuring moderate strength, density, elasticity, and the ability to maintain the desired shape and initial size, showed varying biodegradation rates. Sample 1c, externally, had a higher porosity chitosan, while inside it contained a denser material; the external loose shell was completely biodegradable on Day 7; the denser core — on Day 14. Due to its large porosity and hygroscopic properties, the outer shell ensured high adhesion of the sample to the surrounding tissues when introduced into the surgical area. The core of Samples 1c and 2c was modified via introducing into the central part a 10% iodopyron aqueous solution. The capillary effect helped the drug penetrate deep into the sample, which led to swelling and increased chitosan elasticity in this area; subsequent drying of the sample through the surface tension of the solution resulted in larger pores in the central (axial) part. All this ensured a draining and a prolonged antiseptic effects. The external, unmodified and more rigid shell served the frame function for the biomaterial.

Sample 2c, on the contrary, was a structure, whose outer layer contained a more dense porous material, while the inner one featured a lower specific density.

Under aseptic conditions and general anesthesia (premedication: Atropine Sulfate 0.1 mg/kg; Prednisone 0.1 mg/kg; Sedamidine 0.05 mg/kg and anesthesia: Telazole 0.05 mg/kg intramuscular) the animal (according to the developed method) was fixed on the operating table in a position on its side. After the surgical field was prepared (triple treatment of the perioral area with a 5% aqueous solution of iodopyron, once — the oral mucosa with a 3% aqueous solution of chlorhexidine bigluconate), the upper central incisor (right or left) was extracted with the experimental and control samples introduced into the hole to a predetermined depth (Fig. 2).

The effectiveness of wound coverings was evaluated both in an aseptic wound and under purulent inflammatory conditions. In the latter case, after the tooth extraction, the bacterial culture Ps. aeruginosa was introduced into the hole (concentration – 109 CFU/ml) 3 days before the introduction of the wound covering sample. The gum mucous membrane above the hole was sutured with apposition interrupted sutures (atraumatic Prolene 3/0). In order to reduce the sedative effect of the injected drugs, after the procedure, the animals were injected with Antisendan (0.05 mg/kg). To relieve the pain in the early postoperative period, the animals were administered Flexoprofen (2.5%, 0.08 mg/kg). Through the 14 postoperative days, the animals were monitored with free access to water and food.

The experimental and control samples were studied in the operating room on Day 14.

MORPHOLOGICAL ANALYSIS

The preparations fixed for 7 days in a 10% solution of neutral formalin were washed in running water for 60 minutes, after which they were placed in a SoftiDec decalcifying solution (ErgoProduction, Russia), with the degree of demineralization in the peripheral areas checked with a metal needle every 20 minutes. After decalcification, experimental specimens were cut out. Then, an incision was made in the sagittal

Oral cavity treatment prior to extracting the incisor

The hole after the incisor extraction

Introduction of the samples into the dental hole

Gum soft tissue suture

Fig. 2. *Experiment stages*

plane through the middle of the tooth hole filled with the sample. The materials were processed and paraffin-embedded employing an automatic method using a Leica TP1020 histoprocessor (Germany) subject to a standard procedure. Then, the samples were poured into paraffin to obtain paraffin blocks on a Leica EG1150H modular unit (Germany). 5 μm thick paraffin sections were obtained using a Leica RM2235 rotational microtome (Germany). For general histological evaluation, the preparations were dewaxed and hydrated. The obtained sections were stained with hematoxylin and eosin following the standard methods. The micropreparations were studied on an Olympus CX41 microscope (Japan).

RESULTS AND DISCUSSION

The wound covering Gelatamp proved to be satisfactory for an aseptic wound, serving a good frame function to stabilize the blood clot. In an animal experiment with a purulent wound, this covering did not provide good antimicrobial effect, despite the presence of silver as an antiseptic, which was proven histologically (multiple microabscesses in soft tissues (Fig. 3a).

Compared to the chitosan Sample 1c, the Alvostaz wound covering provides a skeleton function due to a homogeneous, denser fibrous structure, as well as chitosan Sample 2c. Almost complete biodegradation of the material was noted on Day 14 into the experiment. The antimicrobial effect was unsatisfactory: histologically verified microabscesses were observed in the drug injection area. The underlying muscle tissue was ischemic; phenomena of venous stasis and transvascular lympho-macrophage infiltration were to be observed (Fig. 3b).

A comparative evaluation of chitosan samples revealed higher efficiency regarding conventional wound coverings (*Alvostaz*, *Gelatamp*) in animal experiments (rabbits). The developed wound coverings provided a skeleton function, revealed permeability, biodegradability and the ability to be a carrier matrix for the drug introduced into their structure. At the same time, Sample 2c, if matched against Sample 1c, proved the most effective performing a fusing function due to a looser internal structure. During the first 3 days, complete rehabilitation of the wound hole surface was observed, with further effective drainage maintained. The dense outer surface of the structure avoided premature adhesion of soft tissues through further observation time, too. On Day 14 into the experiment, almost complete biodegradation of the material was to be observed in the tissues. No inflammatory changes, be that in the bone or soft tissues, were registered (Fig. 3c.).

The above means that the proposed samples of chitosan-based wound coverings revealed sufficient efficiency on the model of a wound process in the hole of an extracted tooth. Sample 2c was recognized as most reliable because, due to the dense external material, the structure would retain frame functions for a long time, offering proper drainage from the pathological focus. At the same time, the loose chitosan material filling the inner diameter of the endoprosthesis undergoes earlier biodegradation, providing, on the one hand, moderate compliance and elasticity of the external shape, while on the other hand (due to the transformation of chitosan into a gel with a highly ordered micellar-type internal nanostructure) its prolonged function was ensured as a matrix carrier of the drugs introduced into the wound covering during implantation. This type of wound covering proved the most reliable to be used in case of a purulent inflammatory process.

Sample 1c was recognized as more promising in cases where no inflammatory process was observed in the extracted tooth hole, where initially high adhesion with surrounding tissues was required, which ensures tightness and keeps the blood clot in the wound. Note to be made that due to the rapid biodegradation of the outer shell, the sample lost its shape, which created conditions for its coming out of the tooth hole on Day 3—5.

CONCLUSION

An analysis of the obtained data suggests the following conclusion: the studied experimental chitosan-based materials revealed high wound healing activity, biocompatibility, biodegradability, bioadhesive capacity and permeability. In addition, a comparison of chitosan-based samples with conventional wound coverings (*Alvostaz*, *Gelatamp*) done through experiments involving laboratory animals (rabbits), revealed that a wound covering Sample 2c showed higher efficiency in both clean and purulent wounds (with preliminary introduction of a 10% aqueous solution of iodopyrone into the wound covering). Due to the combination in the wound coverings of two different types of chitosan, which differ in biodegradation rate and other physical & chemical properties, the tested sample was found as promising for dental practice, in particular, in the surgical treatment of purulent inflammatory maxillofacial issues. The external frame of the sample, due to higher rigidity and later biodegradation (up to 14 days) provides adhesion to the wound walls as well as drainage of the surgical area; the internal loose chitosan offers a sustained local pharmacological effect, while serving a depot for medications. Further on, the sample proved completely biodegradable without impeding healing in the surgery area. Sample 1c was recognized as promising in cases featuring no inflammation in the extracted tooth hole, where initially high adhesion of the biomaterial to the surrounding tissues is required.

REFERENCES

1. **Semkin V.A., Cousin A.V., Gurin A.N., Besrukov A.A.** Modern wound coatings in surgical dentistry Dentistry 2016; 4: 87-90. DOI:10.17116/stomat201695487-90 p. (In Russ.).
2. **Davydov B.N., Domenyuk D.A., Bykov I.M., Ivchenko L.G., Dmitrienko S.V.** Modern possibilities of clinical-laboratory and x-ray research in preclinical diagnostics and prediction of the risk of development of periodontal in children with sugar diabetes of the first type. Part I. Periodontology, 2018; Vol. 23; 3-23(88): 4-11. DOI:10.25636/PMP.1.2018.3.1
3. **Domenyuk D.A., Porfyriadis M.P., Budaychiev G. M-A.** Contemporary methodological approaches to diagnosing bone tissue disturbances in children with type 1 diabetes. Archiv EuroMedica, 2018; 8(2): 71–81.
4. **Kupryakhin S.V., Lepilin A.V., Kupryakhin V.A., Domenyuk D.A.** Optimization of dental implantation combined with closed sinus lift in patients with low maxillary sinus floor // Archiv EuroMedica. 2019. Vol. 9; 2: 117–121. https://doi.org/10.35630/2199-885X/2019/9/2/117

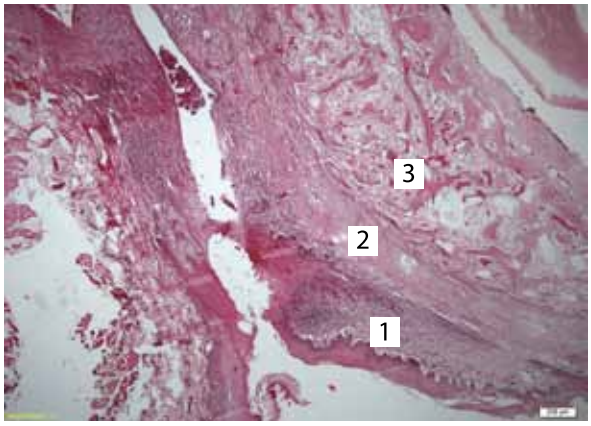

Fig. 3a. *Morphological status after administration of the Gelatamp preparation (mucous membrane of the cavity with a partially biodegraded implant (1); microabscesses in soft tissues (2); spongy bone, capillaries hyperemic, with stasis (3).*

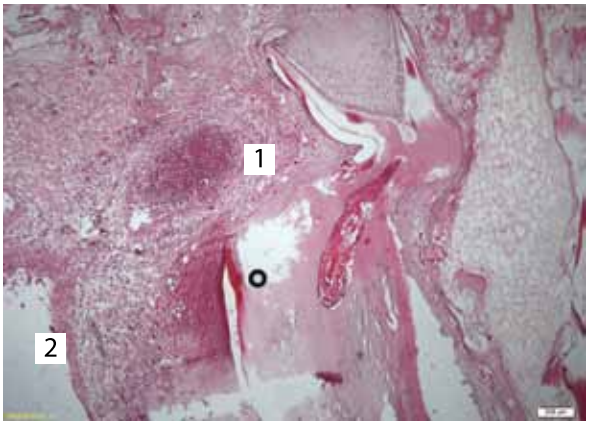

Fig. 3b. *Morphological status after administration of the Alvastaz (abscess wall (1), consisting of granulation tissue with an increased number of cellular elements — a macrophage row of thin-walled capillaries with stasis effects; implant (2) is biodegradable; surrounding adipose tissue featuring a state of fat necrosis).*

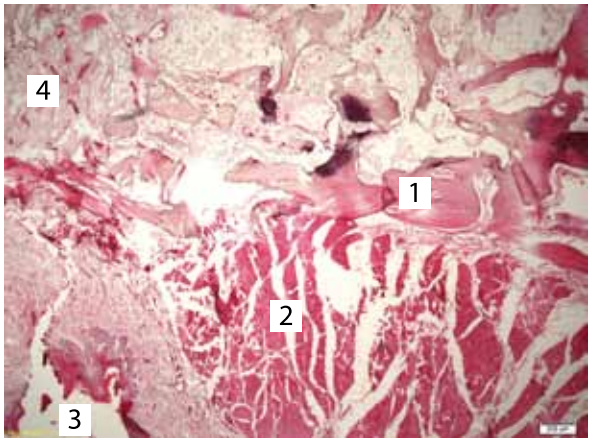

Fig. 3c. *Morphological status after introduction of chitosan Sample 2c (the mucous membrane of the oral cavity reveals no sign of inflammatory change (1). In the submucosal layer and the adjacent loose fibrous connective tissue, through its entire length, infiltration of lymphocytes and macrophages can be observed; muscle tissue shows signs of edema (2); lamellar bone (3); spongy bone, capillaries are hyperemic, with stasis (diameter 16–80 microns). Total biodegradation of chitosan can be observed).*

Fig. 3. *Morphological analysis of tissues on Day 14 into the implantation of the compared samples of wound coverings (stained with hematoxylin and eosin. Magnification, x 200).*

5. **Kupryakhin S.V., Lepilin A.V., Kupryakhin V.A., Postnikov M.A., Domenyuk D.A.** Potential introduction of cell technologies to improve dental implant surface preparing // Archiv EuroMedica. 2019. Vol. 9; 2: 122–129. https://doi.org/10.35630/2199-885X/2019/9/2/122

6. **Lepilin A.V., Rajgorodskij Yu.M., Grigoryeva D.A., Erokina N.L., Bakhteeva G.R., Domenyuk D.A.** Reasoning for the application of violet laser physiotherapy device following surgeries in the oral cavity. Archiv EuroMedica, 2018; 8(2): 111–114.

7. **Lipatov V.A., Lazarenko S.V., Sotnikov K.A., Severinov D.A., Yershov M.P.** To the Issue of Methodology of Comparative Study of the Degree of Hemostatic Activity of Topical Hemostatic Agents. Novosti khirurgii. 2018; 26(1): 81–95 (In Russ., English abstract).

8. **Scriabin K.G., Mikhailov S.N., Varlamov V.P., editors.** Khitozan. M.: Tsentr "Bioinzheneriya" RAN; 2013. 593 p. (In Russ.).

9. **Borda, L.J., Macquhae, F.E., Kirsner, R.S. Wound Dressings: A** Comprehensive Review. Curr. Derm. Rep. 2016; 5(4): 287–297. DOI:10.1007/s13671-016-0162-5

10. **Legon'kova O.A., Alekseyev A.A.** Modern wound dressings: properties and features. Vestnik Roszdravnadzora. 2015; 6: 66–68 (In Russ., English abstract).

11. **Singh R., Singh A., Shitiz K.** Chitin and chitosan: biopolymers for wound management. International Wound Journal. 2017; 14(6): 1276–1289. DOI:10.1111/iwj.12797

12. **Anjum S., Arora A., Alam M.S., Gupta B.** Development of antimicrobial and scar preventive chitosan hydrogel wound dressings. International Journal of Pharmaceutics. 2016; 508(1–2): 92–101. DOI:10.1016/j.ijpharm.2016.05.013

13. **Azuma K., Izumi R., Osaki T., Ifuku S., Morimoto M., Saimoto H., Minami S., Okamoto Y.** Chitin, Chitosan, and Its Derivatives for Wound Healing: Old and New Materials. J. Funct. Biomater. 2015; 6(1): 104–142. DOI:10.3390/jfb6010104

https://doi.org/10.35630/2199-885X/2019/9/3.25

MATRIX METALLOPROTEINASES AND THEIR TISSUE INHIBITORS IN THE PATHOGENESIS OF PERIODONTAL DISEASES IN TYPE 1 DIABETES MELLITUS

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ABSTRACT — The item presents the results of a comparative immune enzymometric assay of the matrix metalloproteinases (MMP-1, MMP-2, MMP-8, MMP-9) and tissue inhibitors (TIMP-1, TIMP-2) levels in blood serum, oral fluid of children belonging to Health Groups I and II and children with type 1 diabetes mellitus (disease course within the range of 1 to 10 years) in projection onto the level of hygiene and the periodontal status. The role of MMP-2, MMP-8, MMP-9 in the pathogenetic mechanisms of inflammatory periodontal diseases development has been identified. Children with a short experience of endocrinopathy were found to have a balanced synthesis of matrix metalloproteinases and their tissue inhibitors in case of reversible inflammatory alterations in periodontal tissues. Children with a longer disease course were found to feature an imbalance between matrix metalloproteinases and tissue inhibitors, which provokes disturbances in remodeling and structural organization of the extracellular matrix in periodontal tissues, along with the development of inflammatory destructive issues.

KEYWORDS — child population, type 1 diabetes mellitus, periodontal issues, matrix metalloproteinases, tissue inhibitors, oral fluid, blood serum

INTRODUCTION

Type 1 diabetes mellitus (DM) in children is one of the most complex and urgent issues faced by medical science, health care and social protection, while its importance has been enforced through international regulatory documents (WHO St. Vincent Declaration, 1989; Weimar Initiative, 1997; UN Resolution, 2007). As stated by the International Diabetes Federation (IDF, 2016), the number of reported Type 1 diabetes cases in the world's child population has reached 549,000, whereas annual diabetes costs have exceeded 12% of total global health care spending. According to the data provided by the Federal National Register, by the year 2017, there had been 22,969 children and 8,758 adolescents registered as outpatients suffering from Type 1 DM, while the annual increase rate was 2.82% in children, and 0.97% in adolescents, i.e. 86.73 and 203.29 per 100,000, respectively. The dramatic part about Type 1 DM in children is due to clinical polymorphism, widespread prevalence, the progressing increase in the incidence, significant lability of the disease course, a tendency to the development of autoimmune reactions combined with increased responsiveness of the immune system, the trouble in achieving clinical and metabolic compensation, which results in complications and early disability within a life period that is active from the social stance, reduced life expectancy and quality, impaired sexual and physical development, and increased mortality rate [3,5,10,14,18,21,35,37].

The WHO experts claim (2015) that over 94% of children with Type 1 DM have periodontal issues of inflammatory, dystrophic, and tumor origin. The etiopathogenesis of periodontal diseases in childhood is due to the fact that the disorders develop in constantly rearranging, rapidly growing, morphologically and functionally immature tissues, which are not capable to offer a proper response even to minor damaging factors. Besides, periodontopathies can develop against oral microbiocenosis issues, endocrine and neurohumoral regulation, hemodynamics changes, connective tissue metabolism, mineral metabolism, vitamin deficiency, poor nutrition, occlusion anomalies, imbalanced growth and maturation of the elements that make up the periodontal structure [1,4,6,15,17,20,33,36].

All the above leaves no doubt regarding the relevance of well-planned diagnostics and treatment of dental diseases in the child population, viewing the body as a whole [11,19,22-32,38-40,46-51].

