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EDITORIAL



Dear clinicians, research fellows, colleagues and friends!

Development and introduction of novel diagnostic techniques aimed at detecting heritable disorders in children are priority tasks of modern pediatrics. Identifying susceptibility to latent pathological conditions is crucial for prevention and interrupting their chronicity. In this connection the issues of studying heritable disorders such as connective tissue dysplasia (DCT) in children population are relevant and timely. DCT symptoms, which are frequently combined with a number of somatic diseases, dramatically affect their severity and course.

Differentiated hereditary diseases of connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, Stickler syndrome, osteogenesis imperfecta) are well-studied. They have clinical phenotypes formed due to heritable disruptions in biosynthesis and collagen degradation on structural and metabolic levels. On the contrary, many facets of undifferentiated dysplasia remain understudied. These subjects, however, have attracted great interest in different medical areas including pulmonologists, cardiologists, ophthalmologists, pediatricians, orthopedic trauma physicians, nephrologists, gastroenterologists, sonographers.

Patients with undifferentiated forms of DCT represent a large heterogenic group encompassing simple as well as complicated conditions. Whereas phenotypic and clinical manifestations confirm the defect of connective tissue, on the other side, they do not match any known syndrome among genetically induced syndromes of mesenchymal cell deficiency. DCT is not a nosological unit, it presents an ontogenetically systemic progredient process resulting in structural and functional changes of organs and tissues. The variety of clinical symptoms in patients with connective tissues diseases indicates on systemic damage, as the connective tissue accounts for 50–80% of the body mass. Its functions (biomechanical, trophic, barrier, plastic, morphogenetic) are the major ones for a human body. Clinical manifestations of undifferentiated connective tissue are extremely varied and have a polysystemic nature. DCT is not a separate disease; it is a set of symptoms determined by an inherited qualitative or/and qualitative defect in protein synthesis defects.

There is dependence between external phenotypic manifestation of DCT and detected pathology of internal organs. Clinical systems of DCT may be displayed during years, whereas functional decline is progressing with the age of the patient.

Specialists observe DCT dependence with cardio-respirative syndromes, urological and gastroenterological diseases, bronchial asthma, and vegetative disorders.

It is scientifically proved that most of the craniofacial tissues are composed of connective tissues. Their structural and functional components play an active part in inflammatory, destructive and protective processes which develop at acute and chronic pathological conditions. There is evidence that CDT facilitates incidence of teeth and jaw abnormalities, diseases of periodontium, occlusion and temporomandibular joint.

In the current issue of our journal you may read about new data on pathogenetic mechanisms causing the development of craniofacial malformations. The authors have systemized external phenotypes and morphological features in children with different severity of CTD. It will allow forming groups of patients with a high risk of development of polyorgan pathology. Therefore, *pre-clinical* diagnosis in children aimed at early detection of latent hereditary diseases can reduce risk and frequency of disability; improve quality of life and social adaptation in children with CTD, as well as save the costs of medical treatment.

Executive Editor

Prof. Dmitry Domenyuk

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ERYTHROCYTES AS A TARGET OF SARS COV-2 IN PATHOGENESIS OF COVID-19

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ABSTRACT — The paper considers the possible mechanism of the pathogenesis of COVID-19 caused by SARS-COV-2, associated with damage to red blood cells, which the authors attribute to the main key target that triggers a cascade of reactions leading to multiple organ failure. The paper presents morphological evidence for the presence of pathological forms of erythrocytes characteristic of various anemias in the blood vessels and parenchyma of damaged lungs of patients with COVID-19. The death of red blood cells leads to cell ischemia and anemia. The defeat of brain neurons, blood vessels and hematotissue barriers in organ systems is a consequence of ischemia due to the impossibility of transferring hemoglobin by damaged erythrocytes and ends at the terminal stages of the development of the disease with their dysfunction. Adaptive erythropoiesis with an increase in erythropoietin secretion is especially dangerous for patients suffering from hypertension, and then it is impossible, since all organs involved in the synthesis of erythropoietin are damaged. In this case, the synthesis of hemoglobin is also disrupted due to a deficiency of iron and cyancobolamin, whereas toxic iron and hemosiderin are deposited in the tissues.

KEYWORDS — COVID-19, SARS-COV-2, erythrocytes, hemoglobin, erythropoiesis, viruses, pathogenesis of COVID-19.

RELEVANCE

In the world, the number of cases of COVID-19 has reached 16.4 million. The number of coronavirus victims worldwide exceeds 600 thousand, including children [1, 5, 16]. Madabhavi I., Sarkar M., Kadakol N. (2020) identified the pandemic as a catastrophe

of global significance [6], which indicates the high urgency of the problem under study [9, 12, 21]. It is generally accepted that viruses multiply in the cell, specializing in certain cell types: HIV infects T-lymphocytes, the influenza virus infects the epithelium of the larynx and lungs, coronavirus destroys the epithelium of the upper respiratory tract, lungs and gastrointestinal tract, herpes affects the nerves and causes neuroinfections, hepatitis viruses infect liver cells, etc. [17, 20]. With COVID-19 caused by SARS-COV-2, multiple organ disorders occur in various structures, including nerve structures [3, 14]. Burness A. T. and Pardoe I. U. (1981) established the possibility of attachment of the influenza virus to human erythrocytes, followed by hemagglutination of the cells [4]. Allaway G.P., Burness A.T. (1986) showed that the main type of glycoporphins, glycoporphin A, is a receptor for the attachment of influenza and encephalomyocarditis (EMS) viruses to human erythrocytes [2, 4]. The attachment of the EMS virus to glycoporphin A includes a region containing amino acids 35 to about 70 (numbered from the end of NH₂), four of which (amino acids 37, 44, 47 and 50) are glycosylated. In addition, there is evidence that segments containing amino acids 35 to 39 with an oligosaccharide side chain on threonine-37 are particularly important for the attachment of EMS virus. However, in the available scientific literature against the background of the available pathomorphological data on the destruction of lung tissue, death of alveolocytocytes, fibrotic changes in the lungs, there is no assessment of erythrocytes located both in the lumen of blood vessels and released into the parenchyma of affected organs [5, 19, 24]. Given the multiple organ failure that develops in COVID-19 [7, 18], the absence of a key morphological target for SARS-COV-2 [8], as well as controversial data on the nature of the virus itself, we directed our research to study changes in the red blood cell pool against the background of COVID-19. According to Rodríguez-Nóvoa S., Morello J., González M., et al (2008), the use of antiviral drugs causes hemolysis and increases hyperbilirubinemia [13]. According to them, treatment of HIV/hepatitis-C infected patients led to an increase in hyperbilirubinemia from 9% to 45% after starting treatment for hepatitis C. Anemia has a multifactorial nature [10, 15], which explains the

cases of unsuccessful attempts to empirically use erythropoietin in the treatment of patients with hepatitis C and HIV-infected [11]. All this dictates an expansion of the range of measures aimed at studying the etiology and pathogenesis of COVID-19 for the development of pathogenetically justified prevention and treatment that is absent at the present stage [22, 23].

Purpose of the study:

To study the role of red blood cells in the pathogenesis of COVID-19.

MATERIAL AND METHODS

The paper analyzes and discusses the results of our own studies of lung biopsies of 11 patients who died from COVID-19 caused by SARS-CoV-2, with PCR confirmation, obtained in accordance with the order of the Ministry of Healthcare of the Russian Federation dated 04.29.94 N 82 *On the procedure for conducting pathological autopsies*, which regulates the procedure for autopsies in medical institutions. The control group consisted of 14 patients who died as a result of injuries incompatible with life, presumably without somatic pathology at the age of 24 to 76 years. The biopsy specimens were fixed immediately after collection in accordance with the preparation protocol for histological examination. The exclusion of possible artifacts is based on data obtained during a special study on dogs, indicating that when corpses are stored at a temperature of 4–7° C for 4–6 hours, microscopically visible changes in the morphology of various organ systems are not observed, except for a slight decrease in the intensity of specific reactions on enzymatic activity. We used classical histological research methods with hematoxylin-eosin staining to obtain a general morphological picture.

The material was analyzed using an Olympus-Bx82 microscope and a CDx82 digital camera with proprietary software. The morphological method of the study consisted in the preparation of sections from paraffin blocks of lung biopsies from SARS-CoV-2 victims, followed by staining with hematoxylin and eosin in accordance with the classical protocol. Analysis of preparations and production of illustrations were carried out using an Olympus Bx52 microscope and a DP25 digital camera.

RESULTS OF OUR OWN RESEARCH

We have found that erythrocytes are one of the targets damaged by SARS-COV-2. Anisocytosis and poikilocytosis of erythrocytes are noted, macrophages with hemosiderin, hypochromic and hyperchromic erythrocytes are identified. Erythrocytes in the form of a sickle are identified (in Fig. 1 it is indicated by an

arrow), as well as spherocytes, macro and microcytes. The appearance of sickle erythrocytes may be associated with disturbances in the B-chains of globin and the replacement of glutamine with valine. The solubility of such globin decreases 25 times, depending on the partial pressure of oxygen in the blood and the concentration of HbS in the erythrocyte. The distribution of hemoglobin in the cytoplasm of erythrocytes is uneven, bright oxyphilia is observed both in the center of erythrocytes and in the periphery. Thickening of the erythrocyte membrane, chromophobic courtyard around the red blood cells. Kebot's rings are identified, staining red. Kebot's rings are characteristic and are found mainly in megaloblastic anemia and metal intoxication (Pb). Under COVID-19 conditions, this toxic effect is exerted by the hemoglobin of dying erythrocytes, transferrin and iron, as well as hemosiderin. We have established that Howell-Jolly bodies are identified on lung preparations, which are small round violet-red inclusions 1–2 microns in size, less often found in 2–3 in one erythrocyte. It is known that Howell-Jolly bodies are the remainder of the erythrocyte nucleus after removal of its RES. Revealed more often with intense hemolysis and with megaloblastic anemia (Fig. 1).

Some of the erythrocytes have a swollen membrane at one of the poles with the formation of a vacuole (Figure 1, indicated by blue arrows). In addition, all degenerative forms of erythrocytes with a characteristic location of hemoglobin are observed: hypochromic with a hole, ring, and also in the form of shadows, indicating iron deficiency and B12 anemia; hyperchromic with an arrangement of hemoglobin in the form of a ring with and without enlightenment (Fig. 2).

This explains the severity of clinical manifestations when the gastrointestinal tract is involved in the pathological process, since the participation of cyanocobalamin in the normalization of erythropoiesis is inhibited. The presence of spherocytes in the lung parenchyma and in the lumen of blood vessels indicates hyperhydration of the erythrocyte, increased permeability of the erythrocyte membrane for Na⁺ and Ca²⁺ ions, followed by the acquisition of spherical erythrocytes with the inability to plasticity and deformation in the microvasculature, with a decrease in life expectancy. It is known that with such changes, the developing membranopathy is mainly due to a significant change in the content of the spectrin protein, a violation of its binding to other proteins of the erythrocyte membrane. Since glycolysis is the leading pathway for ATP resynthesis in erythrocytes, a lack of ATP energy causes a violation of the transmembrane transfer of ions, a decrease in the activity of enzymes of the pentose phosphate cycle. Their imbalance develops, leading to overhydration and swelling of

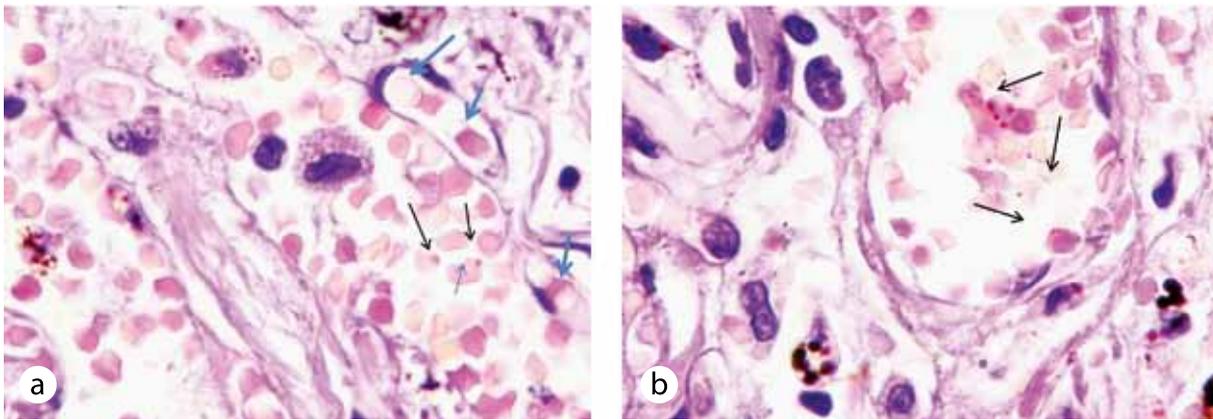


Fig. 1. Lung parenchyma of patients a) 53 years old; b) 74 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto, ×400. Howell-Jolly bodies are identified (indicated by black arrows)

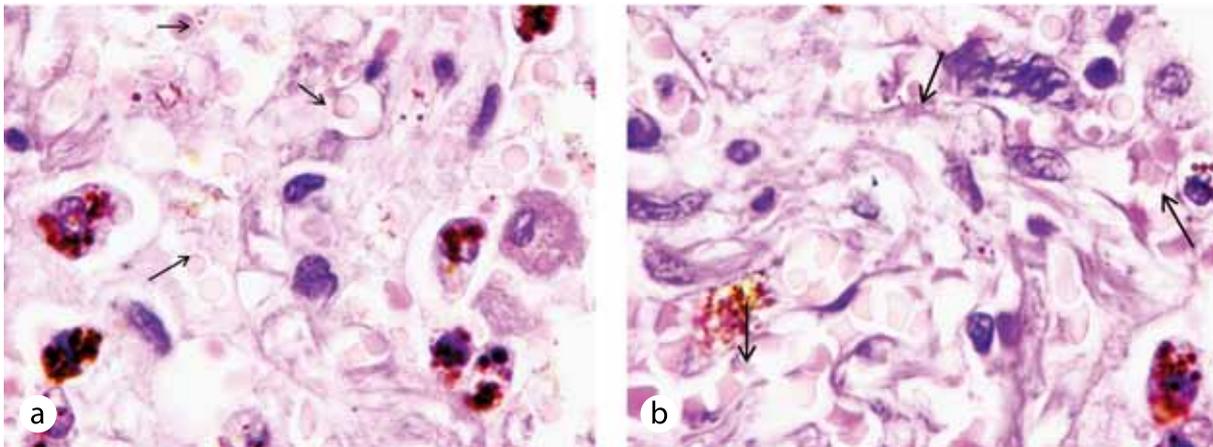


Fig. 2. Lung parenchyma of patients a) 56 years old; b) 64 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto, ×400. Spherocytes, microcytes, hypo- and hyperchromic erythrocytes are identified

erythrocytes. In addition, we noted the distribution of hemoglobin at opposite poles of cells or at one of the poles, typical for erythrocytes located both in the lumen of blood vessels and in the parenchyma of the lung. Also, cell nuclei are identified, the morphology of which is characteristic of those damaged by viruses, has a ring-shaped shape, or inclusions (Fig. 3).

Damage to erythrocytes does not have the character of artifacts resulting from non-technological implementation of methods in violation of the recommended protocol, as evidenced by the presence of normocytes, as well as a clear morphology of macrophages and other cells containing hemosiderin, a product of erythrocyte destruction (Fig. 4).

In addition, hemosiderin is contained not only in the cytoplasm of macrophages, but also in the lumen of blood vessels (Fig. 5, 6).

The presence of macrophages with hemosiderin in the cytoplasm, as well as free hemosiderin in the lumen of blood vessels, indicate that the death of erythrocytes begins not in the lung parenchyma, but at the stage of circulation and oxygen delivery to the tissues. The consequence of this is the generalization of the pathological process, leading to multiple organ failure. Thus, for the causative agent of COVID-19 SARS COV-2 in starting the cascade of pathogenesis, one of the main targets is the erythrocyte, in which membranopathy, fermentopathy and hemoglobinopathy are clearly manifested. Adaptive erythrocytosis, an increase in the number of reticulocytes and arterial hypertension are accompanied by a decrease in blood plasma volume when the body loses fluid as a result of diarrhea, vomiting, and plasmorrhage. In our observations, 3 out of 11 patients developed anemia with a

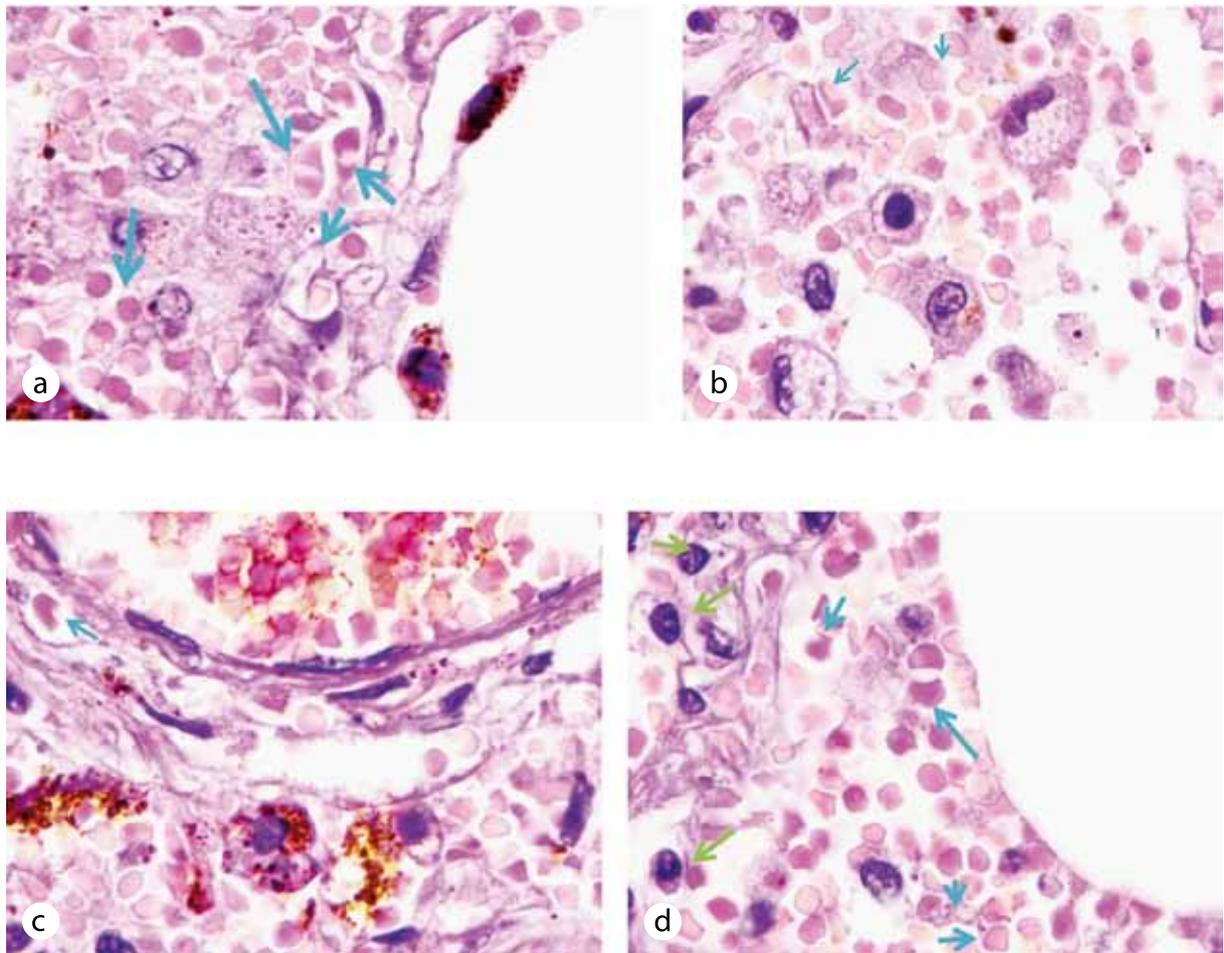


Fig. 3. Lung parenchyma of patients a) 39 years old; b) 56 years old; c) 64 years old; d) 71 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto, $\times 400$. Spherocytes, microcytes, hypo- and hyperchromic erythrocytes are identified. The uneven distribution of hemoglobin at the poles of erythrocytes is indicated by blue arrows, and the nuclei of cells affected by viral RNA are indicated by green arrows

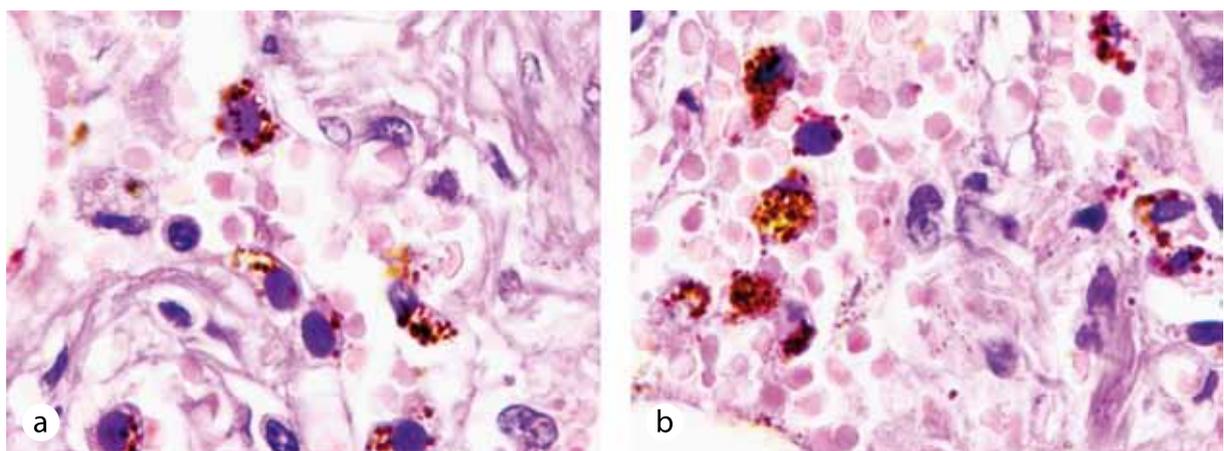


Fig. 4. Lung parenchyma of patients a) 51 years old; b) 56 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto

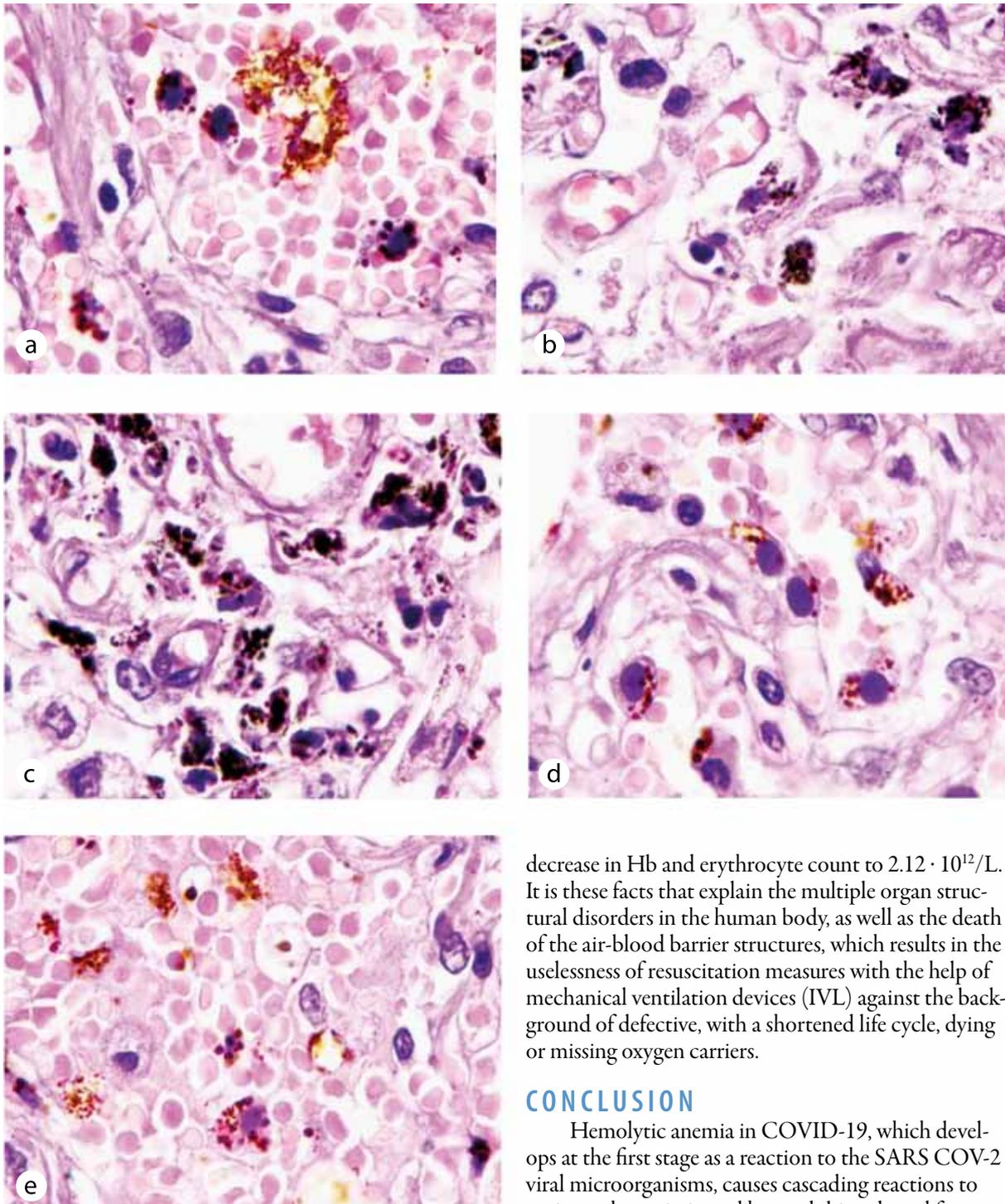


Fig. 5. Lung parenchyma of patients a) 51 years old; b) 56 years old; c) 64 years old; d, e) 74 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto, $\times 400$. Macrophages with hemosiderin granules in cytoplasm are identified against the background of degenerative forms of erythrocytes

decrease in Hb and erythrocyte count to $2.12 \cdot 10^{12}/L$. It is these facts that explain the multiple organ structural disorders in the human body, as well as the death of the air-blood barrier structures, which results in the uselessness of resuscitation measures with the help of mechanical ventilation devices (IVL) against the background of defective, with a shortened life cycle, dying or missing oxygen carriers.

CONCLUSION

Hemolytic anemia in COVID-19, which develops at the first stage as a reaction to the SARS COV-2 viral microorganisms, causes cascading reactions to toxic erythropoietin and hemoglobin released from erythrocytes in the bloodstream, and then to hemosiderin released due to the death of erythrocytes in the tissue. The process ends with a decrease in the synthesis of erythropoietin in the decaying liver and kidneys, in the absence of the necessary vitamin B12 due to the pathology of its secretion in the gastrointestinal tract. The characteristic signs of damage to red blood cells in conditions of infection with COVID-19 indicate

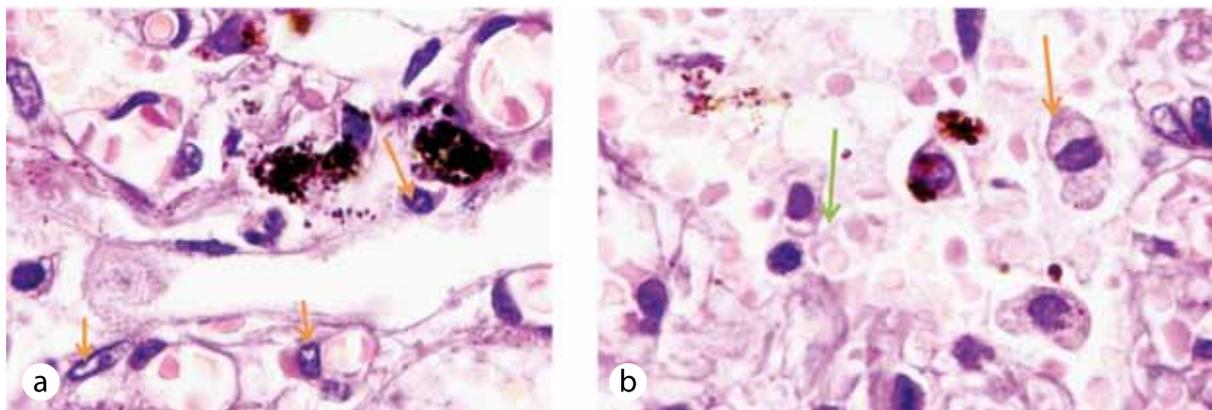


Fig. 6. Lung parenchyma of patients a) 64 years old; b) 71 years old with COVID-19. Staining with hematoxylin and eosin. Microphoto, $\times 400$. (Green arrow indicates sickle-shaped erythrocyte. Orange arrows indicate viral inclusions in cell nuclei)

disruption of erythropoiesis, with developing iron deficiency and B12 anemia. The synthesis of hemoglobin lags behind the differentiation of erythrocytes, which in the initial period of the disease induces an increase in the secretion of erythropoietin, which has a hypertensive effect; increases blood viscosity and leads to impaired blood microcirculation, which is why patients with essential hypertension are the main risk group. This underlies the inability to use erythropoietin-based drugs to treat patients with anemia in the context of COVID-19 infection. Pathological changes in erythrocytes infected with viruses are caused by specific and non-specific processes. Reactions caused by the configuration of the permeability of the plasma membrane of erythrocytes, margination of chromatin in the form of Howell-Jolly bodies, and vacuolization of the cytoplasm are nonspecific. SARS COV-2, like SV40, can be attributed to *vacuolizing viruses*, but only erythrocytes, since the virus has a particularly peculiar and pronounced character of inducing vacuolization. Specific changes are oxyphilic viral inclusions in cell nuclei, leading to cell destruction through a rapid and deep effect on the synthesis of cellular proteins.

CONCLUSIONS

1. The key target for SARS COV-2 is erythrocytes.
2. Multiorgan failure is the result and consequence of SARS COV-2 virus damage to erythrocytes, which develops against this background of ischemia and anemia with cell death of various organ systems.
3. The use of erythrocyte mass for the treatment of COVID-19 is pathogenetically substantiated.

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PRIMARY HEALTH CARE IN GHANA: THE STRUCTURE AND FUNCTIONS IN RELATION TO PREVENTING NEGLECTED TROPICAL DISEASES

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ABSTRACT — There are three main levels of primary health care in Ghana: The district level health care which is the highest level of primary health care in Ghana serve an average population of 100,000–200,000 people in a clearly defined geographical area. A District Hospitals provide Curative care, preventive care, and promotion of health of the people in the district. The second level is the Subdistrict health care which serves a population of approximately 20,000. They augment their service coverage with outreach services and refer severe and complicated conditions to the district level. The final and basic unit of the PHC in Ghana is the Community-based Health Planning and Services (CHPS) which aims to improve access to promotive and preventive health care at the community level of an average population 3000–4500 representing two- or three-unit committees of the subdistrict assembly. Mass drug administration is main preventive measure for eradicating neglected tropical diseases in endemic regions of Ghana of which it is best administered through primary and community health care systems in these hotspots areas, according WHO. The CHPS concept places emphasis on delivering essential community-based health services through the active participation of communities' Primary health care is considered in this article as a tool for the prevention of neglected tropical infectious diseases.

KEYWORDS — Community health nurse, Community based health planning services (CHPS), Ghana health service (GHS), community health offices (CHO) Primary health care, neglected tropical infectious diseases.

INTRODUCTION

In 1996 an act of Parliament created the Ghana Health Service (GHS) as an extra-ministerial agency that is outside the civil service, allowing the health sector to change, innovate, and reform health care operations in Ghana. The GHS has adopted a model for community-based service delivery known as then Community-based Health Planning and Services (CHPS) Initiative. The CHPS initiative characterizes the key strategy for changing primary health care and

family planning from a focus on clinical care at district and sub-district levels to a new focus on convenient and high-quality services at community and doorstep locations. This national program of service delivery change is achieved by forging partnerships between health care providers and the communities they serve. This was necessary because of the problems that existed then which included:

— In Ghana, geographic access is a major barrier to health care and excess childhood mortality is related to service inaccessibility. Fully, 70 percent of the population resides in communities that are over 5 kilometers from the nearest health facility. Childhood mortality in such communities is 40 percent higher than in communities located within 5 kilometers of health facilities.

— There is great disparity in health status between urban and rural areas. As Ghana entered the 21st century, infant mortality rates in rural areas were 60 percent higher than rates prevailing in urban areas.

— Globally, mortality in rural West Africa is the highest of any region in the world. Preventable morbidity among children explains much of the excess mortality.

— Fertility in West Africa remains the highest of any region in the world. The global fertility transition has yet to begin in rural West Africa, where rural total fertility rates are double the rates observed elsewhere in the developing world.

— Ever since the Alma Ata Conference, Ghana has had a policy of making community-based services available to all through community-based care. With the introduction of the Navrongo Experiment, a feasible means of implementing this policy was successfully demonstrated.

— Effective means of utilizing African traditions of social organization and leadership for organizing and promoting family planning and health services are lacking.

CHPS therefore becomes the adopted model for community-based service delivery by the Ghana health service. It represents the health sector component of the national poverty alleviation program.

The inability of most low- and middle-income countries to achieve the health Millennium Development Goals (MDGs) including Ghana is attributed largely to weak health systems that are not able to provide good-quality, accessible, comprehensive and integrated care. The 2008 World Health Organization (WHO) World health report reaffirmed the importance of primary health care (PHC) systems in improving the health of individuals, households and populations, and proposed four areas for reforms: universal coverage, service delivery, leadership and public policy. Other authorities have described PHC as the foundation of health systems, as it ensures that all people stay as healthy as possible and obtain care when needed. The Primary Health Care Performance Initiative describes a working PHC system as: When primary health care works, people and families are connected with trusted health workers and supportive systems throughout their lives, and have access to comprehensive services ranging from family planning and routine immunizations to treatment of illness and management of chronic conditions. Health systems built on strong primary health care are more resilient, efficient and equitable. Primary health care meets the vast majority of communities' diverse health needs, and ultimately, saves lives. Ghana has made significant progress in health care delivery though there is still more to be done. This paper seeks to showcase the current state of primary health care in Ghana and the shortcomings that needs to be addressed and its role in preventing infectious diseases.

MATERIAL AND METHOD

Analysis of Annual report Ghana health service (2013-2017), Primary Health Systems-Comprehensive case study of Ghana pg. 30), Ghana health service: Community based health planning services operational policy (CHPS), Ghana health: Community based health planning services. Training manual.

RESULT AND DISCUSSION

PHC implementation in Ghana is primarily designed at the district level as a three-tier system where health services are provided at district, sub-district and community levels.

First Level: District level health care:

The highest level of healthcare provision is at the district level where district hospitals provide comprehensive healthcare within the district.

Functions and Roles:

District hospitals are the facilities for clinical care at the district level. District hospitals of Ghana serve an average population of 100,000–200,000 people in a

clearly defined geographical area. The number of beds in a district hospital is usually between 50 and 60. It is the first referral hospital and forms an integral part of the district health system. There is a district disease control team in charge of control and prevention of infectious diseases including neglected tropical diseases.

A District Hospitals provide the following:

- Curative care, preventive care, and promotion of health of the people in the district (Including neglected infectious diseases)

- Quality clinical care by a more skilled and competent staff than those of the health centers and polyclinics

- Treatment techniques, such as surgery not available at health centers are available at the district level.

- Laboratory and other diagnostic techniques appropriate to the medical, surgical, and outpatient activities of the district hospital, Outpatient and inpatient.

District Health Management Team (DHMT) are instrumental in devising innovative strategies to implement CHPS and improve service delivery at the community level. These include:

- Mobilizing communities to construct community health compounds or clinics. (CHC).

- Low-cost community construction has greatly expanded health service coverage.

- Building political support for health has led to collaboration between District Assemblies and DHMT in marshalling district development funds for CHC construction. In a few districts, this innovative mechanism permits the participation of grass-roots politicians in health development, and utilizes mechanisms of international development donors, such as the European Union, for innovation in health services.

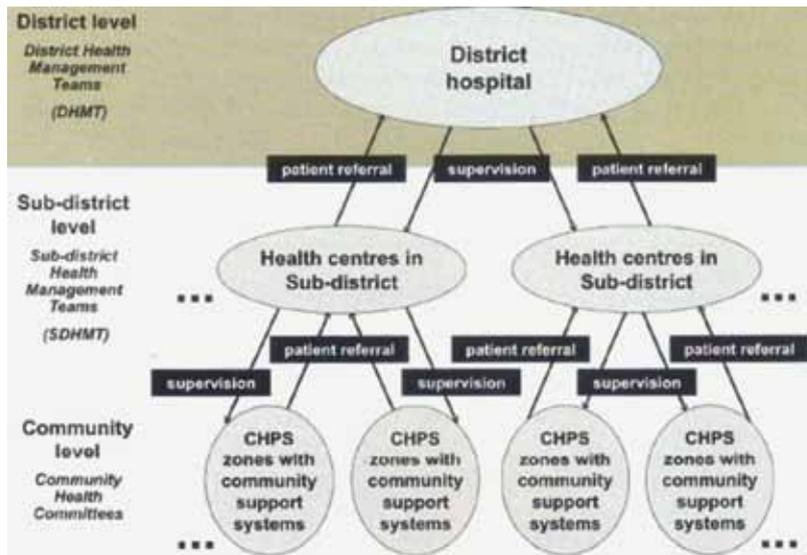
- Community-based planning improves DHMT utilization of

- resources and develops activities that are in connection with local cultural conditions and local needs.

The second level: Subdistrict-Health center and health post: This second level is effective in terms of preventing infectious disease.

The health center has traditionally been the first point of contact between the formal health delivery system and the client. It is headed by a Medical Assistant and staffed with program heads in the areas of midwifery, laboratory services, public health, environmental, and nutrition. Each health center serves a population of approximately 20,000. They provide basic curative and preventive medicine for adults and children as well as reproductive health services. They

Structure of primary health care in Ghana



provide minor surgical services such as incision and drainage. They augment their service coverage with outreach services and refer severe and complicated conditions to appropriate levels usually.

Functions and role in preventing and eradicating neglected tropical infectious diseases include:

1. Collecting data on community health and volunteer programs for the district health manage, end team on neglected tropical diseases in this area.
2. The manage supplies and monitor usage of the medication for chemotherapy in preventing neglected tropical diseases as well as other diseases.
3. They, in collaboration with the district health management team and the community-based health and planning service (CHPS) draw up the program for the preventive chemotherapy within the sub district.
4. They, in collaboration with community-based health planning services (CHPS) recruit volunteers to help in the mass drug administration.
5. They also with the CHPS program plan programs for health education in the subdistrict on different health issues including neglected tropical disease
6. Writing reports on any progress made with regards to tropical infectious diseases to the district health management team
7. They monitor the work of the community-based health planning services program in dealing with disease control including tropical diseases.

The third Level: Community-based Health Planning and Services (CHPS):

In Ghana, the Community-based Health Planning and Services (CHPS) approach to healthcare provision remains the major strategy being adopted for the provision of primary healthcare services. The CHPS concept places emphasis on delivering essential community-based health services through the active participation of communities. The CHPS initiative characterizes the key strategy for changing primary health care and family planning from a focus on clinical care at district and sub-district levels to a new focus on convenient and high-quality services at community and door-

step locations. This national program of service delivery change is achieved by forging partnerships between health care providers and the communities they serve

The sanitary, anti-epidemic and preventive functions against neglected tropical diseases include:

1. They educate the people on the need to keep their sanitation clean as a way of preventing the tropical infectious diseases.
2. They visit the communities, houses and neighborhood with the community task force on sanitation to ensure that people adhere to sanitary measures and failure to do so will lead to the person paying a penalty.
3. They in collaboration with the sub district and district health management team as well the community political leaders to ensures that proper water facilities, toilet facilities, waste facilities and other sanitary facilities necessary are provided.
4. They visit churches, radio stations, organizes durbars to educate the people on prevailing health issues and how to prevent them.
5. They in collaboration with the subdistrict and district disease control unit give out the medications for the preventive chemotherapy by going from house to house in their designated communities and ensures the medications are taken by the people.
6. They also help in giving out mosquito net to prevent malaria and other mosquito related disease like Lymphatic Filariasis.

By 2002, the CHPS program was providing doorstep health care in all regions of Ghana through a program that is supported by Government of Ghana and community resources. The Community-Based Health Planning and Services (CHPS)

Initiative is a national program for reorienting and relocating primary health care from sub-district health centers to convenient community locations. The CHPS organizational change process relies upon community resources for construction works, labor, service delivery, and program oversight. As such, it is a national mobilization of grass-roots action and leadership in health and family planning.

The CHPS initiative enables the Ghana Health Service (GHS) to reduce health inequalities and promote equity of health outcomes by removing geographic barriers to health care. CHPS is a component of government policy agendas, such as the Ghana Poverty Reduction Strategy (GPRS) — which identifies CHPS as a key element in pro-poor health services.

In addition, various sector performance reviews in 2002 commended CHPS as an appropriate way to deliver health care to communities in undeveloped and deprived areas distant from health facilities. The specific elements of the CHPS service delivery model are based on research results demonstrating that placing a nurse in the community substantially reduces childhood mortality and combining with nurse outreach, traditional leader and volunteer involvement builds participation in family planning and improves health service system accountability.

Adopting and implementing the CHPS program begins with District Health Management Team program planning in the most remote and deprived communities of a given district. Communities are mapped, problems are assessed, and a process *community entry* is launched which involves dialogue between health care providers and community leaders. Once leadership responsibilities are clarified, communities are encouraged to raise revenue and convene teams of volunteers to construct village clinics known as *Community Health Compounds (CHC)*. Successful completion of a CHC is followed by posting a nurse to the CHC. These nurses, termed Community Health Officers (CHO), then become community-based front-line health workers who visit households, organize community health services, and conduct CHC clinics.

Under CHPS, CHO receive advanced clinical and community organizational training enabling them to assume their additional duties and responsibilities as they become resident in the community. These strategies have been developed, tested and have become the success story of CHPS:

— Midwifery training is provided so that CHO can supervise births in the community setting. In Nkwanta and several other districts, the DHMT has trained CHO to be midwives capable of performing the procedure for manual removal of placenta, oxytocin injection for labor management, and emergency obstetric referral.

— CHO work in partnership with community leaders. Practical means of utilizing traditional leadership and communication systems for health and family planning promotion have been developed and disseminated through the CHPS Initiative. Traditional *durbars* are now used throughout Ghana to build community consensus and involvement in health care reform.

— CHO services greatly expand access to family planning by providing comprehensive family planning services at the doorstep.

— CHO community services expand access to primary health care, including immunization coverage. By mobilizing community participation, CHPS improves the efficiency and effectiveness of childhood immunization services. Strategies for mobilizing the participation of men in family planning include outreach to chiefs and elders for the purpose of organizing community *durbars* where leaders speak out for family planning and responsible parenthood. All existing forms of social organization are mobilized in the CHPS initiative for supporting CHO work, including organization of men and women's social networks for family planning and health promotion, and deployment of volunteers for health.

— In the past, attempts to organize volunteer services have been ineffective or even detrimental to child health. CHPS demonstrates ways to develop CHO supervision and referral services that improve the quality of volunteer services and community participation in managing volunteerism.

— In the CHPS approach, volunteer effort is focused on mobilizing labor for clinic construction, mobilizing male participation in family planning promotion, and supporting CHO community health service activities.

— Investment in manpower development: CHO training was initially centralized into program at three training centers. Various problems were associated with the centralized approach: National recruitment and posting procedures result in the assignment of nurses to localities that are far from their homes, where languages, social customs, and community organizational arrangements are unfamiliar. Moreover, the centralized approach deprives communities of involvement in CHO selection and posting.

Currently the national recruitment and posting is done at the district level, where they are familiar with the language, social customs and community organization. Community health workers are only posted within the district they come from or live right after graduating and passing the registered nurses' exams.

Having access to remote villages have been made possible through CHPS program with the available

resources they have. Organizing weekly visits to each community, giving primary care to these people and when necessary refer them to the health post or the district hospitals have been very effective under the CHPS program.

The CHPS program also makes it possible for the community health officers to involve various religious bodies in health education by visiting their meetings to give health talk on important health issues.

THE COMMUNITY HEALTH OFFICERS

the functions of sanitary anti-epidemic and preventive against infectious diseases

They work on these

1. Collecting data on community health and volunteer programs for the district health management team on neglected tropical diseases in this area.

2. The manage supplies and monitor usage of the medication for chemotherapy in preventing neglected tropical diseases.

3. They in collaboration with the district health management team and the community-based health and planning service (CHPS) draw up the program for the preventive chemotherapy within the sub district.

4. The in collaboration with community-based health planning services (CHPS) recruit volunteers to help in the mass drug administration.

5. They also with the CHPS program plan programs for health education in the subdistrict

6. Writing reports on any progress made with regards to tropical infectious diseases to the district health management team

7. They monitor the work of the community-based health planning services program in dealing with disease control including tropical diseases.

These are trained health providers who are to deliver a defined package of health care services. They could be from public or private segment of the health sector though currently almost all of them are from the government sector. They include the community health nurse (CHN), community health nurse midwives (CHNM), midwives, enrolled nurses, field technicians etc. TH frontline staffs are given standard conversion courses with additional midwifery skills in case they don't have them already before being re-deployed into their community as community health officers.

The technical service provision will be supported by others within the community especially the following: Community based volunteers, community members, community health committee, mothers and children and community/traditional health delivery

personnel (native doctors, traditional birth attendants, herbalists etc.)

The community health officers are expected to deliver a package of essential primary health care and promotion services at the community level. They are expected to pursue a work routine that revolves around home visiting and has its base in outreach by the health provider, rather than a static service base for the client to attend. The idea is to take service to the clients rather than follow the traditional method of expecting the client to seek out the health care provider.

Roles of CHO in the CHPS Zone

1. Planning health services and program with community members

2. Implementing health program with community participation

3. Supervising community level health workers, including health care assistants, TBAs, volunteers, and health committee members

4. Preparing and submitting monthly CHPS activity reports to sub-district

the functions of sanitary anti-epidemic and preventive against infectious diseases

Direct activities

1. House to house Visits

2. Immunization status

3. Health Education

4. Community sensitization on specific health diseases like prevailing infectious diseases

5. Community mobilization for cleanup activities in the community

6. Distribute medication of preventive chemotherapy for neglected tropical diseases

7. Collaborate with community leaders to disinfect water bodies, keep water bodies clean and construct a good toilet and waste facilities

CHALLENGES OF PHC IN GHANA

1. The first relates to the general misunderstanding of the CHPS strategy. Its implementation has largely focused on building compounds (providing infrastructure) and providing clinical services with minimal attention to outreach services which promote preventive and promotive care. This condition, the health sector admits, is the result of constant changes in the standard basic package of interventions to be delivered in a CHPS zone.

2. Additionally, questions have been raised on CHPS service coverage across the country.

In 2012, the health sector estimated that approximately five per cent of Ghana's population had

been reached by CHPS services. In 2016, The number of functional CHPS zones increased by 11%, from 3,951 in 2015 to 4,400 in 2016, although it fell short of achieving the 6,000 CHPS targeted. This raises questions as to whether the strategy is efficient and cost effective in providing PHC services which are supposed to be available and accessible to all.

3. PHC implementation in Ghana is still largely focused on curative care where the emphasis is on removing the immediate cause(s) of signs and symptoms of a disease in an individual. Efforts at addressing the social and behavioral determinants of health are still limited. An individual's health is determined by a complex interaction between individual characteristics, lifestyle and the physical, social and economic environment. These broader determinants of health are also important in ensuring total health care.

4. Inadequate providers (physicians and nurses) to patient ratio, physicians and nurses lacking professionalism, mal-distribution of providers, bad or lack of technology

5. Health Care financing has been a challenge. The national insurance scheme (NHIS) was meant to tackle this issue remains underfunded.

6. Inadequate logistics and transport for the sub-district and community health nurses who will have to travel to different communities to provide health care due.

7. Other challenges include insufficient training for health workers and volunteers, significant deficiencies in working conditions, high level of bureaucracy.

Inadequate primary health care delivery mainly leads to increase in morbidity and mortality.

CONCLUSION

Generally primary health system in Ghana has improved in the past decade in terms of coverage mainly through the community-based health planning services (CHPS) program. The introduction of National health insurance scheme though underfunded has been a huge relieve especially to the poor communities. If the stakeholders: the Ministry of Health, Ghana health service, World health organization and the international partners can address the challenges listed above and conduct more research as to areas where the CHPS program can improved and also extend to CHPS project to any area yet to benefit from the CHPS program, it will be a great achievement for the country's health sector which will have effect on the basic health indexes in the country like infant mortality, morbidity and mortality rate etc. This will eventually have positive effective in implementing the recommendations of WHO for preventing neglected tropical diseases.

We need to develop health education programs and initiatives by the community:

1. Health talk on Radio stations that can be accessed by the community
2. Using megaphones to announce the date and importance of the chemotherapy in the communities
3. Health talks in churches and other religious gatherings
4. Organising durbars in the communities and talking about health issues
5. Health talks in schools, churches, mosques, public gathering within the communities.
6. Erecting bill boards with billboards with pictures of people infected to draw attention to create awareness of the effect of these diseases.

Functions of sanitary anti-epidemic and preventive against infectious neglected diseases

1. Clean up exercises during days that the community people do at home like weeding places that are grown, draining gutters and places that harbor mosquitoes.
2. House visits to ensure the environment is clean and people made to pay penalty if their surroundings are dirty and weedy
3. Disinfection of water bodies and important places against the vectors
4. Provision of free mosquito nets and other mosquito repellants
5. Education or training for medical personnel involved in the mass drug administration for the prevention of neglected tropical diseases.

