2/2019

Deutscher Wissenschaftsherold

German Science Herald

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Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.dnb.de .

Information bibliographique de la Deutsche Nationalbibliothek
La Deutsche Nationalbibliothek a répertorié cette publication dans la Deutsche Nationalbibliografie; les données bibliographiques détaillées peuvent être consultées sur Internet à l'adresse http://dnb.dnb.de .

Informazione bibliografica della Deutsche Nationalbibliothek
La Deutsche Nationalbibliothek registra questa pubblicazione nella Deutsche Nationalbibliografie; dettagliati dati bibliografici sono disponibili in internet in http://dnb.dnb.de .

Библиографическая информация Немецкой Национальной Библиотеки
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Información bibliográfica de la Deutsche Nationalbibliothek
La Deutsche Nationalbibliothek recoge esta publicación en la Deutsche Nationalbibliografie. Los datos bibliográficos están disponibles en la dirección de Internet http://dnb.dnb.de .

ISSN 2509-4327 (print)
ISSN 2510-4780 (online)

Deutscher Wissenschaftsherold
German Science Herald

№ 2/2019

Die Zeitschrift „Deutscher Wissenschaftsherold" ist eine Veröffentlichung mit dem Ziel ein breites Spektrum der Wissenschaft allgemeinverständlich darzustellen. Die Redaktionsleitung versteht sich als Vermittler zwischen Wissenschaftlern und Lesern. Durch die populärwissenschaftliche Bearbeitung wird es möglich unseren Lesern neue wissenschaftliche Leistungen am besten und vollständigsten zu vermitteln. Es werden Untersuchungen, Analysen, Vorlesungen, kurze Berichte und aktuelle Fragen der modernen Wissenschaft veröffentlicht.

Impressum
Deutscher Wissenschaftsherold – German Science Herald
Wissenschaftliche Zeitschrift
Herausgeber:
InterGING
Sonnenbrink 20
31789 Hameln, Germany
Inhaber: Marina Kisiliuk
Tel.: + 49 51519191533
Fax.:+ 49 5151 919 2560
Email: info@dwherold.de
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Chefredakteur:
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Korrektur:
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Gestaltung:
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Auflage: № 2/2019 (September) – 20
Redaktionsschluss September, 2019
Erscheint vierteljährlich
Editorial office: InterGING
Sonnenbrink 20
31789 Hameln, Germany
Tel.: + 49 51519191533
Fax.:+ 49 5151 919 2560
Email: info@dwherold.de
Deutscher Wissenschaftsherold – German Science Herald is an international, German/English language, peer-reviewed journal and is published quarterly.
№ 2/2019
Passed in press in September, 2019
Printed in September
Druck: WIRmachenDRUCK GmbH
Mühlbachstr. 7
71522 Backnang
Deutschland

INDEXING: Index Copernicus, Google Scolar, Ulrich's Periodicals Directory, Fachzeitungen, MIAR.

http://miar.ub.edu/issn/2509-4327

REDAKTIONSKOLLEGIUM / INTERNATIONAL EDITORIAL BOARD:

Lists of references are given according to the Vancouver style

DOI:10.19221/201921

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GASTROINTESTINAL MICROFLORA AND FACTORS AFFECTING INTESTINAL NORMAL FLORA IN CHRONIC DERMATOSES

Abstract. *The microflora of the digestive tract and the role of bacterial and viral agents in the formation of chronic dermatosis is described. The role of parasitic invasions and other factors of exogenous and endogenous nature that cause dysbiotic changes and play an important role in the pathogenesis of skin lesions is indicated.*
Key words: *microflora, digestive tract, skin covers, lambliosis.*

Introduction. Considerable attention is paid to the study of the etiology and pathogenesis of chronic skin diseases throughout the world, since the correct tactics of their treatment depends on the solution of these issues [19, 23]. Despite all the successes in the diagnosis and treatment of dermatoses, these diseases are extremely difficult to treat. There is still no single view on the causes and mechanisms of chronicity of these pathologies. Against the background of the processes that develop in the patient's skin, there is a pronounced proliferative activity of epithelial cells, regulated by numerous factors, which are complex elements of pathogenesis.

Currently, hereditary, neurogenic, immune factors, endotoxemia, etc., are of great importance in the mechanisms of dermatosis formation [22, 26]. According to one of the leading theories of the development of skin diseases, infectious, the focus is on bacterial and viral agents. In recent years, there have been separate reports on the effect of parasitic invasions on chronic inflammatory processes, data on the significant role in the pathogenesis of chronic skin processes of parasitic intestinal invasions (helminthiasis, lambliosis), which initiate or support chronic dermatoses [3,16,21], have been obtained.

Currently, there is a significant increase in the incidence rates of chronic dermatoses. According to Yu.K. Skripkin, Yu.S. Butov [19], in 48-67% of dermatological patients, the pathological process is chronic. Most often, the states associated with allergic status (allergic contact dermatitis, atopic dermatitis, true and microbial eczema) are recorded in the structure of skin nosologies.