The search for diagnostically significant periodontal disease markers is due to investigating the role that collagen metabolism disorders play in the periodontopathy pathogenesis. The biological functions of collagen, the basic structural protein of the intercellular matrix, include the support & mechanical role, involvement in the intercellular interaction, effect on cell proliferation and differentiation, as well as organs

and tissues morphogenesis through the body growth and development. The rate of the metabolism of collagen, an actively renewing protein, depends on both biosynthesis and biodegradation, while the content of collagen fractions allows making judgment not only concerning the periodontal bone tissue inflammatory destruction, yet also regarding the osteoblasts functional activity. Type I collagen proteolytic degradation has been proven to be one of the key factors in the uncontrolled destruction of the extracellular periodontal matrix [9, 16, 34, 41, 42].

Collagenolytic activity is typical of Matrix metalloproteinases (MMP), extracellular Zn^{2+}- and Ca^{2+}-dependent endopeptidases containing 25 isoforms and involved in connective tissue remodeling through destroying its organic components at physiological pH values. Together with other extracellular proteinases, MMPs under physiological conditions play a key role in the following processes: morphogenesis (embryogenesis); tissue resorption and remodeling; proliferation; membrane receptors cleavage; connective tissue protein metabolism; apoptotic ligands release; cell migration and differentiation; protein matrix proper development and functioning; oncogenic transformation; angiogenesis; immune response implementation; coagulation; cytokines and chemokines deactivation and activation. In case of inflammation, MMPs are involved in the destruction of all types of extracellular matrix proteins. The regulation of MMP activity is carried out at various levels, including protein activation, transcription, and interaction with specific endogenous tissue inhibitors of metalloproteinases (TIMP) — structurally related proteins, three of which (TIMP-1, 2, and 4) are secreted in a soluble form, with another one (TIMP-3) being associated with the extracellular matrix [8, 12, 43, 45].

Neutrophilic collagenase (MMP-8), which is closely associated with pathological changes in periodontium, has the highest proteolytic activity in relation to Type I collagen. A significant contribution to the destruction of collagen fibrils and the degradation of the collagen matrix through periodontitis is made by interstitial collagenase (MMP-1), which is capable of hydrolyzing Types I, II, III collagen, as well as gelatinase (MMP-2 and MMP-9), for which Type IV collagen is a substrate. The wide substrate specificity of MMPs determines their involvement not only in the processes of periodontal destruction, yet also in inflammatory response modulation [2, 7, 13, 44].

Experts claim that examination of the oral fluid is an informative and non-invasive way to assess the proteolytic status and activity in periodontium. Molecular & biochemical changes in the oral cavity have been proven to be affected not by the actual pathological processes in the periodont only, but also by somatic diseases, Type 1 DM in particular. Monitoring the collagen content by the level of MMP and their tissue inhibitors in children with Type 1 DM will allow proper assessment of the imbalance between the MMP and TIPM activity as projected onto the periodontal status. This will facilitate the identification of children with Type 1 DM with a high risk of developing periodontal diseases, also allowing prediction of the course and evaluating the effectiveness of treatment and preventive measures for periodontopathy.

Aim of study:
to identify the dependence between the content of matrix metalloproteinases, their tissue inhibitors and the periodontological status in children with Type 1 DM through different endocrinopathy stages.

MATERIALS AND METHODS

Subject to informed consent obtained from the parents, 129 children (57 boys, 72 girls) aged 8–12 were examined. The objectification of periodontal status in children in a mixed occlusion was performed taking into account the range and classification of periodontal pathology approved by the Presiding Panel of the Periodontics Section, Dental Association of Russia (2001) based on ICD-10 (WHO, 1997) using radiological criteria for evaluating the disease severity (Rabukhina N.A., Arzhantsev A.P., 2003). The oral hygiene status was evaluated based on indicators of the Oral Hygiene Index-Simlified (OHI-S, Green-Vermillion, 1964) and the Hygiene Index (HI, Yu.A. Fedorov, V.V. Volodkina, 1976). The clinical assessment of the periodontal tissues status was calculated by adding up the following values: Periodontal Index Russell (PI Russel, 1956); Papillary Marginal Alveolar Periodontal Index (PMA, Schour, Massler, 1948) Parma modification (C. Parma, 1960); Silness & Loe Plaque Index (PI J. Silness, H. Loe; 1964); Sulcus Bleeding Index (SBI Muhlemann and Son, 1971) modified by Cowell (1975); Schiller-Pisarev test and Svrakov Iodine Value (D. Svrakov, Yu. Pisarev, 1963); Community Periodontal Index of Treatment Needs (CPITN, WHO, 1989). 2% solution of methylene blue and 5% solution of erythrosine pink were used as plaque indicators.

Apart from the dental patient medical record, each child had an electronic periodontal chart filled out for them, containing information about the periodontal status at examination with the Florida probe automated system (FloridaProbe Corporation, USA). To identify the intensity of the inflammatory pathology in the periodont, orthopantomography was performed with a panoramic X-ray device Orthophos XG Plus DS / Ceph (Sirona).

The examined children were divided into two groups. The comparison group included 38 healthy children (Group I health) and basically healthy (Group II health) (Y.E. Veltishchev, 1994). In the comparison group, the diagnosis to the patients was given based on the pediatrician's conclusion. The main group (91 persons) included children with a diagnosis of Type 1 DM, who were undergoing treatment in the endocrinology department of Filippsky Child Clinical Hospital (City of Stavropol, Russia) within the period of 2010–2019. The diagnosis of Type 1 DM was given by endocrinologists following the clinical and laboratory criteria of WHO (1999). Depending on the duration of Type 1 DM, the patients in the main group were divided into two subgroups. The first subgroup included 43 children (47.3%) who had had the disease for up to two years; the other subgroup — 48 children (52.7%) with the disease duration of 3–10 years.

The material for the study was blood serum and unstimulated oral fluid (UOF). Blood sampling was done from the ulnar vein using a BD Vacutainer® vacuum system (BectonDickinson) with a clotting accelerator (Sarstedt) following the algorithm for morning vein blood sampling (on at empty stomach). UOF, too was taken on an empty stomach in the morning into the Saliva RNA Collection and Preservation Devices (Norgen Biotek) system. The collected UOF was poured into 200–250 μl aliquots in plastic tubes and stored frozen at –80° C. Further, the UOF aliquots were thawed at room temperature and centrifuged at 10,000 rpm for two minutes. The levels of MMPs and their tissue inhibitors in blood serum and in the supernatant were assessed by enzyme-linked immunosorbent assay (ELISA) following the manufacturers' requirements. The following standard kits were used: for MMP-1 — RayBio® Human Fas ELISA; for MMP-2 — Human/Mouse/Rat MMP-2 (total) (Quantikine, Research & Diagnostics Systems, Inc.); for MMP-8 — Human MMP-8 (total) (Quantikine, Research & Diagnostics Systems, Inc.); for MMP-9 — Human MMP-9 (Quantikine, Research & Diagnostics Systems, Inc.); for TIMP-1 — Human TIMP-1 (Quantikine, Research & Diagnostics Systems, Inc.); for TIMP-2 — Human TIMP-2 (Quantikine, Research & Diagnostics Systems, Inc.). The optical density was measured on a Sunrise (Tecan) automatic universal microplate reader at λ = 450 nm with correction at λ = 540 nm, followed by data processing with specialized Magellan™ software. The measurements calculation was performed subject to the formula below:

$$Y = a + bX + cX2$$

Y, the optical density; X, the level of MMP and tissue inhibitors.

The statistical analysis was performed using the SPSS Statistics 21.0 software package. The nature of the sample distribution was identified through the Shapiro-Wilk test. The comparison of groups with a normal distribution of quantitative traits was evaluated based on the Student t-test. The results are presented as the arithmetic mean and its standard error. An investigation of the relationship between the MMPs activity indicators and their tissue inhibitors, as well as index assessment of the periodontal status were carried out employing Pearson's parametric correlation analysis for normally distributed quantitative characteristics. To identify the differences between the two groups, the Mann-Whitney U-test was used; in case of over two groups, the Kruskal-Wallis test was used. Group differences were considered statistically significant at a 95% probability of an error-free forecast ($p < 0.05$).

RESULTS AND DISCUSSION

Table 1 below offers a view on the index evaluation of the oral cavity hygienic status.

An analysis of the oral hygiene status indicates that in Health Groups I and II, "very poor" and "poor" hygiene level were observed in 3 (7.9%) and 7 (18.4%) children, respectively. In the 1st subgroup of the main group, "very poor" and "bad" hygiene levels were detected in 6 (14.0%) and 9 (20.9%) children, in the 2nd subgroup – in 4 (8.3%) and 8 (16.7%) children, respectively. It is to be noted that the "good" level of hygiene was observed most often in Groups I and II – 15 (39.5%) children, while in the 1st subgroup this indicator was 14 (32.6%) children; in the 2nd subgroup — 9 (18.8%) children. Therefore, an increase in the disease severity in children with Type 1 DM is associated with a slight deterioration in the hygiene status, which is due to lacking full-range individual hygiene resulting from pain in the oral cavity; a decrease in the protective, secretory function of the salivary glands, and weakened motivated control.

Table 2 shows index evaluation of the periodontal tissues status.

Analysis of the periodontal pathology structure revealed that in the comparison group the ratio of children with periodontopathy (11 children – 29.0%) and children with intact periodontium (27 children — 71.0%) was 0.4 units. In Groups I and II, chronic catarrhal gingivitis was diagnosed in 7 (18.4%) children, exceeding the prevalence of hypertrophic gingivitis (2 children — 5.3%) by 3.5 times. In the 1st subgroup, periodontopathy was observed in 13 (65.1%) children, while periodontal disease was not detected in 25 (34.9%) children. The ratio of children with periodontopathy against the number of children with intact periodont in the 1st subgroup (1.8 units)

went beyond the same index in the comparison group by 4.5 times. In the 1st subgroup only reversible inflammatory changes (chronic catarrhal and hypertrophic gingivitis) were detected, while the chronic catarrhal gingivitis incidence (19 children – 44.2%) exceeded the occurrence of hypertrophic gingivitis (4 children — 9.3%) by 4.7 times. In 7 (35.4%) children of the 2nd subgroup, inflammatory and irreversible destructive periodontal lesions were diagnosed — chronic localized mild periodontitis was detected in 4 (8.3%) children; chronic localized periodontitis of moderate severity — in 7 (14.6%) children; chronic generalized periodontitis – in 6 (12.5%) children. The incidence of chronic catarrhal gingivitis (18 children – 37.5%) in children of the 2nd subgroup exceeded the occurrence of hypertrophic gingivitis (5 children — 10.4%) by 3.6 times, while in comparison with similar parameters in the 1st subgroup there was a decrease in these values by 1.2 and 1.1 times, respectively. The recession as a nosological type of periodontopathy was recorded in 8 (16.7%) children of the 2nd subgroup, compared with 5 (11.6%) children of the 1st subgroup and 2 (5.3%) children in the comparison group.

Analysis of periodontal status indicates that children with Type 1 DM had a worsening periodontal status along with an increase in the disease course. In the 1st and 2nd subgroups, gum recession was diagnosed, as well as chronic catarrhal and hypertrophic gingivitis. The 3rd subgroup children featured a tendency towards transition of reversible inflammatory forms into irreversible inflammatory and destructive periodont lesions. The following factors determine periodontal status deterioration in children with a long-term course of Type 1 DM:

— Diabetic microangiopathies. The plasmorrhages that underlie microcirculatory disorders are manifested by primary plasma lesions of the vascular bed basal membrane, as well as vascular wall hyalinosis and sclerosis. These morphological changes against the unchanged vascular lumen reduce the transcapillary exchange intensity, contribute to thickening of the blood vessels walls, reducing their permeability. This slows down the nutrients transport, reduces tissue resistance to endotoxins produced by conditionally pathogenic (pathogenic) microflora of the gingival sulcus, aggravating the severity of inflammatory and destructive changes in periodontal tissues.

— Dysbiotic disorders. Hyposalivation, increased level of glucose in the gingival fluid and saliva, occurring against carbohydrate metabolism decompensation, change the microbiota composition. These changes, combined with an increase in the non-enzymatic proteins glycation, reduce the local protection of the oral cavity. This is accompanied with a decrease in the level of normal symbionts (dysbiosis), followed by colonization with conditionally pathogenic microflora. It is important to note that patients with decompensated diabetes have an increased level of spirochetes and motile bacteria localized in the apical part of the periodontal pockets. Given increased phagocytosis, the Porphyromonas gingivalis bacteroid and the Treponema denticola spirochete, belonging to the resident microflora, activate the MMPs neutrophilic matrix, aggravating the inflammation.

— Impaired immune response. Given carbohydrate metabolism decompensation, there is a decrease in the function of monocytes/macrophages, neutrophils, polymorphonuclear neutrophilic leukocytes; an increase in the content of IgA, IgG; a decrease in the level of IgM, T and B lymphocytes, while the synthesis of glycosaminoglycans and collagen is getting reduced. Besides, due to non-enzymatic glycation, there is also weakening in the function of cells involved in the immune defense system.

— Oxidative stress. Decreased production of reactive oxygen species, a decrease in the oxygen-dependent phagocyte metabolism activation, incomplete phagocytosis mechanisms, correlating with an increase in the area of insulin-producing β-cells destruction in patients with long-term experience of Type 1 DM, indicates the onset of Stage 3 (depletion stage) in oxidative stress.

Table 3 shows the level of matrix metalloproteinases and their tissue inhibitors in blood serum.

Table 4 offers a view on the level of matrix metalloproteinases and their tissue inhibitors in the oral fluid.

Analysis of the MMP-1 (intestinal collagenase) level in children with Type 1 DM in blood serum and UOF, if compared with children of Health Groups 1 and 2, shows overproduction of MMP-1, while the increase in the indicators in the 2nd subgroup (38.6 ± 3.7% and 176.2 ± 10.4%, respectively) reaches the highest level with respect to the growth in patients of the 1st subgroup (6.8 ± 0.9% and 14.3 ± 1.3%). The increase in the level of MMP-1 along with an increase in the disease duration, which correlates with deteriorating periodontal status, is due to an increase in collagen fibrils degradation through remodeling of extracellular matrix and the development of a chronic inflammatory process in periodontal tissues.

Compared to the children in Health Groups I and II, children with Type 1 DM had a statistically significant increase in the MMP-2 (Gelatinase-A) level only in the oral fluid (children of the 1st subgroup – 120.6±8.3%; children of the 2nd subgroup — 696.9±37.2%), while there was no statistically significant increase in the serum MMP-2 levels in children of the 1st and 2nd subgroups. An increase in the level of MMP-2 involved in

Table 1. *Index evaluation of the oral cavity hygienic status (points), (M ± m)*

Index	Children I, II Health groups	Children with experience of type 1 diabetes up to 2 years	Children with experience of type 1 diabetes 3–10 years
OHI-S, Green-Vermillion	1,27±0,03	1,61±0,04*	2,29±0,07*
HI, Yu.A. Fedorov, V.V. Volodkina	1,74±0,16	2,08±0,13*	2,43±0,12*

Note: ** — p≤0.05 is statistically significant in comparison with the patients of the comparison group (Newman-Cales test, Dunn test).*

Table 2. *Index evaluation of the periodontal tissues status, (M ± m)*

Index	Children I, II Health groups	Children with experience of type 1 diabetes up to 2 years	Children with experience of type 1 diabetes 3–10 years
PI Russel, points	1,44±0,13	2,91±0,28**	3,86±0,17**
PMA Parma C., %	18,21±1,07	27,56±1,73*	43,97±3,09*
PI J. Silness, H. Loe, points	0,43±0,02	0,94±0,04**	2,17±0,07**
SBI Muhlemann-Cowell, points	0,76±0,04	1,23±0,06**	2,08±0,13**
CPITN, WHO, points	0,24±0,03	0,73±0,07**	1,36±0,16*
Schiller-Pisarev test and Svrakov Iodine Value, points	1,29±0,08	1,76±0,13*	3,62±0,21*

Note: ** — p≤0.05 is statistically significant in comparison with the performance of patients in the comparison group; ** — p≤0.01 is statistically significant in comparison with the patients of the comparison group (Newman-Keyles test, Dunn test).*

Table 3. *The level of matrix metalloproteinases and their tissue inhibitors in blood serum (ng/ml), (M ± m)*

Index	Children I, II Health groups	Children with experience of type 1 diabetes up to 2 years	Children with experience of type 1 diabetes 3–10 years
MMP-1	8,68±0,11	9,27±0,52*	12,03±0,94*
MMP-2	231,96±14,27	234,41±17,13*	249,82±13,67*
MMP-8	9,27±1,08	11,06±2,74*	27,48±6,41*
MMP-9	326,13±18,53	339,48±32,28*	386,35±24,31*
TIMP-1	161,35±12,84	174,06±8,97*	213,16±17,36*
TIMP-2	116,74±8,73	129,64±10,69*	187,43±16,28*

Note. ** - p≤0.05 is statistically significant in comparison with the patients of the comparison group (Newman-Cales test, Dunn test).*

Table 4. *The level of matrix metalloproteinases and their tissue inhibitors in the oral fluid (ng/ml), (M ± m)*

Index	Children I, II Health groups	Children with experience of type 1 diabetes up to 2 years	Children with experience of type 1 diabetes 3–10 years
MMP-1	0,21±0,02	0,24±0,03*	0,58±0,11*
MMP-2	0,97±0,33	2,14±0,19*	7,73±2,86*
MMP-8	187,62±16,71	241,91±19,44*	352,47±24,06*
MMP-9	294,83±21,23	370,63±41,71*	533,29±47,88*
TIMP-1	190,54±14,68	217,36±20,32*	261,83±31,27*
TIMP-2	19,36±3,04	26,58±4,29*	41,66±7,01*

Note: ** — p≤0.05 is statistically significant in comparison with the patients of the comparison group (Newman-Cales test, Dunn test).*

the degradation of collagen in UOF — which offers a proper reflection of the inflammatory and destructive process intensity in periodontal tissues — is associated with activation of local compensation & regulatory mechanisms, which is aimed at restoring periodontal tissues. The change dynamics pertaining to the MMP-2 content in the oral fluid offers a reliable reflection of clinical manifestations (the depth of periodontal pockets, the degree of bleeding of the gums), and can be used in clinical practice as a marker to evaluate the effectiveness of dental treatment.