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ACTUALIZATION OF THE PROBLEMS OF DEVELOPMENT OF HIGH-TECH MEDICAL CARE IN RUSSIA

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ABSTRACT — Accessibility of high-tech medical care for the population is one of the main indicators of socio-economic development of the state. The current legislative framework of the Russian Federation guarantees every citizen the opportunity to receive high-tech medical care. However, the centralization of state medical organizations with the right to provide this type of medical care makes it difficult for citizens to access it. One of the promising areas of development is the increase of the share of private medical organizations entitled to provide high-tech medical care in remote regions. Active implementation and modernization of information systems will increase the availability of high-tech medical care to the population under state guarantee.

KEYWORDS — high-tech medical care, healthcare, state guarantees, information systems, quality of medical care.

INTRODUCTION

Providing medical care to the population is one of the important tasks of a developed state. There are several models for health care financing. In developing countries, government spending on health care is minimal [1, 8]. A number of World Health Organization programs reduce inequalities in health care delivery. Developed countries spend significant sums on financing medicine [5]. The most promising is the development of a universal health insurance system [11].

Germany is an example of a balanced approach to the allocation of health care costs. The basic principle of German health care is the principle of solidarity. Medical care is available to all segments of the population, regardless of their financial situation. Funding is provided by employee and employer insurance premiums. For unemployed citizens, the insurance policy is fully paid by the state. High-tech medical care is available to all citizens of the country. [6, 13].

In other European countries, health care funding is not as high as in Germany. Most high tech medical procedures are not covered by basic insurance [2, 14].

Canada is an example of significant reductions in administrative health care costs. Canada's Medicare program helps fund emergency physician and hospital services. This increases the availability of basic health care for the entire population of the country. Funding for most modern medical operations requires the involvement of the patient himself [10].

In the United States, the implementation of Medicare for All and the Affordable Care Act (ACA) has led to short-term improvements in the availability of health care for the population. High-tech medical care is paid for by the patient himself or by charitable foundations [4, 7, 21].

The Russian Federation faces a choice of a health financing model. Will it follow the path of Germany, or will she choose the equivalent of Medicare for All? Consider the financing of high-tech medical care in modern Russia.

DISCUSSION

We tried to analyze the existing experience of financing healthcare and high-tech medical care in Russia. Population health care is one of the fundamental principles laid down in the updated legislative framework of the Russian Federation. One of the main directions of national health care development for the period 2020–2025 is the improvement of the provision of medical care to patients with serious diseases requiring a long and expensive treatment [12].

In Federal Law 323-FZ dated November 21, 2011 *On the Basics of Protecting Citizens' Health in the Russian Federation*, high-tech medical care is defined as *a part of specialized medical care, which includes the usage of new complex and (or) unique treatment methods, as well as resource-intensive treatment methods with scientifically proven effectiveness, including cell technology, robotic technology, information technology and genetic engineering methods, developed on the basis of the achievements of medical science and related branches of science and technology* [18].

Nowadays, federal legislation guarantees the citizens of the Russian Federation providing high-tech medical care for a significant list of diseases at the

expense of the federal budget [20]. At the same time, the use of other sources of financing for the provision of high-tech medical care is not prohibited — the use of personal monetary resources of citizens, as well as of public associations and funds, means provided by non-governmental organizations of various forms of ownership.

The provision of high-tech medical care can be carried out both in medical institutions of the Ministry of Health of the Russian Federation and a number of other ministries and departments, as well as in the framework of the main or additional activities of private medical organizations.

High-tech medical care according to the nomenclature of its types stated in the basic program of compulsory medical insurance is provided by medical organizations included in the Register of medical organizations operating in the field of compulsory medical insurance.

High-tech medical care according to the nomenclature of its types that are not included in the basic program of compulsory medical insurance is provided both by federal state institutions, the list of which is approved by the Ministry of Health, and medical organizations, the list of which is approved at the regional level [9]. Every year, the nomenclature of high-tech medical services funded by compulsory health insurance is expanding. It should be noted that medical institutions that have received the right to provide high-tech medical care can provide it as a part of paid medical service program, which, on the background of a gradual decrease in quotas for compulsory medical insurance, allows a large federal medical institution to receive additional income.

The existing system of high-tech medical care state financing is based on quotas for the guaranteed compensation of the medical institution expenses for integrated nosological units.

This system of medical organizations financing has the following disadvantages:

- the mismatch between the volume of quotas and the real needs of the population, which is especially noticeable in the example of the Far Eastern Federal District [19],
- subjectivity in determining the patient's need for high-tech medical care,
- uneven distribution of institutions eligible to provide high-tech medical care in the region, with their concentration in administrative centers of the federal and regional levels,
- the difficulty of fulfilling all the requirements for a preliminary examination of the patient at the local level.

It should be noted that not only institutions within the jurisdiction of the Ministry of Health of the Russian Federation, but also medical institutions of different departmental subordinations, as well as non-state medical institutions may be involved in the provision of high-tech medical care.

An analysis of Russian medical literature testifies the successful experience of organizing the provision of high-tech medical care in the above-mentioned medical institutions. So according to Shalygin L.S. et al. (2015) the opening of a public-private partnership in the field of *traumatology and orthopedics* on the basis of I.L. Tsvyvan Novosibirsk NIITO has significantly increased the availability of high-tech medical care in the field of *traumatology and orthopedics* both in this region and in neighboring ones [16].

Significant progress in improving the efficiency and quality of the provision of high-tech medical care may be due to greater flexibility in the response of non-state medical institutions to the changing needs of the high-tech medical care market [16, 19].

However, the access of a non-governmental medical institution to the provision of high-tech medical care in the framework of financing under compulsory health insurance programs is hampered at the legislative level.

One of the most controversial criteria for admitting a medical organization to a state-guaranteed order for the provision of high-tech medical care is the availability of full-time specialist doctors. In addition, a separate requirement for specialists of commercial medical institutions is a minimum length of service in the provision of high-tech medical care for at least three years.

Another problem of providing high-tech medical care in a non-governmental medical institution is the low cost-effectiveness of the service and poor return on the initial costs of the organization.

It should be noted that the funds received under the compulsory medical insurance program do not cover all expenses of the medical organization for the provision of high-tech medical care — the costs of developing and maintaining innovative medical equipment, etc. are not completely taken into account.

Improving the profitability by increasing the turnover of beds in this case is impossible. At the same time, large budgetary medical institutions can afford to maintain rarely required equipment and specialists, which leads to excessive centralization and reduced availability of high-tech medical care in the regions [3].

One of the possible ways to level the inequality of the population in terms of access to high-tech medical care is the introduction and improvement of

global information systems. Significant progress in this matter has been achieved in M.F. Vladimirovsky Moscow Regional Research and Clinical Institute (MONIKI) under the guidance of A. Gurov. Integration of his pilot projects with the Unified State Health Information System allows to significantly simplify and speed up the process of obtaining high-tech medical care for various categories of the population of the Moscow region [17].

CONCLUSION

The presented data allow us to conclude that there is no clear understanding of the procedure for financing high-tech medical care in the Russian Federation. Excessive centralization and delays in decision-making do not allow the majority of citizens of the Russian Federation to receive timely high-quality high-tech medical care. This problem can be solved by attracting private medical organizations to provide high-tech medical care using state funding. A promising direction is the creation of public-private partnerships in healthcare.

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ANTITUMOR EFFICACY OF LIPOSOMAL DOXORUBICIN HYDROCHLORIDE IN COMBINATION WITH TAMOXIFEN. EXPERIMENTAL STUDY

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ABSTRACT — In this paper we evaluated the effectiveness of adjuvant chemotherapy in animals (n=30), which created a model of cancerogenesis. We created 3 equal studies: the 1st group control (n=10) – animals were monitored without treatment; the 2nd group (n=10) — animals received adjuvant therapy with a combination of drugs: liposomal doxorubicin hydrochloride+tamoxifen; the 3rd group (n=10) — animals received adjuvant therapy in a combination of doxorubicin hydrochloride (non-liposomal)+tamoxifen. All animals were monitored for a total of 30 days. As a result, the volume of the tumor in the group of animals treated with liposomal doxorubicin hydrochloride was almost 3 times less than in the control group, and 2 times less than in the rats treated with simple doxorubicin. We also recorded a significantly lower number of lung metastases in animals of the second group compared to other groups. **CONCLUSION.** Treatment of Walker 256 tumors with liposomal doxorubicin showed better efficacy and safety compared to non-liposomal doxorubicin.

KEYWORDS — Liposomal doxorubicin hydrochloride, adjuvant chemotherapy, breast cancer, tumor of the Walker strain, metastasis.

INTRODUCTION

Breast cancer (BC) takes the 1st place in the structure of oncological diseases in women [1, 2, 3, 4]. The incidence of breast cancer has been steadily increasing by 1–2% every year [3]. Every year, oncologists all over the world register more than 1 million new cases of breast cancer [1, 5]. Over the last ten years, there has been an increase in the incidence of breast cancer in Russia by 29.1% [5]. Adjuvant chemotherapy is actively used in the treatment of BC [2]. Doctors

use adjuvant chemotherapy to achieve several goals: reducing the volume of the primary tumor; reducing the size and number of affected lymph nodes; increase in the number of conservative surgical interventions; elimination of distant micrometastases, etc. [3, 6, 7].

According to modern rules of adjuvant chemotherapy, it is recommended to use a combination of chemotherapy drugs to potentiate the antitumor effect and reduce toxic effects. Thus, a combination of cytostatic and antiestrogenic drugs is most often used in adjuvant chemotherapy of BC.

Aim:

To evaluate the effectiveness of combined adjuvant chemotherapy using liposomal doxorubicin hydrochloride in combination with tamoxifen.

METHODS

This was an experimental study that we conducted on 30 non-linear white rats weighing 200–250 g, which were kept in the vivarium of the National Research Ogarev Mordovia State University (Republic of Mordovia, Russian Federation). All manipulations with animals were carried out in accordance with the Guidelines for the maintenance and use of laboratory animals. All interventions that cause pain in animals were performed under anaesthesia.

At first, we created a model of a tumor in animals by injecting 1.2 ml of suspension into the hind right paw, which contains 2 tumor strains (solid Walker 256 tumor strain and solid transferable tumor strain). We examined all the animals daily and registered the appearance of tumors. Every three days we examined all the rats. The tumor model was formed on the 5th day, after which all the rats were divided into three groups:

The 1st group: the control group rats (n=10) that were observed and didn't receive any therapy,

The 2nd group: the rats (n=10) which received neoadjuvant therapy with a combination of drugs: tamoxifen + liposomal doxorubicin hydrochloride (5mg/kg/ml) intravenously one time on the 5th day after tumor transplantation.

The 3rd group: the rats (n=10) which received neoadjuvant therapy with a combination of drugs:

tamoxifen + doxorubicin hydrochloride (non-liposomal) at a dose of 5 mg/kg/ml intravenously one time on the 5th day after tumor transplantation.

In animals of the 2nd and 3rd groups, we used tamoxifen in the neoadjuvant mode. The drug was administered daily, in the abdominal cavity, at a dose of 0.5 mg/kg from 5th to 30th days of the experiment. We evaluated the effectiveness of antitumor therapy by measuring the size of tumors and the dynamics of their regression. We also calculated the number of lung metastases after the experiment was completed. The reliability of differences between quantitative indicators was assessed using the Mann–Whitney test. The differences were considered significant at $p < 0.05$.

RESULTS

Our observation showed stable tumor growth in a control group of animals (Fig. 1). We recorded a significant inhibition of tumor node growth in the second group of rats on the 18th day from the beginning of the experiment compared to the first and third groups: 36604.90, 71652.26 and 69781.11 mm³, respectively ($p < 0.05$). We also noted by the end of 3 weeks of the experiment the formation of a tumor regression tendency in the 2nd and 3rd groups of animals, which was reliably maintained until the end of observation (Fig. 1). In the 2nd group, where rats were treated with liposomal doxorubicin hydrochloride in combination with an antiestrogenic drug, the volume of tumors was the smallest at the end of the experiment (Fig. 1). Consequently, the liposomal doxorubicin has the ability to suppress tumor growth.

We recorded a significant difference in the number of lung metastases between groups ($p < 0.05$) (Fig. 2).

The absence of lethal outcomes among animals of the second group is an indicator of the advantage of combined adjuvant therapy with liposomal doxorubicin hydrochloride. In the control group of rats, there were 20% fatalities, and in the third group (treatment with non-liposomal doxorubicin hydrochloride) — 40% ($p < 0.05$).

DISCUSSION

Doxorubicin-based chemotherapy is one of the most effective antitumor agents for various stages of breast cancer [8]. However, the clear cytostatic benefits of doxorubicin hydrochloride were limited by the drug's toxicity, especially the risk of heart and liver complications. Previously, researchers tried to reduce the toxicity of doxorubicin by changing its dosage [2]. Currently, it is possible to use modified liposomal doxorubicin hydrochloride to improve the antitumor effectiveness of the drug and reduce its cardiotoxicity [9]. Liposomal doxorubicin hydrochloride contains

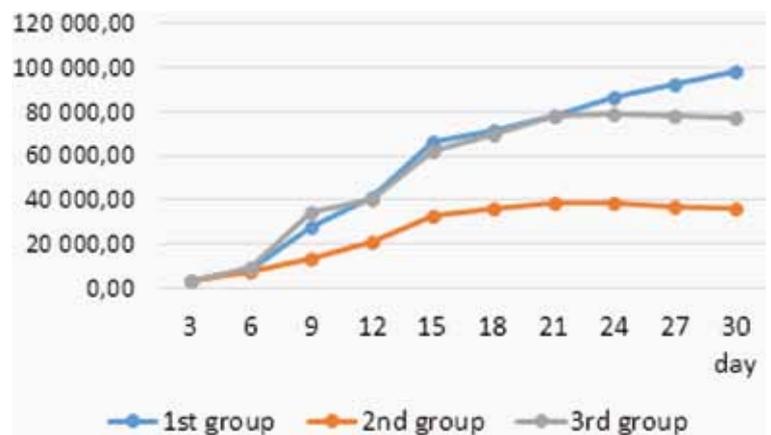


Fig. 1. Dynamics of tumor growth (mm³) depending on the type and duration of adjuvant combination therapy

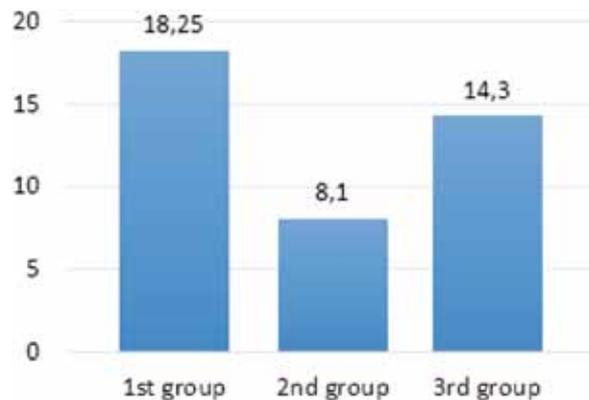


Fig. 2. The number of lung metastases in rats on 30th days of the study

hydrophilic polymers of methoxypolyethylene glycol (liposomes) in contrast to non-liposomal doxorubicin hydrochloride. This creates an advantage for the first drug, since the protection of the molecule from the reaction of the host phagocytic system is formed, which allows extending the time of circulation of the cytostatic substance in the bloodstream and ensuring its higher concentration in the tumor tissue [3]. Fukuda A. et al. claim that liposomal doxorubicin hydrochloride causes less pronounced myelosuppression, cardiotoxicity, and alopecia compared to non-liposomal doxorubicin [9]. Later, Franco YL et al. confirmed that liposomal doxorubicin hydrochloride has low cardiotoxicity, which makes it possible to use this drug in elderly patients [8]. Our study showed that in the group of animals treated with liposomal doxorubicin hydrochloride, the volume of the tumor was almost 3 times less than in the control group, and 2 times less than in the rats treated with simple doxo-

rubicin. We also recorded a significantly lower number of lung metastases in animals of the second group by almost 2.5 and 2 times compared to the first and third groups, respectively. According to Lu YC et al. the use of liposomal doxorubicin hydrochloride may extend the period of relapse-free survival in patients with stage I–III breast cancer [10].

CONCLUSIONS

The most effective combination of antitumor drugs in the treatment of Walker 256 tumors in white rats is a scheme that includes liposomal doxorubicin in combination with tamoxifen in a therapeutic mode. Liposomal doxorubicin provides high safety and effectiveness in tumor growth inhibiting.

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EFFECTS OF NEUROPEPTIDES ON BEHAVIOR OF RATS IN OPEN FIELD TEST AND EXPERIMENTALLY INDUCED SOCIAL STRESS

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ABSTRACT — The experiment is devoted to the study of the effect of neuropeptides on the psychoemotional state of rats exposed to experimental social stress. In the process of modeling social stress, inter-male confrontations were observed, as a result of which groups of animals with aggressive and submissive types of behavior were formed. The psychoemotional state of animals which were injected with the registered neuropeptides Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro), as well as new synthetic compounds of neuropeptide structure — His-Phe-Arg-Trp-Pro-Gly-Pro, Pro-Gly-Pro and Pro-Gly-Pro-Leu were assessed with the help of open field test based on the results of behavioral responses. It was found that the studied neuropeptides (Semax, Selank, His-Phe-Arg-Trp-Pro-Gly-Pro, Pro-Gly-Pro and Pro-Gly-Pro-Leu) exhibited a psychomodulatory effect and relieved symptoms of anxiety-depressive disorders caused by exposure to social stress.

KEYWORDS — experimental social stress, neuropeptides, Semax, Selank, psychomodulatory effect.

INTRODUCTION

Despite a significant number of experiments and publications devoted to various aspects of the problem of stress, the assessment of the level of human stress resistance, especially its behavior under exposure to stress is becoming increasingly important and requires detailed study [1, 2].

One of the main aspects of considering stress is the fact that stress is a complex of psychological and behavioral responses that reflect a state of inner anxiety or suppression. The behavioral response, being the most flexible and diverse in form, serves as one of the mechanisms for protecting the body from the action of various stress factors. According to a number of

researchers its elements are present at all stages of the adaptation process, they are especially pronounced at the stage of disadaptation [3, 4].

Currently, researchers pay great attention not only to the study of the factors that cause stress-induced states, but also the way to eliminate them [5, 6, 7]. In this connection a promising option for stress-protective agents has been suggested by a group of neuropeptides, which are endogenous, playing a role in the formation of compensatory-adaptive forces of the body and regulating important homeostatic functions [8, 9, 10, 11, 12, 13, 14]. The study of the functions of neuropeptides demonstrates their ability to regulate learning, attention and behavior, and to exhibit neuroprotective, neuroregenerative and other types of activity [15, 16, 17, 18]. Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) are registered representatives of neuropeptides which were developed at the Institute of Molecular Genetics of the Russian Academy of Sciences and used in clinical practice. Along with the already registered drugs new synthetic compounds of neuropeptide structure - His-Phe-Arg-Trp-Pro-Gly-Pro, Pro-Gly-Pro and Pro-Gly-Pro-Leu are of significant interest from the standpoint of the prospects for practical implementation in clinical pharmacology.

The aim of research: to study the effect of neuropeptides on the psychoemotional state of laboratory animals exposed to a model of social stress.

Material and methods. The study was carried out on 130 white male rats. The animals were divided into groups (n = 10): group 1 - intact animals (control); group 2 - rats exposed to social stress for 20 days and 5 groups of experimental animals exposed to social stress and receiving neuropeptides at doses of 100 µg / kg per day intraperitoneally for 20 days: registered drugs Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro), as well as new compounds His-Phe-Arg-Trp-Pro-Gly-Pro, Pro-Gly-Pro and Pro-Gly-Pro-Leu.

In our experimental model of social stress rats were paired-housed in cages separated by a transparent partition with holes, which enabled rats to see, hear and smell each other, but at the same time prevented

physical interaction. The septum was removed for 10 minutes every day, resulting in inter-male confrontation. As a result, groups of animals with aggressive and submissive behaviors were formed.

The psychoemotional state of the animals was assessed by the results of studying behavior in the open field test.

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

The results of the study of the effect of neuropeptides on the psychoemotional state of laboratory animals under experimental social stress are presented in the table.

Analysis of the obtained data showed that the formation of social stress led to the development of a state of increased anxiety in rats. So in animals with aggressive behavior we registered a decrease of horizontal and vertical motor, specific hole activity by 40% ($p_1 < 0.01$), 30% ($p_1 < 0.05$) and 35% ($p_1 < 0.01$) respectively and transitions through the central zone of the test is 35% ($p_1 < 0.01$) in comparison with the control group of animals. The intensification of short-term grooming and the increase in the number of fecal boluses of almost 1.8 ($p_1 < 0.05$) and 2 ($p_1 < 0.01$) times respectively were additionally noted. These changes were also observed in animals with submissive behavior: a decrease in horizontal motor, vertical motor, specific hole activity by almost 50% ($p_1 < 0.01$) and transitions through the central zone of the test by 45% ($p_1 < 0.01$) as well as increased grooming and an increase in the number of fecal boluses by 2.5 ($p_1 < 0.05$) and 1.5 ($p_1 < 0.01$) times respectively in relation to the control.

Table. The effect of neuropeptides on the emotional state of rats under conditions of social stress

Experimental groups of animals	Behavioral indicators (M ± m)					
	Horizontal motor activity	Vertical motor activity	Specific hole activity	Crossings through the center	Short-term grooming	Fecal boluses
Control	61,67 ± 5,8	18,37 ± 1,6	9,3 ± 0,8	2,3 ± 0,2	1,12 ± 0,1	1,17 ± 0,2
Animals with an aggressive type of behavior						
"Social" stress	37,0 ± 3,0**	12,75 ± 1,16*	6,2 ± 0,5**	1,5 ± 0,1**	2,0 ± 0,23*	2,33 ± 0,25**
"Social" stress + Semax	51,11 ± 4,14#	17,87 ± 1,52#	8,81 ± 0,64##	2,1 ± 0,19#	1,21 ± 0,17#	1,33 ± 0,1##
"Social" stress + Selank	46,83 ± 3,72#	15,29 ± 1,21	7,67 ± 0,62	1,67 ± 0,14	1,33 ± 0,1#	1,57 ± 0,11#
"Social" stress + His-Phe-Arg-Trp-Pro-Gly-Pro	47,2 ± 4,04#	16,33 ± 1,36#	8,29 ± 0,73#	2,0 ± 0,18#	1,2 ± 0,1##	1,63 ± 0,14#
"Social" stress + Pro-Gly-Pro	51,2 ± 4,73#	17,43 ± 1,81#	8,75 ± 0,62##	2,4 ± 0,21##	1,25 ± 0,11#	1,6 ± 0,18#
"Social" stress + Pro-Gly-Pro-Leu	48,57 ± 4,65#	15,33 ± 1,36	9,25 ± 0,82##	2,0 ± 0,15#	1,5 ± 0,14	1,67 ± 0,15#
Animals with a submissive type of behavior						
"Social" stress	33,0 ± 3,03**	10,25 ± 0,82**	5,67 ± 0,45**	1,33 ± 0,1**	2,83 ± 0,37***	1,8 ± 0,15**
"Social" stress + Semax	45,21 ± 3,88#	13,63 ± 1,0#	7,83 ± 0,58#	2,2 ± 0,17###	1,24 ± 0,12###	1,18 ± 0,1##
"Social" stress + Selank	44,2 ± 4,11#	14,0 ± 1,24#	7,25 ± 0,58#	1,5 ± 0,14	1,67 ± 0,14#	1,5 ± 0,14
"Social" stress + His-Phe-Arg-Trp-Pro-Gly-Pro	43,33 ± 4,19#	13,33 ± 0,93#	8,4 ± 0,93#	1,67 ± 0,15	1,78 ± 0,14#	1,27 ± 0,1#
"Social" stress + Pro-Gly-Pro	49,17 ± 4,37##	14,71 ± 1,21##	8,5 ± 0,6##	2,0 ± 0,18##	1,5 ± 0,11##	1,17 ± 0,1##
"Social" stress + Pro-Gly-Pro-Leu	42,75 ± 3,72#	11,83 ± 0,82	8,25 ± 1,06#	1,5 ± 0,11	2,0 ± 0,18#	1,44 ± 0,11

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).

When introducing neuropeptides, results were obtained indicating their ability to eliminate depressive-like disorders in animals developing under induced social stress, both in animals with aggressive and submissive behavior. It was found that in animals with an aggressive type of behavior the administration of Semax and Pro-Gly-Pro contributed to an increase in horizontal motor activity by an average of 40% ($p_2 < 0.05$), Selank, His-Phe-Arg-Trp-Pro-Gly-Pro and Pro-Gly-Pro-Leu — on average by 30% ($p_2 < 0.05$) in comparison with the stressed group of animals. The vertical locomotor activity of rats also increased under the influence of neuropeptides: administration of Semax and Pro-Gly-Pro — by an average of 40% ($p_2 < 0.05$); His-Phe-Arg-Trp-Pro-Gly-Pro — almost 30% ($p_2 < 0.05$); Selank and Pro-Gly-Pro-Leu — by 20% however these changes were not statistically significant. It should be noted that in animals with the submissive type, the same tendencies in changes in behavioral parameters were observed: the introduction of Pro-Gly-Pro promoted an increase in horizontal motor activity by almost 50% ($p_2 < 0.01$), the introduction of other neuropeptides (Semax, Selank, His-Phe-Arg-Trp-Pro-Gly-Pro and Pro-Gly-Pro-Leu) — on average by 35% ($p_2 < 0.05$) in comparison with the stressed group of animals. The vertical locomotor activity of rats increased under the influence of Semax, Selank and His-Phe-Arg-Trp-Pro-Gly-Pro by an average of 35% ($p_2 < 0.05$); Pro-Gly-Pro — by almost 45% ($p_2 < 0.01$); Pro-Gly-Pro-Leu — by 15% ($p_2 > 0.05$).

The specific hole activity under the stress and the influence of neuropeptides also increased in comparison with the stressed group of animals. It was found that animals with an aggressive type of behavior under the influence of Semax, Pro-Gly-Pro and Pro-Gly-Pro-Leu showed an increase in this activity by an average of 45% ($p_2 < 0.01$), His-Phe-Arg-Trp-Pro-Gly-Pro — by more than 30% ($p_2 < 0.05$), Selank — by more than 20% ($p_2 > 0.05$), in animals with a submissive type under the influence of Selank, an increase in activity by almost 30% ($p_2 < 0.05$), under the influence of the rest of the studied neuropeptides by an average of 45% ($p_2 < 0.05$).

Against the background of the introduction of the studied compounds under stress conditions in animals with an aggressive type of behavior an increase in the number of transitions through the central zone was noted: Semax, His-Phe-Arg-Trp-Pro-Gly-Pro and Pro-Gly-Pro-Leu increased this indicator in on average by 35% ($p_2 < 0.05$); Pro-Gly-Pro — by 60% ($p_2 < 0.01$); under the influence of Selank there was a tendency to increase ($p_2 > 0.05$). When studying changes in this indicator in animals with a submissive type of behavior, the same changes were observed but less pronounced.

When assessing the intensity of short-term grooming and the number of fecal boluses under conditions of administration of neuropeptides against the background of social stress in animals with both aggressive and submissive types of behavior, there were changes in the direction of a decrease in these indicators relative to the stressed group by an average of 40% and 30%, respectively.

CONCLUSION

Thus, the results obtained confirm the ability of the studied neuropeptides (Semax, Selank, His-Phe-Arg-Trp-Pro-Gly-Pro, Pro-Gly-Pro and Pro-Gly-Pro-Leu) to exhibit a psychomodulatory effect correcting symptoms of anxiety and depression arising under induced social stress.

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INFLUENCE OF NEUROPEPTIDES ACTH(4-7)-PRO-GLY-PRO AND ACTH(6-9)-PRO-GLY-PRO ON THE INTENSITY OF REDOX REACTIONS UNDER EXPERIMENTAL DEPRESSION

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ABSTRACT — The experiment is devoted to the study of the antioxidant properties of neuropeptides from melanocortins ACTH(4-7)-Pro-Gly-Pro (Semax) and ACTH(6-9)-Pro-Gly-Pro under conditions of experimental depression. The study was carried out on white outbred male rats. In the process of modeling experimental depression (social stress) inter-male confrontations were observed as a result of which groups of animals with aggressive and submissive behaviors were formed. The free radical oxidation processes were assessed by determining the activity of catalase, the initial content of malondialdehyde (MDA), the rate of spontaneous and ascorbate-dependent lipid peroxidation (LPO) in the hypothalamic and prefrontal regions of the brain by spectrophotometric method. It was found that under the influence of melanocortins, there is a pronounced suppression of the processes of free radical oxidation in the hypothalamic and prefrontal regions of the brain, which arose against the background of a stressful load which is manifested by a decrease in the indicators of the oxidative process.

KEYWORDS — experimental depression, experimental social stress, antioxidant activity, lipid peroxidation, neuropeptides, melanocortins, Semax.

The problem of studying the processes of free radical oxidation is of particular interest from scientists. Numerous studies have shown that oxidative processes occur in a living organism at a constant rate and its change is one of the leading mechanisms of damage to biological membranes [1, 2, 3]. It has been established that an imbalance between prooxidant and antioxidant processes is a pathogenetic link of different diseases, which is most pronounced in the development of autoimmune neurodegenerative, oncological and many other pathological conditions [4, 5, 6]. It has

been proven that the development of free radical processes in the body is directly associated with the impact of various stress factors. Thus, scientific research has shown that any stress response is accompanied by an increase in the level of reactive oxygen species and the development of oxidative stress [7, 8].

Thus the need to create drugs with antioxidant activity is an urgent task of modern medicine. Neuropeptides are of particular interest. Being in fact regulatory peptides and synthesized in almost all tissues of the body they have undeniable advantages, such as high efficiency, lack of toxicity and safety. It has been established that this type of biologically active compounds is involved in such processes as the regulation of metabolism, maintenance of homeostasis, impact on immune processes and functions of the higher nervous system (memory, learning, sleep) and much more [9, 10].

ACTH(4-7)-Pro-Gly-Pro is one of representative of the neuropeptides of the melanocortin family. It is the registered drug Semax, which is an analogue of the ACTH4-10 fragment completely devoid of hormonal activity and with proven neurometabolic, neuroprotective, psychostimulating, immunotropic and other pharmacological effects. Along with the already registered drug Semax, a new synthesized compound from the melanocortin family ACTH(6-9)-Pro-Gly-Pro is being actively studied [11].

Aim

In this connection the aim of this work was to assess the antioxidant activity of neuropeptides of the melanocortin family ACTH(4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro under conditions of experimental social stress.

MATERIAL AND METHODS

The study was carried out on white outbred male rats. Animals were divided into groups (n = 10): 1st group — intact control; 2nd group — rats exposed to experimental depression for 20 days, 3rd group — experimental animals exposed to experimental depression and receiving ACTH(4-7)-Pro-Gly-Pro at a dose of 100 µg/kg per day intraperitoneally for 20 days; 4th group — rats exposed to experimental depression

and receiving ACTH(6-9)-Pro-Gly-Pro at a dose of 100 µg/kg per day intraperitoneally for 20 days. For modeling experimental depression (social stress) animals were placed in pairs in cages separated by a transparent partition with holes which allowed rats to see, hear and perceive each other's smells but at the same time prevented physical interaction. The septum was removed for 10 minutes every day resulting in inter-male confrontation. As a result groups of animals with aggressive and submissive behaviors were formed.

The intensity of free radical oxidation processes was assessed by determining the activity of catalase, the initial content of malondialdehyde (MDA), the rate of spontaneous and ascorbate-dependent lipid peroxidation in the hypothalamic and prefrontal regions of the brain by the spectrophotometric method.

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

The results of a study to determine the intensity of indicators of peroxidation and catalase activity in the hypothalamic region of the brain under the influence of ACTH(4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro under conditions of social stress are presented in the table 1.

Modeling of experimental depression in the form of long-term exposure to social stress led to a statistically significant increase in the content of peroxidation products in the hypothalamic region of the rat brain both in the group with aggressive and submissive behaviors as compared with the control group of animals: the initial MDA level increased by 55% ($p < 0.001$) and 63% ($p < 0.001$), respectively; the rate of spontaneous LPO — in both groups more than 2 times ($p < 0.001$); the rate of ascorbate-dependent LPO by 47% ($p < 0.01$) and 68% ($p < 0.001$), respectively, and the catalase activity increased by 53% ($p < 0.01$) and 49% ($p < 0.01$), respectively.

In the group of animals with an aggressive type of behavior upon administration of ACTH(4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro there was a decrease in the baseline MDA level by 32% ($p < 0.05$) and 25% ($p < 0.05$), respectively. The rate of spontaneous and ascorbate-dependent LPO also decreased in comparison with the group of animals with experimental social stress: by 50% ($p < 0.01$), 30% ($p < 0.01$) and 42% ($p < 0.01$), 28% ($p < 0.05$) respectively. When assessing the activity of catalase a decrease in this indicator was

observed on average by 30% ($p < 0.05$) in comparison with the group of stressed animals.

In the group of animals with a submissive type of behavior identical statistically significant changes were observed. Thus the initial level of TBA-reactive products decreased under the influence of melanocortins by an average of 30% ($p < 0.05$) relative to the stress group. The rate of spontaneous and ascorbate-dependent LPO during exposure to ACTH(4-7)-Pro-Gly-Pro decreased by more than 40% ($p < 0.01$); under the influence of ACTH(6-9)-Pro-Gly-Pro these indicators decreased by an average of 35% ($p < 0.05$). The introduction of the studied neuropeptide compounds led to a statistically significant decrease in catalase activity by almost 30% ($p < 0.05$) in comparison with stressed animals.

The results of the study of lipid peroxidation and catalase activity in the prefrontal zone of the brain under the influence of ACTH(4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro under conditions of experimental depression are presented in Table 2.

When studying the processes of free radical oxidation in the prefrontal zone of the brain of rats under conditions of experimental social stress an increase in the products of peroxidation was noted in comparison with the control in groups with aggressive and submissive behaviors. It was found that the baseline MDA level increased by 76% ($p < 0.001$) and 50% ($p < 0.01$); the rate of spontaneous LPO — 1.7 and 1.9 times ($p < 0.001$); the rate of ascorbate-dependent LPO by an average of 65% ($p < 0.01$) and the catalase activity increased by 59% ($p < 0.05$) and 72% ($p < 0.01$), respectively.

In the group of animals with an aggressive type of behavior under the influence of ACTH(4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro there was a change in all indicators of free radical oxidation in comparison with the group of stressed animals: the initial level of malonic dialdehyde decreased by almost 40% ($p < 0.01$); the rate of spontaneous and ascorbate-dependent lipid peroxidation decreased by almost 40% ($p < 0.05$); catalase activity decreased by 34% ($p < 0.05$) and 28% ($p < 0.05$) respectively.

A similar trend in changes in the indices of the free radical oxidation process was observed in the group of animals with a submissive type of behavior. Against the background of the introduction of ACTH(4-7)-Pro-Gly-Pro the initial level of MDA decreased by 21% ($p < 0.05$), the rate of spontaneous and ascorbate-dependent LPO — by 40% ($p < 0.01$) and 25% ($p < 0.05$) respectively, catalase activity — by 40% ($p < 0.01$) in comparison with the stress group. The neuropeptide compound ACTH(6-9)-Pro-Gly-Pro reduced the listed parameters by an average of 30% ($p < 0.05$).

Table 1. Influence of melanocortins on lipid peroxidation indicators and catalase activity in the hypothalamic area of the brain under experimental 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	
Control	26,5±2,1	2,2±0,3	14,6±1,0	5,5±0,5
Animals with an aggressive type of behavior				
Social stress	41,1±3,1***	5,0±0,6***	21,5±1,5**	8,4±0,8**
Social stress + ACTH(4-7)-Pro-Gly-Pro	28,1±3,1#	2,5±0,3##	15,1±1,2##	5,9±0,6#
Social stress + ACTH(6-9)-Pro-Gly-Pro	30,8±2,9#	2,9±0,3##	15,4±1,3#	6,1±0,6#
Animals with a submissive type of behavior				
Social stress	42,3±3,6***	4,7±0,6***	24,5±2,1***	8,2±0,9**
Social stress + ACTH(4-7)-Pro-Gly-Pro	30,1±3,2#	2,6±0,2##	14,2±0,8###	5,9±0,8#
Social stress + ACTH(6-9)-Pro-Gly-Pro	29,7±3,1#	3,0±0,3#	16,2±0,7##	6,1±0,5##

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).

Table 2. Influence of melanocortins on lipid peroxidation indicators and catalase activity in the prefrontal zone of the brain under experimental 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	
Control	18,2±1,5	4,5±0,4	14,3±1,3	6,5±0,7
Animals with an aggressive type of behavior				
Social stress	32,1±3,2***	7,8±0,8***	24,2±2,1***	10,3±1,1*
Social stress + ACTH(4-7)-Pro-Gly-Pro	20,3±2,1#	4,9±0,6#	14,7±1,5##	6,8±0,9#
Social stress + ACTH(6-9)-Pro-Gly-Pro	19,7±2,7##	5,5±0,8#	15,3±1,7##	7,4±0,8#
Animals with a submissive type of behavior				
Social stress	27,3±2,1**	8,7±0,8***	23,1±1,8**	11,2±1,2**
Social stress + ACTH(4-7)-Pro-Gly-Pro	20,7±1,7#	5,2±0,5##	17,3±1,2#	6,7±0,8##
Social stress + ACTH(6-9)-Pro-Gly-Pro	19,0±1,7##	5,8±0,7#	15,2±1,3#	8,1±0,7#

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).

CONCLUSION

Taking into account the results obtained it can be concluded that pronounced inhibition of free radical oxidation processes in the hypothalamic and prefrontal regions of the brain that arose against the background of experimental depression which is manifested by a decrease in the indicators of the oxidative process, is observed under the influence of neuropeptide drugs of the melanocortin family ACTH (4-7)-Pro-Gly-Pro and ACTH(6-9)-Pro-Gly-Pro.

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AGE-RELATED VARIABILITY OF SOMATOTYPE FEATURES IN FEMALES

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ABSTRACT — Aiming to identify the variability patterns in the physique and somatotype of females aged 18–50 (Saratov Region, Russia) by anthropo- and bioimpedance methods the following parameters were determined: age; body length; body weight; waist circumference; hip circumference; body mass index; waist/hip circumference index; endo-, ecto- and mesomorphy indicators. The women were divided into groups as follows: Group I, 18–20 years old, 37 participants; Group II, 21–30 years old, 41 participants; Group III, 31–40 years old, 43 participants; Group IV, 41–50 years old, 57 participants. The least variable feature of the total body sizes was found to be the body length; the variability index in the age groups did not reveal much of change — from 3.1 to 3.8 (low). The exo- and mesomorphy indicators featured low variability (Cv % — 8.8 and 5.5, respectively). The body weight (Cv % — 12.8 to 24.9), the BMI (Cv % = 22.7) as well as the waist/hip index (Cv % = 10.1) showed an average variability, while the variability value for the endomorphy index (CV%=32.4) proved to exceed the average one. Therefore, the total body measurements, such as the body weight, waist and hip circumference, endo-, exo- and mesomorphy indicators for those aged 18–40 increased significantly to get stable in the IV age group, except for the body length, which changed slightly along with ageing. The body mass index, too, went up until the age of 40 and then stabilized, while the waist/hip index showed a statistically significant increase only within the I and II age groups. Along with the age, the waist/hip index increased, as well as goes up the number of those overweight, obese, and people with the transition and the android body types.

KEYWORDS — age variability, women, physique, somatotype.

INTRODUCTION

The constitution typology of the human body refers to a relevant subject dealing with the current progress of the medical science. At the same time, the anthropological area in terms of research has been developing fast. The subject of study for morphologists now is the somatic type for normal and various pathological conditions. The somatic type, which is shaped through the heredity program within a specific environment, reflects the level and the harmony of physical development, both for the individual and the population taken as a whole [11–16].

Currently, anthropometric methods are widely employed in preventive medicine, which is done both to identify the risk groups and to assess the effectiveness of preventive measures [8, 9]. By the age of 18–20, people mostly stop growing, and until the age of 30 the length of the body reveals only a slight increase (up to 0.5 cm per year), which is largely due to the spine lengthening. At the age of 30–50, the body length remains constant, and then it decreases gradually (by about 1 cm over 10 years) [4], which mainly happens through the spine shortening because of its increased bending, reduced elasticity and flattening of the intervertebral discs, as well as due to emerging osteoporosis [9]. Since the growth of the human body individual parts is uneven, the body proportions change over time. The body weight is one of the most important indicators of the physical development, and it depends on the age, the body morpho-functional features, and allows making some indirect judgment concerning the health status. The body mass index (BMI) is calculated as the ratio of the body weight (kg) to the body length (m²): BMI = body weight (kg) / body length (m²). The BMI allows an objective assessment of the individual's nutrition status, and is an important indicator when it comes to evaluating the risk of developing certain diseases associated with the body weight [1, 2, 3].

The waist circumference is a reliable indicator of excess fat accumulated in the abdominal area (abdominal fat). In females, the waist circumference exceeding 88 cm is a risk factor signaling potential development and progression of CAD and type II diabetes. The waist-to-hip (W/H index) is a simple indicator of the fat distribution pattern [6, 7]. Obesity, especially

abdominal, is a risk factor behind diabetes and cardiovascular diseases [10]. An increase in the W/H index is of a protective effect that it has on the bone tissue, and is a factor in osteoporosis development [3].

Based on the somatic status analysis involving healthy people, a classification of somatotypes has been proposed, the basis of that being the ratio of the human body tissues developing from three primitive tissue layers – endo-, meso- and ectoderm. The endomorphic type can be described as featuring predominance of organs that develop based on the inner layer (internal organs and adipose tissue). The mesomorphic somatotype features the predominance of derivatives coming from the mid-layer, which is the basis for the skeleton and muscles. The ectomorphic type reveals the predominance of the outer leaf, from which the nervous system and integument develop [5].

Aim of study:

to identify the physique and somatotype variability patterns for females aged 18-50 residing in the Saratov Region.

MATERIALS AND METHODS

The study included women aged 18-50 (n=178) residing in the Saratov Region, who underwent bioimpedance diagnostics at the Center for Medical Prevention (City of Engels, Russia). The participants were divided into groups: Group I, 18–20 years old, 37 participants; Group II, 21–30 years old, 41 participants; Group III, 31–40 years old, 43 participants; Group IV, 41–50 years old, 57 participants [4]. The methods used included anthropo- and bioimpedanceometry [7]. The following indices were identified: age (A, years), body length (BL, cm), body weight (BW, kg), waist circumference (W, cm), hip circumference (H, cm), body mass index (BMI), waist-to-hip ratio (W/H), endo- (viscerotonia), ecto- (cerebrotonia) and mesomorphy (somatonia) indices.

The variation and statistical processing of the outcomes was performed using the Statistica 10.0 application software package. The distribution normality was checked using the Shapiro-Wilk test. Given that the groups differed in the number of participants, as well as due to the fact that the distribution of features does not always follow the normal distribution pattern, the median (Me), 25 and 75% percentiles were identified [25.0 75.0]. The statistical significance of differences was calculated through the Mann-Whitney test. The differences were considered statistically significant at 95 and 99% probability limits. Besides, correlation analysis was applied, where correlations were considered strong (tight) at $r > 0.75$; significant — at r ranging from 0.5 to 0.75; average — at r falling within the

range of 0.25 to 0.49; weak — at $r < 0.25$; the variation and extensiveness coefficients were identified.

RESULTS AND DISCUSSION

The body length of adolescent females (Group I) featured on average of 163.5 cm; in Groups II and III it was slightly more (by 0.9 and 0.7%, respectively); in Group IV — less by 1.4% compared to Group III (the differences in adjacent groups were statistically insignificant, $p > 0.05$). The body weight showed a statistically significant increase ($p < 0.01$) changing from 55.0 kg in Group I by 11.0% in Group II and 15.7% in Group III, and basically revealed no change in Group IV if matched against Group III ($p = 0.4$). The BMI also went up every 10 years — starting from 20.6 in the youth group, and going up 9.6; 15.5 and 2.9%; the differences between Groups I and II, II and III proved statistically significant ($p < 0.05$), while between Groups III and IV they were insignificant ($p = 0.4$). In case of the adolescent period, the majority of the females (81.5%) had BMI values within the normal range; 14.8% of the cases had weight deficit, while 3.7% proved overweight; in Group II the share of those with the body mass deficit persisted; the number of females with normal index values decreased, while the number of those overweight increased; in Groups I and II no obese cases were observed.

The group of those aged 31–40 featured an equal distribution of females with normal BMI values and those who were overweight (37.2%); the number of participants with a body mass deficit went down significantly, and then there appeared participants with obesity (Degree I and II; 11.6%). The group of females aged 41–50 had no persons with a body mass deficit; one third of the group had a normal body weight, 38.9% were overweight, as well as there were patients with obesity of Degree I — 18.5%; II — 5.6%, III — 3.7%. The results obtained were partially compared with the outcomes of the study conducted by N.N. Tyatenkova et al. (2018) involving residents of the Yaroslavl Region, while that study, too, relied on the age-based periodization of 10 years. The BW in the group of females aged 20–29 was 61.2 kg (according to our data — 61.8 in females aged 21–30); in those aged 30–39 the BW was 67.9 kg (73.3 kg), while 40–49-year-old participants had a BW of 72.0 kg (73.1 kg) (see Table 1).

The waist circumference increased up to the age of 40, changing from 63.4 cm in the youth group to 80.0 cm (the inter-group differences were statistically significant ($p < 0.001$) and goes on increasing slightly in Group IV. The differences, though, do not come to be statistically significant ($p = 0.6$). The hip circumference also increases by the age of 30 years (+3.5%;

Table 1. Age-related anthropometric and bioimpedance variability in females aged 18–50

Index	Age groups			
	I	II	III	IV
A (yrs)	18.8 [18.0 19.0] *	25.6 [23.0 29.0] *	35.7 [33.0 38.0] **	46.9 [45.0 49.0] ***
BL (cm)	163.5 [160.0 167.0]	164.9 [160.0 168.0]	164.6 [161.0 169.0]	162.3 [157.0 167.0]
BW (kg)	55.0 [48.1 61.9] *	61.8 [53.2 67.1] *	73.3 [59.2 80.1] **	73.1 [63.0 81.0]
BMI	20.6 [18.7 22.4] *	22.8 [19.5 24.4] *	27.0 [22.5 29.8] **	27.8 [24.2 31.1]
W (cm)	63.4 [60.0 66.0] *	71.5 [65.0 75.0] *	80.0 [70.0 88.0] **	81.3 [73.0 87.0]
H (cm)	91.4 [87.0 96.0] *	94.7 [90.0 99.0] *	103.3 [96.0 107.0] **	103.2 [98.0 110.0]
W/H	0.69 [0.67 0.73] *	0.75 [0.71 0.79] *	0.77 [0.71 0.83]	0.79 [0.73 0.82]
Endo-	1.07 [0.55 1.49] *	1.61 [0.90 1.88] *	2.45 [1.40 3.03] **	2.61 [1.74 3.45]
Exo-	6.21 [5.85 6.58] *	6.52 [6.25 6.70] *	6.86 [5.35 7.32] **	6.78 [6.31 7.17]
Meso-	4.29 [4.21 4.42] *	4.42 [4.31 4.53] *	4.62 [4.38 4.71] **	4.58 [4.42 4.70]

Note. * — statistically significant age-related differences among the groups (* — between Groups I and II, ** — II and III, *** — III and IV).

$p=0.05$), and then within the next 10 years — by 8.3% ($p=0.001$), whereas in Group IV it reveals basically no change ($p=0.9$). The W/H index is one of the most reliable indicators of females' health and fertility, as well as it is the aesthetic optimum, which is a reliably indicating of the reproductive status and reproductive capacity. Given the effect of estrogen, fat accumulation in the abdomen is suppressed, while it is stimulated (gynoid fat) at the thighs and buttocks, serving an energy reserve for pregnancy and subsequent lactation. Depending on this index value, there are three types of physique to be identified. At the W/H index <0.8 , the body type is considered gynoid; >0.9 — android, while it is transition type if the index falls between 0.8 and 0.9. The W/H index has a statistically significant increase ($p=0.001$) from 0.69 in Group I to 0.75 in Group II, and continues to grow up to Group IV. However, the differences are statistically insignificant ($p>0.05$). In adolescence, all the girls had the gynoid body type; the females aged 21–30, too, mostly belonged to the gynoid type (78.0%); 19.5% of the participants had the transition type of the body, while in some cases (2.5%) the body type could be described as android. The females above 30, showed a decrease in the gynoid body type share along with an increase in the number of those with the transition and android types. The endomorphy index had an average statistically significant increase from 1.07 in Group I to 1.61 (by 33.5%, $p=0.01$) in Group II, to 2.45 (by 34.3%, $p=0.003$) in Group III, while there were no statistically significant differences between Groups III and IV ($p=0.6$) observed. The intergroup differences in the exo- and mesomorphy indicators in Groups I-III were also statistically significant ($p<0.05$), and these indicators were to get stable in Group IV ($p>0.05$). If

we accept the endomorphy index in the age groups as 1.0, then the ratio of the endo-, ecto- and mesomorphy components will be respectively as follows: 1.0:5.8:4.0; 1.0:4.0:2.7; 1.0:2.8:1.8; 1.0:2.6:1.7. It is obvious that the relative values of the exo- and mesomorphy decrease along with age.

Over age, females undergo change not only in the total body dimensions and somatotype indicators, yet also in the number and strength of the correlations between the parameters. In Group I, there was no significant correlation of the W/H index with the BMI and the indicators of endo-, exo- and mesomorphy identified ($p>0.05$); significant correlation was to be observed between the BMI and the indicators of exo- and mesomorphy, as well as between the indicator of endomorphy and the indicators of exo- and mesomorphy. Following every 10 years, the strength of direct correlation increased; in the general sampling, the correlations are overall stronger when compared among the groups. Of the overall body dimensions, the least variable feature was body length — the variability coefficient through the age groups varied little (from 3.1 to 3.8; low). Exo- and mesomorphy indicators had low variability (Cv% being 8.8 and 5.5, respectively). The BW (Cv% from 12.8 to 24.9), the BMI (Cv%=22.7), the W/H index (Cv%=10.1) revealed average variability, while the variability coefficient in the endomorphy index exceeded the average value (Cv%=32.4).