The objective of the study is to define the features of the clinical course of chronic allergic dermatosis on the background of lamblia invasion.

It is known that the normal human microflora was formed in the process of evolution as a result of the interaction of the host microorganism and the microorganisms surrounding it [17, 32]. Of all the diversity of microbes in the environment, a selection was made of species that can colonize the surface epithelium of the mucous membranes of certain biotopes. An adult human organism consists of a huge number of cells - about 10^{13}, and the total number of representatives of the microecological system reaches 10^{15}. The microflora of mucous membranes of various ecological niches differs in qualitative and

quantitative composition - this is determined by the physiological characteristics of the host organism and the features of microbial associations [44, 49, 51]. The most complex microbiocenosis is the microbiota of the colon, nasopharynx, and mouth. According to researchers, about 60% of the microflora populates various niches of the digestive system, and the weight of these microorganisms is 1.5-3.0 kg in an adult [20].

Discussion. For several centuries, researchers from different countries devote their work to studying the composition of normal microflora and its disorders. Attention of clinicians drawn to this problem is not accidental. In addition to the widespread introduction into the clinical practice of drugs with antimicrobial activity, the results of scientific and technological progress and improvement of technology significantly affect the microflora, and this effect is not always positive. Changes in the normal intestinal microflora in recent years have been increasingly observed [11,39,53] and are accompanied by various symptoms.

Intestinal microflora is formed in the first days of the life of a newborn, with breastfeeding the infant being the most important condition. In healthy newborns, microorganisms in the colon appear on the first day of life [13, 25, 28].

The quantitative composition and species diversity of microbial associations in different parts of the gastrointestinal tract differ significantly. This phenomenon is explained by the fact that as the intestinal tube moves to the distal parts, the partial pressure of oxygen decreases and the pH value of the medium increases, as a result of which the proximal parts are colonized by aerobic bacteria, then optional anaerobes are located, and even lower - only anaerobes themselves. The diversity of these representatives can be judged by the researchers: in 1 g of the contents of the cecum, you can find representatives of 17 families, 45 genera and more than 400 species of microorganisms. It has been established that with food, water and saliva a person swallows up to 1-10^9 microbes per day, and about 5-10^{13} - 8-10^{14} are eliminated from the body. However, the microflora of the human digestive tract is relatively stable [11, 12, 15].

The microflora of the oral cavity is quite rich in its composition - more than 300 species of microorganisms are found here. Basically it is represented by bacteria that can exist in an environment containing oxygen. A peculiar reservoir of microbes is gingival “pockets” and palatine tonsils. The number of microbial cells in saliva can reach 10^9. The role of microflora in the pathology of the oral mucosa has been studied and proved [10, 18, 41].

The microflora of the esophagus, according to the researchers, is not constant and stable, since it depends mainly on the nature of the food. The main bacteria are representatives of the oral cavity. Microorganisms belonging to 11 genera were found in healthy people: staphylococcus, *H. pylori*, streptococci, lactobacilli, bacteroids, stomatococci, enterobacteria, corynebacteria, micrococci, neisserias, veilonella [32].

The microflora of the stomach is not different in variety and number. This situation is determined by the low pH value (should not exceed 3.5-4.0) and the effect of lysozyme, which leads to the main growth-limiting and bactericidal effect. With a normal concentration of hydrochloric acid, the number of microbial cells in 1 ml of gastric contents is about 10 and they live mainly in the pyloric department. Gastric flora is mainly represented by acid-resistant aerobes and facultative anaerobes: staphylococci, streptococci, lactic acid lactobacilli, yeast and yeast-like fungi, as well as bacilli, bacteroids, corynebacteria, micrococci, enterobacteria. According to researchers, healthy people with biopsy specimens of the gastric mucosa in 33-44% sow bacteria *H. pylori* [29, 33].

After eating, the number of microorganisms can dramatically increase to 105-107 cells in 1 ml of the contents, but quickly returns to its original level. When the pH value is more than four units, the proteolytic activity of bacteria and the ability to multiply increase, the number of microorganisms of the biotope increases.

Information about the microflora of the duodenum in healthy people, according to different authors, is quite contradictory. There is an opinion about the absence of microorganisms in this biotope. Most researchers believe that the microbial spectrum of the duodenum is scanty. Recently, the authors note that no more than 10 different types of bacteria can be present in 1 ml

of duodenal contents [1, 31]. The species composition of bacteria in healthy people includes streptococci, staphylococci, lactobacilli, micrococci, enterobacteria, *Candida fungi*, corynebacteria, bacteroids, sometimes actinomycetes, bacilli, *H. pylori* [35,38,43]. That is, the microbial spectrum of the duodenal mucosa is similar to the landscape of the gastric mucosa.