Evaluation of the MMP-8 (neutrophilic collagenase) content taken as a marker for chronic periodontitis, and a marker for impaired neutrophil secretion, in the children with Type 1 DM (in blood serum and UOF), if compared to the children in Groups I and II, revealed an overproduction of MMP-8, while an increase in the values in the 2nd subgroup (196.4 ± 10.4% and 87.8 ± 6.1%, respectively) went up to the most significant level, if matched against a similar increase in the 1st subgroup (19.3 ± 1, 7% and 28.9 ± 1.9%). An increase in the salivary and serum MMP-8 levels along with the progression of endocrinopathy, as a key factor in the extracellular matrix destruction, is due to inflammatory activity in the pancreas islet β-cells, which is accompanied with resorption and destruction of the alveoli osteoid tissue along with activated osteoclast function, as well as dental plaque development, increased dentine demineralization and inflammatory response in the gum tissue. A significant increase in the MMP-8 level and the transition to the active form is a marker of chronic generalized periodontitis in its acute stage and rapidly progressive periodontitis, which can be used as an informative indicator for the pathological process intensity (resorption of interalveolar septa; expansion of periodontal cracks; damage to the bone tissue of the jaw alveolar processes, cortical plates destruction, and presence of osteoporosis foci).

Compared with the children of Health Groups I and II, the children with Type 1 DM had their serum and UOF overproducing MMP-9 (Gelatinase-B), while the increase in the indicators in the 2nd subgroup (18.5 ± 1.4% and 80.9 ± 6.3%, respectively), matched against the children of the 1st subgroup (4.1 ± 0.3% and 25.7 ± 1.6%), appeared the most significant. MMP-9 been proven to be involved in processes like inflammation, recovery, remodeling and osteoclastic bone resorption, while the presence MMP-9 in gingival fluid with periodontitis (up to 99%) and squamous cell carcinoma (up to 93%), allow it to be classified as a marker risk for progression of inflammatory periodontal diseases and marker of squamous cell carcinoma. An increase in the MMP-9 concentration at the local and systemic levels with an increase in Type 1 DM experience in children serves a proper reflection of a decrease in the number of degradation products of native collagens (Type IV, V, VII, X, XI), which means an increase in the intensity of inflammatory and destructive processes in periodontal tissues along with physiological protective and adaptive mechanisms failure. An increase in the levels of TIMP-1 and TIMP-2 involved in the MMP enzymatic activity regulation, in the blood serum and UOF of children with Type 1 DM who belong to Health Groups I and II, means accumulation of extracellular collagen along with extracellular matrix destruction, an increase in the antigenic load, an increased inflammatory response, periodontal tissues degradation, as well as the development of vascular intimal hyperplasia. The most significant increase in TIMP-1 (blood serum, 32.1 ± 1.8%; UOF, 37.4 ± 2.1%) and TIMP-2 (blood serum, 60.6 ± 3.4%; UOF, 115.2 ± 6.3%) was recorded in the 2nd subgroup, which reflects the degree of Type 1 DM advance and the intensity of the morphological structure destruction in the periodont, along with disturbed protective, barrier, trophic, plastic and shock-absorbing functions. Along with an increase in Type 1 DM history, the most significant increase in the serum and UOF TIMP-2 — compared with TIMP-1 — was due to the following factors: the production of TIMP-1, which is involved in the native collagen breakdown, prevails in children with a short disease history, where reversible inflammatory changes in periodontal tissues are dominant; the expression of TIMP-2, which is involved in the denatured collagen breakdown, dominates in children with a long history of endocrinopathy, where (along with the initial signs of inflammation) inflammatory and destructive irreversible periodontal lesions are diagnosed, too. The prominent response of TIMP-2, which is an inhibitor of MMP-2 and MMP-9, can be accounted for by the accumulation of high molecular weight collagen and its degradation products, as well as by the duration and the chronic nature of the inflammation.

Table 5 shows the ratio (matrix metalloproteinases / tissue inhibitors) in blood serum and UOF.

An analysis of the MMP/TIMP quantitative ratios revealed that under physiological conditions, no active MMPs were to be found in the tissues, while the level of the precursors (pro-MMP) was minimal. As long as the length of Type 1 DM history in children increases, the ratio dynamics proves multidirectional: for the blood serum there is an increase in MMP-1/TIMP-1; MMP-8/TIMP-1; MMP-8/TIMP-2; decrease in MMP-2/TIMP-1; MMP-9/TIMP-1; MMP-1/IMP-2; MMP-2/IMP-2; MMP-9/IMP-2; for the oral fluid there is an increase in MMP-1/TIMP-1; MMP-2/TIMP-1; MMP-8/TIMP-1; MMP-9/

Table 5. *The MMP/TIMP ratio in blood serum and UOF*

Index	Children I, II Health groups	Children with experience of type 1 diabetes up to 2 years	Children with experience of type 1 diabetes 3-10 years
Blood serum			
MMP-1/TIMP-1	0,053 (1:18,7)	0,053 (1:18,7)	0,056 (1:17,7)
MMP-2/TIMP-1	1,44 (1,4:1)	1,34 (1,3:1)	1,17 (1,1:1)
MMP-8/TIMP-1	0,057 (1:17,4)	0,063 (1:15,7)	0,129 (1:7,8)
MMP-9/TIMP-1	2,021 (2,0:1)	1,950 (1,9:1)	1,812 (1,8:1)
MMP-1/TIMP-2	0,074 (1:13,4)	0,071 (1:13,9)	0,064 (1:15,6)
MMP-2/TIMP-2	1,987 (1,9:1)	1,808 (1,8:1)	1,332 (1,3:1)
MMP-8/TIMP-2	0,079 (1:12,6)	0,085 (1:11,7)	0,146 (1:6,8)
MMP-9/TIMP-2	2,793 (2,8:1)	2,618 (2,6:1)	2,061 (2,0:1)
Unstimulated oral fluid			
MMP-1/TIMP-1	0,001 (1:904,8)	0,001 (1:904,1)	0,002 (1:450,0)
MMP-2/TIMP-1	0,005 (1:196,4)	0,009 (1:101,6)	0,029 (1:33,8)
MMP-8/TIMP-1	0,98 (1:1,1)	1,11 (1,1:1)	1,34 (1,3:1)
MMP-9/TIMP-1	1,55 (1,5:1)	1,71 (1,7:1)	2,03 (2,0:1)
MMP-1/TIMP-2	0,011 (1:92,2)	0,009 (1:110,7)	0,014 (1:71,8)
MMP-2/TIMP-2	0,05 (1:19,9)	0,08 (1:12,4)	0,18 (1:5,4)
MMP-8/TIMP-2	9,69 (9,7:1)	9,10 (9,1:1)	8,46 (8,5:1)
MMP-9/TIMP-2	15,23 (15,2:1)	13,94 (13,9:1)	12,80 (12,8:1)

TIMP-1; MMP-1/TIMP-2; MMP-2/TIMP-2; decrease in MMP-8/TIMP-8; MMP-9/TIMP-2. The MMP–TIMP imbalance results in activated proteolysis system, which comes accompanied with disturbed connective tissue protein metabolism, increased bone resorption and remodeling processes, proteolytic degradation of Type I collagen, as the major factor involved in the uncontrolled destruction of the intercellular matrix, followed with periodontal structure disturbed arrangement.

In the 1st subgroup, the activity of tissue inhibitors and MMPs, which play a key role in chronic inflammation development and maintenance, is mainly observed in the early stages – *expression; proenzymes activation; matrixin active forms accumulation*. Compared with the children in Health Groups I and II, the change in MMP / TIMP ratios in blood serum and UOF, which reflects the mature enzyme activity forms suppression by tissue (endogenous) inhibitors through direct interaction with their active centers, was insignificant. The compensatory production of TIMP, which is sufficient to inactivate the active forms of MMP, supports proteolytic activity inhibition and prevents intercellular matrix proteins degradation in children at the initial stages of Type I DM course.

In the 2nd subgroup, serum and UOF revealed hyperproduction of the active matrixins and their tissue inhibitors. A significant difference in the MMP/TIMP ratios, if compared with Health Groups I and II, indicates a significant imbalance between the metalloproteinases production and their tissue inhibitors. Excessive or low expression of tissue inhibitors in the 2nd subgroup, including due to blockade by salivary proteolytic enzymes, does not offer a proper blockage of the active MMP forms. The accumulation of extracellular matrix proteins, which indicates the *proteolysis* activation and overstrain in the protective and adaptive mechanisms, confirms the key role played by morphological disorders of the intercellular matrix in the pathogenesis of inflammatory and destructive changes taking place in periodontal tissues in case of a long Type 1 DM history.

CONCLUSIONS

1. Children with Type 1 DM, under hyperglycemia and with a long disease history, feature disturbed regulation of matrix metalloproteinases synthesis (MMP-1, MMP-2, MMP-8, MMP-9) as well as their tissue inhibitors (TIMP-1, TIMP-2), which is due to disorders in the multicomponent system of intercellular matrix catabolism, and malfunctioning of its regulatory mechanisms with failure to maintain proper phase changes.
2. The expression of matrix metalloproteinases and their tissue inhibitors in blood serum and oral fluid reveals significant individual variability not in healthy

children alone, yet also in children with Type 1 DM.
3. The balance in the synthesis of matrix metalloproteinases and their tissue inhibitors in blood serum and oral fluid in children with short experience of Type 1 DM can be seen from the lack of statistically significant differences when compared with similar indicators for children of Health Groups I and II.
4. The biological fluids of children with long-term experience of Type 1 DM against chronic hyperglycemia and insulin hypoproduction reveal a statistically significant increase in matrix metalloproteinases (1.1–7.9 times), their tissue inhibitors (1.3–2.2 times), if compared with similar indices in children belonging to Health Groups I and II, indicating the proteolysis system activation.
5. An increase in the MMP-1, MMP-2, MMP-8, MMP-9, TIMP-1, TIMP-2 levels in blood serum and oral fluid along with an increase in the Type 1 DM history in children is accompanied by progressing inflammatory and destructive changes in periodontal tissues, which is associated with an imbalance between matrix metalloproteinases and their tissue inhibitors, impaired remodeling processes and structural organization of the extracellular matrix.
6. Rising index ratios (blood serum, MMP-8/TIMP-1, MMP-8/TIMP-2; oral fluid, MMP-2/TIMP-1, MMP-2/TIMP-1) can be considered as an early diagnostic sign (predictor) of inflammation, as well as a criterion for developing groups of *patients with a high risk of developing Type 1 DM*.
7. The MMP-8, MMP-9 levels in biological fluids offer a proper reflection to the severity of pathologies within periodontal disease, while an increase in the MMP-9 activity is a diagnostically significant marker for the progression of inflammatory and destructive changes in periodontal disease, accompanied by a decrease in the carbohydrate metabolism compensation.
8. An increase in MMP/TIMP ratios with an increase in Type 1 DM history means, on the one hand, a decrease in the tissue inhibitors receptor control, and on the other – proteolytic degradation of the extracellular matrix, as a result of a complex chain of reactions where MMP-2 and MMP-9 act synergistically, through a fibronectin-like fragment, taking a feedback-like turn and regulating the mechanism in vivo.

REFERENCES

1. **Alves C., Brandao M., Andion J., Menezes R.** Oral health knowledge and habits in children with type 1 diabetes mellitus // Braz Dent J. – 2009. – Vol. 20, № 41. – P. 70–73.
2. **Anderson S.S., Wu K., Nagase H. et al.** Effect of matrix glycation on expression of type IV collagen, MMP-2, MMP-9 and TIMP-1 by human mesangial cells. Cell Adhes Commun 1996; 4: 2: 89–101.
3. **Basov A.A., Ivchenko L.G., Domenyuk D.A., Dmitrienko T.D., Nuzhnaya C.V.** The role of oxidative stress in the pathogenesis of vascular complications in children with insulinable sugar diabetes // Archiv EuroMedica. 2019. Vol. 9; 1: 136–145. https://doi.org/10.35630/2199-885X/2019/9/1/136
4. **Bykov I.M., Gilmiyarova F.N., Domenyuk D.A., Dmitrienko S.V., Ivanyuta S.O., Budaychiev G. M-A.** Evaluation of cariogenic situation in children with type 1 diabetes mellitus given the mineralizing potential of saliva and enamel resistance. Kubanskij nauchnyj medicinskij vestnik. 2018; 25(4): 22–36. (In Russ., English abstract). DOI: 10.25207 / 1608-6228-2018-25-4-22-36.
5. **Bykov I.M., Ivchenko L.G., Domenyuk D.A., Kostyukova N.Y., Storozhuk A.P., Ilijev D.M.** Features of free radical oxidation and antioxidant protection in children with sugar diabetes of the first type. Kuban Scientific Medical Bulletin. 2017; (4): 27–38. (In Russ., English abstract). DOI: DOI:10.25207/1608-6228-2017-24-4-27-38.
6. **Bykov I.M., Ivchenko L.G., Domenyuk D.A., Kostyukova N.Y., Storozhuk A.P., Ilijev D.M.** Salivary the level of proinflammatory cytokines in children with autoimmune diabetes mellitus in different phases of compensation endocrinopathy. Kuban Scientific Medical Bulletin. 2017; 24(4): 39–48. (In Russ., English abstract). DOI: 10.25207/1608-6228-2017-24-4-39-48.
7. **Brew K., Dinakarpandian D., Nagase H.** Tissue inhibitors of metalloproteinases: evolution, structure and function // Biochim. Biophys. Acta. – 2000. – Vol. 1477 (1-2). – P. 267–283.
8. **Chung A.W, Yang H.H., Sigrist M.K. et at.** Matrix metalloproteinase-2 and -9 exacerbate arterial stiffening and angiogenesis in diabetes and chronic kidney disease. Cardiovasc Res 2009; 84: 3: 494–504.
9. **Chandna S., Bathla M., Madaan V., Kalra S.** Diabetes Mellitus – a risk factor for periodontal disease // Internet J Family Prac. – 2010. – Vol. 9, № 1.
10. **Cooke D. W.** Type 1 diabetes mellitus in pediatrics / D. W. Cooke, L. Plotnick // Pediatr Rev.– 2008.– Vol. 29(11).– P. 374–384.
11. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V., Korobkeev A.A., Arutyunova A.G.** Morphological peculiarities of facial skelet structure and clinical and diagnostic approaches to the treatment of dental anomalies in children in the period of early change. Pediatric dentistry and prophylaxis. 2019; Vol. 19; 1 (69): 26–38. (In Russ.) DOI: 10.33925/1683-3031-2019-19-69-26-38
12. **Davydov B.N., Gilmiyarova F.N., Domenyuk D.A., Ivchenko L.G.** Clinical and diagnostic significance of the activity of matrix metalloproteinase and their tissue inhibitors in assessing the condition of periodontal tissues in children with type 1 diabetes mellitus. Part I. Pediatric dentistry and prophylaxis. 2017; Vol. XVI; 4 (63): 14–19. (In Russ.).

13. **Davydov B.N., Gilmiyarova F.N., Domenyuk D.A., Ivchenko L.G.** Clinical and diagnostic significance of the activity of matrix metalloproteinase and their tissue inhibitors in assessing the condition of periodontal tissues in children with type 1 diabetes mellitus. Part II. Pediatric dentistry and prophylaxis. 2018; Vol. XVII; 1 (64): 37–46. (In Russ.).

14. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part I. Periodontology, 2019; Vol. 24; 1–24(90): 4–10. DOI: 10.25636/PMP.1.2019.1.1

15. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part II. Periodontology. 2019;24(2):108–119. (In Russ.) DOI:10.33925/1683-3759-2019-24-2-108-119

16. **Davydov B.N., Domenyuk D.A., Bykov I.M., Ivchenko L.G., Dmitrienko S.V.** Modern possibilities of clinical-laboratory and x-ray research in preclinical diagnostics and prediction of the risk of development of periodontal in children with sugar diabetes of the first type. Part I. Periodontology, 2018; Vol. 23; 3–23(88): 4–11. DOI:10.25636/PMP.1.2018.3.1

17. **Davydov B.N., Gilmiyarova F.N., Domenyuk D.A., Ivchenko L.G.** Optimization of diagnostics of type I diabetes in children according to the results of cytomorphological studies of buccal epithelium and processes of oxidative stress in the oral cavity. Pediatric dentistry and prophylaxis. 2017; Vol. XVI; 3(62): 9–18. (In Russ.).

18. **Dedov I.I., Shestakova M.V., Vikulova O.K.** Standards of specialized diabetes care. Edited by Dedov I.I., Shestakova M.V. (7th edition). Diabetes mellitus. 2015;18(1S):1–112. doi: 10.14341/DM20151S1-112.

19. **Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Sumkina O.B., Budaychiev G. M-A.** Changes of the morphological state of tissue of the paradontal complex in the dynamics of orthodontic transfer of teeth (experimental study). Periodontology, 2018; Vol. 23; 1–23(86): 69-78. DOI:10.25636/PMP.1.2018.1.15

20. **Domenyuk D.A., Zelensky V.A., Rzhepakovsky I.V., Anfinogenova O.I., Pushkin S.V.** Application of laboratory and x-ray gentral studies un early diagnostics of metabolic disturbances of bone tissue in children with autoimmune diabetes mellitus. Entomology and Applied Science Letters. 2018; 5(4): 1–12.

21. **Domenyuk D.A., Zelensky V.A., Dmitrienko S.V., Anfinogenova O.I., Pushkin S.V.** Peculiarities of phosphorine calcium exchange in the pathogenesis of dental caries in children with diabetes of the first type. Entomology and Applied Science Letters. 2018; 5(4): 49–64.

22. **Domenyuk D.A., Konnov V.V., Pichugina E.N., Anfinogenova O.I., Goncharenko A.N., Pushkin S.V.** Microcomputed tomography in qualitative and quantitative evaluation of dental enamel demineralization. Entomology and Applied Science Letters. 2018; 5(4): 72–83.

23. **Domenyuk D.A., Davydov B.N.** Possibilities of microcomputer tomography in the diagnostics of early forms of caries of a chewing surface of permanent molars in children. Part I. Pediatric dentistry and prophylaxis. 2018; Vol. 18; 4 (67): 61–64. (In Russ.) DOI: 10.25636/PMP.3.2018.4.12

24. **Domenyuk D.A., Davydov B.N.** Possibilities of microcomputer tomography in the diagnostics of early forms of caries of a chewing surface of permanent molars in children. Part II. Pediatric dentistry and prophylaxis. 2019; Vol. 19; 2 (70): 4–12. (In Russ.) DOI: 10.33925/1683-3031-2019-19-2-04-12

25. **Domenyuk D.A., Davydov B.N., Gilmiyarova F.N., Ivchenko L.G., Vedeshina E.G.** Diagnostic and prognostic value of crystalline structures of the oral fluid in children with anomalies of occlusion. Pediatric dentistry and prophylaxis. 2017; Tom XXI; 2(61): 9–16. (In Russ.).