CONCLUSION

The total body dimensions, such as the BW, the waist and hip circumference, the endo-, exo- and mesomorphy indicators increase significantly through the age period of 18 to 40 to get stable in Group IV, except for the BL, which changed slightly with the age (there

were no statistically significant differences identified in the groups). The BMI increased, too, until the age of 40, and then stabilized, while the W/H index showed a statistically significant increase only between Groups I and II, and then also went on increasing, yet the differences did not reach statistical significance. Over age, following an increase in the BMI, the W/H index increased, so the number of people with excessive BW, obesity, as well as the number of those belonging to the intermediate and android body types, increased.

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MORPHO-TOPOMETRIC VARIABILITY OF ANATOMICAL STRUCTURES IN THORACIC SPINE

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ABSTRACT — We studied the size-related features (body height, intervertebral discs, horizontal and vertical diameters of intervertebral foramina) on CT-grams of the thoracic spine in people whose age belongs to the first adulthood period (60 men aged 22–35 and 65 females aged 21–35) with no signs of the spine disease or any systemic and traumatic lesions. We have identified topographical variability, gender dimorphism as well as the interconnection of the parameters under study.

KEYWORDS — thoracic spine, vertebrae body, intervertebral discs, intervertebral foramen.

INTRODUCTION

Modern medical science can be described by rapid progress and clinical implementation of highly reliable advanced technological diagnostic methods, which feature their possible use in studying the normal anatomy and structure variability in human organs and systems [12–15].

The thoracic region is the longest part of the vertebral column and is relatively stable compared to the cervical and lumbar regions [1,2,5]. The typical thoracic vertebrae — from II to X (Th_{II}–Th_X) — join the ribs through combined costal-vertebral joints, while the rib head joint is complex (the rib head articulates with two adjacent vertebrae); the first vertebra (Th_I) articulates with the first atypical rib through two simple joints, and the XI and XII vertebrae (Th_{XI}–Th_{XII}) articulate with the respective oscillating ribs with simple non-combined joints. Given that, the thoracic vertebrae, the ribs, and the sternum make up a

relatively mobile, yet a strong structure. Besides, the articular processes that form facet joints are oriented within the frontal plane; the intervertebral discs are of low height, whereas the long spinous processes are tilted and overlap similar to tiles on the roof, which also reduces the thoracic spine mobility [4].

Adjacent vertebrae notches and the intervertebral disc limit the intervertebral foramen, which makes a passage for the spinal nerves and veins to exit, and for the segmental arteries to enter. Specific features of the thoracic vertebral bodies anatomy ensure the thoracic kyphosis [2]. The thoracic part is mainly involved in lateral (mostly lower-thoracic) and rotational (specifically upper-thoracic) movements [8]. When the spine is bent, it is only the thoracic part that bends, while the cervical and the lumbar parts straighten up; in case of extension, on the contrary, the cervical and the lumbar parts unbend, while the thoracic part straightens up [3, 7]. Compared to other parts of the column, the thoracic part gets affected less often, while it takes a larger factor to traumatize it [4].

Respective literature offers basically no detail on complex investigation into the laws of topographic, gender-related and individual-typological variability, as well as on the nature of the relationships and the ratio of the shape and the morpho-topometric features of the thoracic spine anatomical structures. The variability of the morpho-topometric patterns in the thoracic spine structure due to its complex kinematics and biomechanical properties is an urgent issue faced nowadays by functional anatomy, neurovertebrology, orthopedics and forensic studies [6,10]. These data are of important theoretical and applied value in practical health care in terms of diagnosing and correcting the thoracic spine lesions [9, 11].

Aim of the Study:

to identify the variability patterns of morpho-topometric features in the thoracic spine anatomical structures through the first adulthood period.

MATERIALS AND METHODS

We studied thoracic spine CT-grams obtained from people in their first adulthood period (60 men aged 22–35 and 65 females aged 21–35) who featured no sign of any spine disease, systemic or traumatic le-

sion, as well as we identified the size-related specifics of the thoracic spine anatomical features — the vertebrae body height, the intervertebral discs, as well as the horizontal and vertical diameters of the right intervertebral foramen.

The variation-statistical processing of the outcomes was done using descriptive statistics on the Statistica 10.0 platform; the median (Me), the upper and lower quartiles [25.0; 75.0%], as well as the variation coefficient (Cv%) were identified. At $Cv% < 10\%$, the samples were slightly variable; at $Cv%$ from 10 to 20% they revealed average variability, and at $Cv% > 20\%$ the variability was strong. To identify the link between the studied parameters, a correlation analysis (Pearson's criterion) was employed; the correlation was considered weak at $r < 0.25$; average — at r ranging from 0.25 to 0.5; significant — in case of r falling within 0.5 to 0.75, and strong — at $r > 0.75$. The normality test was performed using the Shapiro-Wilk test. The differences in the variables were considered statistically significant at $p < 0.05$; 0.01; 0.001 (Mann-Whitney test).

RESULTS

The height of the thoracic vertebrae bodies increases gradually towards the cervical-lumbar region from 13.7 mm [12.4; 15.2] to 22.2 mm [21.1; 23.1] in females (a significant relative increase was noted distal of vertebra Th_{VIII}) and from 16.5 mm [14.8; 18.0] at the Th_I level to 25.2 mm [23.5; 26.6] at the Th_{XII} level in men (the maximum relative increase was noted below the Th_X level). The gender-related differences, which are manifested in the predominance of the trait in males, are statistically significant at all levels of the thoracic spine with a 99% probability threshold ($p < 0.01$). In the female group, the trait variability is average, Cv% being within the range of 10.5 to 13.4%. In the male group, the variability of the vertebrae body height at the level of Th_I–Th_{VIII} is average (Cv% ranging from 10.0 to 13.5%), and distal of that, the variability is below average (Cv% varies from 8.9 to 9.5%).

The height of the thoracic spine intervertebral discs in females increases from disc Th_{I-II} to the thoraco-lumbar junction level (Th_{XI-XII}) from 4.1 mm [3.6; 5.0] to 6.5 mm [5.6; 7.1]; in males the disc height goes up from 4.6 mm [4.0; 5.2] in Th_{I-II} to 4.8 mm [3.9; 5.1] in Th_{II-III}, then decreases to the thoracic kyphosis apex level and ranges at the level from Th_{III-IV} to Th_{VII-VIII} between 4.3–4.6 mm, and distal of that it goes again up to 6.8 mm [5.9; 7.5] at the level of Th_{XI-XII}. The gender-related differences are statistically significant at all levels of the thoracic spine; at the levels of discs I-II–IV-V and I X-X-XI-XII, the parameter prevails in males, while at level of discs V-VI-VIII-IX — in females

($p < 0.01$). The trait variability is average and above average (Cv%, from 18.7 to 22.9%).

The vertical diameter of the I-II intervertebral foramen in females is 10.3 mm [9.2; 11.6], which decreases to 9.9 mm [8.8; 11.5] by foramina II-III, and then gradually goes up to 14.8 mm [13.1; 16.2] at the level of foramina XI-XII; in males, the foramen diameter decreases as well from 11.3 mm [10.3; 12.3] at foramina I-II to 10.6 mm [10.0; 11.5] at the II-III, and then gradually increases to 15.4 mm [13.4; 16.8]; the maximum relative increase is to be observed at the level of foramina X-XI and XI-XII, both in females and in males. Males have a slightly larger vertical foramen diameter than females, yet the differences do not reach statistical significance ($p > 0.05$). The trait variability is average both in females and in males (Cv% varies from 11.8 to 20.0%).

The horizontal diameter of the I-II intervertebral foramina in females is 5.9 mm [5.2; 6.7], in males — 5.5 mm [4.9; 6.4]; by foramina II-III, the parameter decreases down to 5.6 mm [5.0; 6.3] and to 5.3 mm [5.0; 6.3], to vary from 5.2 to 6.1 mm and from 5.1 to 5.6 mm in the respective gender groups; at the level of XI-XII, the foramina increases significantly to 6.8 mm [5.5; 7.6] in females and to 6.7 mm [5.2; 7.5] in males. In the female group, this parameter is somewhat prevalent compared to the male group, yet the differences do not come up to statistical significance ($p > 0.05$). The trait variability up to the level of foramina IX-X is average (Cv% ranges from 13.1 to 20.0%), while at the level of the last two thoracic intervertebral foramina, the variability goes beyond average (Cv% ranging from 22.0 to 25.6%).

A correlation analysis revealed no significant correlation between the height of the bodies and the height of the intervertebral discs in females; in males, the relationship between the height of the disc and the height of adjacent vertebrae does not exceed the inverse average correlation (r within the range of -0.4 to -0.5). There were significant direct connections detected between the height of the vertebral bodies and the vertical diameter of the intervertebral foramen below the level of the thoracic kyphosis apex (r ranging from 0.5 to 0.7).

CONCLUSION

In view of the above, the size-related features, the variability and the connections of anatomical parts of the thoracic spine have been analyzed here. The height of the vertebral bodies gradually increases towards the lumbar region; this feature increases through the thoracic spine — 1.6 times (by 38.3%) in females and 1.5 times (by 34.5%) in males. The height of the intervertebral discs, too, increases in females 1.6 times

(by 36.9%); in males the height of the discs decreases at the level of the thoracic kyphosis apex in relation to the upper (1.1 times, by 6.5%) and lower (1.6 times, by 36.8%) thoracic vertebrae. The vertical diameter of the intervertebral foramina first decreases 1.04 times (by 3.9%) from I-II to II-III in females and 1.07 times (by 6.2%) in males, then increases towards the lumbar region 1.6 times (by 33.1%) in females and 1.5 times (by 31.2%) in males. The foramina horizontal diameter varies up to the X-XI level falling within the range of 5.2–6.1 mm for females and 5.1–5.6 mm for males, and increases at foramina XI-XII level up to 6.8 mm for females and 6.7 mm for males. The gender differences reveal a statistically significant predominance of the vertebra height and the intervertebral disc in males; the foramen vertical diameter also prevails in males, while the horizontal diameter was found to be prevailing in females; however, the differences do not reach statistical significance. The studied parameters mostly feature average variability.

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CLINICAL ASPECTS OF AGE-RELATED SPHENOID BONE STRUCTURE VARIABILITY IN CHILDREN

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ABSTRACT — Aim of our study was to identify the morphometric variability of the parameters pertaining to the sphenoid bone body structures in children of different ages, in order to improve access to the skull internal base as well as to the adjacent structures during endoscopic interventions. The craniometry method was used to study 87 child skulls, age 1–21, without regard to gender (65 skulls from the fundamental Museum of the Department of Anatomy, the Saratov State Medical University, and 22 skulls from the Department of Normal Anatomy, Military Medical Academy (Saint Petersburg), broken into 6 age periods. The length of the sphenoidal yoke, as well as its width along with the front and back edges, and the length and width of the prechiasmatic sulcus, tuberculum sellae, its width and height, and the length and width of the sella turcica were identified.

The results of the study has revealed that most of the examined structures feature stable values until the age of 7 years (linear parameters of the sphenoidal yoke, the width of the prechiasmatic sulcus, the length and width of the saddle tubercle); these anatomical formations show intensive growth only at the age of 8–12. The height of the tuberculum sellae changes at the age of 4–7, reaching the final value; the length of the prechiasmatic sulcus grows at the ages of 4–7 and 13–16 and does not change in adolescence. The width of the Turkish saddle increases at the ages of 4–7 and 13–16; its length features the same values by the age of 12, increasing only within the period of 13–16, reaching stable values in adolescence.

KEYWORDS — sphenoidal yoke, prechiasmatic sulcus, tuberculum sellae, sella turcica, endoscopic interventions.

INTRODUCTION

The recent decades have witnessed much interest taken in the clinical anatomy of the head, which is based on morphometric studies of the skull deep structures [2–6, 10, 15, 17, 19, 23–26] employed in clinical practice to develop better access to hard-to-reach structures of the brain and neurovascular structures to be found at the skull base [7, 22]. Endoscopic endonasal approaches to the skull internal base in children with craniopharyngiomas, pituitary adenomas, and congenital encephalocele have already been proven to be highly effective and safe as treatment methods [12–14, 20]. The area of the sella turcica, which is located in the center of the skull base, is a relatively small anatomical structure that includes functionally meaningful neurovascular and endocrine formations. The complexity of this area, the depth of its location in the human skull, the availability of a single anatomical passage to it (transnasal-transsphenoidal) point at the value of studying its morphotopometric features and the adjacent structures of the internal cranial base through each period of childhood in order to develop the minimum invasive approaches to tumors and other pathologies occurring in this anatomical region [11]. The respective literature offers fairly sufficient anatomical data of the sphenoid bone in adults and only some works describe the variability of the sella turcica in childhood [8, 9, 18, 21]. Given the lack of knowledge regarding this issue in children, it appears relevant to study the anatomical age variability of the sphenoid bone structures within different childhood periods, which will serve the basis for planning and developing proper surgical access to the deep structures of the skull base in children [14].

Aim of study:

to identify the morphometric variability of the parameters pertaining to the sphenoid bone body structures in children of different ages, in order to improve access to the skull internal base as well as to the adjacent structures during endoscopic interventions.

MATERIALS AND METHODS

The object of study included 87 child skulls (age — 1 through 21, with no regard to gender; 65 skulls from the fundamental Museum of the Department of

Anatomy, the Saratov State Medical University, and 22 skulls from the Department of Normal Anatomy, Military Medical Academy (Saint Petersburg)), broken into 6 age periods. The entire material was divided into 6 age groups following the conventional age classification approved at the VII All-Union Congress of Anatomists, Histologists and Embryologists (1965): Period I — infancy (1–1.5 years old); Period II — early childhood (2–3 years old); Period III — first childhood (4–7 years old); Period IV — second childhood (8–12 years old); Period V — adolescence (13–16 years old); Period VI — youth (17–21 years old). Craniometry was performed subject to the method generally accepted in craniology: with a technical caliper and a metal ruler with a division step of 0.01 mm [1].

The anatomical material was used to study the following parameters of the middle cranial fossa: the sphenoidal yoke length (SYL) — the distance between the elevation front and rear points located in the sagittal plane; the width of its front edge (FEW) — the distance between the front side points of the elevation and width of its rear edge (REW) — the distance between the rear side points of the elevation in the frontal plane; the prechiasmatic sulcus length (PSL) — the distance between the front and rear edges in the sagittal plane and its width (PSW) — the distance between the medial points of the visual channels; the length of the saddle tubercle (STL) — the distance between the two most distant points of the tubercle in the sagittal plane, its width (STW) — the distance between the most distant points of the tubercle in the frontal plane and the height (STH) — the perpendicular from a line passing through the most prominent point of the tubercle to the bottom of the sella turcica; length of the sella turcica (LTS) — the distance from the front and rear of the remotest points of the saddle in the sagittal plane and its width (TSW) — the distance between the lateral points of the carotid groove in the frontal plane. The obtained data was processed employing the STATISTICA 7.0 application software package and the Excel MO table editor. The major variational and statistical features were identified: the arithmetic mean, the mean square deviation, the variation coefficient, the average sampling error, as well as the relative growth rate of the average values of indicators through the transition from one age group to another (%). Since the distribution in the sample did not differ from normal, parametric confidence criteria (Student's criterion) were used to assess the reliability of the differences between the data series. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The length of the sphenoidal yoke at the age of 1–1.5 is 8.8 ± 0.5 mm, keeping the values through the age of 2–7 within the range of 8.8–9.8 mm. At the age of 8–12, the length increases by 1.7 mm (10.6 ± 0.4 mm; $p < 0.05$), and at 13–16 — by 2.9 mm, compared to the age of 2–3; the relative increase over the indicated age periods was 19.1% and 32.6%, respectively. At the age of 17–21, the parameter values were stable. Over the period from 1–1.5 through 17–21, the length of the sphenoid platform went up 1.2 times.

The width of the sphenoid yoke along the front edge at the age of 1–1.5 is 10.8 ± 0.6 mm and does not change through the age period of 2 to 7 years revealing fluctuations in the values from 10.2 to 10.7 mm. At the age of 8–12, the area expands by 2.0 mm (12.7 ± 0.8 mm; $p < 0.05$) with a relative increase of 18.7%, maintaining stable values with minor fluctuations in older ages (12.3–13.4 mm). Within the period of 1–1.5 to 17–21, the width of the elevation in the front increased 1.2 times.

The width of the sphenoid yoke along the posterior edge at the age of 1–1.5 is 14.2 ± 0.7 mm, retaining the values through the age of 2 to 7 within the range of 14.0–14.8 mm. At the age of 8–12, the site expands by 2.1 mm (16.9 ± 0.5 mm; $p < 0.05$), whereas the relative increase is 14.2%. At 13–16 and 17–21 years, the values remain stable and fluctuate from 15.6 mm to 17.9 mm. For the age period of 1–1.5 through 17–21, the width of the yoke at the posterior part increased 1.1 times.

The length of the prechiasmatic sulcus at the age of 1–1.5 is 3.0 ± 0.2 mm. At the age of 4–7, there is an increase of 0.7 mm (3.7 ± 0.2 mm; $p < 0.05$) and then, at 13–16 — an increase by 0.6 mm (4.3 ± 0.1 mm; $p < 0.05$), while the relative increase over these age periods is 19.4% and 16.2%, respectively. After the age of 16, the values remain stable. For the age period of 1–1.5 through 17–21, the width of the visual intersection increased 1.5 times.

The width of the sulcus at the age of 1–1.5 years is 16.5 ± 0.8 mm, and it features no change through the period of 2 to 7, the values remaining at 16.8 mm. At the age of 8–12, the length increases significantly by 1.7 mm (18.5 ± 0.4 mm; $p < 0.05$), and at age of 13–16 — by another 2.0 mm (20.5 ± 0.5 mm; $p < 0.05$) with a relative increase of 10.1 and 10.8% over the indicated age periods. After the age of 16, the values remain stable. Over the age period of 1–1.5 to 17–21, the length of the chiasma opticum increased by 1.2 times.

At the age of 1–1.5 the length of tuberculum sellae is 3.0 ± 0.2 mm; within the period of 2 to 7, it increases slowly with 3.3–3.4 mm fluctuations in the

values. At the age of 8–12, it expands significantly — by 0.6 mm (4.0 ± 0.2 mm; $p < 0.05$); the relative increase was 17.6%. At the age of 13–16, the parameter is stable. At 17–21, there is an increase in the average width by 0.5 mm with a relative increase of 12.5% (4.5 ± 0.3 mm; $p > 0.05$), which, however, is not reliable. For the period from 1–1.5 to 17–21, the width of the sella turcica revealed a 1.5-times increase.

The width of the sella turcica at the age of 1–1.5 features values of 12.7 ± 0.7 mm, and from 2 to 7 it retains the values of 12.8–13.1 mm. At the age of 8–12, the length shows a significant increase by 1.0 mm (14.1 ± 0.3 mm; $p < 0.05$) with a relative increase of 7.6%, and reaches stable values in the said age period. During the period from 1–1.5 to 17–21, the length of tuberculum sellae increased by 1.1 times.

The height of sella turcica at the age of 1–1.5 has a value of 5.4 ± 0.4 mm. At the age of 4–7, it goes up significantly by 1.0 mm (6.6 ± 0.2 mm; $p < 0.05$) with a relative increase of 17.9%, the values were stable within the following age groups (6.0–6.8 mm). Within the age period between 1–1.5 and 17–21, the height of sella turcica increased by 1.3 times.

The length of sella turcica at the age of 1–1.5 is 7.6 ± 0.4 mm. Within the age range of 2 to 12, the values vary slightly between 7.5–8.2 mm. At 13–16, the length increases by 0.8 mm (9.2 ± 0.3 mm; $p < 0.05$) compared to the period of 8–12 years and the relative increase is 15.0%. At the period of 17–21, the sella turcica continues to grow by 0.7 mm with a slight relative increase of 7.6% (9.9 ± 0.5 mm; $p > 0.05$), yet this is not reliable. Within the period from 1–1.5 to 17–21, the length of sella turcica increased by 1.3 times.

The width of the sella turcica at the age of 1–1.5 years is 15.2 ± 0.9 mm. With the age of 4–7 it increases by 1.3 mm (17.5 ± 0.4 mm; $p < 0.05$), and at 13–16 — by another 2.4 mm (19.9 ± 0.4 mm; $p < 0.05$), the relative increase over these age periods being 8.0% and 11.8%. After the age of 16, the values remain stable. For the period between 1–1.5 and 17–21, the width of the sella turcica increased by 1.3 times.

The study outcomes show that at the age of 1.5, the width of the sella turcica prevails over its length by 2 times. In further age groups, the linear dimensions gradually increase until the age of 16, maintaining a similar ratio. The literature also describes the predominance of the sagittal size of the sella turcica over its vertical size, starting from the newborn period up until the age of 16, while the mismatch in the size features does not allow making a comparative analysis [16]. According to V. S. Maykova-Stroganova and D. G. Rokhlin (1955) the length of the sella turcica in children aged 4–18 is 10–14 mm, whereas the transverse size is 9–18 mm [16]. Fluctuations in the average

values of the sella turcica parameters that were to be observed on our material are less variable compared to the data mentioned in the respective literature, and range as follows: width — from 15.2 mm to 19.9 mm; length — from 7.6 mm to 9.9 mm, which can be explained by different measurement approaches.

CONCLUSION

In view of the above, most structures of the sphenoid bone body feature stable values up to the age of 7, namely, the linear parameters of the sphenoid yoke like the width of the prechiasmatic sulcus, the length and width of sella turcica. Growth of these anatomical formations occurs only at the age of 8–12, while the values remain stable in older age groups. At the same time, the height of the sella turcica changes within the age of 4–7, reaching the final value in the same age group, whereas the prechiasmatic sulcus length increases at the age period of 4–7 and 13–16, remaining stable in adolescence. The width of the sella turcica increases at the age period of 4–7 and 13–16, while its length does not feature much of age-related change, and retains the same values up until the age of 12, increasing only within the age period of 13–16. The sella turcica parameters reach stable values by adolescence.

The obtained data can be useful for practitioners who perform surgeries on the skull basis in children. The choice of the surgical access and the diameter of tools instruments will depend on the knowledge regarding age-related variability in the size features of anatomical formations in the area of sella turcica in children.

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ANALYSIS OF AGE-RELATED CHANGES IN THE CORTICAL THICKNESS OF THE HUMAN CEREBRAL AND CEREBELLAR CORTEX IN AREAS ASSOCIATED WITH FACE RECOGNITION

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ABSTRACT — AIMS. Perception and recognition of faces is supported by a network of nerve centers in the human brain that have different maturation periods in postnatal ontogenesis. In this article, we analyze the relationship between changes in the thickness of the cortex in facial recognition centers in children from birth to 12 years old. **METHODS.** Histological material was obtained from the left cerebral hemispheres and bilaterally from the cerebellum of 62 boys who died from injuries without brain damage. The material was grouped at annual intervals. Measurements of the cortical thickness were carried out in field 37a in the fusiform face area on the medial surface of the occipital lobe, in field 10 on the lateral surface of the frontal pole, as well as in the lateral right and left parts of the posterior quadrangular lobule (H VI) of cerebellum. Morphometry was performed on virtual images of sagittal paraffin sections, stained with Nissl cresyl violet. The mean, standard error and confidence interval were calculated for the indicators of different age groups.

RESULTS. The most significant increase in cortical thickness in fields 37a and 10 occurs during the first year of life, at 2–3 and 6 years. Increases in cortical thickness in the lobule H VI of the on the right cerebellum are observed at 1, 2, and 7 years, on the left during the first two years of life. Evaluation of the relationship between age-related changes in cortical thickness using Spearman's rank correlation analysis showed that the strongest, direct and significant two-way relationship is between the indicators in the pairs field 37a & field 10 and field 10 & H VI on the right, a moderate significant relationship in the pair field 37a & H VI on the left.

CONCLUSIONS. It is assumed that age-related changes in the cortical thickness in the centers of face recognition and their relationship reflect the stages of the formation of the facial processing in children.

KEYWORDS — cerebral cortex, cerebellar cortex, cortical thickness, facial recognition centers, children, postnatal ontogenesis.

INTRODUCTION

Recognizing facial features, understanding and interpreting facial expressions allows you to obtain a large amount of socially significant information. This function is gradually formed in children until adolescence [5]. The analysis of invariant facial features associated with facial identity is supported by a network of nerve centers, among which several areas of the cerebral cortex and cerebellum play a particularly important role [6].

Postnatal changes in the cortical thickness make it possible to trace the rates and timing of structural transformations of the cortical centers involved in face recognition. The most interesting is the fusiform face area (FFA), damage to which can cause prosopagnosia (face recognition impairment) [9]. The dorsolateral prefrontal cortex is involved in cognitive operations related to the renewal of working memory, recognition and storage of facial features [8]. The oculomotor area of the cerebellar cortex in the region of the posterior quadrangular lobule (H VI) is also included in the facial recognition neural network [1, 10]. In the system of neural networks that carry out face processing, specialized cortical centers of different levels functionally interact due to the variety of anatomical connections.

It was important to understand how the changes are interconnected in the cortical thickness in different centers of face recognition in the process of age development in children. The aim of this work was to study quantitative changes in cortical thickness in the areas of the brain and cerebellum involved in facial processing in children of different ages and to assess the closeness of the relationship between these changes.

METHODS

The material consisted of the left cerebral hemispheres and cerebellum of boys aged from birth to 12 years (62 cases) who died from injuries without brain damage. The collection of sectional material was authorized by the ethical commission of the Institute of Developmental Physiology of the Russian Academy of Education.

The brain was fixed in 10% neutral formalin. Fragments of tissue were excised in field 37a of the

lateral occipitotemporal gyrus, where the fusiform face area is located [4], and also in field 10 of the prefrontal cortex on the inferolateral surface of the frontal lobe. The cerebellar cortex was examined in the posterior quadrangular lobule on the right (HVI_R) and left (HVI_L) in the lateral regions of the hemisphere of cerebellum. The histological material was grouped at annual intervals.

Cortical thickness was measured on sagittal paraffin sections stained with Nissl cresyl violet using programs Image Tools (NIH, USA) and Image-Expert™ Gauge (NEXSYS, Russia). The number of measurements for each section was at least 10, for each preparation at least 40, for each age at least 120. Statistical analysis of the obtained quantitative data was performed using the SigmaPlot software package (SYSTAT Software, USA). For indicators of different age groups, we calculated the mean, standard error and confidence interval, while checking compliance with the normal distribution of values in the compared samples, analyzed the probability distribution of quantitative data [7]. We also determined the significance of differences between the average values of different age groups using a two-sample t-criterion (Student's t-test) at $P \geq 95\%$ ($p < 0.05$).

To evaluate the relationship between age-related changes in cortical thickness in the compared cortical zones, we calculated Spearman's rank correlation coefficient (Rs) and its statistical significance using the Student's table of critical values.

RESULTS

By the time of birth, the cortical thickness in field 37a in the fusiform face area averaged $1477 \pm 28 \mu\text{m}$, in field 10 of the prefrontal cortex $1611 \pm 82 \mu\text{m}$. In newborns, there were no statistically significant differences in the mean group parameters of cortical thickness between field 37a and field 10 of the neocortex in the left hemisphere. In the cerebellum of newborns, the cortical thickness averaged $295 \pm 11 \mu\text{m}$ in the posterior quadrangular lobule on the right (HVIR), and $244 \pm 11 \mu\text{m}$ in the same lobule on the left (HVIL). The cortical thickness in the posterior quadrangular lobule on the right was significantly greater than on the left ($p < 0,01$).

During the first year of life, cortical growth in thickness in the studied cortical zones occurred with different intensities. By 12 months, in the 37a field the cortical thickness increased by 1.6 times, in the 10 field — 1.2 times, in HVI_R — 1.3 times, in HVI_L — 2.4 times compared to newborns. In children over 1-year-old, the cortical thickness increased by 1.7 times in 37a field at age 3 years and 1.8 times by 6 years compared to newborns. In the field 10, the cortical thickness

increased 1.4 times by 2 years, and 1.5 times by 6 years. At the HVI_R area the cortical thickness increased by 2.3 times by 2.3 years, at age 7 years by 2.7 times, and in the HVI_L area at age 2 years by 3.1 times.

The cortical thickness in the neocortex stabilized after 6 years. By the age of 12, the cortical thickness in field 37a averaged $2660 \pm 54 \mu\text{m}$, and in field 10 $2482 \pm 106 \mu\text{m}$. In the cerebellar cortex, the cortical thickness stabilized in the HVI_R after 7 years, and in the HVIL after 2 years. By the age of 12, the cerebellar cortex thickness in HVIR was $781 \pm 43 \mu\text{m}$, and in the HVI_L region, $821 \pm 45 \mu\text{m}$.

We used Spearman's rank correlation analysis to evaluate the relationship between the rate of cortical thickness growth in facial treatment centers in children from birth to 12 years of age. Rs correlation coefficients between mean cortical thicknesses in annual intervals and on a rank scale are shown in the table.

Table. Correlation matrix of age-related changes in the thickness of the cerebral cortex in fields 37a, 10 and in the posterior quadrangular lobule of the cerebellum on the right (HVI_R) and on the left (HVI_L) in children from birth to 12 years

n=13	Field 37a	Field 10	HVIR	HVIL
Field 37a	1,000 (0,00)	0,836** (0,8)	0,682* (0,57)	0,287 (0,75)
Field 10	0,836** (0,8)	1,000 (0,00)	0,88** (0,7)	0,34 (0,74)
HVIR	0,682* (0,57)	0,88** (0,7)	1,000 (0,00)	0,33 (0,74)
HVIL	0,287 (0,75)	0,34 (0,74)	0,33 (0,74)	1,000 (0,00)

Note: n is the number of rank pairs of compared values; the top indicator is the correlation coefficient (Rs); bottom (in brackets) is t-stat (Student's t-test). Two-sided level of significance (p-value): * 0.05; ** 0.001

It follows from the table that there is a strong and direct two-way relationship ($R_s = 0.836$; $p = 0.001$) between age-related changes in the thickness of cerebral cortex in fields 37a and 10. This indicates the conjugate development of two cortical centers in the left cerebral hemisphere including the frontal center, which controls working memory during facial processing, and the occipitotemporal visual center, for recognizing facial features.

The correlation between age-related changes in cortical thickness in field 37a and HVI_R is moderate and direct ($R_s = 0.682$; $p = 0.05$). A weak direct two-way relationship was found between changes in cortical thickness in field 37a and HVIL ($R_s = 0.287$; $p > 0.05$). Obviously, in the process of postnatal development, functional connections between FFA on the left side are maintained with the right lateral part of the oculomotor visual center in the cerebellar cortex. This relationship corresponds to a system of anatomi-

cal projection connections between the cerebral left hemisphere and cerebellum.

There was a strong and direct two-way relationship between changes in cortical thickness in field 10 and in the HVI_R lobule ($R_s = 0.88$; $p = 0.001$). A weak and direct relationship was determined between changes in cortical thickness in field 10 and in the HVI_L lobule ($R_s = 0.34$; $p > 0.05$). This means that the prefrontal field 10 of the left hemisphere, as well as field 37a of the occipital-temporal cortex, is characterized by a closer functional interaction with the visual area of the cerebellar cortex in its contralateral hemisphere in the system of distributed systemic connections in comparison with the homolateral hemisphere.

DISCUSSION

Our study showed that the most significant changes of the cortical thickness in fields 37a and 10 of the cortex in the left cerebral hemisphere, which are involved in facial processing, occur in children during the first year of life, as well as at 2–3 years and 6 years.

Our assessment of the relationship between age-related changes in cortical thickness using Spearman's rank correlation analysis allows us to conclude that the strongest two-way relationship is between the indicators in the pair field 37a of the occipitotemporal cortex & field 10 of the prefrontal cortex. The presence of a functional connection between the dorsolateral prefrontal cortex and the occipitotemporal cortex in face recognition is confirmed by physiological studies [11], which demonstrate their interaction in the implementation of a cognitive operation related to the categorization of visual stimuli during facial processing [2].

The growth of the thickness of cerebellar cortex in the lateral part of the posterior quadrangular lobule (H VI) has different durations on the right and left. The anticipatory cortical growth in the H VI lobule of the left cerebellum from birth to 2 years compared to its right hemisphere is of interest due to the participation of the left oculomotor zone of the cerebellar cortex in the classification of facial emotional expressions, that has been shown in experiments with transcranial magnetic stimulation of the left cerebellum [3]. The longer growth of the cortical thickness in lobule VI of the right cerebellum, which lasts up to 7 years, compared with the left cerebellum, may be due to the close functional interaction of right cerebellum with the left cerebral hemisphere, the role of which in the processing of the face differs from that of the right hemisphere [2].

CONCLUSIONS

We assume that age-related changes in cortical thickness in facial recognition neural networks reflect stages of improvement in facial processing in children

with age. The interaction of cortical facial processing centers occurs in the system of associative connections between the occipitotemporal cortex and the prefrontal cortex, as well as in the system of forward and backward projections between the cerebral cortex and cerebellar cortex.

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MAGNETIC RESONANCE AND ULTRASOUND IMAGING: DO THE LINEAR LIVER MEASUREMENTS DIFFER IN MEN AND WOMEN?

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ABSTRACT — Magnetic resonance and ultrasound measurements of the liver were performed and compared in 58 adult healthy volunteers (26 men и 32 women). The aim of this study was to distinguish differences in linear liver measurements between men and women. Statistically significant gender differences were found in the following liver diameters: anteroposterior diameter of the left lobe, thickness of the caudate lobe, anteroposterior and oblique maximum craniocaudal diameters of the right lobe. In men all these diameters are larger than in women.

KEYWORDS — magnetic resonance imaging, ultrasound imaging, linear measurements of the liver, men and women, gender differences.

INTRODUCTION

Knowledge of the liver size is an important factor in the diagnosis of wide range of pathologies and one of the most significant criteria for determining its condition. Far back as 1983 Dittrich M. et al. [1] informed that evaluation of liver's sizes by palpation and percussion is unreliable and suggested ultrasound morphometry which can be used successfully to determine the liver size as well as to detect partial enlargement of organ. In 2010 Silva R.M. et al. [2] showed that liver measurements obtained by clinical examination correlates well with ultrasound method, but underestimated the actual liver size in adults, which can be demonstrated by the statistically significant difference between the final mean value obtained by clinical observation and that obtained by ultrasound method. A 2013 study of Mouratev et al. [3] demonstrated that medical students with less than two hours training

could obtain liver size measurements using ultrasound that were more accurate and had less variability than physicians with 10 to 20 years of clinical experience) using physical examination, including palpation, percussion and auscultation scratch techniques.

Computed tomography (CT) and magnetic resonance imaging (MRI) are regarded as a gold standard to determine liver size and volume. However, both methods have contraindications and CT/MRI equipment are very expensive and not mobile. Moreover, CT brings the risk of ionising radiation.

Thus, ultrasound (US) is currently considered to be the first tool of visualization technique after clinical suspicion of hepatomegaly [4] due to numerous advantages, including availability of ultrasound devices in most medical institutions, as well as mobile devices; safe (absence of contraindications and the risk of ionising radiation), inexpensive, provides rapid results and the possibility of repeatedly ultrasonography examination for dynamic monitoring.

Body composition differs between men and women [5]. In relation to liver size it depends on several factors: age, sex, body size and shape, as well as the particular examination technique utilized (physical examination versus radiographic) [6]. We were interested if the definite liver measurements differs in men and women.

The aim of this study

is comparing linear liver's measurements in men and women performed by magnetic resonance and ultrasound imaging.

MATERIALS AND METHODS

In 58 adult healthy volunteers (26 men и 32 women) in MRI and US of abdominal organs were carried out linear liver's measurements. In left lobe were measured: craniocaudal diameter (CC, length), anteroposterior diameter (AP, depth) and thickness of the caudate lobe (CL). In right lobe were measured: craniocaudal diameter (CC, length), anteroposterior (AP) and oblique maximum craniocaudal (OCC max) diameters. Right lobe measurements were performed in the right midclavicular line (MCL) and

in the right anterior axillary line (AAL). All measurements of liver were taken at the widest points. To exclude changes in the liver sizes over the time MRI and US were performed in one day (all participants were fasting before examinations).

Ultrasound liver measurements were performed with convex transducers using Aixplorer (SuperSonic Imagine, France) and SonoScapeS6 (China) ultrasound systems. All volunteers were investigated in the supine position with the both arms placed above the head, the stretched legs and with quiet breathing.

Magnetic resonance imaging (MRI) were performed on the MRI System GE Optima MR 450w 1.5T 70 cm. MRI measurements were performed according to the generally accepted method of ultrasound diagnostics (fig. 1, fig. 2)

Determination of liver linear diameters obtained on MRI was performed on iMac 27 Retina 5K using Osirix DICOM Viewer software. We compared liver linear diameters, obtained on MRI with linear diameters obtained on US.

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software recommended for analysis of biomedical data. For each parameter studied, the average values and standard error of the mean were calculated. The significance of differences in the mean values of independent samples was evaluated using the nonparametric Mann-Whitney test, p-values of less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Results of liver examination in healthy volunteers performed by MRI and US are shown in Tables 1 and 2.

The table 1 shows us that all linear diameters of the left liver lobe obtained by MRI are similar with the same diameters by US, except for one. In women AP diameter using US on average by 9% less than MRI.

CC diameter of the left liver lobe could be considered comparable in men and women. In women AP diameter of the left lobe and thickness of the CL on average by 15–20% less than in men. Additionally, the difference between all diameters does not depend on the imaging technique.

OCC max diameter are almost the same by MRI and US for women as well as for men. However, in men this diameter more on average by 7–8%. This statement is true for measurements in MCL and in AAL.

In men AP diameter using US on average by 10% less than MRI in MCL and on average by 5% in AAL. In women AP diameter of the right lobe by US on average by 10% less than using MRI in the MCL.

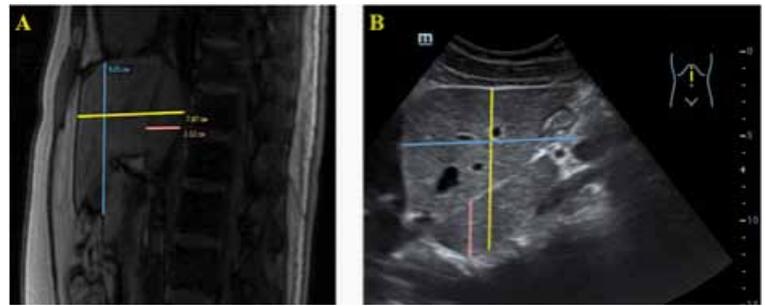


Fig. 1. Measurements of the left liver lobe in a volunteer M., 27 years old: A — MRI, B — US (transducer orientated longitudinally in the midline under xiphisternum). Yellow color indicates the anteroposterior diameter of the left lobe, blue — the craniocaudal diameter of the left lobe, pink — the thickness of the caudate lobe

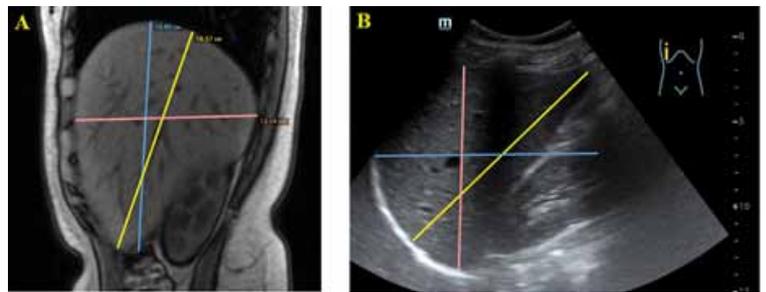


Fig. 2. Measurements of the right liver lobe in volunteer K., 23 years old: A — MRI, B — US (transducer orientated longitudinally in the VII-X intercostal spaces in the anterior axillary line). Yellow color indicates the oblique maximum craniocaudal diameter, blue — the craniocaudal diameter, pink — the anteroposterior diameter

Measurements of AP diameter in AAL for women, by MRI and US, are comparable.

In men AP diameter of the right liver lobe on average by 10 % more than in women by MRI and US as well as in MCL and in AAL. For CC diameters of the right lobe we have mixed results that means this is the most variable diameter of the right lobe.

CONCLUSIONS

It can be concluded that linear liver measurements statistically significant differ in men and women: anteroposterior diameter of left lobe, thickness of the caudate lobe, anteroposterior and oblique maximum craniocaudal diameters of the right lobe. In men these diameters are larger than in women.

Linear diameters of right liver lobe by ultrasound obtained in the anterior axillary line are more comparable with the same diameters by magnetic resonance imaging for males and females.

Table 1. Comparative average linear diameters of the left liver lobe in women and men by MRI and US ($M \pm m$, mm)

Imaging technique	Diameter	Women	Men	p-value
MRI	CC	93,7±2,77	94,08±2,49	p = 0.92
	AP	67,73±1,89	81,96±2,22	p < 0.001
	thickness of CL	21,17 ±0,71	24,68±0,86	p = 0.003
US	CC	92,41±3,86	91,19±3,35	p = 0.81
	AP	61,88±1,81*	77,23±2,28	p < 0.001
	thickness of CL	21,06±0,63	23,79±0,73	p = 0.007

* — statistical significance of differences in average values between MRI and US, $p < 0.05$

Table 2. Comparative average linear diameters of the right liver lobe in women and men by MRI and US ($M \pm m$, mm)

Imaging technique	Diameter	Women	Men	p-value
Measurements in the right MCL				
MRI	OCC max	150,4±2,58	162,56±2,57	p = 0.002
	CC	130,17±3,75	140,24±5,10	p = 0.13
	AP	125,33±2,00	139,56±2,44	p < 0.001
US	OCC max	151,19±2,91	161,81±2,48	p = 0.007
	CC	140,31±3,12*	143,46±3,23	p = 0.49
	AP	113,28±1,66**	126,73±2,30**	p < 0.001
Measurements in the right AAL				
MRI	OCC max	146,73±2,69	157,84±3,13	p = 0.01
	CC	134,93±3,96	145,56±4,39	p = 0.09
	AP	115,1±1,93	131,16±2,62	p < 0.001
US	OCC max	152,52±3,15	164,92±2,68	p = 0.004
	CC	140,00±3,58	150,77± 3,02	p = 0.03
	AP	110,71±1,83	122,85±2,29 *	p < 0.001

* — statistical significance of differences in average values between MRI and US, $p < 0.05$

** — statistical significance of differences in average values between MRI and US, $p < 0.001$

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NO-DEPENDENT FACTOR IN REGULATION OF MICROCIRCULATION DURING EXPERIMENTAL THERMAL TRAUMA

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ABSTRACT — The aim of the study was to evaluate the microcirculatory response to experimental thermal trauma by using laser Doppler flowmetry. The conducted research allowed us to verify the non-linear nature of changes in the intensity of microcirculation in a burn wound, demonstrating both a stress and compensatory responses. It is revealed that NO-dependent mechanisms can play a key role in their provision.

KEYWORDS — burn, wound, microcirculation, nitric oxide, laser Doppler flowmetry.

INTRODUCTION

It is known that microcirculation disorders serve as an important link in the pathogenesis of thermal trauma, appearing both locally (in the tissues of the burn wound and the parawound zone) and systemically [1, 4]. At the same time, the mechanisms for forming such shifts differ significantly [1, 2, 4–6]. Thus, systemic dysfunction of the microcirculatory bed in severe burns is primarily due to the centralization of blood circulation and endotoxemia. On the contrary, microcirculatory disorders in the burn wound area are mainly associated with direct tissue damage, blood stasis, and progressive DIC syndrome [1, 4]. On the other hand, regardless of the mechanism, the severity of these disorders needs to be assessed in a timely manner, since it affects the choice of treatment tactics (including drug therapy) [2, 6, 7]. Also, verification of the state of the microcirculation system serves as a tool for monitoring the effectiveness of local treatment [3, 6, 7]. In addition, understanding the nature and dynamics of the microcirculatory response to thermal trauma is important for the development of innovative methods of sanogenetic impact [2, 5]. At the same time, most of the existing methods for studying the state of microcirculation are either complex in execution and require the use of exclusive equipment

[1, 2, 6], or do not have sufficient depth of penetration and, consequently, informativity [5, 7]. In this regard, the *aim of the study* was to evaluate the microcirculatory response to experimental thermal trauma by using laser Doppler flowmetry.

MATERIAL AND METHODS

The study was performed on 20 male Wistar rats divided into two equal groups. Only a single measurement of microcirculation parameters was performed in the first (control) group of animals. The rats of the second (main) group under combined anesthesia (zoletil + xylavet) sustained simulated thermal burn on the pre-epilated surface of the back (area — 20% of the body surface, depth — II degree) according to the previously developed and patented method (Peretyagin S.P. et al., 2009). Starting from the first day, all animals of the second group were treated locally (*levomekol* liniment).

The microcirculation parameters were registered for 3 minutes using laser Doppler flowmetry on the "LAKK-02" device (Moscow, Russia) [3]. The intensity of blood flow through microvessels was estimated by the microcirculation index (measured in perfusion units). The role of individual factors in ensuring microcirculation was also studied using amplitude-frequency analysis: intravascular (endothelial, neurogenic and myogenic) and external (cardiac and respiratory) components.

Statistical analysis of the results was performed using the program Stastica 6.1 for Windows.

RESULTS

It was found that after applying the burn, the main integrative parameter (the microcirculation index) demonstrates nonlinear dynamics (Fig. 1). In the immediate post-traumatic period (after 1 hour), a sharp decrease in the intensity of microcirculation was observed (by 2.99 times; $p < 0.05$), followed by a compensatory increase almost to the physiological level by 24 hours. However, in the future, a progressive decrease in the indicator was registered.

Analysis of the regulatory components allowed us to establish that the maximum coincidence of the dynamics of the microcirculation index occurs for the endothelial component (Fig. 2), the level of which is

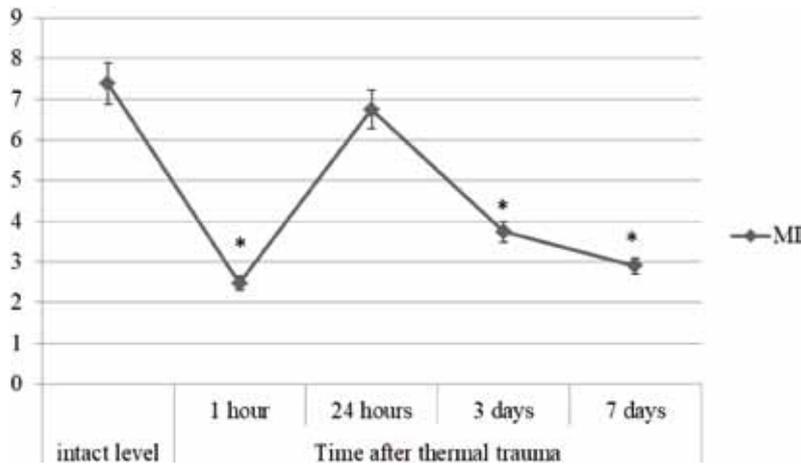


Fig. 1. Dynamics of the level of microcirculatory index (MI) during experimental burn (asterics indicates statistically valued differences, $p < 0,05$)

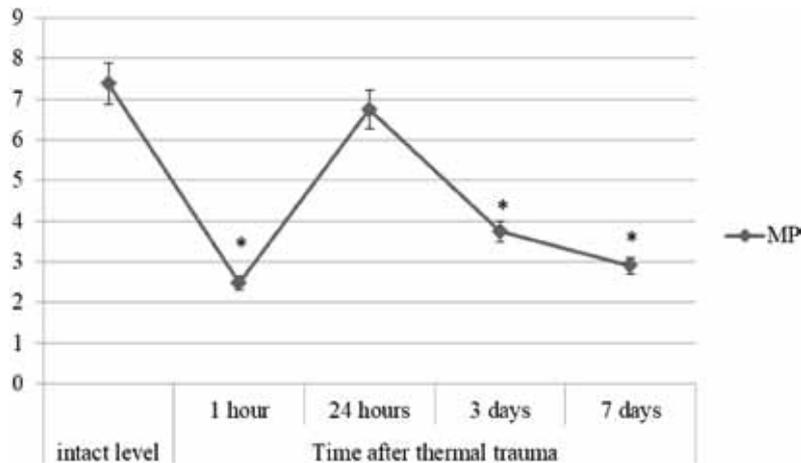


Fig. 2. Dynamics of the endothelial component of microcirculation regulation during experimental burn (asterics indicates statistically valued differences, $p < 0,05$)

directly determined by the release of NO by endothelial cells. The correlation coefficient of these parameters was 0.96, which suggests a key role of this compound in regulating the intensity of blood flow through the microvessels of a burn wound in the dynamics of regenerative processes.

CONCLUSION

The conducted research allowed us to verify the non-linear nature of changes in the intensity of microcirculation in a burn wound, demonstrating both a stress response and compensatory responses. It is revealed that NO-dependent mechanisms can play a key role in their provision.

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A COMPARATIVE STUDY OF PATHOLOGICAL CHANGES IN INFORMATIONAL PARAMETERS OF RAT LIVER DUE TO EXPERIMENTAL EXPOSURE DURING REPRODUCTIVE AND SENILE PERIODS

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ABSTRACT — The informational parameters characterizing the adaptive-compensatory resources of the liver of Wistar rats in the reproductive period and the period of pronounced senile changes in norm and pathological conditions were studied. The same informational parameters were also determined for some non-oncological pathologies, for hepatocellular adenoma and for hepatocellular carcinoma at both ages. It is established that in ontogenesis there is an increase in the level of real structural diversity (H) and coefficient of relative entropy of the system (h). At the same time a decrease of level of organization of system (S) and coefficient of relative organization of system (R) are noted. In the studied periods of ontogenesis, at similar pathologies and pathological processes in liver, in reproductive period of ontogenesis the organ is characterized by fewer deviations from the norm and higher level of adaptation and compensative abilities than in the period of pronounced senile changes. Changes in informational condition of liver at hepatitis have the same direction as ontogenetic changes. They lead to an increase in the disorder of the system and a decrease in the level of its integrity, which results in a decrease in the level of adaptive and compensatory resources. In tumors, a decrease in H and h was found with a simultaneous increase in S and R compared to age norms, which are more pronounced in malignant neoplasms. For all the studied pathologies, changes in the information state are more prominent in the liver of rats in the period of pronounced senile changes.