The microflora of the empty and proximal parts of the ileum is also fairly simple and few. The total number of bacteria is not more than 103-105 in 1 ml of chyme, localized mainly near the wall [4,30]. Streptococci and lactobacilli dominate in this biotope, while obligate anaerobes and members of the enterobacteria family are practically absent. The distal ileum bacteria concentration is 110 to 1 ml of the intestinal contents, flora of the internal lumen predominates over the wall, the amount of anaerobic bacteria (bifidobacteria, bacteroides, peptococci, peptostreptococci, Clostridium, some eubacteria) and aerobic, facultative anaerobes (enterobacteria, lactic acid bacteria, streptococci, staphylococci, fungi) are about the same [32].

The growth of the bacterial flora in the small intestine is influenced by such factors as the action of hydrochloric acid of the stomach, bile, fast (evacuation from the food lump) and delayed intestinal motility; enzyme activity; elimination with mucus that is secreted by goblet cells; secretion into the lumen of immunoglobulins. Also, to prevent excessive bacterial growth in the ileum, the normal functioning of the ileocecal valve, which separates two biotopes that differ in anatomical, physiological and ecological features, is of great importance [30, 31].

The large intestine is an ecosystem with a large number of biotope microorganisms, from 400 to 500 individual bacterial species live there. The biomass of microorganisms inhabiting the human intestine is about 5% of its own weight [10]. More than 1/3 of the dry mass of feces falls on viable bacteria. Among the representatives of microflora anaerobes are predominant: bifidobacteria, bacteroids, lactobacilli, veilonella, peptostreptococci, clostridia, which constitute 95-99% of the total number of microorganisms of the biotope. Aerobic microorganisms (Escherichia, opportunistic enterobacteria, enterococci (fecal streptococci), staphylococci, yeast-like fungi, etc.) account for 5-10% of the total biotope composition of the colon.

The entire intestinal microflora is divided into obligate (main, autochthonous, indigenous, resident, permanent), optional (additional, concomitant, conditionally pathogenic and saprophytic) and transient (random, allochtonic, residual).

Under physiological conditions, the intestinal mucosa is covered with a biofilm, bacterial glycocalyx, inside which there is an exopolysaccharide matrix of microbial origin and mucin of goblet cells of the mucous membrane of the large intestine. The thickness of this film is from fractions up to several tens of microns, but the number of microcolonies of indigenous normoflora in it reaches several hundreds or even thousands [20, 42]. It should be noted that the resistance of microorganisms to the effects of adverse factors of bacterial glycocalyx is much higher compared with the representatives of the free-living flora. Unlike non-immobilized bacteria, they have the ability to be fixed on the mucous membranes only at certain receptors, the number of which is limited. Moreover, the anatomical and species specificity of adhesion is clearly expressed, which is genetically determined by the peculiarity of membrane receptors of epithelial cells.

Thus, in the microbiocenosis of the human gastrointestinal tract, mucosal (parietal) and lumen microflora are distinguished. Their composition is somewhat different. The parietal microflora is more stable, mainly represented by bifidobacteria and lactobacilli, which prevent penetration of the mucous membrane of the colon by pathogenic and conditionally pathogenic bacteria, competing with the latter for communication with epithelial cell receptors. The lumen flora includes all representatives of the obligate, facultative and transient microflora.

The most significant representatives of obligate microflora in the intestines of children and adults are bifidobacteria [45, 47]. It is known that in normal newborns, 95-98% of the total microbiocenosis is bifidoflora; the total mass of other microorganisms (Escherichia coli, lactobacilli, streptococci, enterococci and staphylococci) does not exceed 5% in total. In children older than one year, the indices of the quantitative composition of microflora are close

to those in adults, and the final age-related development of the microbiocenosis occurs up to 4-7 years [46].

Bifidobacteria are present in the human intestine throughout life. Mostly bifidobacteria are in the colon, being in the composition of the parietal and lumen microflora. The main products of vital activity are lactic, acetic, formic and succinic acids, which lead to a decrease in the pH of the medium to 3.8-4.0 [48, 51].

Lactobacilli are also representatives of the obligate microflora of the gastrointestinal tract. Lactoflora colonizes the body of the newborn in the early postnatal period and lives, starting with the oral cavity and ending with the colon, where it maintains a pH of 5.5-5.6. The disappearance of lactobacilli leads to alkalization of the environment in the colon, which drastically reduces the mucosal utilization of biologically active compounds [5, 14]. High levels of lactobacilli are revealed in people adhering to a strict vegetarian diet.

Propionobacteria are another representative of anaerobes, together with bifidobacteria and lactobacilli they belong to the group of normal acid-forming bacteria that produce organic acids (the final cleavage products for propionobacteria are propionic and acetic acid).

Escherichia (*Escherichia coli*), an extensive group of bacteria that are similar in biological properties. Non-pathogenic E. coli appear in the human intestine in the first days after birth. In a healthy body, their habitat is the colon and distal small intestine, the identification of microorganisms in other parts of the digestive tract indicates a disruption of eubiosis. Enteropathogenic Escherichia, enterotoxigenic, enteroinvasive, enterohemorrhagic, enteroaggregative are conditionally pathogenic microorganisms for humans.