26. **Dmitrienko S.V., Domenyuk D.A., Fischev S.B., Subbotin R.S.** Dynamics of periodontal fixing capacity through orthodontic treatment employing edgewise technique // Archiv EuroMedica. 2019. Vol. 9; 1: 151–152. https://doi.org/10.35630/2199-885X/2019/9/1/151

27. **Dmitrienko S.V., Fomin I.V., Domenyuk D.A., Kondratyuk A.A., Subbotin R.S.** Enhancement of research method for spatial location of temporomandibular elements and maxillary and mandibular medial incisors // Archiv EuroMedica. 2019. T. 9. № 1. P. 38–44. https://doi.org/10.35630/2199-885X/2019/9/1/38

28. **Dmitrienko T.D., Domenyuk D.A., Porfyriadis M.P., Arutyunova A.G., Kondratyuk A.A., Subbotin R.S.** Connection between clinical and radiological torque of medial incisor at physiological occlusion // Archiv EuroMedica. 2019. Vol. 9. № 1. P. 29–37. https://doi.org/10.35630/2199-885X/2019/9/1/29

29. **Fomin I.V., Dmitrienko S.V., Domenyuk D.A., Kondratyuk A.A., Arutyunova A.G.** Effect of jaw growth type on dentofacial angle in analyzing lateral teleradiographic images // Archiv EuroMedica. 2019. Vol. 9; 2: 136–137. https://doi.org/10.35630/2199-885X/2019/9/2/136

30. **Fischev S.B., Puzdyryova M.N., Dmitrienko S.V., Domenyuk D.A., Kondratyuk A.A.** Morphological features of dentofacial area in peoples with dental arch issues combined with occlusion anomalies // Archiv EuroMedica. 2019. Vol. 9; 1: 162–163. https://doi.org/10.35630/2199-885X/2019/9/1/162

31. **Gavrilova O.A., Domenyuk D.A.** Specific features of oral cavity microbiocenosis in children using non-removable orthodontic appliances. Archiv EuroMedica, 2018; 8(2): 91–92.

32. **Gavrilova O.A., Domenyuk D.A.** Microbiological verification for the use of thermoplastics in prosthetic treatment of dentition issues in children. Archiv EuroMedica, 2018; 8(2): 88–90.

33. **Gilmiyarova F.N., Davydov B.N., Domenyuk D.A., Ivchenko L.G.** Influence of severity of type I diabetes mellitus in children on dental status and immunological, biochemical parameters of blood serum and oral fluid. Part I. Periodontology. 2017; Vol. XXII; 2 (83): 53–60. (In Russ.).

34. **Gilmiyarova F.N., Davydov B.N., Domenyuk D.A., Ivchenko L.G.** Influence of severity of type I diabetes mellitus in children on dental status and immunological, biochemical parameters of blood serum and oral fluid. Part II. Periodontology. 2017; Vol. XXII; 3 (84): 36–41. (In Russ.).

35. International Diabetes Federation. Diabetes Atlas 7th Edition. 2015.

36. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes. 2014; 15(Suppl. 20): 1–290.

37. **Ivchenko L.G., Domenyuk D.A.** Diagnosis of immunometabolic disorders in children with type I diabetes mellitus. Kuban Scientific Medical Bulletin. 2017; 1(2): 73–82. (In Russ., English abstract). DOI:10.25207/1608-6228-2017-2-73-82.

38. **Karslieva A.G., Domenyuk D.A., Zelensky V.A.** Mixed saliva trace element composition in children with dentoalveolar anomalies through apparatus-involved treatment. Archiv EuroMedica, 2014; 4(1): 29–35.

39. **Korobkeev A. A., Domenyuk D. A., Shkarin V. V., Dmitrienko S. V., Mazharov V. N.** Variability of odontometric indices in the aspect of sexual dimorphism. Medical News of North Caucasus. 2019;14(1.1):103-107. DOI – https://doi.org/10.14300/mnnc.2019.14062 (In Russ.)

40. **Korobkeev A.A., Domenyuk D.A., Shkarin V.V., Dmitrienko S.V.** Types of facial heart depth in physiological occlusion. Medical news of North Caucasus. 2018. – Vol. 13. – № 4. – P. 627–630. (In Russ., English abstract). DOI – https://doi.org/10.14300/mnnc.2018.13122

41. **Kulikova, N.G.** Evaluation of the effectiveness of pharmaco-physiotherapeutic treatment of catarrhal gingivitis on the results of the condition of mucosal immunity of oral cavity in women in the postpartum period / N.G. Kulikova, D.A. Domenyuk, V.A. Zelensky, A.S. Tkachenko // Medical news of North Caucasus. 2017. – Vol. 12. – № 4. – P. 417–421. (In Russ., English abstract). DOI: 10.14300/mnnc.2017.12117.

42. **Lalla E., Bin C., Shantanu L. et al.** Periodontal changes in children and adolescents with diabetes: a case-control study // Diabetes Care. – 2006. – Vol. 29, № 2. – P. 295–299.

43. **Makela M., Salo T., Uitto V.J., Larjava H.** Matrix metalloproteinases (MMP-2 and TIMP-9) of the oral cavity: cellular origin and relationship to periodontal status // J. Dent. Res. – 1994. – Vol. 73, No. 8. – P. 1397–1406.

44. **Nagase H., Woessner J.F.** Matrix metalloproteinases // J. Biol. Chem. – 1999. – Vol. 274, No. 31. – P. 21491–21494.

45. **Sorsa T., Tjaderhane L., Salo T.** Matrix metalloproteinases in oral deseases // Oral. Dis. 2004. – Vol. 10, No. 6. – P. 311–318.

46. **Shkarin V.V., Ivanov S.Yu., Dmitrienko S.V., Domenyuk D.A., Lepilin A.V., Domenyuk S.D.** Morphological specifics of craniofacial complex in people with varioustypes of facial skeleton growth in case of transversal occlusion anomalie // Archiv EuroMedica. 2019. Vol. 9; 2: 5–16. https://doi.org/10.35630/2199-885X/2019/9/2/5

47. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of transversal and vertical parameters in lower molars crowns at various dental types of arches // Archiv EuroMedica. 2019. Vol. 9; 2: 174–181. https://doi.org/10.35630/2199-885X/2019/9/2/174

48. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of grinder teeth rotation at physiological occlusion of various gnathic dental arches // Archiv EuroMedica. 2019. Vol. 9; 2: 168–173. https://doi.org/10.35630/2199-885X/2019/9/2/168

49. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of joint space in patients with physiological occlusion on computed tomogram head image // Archiv EuroMedica. 2019. Vol. 9; 2: 182–183. https://doi.org/10.35630/2199-885X/2019/9/2/182

50. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of central point location between incisors in people with physiological occlusions // Archiv EuroMedica. 2019. Vol. 9; 2: 165–167. https://doi.org/10.35630/2199-885X/2019/9/2/165

51. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko T.D., Domenyuk D.A., Fomin I.V.** Craniofacial line of teleradiography and its meaning at cephalometry // Archiv EuroMedica. 2019. Vol. 9; 2: 84–85. https://doi.org/10.35630/2199-885X/2019/9/2/84

https://doi.org/10.35630/2199-885X/2019/9/3.26

DEPENDENCE OF FACIAL MORPHOMETRIC PARAMETERS FROM MASTICATORY MUSCLES TONE IN PEOPLE WITH HORIZONTAL TYPE OF INCREASED DENTAL ABRASION

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ABSTRACT — The work offers qualitative indicators of masticatory muscles myotonometry, which were recorded in patients in their second mature age with a compensated and decompensated type of increased dental abrasion. The obtained results are compared with similar parameters of patients with physiological occlusion. A characteristic feature of patients with a compensated type of increased dental abrasion is the absence or a slight decrease in the height of the gnathic part of the skull due to false hypertrophy (an increase in the jaw bone porosity). This category features an increased tone of the masticatory muscles, both at rest and during tension. In patients with a compensated type of increased dental abrasion, the parafunction of the masticatory muscles and tongue are combined with symptoms of temporomandibular joint damage. A decompensated type of increased dental abrasion combines clinical and functional symptoms with a decrease in the lower face height. The study outcomes are of an applied focus in terms of selecting the tactics and principles of reasonable treatment when dealing with patients revealing a horizontal type of increased dental abrasion.

KEYWORDS — increased dental abrasion, face morphometric study, interalveolar height, intergnathic distance, myotonometry

INTRODUCTION

Increased dental abrasion (IDA) is quite common in dental practice. This is less common among young people (6.3%) compared to people of middle age (32.7%), as well as to those belonging to older age groups (11.8–20.6%) [1, 2, 19, 22].

IDA occurrence may be associated with the teeth functional overload, harmful professional factors, impaired development of hard dental tissues, the functional status of the masticatory muscles, etc. [3, 9–13, 17, 30].

A decompensated abrasion reveals a decrease in the interalveolar height, while a compensated abrasion shows a slight decrease in the height of the gnathic part due to the jaws alveolar parts hypertrophy. This hypertrophy may disappear or decrease when the alveolar ridge gets proper strain, since bone tissue false hypertrophy develops through increased bone porosity [18, 20].

The following affects a decrease in the lower face height: the dental abrasion degree, abnormal occlusion; changes occurring through loss of antagonist teeth; the functional status of the masticatory muscles [4–8, 14–16, 21, 23–29]. The purpose of this study can be explained with the lack of systematic data available in the respective research literature focusing on the masticatory muscles tone in patients with IDA.

Aim of study

to identify the masticatory muscles tone status and its effect on the face vertical parameters in patients with horizontal IDA.

MATERIALS AND METHODS

A morphometric study of the face and masticatory muscles myotonometry was carried out involving 66 patients (27 males and 39 females) in their second mature age (35–60) with a horizontal type of increased dental abrasion, where 30 patients (14 males and 16 females) had a decompensated type with another 36 (13 men and 23 women) featuring a compensated type of dental abrasion. The comparison group included 64 people in their second half of adulthood (27 males and 37 females) with physiological occlusion. Cefalometric measurements were done subject to the generally accepted method by Ya.Ya. Roginsky (1968), F.Ya. Khoroshilkina (1991) using a caliper with a scale unit value of 0.01 mm. The generally accepted measuring points were used through the cephalometry (Fig. 1).

The measurements between the cephalometric points allowed evaluating the gnathic parameters. The

functional status of the masticatory muscles was evaluated through myotonometric measurements for which purpose a SZIRMA myotonometer (Hungary, METRIMPEX) was used. We involved the motor points (the most prominent areas of the masticatory and temporal muscles, at the maximum teeth compression), and then, using the device's submersible probe we measured the rest tone (Tr) and the stress tone (Ts) in grams (Fig. 2).

The study outcomes were statistically processed using the SPSS 17.0 software package at a 0.05 significance level. When performing quantitative description, the mean value (M) and the standard mean error (m) were used. The statistical processing was carried out using descriptive statistics, analysis of variance (Student's t-test), correlation analysis (Pearson and Spearman's paired correlation coefficients), and with nonparametric statistics methods (Mann-Whitney and Wilcoxon).

RESULTS AND DISCUSSION

The relationship between individual morphometric head and face parameters in patients with physiological occlusion of permanent teeth was identified. Table 1 shows the results of studying the head and face parameters in patients with permanent teeth physiological occlusion.

In females, the morphometric head and face parameters had lower values than in males. The height of the nasal part and the height of the face in males exceeded that of females, while the height of the gnathic part revealed no significant difference between the two genders. The face height (n–me) in males was 125.64±6.3 mm, while in females it was 111.87±2.26 mm ($p < 0.05$). The gnathic part of the face was 55.84±4.5 mm in males vs. 53.16±1.54 mm in females. The mean value of the interocclusal gap was 3.2±0.85 mm. The sum of the dentoalveolar parts height, maxillary and mandibular, corresponded to the size of the mandible height and, according to these signs, no gender dimorphism was identified.

Myotonometry was performed with the rest tone (Tr) and the stress tone (Ts) of the masticatory muscles. Table 2 offers a view on the respective outcomes.

Compared with the temporal muscles in people of both genders, the rest tone of the masticatory muscles exceeded it (by 4.2±0.3 grams, $p < 0.05$), thus being 52.3±3.5 grams in

Fig. 1. *Location of cephalometric points in the frontal (a) and sagittal (b) planes.*

Fig. 2. *Mechanical myotonometer Szirmai "Metrimpex" (Hungary).*

males and 43.1 ± 4.2 grams ($p < 0.05$) in females. The stress tone of the masticatory muscles in males was 155.4±18.0 grams. The masticatory muscles stress tone in females was 19.2±2.5 grams ($p < 0.05$) lower than in men. The measurement values for the facial skeleton in patients with decompensated horizontal IDA can be seen from Table 3.

The height of the nasal face part (n–sn) exceeded the height of the lower face part (sn – gn) and the difference in this case was 8.2±1.2 mm ($p < 0.05$). The intergnathic part (sn–spm) decreased by 6.5±0.7 mm ($p < 0.05$). A typical feature for the patients was a decrease in the height of the gnathic part of the face, namely, the intergnathic distance and the mandible height. The interocclusal gap was 7.5±0.95 mm. The study showed that the patients had a normal maxilla position, while the mandible had a slight sagittal shift. The measurement results for the masticatory muscles tone (in grams) in patients with decompensated horizontal IDA are shown in Table 4.

The rest tone and the stress tone in all the patients with decompensated horizontal IDA was 4.5±0.6 grams ($p < 0.05$)

Table 1. *Morphometric head and face parameters in patients with physiological occlusion of permanent teeth, (mm), (M±m), (p≤0,05)*

Morphometric parameters	Face sizes	
	Male face sizes	Female face sizes
n–me (face height)	125,64 ± 6,3	111,87 ± 2,26
gl–me	136,75 ± 3,29	122,34 ± 2,34
n–sn	61,19 ± 2,7	58,57 ± 2,29
sn–spm (intergnathic height)	55,84 ± 4,5	53,16 ± 1,54
gn–me	6,52 ± 1,29	6,02 ± 1,19
gl–n	12,38 ± 2,62	10,38 ± 2,42
zy–zy	143,57 ± 5,1	138,41 ± 3,72
sn–gn	65,46 ± 1,43	63,28 ± 2,16

Table 2. *Masticatory muscles tone in patients with physiological occlusion of permanent teeth, (gramme), (M±m), (p≤0,05)*

Muscle	Patients	Muscle tone	
		Resting tone, (Tr)	Voltage tone, (Ts)
Chewing muscles proper	Women	46,3 ± 1,4	159,0 ± 4,8
	Men	55,4 ± 2,5	175,6 ± 3,7
Temporal muscles	Women	44,3 ± 1,2	145,2 ± 4,1
	Men	52,7 ± 2,3	166,5 ± 3,9

Table 3. *Morphometric head and face parameters in patients with decompensated horizontal IDA, (mm), (M±m), (p≤0,05)*

Morphometric parameters	Face sizes	
	Male face sizes	Female face sizes
n–me (face height)	112,5 ± 3,13	108,96 ± 2,26
gl–me	123,88 ± 3,29	118,34 ± 2,34
n–sn	55,18 ± 3,39	54,22 ± 3,29
sn–spm (intergnathic height)	46,35 ± 3,45	43,41 ± 2,14
gn–me	6,12 ± 1,54	5,24 ± 1,31
gl–n	12,38 ± 2,62	10,38 ± 2,42
zy–zy	136,57 ± 6,39	132,57 ± 6,76
sn - gn	57,30 ± 2,06	54,76 ± 1,59

lower compared with the norm, and the stress tone was 31.1±3.3 grams lower ($p < 0.05$) in males and females. Table 5 offers a view on the head and face morphometric parameters in patients with compensated horizontal IDA.

The face nasal area (n–sn), taken vertically, corresponded to the height of the lower part of the face (sn–gn) and the difference in these values was 1.75±0.2 mm ($p < 0.05$). The intergnathic part (sn–spm) decreased by 2.1±0.12 mm ($p < 0.05$). The interocclusal gap was 1.5±0.3 mm. This group of patients had a slight decrease in the interalveolar height, especially the height of the mandible and the intergnathic distance. An analysis of indicators showed that the patients had the mandible and maxilla positions corresponding to the normal values. The values for the masticatory muscles tone (in grams) in patients with compensated horizontal IDA are listed in Table 6.

The study revealed that the rest tone and the stress tone in almost all the patients with compensated horizontal IDA was elevated. The patients showed an increase in the rest tone as compared with normal values, by 21.2±1.8 grams ($p < 0.05$), and the stress

Table 4. *Myotonometry results in patients with decompensated horizontal IDA, (gramme), (M±m), (p≤0,05)*

Muscle	Patients	Muscle tone	
		Resting tone, (Tr)	Voltage tone, (Ts)
Chewing muscles proper	Women	42,7 ± 1,3	134,6 ± 3,8
	Men	51,3 ± 1,1	155,4 ± 2,7
Temporal muscles	Women	39,7 ± 2,5	118,8 ± 4,7
	Men	42,3 ± 2,4	126,3 ± 4,7

Table 5. *Morphometric head and face parameters in patients with compensated horizontal IDA, (mm), (M±m), (p≤0,05)*

Morphometric parameters	Face sizes	
	Male face sizes	Female face sizes
n–me (face height)	123,34 ± 6,2	110,57 ± 2,16
gl–me	134,65 ± 3,27	121,36 ± 2,14
n–sn	59,69 ± 2,5	55,27 ± 2,26
sn–spm (intergnathic height)	52,81 ± 4,5	52,15 ± 1,64
zy–zy	142,57 ± 6,1	137,51 ± 3,82
sn–gn	62,45 ± 1,23	53,27 ± 2,36

Table 6. *Myotonometry results in patients with compensated horizontal IDA, (gramme), (M±m), (p≤0,05)*

Muscle	Patients	Muscle tone	
		Resting tone, (Tr)	Voltage tone, (Ts)
Chewing muscles proper	Women	66,3 ± 2,5	168,3 ± 3,8
	Men	73,7 ± 1.8	186,3 ± 3,4
Temporal muscles	Women	56,5 ± 2,6	158,8 ± 4,8
	Men	65,7 ± 3,4	176,6 ± 4,5

tone was higher by 12.5±1.15 grams (p <0.05), both in males and females. This can be viewed as a compensatory response that the maxillofacial area had to hypertrophy of the jaws alveolar ridges. The stress tone in males was 21.6±2.1 grams (p <0.05) higher than in females. The interocclusal gap was an average of 1.5±0.3 mm

CONCLUSIONS

1. The specific feature in the patients with decompensated horizontal IDA was a decrease of 6.5± 0.7 mm (p <0.05) in the interalveolar height with changes in the face vertical parameters. The interocclusal gap was within 7.5±0.95 mm. At the same time, the rest tone in these patients was 4.5±0.6 grams (p <0.05) lower if compared with the normal values, while the stress tone — by 31.1±3.3 grams (p <0.05) in patients of both genders.