KEYWORDS — liver, entropy, hepatocyte, hepatitis, morphometric measurement, tumor.

INTRODUCTION

The morphofunctional changes in pre- and postnatal ontogenesis are increasingly considered as phenomena caused by the dynamics of adaptive and compensatory capabilities of living systems of various hierarchical levels [2, 18]. The adaptive-compensatory abilities of biological systems largely determine the success of maintaining homeostasis through ensuring the structural and functional unity of the system components, both in normal condition and in pathology [8, 13].

Various criteria are used to assess the adaptive-compensatory resources of these systems, but each of them is not completely objective and integrative and does not allow a comprehensive assessment of the potential capabilities of the studied system in the process of adaptation and/or compensation, reflecting mainly its functional and/or morphological features.

At the same time, the concept of *information* has become one of the key concepts for actively developing branches of biology. Information parameters can be considered as diagnostic criteria for pathological conditions. The use of information parameters as criteria for assessing the state of various systems and organs of a mammal is increasingly noted. Among the systems of information parameters used to characterize the adaptive and regenerative capabilities of systems, the concept of entropy is most often used [10–14].

It can be assumed that namely the entropy of biosystems can be the criterion that comprehensively characterizes the complex of adaptive-compensatory capabilities of bio-systems under various functional states. G.G. Avtandilov put into practice several information parameters that are derivatives of entropy that can be used for the informational characterization of systems. Our previous studies suggest that the above informational criteria are quite informative indicators characterizing the level of adaptive-compensatory resources of the organism [3–6].

Moreover, it has been reported that it is advisable to calculate the information parameters of organs and tissues based on variations in the volume of hepato-

cyte nuclei. The cell nucleus is the most labile and significant indicator of the morphofunctional state of the cell. The shape and size of the nucleus are those indicators by which it is possible to determine the state of the cell itself, one or another stage of its life cycle. The change in the average size of the nuclei or the cells themselves (cross-sectional area or volume) is an integral derivative of two factors. First, it may be due to a true functional fluctuation in the size of the nuclei. Secondly, a change in the average size of cell nuclei occurs due to a change in the ratio of di- and polyploid cells (partial polyploidy). Both the first and second factors are very important for assessing the adaptive reserves of an organism [9, 15, 16, 17, 20, 21].

In this regard, we considered as the subject of current interest the study of the informational state of the liver of white Wistar rats, which characterizes the level of adaptive and compensatory resources of organ in norm, at chronic and leptospiral hepatitis, hepatocellular adenoma and hepatocellular carcinoma in the reproductive period and the period of pronounced senile changes.

MATERIALS AND METHODS

All the experimental protocols were performed in accordance with ethical guidelines approved by the Ethics Committee of the Research Center for Biology of Cells and Applied Biotechnology, Moscow Region State University, (Moscow, Russia) prior to conducting the experiments. Experiments were performed as per "Directive 2010/63/EU of the European Parliament for animal use for scientific purpose" and "NIH Guidelines for the Care and Use of Laboratory Animals." In the description of the neoplasms, the WHO International Histological Classification of Tumors of Domestic Animals (AFIP, Washington, DC, 1999.) was used. Qualitative and quantitative characteristics of the studied material are presented in Table 1.

pathologies in the reproductive period and the period of pronounced senile changes the pathologic materials from the archives of the cell biology laboratory at the Research Center for Biology of Cells and Applied Biotechnology, Moscow Regional State University; and the laboratory of experimental biology and biotechnology at the Research and Educational Center, Moscow Region State University were used.

The liver of animals with leptospiral hepatitis was obtained from animals infected in-traperitoneally with a LD50 of five-day culture of *Leptospira* of following serological groups — *Canicola*, *Icterohaemorrhagiae*, *Grippotyphosa* [19].

Chronic hepatitis was induced by subcutaneous administration of CCl₄ (Adams et al., 2016). For euthanasia, a CO₂ camera equipped with an overhead gas supply was used. The chamber volume was filled with gas (100% CO₂) at a rate of 20% per minute to avoid dyspnea and pain in animals. To determine the informational status at focal lesions of the liver, pieces of tissue were taken from the least altered areas on the border of macroscopically visible lesions. In case of visual homogeneity of organ, the material for research was taken from random part of it. The criteria for the inclusion of archival material in the study were the verified diagnosis and accurate information about the age of the animal from which the material for study was obtained. For further research, the histological preparations stained with hematoxylin-eosin were prepared by standard methods.

The following informational parameters were determined: H_{\max} — maximal structural entropy of the system (informational morphological capacity), H — informational morphological entropy (real structural diversity of the system), S — informational morphological organization (the indeterminacy, implemented in the system), h — the relative morphological entropy (coefficient of compression of information), R —

Table 1. Qualitative and quantitative characteristics of the material studied to determine the informational condition of the rat liver in the reproductive period and the period of pronounced senile changes in normal and pathological conditions

Period of ontogenesis	The number of animals used in the study in the norm and in pathologies and pathological conditions.				
	Norm	Chronic hepatitis	Leptospiral hepatitis	Hepatocellular adenoma	Hepatocellular carcinoma
I (6–18 months)	20	10	5	8	5
II (24–40 months)	20	10	9	10	6

Hereinafter: I — parameters of the organ in the reproductive period of ontogenesis, II — parameters of the organ in the period of pronounced senile changes

Rat liver in normal condition was obtained from healthy animals of the corresponding age periods. In research of the informational state of rat liver at

coefficient of the relative organization of the system (or coefficient of redundancy), e — informational morphological equivocation (value of system reliabil-

ity). Since the principles and methods for calculating of entropy parameters were proposed and developed in the framework of classical thermodynamics, the traditional letter designations of the quantities were also used. As a unit of information, a bit was used, as suggested by G.G. Avtandilov [3–5].

For determining the above parameters, a karyometric analysis of histological preparations stained with hematoxylin-eosin was carried out with a further disaggregation of the obtained data into classes. For further analysis, the H_{max} is calculated, i.e. the *maximum structural diversity*, according to the formula: $H_{max} = \log_2 n$; where n — number of classes. This parameter, calculated with use of a real number of classes, reflects the structural diversity for the organ with an already embedded account of the individual characteristics of the organism.

Then the calculation of *real structural diversity of the system (informational morphological entropy)* H is made, which is characterizing the degree of determinacy of a morphofunctional system in time and space. Calculation was made by formula: $H = -\sum P_i \log_2 P_i$; where $\sum P_i$ — the sum of the probabilities of stay of the measured cell parameter in one of the presented classes; $\log_2 P_i$ — the logarithm of the probability of presence in one of the possible classes. Moreover, P_i is defined as the classical probability. Knowing the maximum and actual structural diversity, we can calculate the organization of system (S), — the indeterminacy, implemented in the system: $S = H_{max} - H$. Then the *coefficient of relative entropy of system (coefficient of compression of information)* h is defined by formula $h = H/H_{max}$. A high level of relative morphological entropy indicates a disordered in system and a significant decrease in the level of its structural integrity. *Coefficient of the relative organization of the system (coefficient of redundancy)* R is calculated by formula: $R = (S/H_{max}) \times 100\% = (1-h)/100\%$. Knowing these data, the researcher is given the opportunity to calculate equivocation of system (value of system reliability) e : $e = H_n - H_p$; where H_n — real structure diversity in norm, H_p — real structure diversity at pathology (Avtandilov, 2006).

Microscopy of histological preparations was carried out on a Nikon Eclipse 80I digital microscope using a Nikon DL-FI digital camera (Japan). From each studied preparation, 10 digital images of randomly selected fields of vision were made at a magnification of $\times 400$, $\times 1000$. For morphometric studies, the ImageJ program (USA) was used [7]. Statistical analysis of the data was performed using GraphPad Prism V6.01 for Windows. The data are presented in the form $M \pm m$ where m is the standard deviation. To assess the significance of differences, the Student t-test was used. Changes were considered reliably significant at $p \leq 0.05$.

RESULTS

For liver of rats in the reproductive period the following indicators are characteristic — H_{max} — 3.32 ± 0.00 bits, parameter H makes 2.552 ± 0.014 bits, consequently, S is 0.768 ± 0.014 bits, h — 0.7687 ± 0.0042 bits, R is equal to $23.13 \pm 0.42\%$. In period of pronounced senile changes in liver at H_{max} , equal to 3.32 ± 0.00 bits the H increases to 2.732 ± 0.010 bits, S decreases to 0.588 ± 0.01 bits, h raises to 0.8229 ± 0.0022 bits, but at the same time the decrease in parameter R to $17.71 \pm 0.22\%$ is noted (Fig. 1).

In case of the considered non-tumor pathologies and tumor pathological processes, we found similar changes in the studied parameters, relative to age norms (Fig. 2).

In particular, we found an increase in the levels of real structure diversity (H) and coefficient of relative entropy of system (h). At the same time a decrease in levels of organization of system (S) and coefficient of relative organization of system (R) are noted. The noted changes have different degrees of severity in the studied periods of ontogenesis. In the reproductive period, an increase of H and h is on average $5.71 \pm 1.01\%$, and in the period of pronounced senile changes, the increase is significantly higher — $9.01 \pm 1.03\%$. Decrease of S and R makes $18.98 \pm 4.78\%$ in first and $41.72 \pm 6.98\%$ in second studied period of ontogenesis. Value of equivocation of system (e) averages 0.163 ± 0.02 bits and 0.275 ± 0.020 bits respectively. Thus, with unidirectional changes in information parameters at pathologies, the level of adaptive resources of organs is higher in reproductive age (Fig. 3).

Analysis of the informational state of the liver in neoplasms made it possible to establish a decrease in values H and h , and, consequently, increase in values of S and R (Fig. 4).

The degree of difference between the studied parameters and the age norm depends on the period of ontogenesis and the type of pathology. So, in liver with adenoma the values of H and h are less than the age norm by $6.3 \pm 0.80\%$ and $15.93 \pm 1.21\%$ in each of the studied periods of ontogenesis, but in case of cancer these differences are $15.71 \pm 2.21\%$ and $33.93 \pm 4.85\%$ respectively. Similarly, S and R are over the age norm by $20.96\% \pm 3.81$ and $72.45\% \pm 8.22$ at adenoma, and by $52.21\% \pm 5.22$ and $157.65 \pm 9.84\%$ at carcinoma. Equivocation makes -0.161 ± 0.013 bits at adenoma in reproductive period of ontogenesis, and -0.432 ± 0.01 bits in period of pronounced senile changed, and at cancer this value makes -0.401 ± 0.013 bits and -0.927 ± 0.054 bits respectively (Fig. 5).

DISCUSSION

Our study demonstrates that during ontogenesis at norm the liver as a biological system tends to

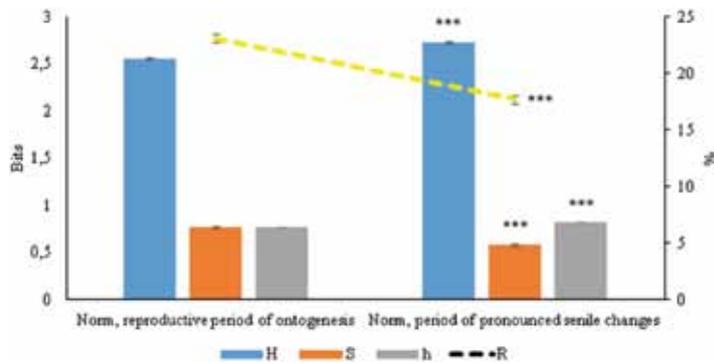


Fig. 1. Informational parameters characterizing the liver of rats in norm in the reproductive period of ontogenesis and in the period of pronounced senile changes. Note: $^*(P \leq 0,05)$; $^{**}(P \leq 0,005)$; $^{***}(P \leq 0,0005)$ — statistical significance of differences in comparison with parameters in the reproductive period of ontogenesis

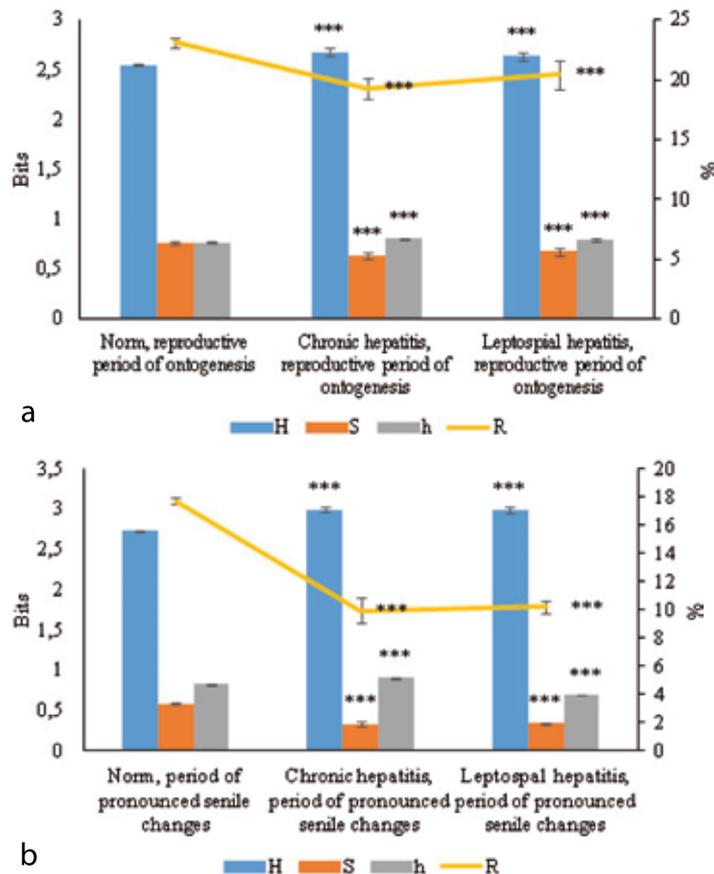


Fig. 2. Changes in informational parameters at chronic and leptospiral hepatitis in reproductive period of ontogenesis (A) and in period of pronounced senile changes (B) Note: $^*(P \leq 0,05)$; $^{**}(P \leq 0,005)$; $^{***}(P \leq 0,0005)$ — statistical significance of differences in comparison with parameters at norm

destruction, loss of structural integrity and functional interconnection of elements, reduction of the reliability of the system, increased risk of disruption of compensatory processes, and a decrease in adaptive reserves and system organization degree.

In studied periods of ontogenesis, at similar pathologies and pathological processes in liver, in reproductive period of ontogenesis this organ is characterized by fewer deviations from the norm and higher level of adaptation and compensative abilities, then in period of pronounced senile changes.

Changes of informational condition, revealed in liver with hepatitis, have the same direction, as ontogenetic changes, and testify about increase in disorder in the system and a decrease in the level of its integrity, and generally about a decrease in the level of adaptive and compensatory resources.

In both considered types of neoplasms, the information parameters of the organ characterize the systems as aimed at a progressive increase in the number of structural elements of the system. Thus, with tumors, a simplification of the informational system of the liver occurs and, as a result, an increase in its reliability, ordering, and the system itself is aimed for growth. In all cases considered by us, in tumor pathologies there is a change in the existing structural diversity, i.e. there is a decrease in the number of system components, its simplification. Such a system is aimed at maintaining functional activity, but at the same time weakly responds to influences from the external and internal environment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

COMPLIANCE WITH ETHICS GUIDELINES

All the experimental protocols were performed in accordance to ethical guide-

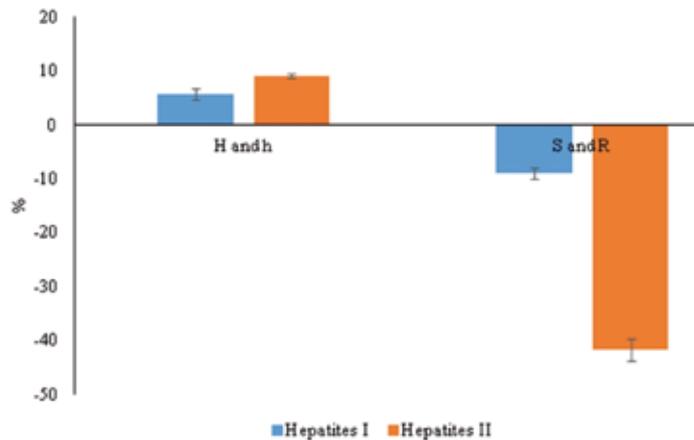


Fig. 3. Changes in some information parameters of rat liver in comparison with the age norm at non-tumor pathologies and pathological processes

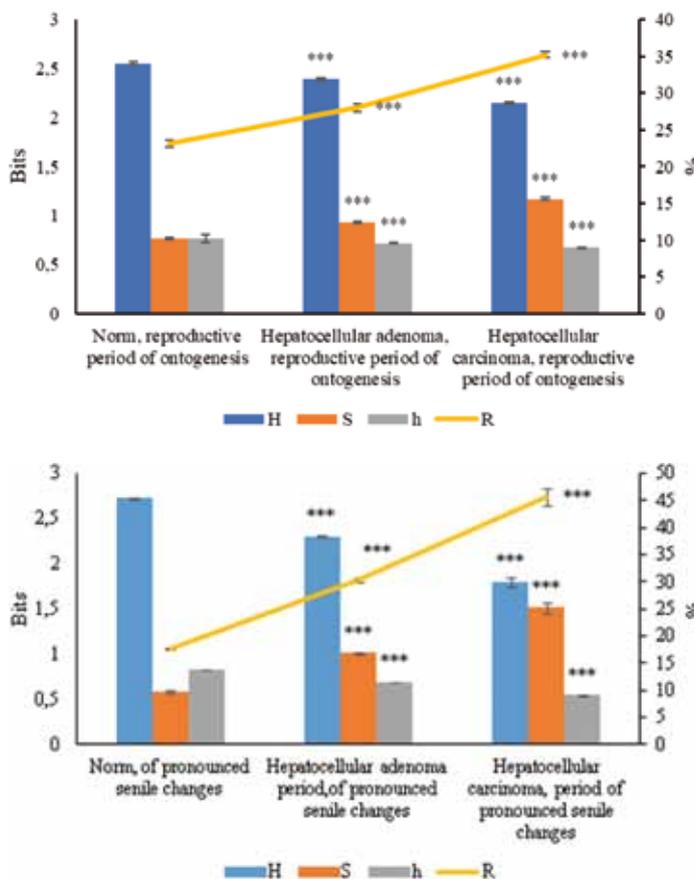


Fig. 4. Changes in informational parameters at hepatocellular adenoma and hepatocellular carcinoma in reproductive period of ontogenesis (A) and in period of pronounced senile changes (B)
Note: *($P \leq 0,05$); **($P \leq 0,005$); ***($P \leq 0,0005$) — statistical significance of differences in comparison with parameters at norm

lines approved by the Research and Ethics Committee of the Moscow State Regional University. Experiments were performed as per “Directive 2010/63/EU of the European Parliament for animal use for scientific purpose” and “NIH Guidelines for the Care and Use of Laboratory Animals”. In the description of the neoplasms, the WHO International Histological Classification of Tumors of Domestic Animals (AFIP, Washington, DC, 1999.) was used.

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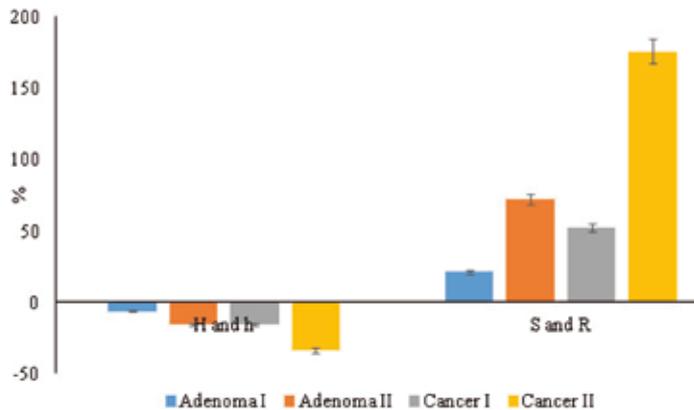


Fig. 5. Changes in some informational parameters of rat liver with tumor pathologies relative to the age norm

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LINEAR ULTRASOUND MEASUREMENTS OF LIVER IN PATIENTS WITH CHRONIC VIRAL HEPATITIS AND CIRRHOSIS

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ABSTRACT — Ultrasound measurements of the liver were performed in 58 healthy volunteers, 31 patients with chronic viral hepatitis and 15 patients with cirrhosis. Statistical differences were detected in anteroposterior diameter of the left lobe, the thickness of the caudate lobe and anteroposterior diameter of the right lobe between healthy volunteers and patients with chronic viral hepatitis and cirrhosis ($p < 0.05$). In healthy volunteers due to the elasticity of the liver parenchyma anteroposterior and craniocaudal diameters of the left lobe and anteroposterior diameter of right lobe significantly differ with quiet breathing and deep breath whereas in patients with cirrhosis these differences was not found ($p < 0.05$) that indicates significant liver's fibrosis and a loss of ability to change configuration with deep breath.

KEYWORDS — ultrasound, liver, linear measurements of the liver, chronic viral hepatitis, cirrhosis.

INTRODUCTION

Chronic liver diseases frequent causes morbidity, deterioration of the quality of life, disability and mortality worldwide [1, 2, 3, 4]. The liver sizes indicates its condition and they can vary significantly even in healthy people and certainly according to the different pathological processes.

We were interested in whether chronic diffuse liver diseases change the definite linear liver sizes. And also, is it possible at the moment of deep breath to affect changes in the linear measurements of the liver?

The aim of this study is to investigate whether the presence of chronic viral hepatitis and cirrhosis in a patient is reflected in linear measurements of the liver, including their possible changes that could occur in deep inspiration breathing.

Materials and methods. We studied 58 healthy volunteers without pathologies of the hepatopancreatobiliary system, 15 patients with cirrhosis, 31 patients

with chronic viral hepatitis (CVH), which included patients infected with hepatitis B virus (HBV), hepatitis C virus (HCV), HBV/HCV coinfection and HBV/HDV (hepatitis D virus) coinfection. All participants were fasting before ultrasound examination.

Liver measurements were performed with convex transducers using Aixplorer (SuperSonic Imagine, France) and SonoScapeS6 (China) ultrasound systems in the supine position of participants on an examination bed with the both arms placed above the head and the stretched legs. All measurements of liver were taken at the widest points. Measurements were started from the left liver lobe with the transducer orientated longitudinally in the midline of abdominal wall just under xiphisternum. The craniocaudal diameter (CC, length), anteroposterior diameter (AP, depth) and caudate lobe (CL) thickness were measured according to the preliminary *frozen* sonographic images. From the same position of the transducer similar measurements were taken in the end of deep inspiration — when the diaphragm takes the lowest position. Before it all participants were instructed to take a deep breath and hold the air for a few seconds in the end of breath.

Measurements of the right lobe began from the positioning of the transducer in a longitudinal orientation in the right midclavicular line (MCL) in the VII-X intercostal spaces during quiet breathing. In a deep breath the liver displaced downward that is why the transducer was moved down from the intercostal access to the right hypochondrium under the costal margin while maintaining its longitudinal position in the MCL. The following parameters were measured on *frozen* ultrasound images: anteroposterior (AP) and oblique maximum craniocaudal (OCC max) diameters. The OCC max is the oblique maximum distance of diaphragmatic dome to the lower edge of the liver [5]. Further similar measurements were carried out with the transducer orientated longitudinally in the right anterior axillary line (AAL) in quiet breathing and in the end of deep breath.

The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS)

software recommended for analysis of biomedical data. For each parameter studied, the average values and standard error of the mean were calculated. The significance of differences in the mean values of independent samples was evaluated using the nonparametric Mann-Whitney test, p-values of less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

We combined all the obtained measurements into tables. Mean linear diameters of the left lobe can be seen in table 1.

with cirrhosis on average are 30–40% higher than in volunteers without liver pathology, and in patients with CVH the values of AP diameter are also more than in healthy volunteers but only 15–25% by an average. The values of the thickness of CL in patients with cirrhosis increase on average by 35–45%, and in patients with CVH on average by 10–20% compared with the group of healthy volunteers.

Holding the air in the end of deep breath for healthy volunteers shown the CC diameter of left lobe elongation by on average of 15% and the AP diameter of left lobe decreases by on average of 10%. While pa-

Table 1. Ultrasound linear measurements of the left liver lobe for healthy volunteers, patients with CVH and cirrhosis at the type of breath ($M \pm m$, mm)

Breath	Diameter	Healthy volunteers	Patients with CVH	Patients with cirrhosis
Quiet breath	CC	91,86 ± 2,58	84,34 ± 3,64	101,93 ± 4,33*
	AP	68,76 ± 1,74	81,48 ± 3,16°	101,86 ± 4,29*, °
	CL	22,28 ± 0,50	24,82 ± 1,21	34,93 ± 1,88*, °
The end of deep breath	CC	106,71 ± 1,90 #	98,23 ± 3,77 #, °	106,57 ± 5,03
	AP	63,74 ± 1,26 #	78,47 ± 3,05°	97,21 ± 3,77*, °
	CL	21,55 ± 0,50	26,3 ± 1,18°	34,21 ± 2,79*, °

* — statistical significance of differences in average values between patients with CVH and cirrhosis, $p < 0.05$

° — statistical significance of differences in average values between patients with CVH and cirrhosis with healthy volunteers, $p < 0.05$

— statistical significance of differences in average values with quiet breathing and in the end of deep breath, $p < 0.05$

In patients with liver cirrhosis, the following linear measurements of left lobe are statistically significant larger compared with patients with CVH ($p < 0.05$) and compared with healthy volunteers ($p \leq 0.001$): anteroposterior diameter of left lobe, the thickness of the caudate lobe, despite of the phase of the respiratory cycle. The values of AP diameter in patients

with chronic viral hepatitis only had elongation CCS on average also 15%. Cirrhosis was the reason why all these parameters were almost unchanged that indicates significant liver fibrosis and a loss of its ability to change configuration even in a state of deep breath.

Linear diameters of the right lobe are shown in Table 2.

Table 2. Ultrasound linear measurements of the right liver lobe in healthy volunteers, patients with CVH and cirrhosis at different positioning of the transducer and the type of breath ($M \pm m$, mm)

Breath	Diameter	Healthy volunteers	Patients with CVH	Patients with cirrhosis
Transducer positioning in the right MCL				
Quiet breath	OCC max	155,95 ± 2,06	155,83 ± 3,35	156,5 ± 7,02
	AP	119,31 ± 1,63	128,63 ± 2,66°	131,79 ± 5,46°
The end of deep breath	OCC max	150,43 ± 2,08	153,79 ± 3,47	146,91 ± 7,68
	AP	112,31 ± 1,59 #	128,00 ± 2,5°	127,09 ± 5,09°
Transducer positioning in the right AAL				
Quiet breath	OCC max	158,17 ± 2,24	159,93 ± 2,97	156,93 ± 7,35
	AP	116,25 ± 1,63	122,73 ± 2,40°	122,07 ± 5,29
The end of deep breath	OCC max	155,28 ± 1,92	157,64 ± 3,14	146,00 ± 7,96
	AP	110,10 ± 1,66#	124,04 ± 2,28°	124,42 ± 4,15°

° — statistical significance of differences in average values between patients with CVH and cirrhosis with healthy volunteers, $p < 0.05$

— statistical significance of differences in average values with quiet breathing and in the end of deep breath, $p < 0.05$

The linear measurements of the right lobe (OCC max and AP) in patients with CVH and cirrhosis could be considered comparable. In patients with CVH and in patients with cirrhosis, there was no change in these sizes during a deep breath, and also in both groups, the values of OCC max and AP diameters did not change depending on access (according to MCL or AAL). We have previously obtained similar results that at the level of MCL and AAL for the right liver lobe, the average values are comparable ($p < 0.05$) [6].

Comparison of the liver measurement values between patients with CVH, cirrhosis and healthy volunteers shows that only the AP diameter of the right lobe differs statistically significant ($p < 0.05$). This size increases on average by 5–10% in liver pathology.

With a deep breath AP diameter of the right lobe in healthy volunteers decreases on average by 5–6%. In patients with CVH and cirrhosis we did not find statistically significant changes in this size that also confirms organ fibrosis.

Thus, in patients with CVH and cirrhosis, the liver tissue becomes stiffer, which was shown during deep breath including both liver lobes but mainly by left that is more changeable in healthy volunteers.

CONCLUSIONS

1. Anteroposterior diameter of the left lobe, the thickness of caudate lobe and anteroposterior diameter of the right lobe are increased in patients with chronic viral hepatitis and liver cirrhosis.
2. In healthy volunteers due to the elasticity of the liver parenchyma anteroposterior and craniocaudal diameters of the left lobe and anteroposterior diameter of right lobe significantly differ with quiet breath and deep breath. In patients with cirrhosis the differences of liver measurements with quiet breath and deep breath were not found.
3. We propose to use the absence of changes in the liver measurements with quiet breath and deep breath as ultrasound criterion of cirrhosis that reflects the loss of liver elasticity.

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DIGITAL TECHNOLOGY OF PERSONALIZED ADMINISTRATION OF VITAMIN AND MINERAL COMPLEXES: PRINCIPAL ALGORITHM

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ABSTRACT — This work is devoted to the discussion of our algorithm for personalized selection of the composition of vitamin and mineral complexes using the laboratory parameters of the patient. For this purpose, we have formed a three-stage scheme based on the gradation of a wide range of laboratory indicators and the selection of components depending on whether the values of indicators fall into certain ranges. Given the complexity of analyzing and interpreting this information, the algorithm was implemented as a special computer program, the functionality of which is illustrated in this article.

KEYWORDS — vitamin, mineral, homeostasis, correction, personification, algorithm.

INTRODUCTION

Currently, much attention is paid to vitamin and mineral homeostasis and its maintenance at the physiological level [1, 2, 7]. This is facilitated by both the normalization of metabolism in whole, and the targeted introduction of missing micronutrients and other necessary compounds into the body [1, 5–7]. At the same time, the focus of research and clinical practice in this area is clearly shifted towards the correction of vitamin deficiency. As a result, synthetic and natural mono- and poly-component vitamin preparations are now widely represented on the pharmaceutical market [1–3, 6, 7]. On the contrary, the issue of correcting shifts of mineral, in particular microelement, homeostasis is not fully explained [1, 2, 7]. At the same time, in our previous cohort studies and according to other authors, the prevalence of micronutrient insufficiency is also quite high, reaching 50–60% of the surveyed individuals for individual elements [1, 3, 4]. On the other hand, the profile of shifts in vitamin-mineral homeostasis shows significant individual variations [1, 3, 5, 7].

On this basis, it is appropriate to use a personalized approach to the appointment and composition of vitamin and mineral complexes, which was the *purpose of this work*.

MATERIAL AND METHODS

To solve this problem, we have introduced a basic three-stage algorithm for preparing individual vitamin and mineral complexes, including the following components:

- 1) preliminary comprehensive laboratory examination (determination of more than 50 biochemical parameters of blood with an emphasis on indicators that characterize the state of pro- and antioxidant systems, as well as the plasma level of 23 macro- and microelements);
- 2) analysis of the obtained panel of biochemical indicators and the level of microelements in blood plasma relative to the standards, taking into account the age and gender of patients using our own software developed by Bioniq Health-Tech Solutions Ltd. (London, United Kingdom) and allowing to grade the level of parameter shifts for the subsequent selection of components of the vitamin and mineral complex;
- 3) formation of the conclusion about the patient's present metabolic shifts, as well as the individual profile of vitamin and mineral insufficiency. On the basis of this conclusion, a personal complex for course admission is created.

RESULTS

The basis of this algorithm is the analysis of multi-factorial results of laboratory examination of the patient, and the value of each parameter is graded at standardized intervals (from three to seven, depending on the indicator). This gradation allows us to apply a differentiated approach to the choice of dosage or the exclusion of individual components of the complex that compensate for the observed shifts in vitamin and mineral homeostasis. Based on this, a complex network of interactions of parameters and their gradations is formed, which directly determines the composition of the individual complex. The complexity

of the considered algorithm for manual analysis and interpretation predetermined the need for its computerization, which was realized in the development of special software that allows you to automate this procedure and integrate the second and third stages of the algorithm. This makes it possible to objectify and standardize the procedure for analyzing and prescribing individual vitamin and mineral complexes. A part of the functional (internal structure) of the program is shown in Fig. 1 on the example of a fragment concerning ferritin and C-reactive protein. So, low or critically low levels of ferritin or its lower value in conjunction with high or extremely high levels of C-reactive protein suggests the inclusion of three portions of iron and one portion of vitamin C in the complex. On the contrary, the presence of normal or elevated levels of ferritin excludes from the formed complex iron-containing component, and in case of detection of a critically high level, the program provides an urgent notification of the physician.

personal complex, and the effectiveness of its application is controlled by a step-by-step and final laboratory examination of the patient, which is carried out with the determination of the same parameters as in the preliminary testing.

CONCLUSION

Thus, we have formed a three-stage scheme of personalization of vitamin and mineral complexes, based on the gradation of a wide range of laboratory indicators and the selection of components depending on whether the indicators fall into certain ranges. The effectiveness of the complex is evaluated based on the dynamic analysis of this set of laboratory parameters. Given the complexity of analyzing and interpreting this information, the algorithm was implemented as an original computer program which can be used by physicians for evidence-based conclusions.

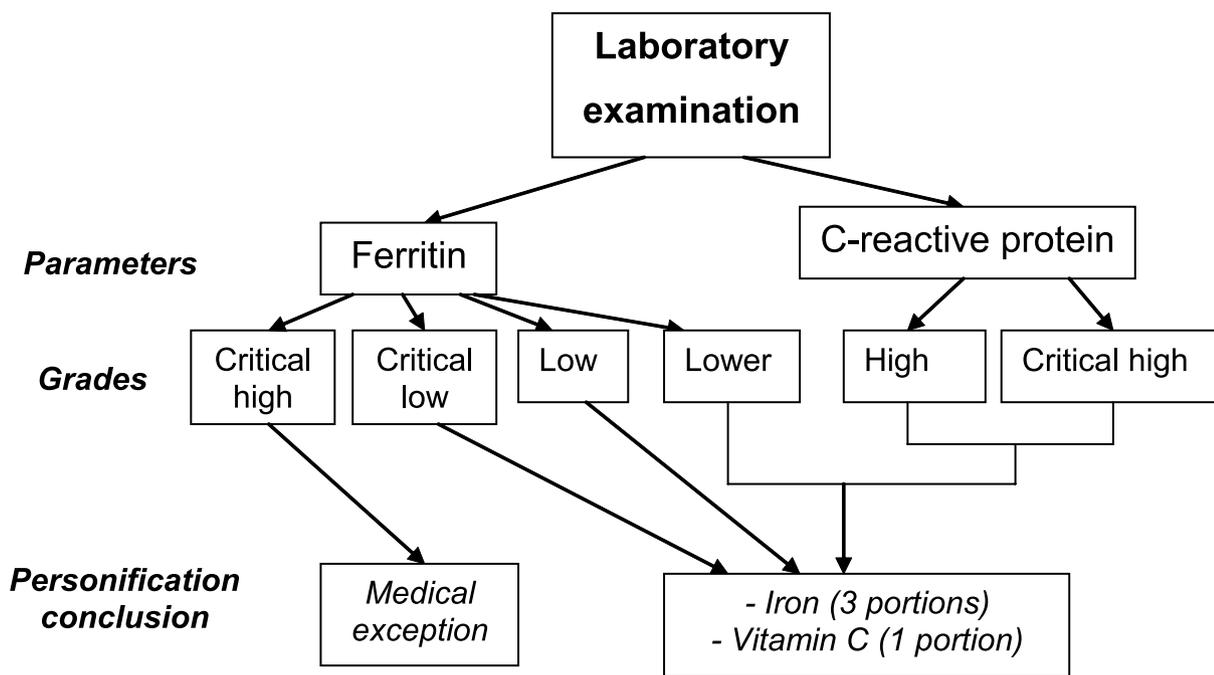


Fig. 1. Fragment of individualization scheme for our vitamin and mineral complex

Software processing of the entire panel of laboratory indicators allows us to make an integrative reasoned conclusion about the totality of the obtained gradations of each parameter and, consequently, the components of the complex necessary for this patient. This information is used for the production of a

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CHARACTERISTICS OF SINUS BRADYCARDIA IN YOUNG ATHLETES WITH COMORBIDITIES

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ABSTRACT — 36 young athletes with sinus bradycardia accompanied by comorbid conditions (vegetative symptoms and visceral manifestations of heart dysplasia) underwent an assessment of creatine kinase-MB levels in their blood serum and the condition of the spectral components of heart rate variability (HRV). It has been discovered that sinus bradycardia is more dependent on vegetative symptoms and high sport loads than on visceral manifestations of connective tissue dysplasia (CTD). However clinical features of vagotonia and visceral manifestations of CTD may serve as risk factors for development of sinus bradycardia in young athletes.

KEYWORDS — sinus bradycardia, comorbid conditions, vegetative symptoms, connective tissue dysplasia (CTD), creatine kinase-MB, spectral components of HRV, young athletes.

INTRODUCTION

Bradycardia is known as either heart rate fall by 10–40% below normal heart rates or these values being less than 10 percent in children. Vagotonic-type vegetative disturbances or cardiac remodeling among young athletes as well as other reasons [1, 3, 5, 6] may also account for slowing of the heart rate.

From the contemporary point of view, the syndrome of connective tissue dysplasia CTD refers to prolapsus of cardiac valves, atrial septal aneurysm, aneurysm of the aortic sinus and ectopic cords of mitral valve. [1, 2, 4, 5].

In young athletes it is difficult to identify the causes for development of sinus bradycardia: whether it attributed to training loads or vegetative disturbances and dysplasia of heart connective tissue. Their manifestations in schoolchildren are interrelated and may significantly facilitate the development of sinus bradycardia [2, 6]. All these factors justify the relevance of our research.

Aim of the investigation:

To define the characteristics of sinus bradycardia caused by vegetative symptoms and CTD disorders in children participating in sport.

CHARACTERISTICS OF CHILDREN AND METHODS OF INVESTIGATION

83 children aged 8–12 years (the mean age was $10 \pm 2,0$), with 2–3 years of football training were under observation. Bradycardia on the base of vegetative symptoms and dysplasia of connective tissue was identified in 36 children. The investigation was carried out at N.N. Silischeva Regional children clinical hospital and Regional sports medicine dispensary of the city of Astrakhan.

All children were observed in dynamics by a pediatrician and consulted by a pediatric cardiologist. Additionally to clinical-anamnestic estimation of a cardio-vascular condition we studied the signs of vegetative symptoms by means of measuring initial autonomic tonus and autonomic reactivity according to conventional methods [1, 5]. CTD was estimated on E.V. Zemschovsky criteria with consideration of phenotypic and visceral characteristics [1]. Laboratory tests included general tests of blood, urine, levels of CRP, liver enzymes; creatine kinase-MB was measured by ELISA kit. Besides, standard ECG. Echo-cardiographic investigation (EchoCG), holter monitoring ECG (ECG HM) were performed. Sinus bradycardia was detected clinically and by ECG data with the frequency of heart contractions from 30 to 47 beats per minute and was confirmed by ECG HM data.

The manifestation of vegetative symptoms and the influence of physical loads on the organism were assessed with spectral analyses of HRV at rest and orthoposition using Poly-Spectrum-12/E Neurosoft. The results of the study were analyzed in accordance with common methods of multivariate statistics.

RESULTS AND DISCUSSION

All observed schoolchildren were divided into three groups, using the method of simple randomization according to age and sex. Finally, only boys were selected for the study.

The first group included 11 boys with manifested bradycardia (decrease of heart contraction frequency by 30–40%). The second group included 25 children with moderate bradycardia (heart rate decreased by 20–29%), and the third group included 20 young athletes (heart rate decreased by 10–19%) and without vegetative symptoms and CTD (the control group).

Analyzing laboratory and instrumental data we identified vegetative symptoms of asympaticotonic type in the first group, whereas visceral manifestations of CTD were observed in all young athletes. 8 to 12 or even more phenotypic features of CTD were detected in 10 (90,9%) children. The children of this group often complained of weakness and fatigue after school. Clinically the suppressed condition and weak sounds of the heart were observed in 10 (90,9%) as well as soft systolic sound at the apex in 9 (81,8%) and moderate widening of heart borders in 6 (54,5%) children. In a laboratory study, a significant decrease in the levels of activity of MB-CPhC in blood serum was established ($p < 0,05$), which could indicate lower energy supply of the body.

ECG was used to detect sinus bradycardia in all young athletes. At the same time there were inversion T wave and depression of segment ST in two and more precordial diversions in 10 cases (90,9%). In 9 children (81,8%) the echocardiogram showed diastolic dysfunction, visceral manifestations of CTD of the heart: prolapse of mitral valve with regurgitation of 1 or 2 degree in 10 (90,9%), abnormal tendon cords of mitral valve in 9 (81,8%), aneurism of interatrial septum in 6 (54,5%).

In analyses of HRV low levels of common power of spectrum ($p < 0,01$) and high data of highfrequent component HF ($p < 0,05$) in comparison with normal state were observed (Table 1).

In the second group of children with moderate bradycardia the features of vegetative symptoms of asympaticotonic type were observed in 17 (60,8%), while the rest of the children showed no signs of vegetative disturbances. CTD was displayed in 20 (80%) boys with the presence of 10 to 14 phenotypic features. In 5 (20,9%) boys there were from 6 to 9 phenotypic features. Isolated visceral manifestations of CTD were found in 24 (96,0%), 2–3 combined criteria were rare or may be single. So, bradycardia was combined with comorbid diseases (vegetative symptoms and CTD). The comparison of frequency in cases of vagotomy and visceral features of dysplasia shows significant correlative connection ($k=0,72$). Laboratory data and levels of MB-CPhC did not change essentially.

ECG showed moderately manifested sinus bradycardia in all children, inversion of T wave in 5 cases (20,2%), in 3 (12%) cases we found depression of segment ST in two and more thoracic directions. EchoCG demonstrated dyastolic dysfunction in 11 (44,1%), prolapse of mitral valve and trycuspid valve in 19 (76,2%), aneurism of interatrial septum in 8 (32,1%), additional cords in 12 (48,2%) cases. Changes of HRV parameters and their spectrograms seemed characteristic for asympaticotonia. The general power of spectrum was decreased moderately TP: ($p < 0,05$) in high level of LF ($p < 0,01$; Table 1). So, the decrease of level in frequency of heart contractions in case bradycardia at rest may be supported by parasymphatic

Table 1. Comparison of laboratory data in the children

Groups	Data				
	MB-CPhC(f/l)	TP(mc2)	VLF (mc2)	HF(mc2)	LF(mc2)
First(n=11)	31,4±0,25**##	2240±508***##	946±208**##	910±210**##	640±124**###
Second(n=25)	40,6±0,5**##	2750±526**##	1120±340*#	790±120*#	880±145**##
Third(n=20)	36,6±0,45	3210±520	1370±410	710±210	718±224

Note: * — reality in comparison of data of the 1st and 2nd groups with the 3rd: * $p > 0,05$, ** $p < 0,05$, *** $p < 0,01$
— reality in comparison of data of the 1st and 2nd groups: # $p > 0,05$; ## $p < 0,05$, ### $p < 0,01$

It proves the prevalence of parasymphatic vegetative influence on sinus node of the heart contractions. The estimation of spectrogram in these children shows a low level of energy supply in the organism observed in manifestations of vegetative symptoms and bradycardia in comorbid conditions with CTD. Bradycardia in this group is closely correlated with manifestations of asympaticotony in estimation of HRV ($k=0,75$) and visceral features of CTD in the heart ($k=0,52$).

influence and sport loads. Manifestations of bradycardia were correlated with signs of VDS ($k=0,61$) and to a lesser extent with CTD ($k = 0,38$). In making up the levels of spectral parameters HRV of this group with the same in the first group it was marked that the changes were more expressed in the first one than in the second ($p < 0,05$). At the same time the frequency of cases with visceral features CTD of the heart in comparative groups didn't greatly differ ($p > 0,05$). So, the presence of expressed dystonia and visceral features

of CTD were the base for formation of bradycardia in young sportsmen.

In the third group (20) among young athletes with no obvious signs of vegetative symptoms and connective tissue dysplasia, a tendency to bradycardia was noted. The MB-CPhC levels in the children of this group were normal. The heart CTD features were diagnosed in single cases with one of the visceral criteria and practically no influence on the heart rhythm. The changes of the heart rhythm were explained by sport loads.

Thus, sinus bradycardia in young athletes may occur due to the influence of comorbid pathology and sports loads. Among comorbid conditions, an important role is played by vegetative symptoms (asymptomatic, in particular). At the same time, vagotonic influences can contribute to the development of pronounced sinus bradycardia, which proceeds against the background of a reduced energy supply of the body at rest and visceral signs of CTD. With moderate signs of vegetative symptoms in young athletes, an important role in the development of sinus bradycardia is played by sports loads and, to a lesser extent, visceral signs of heart dysplasia.

The presence of manifestations of vagotonia and visceral dysplastic symptoms from the side of the heart can serve as factors in the development of sinus brady-

cardia in young athletes. To manage sinus bradycardia, it is important to determine its severity and to assess the state of vegetative manifestations and dysplastic disorders of the heart.

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IMPLEMENTATION AND OUTCOME OF INTERMITTENT KMC- EXPERIENCE AT A SECONDARY LEVEL HOSPITAL IN BANGLADESH

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INTRODUCTION

Kangaroo mother care (KMC) is a low-cost health care method that is practiced in conjunction with conventional newborn care, especially in pre-term and low birth weight (LBW) infants [1]. KMC is widely recognized as an excellent intervention for improving the health and survival chances of premature infants. KMC consists of early, continuous and prolonged skin-to-skin contact between the caregiver and the baby, exclusive breastfeeding or breast milk feeding, and context-appropriate discharge and follow-up provided to the baby and his or her family [2]. KMC has shown to have more advantages over conventional newborn care in preventing neonatal mortality and morbidity especially in resource limited

ABSTRACT — **INTRODUCTION:** The term Kangaroo mother care (KMC) is derived from the practical similarities to marsupial care giving – mother acts as an incubator as kangaroo and put low birth infant vertically in between the chest. It is an effective way to meet baby's needs for warmth, breastfeeding, protection from infection, stimulation, safety and love. **OBJECTIVE:** The general objectives were to see the implementation challenges and outcome of intermittent KMC at a secondary level district hospital. The specific objectives were to observe the nature of family participation, practice pattern of intermittent KMC, length of hospital stay, effect on weight gain, mortality and problem experienced by the newborns and mothers/caregivers during KMC practice. **MATERIALS & METHODS:** This was an observational study for three months at 250 Bedded District Hospital, Moulvibazar, Bangladesh involving 50 preterm (gestational age <37 week) & low birth weight (<2000 g) newborns and their mothers/caregivers. Participants were included and KMC was initiated in stable newborns according to the national KMC guideline. Information related to the study objectives were obtained from examination and interview and the findings were recorded during the hospital stay and follow up visits in a pre-structured data collection sheet. **RESULTS:** Among the studied newborns male female ratio was 1.5:1 and 32 (64%) were out born (delivered at home or any other hospitals). The mean postnatal age at the time of admission was 57.90 h, at the time of initiation of KMC was 115.38 h and at discharge was 227 h. So, there was mean delay of 66 h from admission to initiation of KMC and in 47(94%) newborns. Mostly, the delay was due to absence of mothers or eligible caregivers and unstable clinical condition of the newborns. The mean weight at admission and discharge was 1625.80 g and 1520.60 g respectively. Among the family members, mother practiced KMC in 45(90%) [n=50] followed by grandmother 28 (56%). KMC was practiced in 44 (88%) newborns in the evening shift followed by 43 (86%) & 27(54%) in the night & morning shifts respectively. The mean duration of KMC was 2.58 h in the night shift followed by 2.46 h & 2.46 h in the evening & morning shifts respectively. The mean hospital stay was 109.95 h. Total 32 studied newborns completed up to 3rd follow up after discharge among which 5(15.62%) did not gain weight, 6(18.75%) gained weight at 1st follow up (7th day of age), 14(43.75%) at 2nd follow up (15th day of age) & 7(21.87%) at 3rd follow up (30th day of age). The total mortality was 6(12%). Most of the newborns and mothers/caregivers experienced no problem during KMC practice. **CONCLUSION & RECOMMENDATION:** Family motivation and participation is a key to standard KMC practice. Constant supervision and follow up home visit involving community health personnel until the neonatal age is completed constitute the most important aspect for implementing KMC effectively and reducing the mortality.

countries. KMC improves the lactation in mother, boost the psychological bonding between mother and neonate, improves the sleep cycle and oxygenation in sick preterm and reduces the apneic spells [3].

KMC has three components: Kangaroo position- The kangaroo position consists of skin-to-skin contact (SSC) between the mother and the infant in a strictly vertical position. The infant will be placed between the mother's breasts and under her clothes. SSC should be started as early as possible after birth. It can be two types depending upon the duration which are continuous or intermittent. Kangaroo nutrition- Kangaroo nutrition is the delivery of nutrition to "kangarooed" infants as soon as oral feeding is possible. It is based on exclusive breastfeeding by direct sucking, whenever possible. Goal is to provide exclusive or nearly exclusive breastfeeding. Kangaroo discharge and follow up- Early home discharge in the kangaroo position from the neonatal unit is one of the original components of the KMC intervention [4].

The experience of facility-based KMC in Bangladesh is relatively recent, though there are a few facilities that have been providing KMC services for over a decade. In 2013, the Government of Bangladesh signed onto "A Promise Renewed (APR)" as a sign of its determination and commitment to reduce child deaths to 20 per 1,000 live births by 2035. Through this commitment, KMC is integrated into newborn care for preterm & LBW babies in an effort to decrease preventable neonatal deaths [5]. In 2015, the Bangladesh Every Newborn Action Plan (BENAP) was instituted. There are two main objectives in the BENAP that focus on KMC: the establishment of counseling on KMC practice at facilities including the provision of follow-up KMC services using community health workers (CHWs) and the establishment of centers of excellence for KMC in tertiary and secondary level facilities. The targets for KMC initiation were set at 20% for public health facilities at the upazila health complexes UHC (sub-district level) and above by 2016, and at 50% for public health facilities at the UHC and above to provide KMC services by 2020. In 2016, KMC was included as an essential service for preterm LBW newborns at UHC, district hospitals (DH), and maternal and child welfare centers (MCWC) (Bangladesh Essential Service Package (ESP), MOHFW) [5]. From this point of view, this study was conducted to see the implementation challenges and outcome of KMC at 250 Bedded Hospital, Moulvibazar, a secondary level district hospital in Bangladesh.