Peptostreptococci are non-fermentative gram-positive anaerobic streptococci. Their main location is the large intestine, where they manifest themselves as commensals. In the process of vital activity, they form hydrogen, which in the intestine is converted to hydrogen peroxide, helps to maintain pH 5.5 and below, participate in the proteolysis of milk proteins, and the fermentation of carbohydrates [2, 4]. Hemolytic properties are absent.

Enterococci (fecal streptococci) in the intestines of healthy people metabolize the fermentation type, ferment various carbohydrates to form mainly lactic acid (but not gas), reducing the pH to 4.2-4.6, and, as a rule, are lacto-positive.

Bacteroids are among the most permanent inhabitants of the gastrointestinal tract and live primarily in the colon. The colonization of the intestine with bacteroids occurs gradually: they are usually not recorded in bacterial fecal maps in children of the first 6 month of life. The role of bacteroids is not fully elucidated, but it has been established that they are involved in digestion, break down bile acids, and participate in lipid metabolism [33, 34].

The facultative microflora includes peptococci, staphylococci, streptococci, bacilli. Peptococci metabolize peptone and amino acids to form fatty acids, produce hydrogen sulfide, acetic, lactic, citric, isovaleric and other acids. Staphylococci non-hemolytic (epidermal, saprophytic, etc.) are part of the optional microflora. They are facultative anaerobes (but develop better under aerobic conditions), entering the body from environmental objects, colonize the mucous membranes of the mouth, nose, intestines, and the skin of the newborn in the first hours of life. Staphylococci form enzymes that break down various carbohydrates, proteins, and reduce nitrate to nitrite. Non-pathogenic intestinal streptococci have antagonistic activity to pathogenic bacteria, break down lactose to form lactate, but not gas. Lactic acid and thermophilic streptococci are used for the preparation of fermented milk products. Bacilli can be represented by aerobic and anaerobic microbial species. *Bacillus subtilis*, *Bacillus pumilis*, *Bacillus cereus* are aerobic spore-forming bacteria; *Clostridium difficile*, *Clostridium perfringens*, *Clostridium novyi*, *Clostridium septicum*, *Clostridium histolyticum*, *Clostridium tetanus* are anaerobic. The greatest interest among researchers is caused by *Clostridium difficile*, anaerobic gram-positive spore-forming bacteria with pathogenicity islands (which determines cytotoxicity) can appear in the intestines of healthy children and adults, however, in a clearly limited quantity. Clostridiums produce numerous enzymes that promote the penetration of bacteria

into tissues, from carbohydrates or peptone, they form a mixture of organic acids and alcohols, hydrogen sulfide [36, 37].

Yeast and yeast-like fungi are attributed to both facultative and transient microflora, they are conditionally pathogenic representatives of the flora. In healthy children, the appearance of *Candida fungi* is regarded as a disruption of intestinal eubiosis [8, 13, 20].

Conditionally pathogenic enterobacteria are members of the Enterobacteriaceae family (*Klebsiella*, *Enterobacter*, *Hafhia*, *Serratia*, *Proteus*, *Morganella*, *Providencia*, *Citrobacter*, etc.). They are quite common and may be present in the association [40].

The value of fusobacteria, eubacteria and catenobacteria in the microbiocenosis is not well understood.

Random transient microflora of the human intestine combines many microorganisms that enter the gastrointestinal tract with water and food.

Non-fermentative gram-negative rods (*Pseudomonas*, *Acinetobacter*, *Plesiomonas*) are most often defined as the transient intestinal flora of a healthy person, which easily enter the intestine from the environment.

It should be noted that in addition to bacteria in the stomach and intestines there are about 200 species belonging to 12 families of RNA and DNA of viruses [14, 46].

Most of them do not cause clinical symptoms, however, their significance is normal and their role in pathological processes is not completely understood.

The state of equilibrium in the ecological system - the human body, its microflora and the environment - is characterized by unity and ability to self-regulation, and therefore it has been called eubiosis and is characteristic of a healthy person. This biological equilibrium is affected by a wide variety of exogenous and endogenous factors. The conditions of life in the modern world are characterized by a fairly wide range of factors causing dysbiotic changes, and it is steadily growing.

The quality of the environment largely determines the level of public health in general and the state of the microflora of the skin and mucous membranes in particular. This refers to environmental factors of both natural and man-made origin, and is associated with a large amount of industrial, agricultural, household and other waste to the environment. Epidemiological studies show that even with low levels of these effects, pronounced negative changes may develop in the human body [5, 24, 27]. Also noted in recent years widespread qualitative decline of drinking water. The most common substances (petroleum products, phenols, iron compounds and others) that pollute the environment come from ferrous and nonferrous metallurgy, gas, coal, forestry, agricultural and municipal enterprises, as well as in surface runoff from adjacent territories. Agricultural land, pastures and livestock farms, where various antibiotics and antiseptics are widely used, have a significant impact on the content of biogenic and organic substances in water. The deterioration of water quality leads to an increase in outbreaks of intestinal infections and significantly affects the microbiocenosis in the human body.