2. The patients with compensated horizontal IDA had an insignificant decrease in the height of the gnathic part, as compared with the norm, by 2.1±0.12 mm (p <0.05). The interocclusal gap in the patients was within 7.5±0.95 mm. However, an increase in the rest tone was observed, as compared to the normal values, by an average of 21.2±1.8 g (p <0.05), while the stress tone was an average 12.5±1.15 g higher (p <0.05), both in males and females.

3. The data obtained from the examination of the patients with horizontal IDA will facilitate the selection of reasonable tactics for orthopedic treatment. Patients with decompensated horizontal IDA are recommended treatment with a simultaneous increase in the interalveolar distance with the interocclusal gap maintained within 2–3 mm. As for patients with compensated horizontal IDA, treatment should be delivered in stages with a gradual disintegration of the occlusion, and introduction of teeth under the masticatory muscles tone control.

REFERENCES

1. **Berdin V. V., Dmitrienko S. V. , Sevastyanov A.V., Fishchev B. S., Lepilin A.V.** The main linear parameters of dental arches for the permanent teeth nurmatovtitle // Stomatology of children's age and prevention. 2012. Vol. XI. №3 (48). P. 38–42.
2. **Berdin V. V., Sevastyanov A.V., Fishchev S. B., Dmitrienko D. S., Lepilin A.V.** To the question of determining the size of dental arches in the sagittal and transversal directions // Pediatric dentistry and prevention. 2013. Vol. 12. No. 3. p. 43.
3. **BalakhnichevD.N., Subbotin R.S., Fischev S.B. et al.** Normalization of occlusion in patients with increased dental abrasion // European journal of natural history. 2018. № 4. P. 37–45.
4. **Dmitrienko S.V., Fomin I.V., Domenyuk D.A., Kondratyuk A.A., Subbotin R.S.** Enhancement of research method for spatial location of temporo-mandibular elements and maxillary and mandibular medial incisors // Archiv EuroMedica. 2019. T. 9. № 1. P. 38–44. https://doi.org/10.35630/2199-885X/2019/9/1/38
5. **Dmitrienko S.V., Domenyuk D.A., Fischev S.B., Subbotin R.S.** Dynamics of periodontal fixing capacity through orthodontic treatment employing edgewise technique // Archiv EuroMedica. 2019. Vol. 9; 1: 151–152. https://doi.org/10.35630/2199-885X/2019/9/1/151
6. **Dmitrienko S.V., Domenyuk D.A., Puzdyryova M.N.** Manufacturing methods for individual aligners and trainers from thermoplasts fnd clinical indications for their application // Archiv EuroMedica. 2019. Vol. 9; 1: 153–154. https://doi.org/10.35630/2199-885X/2019/9/1/153
7. **Dmitrienko S.V., Lepilin A.V., Domenyuk D.A., Kondratyuk A.A.** Clinical meaning of methods for identifying variability of mental prominence location // Archiv EuroMedica. 2019. Vol. 9; 1: 45–46. https://doi.org/10.35630/2199-885X/2019/9/1/45
8. **Dmitrienko T.D., Domenyuk D.A., Porfyriadis M.P., Arutyunova A.G., Kondratyuk A.A., Subbotin R.S.** Connection between clinical and radiological torque of medial incisor at physiological occlusion // Archiv EuroMedica. 2019. Vol. 9. № 1. P. 29–37. https://doi.org/10.35630/2199-885X/2019/9/1/29
9. **Fishchev S. B., Orlova I. V., Sevastyanov A. V.** Morphometric parameters of the facial skeleton in humans with a reduced height of gnatichesky part of the person // Pediatr. – 2014. Vol. V. № 3. P. 67–70.
10. **Fishchev B. S., Lepilin A.V., Sevastyanov A.V.,Orlov V. I., Balakhnichev D. N.** The results of treatment of patients with defects of dentition in combination with cross bite with the use of computer modeling // Stomatology of children's age and prevention. 2015. Vol. XIV. No. 3 (46). P. 55–58.
11. **Fishchev B. S., Lepilin A.V., Sevastyanov A.V., Balakhnichev D.N., Agashina M.A.** Prediction of the results of orthopedic treatment of patients with vertical-mesial form of increased teeth abrasion // Parodontologia. 2017. Vol. XXII. №1(82). P. 31–37.
12. **Fischev S.B., Puzdyryova M.N., Dmitrienko S.V., Domenyuk D.A., Kondratyuk A.A.** Morphological features of dentofacial area in peoples with dental arch issues combined with occlusion anomalies // Archiv EuroMedica. 2019. Vol. 9; 1: 162–163. https://doi.org/10.35630/2199-885X/2019/9/1/162
13. **Jacobson A.** Retrospective cephalometric investigation of the effects of soldered transpalatal arches on the maxillary first molars during orthodontic treatment involving extraction of maxillary first bicuspids // American Journal Of Orthodontics add Dentofacial Orthopedics. 2006. № 1. P. 81.
14. **Korobkeev A. A., Domenyuk D. A., Shkarin V. V., Dmitrienko S. V., Mazharov V. N.** Variability of odontometric indices in the aspect of sexual dimorphism. Medical News of North Caucasus. 2019;14(1.1):103-107. DOI – https://doi.org/10.14300/mnnc.2019.14062 (In Russ.)
15. **Lepilin A.V., Fomin I.V., Domenyuk D.A., Dmitrienko S.V., Budaychiev G.M-A.** Diagnostic value of cephalometric parameters at graphic reproduction of tooth dental arches in primary teeth occlusion // Archiv EuroMedica, 2018. Vol. 8. № 1. P. 37–38.
16. **Lepilin A.V., Dmitrienko S.V., Domenyuk D.A., Puzdyryova M.N., Subbotin R.S.** Dependence of stress strain of dental hard tissues and periodontal on horizontal deformation degree // Archiv EuroMedica. 2019. Vol. 9; 1: 173–174. https://doi.org/10.35630/2199-885X/2019/9/1/173
17. **Lepilin A.V., Rajgorodskij Yu.M., Grigoryeva D.A., Erokina N.L., Bakhteeva G.R., Domenyuk D.A.** Reasoning for the application of violet laser physiotherapy device following surgeries in the oral cavity. Archiv EuroMedica, 2018; 8(2): P. 111–114.
18. **Mercado J.** Jefferson skeletal classification system (JSCS) and how it helps in extraction and non-extraction orthodontic cases // Int. J. Orthod. Milwaukee. 2007. № 18(4). P. 31–34.
19. **Porfyriadis M.P., Domenyuk D.A., Arutyunova A.G., Dmitrienko S.V.** Scanning electron microscopy and X-ray spectral microanalysis in dental tissue resistance // Archiv EuroMedica. 2019. Vol. 9; 1: 177–185. https://doi.org/10.35630/2199-885X/2019/9/1/177
20. **Proffit W.R., Fields H. W.** Contemporary Orthodontics, 4rd Edition. Mosby. 2007. 751 p.
21. **Pullinger A. G., Seligman D. A.** Multifactorial analysis of differences in temporomandibular joint hard tissue anatomic relationships between disk displacement with and without reduction in women. / The journal of prosthetic dentistry. 2001. Vol. 86. № 4. P. 407–419.
22. **Sevastyanov A.V., Dmitrienko D. S., Fishchev S. B., Egorova A. V., Rtishcheva S. S.** Match the size of the permanent teeth, dental arch parameters

and the craniofacial complex (the literature review) // Parodontologia. 2010. Vol. XV. No. 2 (55). P. 18-20.

23. **Shkarin V., Domenyuk D., Lepilin A., Fomin I., Dmitrienko S.** Odontometric indices fluctuation in people with physiological occlusion. Archiv EuroMedica, 2018; Vol. 8; 1: 12–18.

24. **Shkarin V.V., Ivanov S.Yu., Dmitrienko S.V., Domenyuk D.A., Lepilin A.V., Domenyuk S.D.** Morphological specifics of craniofacial complex in people with varioustypes of facial skeleton growth in case of transversal occlusion anomalie // Archiv EuroMedica. 2019. Vol. 9; 2: 5–16. https://doi.org/10.35630/2199-885X/2019/9/2/5

25. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of transversal and vertical parameters in lower molars crowns at various dental types of arches // Archiv EuroMedica. 2019. Vol. 9; 2: 174–181. https://doi.org/10.35630/2199-885X/2019/9/2/174

26. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of grinder teeth rotation at physiological occlusion of various gnathic dental arches // Archiv EuroMedica. 2019. Vol. 9; 2: 168–173. https://doi.org/10.35630/2199-885X/2019/9/2/168

27. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of joint space in patients with physiological occlusion on computed tomogram head image // Archiv EuroMedica. 2019. Vol. 9; 2: 182–183. https://doi.org/10.35630/2199-885X/2019/9/2/182

28. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of central point location between incisors in people with physiological occlusions // Archiv EuroMedica. 2019. Vol. 9; 2: 165–167. https://doi.org/10.35630/2199-885X/2019/9/2/165

29. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko T.D., Domenyuk D.A., Fomin I.V.** Craniofacial line of teleradiography and its meaning at cephalometry // Archiv EuroMedica. 2019. Vol. 9; 2: 84–85. https://doi.org/10.35630/2199-885X/2019/9/2/84

30. **Subbotin R.S., Puzdyreva M.N., Fishchev S.B. et al.** Morphometric parameters of the face in patients with decompensated vertical-anterior form of incrised adrasion of teeth // European journal of natural history. 2018. № 5. P. 27–30.

https://doi.org/10.35630/2199-885X/2019/9/3.27

DISTURBED CELL PROLIFERATION AND APOPTOSIS IN PATIENTS WITH CHRONIC PERIODONTITIS AGAINST THE BACKGROUND OF GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT — This study aimed to examine the indicators of gum epithelial cell proliferation in patients with chronic periodontitis against gastroesophageal reflux disease (GERD). The clinical, endoscopic, immunohistological and morphological studies revealed that diseases affecting the esophagus facilitate the development and the progression of periodontal issues. Enhanced apoptosis due to insufficient proliferation of periodontal tissues contributes to the progression of inflammatory and destructive changes in the tissues, against the background of reduced regeneration due to a decrease in the Ki-67 immunopositive cells.

KEYWORDS — periodontitis, gastroesophageal reflux disease, proliferation, apoptosis, Ki-67, Bcl-2

INTRODUCTION

The issues related to the pathogenesis, diagnostics and treatment of inflammatory periodontal diseases still remain relevant due to their prevalence (98%) worldwide, which makes them a serious socio-economic issue [1]. There have been a number of somatic factors identified currently, which add to the development and progression of periodontal diseases, which, in turn, result in stereotypic response revealed as structural shifts once subjected to the effect of various somatic changes in the body [2–6]. The inflammatory periodontal issues incidence in patients with gastroesophageal reflux disease reaches 85.7% of cases [2, 7–9]. Disturbed cell proliferation and apoptosis determine the transition from chronic gingivitis to periodontitis, contributing to chronic diseases progression [10]. Currently, an important role in apoptosis regulation and cell proliferation belongs to the proliferating cells marker — Ki-67, anti-apoptotic protein Bcl-2, and apoptosis [11, 12]. The study of proliferation and apoptosis of gum epithelial cells in periodontal diseases against esophageal pathology will expand the scope of pathogenesis issues, improve early diagnostics of the said diseases, and improve treatment.

Aim of study

to analyze the expression of cell proliferation markers and apoptosis of gum epithelial cells in chronic periodontitis with gastroesophageal reflux disease.

MATERIALS AND METHODS

100 patients were examined; 40 patients had periodontitis on the GERD background; 40 patients had periodontitis with no esophageal pathology; the comparison group included 20 patients with intact periodont. All the patients underwent a comprehensive clinical and instrumental examination with the following index indicators identified: OHI-s (Green J.C., Vermillion J.R., 1964), PMA (Parma, 1960), PI (Russel A.L., 1956) as well as dentition radiological diagnostics. The diagnosis of GERD was given based on the outcomes of a comprehensive clinical and morphological examination. The patients were monitored subject to a single program, including general clinical examination, ultrasound abdominal examination, fibrogastroduodenoscopy, general morphological and cytological, as well as immunohistochemical examination.

The material for morphological diagnostics was taken from the gingival margin mucous membrane, the gingival papillae, as well as the mucous membrane in the transitional gingival fold area. An immunohistochemical study was done using monoclonal mouse antibodies to the proliferating cell marker, Ki-67 and Bcl-2 (Sigma, St. Louis, USA, titer 1: 200). The number of expressing cells was counted in 30 fields within view, and at the indicated magnification; the digital data were counted as per 1 mm^2 using the Video Test-Morphology 4.0 application morphometric software package.

RESULTS AND DISCUSSION

The clinical and instrumental analysis focusing on the periodontal tissues status revealed that periodontal diseases were observed in all (100%) the examined patients with GERD, while the issues were

more severe than in patients without somatic pathology. The anamnesis analysis showed that the severity of the chronic periodontitis course correlates with the GERD history. In case the duration of GERD exceeded 10 years, periodontal diseases of moderate and severe severity were observed in 63.6% of the cases.

Patients with chronic periodontitis complained of bleeding gums, slight pain, and halitosis. An objective examination allowed detecting hyperemia, swelling, bleeding gums. It is to be noted that, at basically equal values in the individual hygiene levels (OHI-s 2.94 ± 0.053), the inflammatory process in the periodont against the GERD background was higher: the PMA index (66.11 ± 1.64); Muhlemann (3.88 ± 0.45); and PI (3.74 ± 0.11), were statistically differed from indicators in patients with periodontitis with no somatic pathology: (OHI-s 2.36 ± 0.34) PMA (33.95 ± 2.35); Muhlemann (1.64 ± 0.28); and PI (1.60 ± 0.13) ($p < 0.05$).

An analysis of the gums immunohistochemical study outcomes revealed that in healthy people, periodontal epithelium shows a low potential for proliferative and anti-apoptotic activity (Ki-67 9.53 ± 0.19); (Bcl-2 2.88 ± 0.10); apoptosis index (Iapt 0.38 ± 0.04). Chronic periodontitis without esophageal pathology featured an increase in the expression of (Ki-67 = 28.88 ± 1.42) and (Bcl-2 8.26 ± 1.19), with a relatively low apoptosis index (Iapt 0.54 ± 0.03). In patients with periodontitis against the GERD background, there was a multiple increase in the gum epithelial cells proliferative potential, which manifested itself through an increase in the number of cells immunopositive to (Ki-67 20.19 ± 0.37). At the same time, apoptosis also increased (Iapt 1.40 ± 0.12); however, the degree of its increase did not correspond to the epithelial cells proliferative activity. The latter could be accounted for by genetic rearrangement of individual cells with them gaining an ability to express an anti-apoptotic molecule (Bcl-2 5.23 ± 0.32). Thus, in patients with inflammatory periodontal diseases observed against the GERD background, cell renewal reveals an epithelial cells apoptosis lagging progressively behind the proliferation rate. The obtained data are consistent with the results obtained through previous studies, which showed that apoptosis increases accordingly to an increase in the severity of periodontal disease inflammatory changes [13, 14]. Activated apoptosis and inhibited proliferation disturb both the physiological and the regenerative function in the mucous membrane of the oral cavity and the stomach.

CONCLUSION

Our data indicate that esophagus diseases contribute to the progression of periodontal disease. The dental status analysis in patients with periodontitis against the GERD background indicates a more pronounced inflammatory lesion of the periodontal complex, if compared with patients without esophageal pathology. An important risk factor triggering and facilitating the course of periodontal disease in people suffering from GERD is the history of the esophagus issue.

The obtained changes in cell proliferation processes and apoptosis largely determine the degree of inflammatory and destructive lesions in periodontal disease against the GERD background, and correlate with the severity of inflammatory periodontal diseases. The leading role in the progression of inflammatory and destructive changes in periodontal tissues against the GERD background belongs to Ki-67, which describes the degree of processes, Bcl-2, which reflects the severity of anti-apoptotic activity, and the apoptosis index, which shows the degree of destruction in the periodontal tissues.

REFERENCES

1. **Gazhva S.I., Guluyev R.V.** The prevalence and intensity of inflammatory periodontal diseases (literature review) // Review. – 2012. – No. 1 (75). – P. 13–14. (In Russ.).
2. **Gorbacheva I.A., Kirsanov A.I., Orekhova L.Yu.** The unity of systemic pathogenetic mechanisms in diseases of internal organs associated with generalized periodontitis // Dentistry. – 2004. – No. 1 (30). – P. 3–7. (In Russ.).
3. **Arutyunov S. D., Pleskanovskaya N.V., Naumov A.V.** Periodontal diseases and "systemic diseases": the past, promising future // Periodontology. – 2009. – No. 1. – T.50. – P. 3–6. (In Russ.).
4. **Mayev I.V., Barer G.M., Busarova G.A.** Dental manifestations of gastroesophageal reflux disease // Clinical medicine. – 2005. – No. 11. – P. 33–38. (In Russ.).
5. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part I. Periodontology, 2019; Vol. 24; 1–24(90): 4–10. DOI: 10.25636/PMP.1.2019.1.1
6. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part II. Periodontology, 2019; Vol. 24; 2–24(91): 108-119. DOI: 10.33925/1683-3759-2019-24-2-108-119
7. **Osipova Yu.L., Bulkina N.V., Tokmakova E.V.** The pathogenetic relationship of inflammatory periodontal diseases with gastroesophageal reflux disease // Basic Research – 2015. – No. 1–7. – P. 1397–1400. (In Russ.).
8. **Lepilin A.V., Bulkina N.V., Ostrovskaya L.Yu., Osipova Yu.L.** Inflammatory periodontal disease

with Helicobacter pylori, an associated gastroduodenal pathology. Clinical - morphological and immunohistochemical examination // Russian Dental Journal. – 2008. – No. 2. – P. 31–34. (In Russ.).