MATERIALS & METHODS:

This was an observational study done with the cooperation of UNICEF, Moulvibazar, involving the

Special Care Newborn Unit (SCANU) and the department of Obstetrics & Gynaecology of 250 Bedded Hospital, Moulvibazar, Bangladesh. The study period was three months, November 2019 to January 2020. A total 50 preterm (gestational age <37 completed weeks) and low birth weight (birth weight less than 2000 g) newborn babies either inborn (delivered at 250 Bedded Hospital, Moulvibazar) or out born (delivered at home or any other hospitals) and their mothers/caregivers were included. The inclusion and exclusion criteria was set according to the Bangladesh National Guideline on Kangaroo Mother Care 2014. Inclusion criteria for the newborns — birth weight >1800–2000 g, if stable, KMC was initiated immediately after birth; birth weight >1200–1800 g, if stable, KMC was initiated immediately, if not, KMC was initiated after stabilization; birth weight <1200 g, most infants suffer from serious morbidities and KMC was initiated after stabilization. Stable newborn was defined according to the guideline-normal heart rate 100–160 per minute, respiratory rate 30–59 per minute (breaths comfortably, no sign of respiratory distress, pink in room air or with 40% oxygen, no prolonged of frequent apnea). Inclusion criteria for the mothers — should be willing to provide KMC after counseling on KMC, health condition allowing full-time availability to provide care, in absence of mother, other family members like father, grandparents, aunts can also provide KMC with obvious extra support for feeding. Exclusion criteria for the newborns were major surgical problem and gross congenital anomalies. Exclusion criteria for the mothers — bad obstetric situation like postpartum hemorrhage, eclampsia, mother suffering from serious illness potentially dangerous to the baby like active tuberculosis, chicken pox, psychosis etc. After taking written informed consent patients were enrolled in this survey from the date of admission. Intermittent KMC was initiated on the decision of the SCANU consultant after fulfillment of the criteria. For KMC to be given intermittently, we divided the 24 h into 3 shifts — 8am to 2.30 pm (morning shift), 2.30 pm to 8 pm (evening shift), 8 pm to 8 am (night shift) according to the duty shifts of hospital nurses. KMC was practiced using standard KMC binder, cap and socks provided by UNICEF. In every shift, the number of hours KMC given, KMC given by whom (caregiver), and problems experienced during KMC by the caregivers were monitored, interviewed and documented by the duty nurses. A fixed digital weight machine was used to measure the initial and daily weight. Day of initiation of feeding either breastfeeding, dropper feeding or nasogastric feeding was recorded. Daily decision regarding overall treatment, KMC and discharge was made by the SCANU

consultant. During discharge, the KMC binder was given to the mother to continue it at home and a pre-scheduled follow up plan was given for day 7th, 15th and 30th. At each follow up conducted by the on duty consultant and a fixed nurse, thorough examination of the newborns was performed, weight was measured, and interview on the duration of KMC, problem related to KMC, etc. were carefully documented on the data collection sheet.

RESULTS

Table 1 shows the baseline characteristics of the studied newborns. Here, the total male newborns were 30 (60%) and female 20 (40%) and the M:F=1.5:1. Most of the newborns 32(64%) were out born, either delivered at home or referred from other hospitals. The mean postnatal age at the time of admission was 57.90 h and the time of initiation of KMC was 115.38 h. So, there was a time difference from admission to the initiation of KMC in 47(94%) newborns and 66 h (mean). In most cases, cause of the time difference was unstable clinical condition at the time of admission or other medical conditions requiring immediate treatment. Regarding the weight, the mean weight at admission and discharge was 1625.80 g and 1520.60 g respectively.

Table 2 shows the caregivers who were involved in KMC practice during the study period. Mostly, KMC was given by mother 45(90%) and grandmother 13(26%). Other family members were also involved in KMC practice namely father, aunt and uncle.

The number of newborns in whom KMC was provided by the caregivers in three shifts is shown in Table 3. In the morning session, 27(54%), in the evening 44(88%) and at night 43 (86%) newborns were given KMC by the caregivers. Table 4 shows the duration of KMC in three different shifts where the mean duration of KMC in the morning shift was 1.97 h and in the evening and night, 2.46 h and 2.58 h respectively.

In Table 5, the length of hospital stay of the studied newborn is revealed where the minimum hospital stay was 5 h, maximum 383 h and the mean duration was 109.95 h. Effect of KMC on weight gain who completed the pre-scheduled three follow up is shown in Table 6. Five newborns (15.62%) did not gained weight throughout the follow up period. Six newborns (18.75%) gained weight at 1st follow up on day 7th, 14(43.75%) at 2nd follow up on day 15th and 7(21.87%) at 3rd follow up on day 30th.

The total death observed in this study was 6 (12%) among which 5 (10%) death occurred after hospital discharge Table 7. Table 8 shows the pattern of problems in the newborn and the mother/caregiver

during KMC practice. Most of the newborns 32(64%) faced no problems during KMC, 5(10%) & 4(8%) experienced excess hot/sweating & excess crying respectively and 2 (4%) had restlessness, breathing problem & umbilical bleeding. Among the caregivers, 45 (90%) experienced no problem, 3 (6%) had physical weakness & hot feeling and 2 (4%) excess sweating & tiredness.

DISCUSSION

In this study, 50 neonates were enrolled where male participants were 60% and female 40% and male female ratio was 1.5:1. Similar gender ratio was observed in the study by Joshi M et al 60% [6]. Among the studied newborns, 36% were inborn, delivered in the obstetric department of 250 Bedded Hospital, Moulvibazar, whereas the rest of the percentage 64% were referred cases (delivered at home or other hospitals).

The minimum postnatal age of the newborns at the time of admission was 0.33 h and maximum age 360 h (mean age 57.90 h). The postnatal age at admission might not be the same as the age of KMC initiation due to some factors- unstable infant at admission, stable but other clinical condition present (under phototherapy due to jaundice, etc), absentee of the mother or eligible caregiver, unwillingness of the caregiver to provide KMC, engagement of the duty nurses with other newborns as there was lacking of nurses at SCANU, etc. Hence, in this study we observed the time delay in 94% patients and 66 h mean. A community base pilot study in India by Rasaily R et al [7] showed that the time of initiation of KMC in 21.8% (n=22) within 24 h, 55.4% (n=56) within 72 h and 13.9% (n=14) after one week whereas we observed it 16% (n=8), 40% (n=20) and 44% (n=22) respectively.

In this study we measured the weight of the newborns at the time of admission which did not necessarily mean the birth weight because in some cases birth weight was unknown due to home or other hospital delivery. The mean weight measured was 1625.80 g whereas Joshi M et al [6] showed the birth weight to be 1359 g. In another study by Subedi K et al [8] the weight of the babies ranged between 1200 g to 2000 g and 50% (n=60) of the total included babies had weight more or equal to 1800 g, in our study the weight ranged between 820 g to 2000 g and 28%(n=14) of the total having weight \geq 1800 g. After enrollment, all the available family members were counseled in details about KMC and we observed that, mother and in case of absentee of the mother, grandmother played the pivotal role for providing the newborns with KMC. In few cases, father, aunt, grand-

Table 1. Baseline characteristics of the studied newborns [n=50]. Data presented as number (%) and mean value

Patient profile	Variables	Number (%)	Minimum	Maximum	Mean
Sex	Male	30(60)			
	Female	20(40)			
Delivery status	Inborn	18(36)			
	Out born	32(64)			
Postnatal age at admission (in hour)			0.33	360	57.90
Time of initiation of KMC (in hour)	< 24 h	8(16)	2.10	560	115.38
	24 h to 72 h	20(40)			
	>72 h	22(44)			
Age at discharge(in hour)			39	877	227
Delay from admission to KMC initiation(in number of patients)		47(94)			
Delay from admission to KMC initiation(in hour)			1.50	459	66
Causes of delay	Mother admitted in another hospital	1(2)			
	Unstable at admission	34(68)			
	Under phototherapy	10(20)			
	Nurse on duty was busy with other babies	1(2)			
	Eligible caregiver unavailable	1(2)			
Weight at admission(gram)	<1200	2(4)	820	2000	1625.80
	1200-1399	8(16)			
	1400-1599	10(20)			
	1600-1799	16(32)			
	≥1800	14(28)			
Weight at discharge(gram)			730	2030	1520.60

Table 2. Pattern of caregivers involved in KMC practice [n=50]. Data presented as number (%)

Caregivers	Number (%)
Mother	45(90)
Grandmother	28(56)
Father	17(34)
Aunt	13(26)
Uncle	1(2)

Table 3. KMC practiced (number of newborns) in three shifts [n=50]. Data presented as number (%)

Shift	KMC practiced, Number (%)	KMC not practiced, Number (%)
Morning 8am–2.30pm	27(54)	23(46)
Evening 2.30pm–8pm	44(88)	6(12)
Night 8pm–8am	43(86)	7(14)

Table 4. KMC practiced (duration) in three shifts

Shift	Minimum duration (hour)	Maximum duration (hour)	Mean duration (hour)
Morning [n=27] 8am-2.30pm	1	4	1.97
Evening [n=44] 2.30pm-8pm	1	5	2.46
Night [n=43] 8pm-8am	0.8	10	2.58

father and uncle provided KMC willingly. Studies by Nimbalkar S et al [2], Pratomo H et al [9] and Urmila K.V et al [3] showed that the caregiver for KMC was mother. Kadam et al [10] and Cattaneo [11] reported that 64% and 83% of husbands accepted KMC and supported their wives respectively.

KMC was practiced by the caregivers intermittently in three shifts, morning (8am–2.30pm), evening (2.30pm–8pm) and night (8pm–8am). In the morning shift, 54% newborns were given KMC, in the evening shift 88% and in the night shift 86%. The mean duration of KMC in the three shifts were 1.97 h, 2.46 h

Table 5. Length of hospital stay [n=50]. Time calculated from the date & time of KMC initiation

Hospital stay	Minimum duration (hour)	Maximum duration (hour)	Mean duration (hour)
	05	383	109.95

Table 7. Mortality pattern [n=50]. Data presented as number (%)

Outcome	Variables	Number (%)
Survival		44(88)
Death	At hospital	1(2)
	At home	5(10)
	Total	6(12)

and 2.58 h respectively which was 7.01 h/day cumulatively. Joshi M et al [6] showed in their study that the duration of KMC among all eligible babies remains around 9 h/day, almost similar to our study. All mothers practiced KMC intermittently; maximum duration (median) of practice/day was 8 h (Odisha) and minimum 3 h (Maharashtra) [7]. Most mothers practiced KMC 2–4 h/day in the morning or evening hours when the temperature is relatively cool [7]. Aliganyira P. et al, in their cross sectional study [12] including 11 health care facilities in Uganda showed that in only 3 facilities KMC was practiced for more than 20 h/day. Heidarzadeh M et al in a study in Iran [13] showed that the duration of KMC was at least 1–3 h which was repeated at least three times a day. Another study by Mekle D et al [14] in India revealed that >1 h KMC was practiced per sitting in 56% studied newborns (n=50) and >4 h/day KMC was practiced in

Table 6. Effect of KMC on weight gaining (who completed up to 3rd follow up) [n=32]. Data presented as number (%)

Changes in birth weight	Number(%)
No weight gain until 3 rd follow up (30 th day of age)	5 (15.62)
Weight gain at 1 st follow up (7 th day of age)	6 (18.75)
Weight gain at 2 nd follow up (15 th day of age)	14 (43.75)
Weight gain at 3 rd follow up (30 th day of age)	7(21.87)

Table 8. Problems during KMC practice. Data presented as number (%)

Problem during KMC	Pattern of problem	Number (%)	
Problem related to newborns[n=50]	No problem	32(64)	One newborn might have multiple problems, so, [n] and Number (%) may be different
	Restlessness	2(4)	
	Vomiting	1(2)	
	Excess hot/ sweating	5(10)	
	Breathing problem	2(4)	
	Excess crying	4(8)	
	Umbilical bleed	2(4)	
Problem related to caregivers[n=50]	No problem	45(90)	One caregiver might have multiple problems, so, [n] and Number (%) may be different
	Restlessness	1(2)	
	Excess sweating	2(4)	
	Physical weakness	3(6)	
	Hot feeling	3(6)	
	Tiredness	2(4)	

14% which was similar to our study result where the mean duration of KMC was 2.3 h per shift and 7 h/day(n=50).

It was observed that the mean hospital stay was 109.95 h (4.58 days). Uwaezuoke SN [15] in a study in Nigeria showed that infants who weighed ≤ 1500 g at birth and received KMC had shorter duration of admission than those who received conventional method of care (4.0 days Vs13.8 days). Randomized control trial demonstrated that KMC infants discharged from hospital earlier than control group [16, 17]. Infants who received conventional care stayed longer in the hospital than the KMC infants [18]. Gupta M et al [19] observed the mean duration of hospital stay was 15.5 days. Similarly, in a study in Merida newborns were discharged at 13.4 days after enrolment [20]. In Delhi studies the average day of hospital stay was 27.2 ± 7 days [17].

Because of loss of extra cellular fluid, around 5–15% of weight loss occurs in newborn babies. The nadir of weight loss occurs by 4–6 days of life and then gradually weight gain starts and birth weight regained by 14–21 days of life [8]. Various other studies had shown that KMC babies had better average weight gain per day [8]. Ramanathan et al [17, 19] found the average weight gain in KMC babies after the first week of life was 15.9 g/day. Another study by Urmila K.V et al [3] revealed that birth weight was regained from 6 to 29 days and maximum number regained birth weight on 14th day. In our study, weight gain started from 7th day of age in 18.75%, from 15th day in 43.75% and from 30th day in 21.87% newborns.

Different studies revealed the mortality pattern in relation to KMC. In a study by Ahmed S et al [21] found that most newborn deaths in the community KMC(CKMC) group occurred in babies who were held skin to skin (STS) ≤ 1 h/day (neonatal mortality rate NMR, 8.4%) or who had missing newborn STS

assessment (NMR 8.1%). NMR was 2.8% in babies held STS between 2 to 6 h/day in the first 2 days of life. Only five newborn deaths (NMR 0.9%) occurred in CKMC babies held STS \geq 7 h/day in the first 2 days of life. Conde-Agudelo A, et al. found no evidence in difference in infant mortality in KMC as compared to conventional care after stabilization [22]. The Cochrane review [23] included seven trials that assessed mortality at discharge or at 40–41 weeks. These trials reported a statistically significant reduction 3.4% in the risk of mortality among KMC infants, compared with 5.7% for babies receiving traditional care. In this study it was observed that the mortality in KMC newborn was 12% (at hospital 2% and at home 10%). During each follow up session mother or the caregivers were interviewed about the problems experienced by themselves or the newborns during KMC practice. Most of the participants (64% newborns, 90% caregivers) experienced no problems. The other problems common to both were restlessness (4% newborns, 2% caregivers) and excess sweating (10% newborns, 4% caregivers). Quasem et al [24] in his study reported that mothers experience discomfort when the infant grows bigger. Urmila K.V. et al [3] reported that 6.2% of mothers experienced physical difficulties for practical implementation compared to 54% who experienced back pain in this study. Trials have shown that infants rarely cry when in KMC [25–30], a Cochrane meta-analysis has confirmed a reduction in crying during KMC [32] whereas we observed that 8% newborns (n=50) cried excessively during KMC. The effect of KMC on infant body temperature has been studied extensively [28, 32–39] which revealed that when the healthy preterm infants are placed in KMC, infant body temperature rises. This finding was consistent with our result (10% newborns experienced excess body temperature/sweating).

Grace JC, et al in their systematic reviews mentioned that there are several barriers to implementing KMC, including the need for time, social support, medical care and family acceptance [40]. KMC should be practiced more systematically and consistently to enhance adoption and to build trust, with motivated trained staff, education of the staff and parents, clear eligible criteria, improved referral practices and creation of communities among KMC participants through support groups. By addressing barriers and by building trust, effective uptake of KMC into the health system will increase and this will help to improve neonatal survival [40].

CONCLUSION & RECOMMENDATION:

It was observed that mothers involved in KMC practice mostly in spite of their household work load,

sometime making KMC inadequate, inappropriate and distressful. Family motivation and participation is a key to standard KMC practice. More focus should be made on morning and evening hours when KMC practice was observed less in terms of number and duration. Constant supervision and follow up home visit involving trained and motivated community health personnel until the neonatal age is completed constitute the most important aspect for implementing KMC effectively and reducing the mortality.

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RESULTS OF THE TREATMENT OF CONGENITAL HYDRONEPHROSIS

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ABSTRACT — The paper evaluates the results of treatment in 92 children with congenital hydronephrosis of grades II and III. Plastic surgery of the adjuvant segment was performed in 67 patients using the Anderson-Hynes-Kucera pyeloplasty, while minimally invasive endoscopic treatment was performed in 25 patients. To diagnose nephrosclerosis in children with hydronephrosis and connective tissue dysplasia, urinary nephrosclerosis factor (TGF- β 1) and glycosaminoglycans were studied. Static nephroscintigraphy revealed changes in the contralateral organ with unilateral lesion.

KEYWORDS — congenital hydronephrosis, minimally invasive endoscopic treatment, nephrosclerosis, connective tissue dysplasia, children.

INTRODUCTION

The problem of treating children with prenatally established hydronephrosis is one of the leading ones in pediatric surgery and urology, due to the complications of its postnatal course. The urgency of the problem is determined not only by the prevalence of the disease (1:500–800 newborns), but also by the complexity of the treatment and diagnostic measures, especially in newborns and children of the younger age group. According to the literature, hydronephrosis tends both to spontaneous resolution with age (up to 1.5–3 years) and to progression with loss of kidney function, despite the elimination of urodynamic obstruction and stabilization of the inflammatory process [1, 2, 3]. In connection with the active development of antenatal diagnosis, treatment is carried out from the first months of the child's life. The priority is the restoration of urodynamics. Scientific information on the diversity of the pathogenesis of congenital hydronephrosis has changed the approaches to its treatment — from open surgical to minimally invasive endoscopic in the form of bougienage and stenting of the ureteral lining of the ureter with the simultaneous use of energy-producing ripening preparations [4]. The

recurrent course of an infection of the urinary system, the late start of treatment — all these are factors that adversely affect the result. Despite the elimination of obstruction, there are manifestations of nephrosclerosis in the renal parenchyma, which is formed in 30–60% of patients with impaired urodynamics. Timely diagnosis and treatment measures to stop the process of nephrosclerosis are important for the morphological and functional state of the kidney, which is especially important in a bilateral process [5, 6, 7]. The search for rational schemes for postnatal examination is an objective reality and it should be aimed at minimal invasiveness when performing both diagnostic and therapeutic procedures, taking into account the age of the main contingent of patients.

Purpose

analysis of hydronephrosis treatment methods and their results.

MATERIALS AND METHODS

The material of this work was the analysis of the results of examination, treatment and observation of 92 patients with grade 2 hydronephrosis (49%), grade 3 (51%) who were undergoing in-patient examination and surgical treatment from January 2016 to September 2018 at the Department of Urology of Children's Regional Clinical Hospital, Tver. The degree of hydronephrosis was established in accordance with the ultrasonic classification system for hydronephrosis developed by the Society of fetal urology (SFU) 1993. Patients were divided into two groups. The first — 67 patients aged from six months to 17 years, operated using the Anderson-Hynes-Kucera technique with the assessment of long-term treatment results from 1 year to 24 years. The second group consisted of 25 patients aged from three months to seven years with prolapse of the parietal segment managed by subsequent placement of a catheter-stent for a period of one to five months as an independent treatment method, which also evaluated the long-term results of treatment from six months to two years. By gender, boys made up 54%, girls — 46%. The average age of patients is 5.6 ± 1.8 years. Left-sided hydronephrosis was found in 62%, right-sided — 38%.

INSPECTION METHODS

The design of the examination of patients included a diagnostic complex that made it possible to verify

the diagnosis, assess the condition of the upper and lower urinary tract, the functional state of the kidneys in the preoperative and postoperative periods, and included: laboratory, ultrasound examination of the kidneys with dopplerography (ultrasound), intravenous urography or computed tomography with contrast amplification, diuretic ultrasonography, static nephroscintigraphy. To diagnose nephrosclerosis in children (37) with hydronephrosis and connective tissue dysplasia, the urinary nephrosclerosis factor (TGF- β 1) was studied. Urinary TGF β was determined by enzyme linked immuno-absorbent assay (ELISA) in children before and after surgery: after 1 year (18). In order to diagnose connective tissue dysplasia, a biochemical urine test was performed — glycosaminoglycans (GAG) — 37, which made it possible to determine the severity of dysplasia. When choosing treatment tactics, the degree of hydronephrosis, the state of the renal parenchyma, the age of the patient, and the degree of connective tissue dysplasia were taken into account. The method of choosing surgical treatment continues to be the Anderson-Hynes-Kucera operation, which was performed in 67 patients. Ureteral stent placement, as an independent method, was performed in 25 patients, of which 14 were young children. In 8 children, at first, the intravesical and parietal segments were bougiended with the ureteral catheter Ch — 3, 4, 5 with its subsequent replacement with the JJ stent Ch — 5 after 5–7 days. Stent patency was monitored using an ultrasound scan of the MVS for 1–3 days after the installation of a stent catheter, a month later, before and after its removal, with an assessment of the size of the CLS. All children were prescribed antibiotic therapy in the pre and postoperative periods to prevent exacerbation of secondary pyelonephritis, taking into account the sensitivity of microflora. The duration of standing of the catheter-stent in the urinary tract was 3 ± 2 months.

RESULTS

The results of treatment of patients with hydronephrosis were evaluated according to the following criteria: good, satisfactory and unsatisfactory. By good the preservation of the renal parenchyma and evacuation ability, remission of pyelonephritis was meant. Under satisfactory — moderate dilatation of the CLS with impaired evacuation function, latent pyelonephritis. Under unsatisfactory — the loss of the anatomical and functional state of the kidney. Good results after Anderson-Hynes-Kucera operation were achieved in 96%, in the 2nd group of patients in 68%. Examination after stenting for adequate assessment of its effectiveness was carried out in 1-3-6-9-12-18-24 months. Ultrasound showed an improvement

in blood flow and IR values ranged from 0.6 to 0.7. When analyzing GAG and urinary TGF β data, all children showed an increase in their level. The indicator of the biochemical marker of mesenchymal dysplasia (GAG) was within the normal range in only 5 (18%) cases, while no relationship was found between its level and age ($p = 0.348$) and the degree of hydronephrosis ($p = 0.857$). This indicator is not a reliable sign of the presence of DST in children with hydronephrosis, but an increase in its level indicates the immaturity of the child. The dependence of the indicator of urinary nephrosclerosis factor (TGF) and the degree of hydronephrosis before surgical treatment was determined: with an increase in the degree of hydronephrosis, the TGF indicator changes: Grade 2 — 10.73 ± 0.83 ; Grade 3 — 11.25 ± 0.64 . (norm 2.6 ± 0.9 pg/ml), in the comparison group 2.24 ± 0.2 , which is the norm of this indicator. An increase in hydrostatic pressure with an increase in the volume of the pelvis triggers the mechanism of pyelovenous, pyelotubular refluxes, contributing to the progression of damage to the parenchyma. A relationship has been established between the degree of hydronephrosis and the level of urinary factor hydronephrosis. This bond is of medium strength ($r = 0.571$; $p < 0.001$). Pearson's linear correlation between the degree of hydronephrosis and the level of urinary factor hydronephrosis was determined by the linear regression formula — level of urinary factor = $4.197 + 3.513 \times$ degree of hydronephrosis. The study of the indicator in the comparison group showed that in patients with hydronephrosis, urinary nephrosclerosis factor remains high compared with children without hydronephrosis 11.07 ± 0.50 and 2.24 ± 0.28 . The differences are statistically significant (Student's test for independent variables ($p < 0.001$)). The urinary TGF 1 year after surgery was reduced from 13.36 ± 0.70 to 11.07 ± 0.50 . Changes are statistically significant (Student's test for paired measurements, $p = 0.006$). For a qualitative assessment of static nephroscintigrams, a classification was used that took into account 3 types of parenchyma lesions [8]. Patients before ureteropyeloplasty (12) with hydronephrosis of 2 and 3 grades in the parenchyma of the hydronephrotic kidney had 2 types of lesions (85.71%) Changes also affected the contralateral kidney, 42.71%. After surgical restoration of the passage of urine, there was an improvement in the functional state of the parenchyma, both operated (type 2 — 55.56%) and the contralateral kidney, 22.22%. In all children, prior to the prolapse of the extracranial segment (25) with hydronephrosis of 2 and 3 grades there were signs of parenchyma lesion, type 2 was 92%, Type 1 — 8%, lesions of the parenchyma of the contralateral kidney were noted in about 36.4% patients. After stenting, the

parameters of static nephroscintigraphy improved in the operated kidney, type 2, 62.5%, type 1, 37.5%; in the parenchyma of the contralateral kidney, there was no positive dynamics, type 36.5%. Positive dynamics of the state of the parenchyma in both kidneys was noted after stenting, which can be explained by a large supply of *sleeping* nephrons due to the younger age.

CONCLUSION

The choice of treatment for hydronephrosis is objectified by the morphological and functional state of the renal parenchyma, the age of the child, and the presence of comorbid conditions. The use of endoscopic minimally invasive techniques is justified for hydronephrosis of 2–3 Grade in children of a younger age group. Anderson-Hynes-Kucera ureteropyeloplasty is the method of choice for grade 3 hydronephrosis in children older than 3 years. A marker for the development of nephrosclerosis in the renal parenchyma is an increase in TGF β , which correlates with the degree of hydronephrosis. Therefore, the study of this indicator should be included in the program of rehabilitation of children with hydronephrosis. An increase in glycosaminoglycans is a marker of the child's immaturity and should be taken into account when choosing a method of treatment and prescribing therapy for ripening, as these children are children of the *late start*.

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EXPERIENCE OF TREATMENT OF SPLENIC CYSTS IN CHILDREN

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ABSTRACT — The problem of treatment of spleen cysts in children has not lost its relevance at the present time. The choice of medical tactics at the present stage is far from unification. 26 children were treated from 2007 to 2020. 23 (88.5%) children were operated on. Sonography was the main diagnostic method. More often primary (true) spleen cysts prevailed. An analysis of our own results showed that the method of choice was laparoscopic fenestration, minimizing the risk of recurrence. In one case (3.8%) there was a complication in the form of bleeding, which required splenectomy. There were no fatal outcomes.

KEYWORDS — spleen cysts, children, laparoscopy, sonography.

INTRODUCTION

Spleen cysts in children are quite rare. They are mainly represented by congenital cysts, lymphangiomas and hemangiomas, post-traumatic hematomas, and, sometimes, echinococcal cysts, angiosarcomas and lymphomas [1]. Spleen cysts, especially large ones, are potentially dangerous, since the risk of organ damage and the occurrence of intra-abdominal bleeding is significantly increased [2]. Such a complication often ends with splenectomy. It is known that the spleen is an immunocompetent organ and its removal leads to a *post-splenectomy* syndrome [3, 4]. Nowadays, splenectomy is not a key option for most surgeons, not only because of spleen damage, but also because of benign neoplasms [5]. The treatment of spleen cysts is a debatable issue, as there is no single treatment tactic [6]. An alternative spleen-preserving option is laparoscopy with fenestration of the cavity [7, 8]. Percutaneous puncture methods are not successful in all cases, because de-epithelialization of the cyst cavity by various aggressive chemical agents is not always able to stop the production of cyst contents. The combined method of laparoscopic fenestration with superselective occlusion of the spleen vessels is not available to a

wide range of pediatric surgeons [9]. The work evaluates the effectiveness of therapeutic methods.

Purpose

analysis of the results and selection of the optimal treatment method for children with non-parasitic spleen cysts.

MATERIALS AND METHODS

From 2007 to 2020, 26 children with non-parasitic spleen cysts aged 6 to 17 years were treated at the Tver Children's Regional Clinical Hospital. There were 14 boys (54%), 12 girls (46%). Cystic spleen damage was most often asymptomatic and was detected by ultrasound of the abdominal cavity and retroperitoneal space for other diseases. Clinical symptoms were manifested in only 8 (31%) patients in the form of pain in the left hypochondrium, which was dragging in its nature. In the anamnesis, only 1 child had spleen damage, treated conservatively, after which a large post-traumatic cyst was formed. On palpation of the abdomen in 2 patients, a tumor-like formation emanating from the left hypochondrium, painless, sedentary, densely elastic consistency was determined. Splenomegaly was detected in three patients. The main diagnostic methods were ultrasound, CT and MRI of the spleen.

In all cases, the diagnosis was made using ultrasound. The localization of the cyst in the upper pole of the spleen predominated, in 17 (65%) cases, in 3 (12%) children the cyst was found in the area of the gate of the spleen, and in 6 (23%) patients in the lower pole. The diameter of the cysts varied from 13 to 150 mm. In 24 (92%) patients, cysts are represented by a single-chamber formation, in 2 (8%) cases with multiple septa. Laparoscopic fenestration was performed in 19 (72%) patients. Laparoports with a diameter of 5 mm with manipulators were installed in the right hypochondrium and left mesogastric regions. Sometimes the installation of a third manipulation laparoport in the epigastric region was required. Visualization was carried out through the umbilical region using a 5 mm telescope (Karl Storz). In all cases, the cyst membranes were excised with ultrasonic scissors along the border with the parenchyma and the maximum destruction of the inner lining by argon plasma coagulation was performed. Additionally, the residual cavity was plugged with a lock of the omentum and a safety drainage to the spleen was installed.

Puncture-sclerosing interventions were performed in 4 (16%) children. Using ultrasound navigation (MySono U6-RUS SAMSUNG MEDISON) the puncture system (Teleflex) No. 8 and a conductor were set up at the site of the smallest thickness of the spleen parenchyma. Drainage was established through this conductor into the cavity, the contents of the cyst were evacuated, and sclerosant was administered. Then, a sclerosant (alcohol 96%) was introduced into the cyst cavity. 3 (12%) children did not undergo surgical treatment due to the small diameter of the spleen cyst.

RESULTS

Our analysis of the treatment results showed that laparoscopic fenestration was successful in 17 (68%), and in one (4%) patient there was a relapse. We believe that relapse occurred because tamponade of the residual cavity with the omentum was not performed in this case. After 6 months, the child was successfully operated on — laparoscopic fenestration was performed with fixation of the omentum in the residual cavity. We believe that these measures are necessary, since tamponing the residual cavity with an omentum strand performs a drainage function, and the established safety drainage is an indicator of delayed intra-abdominal bleeding. After puncture-sclerosing intervention in one (4%) child, relapse was recorded twice. During laparoscopic fenestration, in one (4%) case there was spleen damage, complicated by massive bleeding, which required conversion and splenectomy. There were no fatal outcomes. In two (8%) children with relapse, histological examination revealed cystic capillary lymphangioma (coarse fibrous tissue with hyalinosis, focal lymphoid infiltration with single eosinophils; a large number of closely adjacent erythrocyte capillary vessels was determined in one of the sites; on the inner surface of the capsule endothelial lining preserved in places). In other cases, a histological examination revealed a true spleen cyst.

CONCLUSIONS

Nonparasitic spleen cysts are a rare pathology in children, which requires an individual approach when choosing treatment tactics. To minimize surgical invasion, spleen-preserving interventions should be used, which are associated with the obligatory destruction of the inner lining of the cyst, which reduces the risk of recurrence. The operation of choice is laparoscopic fenestration, and in case of recurrence, it is possible to use endovascular occlusion of the vascular pools of cystic formations.

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SURGICAL TREATMENT FOR LUMBAR DISK HERNIATION IN AN ADOLESCENT PATIENT: CLINICAL CASE STUDY

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ABSTRACT — Osteochondrosis of the spine refers to one of the leading problems of modern medicine. This disease is most characteristic of patients aged 25 to 55 years. It is noted that adolescents are increasingly suffering from osteochondrosis of the spine and its complications in the form of a hernia of an intervertebral disc. The purpose of this report: to analyze the clinical picture and the results of surgical treatment of a rare clinical case in childhood, represented by a hernia of the lumbar intervertebral disc with radicular syndrome. Surgical treatment consisted of a combination of microdiscectomy and foraminotomy under the control of endoscopic techniques.

KEYWORDS — osteochondrosis, herniation of an intervertebral disc, microdiscectomy, foraminotomy.

INTRODUCTION

According to the data of the neurosurgical service of the Russian Federation, about 50 thousand patients per year are operated on for a hernia of an intervertebral disc. Among them, 0.5–2% patients tend to be adolescents under 18 years of age. The article presents a clinical case of successful surgical treatment for a hernia of an intervertebral disc in a 15-year-old adolescent [1–4].

CASE DESCRIPTION

Patient M., 15 years old. Growth and development took place in accordance with gender and age.

Medical history. Back pain started 6 months prior to the first examination. Conservative treatment produced no effect. On admission the MRI of the lumbosacral region showed a paramedian right-sided hernia of the L4–L5 intervertebral disc up to 10 mm with stenosis of the intervertebral foramen on the right and compression on the nerve root.

On examination: complaints of pain in the lumbar region with radiation to the right lower limb, gait disturbance, numbness of the right lower limb. In neurological status, hypoesthesia was noted in the

right lower leg, paresis of the right foot up to 3 points, tingling of the right leg when walking. Weight — 57 kg. Height — 164 cm.

In a preoperative examination, weak myopia, mitral valve prolapse of the I–II degree, and vegetative symptoms were diagnosed.

A microsurgical operation was performed as follows: microdiscectomy L4–L5, foraminotomy, radiculolysis L5 on the right with video endoscopic assistance.

Progress of the operation. A linear incision was made in the lumbar region in the projection L4–L5 ~ 3.5 cm with installation of operating microscope. Radiculolysis of the root L5 was performed. The posterior longitudinal ligament above the herniation of the intervertebral disc was dissected, the latter was removed. The procedure was controlled by of a 30-degree endoscope, Foraminotomy and decompression of nerve structures were performed in the projection of the L5 root.

The postoperative period. Pain syndrome regressed on the first day. The child was vertical on the second day.

Histological examination of a removed hernia of the intervertebral disc revealed signs of connective tissue dysplasia in the form of extracellular matrix disorganization sites.

At discharge (on the 4th day) the patient was at a satisfactory condition, had no complaints; movements and sensitivity in the right lower limb were recovered.

The teenager was discharged with a diagnosis of “Juvenile osteochondrosis: right-sided paramedian hernia of the L4–L5 intervertebral disc with stenosis of the foraminal opening, persistent lumbar ischialgia on the right.”

At the follow-up examination after 3 months no complaints and neurological deficit were observed.

MRI control of the lumbar spine noted no signs of compression of the structures of the spinal cord; spinal canal, foraminal openings was not narrowed.

DISCUSSION

Currently, spinal osteochondrosis in children is considered as one of the common forms of chronic systemic damage to connective tissue [5–8]. Surgical intervention in the form of microdiscectomy in

combination with foraminotomy under the control of endoscopic technique helped to achieve a good treatment effect in this clinical case. In the expanded foraminal opening, a reserve space is created for the nerve root, which reduces the risk of adhesions in the postoperative period, which can manifest as radicular pain [9].

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OPTIMIZATION OF EARLY DIAGNOSIS OF NECROTIC ENTEROCOLITIS IN NEWBORNS

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ABSTRACT — Necrotizing enterocolitis (NEC) is an inflammatory disease of newborns which causes serious damage to the gastrointestinal tract (GIT) leading to development of perforations and intestinal necrosis. In our study, we have focused on early diagnosis of NEC based on imaging and laboratory findings. Elevations in fecal calprotectin can be used as an effective biomarker for diagnosing of NEC. We found that if the level of fecal calprotectin was higher than 1.1 mg/g, NEC can be diagnosed. The level of fecal calprotectin exceeding 1,5 mg/g is considered to be an indication for surgery.

KEYWORDS — NEC, newborns, treatment, diagnosis, fecal calprotectin.

INTRODUCTION

Despite the achievements of medical science and practice there are issues in the clinical medicine that still remain relevant and this refers to necrotizing enterocolitis in newborns.

Relevance of the NEC, despite the progress achieved in diagnosis and treatment, is confirmed by the mortality among the patients after surgery, which reaches 60% and there is no tendency to its reductions [4, 5, 7].

To date, the etiology and pathogenesis of NEC has been the subject of extensive scientific discussion. The main efforts are aimed at finding potential markers to identify NEC in the early stages, to determine the nature of the course and prognosis of the disease [2, 3, 6].

Despite the progress achieved in the diagnosis, the analysis of the immediate and long-term results of treatment of NEC demonstrates that in 16–40% of children the course of the disease is complicated by intestinal perforations, the mortality in which reaches according to different authors from 40–90% [4, 7, 9]. It becomes quite obvious that the success of treatment depends not only on adequate surgical correction,

timely and rational prescription of antibiotics, but also is determined by a complex of diagnostic and therapeutic measures aimed at early detection of signs of complicated course of NEC [1, 6, 8]

It is known that in patients with NEC any parts of the gastrointestinal tract (GIT) can be damaged. The prevailing pathological process in more than 90% of cases is inflammation and coagulation necrosis of the intestinal wall. The proven risk factors in the pathogenesis of NEC are prematurity, early onset of feeding, asphyxia, intestinal ischemia, immune disorders, infection, and low gestational age [1, 5, 9, 4, 6].

Aim:

to optimize early diagnosis and treatment of necrotic enterocolitis in newborns using laboratory and instrumental diagnostic methods.

MATERIALS AND METHODS

Our study encompassed 30 newborns, 10 days old, with necrotic enterocolitis (acute and subacute forms). There were 18 boys (60%) and 12 girls (40%) in the group. All newborns underwent x-ray examination of the abdominal cavity, ultrasound of the abdominal organs. The laboratory tests included: complete blood count (CBC) every 6 hours, clinical urinalysis (UA), coagulogram (thrombin time, activated partial thromboplastin time (APTT), fibrinogen), biochemical blood analysis (C-reactive protein (CRP), glucose, total protein, albumins, triglycerides, bilirubin, creatinine, urea), tests of procalcitonin in the blood on the basis of immunochemiluminescence; bacteriological blood testing for sterility (isolation of pure culture), antimicrobial susceptibility testing of isolated cultures, fecal occult blood test.

The objective of the suggested diagnostic techniques was to identify diagnostic criteria for necrotic enterocolitis (NEC). It is very challenging for pediatric surgeons to reliably assess, whether medical management is possible or surgical intervention is required. This challenge justifies a priority of optimizing diagnosis and treatment of NEC.

RESULTS AND DISCUSSION

To assess the severity of the condition and the stage of the disease, we used the criteria of Bell's

stage. During the first stage, there was a stretching of intestinal loops on the abdominal x-ray survey, CBC: anemia, leukocytosis $+25.4 \times 10^9/l$, leukopenia, $+4.5 \times 10^9/l$, a shift of the leukocyte formula to the left, UA without changes, a biochemical blood test within normal parameters, a fecal analysis for hidden blood-positive. Ultrasound of the abdominal cavity showed the absence of infiltrates and other formations in the abdominal cavity, sluggish intestinal peristalsis. During the second stage, on an overview x-ray of the abdominal cavity, dilation of intestinal loops, an increase in the thickness of the intestinal wall due to edema and inflammation, in the CBC thrombocytopenia is lower than $+150 \times 10^9/l$, UA is unchanged, Biochemical blood test: hypoalbuminemia, hyperbilirubinemia, C-reactive protein $+10 \text{ mg/l}$, increased urea. Ultrasound of the abdominal cavity: reduced peristalsis in the affected segments, uneven, moderate dilatation of intestinal loops. Fecal calprotectin was observed in the range of $1.1-1.4 \text{ mg/g}$. During the third stage, subserous pneumatosis of the intestinal wall with its thickening, fixed intestinal loops, gas in the portal vein system, and pronounced ascites were showed on the x-ray. Ultrasound of the abdominal cavity: pronounced local thickening of the intestinal wall, infiltrates are located, between the loops of the intestine and in the pelvic cavity, CBC neutropenia $+1.5 \times 10^9/l$. Serum electrolytes: hyponatremia, hypocalcemia, hypokalemia. Coagulogram: increase in APTT, thrombin time. Biochemical blood analysis: hypoalbuminemia, hyperbilirubinemia, C-reactive protein $>10 \text{ mg/l}$, increased urea, residual nitrogen, increasing procalcitonin $+2 \text{ ng/ml}$ is a marker of sepsis; ABS of blood pH $+7.2$. The development of intestinal necrosis is indicated by the preservation of metabolic acidosis for more than 4 hours against the background of intensive therapy. In 21 (70%) children a bacteriological blood test gave a positive result. 11 (36.6%) children were operated on. The indicator of fecal calprotectin varied from $1.5-2.5 \text{ mg/g}$. This provides evidence of a deep lesion of the intestinal wall and reflects the severity of the intestinal perforation and enables to select management strategies for newborns.

CONCLUSION

1. Early diagnosis of ulcerative-necrotic enterocolitis in newborns is aimed at determining the level of fecal calprotectin in the stool.
2. If the level of fecal calprotectin is higher than 1.1 mg/g , necrotic enterocolitis is diagnosed (patent RU 2 705 379 C1).
3. If the level of fecal calprotectin is higher than 1.5 mg/g , surgery is considered to be a better option.

Therefore, we have confirmed the feasibility of using fecal calprotectin for early diagnosis of NEC.

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EFFECTIVENESS OF MINIMALLY INVASIVE TECHNOLOGIES IN PATIENTS WITH POSTOPERATIVE GASTROINTESTINAL ARTERIAL BLEEDING

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ABSTRACT — When it comes to treatment of patients with intraluminal bleeding, endovideosurgical methods are the methods of choice. Our hemostasis strategies encompass use of clipping, electrocoagulation, and bleeding vessels tamponing. At the same time, the available literature has offered no information concerning the effectiveness of minimally invasive procedures when treating patients with postoperative gastrointestinal bleeding. Thus, the purpose of this study was to find out the most effective minimally invasive surgery. Our study involved 73 patients with arterial bleeding divided into 3 groups. 23 patients with bleeding from duodenal ulcers (Group 1), 19 patients with bleeding from stomach ulcers (Group 2), while another 31 patients with gastric and duodenum bleeding (Group 3). The study was carried out in accordance with the ethic criteria and a written informed consent obtained from all the patients. The analysis of the effectiveness of the procedures demonstrated the benefit of clipping with the effectiveness of 90.1%. Argon-plasma coagulation proved effective in 80.0% of the cases, combined procedures to achieve homeostasis was effective in 79.2 % of the cases, whereas 66.7% was given to electrocoagulation. Clipping is an effective method to stop suture line bleeding and bleeding resulted from traumatic rupture of mucous membrane. The main indications for using clipping include acute ulceration, with a diameter not exceeding or slightly exceeding the clip size.

KEYWORDS — minimally invasive procedures, postoperative abdominal bleeding.

INTRODUCTION

The quality of medical care, highly competent professionals, advanced innovation-based diagnostics and treatment technologies, high-tech equipment and availability of medical services are the components of healthcare systems in various countries, which positively influence the quality of life [10, 18]. Digital technologies have penetrated all spheres of human life, including medicine. Their potential use in dentistry through all stages includes keeping medical records, diagnostics (radiovisiographs, computer tomographs, virtual articulators, digital cameras), modeling and simulation of clinical situations as well as treatment.

Methods for obtaining and orienting computer 3D models of teeth and dental arches, measuring the height of fissures, tubercles, the shape of their slopes, along with methods for controlling odontopreparation are being developed [11–17].

Minimally invasive technologies have currently found wide implementation in clinical abdominal surgery, which improves significantly the effectiveness of treatment. These technologies are widely used in abdominal surgery managing complications, for comprehensive prevention and treatment [3, 4, 5, 6, 8].

Improving methods and volumes of repeated surgical intervention is an important factor that will be decisive for the outcomes of eliminating the pathological process leading to complications, where special gastrointestinal bleeding is viewed as specifically important [2, 7].

Endovideosurgical methods are used to treat patients with intraluminal bleeding. Researchers believe that endoscopic methods are recommended in case of bleeding, with no reduction in the hemodynamics major indicators. It has been noted that clipping, electrocoagulation, and tamponing of bleeding vessels are used to achieve hemostasis [1].

Experts, in turn, point at the fact that surgical treatment of gastrointestinal bleeding, especially in the postoperative period, is associated with a high mortality rate, and is recommended for cases of unsuccessful endoscopic interventions. It is noted that a differentiated management approach requires improved methods to stop bleeding, including injection, endoclips of various designs, diathermocoagulation, and argonoplasmic coagulation [9]. A combination of these modalities is also possible.

At the same time, the available literature has not contained data on the effectiveness of minimally invasive techniques to manage postoperative gastrointestinal bleeding, which becomes the aim of our study.

Aim:

to improve minimally invasive techniques in the treatment of patients with postoperative gastrointestinal bleeding, as well as identifying the effectiveness of such methods.

MATERIALS AND METHODS

The study involved 73 patients with arterial bleeding. 23 of the patients were diagnosed with bleeding from duodenal ulcers (Group 1), 19 had bleeding from stomach ulcers (Group 2), and another 31 patients had bleeding from the gastric and duodenum suture line (Group 3). The study was performed in accordance with current ethic requirements and with a written informed consent obtained from all the patients.

The treatment relied on the epinephrine injection method, which was applied along the bleeding source perimeter. Fluoroplastic injector was used, which was introduced through the endoscope channel. Patients with a loose red blood clot, had combined treatment with Caproferr (Fig. 1).



Fig. 1. Vessel bleeding in a patient with a flat duodenal ulcer (a) and the method of infiltration of epinephrine solution (b)

The method of clipping was used to stop bleeding from the suture line and the mucosa traumatic ruptures. Indications for administering this method also included acute ulcers with a diameter not exceeding the size of the clip, which allowed clipping in the projection of the bleeding vessel within viable tissues (Fig. 2).

If clipping is not possible, as the most optimal procedure we consider argonoplasmic coagulation combined with paravascular injection, especially in cases where the bleeding source was to be found near large intramural vessels (Fig. 3)

RESULTS AND DISCUSSION

The choice of the method for endoscopic management of bleeding was mostly influenced by the severity, nature and localization of the source of hemorrhage.

The study revealed a positive outcome in 19 out of 23 patients with duodenal ulcer. In this case, clip-

ping was performed in 9 patients, while 3 patients had argonoplasmic coagulation, and in 7 more cases the combination of injection with argon-plasma coagulation was employed. Emergency relaparotomy was performed in 3 patients due to inefficiency of minimally invasive technologies. During the postoperative period, one patient died due to cerebral circulation failure.

Postoperative arterial bleeding from stomach ulcers was identified in 19 patients. The effectiveness of hemostatic manipulations was observed in 16 people. Electrocoagulation was employed in 4 patients, argonoplasmic coagulation – in 5 cases, whereas combined minimally invasive methods were used in 7 patients. It is to be noted that three patients had relaparotomy due to inefficiency of endoscopic hemostasis.

26 patients of Group 3 revealed effectiveness of minimally invasive technologies for bleeding from the suture line. In this case, clipping was performed in 19 patients, and electrocoagulation combined with injection — in 7 cases. Emergency relaparotomy was performed in 5 patients, out of 31 people in Group 3. No lethal outcomes were registered in this group.

The effectiveness analysis of the methods revealed that the most effective procedure is clipping, which displayed the effectiveness of 90.1%. The argon-plasma coagulation proved effective in 80.0% of the cases, while combined procedures were effective in 79.2% of the cases, and electrocoagulation accounted for 66.7%.

CONCLUSIONS

Clipping is an effective treatment option when it comes to stopping bleeding from the suture line and traumatic ruptures of the mucous membrane. At the same time, in order to achieve the best outcome of this procedure, it is necessary to clearly determine the

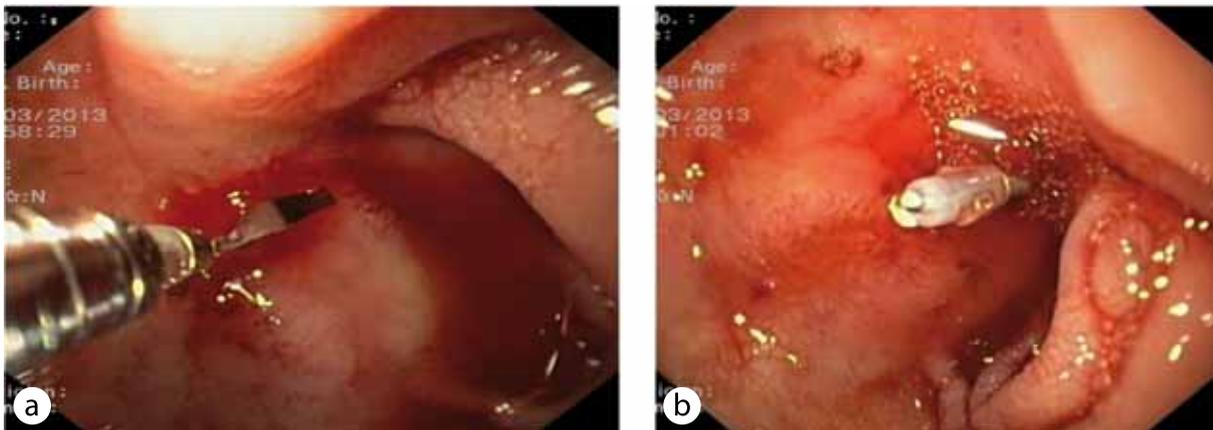


Fig. 2. Attaching the endoclips to the bleeding vessel (a) and the method of applying the clip to the ulcer bottom vessels (b)

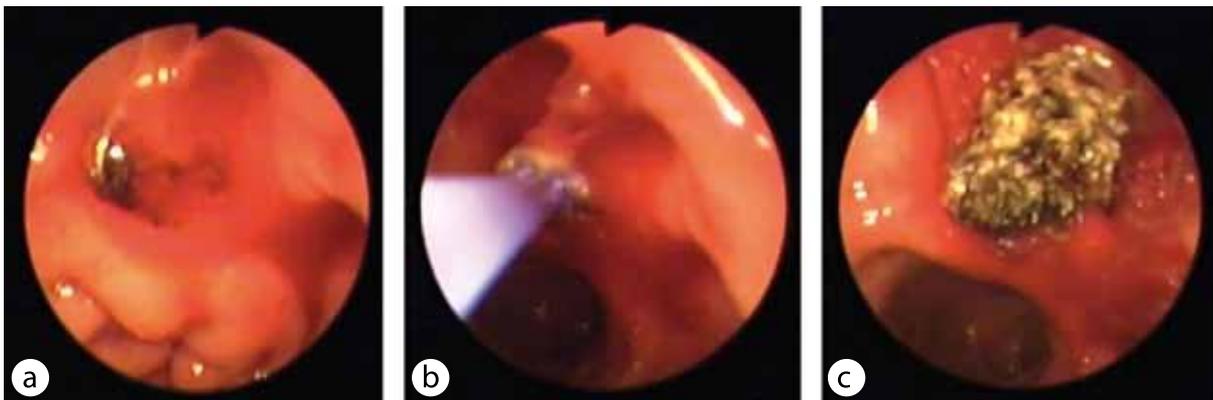


Fig. 3. Duodenal bulb ulcer with a fixed clot and continuous bleeding (a); method of argon-plasma coagulation of the ulcer (b); scab formation after the ulcer coagulation (c)

indications for its use. The main indications, as we see them, also include acute ulceration, with a diameter not exceeding or slightly exceeding the size of the clip, provided it is possible to perform clipping in the projection of the bleeding vessel as well as within the minimally altered viable tissues.