Air pollution is a very significant problem in human activity in the 21st century. The most important for human health is chemical pollution of the air environment, as well as pollution by household allergens (house dust, micro-mites, fungi). Experimental studies confirmed sensitizing, allergenic, as well as potentiating dysbiotic changes in the action of many of the ingredients of polluted air.

In the “era of antibiotics”, another pressing threat appeared for the microflora of the human body - the massive use of antimicrobial substances in animal husbandry, the food industry, and veterinary medicine, which led to their unjustifiably high content in basic foods (meat and dairy). In parallel, a tendency towards uncontrolled intake of antibacterial drugs has formed among the population. Often, without sufficient evidence, focusing on information from commercials and brochures, patients take antibiotics on their own, which certainly contributes to the development of dysbiotic changes and allergization of the body [6, 9, 52].

Numerous man-made disasters lead to increased radiation level and contribute to a negative impact on the human body.

It has been established that the gastrointestinal tract, in particular, its immune

system, is most vulnerable to the effects of radiation. It was revealed that the radiation factor disrupts the antioxidant activity of the membranes of immunocompetent cells, which secrete IgA, the deficiency of which in the blood and coprofiltrates leads to the development of intestinal dysbiosis [4, 30].

In the trigger mechanism of various diseases of infectious and non-infectious genesis, allergic and dysbiotic changes, psychosocial factors are essential.

Significant changes in the biocenosis occur as a result of diseases of the small and large intestine of both infectious and non-infectious nature. The factors that affect the diversity and density of the microflora of the gastrointestinal tract, the researchers attribute the intestinal motility and the lack of possible effects on this process, realized by functional disorders (slowing / accelerating the passage of chyme through the colon) or diseases (gastroduodenitis, diabetes, scleroderma, Crohn's disease, necrotizing colitis, etc. diarrhea [32]. A significant role is played by transient functional disorders of the biliary system, as well as fermentopathies and allergic lesions of the intestinal mucosa [20,27]. It should be noted that congenital and acquired immunodeficiency states, various popular “bowel cleansing” methods, unbalanced nutrition, and other factors negatively affect the intestinal microflora.

The role of some helminth infections in the development of dysbiosis is known, which is accompanied by a disruption of the biocenotic relationships between pathogenic bacteria and normal intestinal microflora, which is one of the most important factors affecting the development of many diseases, especially chronic [23, 50].

Given this, the study of the common protozoal invasion due to parasitism in the small intestine of the simplest *Lamblia intestinalis* is of particular relevance. Clinical forms of lambliosis are noted with a predominance of allergic manifestations in the form of invincible itching, urticaria, bronchial asthma and asthmatic bronchitis, eosinophilic pulmonary infiltrates, blepharitis, atopic dermatitis [7, 25, 27, 50]. Pallor of the skin, especially of the face, is noted in almost all patients, even with high rates of hemoglobin. With a long course of the disease and a high degree of intoxication, a sharp pallor of the skin of the nose (“marble nose”) is highlighted. In patients with prolonged persistence of invasion, follicular hyperkeratosis occurs (localization on the extensor surface of the arms, legs, lateral surfaces of the chest, abdomen), wavy pigmentation of the neck skin, pallor and subicteric hue of the nasolabial triangle, which are pathognomonic symptoms of lambliosis.

Dermatoses, such as atopic dermatitis with lambliosis, have a more severe course in children, are characterized by chronic, torpid, continuously recurring clinical manifestations, and the intoxication syndrome is more pronounced [3,6,16,24]. In young children, eczema is diffuse, widespread, with a continuously-relapsing course [7,50]. There is a long maceration of the skin, severe itching. In most cases, children with eczema and lambliosis clearly show signs of secondary malabsorption syndrome (loose stools, fecal foam with an unpleasant odor). Older children can have neurodermatitis with skin lesions clinically in the elbows and popliteal folds. During the period of exacerbation of neurodermatitis, characteristic symptoms are erythroderma and pronounced “scalping” itching of the skin.

It has been shown that *Lamblia intestinalis* have the ability to produce toxic metabolic products that are absorbed in the intestinal mucosa and enter the bloodstream, causing systemic intoxication [33]. However, this problem still remains virtually unexplored.

The results of the study. The features of the clinical course of chronic allergic dermatosis on the background of lamblia invasion, in particular, the enhancement of pruritus and the appearance of new rash at night, more frequent chronization of the process were studied. The baseline therapy for chronic dermatosis associated with lambliosis was ineffective: in 47.6% of patients without positive dynamics, in 36.9% there was a worsening of the condition with increased pruritus and the appearance of fresh rashes (in patients without a concomitant parasitosis, a positive result was noted in 80 4% of individuals). Resistance to basic therapy, especially in cases of severe chrono-dependence of allergic dermatoses, served as an indication for additional examination of patients for the presence of concomitant lambliosis.