9. **Bulkina N.V., Osipova Yu.L.** Clinical and immunomorphological features of the course of chronic generalized periodontitis on the background of gastroesophageal reflux disease // Basic research – 2012. – No. 5–1. – P. 213–216. (In Russ.).
10. **Nikolaev E.N., Tsarev V.N. Ermolin D.V.** Apoptosis and inflammatory periodontal diseases // Institute of Dentistry. – 2003. – No. 4 (21). – P. 91–93. (In Russ.).
11. **Osipova Yu.L., Akimova S.A.** Cell renewal and gum apoptosis in patients with rapidly progressive periodontitis. // Morphology – 2018. – T. 153. – No. 3. – P. 209–210. (In Russ.).
12. **Osipova Yu.L., Bulkina N.V., Kropotina A.Yu.** Inflammatory periodontal diseases with a non-erosive form of gastroesophageal reflux disease: clinical and immunomorphological aspects // Basic research – 2012. – No. 2–2. – P. 325–327. (In Russ.).
13. Investigation of the molecular mechanisms of reparative-regenerative processes in the wound during stimulation with chitosan / A.P. Vedyaeva, N.V. Bulkina, P.V. Ivanov et al. // Periodontology. – 2017. – T. 22. – No. 4. (85). – P. 35–39. (In Russ.).
14. **Bulkina N.V., Vedyaeva A.P.** Rapidly progressive periodontitis: new aspects of pathogenesis and complex therapy // Periodontology. – 2012. – T. 17. No. 4 (65). – P. 13–18. (In Russ.).

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MORPHO-FUNCTIONAL CHANGES IN TEMPOROMANDIBULAR JOINT IN CASE OF DENTAL DEFECTS COMPLICATED BY LOWER JAW DISTAL SHIFT

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ABSTRACT — In order to identify morphological and functional changes in the temporomandibular joint, 40 patients with disturbed dentition complicated by a mandibular distal shift were examined. This pathology has been found to contribute to morphological and functional changes in the temporomandibular joint, whereas comprehensive treatment requires an individual approach.

KEYWORDS — temporomandibular joint, occlusion

INTRODUCTION

The prevalence of defects in the dentition among the adult population reaches 80.0 - 85.0%, and in the elderly aged beyond 60, the index reaches 100.0%. Loss of the chewing group of teeth is often accompanied by a distal displacement in the mandible, which leads to structural and functional changes in the temporomandibular joint [1–5].

Despite the wide variety of clinical and experimental studies involving the temporomandibular joint, the issue of its morphological and functional status for various pathologies has not been studied to the full yet [6–14].

Aim of study

to identify anatomical, topographic and functional changes in the temporomandibular joint through the treatment of patients with disturbed dentition complicated by the lower jaw distal shift.

MATERIALS AND METHODS

Functional status assessment and X-ray examination of the temporomandibular joint were performed in 40 patients featuring defects in the dentition complicated by a distal shift of the lower jaw. The comparison group included 10 patients with orthognathic bite.

To evaluate the anatomical and topographic status of the temporomandibular joint, we used lateral tomography performed on a universal radiological unit ORTHOPHOS 3 (SIEMENS).

To evaluate the functional status of the temporomandibular joint, a list of clinical dysfunction symptoms was used with the symptoms further assessed in points (Helkimo).

The results obtained through the study were processed by statistical analysis methods. For smaller sampling, nonparametric research methods were used.

RESULTS AND DISCUSSION

Analysis of lateral temporomandibular joint tomograms revealed an asymmetric arrangement of the articular heads in the articular fossa in 60% of cases. In 60% of the cases, at wider mouth opening, the articular head was located behind the articular tubercle apex; in 40% — under its apex. The width of the articular head on the left was 10.77 ± 0.74 mm; on the right — 10.66 ± 0.57 mm. The articular head immersion depth in the articular fossa was 5.00 ± 0.67 mm on the left and 4.77 ± 0.49 mm on the right. The depth of the articular fossa was 2.38 ± 0.36 times that of the previous indicator on the left, and 2.46 ± 0.41 times on the right side.

The articular tubercle height on the left was 9.90 ± 0.34 mm and 10.82 ± 0.84 mm on the right. The articular tubercle inclination angle to the line drawn from the lower edge of the ear canal to the top of the articular tubercle was 59.80 ± 2.97° on the left and 60.00 ± 2.65° on the right.

The anterior articular gap on the left was 3.74 ± 0.22 mm and on the right — 3.89 ± 0.29 mm; the posterior articular gap on the left was 4.71 ± 0.90 mm and on the right — 4.27 ± 0.53 mm. The distance from the articular fossa bottom to the top of the articular head was 5.25 + 0.85 mm on the left and 5.80 ± 0.52 mm — on the right.

The calculations aimed at identifying the dysfunction index in patients of this group revealed that the temporomandibular joint function was impaired in 88.2% of the cases. Mild dysfunction was observed

in 35.3% of the cases; 29.4% of the patients were found to suffer from a moderate degree of the dysfunction, with another 23.5% of the cases featuring a severe degree.

The patient treatment plan was designed individually and in all the cases included two stages. Stage 1 implied correcting the position of the lower jaw and recovery of the interalveolar distance, while Stage 2 involved rational prosthetics.

The treatment contributed to a change in the articular head topography. So, the front position of the articular head increased by 45%, which came along with a decrease in its central and rear positions frequency. The articular heads location symmetry increased by 40%. In 25% of the cases, the position of the articular head was observed at the top of the articular tubercle, which did not allow the treatment to be considered complete, which, in turn, required additional measures to eliminate this position of the articular heads.

The treatment contributed to a change in the anterior and posterior portions of the joint space. The anterior articular gap decreased on the left by 0.71 mm ($p < 0.05$). The posterior articular gap increased on the left by 2.74 mm and on the right — by 2.13 mm ($p < 0.05$).

Due to the treatment, the functional status of the temporomandibular joint changed, evidence to that being an increase of 17.6% in the number of observations revealing no signs of temporomandibular joint dysfunction. There was also a decrease observed in the incidence of moderate and severe dysfunction by 11.7% and 23.5%, respectively.

The study of the temporomandibular joint status in patients with disturbed dentition complicated by the lower jaw distal shift based on X-ray examination, revealed that its elements underwent morphological and anatomical, as well as topographic changes, which manifested themselves through a decrease in the articular tubercle height by 2 mm on the left with $p<0.005$ and 1.08 mm on the right at $p < 0.01$. A decrease in the articular tubercle height led to a reduced articular fossa depth by a similar value of the indicator pointing at these changes.

The joint space width in the anterior section was 1.44 mm wider on the left at $p < 0.005$ and 1.39 mm wide on the right at $p < 0.01$; in the upper section, the increase in the index was 2.15 mm on the left at $p < 0.05$ and 2.80 mm on the right at $p < 0.005$. A change in the articular head topography was also confirmed by a decrease in the articular fossa immersion depth by 2.70 mm on the left and 3.03 mm on the right at $p < 0.005$.

The treatment of the patients went along with a decrease in the incidence of clinical signs of severe and moderate dysfunction by 23.5% and 11.7%, respectively, which resulted in an increase in mild dysfunction and the absence of any dysfunction signs by 17.6%, respectively.

CONCLUSION

The outcomes of our study allow concluding that impaired dentition, complicated by the lower jaw distal shift, contribute to morphological and functional changes in the temporomandibular joint. The developing pathology is rather rigid, which requires a comprehensive approach to treatment.

REFERENCES

1. **Korobkeev A.A., Domenyuk D.A., Shkarin V.V., Dmitrienko S.V., Weisheim L.D., Konnov V.V.** Anatomical features of the interdependence of the basic parameters of the dental arches of the upper and lower jaws of man. Medical news of North Caucasus. 2018. – Vol. 13. – № 1–1. – P. 66–69. (In Russ., English abstract). DOI – https://doi.org/10.14300/mnnc.2018.13019.
2. **Korobkeev, A.A.** Changes in the structural elements of the temporomandibular joint with distal occlusion / A.A. Korobkeev, D.A. Domenyuk, E.G. Vedeshina, V.V. Konnov, O.Yu. Lezhnina, Ya.A. Korobkeeva // Medical news of North Caucasus. 2017. – Vol. 12. – № 1. – P. 72–76. (In Russ., English abstract). DOI – https://doi.org/10.14300/mnnc.2017.12020.
3. Morphofunctional changes in temporomandibular joint correlating with its morphological variations in patients with dentition defects complicated by distal occlusion / V.V. Konnov, A.P. Vedyaeva, D.Kh. Razakov, E.N. Pichugina, T.V. Matytsina, S.N. Salnikova, M.V. Vorobeva, R.N. Mukhamedov, I.V. Matysina // Archiv EuroMedica. – 2019. – Vol. 9, № 1. – P. 52–58. https://doi.org/10.35630/2199-885X/2019/9/1/52
4. Functional status of masticatory muscles at occlusion disturbances accompanied with displaced mandible / S.V. Konnov, D.Kh. Razakov, V.V. Konnov, A.R. Arushanyan, R.N. Mukhamedov, A.S. Khodorich, V.A. Mikailova // Archiv EuroMedica. – 2018. – T. 8, № 1. – P. 41–42.
5. Clinical image of temporomandibular joint dysfunction in patients with dentition defects complicated with displaced mandible / S.V. Konnov, E.N. Pichugina, V.V. Konnov, A.A. Bizyaev, S.N. Salnikova, A.R. Arushanyan, V.A. Mikailova // Archiv EuroMedica. – 2018. – T. 8, № 1. – P. 42–43.
6. Temporomandibular joint morphology at orthognatic bite / A.R. Arushanyan, V.V. Konnov, A.P. Vedyaeva, D.Kh. Razakov, T.V. Matytsina, D.N. Maslennikov, R.N. Mukhamedov, A.S. Khodorich, I.V. Matysina // Archiv EuroMedica. – 2019. – Vol. 9, № 1. – P. 18–19. https://doi.org/10.35630/2199-885X/2019/9/1/18
7. Radiological specifics of temporomandibular joint structure in case of dentition issues complicated with

distal occlusion / S.V. Konnov, A.A. Bizyaev, V.V. Konnov, E.V. Pichugina, S.N. Salnikova, A.S. Khodorich, V.A. Mikailova // Archiv EuroMedica. – 2018. – T. 8, № 1. – P. 39–40.

8. Specifics of occlusion disturbances in adults with distal occlusion due to dentition defects / S.V. Konnov, A.R. Arushanyan, V.V. Konnov, D.Kh. Razakov, R.N. Mukhamedov, E.N. Pichugina, V.A. Mikailova // Archiv EuroMedica. – 2018. T. 8, № 1. – P. 40–41

9. Causes behind distal occlusion / M.V. Vorobieva, V.V. Konnov, N.V. Bulkina, A.A. Bizyaev, D.N. Maslennikov, A.S. Khodorich, E.S. Popko, S.V. Konnov, I.V. Matytsina // Archiv EuroMedica. – 2019. – Vol. 9, № 1. – P. 191–193. https://doi.org/10.35630/2199-885X/2019/9/1/191

10. Clinical manifestations of temporomandibular joint dysfunction in patients with free-end edentulous space / E.N. Pichugina, V.V. Konnov, N.V. Bulkina, T.V. Matytsina, M.V. Vorobeva, S.N. Salnikov, R.N. Mukhamedov, V.A. Mikailova, I.V. Matysina // Archiv EuroMedica. – 2019. – Vol. 9, № 1. – P. 175–176. https://doi.org/10.35630/2199-885X/2019/9/1/175

11. **Dmitrienko T.D., Domenyuk D.A., Porfyriadis M.P., Arutyunova A.G., Kondratyuk A.A., Subbotin R.S.** Connection between clinical and radiological torque of medial incisors at physiological occlusion. Archiv Euro Medica, 2019; Vol. 9; 1: 29–37. https://doi.org/10.35630/2199-885X/2019/9/1/29

12. **Dmitrienko S.V., Fomin I.V., Domenyuk D.A., Kondratyuk A.A., Subbotin R.S.** Enhancement of research method for spatial location of temporomandibular elements and maxillary and mandibular medial incisors. Archiv Euro Medica, 2019; Vol. 9; 1: 38–44. https://doi.org/10.35630/2199-885X/2019/9/1/38

13. **Davydov B.N., Konnov V.V., Domenyuk D.A., Ivanyuta S.O., Samedov F.V., Arutyunova A.G.** Morphometric characteristics and correlation relationships of bone structures of TMJ-jaw joint in extending concepts of individually typological variability // Medical alphabet. Series "Dentistry". - 2019 . – Vol. 3. – 23 (398). – P. 44–50. DOI: 10.33667/2078-5631-2019-3-23(398)-44-50

14. **Konnov V.V., Domenyuk D.A., Ivanyuta I. V., Ivanyuta S. O.** Optimization of treatment tactics of patients with distal occlusion of dentition according to results of functional, clinical and X-ray studies of temporomandibular joint // Medical alphabet. Series "Dentistry". - 2019 . – Vol. 3 . – 23 (398). – P. 58–63. DOI: 10.33667/2078-5631-2019-3-23(398)-58-63

https://doi.org/10.35630/2199-885X/2019/9/3.29

ANALYTICAL APPROACH WITHIN CEPHALOMETRIC STUDIES ASSESSMENT IN PEOPLE WITH VARIOUS SOMATOTYPES

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ABSTRACT — Morphological studies require not only a qualitative description of the object studied, yet also a detailed account of its quantitative features. The outcome of studying lateral head teleradiographies in 127 persons with a complete set of permanent teeth and physiological occlusion was used to develop a method for measuring the jaws in the sagittal plane, as well as a method for identifying the proportion between the alveolar process anteroposterior dimensions of the upper jaw and the alveolar part of the lower jaw. Only 75.59±4.37% of the patients with physiological occlusion were found to have a proportional relationship between the sagittal dimensions of the maxillary alveolar process and the mandibular alveolar part; 14.71±4.29% of the patients had the maxillary sagittal dimensions prevailing, while 8.82±3.44% had the mandibular alveolar part prevailing over the sagittal dimensions of the maxillary alveolar process. People with the neutral type of the facial area, have a mandibular angle of 120.73±1.18°, while the maxillofacial angle shaped by the intersection of the craniofacial and mandibular planes is 43.51±2.87°. People with the horizontal facial growth type feature a significant decrease in the maxillofacial angle to 36.61±2.17°, and in case of the vertical — an increase to 51.24±1.22°. Advanced methods of dentoalveolar anomalies X-ray diagnostics would allow not only minimizing errors associated with instrumental methods employed for measuring the maxillofacial area structure, but also achieving optimal functional and aesthetic outcomes due to the orthodontic treatment predictability.

KEYWORDS — physiological occlusion; type of facial section growth; lateral teleradiography; jaw size; dental jaw segment

INTRODUCTION

The data concerning the laws of human physique development at each stage of the human body constitution knowledge is updated and refined constantly. The constitutional morphological and functional features variability limits arising from the effect of exogenous factors are determined genetically, so the content of the term constitution in modern Anthropology is interpreted as a "fairly stable comprehensive biological specifics of a person, a variant of an adaptive norm that reflects the responsive capacity and the resistance of the body to environmental factors" [13, 16, 38, 45, 49].

The key structural component of the constitution is the somatotype (morphophenotype). The somatotype acts as the most ontogenetically stable macromorphological subsystem of the general constitution, for which anthropometric measurements are available. A quantitative evaluation of a person's constitutional features performed through diagnostic features allows offering a comprehensive description of both the entire population and each individual separately. The somatotype is not only the basis for constitutional diagnosis, a morphological feature and the evaluation of health, yet is also an image of metabolic processes underway in the body. Studying homeostatic mechanisms has different levels of biosystems – from the cell to the entire body, under normal conditions and by way of adjusting to changes in the environment [18, 37, 46].

Traditional instrumental and high-tech anthropometric methods, if employed, allow identifying the qualitative and quantitative morphological features of the somatotype, their age- or gender-related, physiological or pathological variability, which, in turn, would offer a chance for an objective and reliable evaluation of the basic anatomical features [2, 5, 9, 10, 36].

When talking of identifying the somatotype, of equal clinical diagnostic value is the evaluation of the body developmental harmony, which implies proportionate ratios of its dimensional features (head, body, limbs) that make up the individual's specific features [17, 47].

Dentofacial system is one of the top human body systems in terms of the arrangement complexity, anatomical structure and the variety of functions performed. At the same time, dentofacial system, taken as the main craniofacial element, is the initial segment of the digestive and respiratory systems, also being responsible for the interconnection of the speech-related, facial and aesthetic functions [3, 7, 39, 48, 50, 56].

Understanding the growth and development patterns of the jaw bones is an important point in

clinical orthodontics, which often determines the treatment tactics for occlusal anomalies, be that with or without tooth extraction [6, 20, 32, 52]. Research in this direction is relevant in applied dentistry for studying variant anatomy of teeth, jaw bones, dentofacial segments and craniofacial complex as a whole [4, 8, 11, 25, 31, 43, 51, 55].

Improved orthodontic treatment in case of dental arches shape and size anomalies, based on more efficient advanced diagnosing and treatment planning methods, which imply taking into account individual maxillofacial features, will contribute to the long-term stable outcome of complex treatment [12, 24, 30, 42].

In treating occlusion anomalies, the major issue is to identify the forecasted shape of the dental arch, which corresponds to the morphometric maxillofacial parameters, whereas the optimal balance between the morphology, function and aesthetics will facilitate significantly the process of gaining stable treatment outcomes [1, 19, 23, 26, 29, 33, 40, 53].

There have been many methods for morphometric, biometric, x-ray analysis proposed currently to carry out such studies, while each of them feature both advantages and disadvantages that have been discussed widely in respective literature [14, 22, 28, 34, 44, 54].