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REHABILITATION OF PATIENTS WITH APICAL PERIODONTAL CYSTS OF JAWS

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ABSTRACT — The present study shows that the processes of reparative osteogenesis start in the parietal area of the osseous defect and are directed to the apex. Synchronism of these processes is significant which occurs simultaneously being linked with the degree of demineralization of the implant induced into the osseous defect. It has been stated that indigenous bone grafting material «bioOst» with interfacial demineralization in filling of infected bone defects possesses both osteoinductive and osteoconductive properties.

KEYWORDS — apical periodontal cyst, osteoplastic materials, cystectomy.

The problem of bone regeneration is one of the challenging issues in modern dental surgery [1]. Bone tissue insufficiency in the jaws may result from different causes, for instance, after tooth extraction and intrabony defects, periapical surgery [4, 5, 6].

Presently, guided bone regeneration utilized in a variety of bone tissue engineering applications has been proved theoretically and clinically. However, in practice, application of osteoplastic materials does not always lead to an expected positive result. In a number of cases, adverse clinical outcomes such as loss of graft materials and formation of fibrous encapsulation over the graft may develop [3].

Owing to these facts, using indigenous bone grafting material «bioOst» may be a treatment choice in implant dentistry. «bioOst» matrix represents bovine bone tissue subjected to physico-chemically treatment. It is very similar to human bone tissue in its physical, immunologic and chemical composition. A review of the modern literature shows the efficacy of bone grafting material «bioOst» used in the sinus floor elevation and filling of extraction sockets. All papers underlie application of osteoplastic materials only in the absence of any chronic inflammatory process [2].

The objective of the study

is to evaluate the efficacy of bone grafting material «bioOst» in filling of infected bone defects.

MATERIALS AND METHODS

Surgical treatment of 63 patients with apical periodontal cysts of the jaws was performed. In the experimental group (31 — 49,2% of patients) a bone defect was filled with osteoplastic material «OsteoBiol Gen-Os» by TecnoSS (Italy). The material is bone granules with collagen / heterologous cortical-spongius mixed (pigs/horse) in the size of 250–1000 microns.

In the control group (32 — 50,8% of patients) osteoplastic matrix «bioOST-XENOGRAFT Collagen» — bone chips with underlying subtotal osteoinductive demineralization, made by «OOO Cardioplant» (Russia) was employed.

Cystectomy was performed using Parch II technique. Three, six and nine months after surgery a case follow-up was done. Activity in regeneration processes was assessed by taking a dental panoramic radiogram using Adobe Photoshop 7,0 software and calculating the coefficient of the bone mineral density in the parietal and middle area of the osseous defect.

The probability of obtained data was calculated by using the Student t-test (reliable data were at $p < 0,05$).

The conducted survey was approved by the local ethics committee of the Volgograd State Medical University (protocol № 2098-2019 dd 1.03.2019).

RESULTS

It has been estimated that before surgery in both clinical groups tissue density indexes in the parietal and middle area of the osseous defect showed no statistically significant differences ($p > 0,05$) and were 2 times lower than intact bone indexes.

Three months after surgery in both clinical groups the coefficient of the bone mineral density in the parietal area of the osseous defect equaled to $p > 0,05$. At the same time, in the control group difference of the coefficient of the bone mineral density in the parietal area ($128,34 \pm 1,43$ y.e) and middle area of the osseous defect ($124,67 \pm 1,47$ y.e) was statistically invalid, but in the experimental group it was pronounced ($125,41 \pm 1,37$ y.e and $120,27 \pm 1,34$ y.e; $p < 0,05$). The coefficient of the bone mineral density in middle area of the osseous defect in patients of the

control group was significantly greater ($p < 0,05$) than in patients of the experimental group.

Six months after surgery there were no statistically significant differences ($p > 0,05$) between the groups in the coefficient of the bone mineral density over the entire area, but they were lower in the intact bone ($p < 0,001$). Nine months after surgery the coefficient of the bone mineral density over the entire area equaled to the values in the intact bone ($p > 0,05$).

So, the results of the survey showed that processes of reparative osteogenesis started in the parietal area of the osseous defect in both groups, i.e. at the site of a bone grafting material adjacent to the wall of the defect and were directed to the apex. It is termed as *creeping substitution* meaning the initial resorption of the graft followed by secondary ingrowth of a new bone from the osseous defect. Synchronism of these processes must be emphasized which occurs simultaneously being linked with the degree of demineralization of the implant induced into the osseous defect. In series of studies it is noted that resorption of bone grafting materials with total demineralization occurs to a much greater extent than osteogenesis. Partially demineralized bone implants (interfacial, subtotal demineralization) possess higher osteoinductive activity supporting simultaneous occurrence of biodegradation and osteogenesis processes.

In the survey under study, in both groups simultaneous occurrence of biodegradation and reparative osteogenesis processes was established. At the same time, statistical analysis of the obtained data confirmed a pronounced activity of these processes in using indigenous bone grafting material «bioOst» with interfacial demineralization during the first three months after surgery. To the sixth month of monitoring the rate of reparative osteogenesis and resorption of implant material became even. To the ninth month of a post — operative period complete restoration of the osseous defect was observed.

CONCLUSION

Indigenous bone grafting material «bioOst» with interfacial demineralization in filling of infected bone defects possesses both osteoinductive and osteoconductive properties contributing to simultaneous occurrence of biodegradation and reparative osteogenesis processes. The advantage of this material is successful integration during the first three months after surgery. That is very essential in prognosis of clinical complications. This evidence based study underlines the necessity to conduct further investigations to reveal the efficacy of the material in filling of infrabony defects of different original.

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ONLINE COMMUNICATION-BASED REHABILITATION MANAGEMENT FOR PATIENTS WITH REPLACED JOINTS: EXPERIENCE AND OPPORTUNITIES

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ABSTRACT — The purpose of this study is to examine online communication as a tool for managing rehabilitation of patients with musculoskeletal pathologies. We have developed a system of interactive personalized online monitoring and feedback between patients and medical organizations. The system functions as a web application. It has proved successful in the frame of practical tests in 2018–2019. Our outcomes show that the proposed online service is an effective tool for managing rehabilitation after joint replacement. The patients benefited from online medical monitoring and social support during postoperative rehabilitation.

KEYWORDS — rehabilitation, online communication, joint replacement, feedback, social support.

INTRODUCTION

Online communication in medicine is becoming a method to promote social support for patients, as it allows effective information and psychosocial resources exchange to overcome difficult life situations [1]. An essential feature of online communication as a tool for improving the effectiveness of healthcare is rapid feedback between the patient and the medical institution, which encourages patients to take active actions thus shaping a behavior pattern necessary to maintain an acceptable quality of life [2]. One of the areas in medicine where the introduction of online communication services is relevant, includes musculoskeletal pathology, and the share of this issue in the overall burden of diseases was recognized by the UN, WHO and the World Bank as dominant in the late 1990s due to the high rate and severity of negative socio-economic effects, such as disability, reduced personal

and economic independence of patients [3]. Hip and knee joint osteoarthritis has a leading position in the structure of this pathology [4]. It is to be noted that surgery involving medical technologies for large joint replacement appears as no specific issue, in particular in Russia since there are special high-tech medicine programs available, which cover over 120 thousand patients annually [5].

However, systemic factors limiting the availability of health care services, implying, first of all, a lack of funding for rehabilitation at the postoperative stage [6, 7], lead to a problem of identifying a large group of patients with implanted structures that do not have permanent rehabilitation follow-up. The resources available through online communication allow access to healthcare services for patients with osteoarthritis based on personalization through receiving recommendations, asking questions about their own health status, and sharing experiences with other patients [8]. This means that the promotion of online communication at all stages of interaction with the health care provider — diagnostic, treatment and rehabilitation — is a strategy that ensures continuity, consistency and accessibility of health services.

Aim of study

was to examine online communication as a tool for managing rehabilitation in patients with musculoskeletal pathologies.

MATERIALS AND METHODS

A Monitoring and Feedback System (Russian acronym — SIMOS) based on online communication was developed the Research Institute of Traumatology, Orthopedics and Neurosurgery (Saratov, Russia). It is aimed to improve the quality of information exchange between patients and medical institutions through the period of medical care and postoperative rehabilitation. The system was registered with the Federal Institute of Industrial Property (Certificate of registration of computer software # 2019663975 of 13/11/2019). It functions as a web application, which embraces, based on the epidemiological priority, patients with coxarthrosis and gonarthrosis.

The SIMOS organizational technology is based on 2-stage online communication with the patient within the system's functional structure (Fig. 1), which is represented by various modules. At Stage 1, a patient who is to be hospitalized at our Institute gets a personal account, after which it is added to the database of sending SMS messages informing the patient about the access to the service. At Stage 2 of interaction, the patient also receives an SMS notification about access to the SIMOS during the postoperative period.

From July 2018 to April 2019, the SIMOS was tested at the prehospital stage and through the postoperative medical rehabilitation period (6 months following the surgery), which included 381 patients. The statistical data processing was performed using the Statistica 6.1 software package. The data was presented in the "Me (25%; 75%)" format since not all quantitative indicators matched the normal distribution by Shapiro-Wilk test. The category indicators are presented as frequencies expressed in percentage.

RESULTS

General details concerning the participants

The age of the patients was 64 (59; 69); minimum — 19, maximum — 81, the gender distribution revealed women predominating (78.1%). The number of patients with planned total hip replacement surgeries was 36.8%, while the number of patients with knee replacement accounted for 63.2%.

Interpretation of the testing outcomes

The key element of evaluating the performance of the created medical and social service is the investigation and measurement of its demand among patients, which explains the development of a set of criteria in order to solve this task; the criteria were developed to evaluate the effectiveness of the SIMOS. The criteria normative were identified based on the experience of the patients' response to the initial SMS message notification at the prehospital stage (Fig. 2) and in view of the functional structure of the system described above.

The results obtained, using the presented criteria, has allowed us to register an acceptable level of demand for the online service at the prehospital stage and through the period of postoperative rehabilitation (Table 1).

The results of using the SIMOS within the age context have shown that older people can actively use the modern means of communication and that they are open to this type of interaction. At the prehospital stage, the use of personal computers (desktops) (58.8%) prevails when working in the system, whereas mobile devices (56.6%) overtake through postoperative rehabilitation.

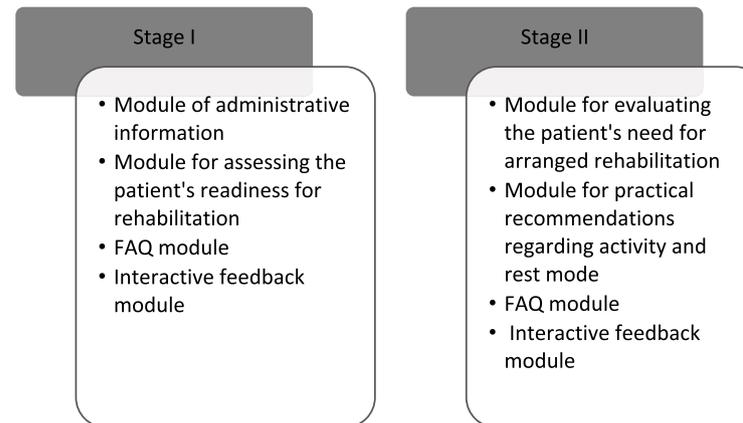


Fig. 1. The SIMOS functional scheme

The study of the acceptability of employing various communication channels by patients to interact with medical specialists shows that after using the SIMOS at the prehospital stage, whereas after the surgery their preferences change from using the traditional means of communication (telephone) to methods involving online interaction (Fig. 3). This change is statistically significant for the methods of communication like Telephone ($p < 0.01$) and Skype ($p < 0.05$).

The SIMOS was used to study the patients' readiness for active postoperative rehabilitation, which proved quite high — 91.3% of the patients confirmed at Stage I of working with the system that they could follow the doctors' recommendations concerning their lifestyle after surgery, etc. Remote online interaction with our experts at the stage of postoperative rehabilitation was considered acceptable by 100% of the patients who had used the SIMOS.

DISCUSSION

The developed and implemented interactive online patient-support service allowed carrying out a study of patients' readiness to interact with a medical institution using digital communication technologies. This system incorporates the major directions of employing online communication through rehabilitation [9], which ensures that patients can obtain social and professional support during this difficult period of recovery. The first area is medical (consultations of specialists, communication with a medical institution, training video programs, assessment of the patient's functional status). The second one is social (protection of the patients' rights and health, information support for patients, prevention of restrictions on everyday social practices). The values of the *recipient's response* indicator observed through testing are consistent with

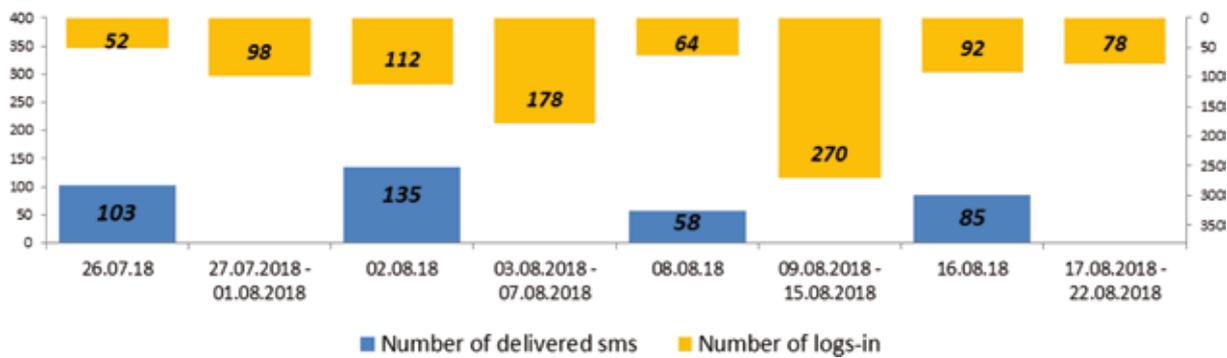


Fig. 2. Dynamics of patients' using the SIMOS at the prehospital stage

Table 1. Demand for the SIMOS by patients

Criterion details	Criterion practical value	Normative value	Result at Stage I	Result at Stage II
Response from the recipient	Evaluates the patient's response to the offer to use the service with a factual log-in	>20%	45.9	19.2
Response time	Estimates the time during which more than 50% of the informed patients logged into the system	<1 day	<1	<1
Reuse ratio	Estimates the development of a stable interest for working with the system in the patient	>1	4.8	1.5
Demand for the system component	Identifies the share of the functional blocks within the system used by the patients	>75%	100	100

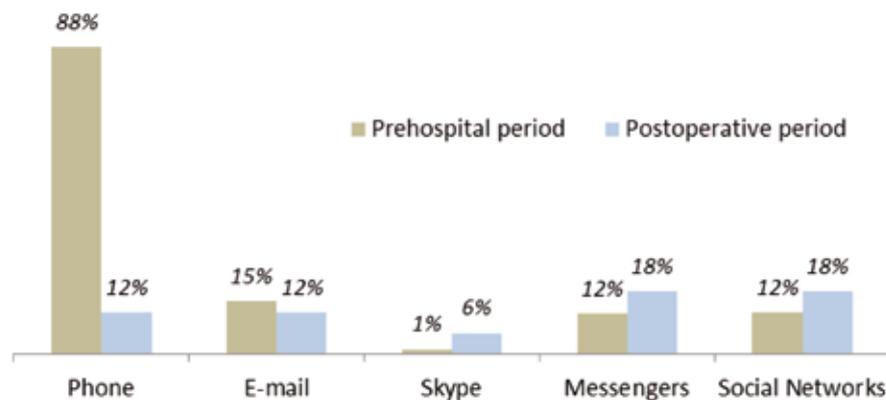


Fig. 3. Acceptance of various communication channels for patients to interact with medical specialists, %

the data reported by other researchers [10, 11], while its decrease at Stage II indicates the need for additional study of patients' response to informing them within an earlier period following the surgery.

The presented monitoring and feedback system has a wide range of functions, which thus allows solving a number of important tasks, including research — it allows acquiring new knowledge and developing vectors for organizing medical care, expanding interaction between the patient and the health system, as well as shaping a patient-centered model of medical care and rehabilitation. The described online service solves an important social issue, which implies increasing the availability of professional medical support for elderly patients [12], creating the conditions for

prolonging their labor activity, which is important in cases where the state runs a policy of increasing the retirement age.

The experience of interaction between patients and medical specialists proves that online services designed for patients solve the most important medical and social issue task related to establishing conditions for reducing the rehabilitation period: monitoring and control by medical specialists, remote professional consultations regardless of geographical location, interactive notification concerning the health status, which serves the basis for patients' self-training, and which, in turn, leads to better compliance [13].

The proposed model serves the basis for quality assurance in medical care and rehabilitation, implementing in practice the fundamental requirements of the ISO 9001-2015 international standard: Understanding the organization and its context (4.1), Understanding the needs and expectations of interested parties (4.2), Customer focus (5.1.2), Actions to address risks and opportunities (6.1), Customer communication (8.2.1), Customer satisfaction (9.1.2), management review (9.3), improvement (10) [14]. In particular, studying the patient's satisfaction with the quality of medical care allows identifying downsides in arranging medical communication and identifying potential areas for its improvement.

Online services for patients implement the philosophy of lean healthcare, ensuring continuity, consistency and accessibility of medical care in view of factors implying territorial remoteness, personnel and infrastructure shortage, while increasing the effectiveness of the available healthcare programs taking no significant investment in the respective industry.

CONCLUSION

Online communication services make an effective tool for managing rehabilitation following joint replacement, offering patients social support during a difficult period of life.

Conflict of interests

The authors herewith declare that there is no conflict of interests involved.

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USE OF SODIUM HYALURONATE IN THE TREATMENT OF CHRONIC CYSTITIS

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ABSTRACT — We prospectively evaluated the efficiency of chronic cystitis therapy in women with 0.1% sodium hyaluronate (Uro-hyal) on the basis of regression of leukocyturia, erythrocyturia, bacteriuria, subjective sensations (according to the QoL scale). We also observed all the patients during 12 months after treatment and recorded the number of recurrences. As a result, we recorded a significant improvement in the quality of life and by 2.5 times decrease in recurrences of the disease after Uro-hyal therapy compared to the control group. Conclusions. The intravesical use of 0.1% sodium hyaluronate contributes to restoring the protective properties of the mucous membrane of the bladder and maintains a long time without recurrence of the disease.

KEYWORDS — chronic cystitis, dysuria, bacteriuria, sodium hyaluronate (Uro-hyal, CLS International), intravesical therapy.

INTRODUCTION

An episode of lower urinary tract infection occurs in almost every third woman under 25 years of age [1]. The inflammation of the lower urinary tract occurs in approximately every second woman during her lifetime [1]. If the patient has more than 3 episodes of chronic cystitis a year, or two episodes in six months, the urologist diagnoses chronic cystitis [2]. Frequent bouts of chronic cystitis significantly reduce the patient's quality of life [3]. The causes of chronic cystitis are the presence of a constant source of bacteriuria, impaired urinary passage, abnormalities of the urinary tract, diabetes mellitus, etc. [4, 5, 6].

The main treatment of chronic cystitis is etiotropic treatment for bacterial infection [7]. However, the frequent use of antimicrobial drugs contributes to their increased resistance, as well as the development of adverse effects (allergic reaction, nausea, diarrhea, dysbacteriosis, etc.). Therefore, antimicrobial therapy does not eliminate all issues in the problem of recur-

rent cystitis and prevention of further damage to the urothelium.

There are many medicines used to prevent and treat bladder mucous membrane damage or to restore it after chronic cystitis. These drugs can be used intravesically [8]. The necessity of such therapy is conditioned by the fact that in chronic cystitis, regardless of etiology, there is a constant destruction of urothelium, lamina propria and the submucosa of the bladder base.

In recent years, a group of drugs that can strengthen the tissue framework of the bladder wall, thereby creating conditions for the restoration of the physiological barrier properties of the urothelium have been intensively studied. One of the most frequently used drugs in this class is sodium hyaluronate.

Aim

Evaluate the efficacy of 0.1% sodium hyaluronate (Uro-hyal, made by the company CLS International in Russia, according to the international standard EN ISO 13485) in treatment of chronic cystitis.

METHODS

We carried out a prospective analysis of the treatment results of chronic cystitis in women (n=72). All patients agreed to the study and data processing. Inclusion criteria are the age of women from 18 to 50 years, presence of bacteriuria at least 10*5 CFU, presence of chronic cystitis in the history at least 1 time a year, presence of cystitis attacks at least 3 times a year. Exclusion criteria are sexually transmitted diseases, cancer, urethral stricture, diabetes mellitus.

All women were divided into two groups by the blind method. The first group (basic group) included 37 women with chronic cystitis, who received five intravesical injections of 50 ml 0.1% sodium hyaluronate solution (Uro-hyal) (one procedure per week) after ten days of antibacterial therapy (taking into account the sensitivity of the detected microorganism). The second group (control group) included 35 women with chronic cystitis, who were offered only a ten-day course of antibacterial therapy (taking into account the sensitivity of the microorganism detected in them).

Patients of both groups at the time of the first visit had no reliable differences in the number of recurrences of cystitis per year (4.1+1.3), leukocyturia (26.1+3.7 cells in the field of vision), erythrocyturia (5.3+2.2 cells in the field of vision), bacteriuria (p>0.05).

We assessed the efficacy of the therapy according to the dynamics of leukocyturia, erythrocyturia, bacteriuria, ultrasound of the bladder, subjective sensations (on the QoL scale) after the end of treatment. We also interviewed women from both groups about the number of cystitis relapses within a year after treatment.

Statistical analysis was performed using Excel and STATISTICA 6.0 spreadsheets. The significance of differences between quantitative indicators was assessed using the Mann–Whitney test. The differences were considered significant at $p < 0.05$.

RESULTS

During the intravesical injection of Uro-hyal, not a single woman reported any discomfort during the procedure or an allergic reaction. After the treatment, we found no leukocyturia or erythrocyturia in women of both groups. Urinary bladder wall thickness at transvaginal ultrasound access in women of the first group was 3.6 ± 0.4 mm, in the second group — 4.2 ± 0.6 mm ($p > 0.05$). Patients of the first observation group noted a significant improvement in the quality of life after Uro-hyal therapy in comparison with the second group (Fig. 1). Thus, in the first group the quality of life improved by 65,5%, in the second group by 51,9% ($p < 0,01$).

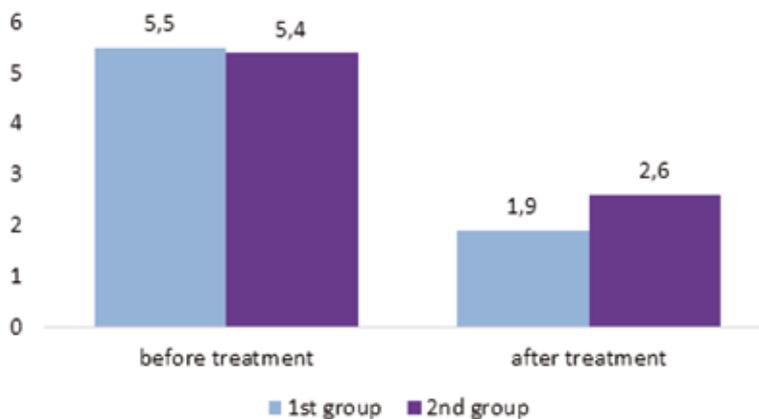


Fig. 1. Dynamics of quality of life of patients (according to the QoL scale) depending on the selected therapy

No urination urges after treatment were reported in 29 (82.8%) control group patients and none of the women in the first group ($p < 0.001$). None of the observed women complained of intolerable or very severe urination pain. However, discomfort after urination persisted in 11 (31.4%) and 6 (16.2%) women in the second and first monitoring groups after the end of treatment ($p < 0.05$). The average number of recurrences of cystitis after Uro-hyal therapy decreased to 1.2 ± 0.5 times per year in the first group of the study, against 2.5 ± 0.8 times in the second group during the whole period of observation ($p < 0.05$).

Discussion. The main pathogenetic component for all variants of chronic cystitis is permanent damage of the mucous membrane of the bladder, which leads to hyperplastic and dysplastic processes in the membrane and increases the frequency of cystitis episodes [1]. Atrophic

and dystrophic changes in the mucous membrane of the bladder create a favourable environment for the development of the bacterial component and progression of urothelial damage. It is known that chronic cystitis results in an increase and change of leukocyte infiltration in mucous and submucous membranes of the bladder. Therefore, in the treatment of chronic cystitis, it is important to use substances that provide protection for urothelium [9]. Currently, medications based on hyaluronic acid (0.1% sodium hyaluronate) have some success. The main clinical effects of sodium hyaluronate are the establishment of mechanical barrier (lubrication), enhancement of regeneration due to restoration of glycosaminoglycan layer of the urothelium, moistening of the mucous bladder due to high degree of water binding, interruption of the pathological circle of inflammatory reaction [10].

Studies by Rooney P. et al. have shown that hyaluronic acid is capable of reducing the production of cytokines by 4–5 times, reduces the intensity or generally prevents the development of inflammatory processes. There has also been an increase by 2 times in the formation of sulfated glycosaminoglycans and a decrease in urothelium permeability without damaging natural barriers [11].

The results of our study showed that when 0.1% sodium hyaluronate was used in the treatment of acute interstitial cystitis, there was a significant improvement in the quality of urination in 70.5% of patients, none of the women had complaints of intolerable or very severe pain ($p < 0.05$) [12].

CONCLUSIONS

Intravesical use of sodium hyaluronate in the therapy of chronic cystitis significantly improves the effectiveness of treatment. Pathogenetically justified combined therapy of chronic cystitis should be carried out in two stages. The first stage is a ten-day course of antibacterial therapy. The second stage is a course of intravesical injections

(at least five) of sodium hyaluronate solution. The use of sodium hyaluronate in the complex treatment of chronic cystitis increases the duration of the recurrence-free intervals of the disease.

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IDENTIFICATION OF BENIGN URETHRAL LESIONS IN FEMALE PATIENTS

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ABSTRACT — AIM: Our study was aimed to identify the types of benign urethral lesions in 92 women of reproductive age.

METHODS. We performed a physical examination and assessment of the external and internal genitals employing laboratory diagnostic methods, ultrasonography (transvaginal and transperineal scanning), and magnetic resonance imaging (MRI) in all women.

RESULTS. Asymptomatic benign urethral lesions of the paraurethral region were detected in 22.8% of women. The remaining 2/3 of the patients complained of dysuria and a sensation of a foreign body in the perineum. The most common complaints and clinical manifestations were predominantly observed in the women within one year after childbirth (72.8%).

CONCLUSIONS. Our findings on the types of benign urethral lesions were 56 urethral diverticula (60.8%) and 34 paraurethral cysts (37.1%). Most such lesions are more likely to occur in the first years after childbirth, so it is necessary to invite women for a pelvic exam during this period.

KEYWORDS — benign urethral lesions, urethral diverticulum, paraurethral cyst, dysuria, dyspareunia.

INTRODUCTION

Diseases of the urethra are common in women [1]. Most common among them are disorders of inflammatory and tumor-associated origin, such as urethritis, cysts, diverticula, polyps, etc. [1, 2, 3]. Special attention should be paid to benign urethral lesions. However, their incidence is difficult to assess due to a high proportion of asymptomatic patients and the absence of specific signs [4]. Such lesions normally have a small size (from 2 to 15 mm), which also makes it difficult to diagnose them [2, 5]. According to foreign and Russian literature they refer to 1% to 8% of cases [1, 2, 6]. Benign urethral neoplasms are often detected in women aged 30–60 years [6]. Their etiology in women in most cases is unclear. Some authors claim that cystic lesions may grow when the periure-

thral glands are blocked during traumatic childbirth, or when there is frequent infection of the lower urinary tract [5, 7, 8].

Difficulties in diagnosing the benign urethral lesions affect the quality of their treatment. [9, 10]. Incorrect interpretation of their clinical symptoms may lead to development of serious complications: formation of an abscess, urethro-vesicovaginal fistulas and a risk of recurrence.

Aim:

to identify and analyze the types of benign urethral lesions in the cohort.

METHODS

The study included 92 women with detected cystic urethral lesions. We have obtained the consent of all patients for the examination. The complaints of all the women (n=92) were carefully collected and recorded. We also employed a physical examination and assessment of the external and internal genitalia, laboratory diagnostic methods (blood, urine and vaginal discharge tests). The exclusion criteria for participation in the study were 1) age under 18 and over 45 years; 2) inflammatory diseases of the lower urinary tract; 3) diseases of reproductive tract.

For the visualization of benign urethral lesions in the women, we were helped by diagnostic imaging techniques such as ultrasound and MRI. We used methods of vaginal and perineal scanning with a 7 MHz sensor for ultrasound examination. Ultrasound scanning was done in different planes, which allowed us to detect the connection of the paraurethral cyst cavity with the urethral lumen. Magnetic resonance imaging (MRI) was performed within the pelvis using an endorectal coil.

Statistical analysis was performed using Excel and STATISTICA 6.0 spreadsheets. Mann–Whitney U test was applied to assess the significance of differences between quantitative indicators. The differences were considered significant at $p < 0.05$.

RESULTS

The average age of all women was 29+7 years. The majority of women had a history of childbirth — 63 (68.4%). 21 (22.8%) women had asymptomatic BPN. The most frequent complaints in patients were: a foreign body sensation in the perineum — 71 (77.1%),

dysuria — 59 (64.1%), pain in the perineum — 26(28.2%), dyspareunia — 24(26%), urinary retention — 13(14.1%). The most frequently mentioned complaints were reported in women within 1 year — 67(72.8%), under 5 years — 19 (20.6%), within 10 years — 6(6.5%) after childbirth.

The types of benign urethral lesions detected in all the patients (n=92) are shown in Fig. 1. In most cases, we diagnosed urethral diverticula — 56 (60.8%). Also, in 2 (2.1%) patients, we suspected a malignant degeneration of the cyst based on the signs: a bumpy surface, limited mobility, and compaction of the walls. The remaining 34 (37.1%) women had paraurethral cysts.

We found quantitative differences in the localization of the lesions in the women (Table 1). The most frequent localization is the distal part of the urethra (84.7%).

Volume masses in the paraurethral region (Fig. 2) were detected by ultrasound in all women. Ultrasound signs showed clear contours of the cyst, a homogenous thin wall, and a hypoechoogenic (without inclusions) internal environment.

DISCUSSION

The occurrence of benign urethral lesions in young and middle-aged women leads to a significant deterioration in their quality of life and reduced ability to work [11]. The frequency with which the lesions may occur seems difficult to estimate due to many missed or misdiagnosed cases. Many studies show a certain number of asymptomatic women although they may have a growth located in the periurethral area [1, 7]. Only in 23% of patients benign urethral lesions cause any symptoms [10]. Laudano M.A. et al in diagnosis of benign urethral lesion and urethral diverticula in particular offer to rely on a triad of symptoms: dysuria, dyspareunia and postvoid dribble [6]. The results of the study by Blaivas J. G. et al show that urethral diverticula is the most common of all periurethral masses (84%) [2].

BPN may assume the guise of various diseases: ectopic ureterocele, pelvic organ prolapse, leiomyoma, adenocarcinoma, etc. [12]. The frequency of malignant neoplasms of the paraurethral zone according to the literature is from 3–6% [6]. For this position, our data almost match the statistics, we found a suspicion of malignization of the lesions in 2.1% of cases.

Our study showed that most patients had a history of childbirth. This means that labor is a risk factor for the development of periurethral lesions. 21 (22.8%) women had asymptomatic benign periurethral lesions. This means that doctors should be active in visualizing BPN in women of reproductive age.

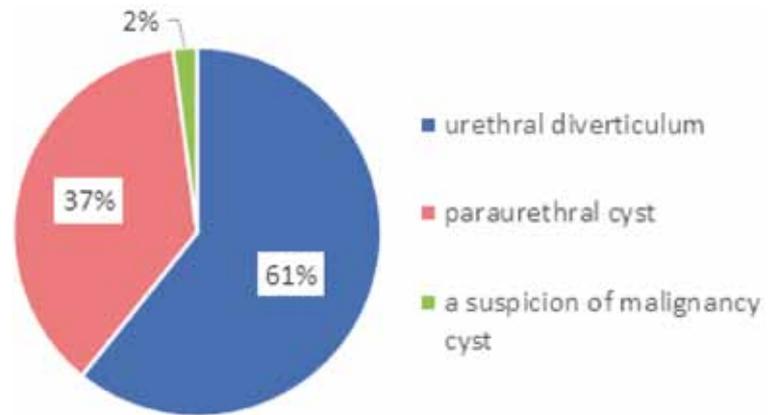


Fig. 1. Types of benign urethral lesions in all patients (n=92)

Table 1.

Localisation of benign urethral lesions	Examination's number (n=92)	
	n	%
Distal part of the urethra	78	84,7
Middle part of the urethra	11	11,5
Proximal part of the urethra	3	3,8



Fig. 2. Ultrasound examination of the cyst of the proximal part of the urethra

The issues of diagnosis and treatment of periurethral entities in women deserve exceptional attention from the point of view of the practical work of a doctor. There is currently no single algorithm for examining patients with these diseases and, often, the entire examination is reduced to collecting anamnesis and routine physical examination.

CONCLUSIONS

Benign periurethral entities often occur under the guise of dysuria, which is characteristic of diseases

of many pelvic organs. Therefore, their diagnosis largely depends on the activity and professionalism of the doctor. Since most benign urethral lesions are more likely to occur in the first years after birth, it is necessary to invite women to a pelvic exam during this period. In 84.7% cases they are identified by a routine examination of the external genitalia. A comprehensive approach to imaging of the urethral lesions using ultrasound, CT, and MRI is also required.

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ASSOCIATION OF DNA FRAGMENTATION OF SPERMATOZOA AND THE SUCCESS OF ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS

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ABSTRACT — The number of men with impaired sperm genetic material is steadily increasing, which is reflected in the increase in the number of assisted reproductive technology (ART) programs and their outcomes. This article presents an analysis of ART program success, depending on the proportion of DNA-sperm fragmentation. As a result, in couples with normal sperm counts (n=43), the frequency of spontaneous abortions was twice lower compared to couples (n=39), where the level of DNA fragmentation was increased (p<0.05) **CONCLUSIONS.** The miscarriage in a spouse in the early stages (up to 12 weeks) is more common in couples with damaged sperm DNA.

KEYWORDS — Male infertility, assisted reproductive technology (ART), DNA fragmentation, reproductive loss, spontaneous abortion.

INTRODUCTION

Every fifth married couple in Europe and every fourth couple in the world need medical help to manage infertility [1, 2]. At the same time, the male factor of infertility is already found equally often with the female one [3]. Male infertility is provoked by many diseases: varicocele, inguinal hernia, sexually transmitted infections, genetic mutations, etc. [4, 5, 6, 7] these diseases often cause oxidative stress, damage and fragmentation of the DNA in germ cells, which is the cause of reduced sperm fertility [7]. In every third case, abnormalities in sperm and DNA fragmentation cannot be eliminated by medication. Therefore, married couples are forced to use assisted reproductive technologies (ART) to overcome childless marriage

[2]. Unfortunately, methods of infertility treatment using ART (IVF/ICSI) are successful only in 32% of cases [8]. One of the factors of ART failures is the poor quality of sperm. Therefore, some authors suggest considering the level of sperm DNA fragmentation as a predictive criterion of ART outcomes [9].

Aim

To estimate the association of DNA fragmentation level in spermatozoa with the successful outcome of ART programs.

METHODS

We retrospectively evaluated the results of ART (ICSI) in 82 married couples. Inclusion criteria: male factor of infertility, absence of reproductive health pathology in the female partner. Exclusion criteria: varicocele, bad habits in men (smoking, alcohol, drugs).

All couples were divided into study groups:

Group 1: the percentage of DNA fragmentation of spermatozoa <15% (n=43)

Group 2: the DNA fragmentation in spermatozoa >15% (n=39)

We performed semen analysis in all patients in accordance with WHO guidelines from 2010. We determined the level of DNA fragmentation of germ cells using the TUNEL method. The standard values of DNA fragmentation were considered to be less than 15%. We evaluated the indicators of embryogenesis (formation of blastocysts at the stage of cultivation), the frequency of clinical pregnancies after the transfer of the native embryo in all married couples. We also recorded the level of reproductive losses.

The statistical analysis was performed using spreadsheets "EXCEL" and "STATISTICA 6.0". The significance of differences between quantitative indicators was assessed using the Mann-Whitney test. Differences were considered significant at p<0.05.

RESULTS

We did not get significant differences in spermogram indicators in men of both study groups. Men of the first group had an average sperm concentra-

tion of $4.9 \pm 3.2 \cdot 10^6$, and the second — $3.8 \pm 2.9 \cdot 10^6$ ($p > 0.05$). The percentage of active-motile spermatozoa in patients of the first group was $17.2 \pm 4.8\%$, in the second group — $14.5 \pm 5.7\%$; the percentage of normal spermatozoa was 4.6 ± 2.3 vs. 2.9 ± 1.7 ($p > 0.05$). The level of DNA fragmentation of spermatozoa in men of the first group was significantly lower than in the second: $11.2 \pm 4.1\%$ vs. $28.5 \pm 7.9\%$ ($p < 0.05$). We demonstrate the effectiveness of ART depending on the level of DNA fragmentation in Table 1. Termination of embryo cultivation after 3 days significantly prevailed in the second group of the study ($p < 0.05$). We found a direct correlation between reproductive losses (spontaneous abortion in early pregnancy) and the level of DNA fragmentation (Fig. 1)

Table 1. The ART results in both monitoring groups

ART Effectiveness indicators	The 1 st study group n(%)	The 2 nd study group n(%)	p
Formation of blastocysts at the stage of cultivation	27(62,7%)	17(43,5%)	$p < 0,05$
Oncoming of clinical pregnancy (%)	22(51,1%)	15(38,4%)	$p < 0,05$
Undeveloped pregnancy	3(6,9%)	5(12,8%)	$p < 0,05$
Spontaneous abortion	5(11,6%)	8(20,5%)	$p < 0,01$

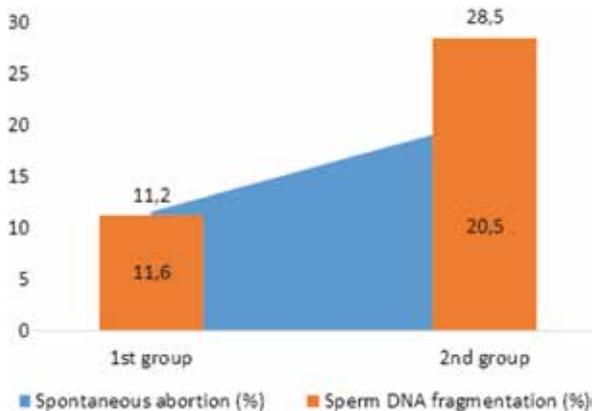


Fig. 1. Correlation between the level of DNA fragmentation (%) and spontaneous abortions (%) in both groups of patients

DISCUSSION

The birth of a healthy child undoubtedly depends on a woman's reproductive health. However, recently, there has been evidence that the frequency of pregnancies and embryo development is influenced by the quality of sperm [8, 9]. It is especially important to exclude violations of the genetic material of sperma-

tozoa in male infertility [6, 10]. Palermo Gianpiero D. et al showed an inverse correlation between DNA fragmentation and sperm mobility [11]. Our study has indicated that there is a negative relation between the rate of DNA fragmentation of spermatozoa and the frequency of onset and development of clinical pregnancy in ART programs. Meta-analysis of the results of treatment of 2969 couples from 16 cohort studies showed a significant increase in the frequency of miscarriage in women who were fertilized with sperm with a high DNA fragmentation index (risk ratio = 2.16 (1.54; 3.03), $p < 0.00001$) [9]. A DNA-fragmentation test can show not only the proportion of damaged germ cells, but also the extent of breaks in the DNA molecule, which often stops the development of the embryo at any time. Ribas-Maynou J. et al. it was proved that the presence of DNA damage in two chains of the molecule leads to a high risk of miscarriage (specificity — 77.5%) [12].

In couples with a high level of DNA fragmentation, additional selection of spermatozoa with an intact DNA chain must be used in order to achieve pregnancy in the ART program, after visual evaluation of progressive motility and native evaluation of germ cell morphology.

CONCLUSIONS

The miscarriage in the spouse in the early stages (up to 12 weeks) is significantly more common in couples where men have a high level of DNA fragmentation of spermatozoa than in couples with intact DNA of germ cells. The determination of DNA fragmentation in infertile men can be used as a predictive marker of fertility and the outcome of ART programs. Men with high levels of DNA fragmentation need treatment before planning ART.

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POSTTRAUMATIC HEADACHES IN MEN

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ABSTRACT — The status of emotional sphere, cognitive functions and the quality of life was evaluated in 19 men with post-traumatic cephalalgia. The following instruments were used: The Zung Self-Rating Depression Scale (adapted in Russian), Hospital Anxiety and Depression Scale, Recovery Locus of Control, Psychological General Well-Being Index, MMSE (Mini - Mental State Examination), Luria Test, Shulte Tables. Our main findings were as follows: average age of the group was 38.7 ± 11.1 years against the mean duration of pain 10.8 ± 4.7 years. Gross cognitive deficits were reported in 5 (26.3%) men with severe brain injuries. An increased level of anxiety was found in 6 (31.6%) whereas clinical depression was diagnosed in 7 men. Thus, different types of cephalgia are attributed to the presence and various rates of anxiety, depression and cognitive disorders.

KEYWORDS — posttraumatic headaches (cephalgia), emotional sphere, cognitive functions, anxiety, depression and cognitive disorders.

INTRODUCTION

Headaches (cephalgia) are a characteristic symptom of all forms of craniocerebral trauma. It usually occurs immediately (less often — during the first two weeks from the moment of injury) or, if there was a loss of consciousness, when the consciousness returns to the patient.

In acute craniocerebral trauma, headaches can be caused by the damage to the soft tissues of the head and neck, the changes in cerebrospinal fluid dynamics, and in brain injuries or intracranial hematomas by the structural changes with an involvement of the blood vessels, meninges, sensitive cranial and spinal nerves [1, 2, 3, 4]. Clinically, immediately after the injury, various kinds of pain may occur, some of which proceed as the type of primary headache — most often as the

type of tension headache, the cases of migraine with or without an aura, bundle headache have been described.

Cephalgic syndrome in men is an urgent problem of clinical neurology, the significance of which is determined by such circumstances as the high prevalence of headache in the population, the low attendance of men for medical care and the preference to be treated independently or not to be treated at all. Most men, especially those of a young working and socially active age, do not consider headaches as a serious enough reason to see a doctor, or, on the contrary, are afraid of identifying any serious illness [9].

The objective

of this work was to study characteristics of the clinical picture, the emotional status and cognitive functions, as well as to assess the quality of life in men of young (25–44 years old according to WHO) and middle (45–59 years old according to WHO) age with post-traumatic headache.

MATERIALS AND METHODS

19 men with post-traumatic cephalalgia were examined.

The neurological status was studied according to the classical scheme of the examination of a neurological patient. Nosological affiliation was determined in accordance with the International Classification of Headaches (ICHD, 2003, 2013) [5] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10, 1995) [6]. The statistical processing of the material was carried out using Excel 2007.

In addition to standard neurological examination and paraclinical examination methods, all patients underwent an assessment of emotional status and cognitive sphere.

The battery of tests for assessing the emotional status and quality of life of patients with post-traumatic headaches (HA) included the self-questionnaires [7] — The Zung Self-Rating Depression Scale (Russian adaptation by A.F. Kudryashov, 1992), The Hospital Anxiety and Depression Scale, HADS, Zigmond A.S., Snaith R.P., 1983, consisting of the Subscale of anxiety and the Subscale of depression, CL, «Recovery Locus of Control» Patridge C., Johnstone M., 1989; Wade D., 1992 and the PGWB (The Psychological General Well-Being Index), Dupuy H., 1984).

The complex of neuropsychological examination to assess cognitive impairment included the following methods: MMSE (Mini-Mental State Examination), Digit span test from Wechsler Intelligence Scale for adults and Wechsler Memory Scale [7], the study of short-term memory according to the method of A.R. Luria (test of 10 words, A.R. Luria, 1973) [8] and the Schulte Tables (adapted by S.Ya. Rubinshtein, 1970) [9].

RESULTS AND THEIR DISCUSSION

We examined 19 patients with a history of traumatic brain injury aged 24 to 58 years — the average age of the group was 38.7 ± 11.1 years.

All the patients examined suffered a traumatic brain injury of varying severity. Based on the history, nature and mechanism of the injury, the patients were divided into 3 injury subgroups:

- a concussion of a domestic nature (falling from a height, including from a height of one's own height, blows to the head) — 8 patients (42.1%);
- a severe open or closed craniocerebral injury due to a car accident, accompanied by a brain contusion, traumatic subarachnoid hemorrhage or traumatic intracerebral hematoma, damage to the cranial nerves, fractures of the skull and facial skeleton, with trepanation of the skull — 5 patients (26.3%);
- a mine-blast injury, accompanied by a concussion or bruise of the brain, a fracture of the bones of the skull or facial skeleton, rupture of cranial nerves, gunshot and fragmentation wounds of the trunk and extremities — 6 people (31.6%).

In all the patients examined, the headache appeared either immediately after the injury (with severe injury) or gradually over a period of 3 months, remaining in varying degrees of severity to date, and therefore in all 19 cases it was classified as a chronic post-traumatic headache, which includes in the composition of post-traumatic syndrome [5].

By age, the examined patients with post-traumatic headache were as follows: 20–29 years old — 5 (26.3%), 30–39 years old — 6 (31.6%), 40–49 years old — 4 (21%) patients, 50–59 years old — 4 (21%) patients.

The duration of the disease varied widely — from 2 to 20 years and the group average was 10.8 ± 4.7 years. Up to 5 years, 2 patients suffered from headache, 5–10 years — 5 patients (26.3%), 10–15 years — 9 patients (47.4%), 15–20 years — 3 patients.

Cognitive functions in patients with post-traumatic headache

When performing the MMSE test, the 26.7 ± 2.9 points were determined as the normal level but the low

one taking into account the age of the patients. At the same time, 5 of the examined men (26.3%) who had severe traumatic brain injury showed signs of gross cognitive deficit from the border level of 24 points (3 people) to 20 points (2 people).

In the process of studying the auditory — speech memory using the *10 words* test by A.R. Luria, the patients with post-traumatic headache, despite their young age, on average memorized 6.6 ± 1.9 words for five presentations. When performing a Wechsler test for attention and auditory memory for numbers, the patients correctly called in direct order an average of 54.1 ± 6.4 digits (at 60 maximum possible digits), in the opposite - 41.1 ± 11.5 digits (at 50 maximum possible digits).

When assessing the attention and performance using a sample with Schulte Tables, the patients performed one table in 41.5 ± 3.4 seconds (norm) on average.

Psychological status in patients with post-traumatic headache

When assessing the emotional status of patients with post-traumatic headache using HADS, despite the severity of the traumatic brain injury, the group as a whole showed no anxiety 6.3 ± 4.4 points on the Anxiety Scale and no depression 7.1 ± 2.98 score on the Depression Scale.

Nevertheless, with a detailed analysis of the Anxiety Scale, an increased level of anxiety was detected in 6 (31.6%) of the 19 patients examined: in 2 patients, a subclinical level of anxiety was detected and in 4 patients a clinically expressed level of anxiety was detected.

A detailed analysis of the The Zung Self-Rating Depression Scale (Russian adaptation by A.F. Kudryashov, 1992) revealed depression in 7 patients (36.8%), of which subclinically expressed depression was noted in 4 patients and clinically expressed depression in 3.

In 2 patients out of 19 examined, a simultaneous increase in both indicators to the levels of subclinical and clinical anxiety and depression was noted.

When analyzing the level of depression on the The Zung Self-Rating Depression Scale (Russian adaptation by A.F. Kudryashov, 1992) as a whole in the group, a state without depression was also recorded as 44.6 ± 10.4 points. At the same time, the mild depression (50–59 points) was revealed in 4 patients from the group and a subdepressive state (60–69 points) in 2 patients.

In 4 of the examined patients with post-traumatic headache, the depression detected on this scale coincided with pathology by two HADS scales of varying

severity, in addition, they had extremely low (up to 21 points) levels of the control locus and low levels on the MMSE scale (up to 20 points), which indicates a pronounced cognitive deficit. Previously, all these patients who had suffered a mine-explosive injury were consulted by a psychiatrist and already had a diagnosis of post-traumatic stress disorder, in connection with which they received specialized therapy.