Lambliosis was confirmed by parasitological examination of feces, and bile if medically required. The aggravating effect of lambliosis on the clinical course of dermatosis, characterized by the predominance of severe and chronic forms, has been established. The frequency of lamblia detection in the first study of feces of patients with chronic dermatosis in patients receiving enterosorbents reached 30%, and in patients who avoided taking enterosorbents for 5-7 days prior to examination, lamblia were detected in 91% of patients (P <0.001). In patients with chronic dermatosis with and without lambliosis, a decrease in the percentage of CD3 was found (P <0.01) in the blood (respectively 46.49 ± 0.48 vs. 65.20 ± 4.80 in the control group), CD8 counts (13.28 ± 0.21 versus 20.70 ± 2.10 were lower (P <0.05) against the background of a concomitant parasitosis. An increase in the immunoregulatory index was observed (2.51 ± 0.39 against 1.89 ± 0.03 in the control group). In patients with lambliosis without skin pathology, the percentage of CD3, CD8, CD4 was less than the norm, not differing from the figures in patients with chronic dermatosis. The content of IgE in the serum of patients with dermatoses against lambliosis was more significant (129.51 ± 10.52) than in healthy ones (75.00 ± 5.00 units / ml) (P <0.01), and more than in patients with chronic dermatosis without concomitant lambliosis (70.16 ± 7.68 U / ml) (P <0.01). The quantitative changes in IgA, IgM, IgG in patients with chronic dermatosis did not depend on the presence of concomitant parasitic invasion. Comprehensive treatment of patients with chronic dermatosis against lambliosis with chrono-determined prescription of protocytotic drugs ornidazole derivatives provided clinical recovery of 88.3% of patients against 19.2% without such therapy (P <0.001), improvement of cellular immunity, in particular, relative and absolute indicators CD3 (P <0.01). Indicators of the number of CD4, CD8, CD16 approached the level of the norm.

Conclusions. 1. The aggravating effect of lamblia parasitic invasion on the clinical course of chronic dermatosis, characterized by the prevalence of severe and chronic forms, has been established.

2. Theoretically substantiated solution of the scientific problem, which is to increase the efficiency of treatment of patients with some forms of chronic dermatosis of allergic origin against the background of lamblia invasion and to improve the diagnosis of concomitant parasitosis.

3. The complex therapy of chronic dermatosis must necessarily include the antiparasitic drug ornidazole or its derivatives.

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DOI:10.19221/201922

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CIRCADIAN CHRONORHYTHMS OF FREE-RADICAL HOMEOSTASIS, ADRENAL HORMONES AND FACTORS OF HUMORAL IMMUNITY OF WHITE RATS IN NORMAL AND UNDER THE ACTION OF CADMIUM CHLORIDE

Abstract. *In the experiment, the circadian chronorhythms of free radical homeostasis in rat erythrocytes, adrenal hormones in the plasma of their blood and the indicators of humoral immunity in the blood serum were investigated. It was established that as a result of intragastric administration of an aqueous solution of cadmium chloride at a dose of 5 mg / kg for 14 days, desynchronosis occurs in the activity of the pro and antioxidant systems and other studied parameters, which is explained by increased free radical oxidation of lipids and a decrease in the activity of antioxidant enzymes.*

Key words*: circadian chronorrhythms, desynchronoses, blood, free radical homeostasis, adrenal glands, humoral immunity.*

Introduction. At present, it is likely that the prefix "chrono" (chronotherapy, chronopharmacology, chronophysiology, chronoprophylaxis, etc.) should be used for any biomedical area. Knowledge of biological rhythms provides physicians and biologists with an important tool for assessing the functional state of the body and determining the optimal values of physiological functions in a temporal aspect, both for intended and unpredictable actions [1, 2, 3].

Biological rhythms are periodic reproductions of changes in the nature and intensity of biological processes and phenomena. They are inherent in all forms of all living organisms and are noted at all levels of the organization of living matter. In plants, rhythms are manifested, for example, in the daily movement of leaves, petals, autumn leaf fall, and the like. Animal rhythms are clearly expressed in the frequency of motor activity and many other functions (temperature fluctuations, hormone secretion, RNA synthesis, cell division, etc.). Many physiological processes (daily fluctuations in blood pressure and blood clotting parameters, quantitative lymph indices) have a rhythmic character. Biological rhythms are hereditarily fixed and are the most important factor of adaptation and evolution in general [4, 5].

Biological rhythms occur as a reaction to periodic changes in the environment (exogenous rhythms) or are generated by the body itself (endogenous rhythms). The latter arise on the basis of self-regulating processes in living systems (cells, tissues, etc.). External influences have a limited effect on endogenous rhythms, shift the phase of these biological rhythms and change their amplitude [6, 7].

Disruption in the confinement of human biorhythms to periodic changes in the external environment is called desynchronosis. An example is a flight to a different time zone. The consequences of desynchronosis can be exacerbations of chronic diseases, fatigue and decreased performance. Inconsistency of biorhythms (desynchronosis) is, as researches show, the first signal of biological trouble, which can be considered as pre-pathology or pathology. This allows for the early diagnosis of diseases, more effective treatment and prevention [8, 9].