Most of the available generally accepted and mandatory methods are textbook entries and are inevitable in the treatment protocols for patients with occlusion anomalies, thus complementing the diagnosis and determining the treatment tactics with the orthodontist. Yet, most of the anthropometric diagnostics methods require clarification, expansion and compliance with relevant individual orthodontic requirements, taking into account the patient's individual facial orthodontic features [15, 21, 27, 35, 41].

Further elaboration of the available methods for X-ray diagnostics and treatment planning, in view of the individual maxillofacial features, will improve the effectiveness of orthodontic treatment of patients with abnormal dental arches due to the maxillary vs. mandibular size mismatch.

Aim of study

to develop a new quantitative method for identifying the maxillofacial angle and measuring the jaws in the sagittal direction subject to cephalometric data, along with the selection of the most informative indicators reflecting the structural maxillofacial features pertaining to the individual's somatotype.

MATERIALS AND METHODS

The survey involved 127 patients in their first adulthood stage (men, 22–35 years old; women, 21–35 years old) with a full set of permanent teeth and physiological occlusion. Clinical, X-ray studies were conducted in strict compliance with the ethical principles of biomedical research and obtaining voluntary informed consent of all patients. The developed and approved provisions were fully consistent with the basic ethical legal and regulatory documents required for conducting research with human participation (Nürnberg Code, 1947; World Medical Association Declaration of Helsinki, 1964).

Teleroradiograpy in the lateral projection was performed on an X-ray machine Rayscan Symphony Alpha 3D (South Korea). The results were processed using the RayScanver. 2.0.0.0 software offering the options of receiving, processing and storing data in a DICOM 3.0 compatible format. Shooting features: sensor type — CMOS; resolution detector — 630 × 1024 pixels; focal spot — 0.5 mm; voxel size – 140–230 microns; magnification — 1.3; time — 2–14 seconds; panoramic image size — 148 mm.

To analyze teleradiographies, conventional points were marked — ***N*** (*Nasion*), ***C*** (*Condylion*), ***Ar*** (*Articulare*), ***T1***, ***T2***, ***Pg*** (*Pogonion*). At the same time, the ***N*** point corresponded to the intersection of the nasolabial suture with the anterior median line (or as the frontal and nasal bones junction). The ***C*** point (or *Cond*) was located on articular head top. The ***Ar*** point was the distal articular head contour; the ***T1*** point was located on the posterior superior convexity of the lower jaw angle, whereas the ***T2*** point was located on the posterior lower convexity of the lower jaw angle. The point ***Me*** corresponded to the location of the symphysis contour lower point, and the point ***Pg*** corresponded to the anterior prominent point of the chin protrusion (Fig. 1).

In the horizontal direction, there were two lines drawn. The upper line ran through the (***N***) and (***C***) points, separating the head facial section from the cranial one, and we marked it as the head facial section plane, or the craniofacial line (***KFL***). The mandibular plane (***ML***) passed through the most convex points of the lower edge of the lower jaw body, (***Me***) and (***T2***). The intersection of these lines made up the maxillofacial angle, which could be used as an indicator for the facial growth type (horizontal, vertical and neutral). In the vertical direction, the (***N***) and (***Pg***) points were connected, which we marked as the face vertical line. The tangent line to the lower jaw branch (***Ar–T1***), together with the mandibular plane, formed the lower jaw angle. An angle measuring within 119–123° corresponded to the neutral jaw growth type. A decrease or an increase in the angle pointed at the horizontal or the vertical type of growth, respectively.

Of the variety of research methods, points and reference lines, the major references were selected for

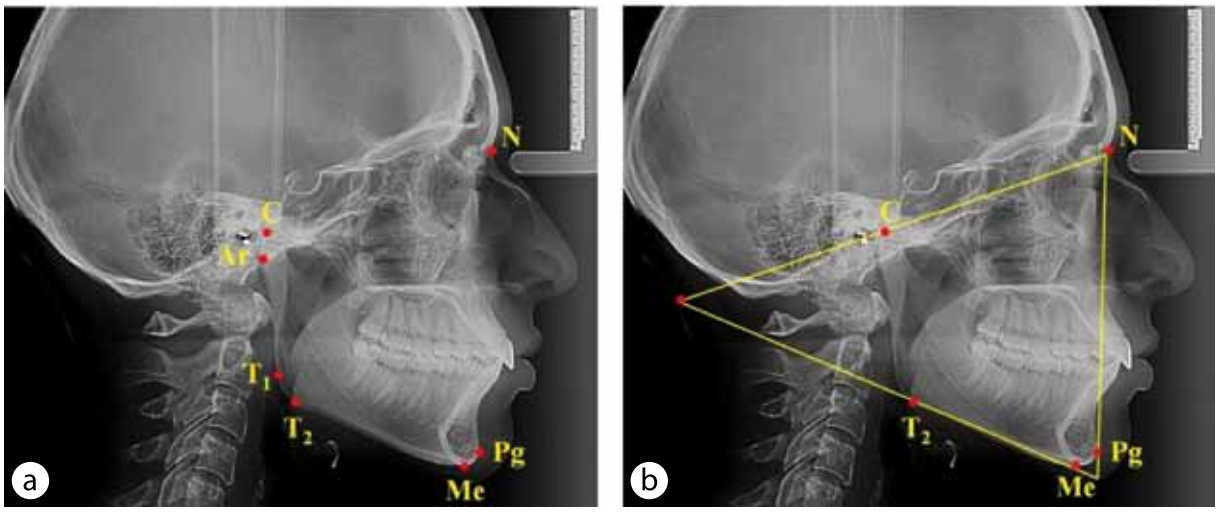

Fig. 1. Major main points (a) and lines (b) of the head lateral teleradiography.

identifying the size of the jaw apical basis: ***A*** point — the apical basis of the upper jaw or the projection of the medial superior incisor root apex on the alveolar process vestibular surface; ***B*** point — the apical basis of the lower jaw or the projection of the medial lower incisor root apex on the vestibular surface of the mandibular alveolar part. The occlusal plane was identified through conventional methods. The distal point was the vestibular distal tubercle apex of the mandibular second molar chewing surface. The anterior (interincisal) point was located in the middle between the cutting edges of the medial incisors of both jaws (Fig. 2).

For statistical analysis of the results, the software products STATISTICA 8.0 and SPSS 22.0 (StatSoft, USA) were used. For each feature, the following were determined: the arithmetic mean value and the arithmetic mean error. To identify the significance of the difference between the averages from the counterlateral sides, Student's t-criterion was identified. To examine the significance of the differences between the mean values, the dispersions analysis (ANOVA) was used.

RESULTS AND DISCUSSION

Based on the study, we proposed a method for identifying the jaw size through lateral teleradiographies.

Technique description. The occlusal plane served as the main reference point employed to identify the jaws size in the sagittal direction. The anterior reference point for the maxillary sagittal size was the structural point shaped through the intersection of the perpendicular against the occlusal plane, running from the subspinal ***A*** point. Similar design from the supramental B point was used for the lower jaw.

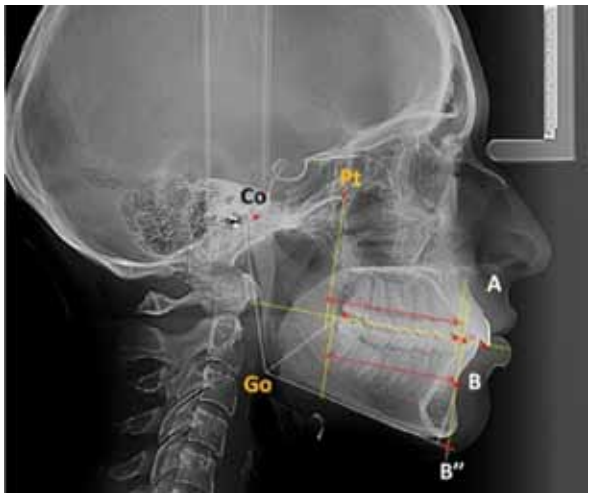

Fig. 2. Localization of points and reference lines on the lateral telegraphy for identifying the jaws size.

From the distal side, for the upper jaw, a perpendicular was drawn to the occlusal plane from the ***TM*** point located on the distal surface bulge of the tuber maxillae on the facies infratemporalis. The distance from the anterior point (***A′***) to the posterior point (***TM′***) determined the sagittal size of the maxillary alveolar process. In the lower jaw, the distal point of the alveolar part was identified at the intersection of the mandibular angle bisector with the occlusal plane. The distance from the anterior point (***B′***) to the distal point (***Go′***) was viewed as the sagittal size of the mandibular alveolar part.

The second part of the study implied identifying the proportion of the anteroposterior sizes of the max-

illary alveolar process and the mandibular alveolar part on the lateral teleradiographies. The ***A′–TM′*** distance was found to correspond to the ***B′–Go′*** length in 96 people within the study group, i.e. 75.59 ± 4.37% of the total number of the patients (Fig. 3).

In 19 people (14.96 ± 3.81%), the sagittal size of the maxillary alveolar process exceeded the size of the mandibular alveolar part, an average by 2.87 ± 1.02 mm. In this case, the occlusal ratio of the antagonists corresponded to the age and physiological norm and, as a rule, was to be found in people with physiological retrusion of the upper medial incisors, which also featured an anterior displacement of the subspinal ***A*** point. In 12 patients (9.45 ± 2.76%) the mandibular alveolar part size was by 1.95 ± 1.08 mm larger than the sagittal size of the maxillary alveolar process, which in our opinion is associated with the physiological protrusion of the upper medial incisors and the upper apical basis posterior displacement (***A*** point).

The cephalometric analysis revealed that people with the neutral type of the facial area, have a mandibular angle of 120.73 ± 1.18°. At the same time, the maxillofacial angle shaped by the intersection of the craniofacial and mandibular planes was 43.51 ± 2.87°. In people with the horizontal type of facial growth, the mandibular angle was significantly smaller, 108.93 ± 3.62° ($p \leq 0.05$), in the group as a whole. A significant decrease in the maxillofacial angle to 36.61 ± 2.17° was observed, too. The vertical type of facial growth contributed to an increase in the studied angles up to 126.11 ± 2.19° and 51.24 ± 1.22°, respectively (Fig. 4).

Attention should be paid to the maxillofacial triangle features in people with various types of the head facial area growth.

People with the neutral type of growth, the height of the triangle (whose base was at the front face vertical (***N-Pg***)), divided it into approximately equal parts. The upper facial part of the maxillofacial triangle, as a rule, matched its lower facial part.

For people with the vertical type of gnathic growth, the upper facial part of the maxillofacial triangle was smaller than its lower facial part. The horizontal type of growth was accompanied by a decrease in the lower facial part of the triangle, if compared with the upper facial part.

CONCLUSIONS

1. A method has been proposed for identifying the size of the jaws in the sagittal plane, whereas the method is based on the proportion of the anteroposterior sizes of the maxillary alveolar process and the mandibular alveolar part, subject to head teleradiographies in lateral projection.

2. 75.59 ± 4.37% of the total number of the examined patients with physiological occlusion were found to have a match between the sagittal dimensions of the maxillary alveolar process and the mandibular alveolar part; 14.96 ± 3.81% of the patients had their maxillary sagittal sizes prevailing, while another 9.45 ± 2.76% of the patients had the mandibular alveolar sizes prevailing over the sagittal sizes of the maxillary alveolar process.

3. An extra criterion has been proposed to identify methods for treating malocclusion. The use of anteroposterior size ratios of the maxillary alveolar process and the mandibular alveolar part appears feasible in terms of identifying methods for treating malocclusion with or without removal of individual teeth following orthodontic indications.

4. The dimensions of the maxillofacial triangle and its components can be used as additional criteria for identifying the head facial area growth type.

5. People with the neutral type of the facial part were proven to have the size of the mandibular angle within the range of 120.73 ± 1.18°, while the maxillofacial angle was 43.51 ± 2.87°. In people with the horizontal type of facial growth, the mandibular angle parameters (108.93 ± 3.62°) and maxillofacial angle (36.61 ± 2.17°) were statistically smaller, whereas the vertical facial growth type implied an increase in the studied angles up to 126.11 ± 2.19° and 51.24 ± 1.22°, respectively.

6. Subject to the results of cephalometric, radiological studies, the localization of the standard (classical) and additional anthropometric points in the sagittal projection has been clarified. Specifying topographic data of the anatomical landmarks on the head X-ray lateral projection patterns allows increasing reliability and accessibility of the measurements; standardize anthropometric studies of the craniofacial structures in people with various somatotypes, as well as obtain a significant amount of reliable data with precise dimension features.

7. Employing X-ray diagnostics for cephalometric analysis expands significantly the current understanding of the anatomical norm variability, as determined by individual variability, gender differences, and age-related alterations, which shall serve the basis for all scientific areas of study dealing with personalized medicine.

REFERENCES

1. **Borodina V.V., Domenyuk D.A., Weisheim L.D., Dmitrienko S.V.** Biometry of permanent occlusion dental arches – comparison algorithm for real and design indicators // Archiv EuroMedica. 2018. Vol. 8. № 1. P. 25–26.

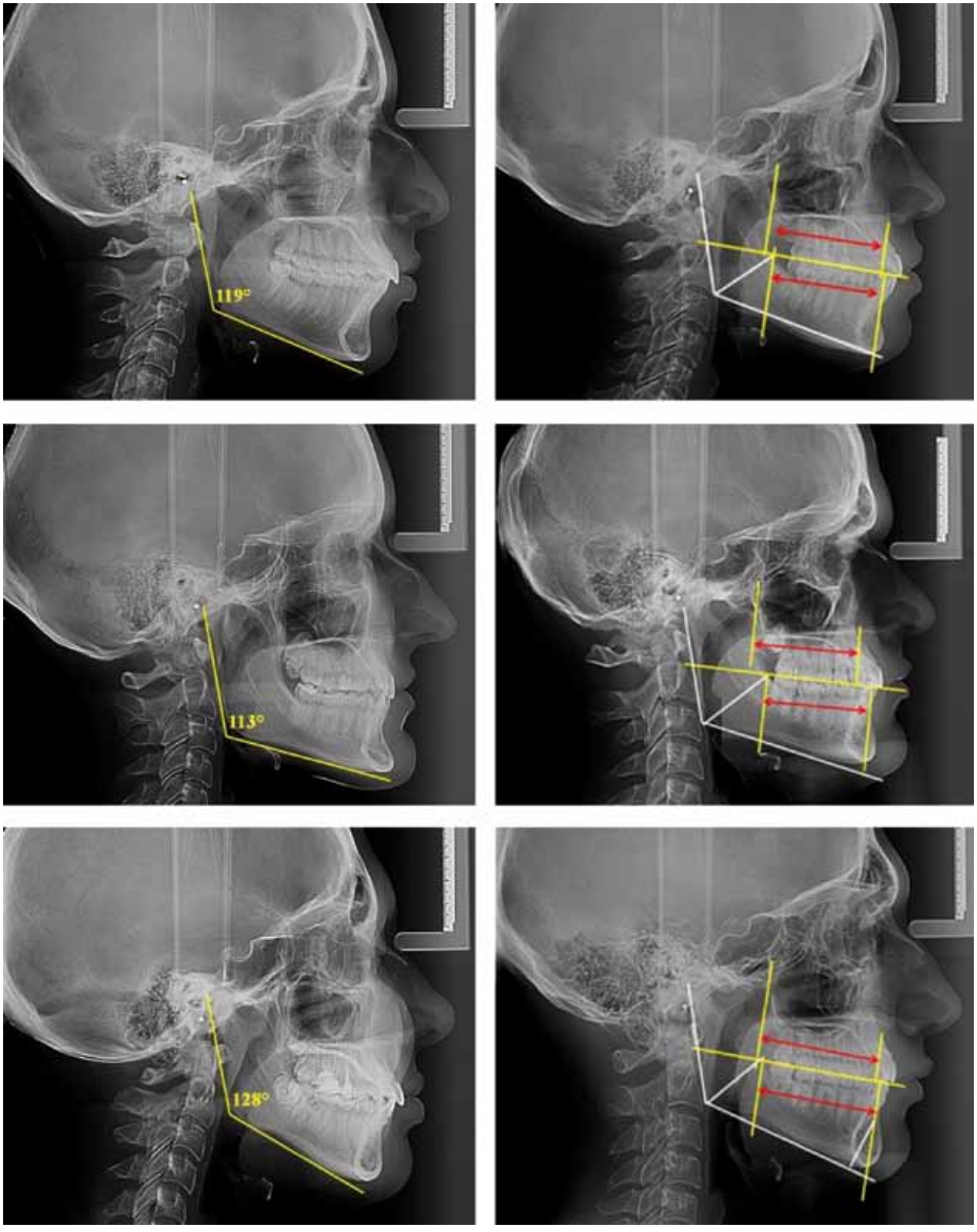

Fig. 3. *Specific features of the jaws size in people with a neutral (a), horizontal (b) and vertical (c) type of growth*