Life quality in patients with post-traumatic headache

In whole by group the Psychological General Well-Being Index (PGWB), reflecting the quality of life of the examined patients, was quite low i.e. 70.6 ± 11.9 points. At the same time, its intensity coincided with the data of the scales for detecting anxiety and depression - it was maximum low (up to 34 points) in patients with clinically pronounced anxiety and depression.

In the group as a whole, in the group of patients with PTHB, the locus of Control (LC) was also low - 24.6 ± 4.2 points, reaching a minimum of 21 points in patients with post-traumatic stress disorder.

The low scores obtained during the survey on the Recovery Locus of Control scales and Psychological General Well-Being Index (PGWB) reflect the psychological status of patients with post-traumatic headache, which is in contradiction with unexpressed levels of anxiety and depression.

CONCLUSION

The obtained results correlate with our findings in previously examined patients with traumatic facial pain (caused by domestic violence, street fights, falls from a height combined with a concussion). There is no significant difference in severity of anxious moods and depression among other forms of headaches and facial pain which can be explained by the relatively young age of the patients, and, despite the traumatic brain injury, the hope for a complete cure [3, 10].

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EFFECT OF WEARING AN OCULAR PROSTHESIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON THE LEVEL OF ACID-BASE BALANCE OF THE CONJUNCTIVAL CAVITY

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ABSTRACT — THE AIM of the study was to study the effect of wearing an eye prosthesis by patients with type 2 diabetes on the level of acid-base balance of the conjunctival cavity. **MATERIALS AND METHODS.** Biomicroscopy of the conjunctival cavity, the pH of the discharge from the conjunctival cavity and HbA1c in the blood were determined.

CONCLUSIONS. The constant presence of an ocular prosthesis in the conjunctival cavity leads to a shift in the acid-base balance to the alkaline side, and the patient's history of diabetes also leads to the same result. The shift in the pH of the conjunctival cavity directly depends on the level of glycated hemoglobin, and the combination of these factors leads to a more aggressive shift of the pH to the alkaline side.

KEYWORDS — ocular prosthetics, anophthalmia, diabetes mellitus.

INTRODUCTION

The prevalence of anophthalmos in Russia reaches 24.47 per 10 thousand population [1, 2] and the only method of medical and social rehabilitation of such patients, today, remains eye prosthetics [3, 4, 5].

There is an increase in the number of patients with diabetes mellitus (DM) in the world. According to the forecasts of WHO experts, by 2025 the number of cases will reach 350 million [6, 7].

In patients with anophthalmos complicated by diabetes mellitus, there is a chronic sluggish inflammatory process, which negatively affects the cosmetic effect of ocular prosthetics and the comfort of wearing an ocular prosthesis [8, 9].

A shift in the acid-base balance (pH) of the conjunctival cavity to the alkaline side leads to chronic inflammatory processes, which lead to permanent

secretions in the conjunctival cavity, in which the prosthesis is constantly located. Finding a prosthesis in such conditions increases the amount of deposits on its surface. It becomes rough and wears out faster. All this, in turn, leads to a shift in the period of planned replacement of an eye prosthesis for a shorter one [8, 9].

The aim of the study

was to study the effect of wearing an eye prosthesis in patients with type 2 diabetes on the level of acid-base balance of the conjunctival cavity.

MATERIALS AND METHODS

The studies were carried out in the period from September 2018 to January 2020 at the Department of Eye Diseases of the RUDN University and at the Center for Eye Prosthetics in Moscow.

The study included 176 people, men and women, aged 19 to 80, with an average age of 58.4 ± 15.2 years. The patients were divided into five groups: 1st group — 36 people who do not use eye prostheses and do not suffer from DM; 2nd group — 33 patients using eye prostheses and not suffering from DM; 3rd/a group — 35 patients who do not use eye prostheses and suffer from type 2 DM with glycated hemoglobin in the blood less than 8%; group 3rd/b — 34 patients who do not use eye prostheses and suffer from type 2 DM with glycated hemoglobin more than 8%; 4th group — 38 patients using eye prostheses and suffering from DM.

All patients underwent the following studies: biomicroscopy of the conjunctival cavity, the pH of the discharge from the conjunctival cavity and HbA1c in the blood were determined.

THE RESULTS OF THE STUDY

The results of the study of the acid-base balance of the conjunctival cavity in both eyes in patients without diabetes mellitus and not using eye prostheses (1st group) showed a normal level of pH of the conjunctival cavity from 6.30 to 7.23 in 97.23% of cases (Table 1).

The results of the study of the acid-base balance of the conjunctival cavity of patients using an ocular prosthesis and not suffering from diabetes mellitus

Table 1. pH Measurement of the conjunctival cavity of 1st group

1 st group, n = 36	pH			
	6–6,5	7–7,5	8–8,5	> 8,5
OD	11 (30,56%)	24 (66,67%)	1(2,77%)	-
OS	13 (36,12%)	22 (61,11%)	1(2,77%)	-

(2nd group) showed in 84.85% of cases a shift in the pH of the conjunctival cavity, in which the prosthesis is located, to the alkaline side, while the pH of the conjunctival the healthy eye cavity was within normal limits (Table 2).

Table 2. pH Measurement of the conjunctival cavity of 2nd group

2 nd group, n = 33	PH				
	6–6,5	7–7,5	8–8,5	9–9,5	> 9,5
Non-prosthetic eye	9 (27,27%)	22 (66,67%)	2 (6,06%)	-	-
Eye with ocular prosthesis	-	5 (15,15%)	21 (63,64%)	7 (21,21%)	-

The results of the study of the acid-base balance of the conjunctival cavity of both eyes in patients with diabetes mellitus and not using an ocular prosthesis (3rd/a and 3rd/b groups) showed a shift in the pH of the conjunctival cavity to the alkaline side in both groups, but in patients with glycated hemoglobin more than 8% (3rd/b group), the pH shift towards the alkaline side was more aggressive, which suggests that the level of glycated hemoglobin in the blood is directly related to the level of pH of the conjunctival cavity (Table 3; Table 4).

Table 3. pH Measurement of the conjunctival cavity of 3rd/a group

3 rd /a group, HbA1c <8% n = 35	PH				
	< 7	7–7,5	8–8,5	9–9,5	> 9,5
OD	-	9 (25,71%)	22(62,86%)	4 (11,43%)	-
OS	-	8 (22,86%)	23 (65,71%)	4 (11,43%)	-
Total	-	24,28%	64,29%	11,43%	-

Table 4. pH Measurement of the conjunctival cavity of 3rd/b group

3 rd /b group, HbA1c >8% n = 34	PH			
	< 8	8–8,5	9–9,5	> 9,5
OD	-	16 (47,06%)	18 (52,94%)	-
OS	-	15 (44,12%)	19 (55,88%)	-

The results of the study of the acid-base balance of the conjunctival cavity of patients using an eye prosthesis and suffering from diabetes mellitus (4th group) showed a shift in the pH of the conjunctival cavity to a more aggressive alkaline side than in all our previous groups. This suggests that a combination of factors of the presence of an ocular prosthesis in the conjunctival cavity and a history of diabetes mellitus lead to a change in the pH of the environment in which the prosthesis is constantly located, and this, in turn, affects the effectiveness of ocular prosthetics and comfort when wearing the prosthesis (Table 5).

Table 5. pH Measurement of the conjunctival cavity of 4th group

4 th group, n = 38	PH			
	7–7,5	8–8,5	9–9,5	10–11
Non-prosthetic eye	3 (7,89%)	17 (44,74%)	18 (47,37%)	-
Eye with ocular prosthesis	-	5 (13,16%)	19 (50%)	14 (36,84%)

CONCLUSIONS

1. The constant presence of an ocular prosthesis in the conjunctival cavity leads to a shift in the acid-base balance to the alkaline side.
2. Hyperglycemia in a patient with diabetes mellitus leads to a shift in the acid-base balance of the conjunctival cavity to the alkaline side, thus, the shift in the acid-base balance directly depends on the level of glycated hemoglobin in these patients.
3. A history of diabetes mellitus in patients using ocular prostheses increases the shift of the acid-base balance to the alkaline side to more aggressive levels, which negatively affects the effectiveness of ocular prosthetics and the comfort of wearing the ocular prosthesis.
4. Supervision of patients using ocular prostheses and suffering from diabetes mellitus should be carried out in conjunction with endocrinologists to achieve the best cosmetic effect from ocular prosthetics and maximum comfort of wearing the prosthesis.

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EXAMINING AND TREATING PATIENTS WITH EPILEPSY AT THE DENTIST'S OFFICE (LITERATURE REVIEW)

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ABSTRACT — Our literature review analyzes the sources focusing on epilepsy, as well as on aspects of working with children suffering from epilepsy at a dentist's appointment. Based on the obtained data, the oral cavity status may indicate previously undetected epilepsy, as the dentist may become a doctor of the first contact. And when managing children diagnosed with epilepsy, it is important to select individual treatment tactics for them. The dentist, therefore, should have basic understanding of the patient's condition, the main symptoms of epilepsy, and be capable of applying first aid tactics in case of an epileptic seizure. Otherwise, epilepsy patients tend to have poor dental health and need regular visits to the dentist.

KEYWORDS — literature review, epilepsy, dentistry, pediatric dentistry, neurology.

INTRODUCTION

Child epilepsy has become a common neurological pathology. However, seizures occur instantly, and not neurologists may have to confront this challenge. One of the causes of seizures is stress that may be triggered in a dentist's office during an appointment. Besides, children with this pathology need special care and treatment tactics from other specialists.

The purpose of this review is to study literature focusing on the issue of epilepsy, as well as the aspects of working with children with epilepsy at the dentist's office. We believe that it is important to analyze the relationship between epilepsy and the dental status of children, and visiting a dentist, which in itself can provoke a seizure.

EPILEPSY, ITS POSSIBLE SYMPTOMS AND EFFECT ON THE DENTAL STATUS OF CHILDREN

In 2005, the International League Against Epilepsy defined epilepsy as a brain disorder featuring a persistent predisposition to epileptic seizures, as well as various neurobiological, cognitive, psychological and social effects. Since 2014, setting a diagnosis of epilepsy has required at least two unprovoked seizures with an interval of more than 24 hours, or one unprovoked seizure and the presence of a risk of repeated attacks (at least 60%) after two spontaneous seizures over the next 10 years, or a diagnosis of epileptic syndrome [1].

In 2017, the well-known classification of epilepsies, epileptic syndromes and similar diseases adopted by the International League Against Epilepsy was revised (New Delhi, 1989) [2]. This classification is multi-level and includes three stages — the type of seizure, the type of epilepsy, and the epileptic syndrome.

Epilepsy is a common childhood brain disorder, which affects between 0.5% and 1% of children at the age of under 16. Its psychological comorbidities include autism spectrum disorders, ADHD, psychosocial issues, and family troubles. Physical comorbid conditions occur, as a rule, against the background of medication intake, and they include loss of bone mass, immunological disorders, hypothyroidism, dyslipidemia and carnitine deficiency, etc. [3–8].

Visiting a dentist is, nowadays, most common routine. Children diagnosed with epilepsy are frequent patients in dental clinics, and the estimated prevalence of epilepsy among those seeking dental care is 0.9%. A study by Subki A. H. suggests that 55.2% of respondents have a poor dental status, whereas 84.4% of children need dental intervention [9]. Poor dental health is largely correlated with factors like cerebral palsy, motor disability, and lack of regular brushing. In patients with epilepsy, poor oral hygiene leads to an increased incidence of caries, tooth loss, and periodontitis [10]. Besides, there is a correlation between the frequency of seizures and periodontal diseases [11].

Severe forms of epilepsy are associated with serious problems in the oral cavity and maxillofacial area. In case of West's syndrome, for instance, there are multiple abnormalities, including disturbed eruption time, poorly developed hard tissues of the teeth, abnormal

shape and position, heavy plaque and calcified debris, abnormal bite and poor oral habits — patients breathe through the mouth and bite their nails [12, 13].

Oral cavity injuries occur due to seizures, and patients with epileptic seizures get injured more often than patients with psychogenic seizures. The rate of maxillofacial area injuries among such patients is 19%. At the same time, face soft tissue damage is most common (52%), while dental damage (18%) and maxillofacial fractures (12%) are not so frequent [14]. In case of comorbid epilepsy conditions, the chances of getting injuries in the maxillofacial area are high as well, which may be accounted for by the combined course of the issue with epilepsy [15]. One of the factors suggesting a child has epileptic seizures is a full examination at the dentist's office, since over 90% of injuries during seizures were those affecting the maxillofacial area. At the time of the seizure, almost none of the children received antiepileptic therapy and trauma occurred at the first seizure [16]. According to Lagunju I. A., over a half of children injured during a seizure were diagnosed with generalized idiopathic epilepsy, while this group of patients requires special care when treated [17].

Biting the soft tissues in the oral cavity is also a common injury in case of an epileptic seizure. Earlier tongue traumas were believed to be a direct indication of epilepsy, yet this can also occur in case of fainting and psychosis. Epilepsy can be more often concluded from injuries on the tongue lateral surface, while injuries on the lateral surface of the tongue and lips indicate fainting and psychogenic attacks [18, 19, 20].

In view of the above, children with epilepsy should visit the dentist on a more frequent basis. According to Mielnik-Błaszczak M., most children with epilepsy do not have regular dental check-ups. Besides, patients with epilepsy are less likely to see dentists compared to the general population, even though they have a higher need for it [21, 22].

Epilepsy is an aggravating factor not only for children and their parents, yet for dentists as well. Various dental interventions involve the risk of convulsions, so dentists should have a basic understanding of the patient's condition. As claimed by Schipper M., 10% of patients had a seizure in a dental practice. At the same time, only 79% of them informed their doctor about epilepsy, whereas 6% of them rejected dental procedures due to the major diagnosis [23].

TACTICS FOR MANAGING A PATIENT WITH EPILEPSY IN THE DENTIST OFFICE

First of all, it is to be noted that people with various neuropsychiatric disorders, including epilepsy,

require more preventive examinations as well as they need to spend more time on their oral hygiene [24].

When handle a child with epilepsy, it is important, first of all, to get a detailed history of the disease, to find out about the type of epilepsy, the earlier seizures, to learn how often they occurred and under what conditions, as well as get some details regarding adherence to therapy and its effectiveness. Gathering details about the disease should be done at each visit, even if the patient visits the same dentist, to see if the disease is progressing [25, 26]. During the examination, the dental chair should be in the supine position and kept at the lowest possible. Lidocaine used as a local anesthetic virtually does not increase the risk of a seizure [27]. Prior to the procedure, a sedative may be needed. Midazolam, for instance, proves effective in 89% of patients with neurological disorders [28].

General anesthesia should only be used in special situations with severe epilepsy and a large number of seizures in the history. When taking some antiepileptic and anticonvulsant drugs, it is to be taken into account that they can have a serious sedative effect, which means the dosage of anesthesia should be reduced [29, 30].

In case of a generalized tonic-clonic seizure, it is important to free up the space around the patient, lift the head, and give oxygen. If a seizure persists for more than 5 minutes or a in case it is a rapidly recurring seizure, buccal injection of Midazolam has to be used (10 mg — for children over 10; 7.5 mg — for children aged 5 to 10; 5 mg — for children under the age of 5). Besides, it is necessary to call an ambulance, since a long-term seizure can turn into an epileptic status [31, 32].

CONCLUSIONS

One of the factors that may help identify epilepsy in a child is a comprehensive examination at the dentist's office, which may reveal injuries in the maxillofacial area related to previously unknown seizures. Obtaining an accurate medical history can offer an additional chance to predict and prevent epileptic seizures. At the same time, we believe that the issue of dental treatment of children with epilepsy has not been fully disclosed, and the material does not provide enough data.

Therefore, managing children with epilepsy in the dentist's office, it is important to take into account the primary disease and, in view of that, adjust the treatment tactics in regard to potential comorbid conditions.

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EFFECTIVENESS OF ENAMEL INFILTRATION AFTER RADIATION THERAPY IN PATIENTS WITH ORAL CAVITY CANCER

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ABSTRACT — Prevention and treatment of dental hard tissue pathologies in patients exposed to combined and radiation treatment of oral cavity and pharyngeal malignancies are an urgent and challenging issue for the clinical dentistry. Deterioration of tooth enamel after radiation is similar to caries in the spot stage, which allows using infiltration of tooth enamel. **AIM OF THE STUDY:** to identify the effectiveness of enamel infiltration with *Icon* in patients subjected to radiation therapy for the oral cavity cancer. **MATERIALS AND METHODS:** enamel infiltration was performed for the vestibular and proximal surfaces of 35 teeth in patients who received radiation therapy for oral cancer (squamous cell tongue carcinoma, squamous cell amygdala carcinoma). The study outcomes were evaluated 6 months, 1 year and 1.5 years following the treatment. **RESULTS AND DISCUSSION:** enamel gloss was recovered in 32 teeth; chalky spots disappeared completely in 28 cases, while another 7 cases featured significantly decreased severity. In total, the progression of the carious process was to be observed in 14.3% of the cases within 1.5 years, mainly on the proximal surfaces of the teeth. **CONCLUSION:** enamel infiltration with *Icon* is an effective treatment for enamel demineralization in patients who underwent radiation therapy.

KEYWORDS — radiation caries, enamel infiltration method.

INTRODUCTION

The recent years have witnessed an increase in the overall intensive incidence of oral cavity and pharyngeal cancer. Treatment of such patients in most cases is combined; as claimed by the WHO, about 70–75% of such patients need radiation therapy [1, 2], which has a number of complications. One of the late effects is radiation caries. The effects of radiation depend on both the radiation nature and its dose, and may have different clinical manifestations [3, 4, 29]. Most often, 3–6 months after radiation therapy, the teeth enamel loses its typical gloss and gets dull, as well as it acquires

some grayish hue. The enamel film becomes more eroded, which leads to enamel fragility on all surfaces of the teeth. As the process progresses, it causes local enamel necrosis, gradually turning into circular lesions of the teeth. The necrosis foci expand gradually, affecting a larger part of the tooth surface. If there are no drastic measures taken to treat the teeth, in 1–2 years over 96% of the teeth will be affected [3].

Modern practical dentistry has made a breakthrough in recent decades not only by introducing new methods of prevention, diagnosis and treatment of dental issues, but also by improving the scientific knowledge and manual skills [10–19]. Comprehensive approach to teeth aesthetic restoration with chemical and technological compatibility of all materials and medication should be applied after diagnosing caries in all treatment stages. It includes a follow-up examination. Such approach is extremely important and requires in-depth study [20–28].

So far prevention and treatment of the dental hard tissue pathology in patients after combined and radiation therapy for oral cavity and pharyngeal cancer remain unresolved [4–6]. All the above mentioned explain the relevance of the problem and a search of effective restoration options.

Relying upon the fact that initial changes in the teeth enamel after exposure to radiation are similar to caries in the spot stage, our idea was to investigate possible use of tooth enamel infiltration to treat the initial stages of radiation caries and prevent the caries progress.

The technique of enamel infiltration with *Icon* implies removing the pseudo-intact enamel layer with 15% hydrochloric acid, then filling the lesion with a mixture of synthetic resins featuring a high penetration coefficient, while their optical properties are to be similar to those of intact tooth enamel [5]. After treatment with the *Icon* system, the tooth shows improved aesthetic properties, whereas the enamel surface is sealed hermetically at the carious spot. This leads to higher stability of the teeth hard tissues and to stabilization of caries progression [7–9]. Therefore, this method seems rather promising for management of initial stages of radiation caries and preventing its progression.

Aim of study:

to identify the effectiveness of enamel infiltration with *Icon* in patients after radiation therapy for the oral cavity cancer.

MATERIALS AND METHODS

The study focused on working with 35 teeth in patients exposed to radiation therapy for oral cancer (squamous cell tongue carcinoma, squamous cell amygdala carcinoma).

For impregnation, the teeth were selected featuring a loss of gloss and enamel transparency, chalky spots as a manifestation of demineralization of the enamel surface layer and without signs of its destruction and defects. Enamel infiltration was performed on the vestibular and proximal surfaces.

Enamel impregnation with *Icon* (DMG, Germany) was carried out as follows. Initially, dental deposits were removed with a brush using the Detartrine paste (Septodont, France), after which the teeth were thoroughly washed with a stream of water and dried.

Afterwards, the teeth were isolated using liquid photopolymerized cofferdam Liquid Dam (Amazing White, USA). Then, some etching gel *Icon-Etch*, containing 15% hydrochloric acid, was applied to the enamel demineralization foci.

The medicine was allowed to have its effect on the tooth enamel for 120 seconds, after which the tooth surface was washed with distilled water for 30 seconds. Then the tooth enamel was air-dried. In order to completely remove the moisture remaining in the enamel pores, some ICOP-Dry air conditioner containing etha-

3 minutes, after which it was photopolymerized for 40 seconds. To increase microhardness and compensate for polymerization shrinkage, the infiltrate was applied again for 1 minute, after which it was photopolymerized for another 40 seconds. Further on, the cofferdam was removed, to be followed with removal of the excess material, the oxygen-inhibited layer; then the teeth were polished with polishing heads and disks.

The patients were recommended to practice good dental hygiene and use a remineralizing toothpaste. The follow-up period was 1.5 years; control check-ups were carried out 6, 12 and 18 months after the procedure of dental infiltration with *Icon*.

RESULTS AND DISCUSSION

After the treatment, the enamel gloss was restored on 32 teeth (91.4% of cases); the chalky spots disappeared completely in 28 cases (80%), and in 7 cases (20%) their severity decreased significantly.

6 months later, there were no cases of caries progression on the treated teeth. 12 months after the enamel infiltration, carious cavities development was registered on the treated surfaces of 3 teeth (vestibular surface of 1 canine, circular caries of 1 premolar, approximal surface of 1 molar).

A study conducted after 18 months revealed 2 more cases of cavity caries (approximal surfaces of 2 premolars), as well as an increase in the chalky spots area on the vestibular surface of 3 teeth treated with *Icon*; the infiltration effectiveness was incomplete.

Fig. 1 below shows the effectiveness of enamel infiltration with *Icon*.



Fig. 1. Oral cavity status after radiation therapy (46-year-old patient) (a), at treatment stage (b), and 6 months after enamel infiltration with *Icon* (c)

nol was applied to the surface, which was further dried by a jet of air supplied from a compressor, which created proper conditions for the polymer resins adhesion.

The lesion infiltration was performed with a component of the *Icon-Infiltrant* medication. For this purpose, a nozzle was screwed onto the syringe, which allowed the infiltration, with some excess, to be applied by rubbing movements onto the enamel surface. The exposure time of the infiltrant on the enamel was

During 1.5 years of monitoring the teeth condition treated with *Icon*, progression of caries was to be observed in 14.3% of cases — mostly on the proximal surfaces of the teeth. Comparing the rate of caries progression after intensive exposure to radiation (without dental treatment, over the course of 1–2 years after the radiation therapy, more than 96% of teeth get affected by radiation caries), we can conclude that treatment of radiation caries with tooth enamel infiltration *Icon*

proves as highly effective. In addition, if it is complemented with procedures aimed at enamel remineralization, this method can significantly reduce the caries progression in irradiated patients.

CONCLUSION

Our clinical observation has proven the effectiveness of enamel infiltration with Icon in treatment of initial stages of radiation caries, especially when it is used on the teeth vestibular surface. This demonstrates a promising potential of further studying of this approach in regard to the hard dental tissue issues in irradiated patients with cancer of the oral cavity tissues and organs.

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A BIOMETRIC APPROACH TO DIAGNOSIS AND MANAGEMENT OF MORPHOLOGICAL CHANGES IN THE DENTAL STRUCTURE

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INTRODUCTION

The issues focusing on studying human constitution features, which are the basis of clinical and anthropological area, attract both theoretical and clinical medicine, while classical anthropometric methods are perfectly complemented by advanced innovation-based research approaches, at the same time enhancing the precision and effectiveness of the obtained outcomes [1, 14, 19, 28, 35].

The goal of personalized medicine, taken as a rapidly progressing field of healthcare, is entitled to improve patient treatment protocols following the constitutional and typological body features, which are determined by a whole set of phenotypic and genetic markers, offer an objective reflection of its morphological, functional and biochemical specifics, are stable in ontogenesis, and reveal individual anatomical variability with minor intra-individual change [3, 11, 13, 23].

Diagnostics and treatment of dental issues with morphological changes should be based not only on a thorough clinical and paraclinical examination, but also on a personalized approach in view of a set of anthropometric and X-ray cephalometric indicators that are mutually complementary [6, 10, 16, 25, 29, 36, 42].

ABSTRACT — Clinical examinations, biometric studies of jaw diagnostic models and cone-beam computed tomography were performed involving 104 people in their first adult period with a full set of permanent teeth, the physiological occlusion and the mesognathic type of dental arches. Clinical and X-ray-morphometric explanation of the proportional parameters of the dental and alveolar triangles, taking into account the medial incisors individual position, allowed us developing, substantiating and testing a biometric diagnostic approach to treat morphological changes in the dental structure. Patients, depending on the interincisal angle, featured the mesotrusion type (interincisal angle, 130°-140°), the protrusion type (interincisal angle below 129°) and the retrusion type of the dental arches (interincisal angle above 141°). The study revealed that the distance between the central points of the dental and alveolar triangles on both jaws could be described with the trusion type of arches. The smallest distance between the peaks of the dental and alveolar triangles was to be observed in people with the retrusion type of the arches and microdontia (upper jaw, 1.5±0.07 mm; lower jaw, 0.5±0.02 mm); the average value was recorded in patients with the mesotrusion type and normodontia (upper jaw, 2.5±0.06 mm; lower jaw, 1.5±0.05 mm); the maximum distance was observed in people with the protrusion type of the arches and macrodontia (upper jaw, 3.5±0.08 mm; lower jaw, 2.5±0.07 mm). The morphometric data interpretation can be used to describe the physiological occlusion, when choosing the tactics and the methods of orthodontic treatment for patients with disturbed shape and size of the dental arches, as well as when designing artificial dental arches for patients with full or partial adentia, thus seeking to achieve a balanced articulation balance.

KEYWORDS — biometric diagnostics, dental arches, alveolar arches, microdontia, macrodontia, normodontia, protrusion of incisors, retrusion of incisors, mesotrusion of incisors.

Lack of highly reliable data on clinical, X-ray and anthropometric examination of patients with maxillofacial pathology under complex clinical conditions explains the need for reviewing conventional diagnostic schemes in order to improve the effectiveness of orthodontic and prosthetic treatment [8, 12, 21, 33, 38].

The basis of the modern concept of *norm* relies on the idea of *optimal individual norm*, i.e. the condition of sufficiently guaranteed morphological, functional and aesthetic balance in the dental system and the facial skeleton as a whole, which should be the aim of orthodontic and prosthetic treatment [40].

Orthodontic and prosthetic treatment is based on knowing the patterns of individual-typological craniofacial variability. The variability of the dental arches' shape and morphometric parameters is the basis for employing orthodontic and prosthetic treatments, while a detailed study of dental arches is not only of fundamental theoretical importance, yet also has applied value in identifying dental anomalies, interpreting biometrics, as well as when through the treatment and rehabilitation of patients with occlusal disorders [2, 15, 22, 26, 32, 39, 43].

A detailed study of the variant anatomy of the shape and morphometric parameters of dental arches allows personalized prosthetic, orthodontic, and surgical intervention, which is of high clinical significance when it comes to diagnosing and planning of further treatment tactics [4, 7, 20, 27, 31, 34, 37, 45].

Lack of effectiveness in orthodontic measures, which is due to non-compliance with the biological principles of the tooth movement (excessive load, reduced retention period), as well as the impossibility of installing teeth in a neutral zone while seeking a balance between the muscles of the external and internal functional circles, will not contribute to improving the dental arches shape and size as well as to the compensation for occlusal relationships, which, in turn, will lead to relapsing dental anomalies [17, 44].

Of reasonable interest are works by researchers who point at correlations between the size of the dental and alveolar arches in the upper jaw, as well as their match with the face parameters. The ratio of the face diagonal dimensions to the similar parameters of the alveolar arches has been found to be 2.5, while the ratio of the frontal-distal diagonal of the upper alveolar arch to the lower one is 1.06. The authors recommend using the obtained data for clinical dentistry when treating patients with dental arches anomalies and defects [18, 30].

Experts present the main parameters of dental arches in children through the period of baby teeth bite, as well as in case of congenital maxillofacial pathology [5, 9, 24, 41].

Analysis of research by national and foreign experts shows that there are no methods for constructing dental and alveolar triangles based on the permanent anatomical marks position in people with physiological occlusion in the permanent teeth bite. There have been no morphometric values identified, which determine the dental and alveolar triangles size, whereas the data on the dependence of the interincisal angle and the dental arches belonging to the trusion type is not complete, which points at the rationale and purpose of the study.

Aim of study:

to develop a diagnostic biometric approach to studying dental and alveolar arches in order to plan the tactics of orthodontic and prosthetic treatment in patients with morphological changes in the dental structure.

MATERIALS AND METHODS

The study involved 104 people in their first adulthood featuring a full set of permanent teeth and physiological occlusion. According to the age periodization of postnatal ontogenesis as approved by the International Symposium on Age Physiology (Moscow, 1965), the first adult period for men is the age of 22–35, and for women — 21–35. All the participants offered their informed consent. The Committee for Bioethics confirmed that the protocols complied with the international and national ethics requirements (Helsinki Declaration of the World Medical Association on the ethical principles of human medical research, 1964) with amendments, the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

The patients were divided into three groups based on the dental arches type and on the individual position of the medial incisors. Group 1 included 39 people with mesotrusion type of dental arches and mesotrusion of the central incisors, with an interstitial angle of 130–140°. In Group 2 (n=34), the patients featured the protrusion type of dental arches with physiological protrusion of the medial incisors, and a decrease in the interincisal angle (less than 129°). In Group 3 (n=31), the patients had an interincisal angle of above 141°, as well as the retrusion type of dental arches with physiological retrusion of the central incisors (Fig. 1).

Teleroentgenograms and cone-beam tomograms were obtained on a 21-slice digital panoramic X-ray machine PaX-i3D SC with the function of a computer tomograph and a cephalostat FOV with accessories (VATECH Global, South Korea) following the scanning Protocol for Sim Plant. Processing, storage and export of the X-ray images were done with the Ez Dent-irm software, multiplanar reconstruction and three-dimensional (3D) reconstruction were performed with the tomograph software for 3D diagnostics Ez 3D-i™; the saved data was viewed, with an option of import done using the Viewertm software. The tomographic section thickness was 1 mm; the reconstruction step was 1 mm, whereas the rotation step was 1 mm.

The main reference point for the biometric study of the dental arches was the anterior incisal (central) point, which was located between the medial incisors at the cutting edge, and which we indicated as *in_a*

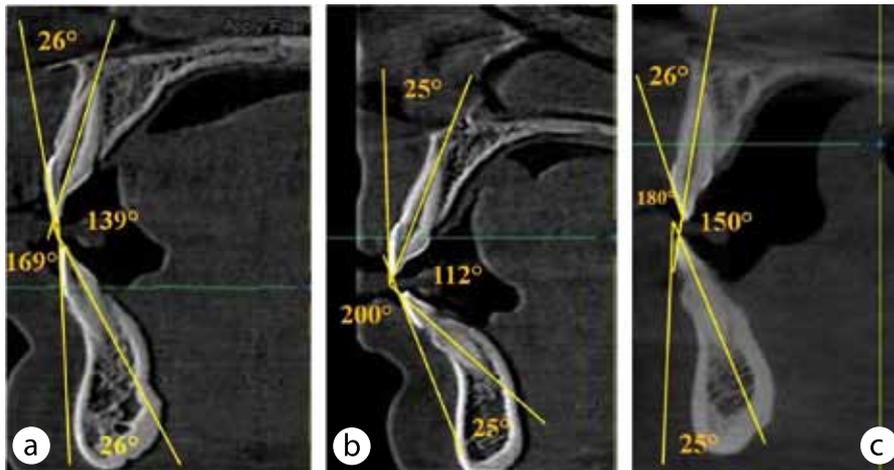


Fig. 1. Cone-beam computed tomography images of patients with mesotrusion (a), protrusion (b) and retrusion (c) of central incisors

(incisus dentale). The tops of the vestibular distal tubercles were marked with the m_d points (molares dentale). The junction of the molar points determined the base of the dental triangle and corresponded to the dental arches width between the second molars. The sides of the dental triangle (which was isosceles, as a rule) matched the frontal-distal diagonal of the dental arch ($in_d - m_d$). The height of the triangle was measured from its top ind to the m'_d point, taken as the intersection of the perpendicular drawn from the ind point to the conditional line between the second molars ($md - md$). To measure and build the alveolar triangle, the central point was put on the alveolar process (alveolar part) in the interdental space between the incisors, and marked as inal (incisus alveolare). The molar alveolar points mal (molares alveolare) were placed on the alveolar process (alveolar part) in the interdental space between the second and third molar on the lingual side. If the third molar was missing, the reference point was placed on the distal surface of the lingual distal odontomer near the tooth neck. The alveolar triangle was built similarly to the dental one (Fig. 2).

The measurements were performed on both jaws using an electronic caliper with a precision of 0.01 mm. The dimensions identified included the base, the height, and the sides of the alveolar and dental triangles, after which they were compared. The distance between the central points of the arches (the apexes of the triangles) was estimated as well.

Statistical data processing was done using the Microsoft Excel 2013 software and the SPSS Statistics (Version 22) statistical software package. To try the normal data distribution hypothesis, the Shapiro-Wilk's test (W-test) was employed. The statistical significance of the intergroup values was calculated using the non-parametric Mann-Whitney U-test with Bonferroni correction, while the reliability of the dynamics

difference-related features was calculated through the Wilcoxon T-test. In other cases, the Student's T-test was used. When identifying correlations among the studied parameters, a non-parametric Spearman rank correlation coefficient was calculated. The critical level of a potential null statistical hypothesis was taken as equal to 0.05.

RESULTS AND DISCUSSION

Following the tasks set, we measured the parameters of the dental and alveolar triangles on cast models of the upper and lower jaws. Note to be made that all patients featured the mesognathic type of the dental arches, while the position of the incisors was due to the differences in the teeth size. The patients of Group 1 with the mesotrusion type arches, typically featured normodontia. In case of the protrusion type of the arches, the macrodontic dental system was to be observed more often, while in case of retrusion it was microdontia, which was reflected in the major indicators of dental and alveolar triangles (Fig. 3).

Table 1 offers the outcomes of studying upper jaw cast models in the groups in question.

The patients with the mesotrusion type of the dental arches had the dental triangle base ($m_d - m_d$) significantly exceeding that of the alveolar triangle ($m_{al} - m_{al}$), measuring 60.61 ± 1.87 mm and 52.13 ± 1.24 mm, respectively ($p \leq 0.05$). Also, the sides of the dental triangle ($in_d - m_d$) were larger than the sides of the alveolar triangle ($in_{al} - m_{al}$) measuring 53.72 ± 1.01 mm and 50.17 ± 1.32 mm, respectively ($p = 0.05$). We observed no statistically significant differences in the arches depth (the heights of the triangles), while the measurement outcomes were as follows: the dental triangle, $in_d - m'_d = 44.35 \pm 1.41$ mm; the alveolar triangle, $in_{al} - m'_{al} = 42.87 \pm 1.14$ mm ($p \geq 0.05$) (Fig. 4).

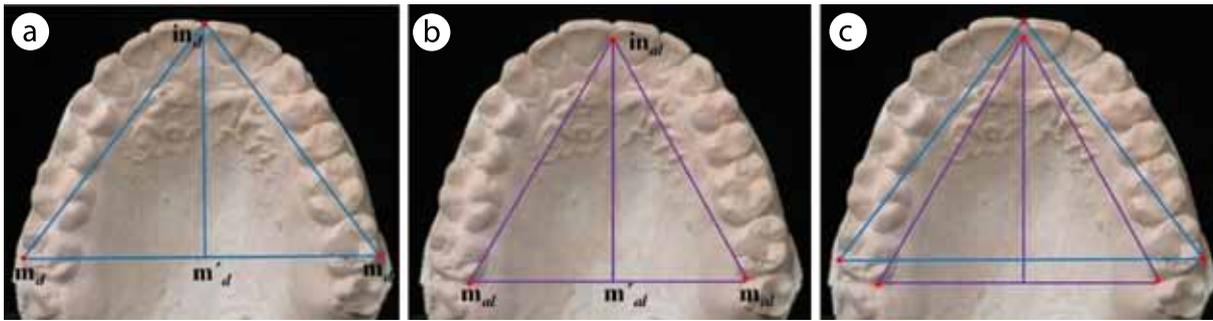


Fig. 2. Methods for building dental (a) and alveolar (b) triangles, and matching them (c)



Fig. 3. Upper jaw cast models in patients with mesotrusion type of dental arches and normodontia (a), protrusion type of dental arches and macrodontia (b), and retrusion type of dental arches and microdontia (c)

Table 1. Biometric parameters of upper jaw cast models in patients with mesotrusion, protrusion and retrusion type of dental arches (M±m, mm)

Major parameters of arcade triangles	Linear dimensions of upper arcade triangles in people with meso-, pro-, and retrusion types of dental arches		
	mesotrusion	protrusion	retrusion
Basis of dental triangle (m _d -m' _d)	60.61±1.87	66.53±1.62*	57.75±1.12*
Height of dental triangle (in _d -m' _d)	44.35±1.41	46.61±1.81*	42.01±1.97*
Side of dental triangle (in _d -m _d)	53.72±1.01	57.26±1.23*	50.98±1.57*
Basis of alveolar triangle (m _{al} -m' _{al})	52.13±1.24	57.69±1.72*	49.36±1.65*
Height of alveolar triangle (in _{al} -m' _{al})	42.87±1.14	43.12±1.53*	41.07±1.71*
Side of alveolar triangle (in _{al} -m _{al})	50.17±1.32	54.87±1.38*	47.91±1.24*

Note: * — statistically reliable regarding the parameters in the patients with the mesotrusion type of the dental and alveolar arches (p ≤ 0.05)



Fig. 4. Images of oral cavity, patient with mesotrusion type of dental arches and normodontia (a — frontal, b — lateral right, c — lateral left projections)

The transversal size values in patients with the protrusion type of the dental and alveolar arches ($m_d - m'_d = 66.53 \pm 1.62$ mm and $m_{al} - m'_{al} = 57.69 \pm 1.72$ mm, respectively) exceed similar values in people with the mesotrusion type ($m_d - m'_d = 60.61 \pm 1.87$ mm and $m_{al} - m'_{al} = 52.13 \pm 1.24$ mm, respectively) ($p \leq 0.05$), while in Group 2, the sides of the triangles ($in_d - m'_d = 57.26 \pm 1.23$ mm; $in_{al} - m'_{al} = 54.87 \pm 1.38$ mm) were significantly larger than identical parameters of patients of the first group ($in_d - m'_d = 53.72 \pm 1.01$ mm; $in_{al} - m'_{al} = 50.17 \pm 1.32$ mm) ($p \leq 0.05$). The sagittal dimensions (the height of the triangles) featured basically no significant differences both within the group and when comparing the patients of Groups 1 and 2 (Fig. 5).

The patients with the retrusion position of the incisors had odontometric indicators that corresponded to microdontia, which predetermined smaller (compared to the other groups) size of the dental and alveolar arches. The biggest decrease in the size values was observed at the triangles' bases ($m_d - m'_d = 57.75 \pm 1.12$ mm; $m_{al} - m'_{al} = 49.36 \pm 1.65$ mm) and the sides ($in_d - m'_d = 50.98 \pm 1.57$ mm; $in_{al} - m'_{al} = 47.91 \pm 1.24$ mm). However, the height of the dental ($in_d - m'_d = 42.01 \pm 1.97$ mm) and alveolar ($in_{al} - m'_{al} = 41.07 \pm 1.71$ mm) triangles slightly differed from respective values in Groups 1 and 2 ($p \geq 0.05$) (Fig. 6).

An analysis of the dental and alveolar arches central point's location (the triangles apexes) revealed that the distance between them belonged to the trusion type of the arches. The patients with the retrusion type had the shortest distance, 1.5 ± 0.07 mm. In case of mesotrusion, the alveolar triangle was displaced by 2.5 ± 0.06 mm, and for the protrusion type the respective value was 3.5 ± 0.08 mm (Fig. 7).

Table 2 offers a view at the outcomes of biometric measurements of lower jaw cast models in the groups in question.

The morphological features that determine the relative positions and symmetry of the dental and alveolar triangles in case of the retrusion, mesotrusion and protrusion arches, involve both the upper and the lower jaw.

An analysis of morphometric indicators of mandibular dental and alveolar arches shows the following displacement of the apex (central point) of the alveolar triangle in relation to the dental triangle apex: 1.5 ± 0.05 mm for the mesotrusion position of the incisors; 2.5 ± 0.07 mm for protrusion position of the incisors; 0.5 ± 0.02 mm for the retrusion position of incisors.

In view of the above, the major parameters of the dental and alveolar triangles are determined by

the types of the arches and odontometric parameters, which is to be taken into account when planning and performing orthodontic and prosthetic treatment, as well as when evaluating the final outcomes of such treatment in patients with maxillofacial anomalies and deformities.

CONCLUSIONS

1. The clinical and X-ray-morphometric explanation of the proportion dependence for the dental and alveolar triangles parameters (width, $m_d - m'_d / m_{al} - m'_{al}$; depth, $in_d - m'_d / in_{al} - m'_{al}$; frontal & distal diagonal, $in_d - m'_d / in_{al} - m'_{al}$), in view of the individual position of the medial incisors, allowed us developing, substantiating and testing a biometric diagnostic approach to studying the dental and alveolar arches in people with physiological occlusion in a permanent teeth bite.
2. The following points were used as the most stable anatomical references through building the dental ($m_d - in_d - m'_d$) and alveolar ($m_{al} - in_{al} - m'_{al}$) triangles: the incisal ind point located between the medial incisors near the cutting edge; the molar md point located at the vestibular distal tubercles apexes; the central inal point located on the alveolar process (alveolar part) in the interdental space between the incisors; the molar mal alveolar point located on the alveolar process (alveolar part) in the interdental space between the second and third molar on the lingual side.
3. In the patients with a physiological occlusion of permanent teeth, the value of the interincisal angle falling within the reference intervals of $130 - 140^\circ$, signals of the mesotrusion type of the dental arches. The patients with a physiological protrusion of the medial incisors and an interincisal angle below 129° , feature the protrusion type of the dental arches, whereas those with the physiological retrusion of the central incisors, and an interincisal angle exceeding 141° had the retrusion type of the dental arches.
4. In patients with the protrusion type of arches, on both the upper and lower jaw, the base ($m_d - m'_d$, $m_{al} - m'_{al}$), as well as the sides ($in_d - m'_d$, $in_{al} - m'_{al}$) of the dental and alveolar triangles exceed statistically reliably the similar indicators identified in people with the mesotrusion and retrusion types of the arches. The patients with the meso-, pro-, and retrusion types of the arches (both jaws) had the sagittal values of the dental ($in_d - m'_d$) and alveolar ($in_{al} - m'_{al}$) triangles revealing no statistically meaningful differences.
5. The patients with complete loss of teeth, due to bone atrophy of the alveolar processes and jaws,



Fig. 5. Images of oral cavity, patient with protrusion type of dental arches and macrodontia (a — frontal, b — lateral right, c — lateral left projections)



Fig. 6. Images of oral cavity, patient with retrusion type of dental arches and microdontia (a — frontal, b — lateral right, c — lateral left projections)

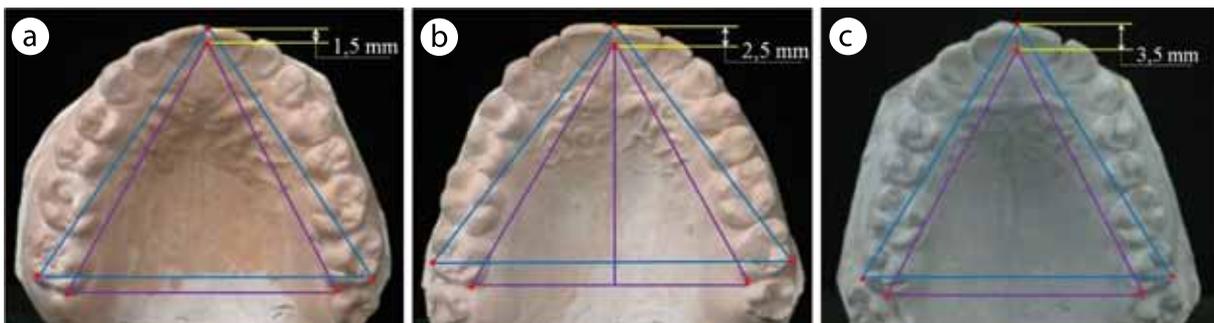


Fig. 7. Mutual position of dental and alveolar triangles for retrusion (a), mesotrusion (b) and protrusion arches (c)

Table 2. Biometric parameters of lower jaw cast models, patients with mesotrusion, protrusion and retrusion type of dental arches ($M \pm m$, mm)

Major parameters of arcade triangles	Linear dimensions of upper arcade triangles in people with meso-, pro-, and retrusion types of dental arches		
	mesotrusion	protrusion	retrusion
Basis of dental triangle ($m_d - m'_d$)	55.27 ± 1.56	$61.05 \pm 1.84^*$	$53.73 \pm 1.67^*$
Height of dental triangle ($in_d - m'_d$)	41.19 ± 1.48	$46.68 \pm 1.81^*$	$38.60 \pm 1.73^*$
Side of dental triangle ($in_d - m_d$)	49.57 ± 1.56	$52.83 \pm 1.45^*$	$47.03 \pm 1.48^*$
Basis of alveolar triangle ($m_{al} - m'_{al}$)	50.45 ± 1.72	$53.15 \pm 1.83^*$	$47.99 \pm 1.64^*$
Height of alveolar triangle ($in_{al} - m'_{al}$)	39.38 ± 1.16	$42.16 \pm 1.51^*$	$37.32 \pm 1.39^*$
Side of alveolar triangle ($in_{al} - m_{al}$)	46.77 ± 1.52	$49.84 \pm 1.39^*$	$44.36 \pm 1.42^*$

Note: * — statistically reliable regarding the parameters in the patients with the mesotrusion type of the dental and alveolar arches ($p \leq 0.05$)

- had their alveolar arches shape and size changed. Employing the identified morphometric reference intervals of the alveolar arches (base, $m_{al}-m_{al}$; side, $in_{al}-m_{al}$; height, $in_{al}-m'_{al}$) as reference points for building dental rows will allow reproducing the volume and the nature of the structure that were to be observed prior to the loss of teeth and bone atrophy in the alveolar processes and jaws, which is important when dealing with manufacturing prosthetic structures that are fully functional and aesthetic.
6. The distance between the central points of the dental (in_d) and the alveolar (in_{al}) triangles on both jaws features the trusion type of the arches. The smallest distance between the dental and alveolar triangles' apexes was to be observed in the patients with the retrusion type of the arches and microdontia (upper jaw, 1.5 ± 0.07 mm; lower jaw, 0.5 ± 0.02 mm); the average value was recorded in the patients with the mesotrusion type of the dental arches and normodontia (upper jaw, 2.5 ± 0.06 mm; lower jaw, 1.5 ± 0.05 mm), whereas the maximum distance was found in the patients featuring the protrusion type of the dental arches and macrodontia (upper jaw, 3.5 ± 0.08 mm; lower jaw, 2.5 ± 0.07 mm).
 7. Morphometric data on the dental and alveolar arches parameters are reliable and diagnostically meaningful values that can be of applied significance in practical dentistry. Interpretation of morphometric data can be used to describe the physiological occlusion when choosing the tactics and methods of orthodontic treatment for patients with disturbed dental arches shape and size, as well as when designing artificial dental arches in patients with full or partial adentia, thus ensuring a balanced articulation function.
 8. Manual reproduction of biometric diagnostics algorithms using conventional measuring tools and the table-based data of the normal values (base, height, side) of the dental triangles in patients with different teeth size (macro-, micro-, normodontia) will allow planning and controlling the course and the scale of teeth movement through all stages of orthodontic measures, thus helping eliminate dental anomalies.
 9. Improved rational prosthetic treatment is reached through following the principle of a proper combination of the constitution-bound alveolar process with the shape of the teeth (Modrach, 1959), and effective harmonious functioning. The inclusion of basic parameters of the alveolar triangles in the treatment standards (protocols) for patients with total absence of teeth would allow

not only reducing the time spent at the stage of installing toothless jaw models in the articulator, and facilitate achieving a proper match between the teeth shape, alveolar arches and the face, yet would also help build a balanced articulation structure, thus ensuring optimal functional and aesthetic outcomes.

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TOOLS AND METHODS OF TELEMEDICINE FOR EARLY DETECTION OF DENTAL ANOMALIES

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Aim of study:

to investigate potential use of telemedicine technologies and to develop software for early detection of dental anomalies under conditions of orthodontist shortage.

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ABSTRACT — This work offers a view at the practical application of telemedicine, especially in rural areas. There is a description and the principle of independent development. The item also contains comparative data on the effectiveness of jaw model analysis performed in the conventional way as matched against doing that with new software employed to detect dental anomalies, with no previously acquired skills. The software can be used by any doctor as it features detailed and clear instructions. This program will be useful in cases where orthodontists are not available.

KEYWORDS — telemedicine, diagnostic software, teledentistry, dentoalveolar issues detection.

INTRODUCTION

Availability of narrowly specialized medical care is an important feature attributing to its quality [7–11]. While in urban areas a specialist's consultation is available to most of the population, rural residents face certain deficits in this respect [1, 2]. Not only rural areas have a worse access to medical centers, but also a shortage of specialists and the insufficient technological infrastructure present a challenge there [3, 4]. The advance in communication technologies in remote areas is still slow compared to what it could be nowadays.

Telemedicine is one of the healthcare arrangements that may serve to improve medical services offered in remote areas that face issues with access to specialized care and appropriate equipment [5, 6].

MATERIALS AND METHODS

We had carried out an analysis of research articles and academic issues, after which software to analyze control and diagnostic models of the jaws were created. To do this, we developed a software program where the points on the images were placed following the instructions. After that, it analyzes the models based on common methods. Later on we compared the calculation accuracy through matching the outcomes obtained by an analog method against those obtained by using our software program. After that the analysis was performed.