Achievements of biorhythmology are important for the organization of a rational mode of work and rest of a person, especially in extreme conditions (working at night, in polar conditions and in space, flying to other time zones, etc.), when the endogenous biological rhythms are disturbed by cyclic changes in the external environment. Daily rhythms of cell proliferation are taken into account, for example, in cancer clinics when prescribing drugs that act on dividing cells [10].

Medicine and biology now closely approach to the consideration of the processes of the norm

and pathology in projection at certain periods of time (during the day, months, seasons, etc.) [11, 12].

An important indicator of the norm and pathology of body functions is the range of their daily fluctuations in the norm. This means that at different times of day, the norm indicator varies in different limits, and, therefore, the same indicator of the function at one time of day will normally have one quantitative characteristic, and another the rest of the time.

Another important indicator is the different sensitivity of the organism to the same physical or chemical effect or to drugs at different times of the day. For example, a higher sensitivity of a person to such well-known antibiotic as penicillin, is registered in the evening and during sleep; dentists know that tooth sensitivity to painful stimuli is maximum at 4 p.m. and minimum in the morning, so they tend to perform the most painful processes in the morning [13].

Preventive medicine is also beginning to take into account the dynamics of biorhythms. For example, doctors have shown that vaccination of children against measles should be carried out only in the first half of the day, since in the second more pronounced negative reactions of the body develop, disrupting the daily regime of physiological functions [14, 15].

For the pathogenesis of many diseases, activation of free radical mechanisms is essential, which is accompanied by an increase in the level of reactive oxygen species in the body [16, 17]. Under normal conditions, the activation of free radical mechanisms is one of the means of reliable protection of the body against various exogenous factors. At the same time, an increased content of free radicals, exceeding the limits of maximum permissible concentrations, adversely affects metabolic processes and may cause the development of pathological changes [18].

It is known that a high content of oxidants causes in the body the activation of lipid peroxidation (LPO) and the accumulation of its products, which can also lead to significant disturbances. In this area, an important role belongs to the mechanisms of protection of cellular structures from the toxic effect of oxidants, antioxidant defense (AOD), which maintains the concentration of reactive oxygen species and peroxidation products at a level safe for the body [19].

At the same time, data on chronorhythmic changes in the parameters of the system of free radical peroxidation both in norm and due to the effect of various stress factors, in particular heavy metal salts, are insufficient.

Due to intensive discharge from industrial enterprises, environmental pollution with cadmium is constantly increasing. As a result, pollution of soil and food products grown on them also increases [20].

Cadmium belongs to highly toxic substances. The main mechanism of cadmium toxic action is the blocking of sulfhydryl groups of enzymes. In addition, the toxic effect of cadmium is associated with its physiological antagonism to zinc. Cadmium has a high ability to cumulate in the tissues in which it is found both in the ionic form (inorganic compounds) and in the complex with thionin [21].

The formation of free radicals, which occurs under conditions of admission of cadmium compounds in the body, accelerates the process of peroxidation, accompanied by damage to the macromolecules and supramolecular components of the cell, depletion of the body's antioxidant defense system, changes in nitrogen, carbohydrate metabolism and intensity of bioenergy processes [22, 23].

Recently, the subject of active study has been the participation of adrenal hormones in the body's response to various adverse effects. In particular, daily, seasonal and other chronorhythms of physiological functions in adrenalectomized animals are being studied [24]. At the same time, information about circadian changes in the functioning of the adrenal glands is insufficient [26, 26].

When a person is exposed to harmful environmental factors, the adaptive responses may be disturbed, leading to an immunopathological process [27, 28].

The human immune system, when in contact with various infectious agents (bacteria, viruses), produces protective proteins (antibodies), so-called immunoglobulins, which specifically interact with microorganisms and help blood cells cope with the infection faster.

The largest molecules are class M

immunoglobulins, they are first produced by contact with microorganisms, so they are called immunoglobulins of the primary immune response. The presence of immunoglobulin M (IgM) in the blood indicates an acute stage of the infectious process in the human body. This class of immunoglobulins begins to be produced before birth, but IgM does not penetrate through the placenta because of its size, so the presence of IgM in the cord blood of a newborn indicates prenatal infection [29, 30].

Class G immunoglobulins are produced in the later stages of the disease, as well as in exacerbation of chronic infections. They are smaller in size than IgM; four subclasses of IgG are distinguished. The presence of IgG in the blood indicates the duration of the pathological process. By the way, this class of immunoglobulins penetrates through the placenta, ensuring the immunity of the child in the first months of life (up to 3-6 months). But the baby itself begins to produce antibodies of this class in sufficient quantity closer to the age of one, therefore the presence of immunoglobulins of class G in the infant's blood only indicates the possibility of prenatal infection, since the baby's mother has these antibodies. The child needs further examination to determine his status.