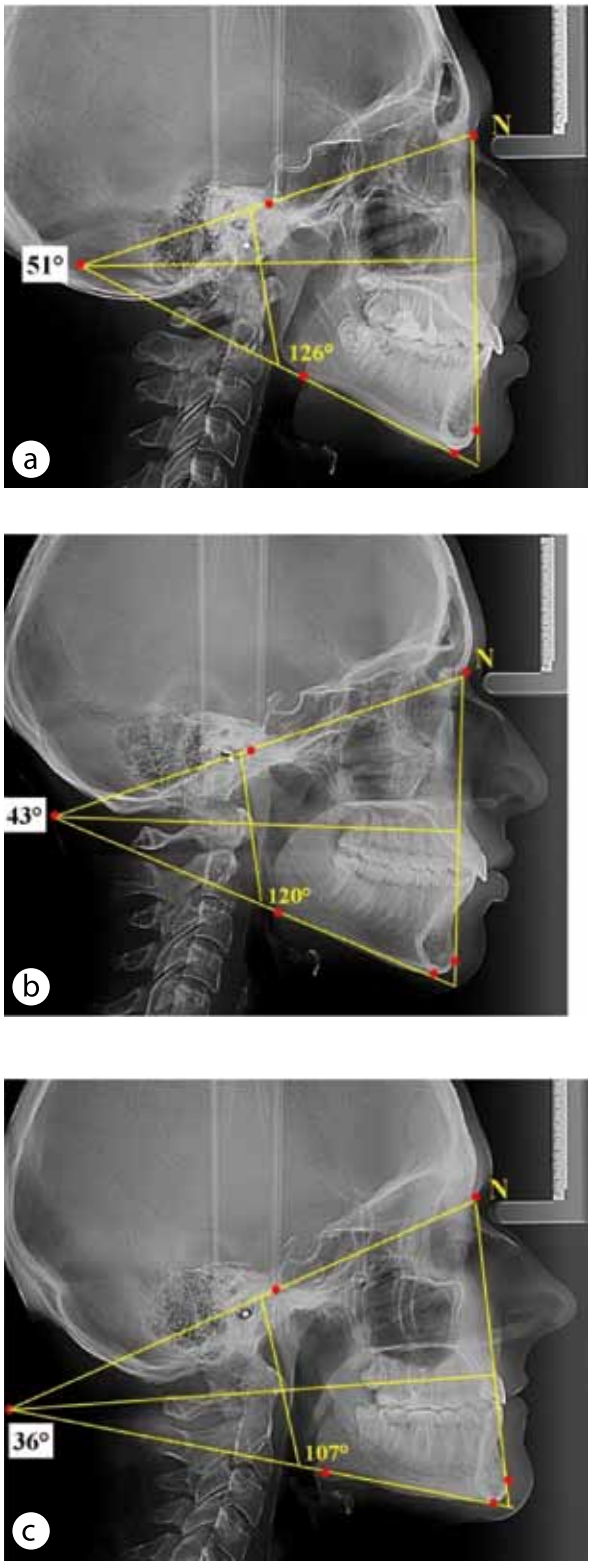

Fig. 4. *Mandibular and maxillofacial angles for vertical (a), neutral (b) and horizontal (c) types of facial growth*

2. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V., Korobkeev A.A., Arutyunova A.G.** Morphological peculiarities of facial skelet structure and clinical and diagnostic approaches to the treatment of dental anomalies in children in the period of early change. Pediatric dentistry and prophylaxis. 2019; Vol. 19; 1 (69): 26–38. (In Russ.) DOI: 10.33925/1683-3031-2019-19-69-26-38

3. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part I. Periodontology, 2019; Vol. 24; 1–24(90): 4-10. DOI: 10.25636/PMP.1.2019.1.1

4. **Davydov B.N., Domenyuk D.A., Dmitrienko S.V.** Peculiarities of microcirculation in periodont tissues in children of key age groups sufficient type 1 diabetes. Part II. Periodontology. 2019;24(2):108–119. (In Russ.) DOI:10.33925/1683-3759-2019-24-2-108-119

5. **Davydov B.N., Domenyuk D.A., Bykov I.M., Ivchenko L.G., Dmitrienko S.V.** Modern possibilities of clinical-laboratory and x-ray research in preclinical diagnostics and prediction of the risk of development of periodontal in children with sugar diabetes of the first type. Part I. Periodontology, 2018; Vol. 23; 3–23(88): 4–11. DOI:10.25636/PMP.1.2018.3.1

6. **Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Sumkina O.B., Budaychiev G. M-A.** Changes of the morphological state of tissue of the paradontal complex in the dynamics of orthodontic transfer of teeth (experimental study). Periodontology, 2018; Vol. 23; 1–23(86): 69–78. DOI:10.25636/PMP.1.2018.1.15

7. **Domenyuk D.A., Zelensky V.A., Rzhepakovsky I.V., Anfinogenova O.I., Pushkin S.V.** Application of laboratory and x-ray gentral studies un early diagnostics of metabolic disturbances of bone tissue in children with autoimmune diabetes mellitus. Entomology and Applied Science Letters. 2018; 5(4): 1–12.

8. **Domenyuk D.A., Zelensky V.A., Dmitrienko S.V., Anfinogenova O.I., Pushkin S.V.** Peculiarities of phosphorine calcium exchange in the pathogenesis of dental caries in children with diabetes of the first type. Entomology and Applied Science Letters. 2018; 5(4): 49–64.

9. **Domenyuk D.A., Konnov V.V., Pichugina E.N., Anfinogenova O.I., Goncharenko A.N., Pushkin S.V.** Microcomputed tomography in qualitative and quantitative evaluation of dental enamel demineralization. Entomology and Applied Science Letters. 2018; 5(4): 72–83.

10. **Domenyuk D.A., Dmitrienko S.V. Porfyriadis M.P.** Major telerenthengogram indicators in people with various growth types of facial area // Archiv EuroMedica. 2018. Vol. 8. № 1. P. 19–24.

11. **Domenyuk D.A., Davydov B.N.** Possibilities of microcomputer tomography in the diagnostics of early forms of caries of a chewing surface of perma-

nent molars in children. Part I. Pediatric dentistry and prophylaxis. 2018; Vol. 18; 4 (67): 61–64. (In Russ.) DOI: 10.25636/PMP.3.2018.4.12

12. **Domenyuk D.A., Davydov B.N.** Possibilities of microcomputer tomography in the diagnostics of early forms of caries of a chewing surface of permanent molars in children. Part II. Pediatric dentistry and prophylaxis. 2019; Vol. 19; 2 (70): 4–12. (In Russ.) DOI: 10.33925/1683-3031-2019-19-2-04-12
13. **Domenyuk D. A., Korobkeev A. A., Dmitrienko S. V., Korobkeeva Ya. A., Grinin V. M., Shkarin V. V.** Anatomical and topographical features of temporomandibular joints in various types of mandibular arches. Medical News of North Caucasus. 2019;14(2):363–367. DOI – http://dx.doi.org/10.14300/mnnc.2019.14089 (In Russ.)
14. **Domenyuk D.A., Lepilin A.V., Fomin I.V., Dmitrienko S.V., Budaychiev G.M-A.** Improving odontometric diagnostics at jaw stone model examination // Archiv EuroMedica. 2018. Vol. 8. № 1. P. 34–35.
15. **Domenyuk D.A., Porfyriadis M.P., Budaychiev G. M-A.** Contemporary methodological approaches to diagnosing bone tissue disturbances in children with type 1 diabetes. Archiv EuroMedica, 2018; 8(2): 71–81.
16. **Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Lepilin A.V., Fomin I.V.** Diagnostic opportunities of cone-box computer tomography in conducting craniomorphological and craniometric research in assessment of individual anatomical variability (Part I). The Dental Institute. 2018; 81(4): 52–55. (In Russ.).
17. **Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Lepilin A.V., Fomin I.V.** Diagnostic opportunities of cone-box computer tomography in conducting craniomorphological and craniometric research in assessment of individual anatomical variability (Part II). The Dental Institute. 2019; 82(1): 72–76. (In Russ.).
18. **Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Lepilin A.V., Fomin I.V.** Diagnostic opportunities of cone-box computer tomography in conducting craniomorphological and craniometric research in assessment of individual anatomical variability (Part III). The Dental Institute. 2019; 83(2): 48–52. (In Russ.).
19. **Dmitrienko S.V., Lepilin A.V., Fomin I.V., Domenyuk D.A., Davydov B.N.** Study of morphology, methods of comparison of tooth and alveolar arcs by results of anthropometry and cellular-beam computer tomography (Part I). The Dental Institute. 2018; 79(2): 68–72. (In Russ.).
20. **Dmitrienko S.V., Lepilin A.V., Fomin I.V., Domenyuk D.A., Davydov B.N.** Study of morphology, methods of comparison of tooth and alveolar arcs by results of anthropometry and cellular-beam computer tomography (Part II). The Dental Institute. 2018; 80(3): 70–74. (In Russ.).
21. **Dmitrienko S.V., Davydov B.N., Domenyuk D.A., Avanisyan V.M., Arutyunova A.G.** Diagnostic value of odontometric data in studying the typological features of dental arts (Part I). The Dental Institute. 2019; 84(3): 46–49. (In Russ.).
22. **Dmitrienko S.V., Davydov B.N., Domenyuk D.A., Ivanyuta I.V., Ivanyuta O.O.** Perfection of algorithms for visualization of the structures of the maxial-facial region when using modern radio diagnostics methods (Part I). The Dental Institute. 2019; 84(3): 56–59. (In Russ.).
23. **Dmitrienko S.V., Domenyuk D.A.** Dentoalveolar specifics in children with cleft palate during primary occlusion period. Archiv EuroMedica, 2018; Vol. 8; 1: 33–34.
24. **Dmitrienko S.V., Domenyuk D.A., Fischev S.B., Subbotin R.S.** Dynamics of periodontal fixing capacity through orthodontic treatment employing edgewise technique // Archiv EuroMedica. 2019. Vol. 9; 1: 151–152. https://doi.org/10.35630/2199-885X/2019/9/1/151
25. **Dmitrienko S.V., Fomin I.V., Domenyuk D.A., Kondratyuk A.A., Subbotin R.S.** Enhancement of research method for spatial location of temporomandibular elements and maxillary and mandibular medial incisors // Archiv EuroMedica. 2019. T. 9. № 1. P. 38–44. https://doi.org/10.35630/2199-885X/2019/9/1/38
26. **Dmitrienko T.D., Domenyuk D.A., Porfyriadis M.P., Arutyunova A.G., Kondratyuk A.A., Subbotin R.S.** Connection between clinical and radiological torque of medial incisor at physiological occlusion // Archiv EuroMedica. 2019. Vol. 9. № 1. P. 29–37. https://doi.org/10.35630/2199-885X/2019/9/1/29
27. **Dmitrienko S.V., Domenyuk D.A., Puzdryova M.N.** Manufacturing methods for individual aligners and trainers from thermoplasts and clinical indications for their application // Archiv EuroMedica. 2019. Vol. 9; 1: 153–154. https://doi.org/10.35630/2199-885X/2019/9/1/153
28. **Dmitrienko S.V., Lepilin A.V., Domenyuk D.A., Kondratyuk A.A.** Clinical meaning of methods for identifying variability of mental prominence location // Archiv EuroMedica. 2019. Vol. 9; 1: 45–46. https://doi.org/10.35630/2199-885X/2019/9/1/45
29. **Dmitrienko S.V., Davydov B.N., V.V. Shkarin, Domenyuk D.A.** Algorithm for determining the size of artificial teeth by the morphometric parameters of the face in people with full adentia. Dentistry. 2018; 97(6): 57–60. DOI – 10.17116/stomat20189706157
30. **Dmitrienko S.V., Porfiriadis M.P., Domenyuk D.A., Budaychiev G.M-A.** Dentoalveolar specifics in children with cleft palate during primary occlusion period // Archiv EuroMedica, 2018. Vol. 8. № 1. P. 33–34.
31. **Fischev S.B., Puzdryova M.N., Dmitrienko S.V., Domenyuk D.A., Kondratyuk A.A.** Morphological features of dentofacial area in peoples with dental arch issues combined with occlusion anomalies // Archiv EuroMedica. 2019. Vol. 9; 1: 162–163. https://doi.org/10.35630/2199-885X/2019/9/1/162

32. Fomin I.V., Dmitrienko S.V., Domenyuk D.A., Kondratyuk A.A., Arutyunova A. Effect of jaw growth type on dentofacial angle in analyzing lateral teleradiographic images // Archiv EuroMedica. 2019. Vol. 9; 1: 136–137. https://doi.org/10.35630/2199-885X/2019/9/2/136

33. Fomin I.V., Ivanov S.Yu., Dmitrienko S.V., Domenyuk D.A., Lepilin A.V. Efficiency of osseointegration properties manifestation in dental implants with hydroxyapatite plasma coating // Archiv EuroMedica. 2019. Vol. 9; 1: 138–139. https://doi.org/10.35630/2199-885X/2019/9/2/138

34. Gavrilova O.A., Domenyuk D.A. Specific features of oral cavity microbiocenosis in children using non-removable orthodontic appliances. Archiv EuroMedica, 2018; 8(2): 91–92.

35. Gavrilova O.A., Domenyuk D.A. Microbiological verification for the use of thermoplastics in prosthetic treatment of dentition issues in children. Archiv EuroMedica, 2018; 8(2): 88–90.

36. Korobkeev A. A., Domenyuk D. A., Shkarin V. V., Dmitrienko S. V., Mazharov V. N. Variability of odontometric indices in the aspect of sexual dimorphism. Medical News of North Caucasus. 2019;14(1.1):103–107. DOI – https://doi.org/10.14300/mnnc.2019.14062 (In Russ.)

37. Korobkeev A.A., Domenyuk D.A., Shkarin V.V., Dmitrienko S.V. Types of facial heart depth in physiological occlusion. // Medical news of North Caucasus. 2018. – Vol. 13. – № 4. – P. 627–630. (In Russ., English abstract). DOI – https://doi.org/10.14300/mnnc.2018.13122.

38. Korobkeev A.A., Domenyuk D.A., Shkarin V.V., Dmitrienko S.V., Weisheim L.D., Konnov V.V. Anatomical features of the interdependence of the basic parameters of the dental arches of the upper and lower jaws of man. Medical news of North Caucasus. 2018. – Vol. 13. – № 1-1. – P. 66–69. (In Russ., English abstract). DOI – https://doi.org/10.14300/mnnc.2018.13019

39. Kulikova, N.G. Evaluation of the effectiveness of pharmaco-physiotherapeutic treatment of catarrhal gingivitis on the results of the condition of mucosal immunity of oral cavity in women in the postpartum period / N.G. Kulikova, D.A. Domenyuk, V.A. Zelensky, A.S. Tkachenko // Medical news of North Caucasus. 2017. – Vol. 12. – № 4. – P. 417–421. (In Russ., English abstract). DOI: 10.14300/mnnc.2017.12117.

40. Lepilin A.V., Fomin I.V., Domenyuk D.A., Dmitrienko S.V., Budaychiev G.M-A. Diagnostic value of cephalometric parameters at graphic reproduction of tooth dental arches in primary teeth occlusion // Archiv EuroMedica, 2018. Vol. 8. № 1. P. 37–38.

41. Lepilin A.V., Dmitrienko S.V., Domenyuk D.A., Puzdyryova M.N., Subbotin R.S. Dependence of stress strain of dental hard tissues and periodontal on horizontal deformation degree // Archiv EuroMedica. 2019. Vol. 9; 1: 173–174. https://doi.org/10.35630/2199-885X/2019/9/1/173

42. Lepilin A.V., Rajgorodskij Yu.M., Grigoryeva D.A., Erokina N.L., Bakhteeva G.R., Domenyuk D.A. Reasoning for the application of violet laser physiotherapy device following surgeries in the oral cavity. Archiv EuroMedica, 2018; 8(2): P. 111–114.

43. Porfyriadis M.P., Domenyuk D.A., Arutyunova A.G., Dmitrienko S.V. Scanning electron microscopy and X-ray spectral microanalysis in dental tissue resistance // Archiv EuroMedica. 2019. Vol. 9; 1: 177–185. https://doi.org/10.35630/2199-885X/2019/9/1/177

44. Porfiriadis M.P., Dmitrienko S.V., Domenyuk D.A., Budaychiev G.M-A. Mathematic simulation for upper dental arch in primary teeth occlusion // Archiv EuroMedica, 2018. Vol. 8. № 1. P. 36–37.

45. Porfyriadis M.P., Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Budaychiev G.M.-A. Variability of cephalometric indices in men and women with mesocefalic form of the head and various constitutional types of face (Part I). The Dental Institute. 2018; 78(1): 70–73. (In Russ.).

46. Porfyriadis M.P., Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Budaychiev G.M.-A. Variability of cephalometric indices in men and women with mesocefalic form of the head and various constitutional types of face (Part II). The Dental Institute. 2018; 79(2): 82–85. (In Russ.).

47. Porfyriadis M.P., Domenyuk D.A., Davydov B.N., Dmitrienko S.V., Budaychiev G.M.-A. Variability of cephalometric indices in men and women with mesocefalic form of the head and various constitutional types of face (Part III). The Dental Institute. 2018; 80(3): 84–87. (In Russ.).

48. Shkarin V., Domenyuk D., Lepilin A., Fomin I., Dmitrienko S. Odontometric indices fluctuation in people with physiological occlusion. Archiv EuroMedica, 2018; Vol. 8; 1: 12–18.

49. Shkarin V.V., Ivanov S.Yu., Dmitrienko S.V., Domenyuk D.A., Lepilin A.V., Domenyuk S.D. Morphological specifics of craniofacial complex in people with varioustypes of facial skeleton growth in case of transversal occlusion anomalie // Archiv EuroMedica. 2019. Vol. 9; 2: 5–16. https://doi.org/10.35630/2199-885X/2019/9/2/5

50. Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A. Specific features of transversal and vertical parameters in lower molars crowns at various dental types of arches // Archiv EuroMedica. 2019. Vol. 9; 2: 174–181. https://doi.org/10.35630/2199-885X/2019/9/2/174

51. Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A. Specific features of grinder teeth rotation at physiological occlusion of various gnathic dental arches // Archiv EuroMedica. 2019. Vol. 9; 2: 168–173. https://doi.org/10.35630/2199-885X/2019/9/2/168

52. Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A. Specific features of joint space in patients with physiological

occlusion on computed tomogram head image // Archiv EuroMedica. 2019. Vol. 9; 2: 182–183. https://doi.org/10.35630/2199-885X/2019/9/2/182

53. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko S.V., Domenyuk D.A.** Specific features of central point location between incisors in people with physiological occlusions // Archiv EuroMedica. 2019. Vol. 9; 2: 165–167. https://doi.org/10.35630/2199-885X/2019/9/2/165

54. **Shkarin V.V., Grinin V.M., Khalfin R.A., Dmitrienko T.D., Domenyuk D.A., Fomin I.V.** Craniofacial line of teleradiography and its meaning at cephalometry // Archiv EuroMedica. 2019. Vol. 9; 2: 84–85. https://doi.org/10.35630/2199-885X/2019/9/2/84

55. **Shkarin V.V, Davydov B.N., Domenyuk D.A, Dmitrienko S.V.** Non-removable arch orthodontic appliances for treating children with congenital maxillofacial pathologies – efficiency evolution // Archiv EuroMedica, 2018. Vol. 8. № 1. P. 97–98.

56. **Zelensky, V.A.** Integral indicator for orthodontic carequality control / V.A. Zelensky, D.A. Domenyuk, M.V. Baturin, I.V. Zelensky, A.V. Kokareva, A.V. Zenina // Medical news of North Caucasus. 2014. – Vol. 9. – № 1. – P. 80–83. (In Russ., English abstract). DOI: 10.14300/mnnc.2014.09022.