RESULTS AND DISCUSSION

One of the tasks within this work implied developing software to detect early signs of dental anomalies by analyzing control and diagnostic cast models in remote areas where residents cannot visit an orthodontist for various reasons.

The major features for the developed software were to be the following ones:

- 1) low system requirements;
- 2) user-friendly interface and easy using (the software is to be used by doctors of any profile);
- 3) minimum time spent by the doctor when using the software;
- 4) open source;
- 5) free distribution model.

The software allows performing analysis by using two photos of jaw cast models with minimal preliminary preparation and no serious technical support. It takes placing the required dots on the image, which is to be done following the detailed description appearing on the screen, after which the software will make its own calculations.

The software employs the main methods of analysis of control & diagnostic models, which require data on the teeth size, on the distance between them and the length of the dental rows. The software requires

measuring 1 centimeter on a ruler, and then, in the image, marking the most prominent points on the teeth mesial and distal surfaces of each jaw (Fig. 1).

After that, points are marked to identify the dentition width (Fig. 2). Further on, points are placed to identify the length of the apical basis, and then the software will require opening the models image in a frontal projection and place points to identify the apical basis width (Fig. 3).

When all the data is specified, the software displays the calculation outcomes based on the methods proposed by Pont, Linder-Harth, Gerlach, Bolton, Snagina, Korkhaus. The data is displayed in terms that are accessible to non-dental specialists (Fig. 4). Further options imply sending the report and save it on the PC.

The major differences between our development and those available on the market include:

- 1) free distribution;
- 2) easy to use; each stage of diagnostics offers graphic instructions in Russian;
- 3) low system requirements; requires 6 megabytes of free hard disk space;
- 4) can be used by doctors of any specialty.

The second stage in the development was to check the analysis accuracy compared to the conventional traditional method of jaw models anthropometry with a caliper.

The test involved ten undergraduate students majoring in Dentistry, who performed measurements on models — first in the traditional way, and then using the respective software. The results showed that the differences between the measurements fell within the range of 2–4%, which is an acceptable tolerance.

The next step implied comparing the time spent on analog analysis and that using the software, which was done by untrained participants. We compared the time the students spent on analyzing 5 models in the traditional way and then — using our software. On average, the conventionally performed analysis took 35–42 minutes, whereas it took 3–4 minutes only to do that with the software, which, actually, means 8–10 times less than usual.

Putting the developed software to practice

- 1) Using this, as well as other similar developments, allows early detection of dental issues, which offers an obvious advantage since the successful outcome of treatment depends largely on the starting time of orthodontic treatment.
- 2) Many parents do not even suspect their children may be suffering from dental anomalies. Given that, another problem can be solved — the patient's awareness.

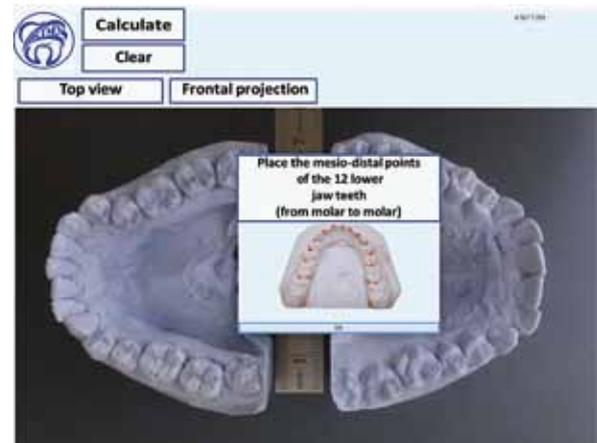


Fig. 1. Example of a popup window with a step-by-step instruction

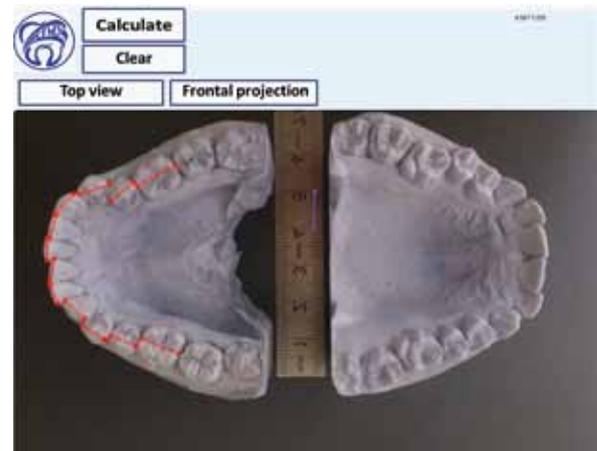


Fig. 2. Diagnostic models with points placed on the mesial and distal teeth surfaces, connected with reference lines

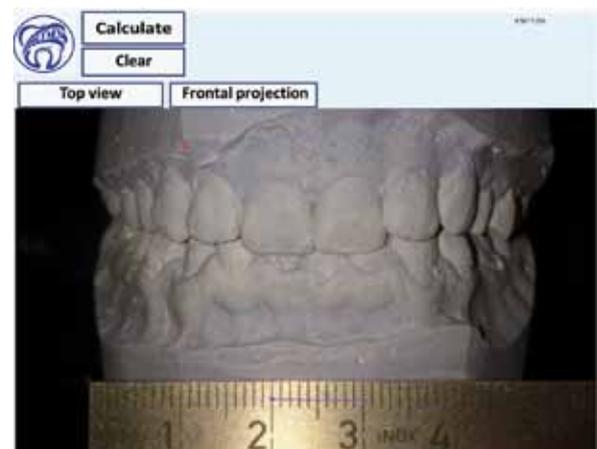


Fig. 3. Opening an image in a frontal projection to measure the apical basis

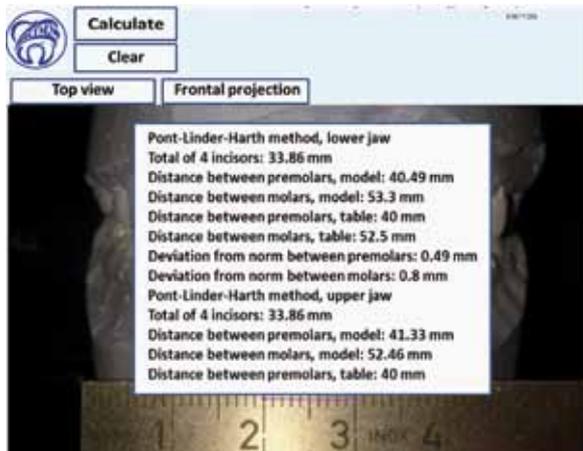


Fig. 4. Software compares measurements with table indices to make further conclusions

Table 1. Comparison of the measuring results for the four upper incisors sum by each student using the software and the conventional analysis

Student	1	2	3	4	5	6	7	8	9	10
Software (mm)	28.5	28	28	29.5	28	28	28.5	28.5	28	29
Conventional method (mm)	28	28.5	28	28.5	28.5	27	28	29.5	27	28.5

- 3) Easy to use. Analyzing models using our software takes having 2 photos of models with a ruler for zooming.
- 4) Maximum simplification of the diagnostics procedure and minimization of the time spent on it.
- 5) Lower cost. Telemedicine technologies in orthodontics may allow saving not only the doctor's time, yet also the patients' money.

CONCLUSION

The proposed development allows analyzing models by a dentist who has no special skills. In view of a shortage of orthodontists to be observed in remote areas with a low population density, this software, if integrated into telemedicine systems, may facilitate detection of dental anomalies, at the same time possibly reducing the number of diagnostic errors.

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MORPHOLOGY OF FACIAL SKELETON IN CHILDREN WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA

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ABSTRACT — In order to determine the major cephalometric and gnathometric features in children with undifferentiated connective tissue dysplasia, a comprehensive clinical-instrumental and X-ray examination was carried out involving 109 children aged 11–16 and featuring a set of signs pointing at connective tissue failure. Depending on the severity of the external phenotypic manifestations as well as clinical and instrumental signs, the patients were divided into groups with mild, moderate and severe undifferentiated dysplasia. The gnathometric and biometric maxillofacial studies were performed employing traditional methods, while the diagnosis was set following the generally accepted classifications.

The head telereöntgenograms (lateral projection) interpretation was performed in the Dolphin imaging software. The analysis of the head telereöntgenograms (lateral projection) was done through the Schwartz S. method subject to the norm indicators proposed by A. A. Anikienko. The nature and the intensity of morphofunctional issues in the craniofacial structures (small stigmas) were found to be determined by the severity of dysplastic connective tissue disorders.

Constitutional and morphological dysgenesis, as a manifestation of connective tissue dysplasia, is the reason behind abnormal development in the anatomical structure of the cranial and facial regions. It is displayed through increasing dolichocephaly with a decrease in the face width and vertical size, poorly developed jaws, distal displacement of the mandible in relation to the skull base combined with a deep incisal overbite, increased sagittal interincisal distance, and the vertical type of jaw growth. Thus, the pathogenetic mechanisms facilitate the development of malocclusions.

KEYWORDS — children, adolescents, undifferentiated connective tissue dysplasia, facial skeleton, cephalometry, gnathometry, maxillofacial region, lateral projection of head telereöntgenogram.

INTRODUCTION

Nowadays, researchers and clinicians are particularly interested in studying the pathogenesis, clinical polymorphism, and hereditary connective tissue diseases, as well as in developing and improving advanced techniques for their diagnosis and pathogenetic treatment [2, 26, 41].

Connective tissue dysplasia (CTD) is a genetically determined condition that features issues in the fibrous structures and in the connective tissue main substance, which leads to disturbed development of organs and systems, and which has a progredient course determining associated pathologies' specifics, as well as the respective medicine pharmacokinetics and pharmacodynamics [4, 7, 30, 39].

CTD development is based on inherited mutations of genes encoding the synthesis and spatial arrangement of collagen, structuring proteins and protein-carbohydrate combinations, as well as mutations of enzyme genes and respective cofactors. From the morphological aspect, these changes reveal improper development of collagen chains, resulting in abnormal collagen trimmers that are unstable to mechanical loads, while elastic fibrils, glycoproteins and proteoglycans with fibroblasts are also subject to irreversible change [5, 29, 47].

CTD clinical manifestations depend on the predominance of lesions in the dense or loose connective tissue, the number and quality of mutations, the nature and severity of fibrillogenesis disturbance. Due to the common presence of connective tissue (skin, bones, cartilage, vascular walls, organs stroma), the disease features a polysystemic nature and a variety of symptoms [3, 6, 8, 27].

Connective tissue, which accounts for 50 to 80% of the body weight, carries vital functions (trophic, plastic, barrier, biomechanical, morphogenetic), determines the morphofunctional integrity of the macroorganism, and responds to almost any pathological and physiological effect. The maxillofacial region features a complex anatomical structure, a large number of involved tissues, and their specific interaction. Embryogenesis and postnatal transformations of the dental apparatus help understand the mechanisms behind dysmorphia development, which is based on an inherited or acquired defect of connective tissue,

and offer a clear confirmation to the dominant shaping role of mesenchymal tissue and its integrating function. Disturbed development of connective tissue is the predetermining factor to dysmorphia involving all types of tissues that make up the organs in the maxillofacial region [1, 25, 31, 40].

The structural and functional components of connective tissue are involved actively in inflammatory, destructive and protective processes in various acute and chronic pathological conditions. Diagnostic dental markers for undifferentiated CTD include anthropometric features of the facial skeleton, dental issues, dental caries, periodontopathy, temporomandibular joint dysfunction, altered oral mucosa, oral cavity small vestibule, congenital short tongue frenulum, and narrowing lower jaw [10, 12, 20, 22–24, 43].

The current stage of development of certain divisions within clinical dentistry shows a significant increase in the role of anthropometric, morphological, genetic and functional research methods when it comes to solving the most urgent problems [11, 13–19, 21, 28, 42].

The priority task that clinicians are facing in view of the current demands implies improving the quality of criteria indicators, better treatment and diagnostic measures and protocols for follow-up cases with dental issues while relying upon principles of personalized medicine, as well as achieving sustainable long-term outcomes of dental treatment and improving patient quality of life [9, 32–38, 44–46].

Despite a significant number of respective research items, the data on the facial skeleton structure in children with CTD remains scattered. Given that, it appears relevant to study diagnostically significant gnathometric and cephalometric indicators in children with CTD of various severity, which would allow forming groups with a high risk of developing a multisystem pathology, as well as improving treatment methods for maxillofacial issues.

Aim of study:

to identify the major cephalometric and gnathometric features in children with undifferentiated CTD, which contribute to development of malocclusions

MATERIALS AND METHODS

Prior to clinical radiological studies involving children, independent informed consent was obtained from their parents.

The work itself implied a set of clinical, paraclinical and laboratory studies involving 109 children (62 girls, 47 boys) aged 11–16, with general somatic pathology, as well as CTD symptoms, who were treated at the Filippky Pediatric Hospital (Stavropol,

Russia). CTD diagnostics was performed following a unified diagnostic algorithm, involving doctors of related specialties. This was important in order to detect details of the lesions affecting organs and systems in this category of children. After excluding differentiated dysplasia with distinct clinical manifestations and detected inheritance (Marfan syndrome, Ehlers–Danlos syndrome, osteogenesis imperfecta, Stickler syndrome), CTD diagnostics included the following symptoms: at least six external phenotypes; multi-organ and multisystem distribution of pathological processes; signs of familial accumulation of collagenopathies; biochemically and immunohistochemically proven disorders of connective tissue metabolism.

The assessment of the CTD severity, depending on the external phenotypic manifestations and laboratory, clinical and instrumental signs, was performed in accordance with the recommendations by L.N. Abbakumova, T.I. Kadurina (2008). Taking into account the external phenotypic signs, as well as laboratory data and clinical examinations, CTD of the mild degree (scores below 30); the medium degree means a score of 30–44, while a score of 45 or above corresponds to the severe degree of CTD. The final diagnosis of CTD took into account the diagnostic tables for the CHILD category in cases where the diagnostic level of +70 was exceeded (E. P. Timofeeva, 1996). Based on the research outcomes, the patients were divided into three subgroups: Subgroup 1 — mild degree of CTD (n=31); Subgroup 2 — medium degree of CTD (n=37); Subgroup 3 — severe degree of CTD (n=41). The control group included 47 children belonging to health groups I and II (Yu.E. Veltischev, 1994), comparable in age and gender.

The diagnostics of dental anomalies relied on the results of clinical examinations, which included medical background evaluation, general examination of the face: symmetry, proportions in the jaw development, the lips position, the severity of nasolabial and chin folds, the degree of mouth opening, and the breathing type. The oral cavity examination included assessing the teeth and periodontium hard tissues status, the teeth position in the dental arch, the dentition shape and size, as well as their ratios. The orthodontic diagnosis was made on the basis of commonly accepted classifications. When making a preliminary diagnosis, we employed the Angle morphological classification, while the final diagnosis was based on the occlusion anomalies classification (Moscow State University of Medicine and Dentistry; 1990) as well as the occlusion anomalies classification by L.S. Persin (1989), recommended by the Resolution of the X Congress of the Professional Society of Russian Orthodontists (2006) as a single classification for orthodontic, surgical and

orthopedic clinics.

The identification of cephalometric indicators included linear and angular measurements of the head and face, along with assessing the head longitudinal and transverse diameter, the face morphological height, the zygomatic diameter, the head index, the facial index, the facial angle, and the nasal index using the conventional Martin and Garson methods.

After placing the head in the Frankfort horizontal, the following cephalometric measurements were performed: *eu-eu* — the head transverse diameter; *g-op* — the head longitudinal diameter; *n-gn* — the face morphological height; *zy-zy* — the face zygomatic diameter. The Garson facial index was identified based on the face morphological height ratio (*n-gn*) to the face width at the zygomatic arches (*zy-zy*). This index was employed to identify the following types of the face: hyperurisopic (<79.9%); euriprosopic (80.0–84.5%); mesoprosopic (85.0–89.9%); leptiprosopic (90.0–94.9%); hyperleptiprosopic (>95.0%). An equally important value in the facial skull is the facial angle, which is shaped through crossing of the line connecting the prosthion (pr) with the nasion (n) and the auricular (Frankfort) horizontal. Depending on the facial angle, the following types of facial skull can be identified: prognathic (70.0–79.9°); mesognathic (80.0–84.9°); orthognathic (85.0–92.9°); hyperorthognathic (>93.0°). Based on the head indicator — the ration of the transverse and longitudinal diameter of the cerebral part of the head, the following craniotypes were identified: dolichocephaly (<75.9); mesocephaly (76.0–80.9); brachycephaly (81.0–85.4); hyperbrachycephaly (>85.5). In anthropometry of the face soft parts, the measurement of the nasal area is of key value. The nasal index was calculated as a ration between the nose width (the greatest distance between the outer points of the piriform opening, or the nose wings) to the nose height (the distance between the upper nasal and the sub-spinal points).

As for the X-ray diagnostics methods, orthopantomography (Fig. 1a) and telereöntgenography of the head (lateral projection) (Fig. 1b) were used on a cone-beam Planmeca ProMax^{3D} Plus computer tomograph with cephalostat (Planmeca). The data was processed using the Romexis Viewer software package, which allows obtaining, processing, storing, and exporting 2D and 3D images in the conventionally accepted medical formats DICOM.

The interpretation of the head telereöntgenograms (lateral projection) was performed in the Dolphin imaging software (USA); the indicators that determine the distal occlusion (Schwartz S.) were studied (Fig. 2).

The lateral projection of the head telereöntgenograms obtained from children with CTD was used

to study linear and angular parameters describing the jaw bones position in the skull space. The analysis of the obtained data was carried out according to the method proposed by Schwartz S. (1955) and employment of the indicators for a norm by Anikienko A.A. (2014).

Studying the linear parameters: *N-A* — the line between points N and A; *N-B* — the line between points N and B; *N-Se* — the length of the skull base anterior segment; *NL* — the plane of the upper jaw base (through Sna and Snp); *NSL* — the line of the anterior skull base, used to measure angular dimensions (continuation of the **NS line**); *H* — the line from the **Or** point to the **C** point; *MP* — the plane of the mandible base; *MP₁* — the tangent to the mandible lower contour; *MP₂* — the tangent to the rear contour of the lower jaw branches; *Pn* — the nasal plane, the plumb line perpendicular to the plane of the skull base front; *OcP* — the occlusal plane dividing the middle of the incisal crossbite and the contacting last teeth tubercle crossbite; *i-I* — the longitudinal axis of the upper central incisor passing through the middle of the tooth apex and canal; *i-I* — the longitudinal axis of lower central incisor passing through the middle of the tooth apex and canal.

Studying the angular parameters: <*SNA* — the angle that describes the position of the upper jaw in the sagittal plane; <*SNB* — the angle, which describes the position of the mandible in the sagittal plane; <*NSeAr* — the angle describing the position of the mandible head in the sagittal direction; <*SeArGo* — the angle, which describes the position of the lower jaw branches in the sagittal direction; <*ArGoMe* — the angle describing the relative positions of the mandible body and branch; <*NSE-SpP* — the angle, which describes the upper jaw slope towards the skull anterior base; <*NSE-MP* — the angle, which describes the mandible body slope to the skull anterior base; the **basal B angle** is the inclination angle of the jaws base to each other (*SpP-MP*), which offers a description of the jaws vertical position; the inclination angle of **Axis 1** to *SpP*; the inclination angle of **Axis I** to *MP*; the interincisal angle *ii* is shaped by the intersection of the long axes of the upper and lower incisors and determines their relative positions; <*NSE-OcP* — the inclination angle of the occlusal plane to the skull base. **The mandibular G angle** is located between the tangent to the mandible lower edge (*MT₁*) and the rear surface of the mandible branches (*MT₂*); the mandible body length (*MT*) — from the projection of the Pg point onto *MP* to the point of its intersection with the tangent to the mandible branch on the *MP* plane; **the maxilla length** — from the intersection point of the perpendicular from the **A** point to *SpP*, up to the **Sn**

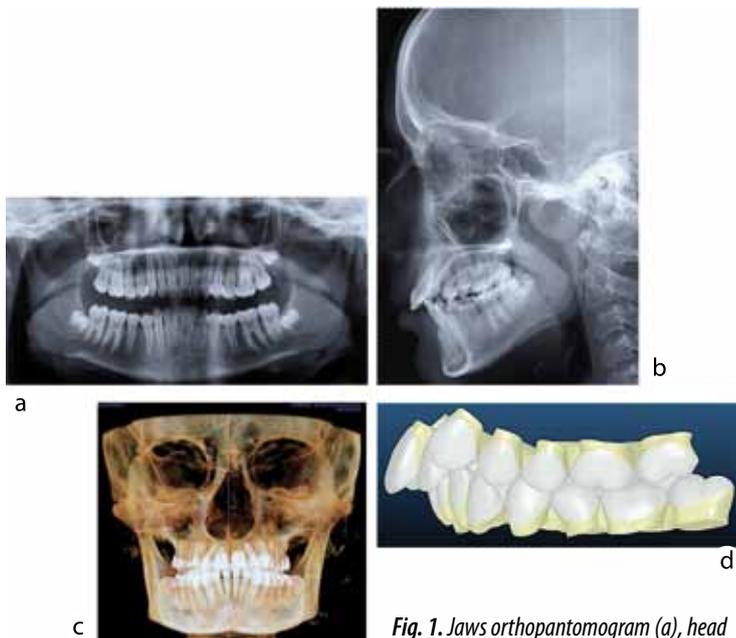


Fig. 1. Jaws orthopantomogram (a), head telereöntgenogram (lateral projection) (b), 3D panorama at FOV 8×15 in Unshaded VR mode (frontal projection) (c) and virtual diagnostic Set-Up model in the file "ORAPIX" 3Txe 2.5.0 (Japan) (d); patient T with CTD, 16 y.o.

point; **the mandible branch height** — the tangent to the branch rear edge from the point of intersection with the MP plane to the C point projection on the tangent; **the sagittal interincisal distance** goes parallel to the Frankfort horizontal between the cutting edges of the upper and lower central incisors; **the incisal overlap depth** — the distance between the projections of the central upper and lower incisors cutting edges on the Pn nasal plane; **the face anterior height** — the interval between the projections of points N and Me, where the point SNA breaks it into the upper (N-SNA) and the lower (SNA-Me) parts; \angle NSeAr — the angle, which describes the position of the mandible head in the sagittal direction; \angle SeArGo — the angle that describes the position of the mandible branches in the sagittal direction; \angle ArGoMe — the angle that describes the relative position of the mandible body and branches. The neutral, horizontal or vertical growth types of the skull facial part in children with distal occlusion were identified by the total Bjork angle — the sum of the three angles (\angle NSeAr, \angle SeArGo, \angle ArGoMe).

For teeth and dentition biometric measurements, diagnostic cast models of the jaws were used (Fig. 3).

When identifying the width of the teeth crown part, the reference was the mesiodistal dimension at the equator area, the exception being the lower incisors, where reference point was the cutting edge. The obtained morphometric outcomes were evaluated in view of individual facial features and their relationship with the odontometric indicators. The proportionality of the permanent incisors width in the lower and upper jaws was calculated using the Tonn

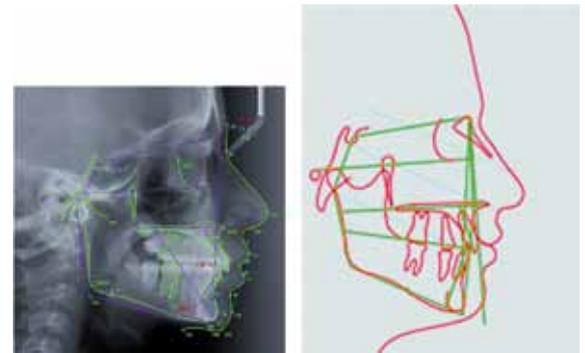


Fig. 2. Head telereöntgenogram analysis (lateral projection), Dolphin imaging software (USA)

and Bolton method. The palate height measurements were based on the index of the palate height index (Persii L.S., 2003). Another value identified was the ratio between the sum of the mesiodistal dimensions of 14 permanent teeth and the diagonal dimensions of the face and the dental arches.

The statistical processing of the obtained data was performed using the SPSS 21.0 software package and methods of variation statistics in Microsoft Excel, adjusted to biomedical research.

RESULTS AND DISCUSSION

The orthognathic bite was detected in 23 children with CTD (the main group) (21.1%). As for the phenotypic signs of the dental system (small stigmas) in children with CTD, the following were detected: narrowed and deformed dental arches — 79 children (72.5%); deformed occlusal Spee curve — 74 children (67.9%); "Gothic" or "arched" palate — 69 children (63.3%); abnormal attachment of the lips and tongue frenulum, true diastema — 66 children (60.6%). Of the pathological bites, the most common were distal and deep incisional occlusion — 81 children (74.3%). Children with CTD who had occlusion pathology, featured a history of early loss of baby teeth, which contributes to the development of dental and speech issues, as well as to a disturbed chewing efficiency. Deviated nasal septum, which was diagnosed in 63 children (57.8%), as well as the growth of lymphoid tissue in



Fig. 3. Diagnostic cast models of jaws, patient S. with CTD, 17 y.o.; lateral right (a), frontal (b) and lateral left (c) projections: prognathic bite, skeletal form, complicated by open bite; distal occlusion. Sagittal inter-incisal distance is increased; narrowed and deformed dentition; lower jaw front teeth — crowded, with mesial position; protruded upper jaw incisors

the nasopharynx, was a predisposing factor behind oral or mixed type of breathing.

The distribution of children in the study groups by type of facial skull (facial index) is shown in Table 1.

The evaluation of the facial skull type with a facial index revealed that the greatest share of patients with moderate and severe degrees of CTD had leptoprosopic and hyperleptoprosopic shapes, while the children in health groups I and II, as well as children with a mild degree of CTD had the mesoprosopic and leptoprosopic face types prevailing.

Table 2 offers a view at the distribution of the children within the groups following the facial skull (facial angle).

Evaluating the facial skull using the facial angle indicator revealed that the orthognathic and mesognathic skull types dominated in all the cases within the groups, while there were no statistically significant differences to be observed among the groups.

Table 3 shows the distribution of the patients based on the skull shape (cephalic index).

The craniotype assessment based on the cephalic index showed that the largest number of patients with moderate and severe CTD featured the dolichocephalic type, while the children belonging to health groups I and II, as well as the children with mild CTD, had an even distribution across the craniotypes.

The major cephalometric features of the children within the groups can be seen from Table 4.

An analysis of the average values for the main cephalometric indicators allowed detecting statistically significant differences among the parameters within the groups for further identification of the direction vector in the maxillofacial changes. An increase in the facial index values from the mild to the severe degree of CTD was indicative of a growing dynamics of

latitudinal indicators decreasing towards the narrow face in children within subgroup 3. The decreasing dynamics for the cephalic index changes along with an increase in the CTD severity reflected the nature of the sign displacement towards the dolichocephalic head shape (dolichocephalization) in the children featuring a severe degree of CTD. The positive tendency towards an increase in the nasal index with progressing mesenchymal dysplasia reflected the dynamics of decreasing face vertical size within subgroup 3 of the main group. The lack of statistically significant differences among the facial angle size features in the groups points at the dominance of the mesognathic (facial angle — 80–84.9°) and the orthognathic (facial angle — 85° or above) types of facial skull with a vertical profile.

A comparative evaluation of the cephalometric parameters within the studied groups showed that the children with CTD, in contrast to the children in health groups I and II, had morphological changes in the maxillofacial area. The change direction vector in the facial and cephalic parts of the skull was towards hypoplastic variants (trends), while the child's body development rate through the postnatal period could be called slow (*retardatio*), due to later anlage of organs. The nature of the detected changes (dolichocephalic; hypoplastic variants of the head facial and cephalic structure; skeletal abnormalities in the maxillofacial area) were the result of a genetically determined set of anatomical, constitutional, dysplastic internal and external phenotypic features.

Table 5 contains gnathometric indicators within the groups.

An analysis of gnathometric parameters in patients with moderate and severe degrees of CTD revealed the following morphological features in the

Table 1. Distribution of patients based on the type of facial skull (facial index)

Facial Skull Type	Research groups			
	Main group 1 st subgroup, n=31	Main group 2 nd subgroup, n=37	Main group 3 rd subgroup, n=41	Control group, n=47
Hyperevipsopic Type	1 (3,2%)	0 (0%)	0 (0%)	1 (2,1%)
Evipsopic Type	2 (6,4%)	1 (2,7%)	1 (2,4%)	2 (4,2%)
Mesoprosopic Type	17 (54,8%)	3 (8,1%)	2 (4,8%)	34 (72,3%)
Leptoprosopic Type	8 (25,9%)	22 (59,5%)	25 (60,9%)	8 (17,2%)
Hyperleptoprosopic Type	3 (9,7%)	11 (29,7%)	13 (31,9%)	2 (4,2%)

Table 2. Distribution of patients based on the type of facial skull (facial angle)

Facial Skull Type	Research groups			
	Main group 1 st subgroup, n=31	Main group 2 nd subgroup, n=37	Main group 3 rd subgroup, n=41	Control group, n=47
Prognathic Type	2 (6,4%)	3 (8,1%)	3 (7,3%)	3 (6,4%)
Mesognathic Type	8 (25,9%)	7 (18,9%)	11 (26,8%)	12 (25,5%)
Orthognathic Type	19 (61,3%)	23 (62,2%)	25 (61,1%)	28 (59,6%)
Hyperorthognathic Type	2 (6,4%)	4 (10,8%)	2 (4,8%)	4 (8,5%)

Table 3. Distribution of patients based on the craniotype (cephalic index)

Skull shape	Research groups			
	Main group 1 st subgroup, n=31	Main group 2 nd subgroup, n=37	Main group 3 rd subgroup, n=41	Control group, n=47
Dolichocephalic Type	10 (32,2%)	26 (70,3%)	30 (73,2%)	14 (29,8%)
Mesocephalic Type	12 (38,7%)	5 (21,6%)	9 (21,9%)	15 (31,9%)
Brachycephalic Type	9 (29,1%)	3 (8,1%)	2 (4,9%)	18 (38,3%)

Table 4. Cephalometric parameters in the groups, ($M \pm m$)

Research indicators	Research groups			
	Main group 1 st subgroup, n=31	Main group 2 nd subgroup, n=37	Main group 3 rd subgroup, n=41	Control group, n=47
Face index	87,9 \pm 0,98*	89,4 \pm 0,96*	92,6 \pm 1,17*	86,9 \pm 0,84
Head index	80,5 \pm 0,31*	77,4 \pm 0,23*	72,3 \pm 0,28*	80,8 \pm 0,27
Nasal index	53,1 \pm 0,77*	53,9 \pm 0,79*	55,7 \pm 0,74*	52,8 \pm 0,72
Face angle	86,6 \pm 0,83*	85,7 \pm 0,79*	86,1 \pm 0,71*	85,1 \pm 0,74

Note. * — $p \leq 0.05$ statistically significant in comparison with the parameters of patients in the control group, (Wilcoxon's T-test).

facial skeleton: the maxilla, if taken in relation to the cranial base, has the right position, being rather horizontal; the mandible, if taken in relation to the cranial base, features some distal displacement, while it is inclined downwards in the vertical plane, which points at the vertical growth of the jaws; the maxillary (basal)

angle, as well as the lower jaw angle, is enlarged; the upper incisors, viewed in relation to the jaw base, have a vestibular inclination; the lower incisors, in relation to the jaw base, have an oral inclination; the interincisal angle is reduced; the occlusal plane has a tilt down toward the skull base; the anterior face height is reduced;

Table 5. Gnathometric indicators in the groups, ($M \pm m$)

Indicators, units	Research groups			
	Main group 1 st subgroup, n=31	Main group 2 nd subgroup, n=37	Main group 3 rd subgroup, n=41	Control group, n=47
Upper jaw length, mm	50,9 ± 0,67*	43,6 ± 0,49*	44,3 ± 0,41*	51,3 ± 0,56
Lower jaw length, mm	66,7 ± 0,78*	59,9 ± 0,42*	59,6 ± 0,49*	67,4 ± 0,81
Lower jaw branch height, mm	59,3 ± 0,64*	52,2 ± 0,51*	51,9 ± 0,73*	60,5 ± 0,77
Sagittal inter-incisal distance, mm	4,3 ± 0,08*	7,6 ± 0,14*	9,1 ± 0,19*	3,2 ± 0,05
Depth of incisal overlap, mm	3,6 ± 0,07*	6,5 ± 0,13*	7,3 ± 0,14*	2,9 ± 0,09
Front face height, mm	112,6 ± 1,79*	107,6 ± 1,23*	105,9 ± 1,74*	113,2 ± 2,03
<SNB	79,1 ± 0,66*	75,2 ± 0,81*	73,3 ± 0,72*	79,9 ± 0,94
<SNA	81,3 ± 0,48*	82,1 ± 0,74*	81,5 ± 0,71*	81,8 ± 0,68
<NSE - SpP	7,7 ± 0,11*	7,3 ± 0,12*	7,0 ± 0,17*	8,2 ± 0,18
<NSE - MP	31,4 ± 0,19*	37,1 ± 0,12*	37,9 ± 0,23*	32,5 ± 0,21
<SpP - MP	26,9 ± 0,12*	32,3 ± 0,19*	34,5 ± 0,23*	26,3 ± 0,17
<I - SpP	81,9 ± 1,24*	73,4 ± 1,06*	73,9 ± 0,97*	80,3 ± 1,19
<I - MP	95,2 ± 1,22*	87,8 ± 1,19*	87,4 ± 1,07*	94,8 ± 1,27
<i - i	128,9 ± 1,25*	120,6 ± 1,17*	119,2 ± 1,19*	129,9 ± 1,18
<NSE - OcP	17,6 ± 0,14*	22,1 ± 0,31*	24,9 ± 0,16*	16,9 ± 0,18
<MT1 - MT2	125,7 ± 0,73*	129,7 ± 0,85*	128,5 ± 0,89*	126,1 ± 0,84

Note. * — $p \leq 0.05$ statistically significant in comparison with the parameters of patients in the control group, (Wilcoxon's T-test).

the upper and the lower jaws, as well as the lower jaw branch, are reduced in size; the cutting depth of the incisal crossbite is increased; the sagittal interincisal distance is increased (Fig. 4–5).

Children with a mild degree of CTD feature cephalometric and gnathometric indicators that fall within the average standard values, except for a small increase in the incisal crossbite and sagittal interincisal distance, as well as an increase in the upper incisors inclination towards the jaw base, and a decrease in the interincisal angle (Fig. 6).

Dolichocephalism processes in children with CTD, if compared to healthy children, is confirmed with the side teleroentgenograms of the head: prevalence of the vertical facial skeleton growth over the horizontal and neutral (the ratio between the posterior and the anterior heights of the face — $SGo/NMe=56-50\%$; hyperdiverging type — a too obtuse NSBa angle (the skull base angle); increased maxillary angle parameters $<NL-ML=33-43^\circ$; increased angle of the mandible body base plane to the anterior skull base — $<ML-NSL=37-47^\circ$; increased lower genial angle $<NGoMe=78-86^\circ$; decrease in the Ricketts facial angle — $<NBa-PtGn=87-81^\circ$; the total Bjork angle — $<NSAr + SArGo + ArGoMe=401-411^\circ$); a convex facial profile due to disproportionate total of the facial skeleton heights; a short narrow mandible branch; the upper jaw moved forward and downward;

reduced dimensional values of the lower dentition apical basis, mandible body, as well as the height and the width of the mandible branches; deepening notch on the outer edge of the mandible body; elongated and thinned symphysis; lack of the cortical layer at the Gn point (Fig. 2 a–e).

An analysis of anthropometric parameters in the facial area the head, the jaw bones, the teeth and dentition in children with CTD has helped identify the following skeletal issues in the facial skull: a distal shift of the mandible in relation to the cranial base, combined with a deep incisal crossbite; poorly developed upper, lower jaws; increased sagittal interincisal distance and the vertical type of jaw growth, which causes a truly prognathic ratio in the jaw bones; deformed and narrowing dental arches; mesial displacement (position) of the teeth; crowded teeth. Note to be made that the intensity of the dentofacial structure changes reveals a correlation with the number of CTD phenotypic manifestations, while the degree of organs and systems involvement in the dysplastic process features a direct relation with the severity of connective tissue disorders.

Based on the lateral projection of the head TRG, the children in health groups I and II, if compared with the main group, had a smoother face profile, their lower jaw being moderately developed, the body of the lower jaw more horizontal, its branches wide, and

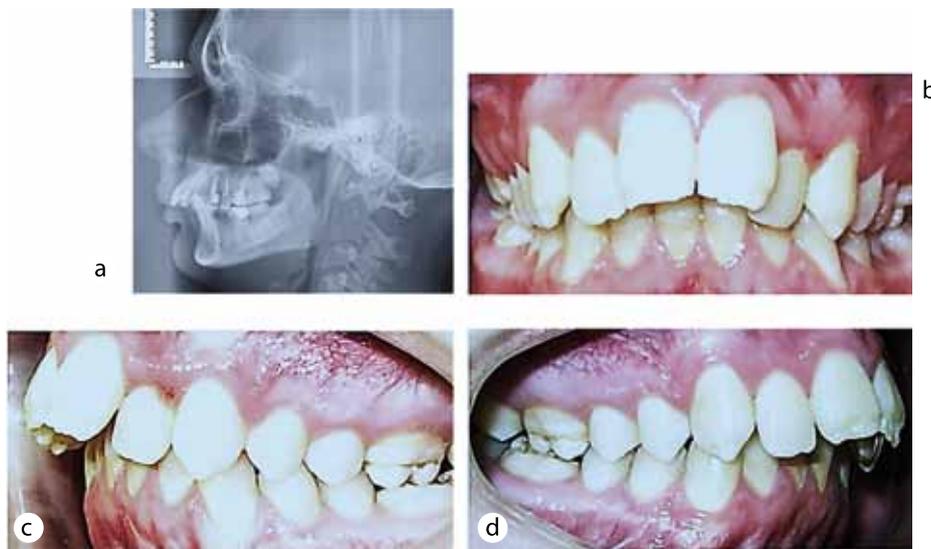


Fig. 4. X-ray and photographic features of dental system, patient M., 15 y.o., with severe CTD. Head telorentgenogram, lateral projection (a), pathological occlusion (b — direct projection, c — left-side lateral projection, d — right-side lateral projection)

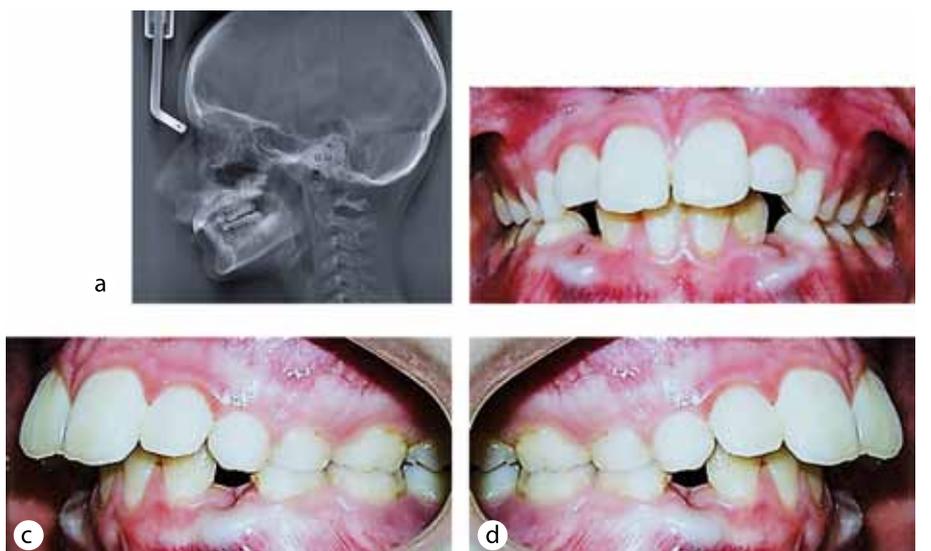


Fig. 5. X-ray and photographic features of dental system, patient A., 11 y.o., with moderate CTD. Head telorentgenogram, lateral projection (a), pathological occlusion (b — direct projection, c — left-side lateral projection, d — right-side lateral projection)

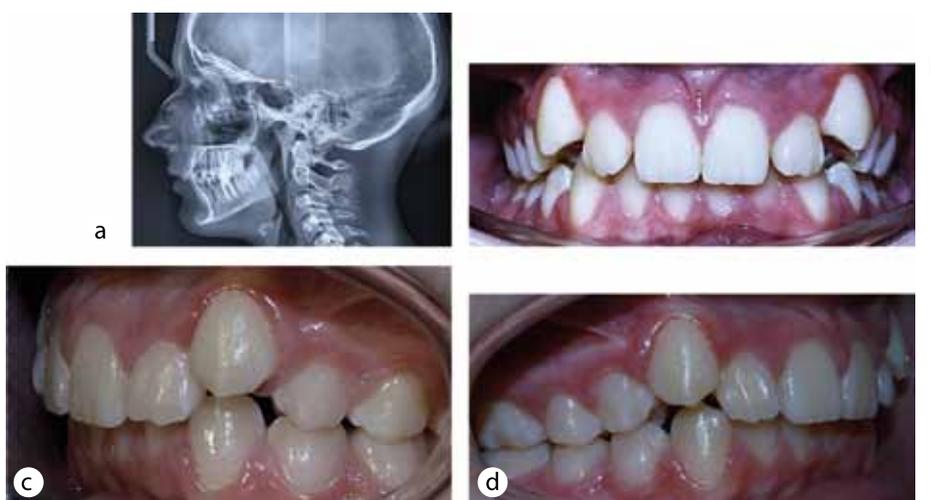


Fig. 6. X-ray and photographic features of dental system, patient S., 14 y.o., with mild CTD. Head telorentgenogram, lateral projection (a), pathological occlusion (b — direct projection, c — left-side lateral projection, d — right-side lateral projection).

the height of the mandible not disturbed. At the Gn point, the cortical layer is expressed significantly, while the mandibular symphysis is wide and short. Children in the comparison group, talking of the neutral facial skeleton type dominating over the vertical one, had the following signs: increased ratio of the front and rear height of the face — $SGo/NMe=62-65\%$; decreased maxillary angle $<NL-ML=25-31^\circ$; reduced angle of the mandible base body plane to the anterior skull base — $<ML-NSL=29-35^\circ$; reduced lower genial angle — $<NGoMe=70-76^\circ$; increased Ricketts facial angle — $<NBa-PrGn=92-89^\circ$; a decrease in the total Bjork angle — $<NSAr + SArGo + ArGoMe=393-399^\circ$ (Fig. 7).

(size, length) of apical basis on both jaws. We believe that the lack of consistency between the jaw bones parameters (shortened and narrowed) with the teeth size (large, elongated) is due to a higher rate of the jaws reduction (upper, lower) prevailing over not so intensive rate of the teeth reduction.

In case of CTD, there is a close relationship between the number of external phenotypic signs (big, small stigmas) and the internal organs pathology, while the functional failure of connective tissue in the organs and systems, which progresses over age, works an inducing effect on the acquired diseases course, thus contributing to early manifestations. This means

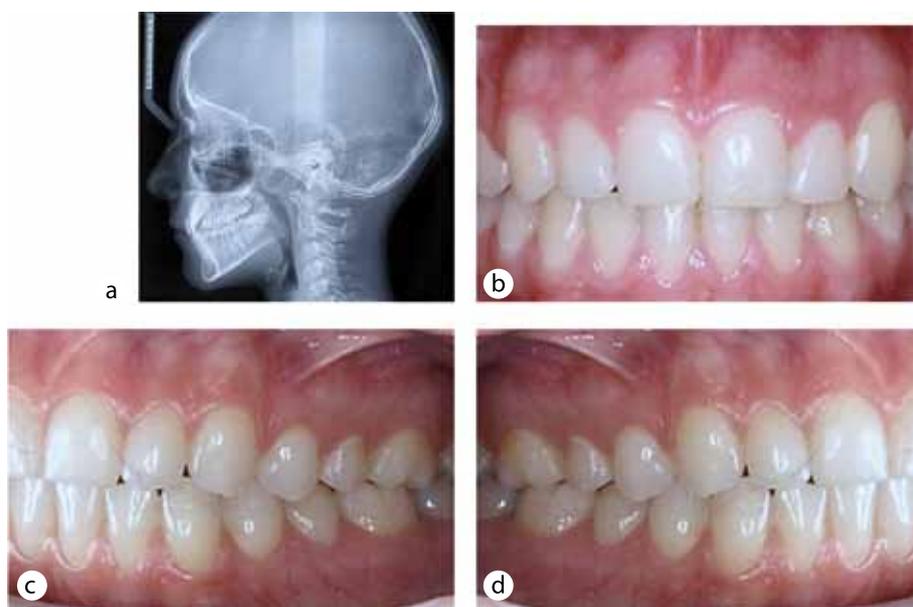


Fig. 7. X-ray and photographic features of dental system, healthy patient K., 16 y.o. Head telereöntgenogram, lateral projection (a), physiological occlusion (b — direct projection, c — left-side lateral projection, d — right-side lateral projection)

The available research data, as well as the outcomes of our own study, allow claiming that there are other pathomorphological signs that are of value in terms of the clinical, diagnostic and prognostic value when we have to deal with external phenotypic manifestations (small stigmas) involving the dentition in patients with CTD featuring permanent teeth bite: increased odontometric parameters of the crown; vestibule-oral lengthening of the teeth crowns in the upper (central incisors, canines, first molars) and in the lower (incisors, canines) jaw; hypomineralized tooth enamel and dentin; pointed, elongated and protruded teeth roots; denticles found in teeth cavities; contracted root canals; enamel hypoplasia of varying severity; elongated front (limited to canines) part of the dental arches on both jaws; decreased width of the dental arches at the level of the first molars and premolars on both jaws; a decrease in the morphological parameters

that underestimating the role of CTD leads to delayed identification of key prognostic conditions, increased risk of developing general somatic complications, insufficient comprehensive prevention measures, improper rehabilitation and management tactics applied to such patients, which finally affects the health of the child population suffering from connective tissue dysplasia.

CONCLUSIONS

1. To improve the algorithm for diagnosing undifferentiated CTD types in children at the first appointment, we have systematized diagnostically significant signs (small stigmas), which determine the morphology of the craniofacial structures: dolichocephaly; hypoplastic types of the facial and cephalic head parts; skeletal anomalies of the maxillofacial area; narrowed and deformed dental arches; a deformed occlusal *Spee* curve; “Gothic”

- or “arched” palate; abnormal lips and tongue frenulum attachment, true diastema; distal and deep incisal occlusion.
2. Constitutional and morphological congenital development issues (dysgenesia), viewed as manifestations of the connective tissue failure, are an etiopathogenetic factor behind the developing abnormalities in the facial and cephalic parts of the skull. The nature and intensity of morphological and functional manifestations in the maxillofacial area (phenotypic features, small stigmas) is determined by the severity of connective tissue dysplasia.
 3. The highest number of patients with the moderate and severe degrees of CTD had leptoprosopic, hyperleptoprosopic facial skulls and a dolichocephalic craniotype, while healthy children and children with a mild degree CTD featured the mesoprosopic and leptoprosopic facial skulls prevailing with a uniform distribution within craniotypes.
 4. The vector for the facial and cephalic skull changes in children with CTD, as observed from cephalometric studies, is oriented towards strengthening hypoplastic trends and dolichocephaly. As a proof to this may serve the following: the vertical growth of the facial skeleton dominating over the horizontal and neutral ones; a convex face profile along with disproportionate total heights of the facial skeleton; reduced width parameters and increased height parameters of the face; a short narrow branch of the lower jaw; upper jaw displaced downwards and forward; reduced size of the apical base in the lower dentition, the lower jaw body, as well as in the lower jaw branches height and width; deepening notch on the outer edge of the lower jaw body; elongated and thinned symphysis; lack of cortical layer at the Gn point.
 5. The gnathometric and biometric studies of the maxillofacial area in children with connective tissue failure, which determine dynamic and static occlusion, revealed the following facial skeleton issues: a distal shift of the mandible viewed in relation to the cranial base, combined with a deep incisal crossbite; poorly developed upper and lower jaws; increased interincisal distance along the sagittal, which determines the prognathic ratio of the jaw bones; deformed and narrowed dental arches; a mesial shift (position) of the teeth; crowded teeth; a mismatch between the teeth size and the dental arch parameters in the transversal and sagittal planes; a mismatch between the true sizes of the maxillary bone (width and length) and the forecasted (optimal) one; disproportionate and disturbed dentition.
 6. Given the increased maxillofacial lability and a high predisposition to developing immediate, long-term complications (improper vascular responses, lengthening of bone remodeling and ossification, a tendency to TMJ dysfunction), orthodontic treatment of dentition anomalies in children with CTD should be carried out in view of the short path and small forces in designing the equipment, expanding the indications for trainers, which is due to the oral mucosa and muscle fibers compliance, as well as due to a longer retention period.
 7. In view of connective tissue failure in cases with undifferentiated dysplasias, traditional orthodontic treatments applied to children with dental issues may lead to a relapse, and will not allow getting a stable expected outcome. Medication pathogenetic therapy, as a mandatory component through the entire period of orthodontic treatment, should be of a substitutive nature and include the following parts: correction of the disturbed glycosaminoglycan synthesis; stimulation of collagen synthesis; regulation of redox mechanisms; stabilization of phosphorus-calcium metabolism.
 8. The identified association between certain constitutional and morphological features and CTD has to be taken into account when examining children and adolescents in organized groups thus aiming to develop groups running a high risk of developing general somatic and dental pathologies. It has been proven that along with progressing severity of connective tissue-related dysplastic disorders the prevalence of dental anomalies and deformities increases.
 9. The patient-oriented approach applied through the stages of diagnostics, treatment and rehabilitation of children with CTD should imply close collaboration with dentists, maxillofacial surgeons, pediatricians, therapists, cardiologists, neurologists, ophthalmologists, gastroenterologists. Interdisciplinary collaboration that allows early detection of pathologies associated with CTD, irreversible morphofunctional changes, dysplastics-dependent disorders that may affect the child's life quality, would allow changing the traditional approach and shifting towards personalized diagnostics and differential treatment of this category of patients, in view of their individual features.

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