Class A immunoglobulins are predominantly located in the mucous membranes and protect the body at the first stage of contact with the infection; the baby receives these immunoglobulins with the mother's milk. These immunoglobulins provide protection against a wide variety of infections; in the presence of such antibodies in the blood, it is possible to judge the presence or absence of infection and its activity [30, 31].

In view of the above, the study of the influence of heavy metals on the state of the immune system, taking into account the chronobiological aspect, is relevant to contemporary issues of biology and medicine.

The purpose of the study is to determine the structure of circadian chronorhythms of free radical homeostasis, adrenal hormones and the dynamics of daily changes in immunological reactivity in white rats under the conditions of the physiological norm, as well as under the influence of cadmium chloride.

Material and methods. The experiments were conducted on 96 adult white male rats weighing 180-200 g, kept in standard vivarium conditions at a constant temperature and humidity, in the usual light mode, with free access to food and water. The test group of animals was intragastrically administered an aqueous solution of cadmium chloride at a dose of 5 mg / kg for 14 days, and the control group was given tap water.

The rats were killed by decapitation in accordance with the requirements of the European Convention for the Protection of Experimental Animals, under light ether anesthesia at 8 a.m. 12 a.m. 4 p.m. 8 p.m. 12 p.m. and 4 a.m.

The blood was stabilized with heparin, centrifuged for 15 minutes at 3000 r.p.m, the plasma was separated from the formed elements. A suspension of red blood cells was obtained by washing three times with a physiological solution of sodium chloride in a ratio of 1:10.

The state of lipid peroxidation was assessed by the content in erythrocytes of malonic aldehyde (MA) and diene conjugates (DC) [32], and the AOD system was evaluated by the level of catalase [33].

The study of the content of epinephrine and noradrenaline in the blood plasma was performed by enzyme immunoassay using the CatCombi ELISA reagent kit from IBL (Hamburg). The level of corticosterone in the blood plasma of rats was determined by radioimmunoassay method using the Corticosterone RIA reagent kit (for rats and mice) from IBL (Hamburg).

For studies, blood serum was also used, in which the level of immunoglobulins IgA, IgG, IgM was determined by the method [34].

Statistical processing of the results was performed by the method of variation analysis with the definition of Student's criterion.

Results and their discussion. As a result of the research, it was revealed that under normal conditions, the indicators of free radical homeostasis in the erythrocytes of white rats change periodically during the studied part of the day. In particular, the smallest amount of MA was detected at 8 a.m. (36.21±0.913 μmol / l), subsequently the level of this indicator gradually increased, reaching a maximum value at 8 p.m. (51.35±0.102 μmol / l). The acrophase of the DK content was observed at 4 p.m. (2.27±0.008 E_{232} /

ml), the batiphase was observed at 12 a.m. (2.03±0.011 E_{232} / ml).

Catalase activity in erythrocytes of intact rats was the smallest at 8 a.m. (2.04±0.035 μmol/min·ml), slightly increased during the next two time intervals, and at 8 p.m. it became almost equal to the initial value (2.08±0.034 μmol / min·ml).

After daily administration of a solution of cadmium chloride to rats for 14 days, significant changes were recorded in the chronorhythms of those indicators of prooxidant and antioxidant homeostasis, which were studied. Thus, the levels of MA and DC significantly increased in all the studied time intervals, and their chronograms, compared with the control, acquired an antiphase character. In both cases, there was a redistribution of acro - and batiphases.

The MA rhythm mezor grew from 44.21±2.525 to 72.80±3.885 μmol / L ($p<0.001$), the amplitude of oscillations increased by 23.4% relative to that of intact animals. The average level of DC rhythm also significantly changed (from 2,18±0,037 до 3,66±0,198 E_{232}/ml, $p<0,001$), its amplitude increased 2.7 times.

All these changes occurred against the background of a decrease in the activity of the enzyme of the AOD catalase system. During the entire study period, the activity of catalase compared with the groups of intact rats was significantly less. The rhythm mezor also significantly decreased in accordance with 2.10±0.018 to 1.39±0.065 μmol / min · ml. The amplitude of chronogram fluctuations grew 5.5 times.

Owing to the conducted research, it was also established that catecholamines and corticosteroids are characterized by daily secretory dynamics, and the phase structure of circadian rhythms of adrenaline and noradrenaline was the same. The peak of catecholamine secretion occurs during the daytime: at 12 a.m., the concentration of adrenaline in the blood plasma was 16.5 ± 0.74 nmol / l, and that of norepinephrine - 55.8 ± 1.03 nmol / l. The batiphase content of these hormones in the blood plasma was observed at 8 p.m., at this time the level of adrenaline was 11.1 ± 0.20 nmol / l, and norepinephrine - 33.8 ± 1.10 nmol / l. The amplitude of secretion of norepinephrine was 43.1 ± 3.17%, adrenaline - 17.5 ± 4.35%.

The data obtained coincide with the literature on the daily rhythms of catecholamine secretion [35, 36], and also correlate with morphometric studies. In the latter, periodic enhancement of metabolic and synthetic processes in the tissue is observed, manifested by an increase in the size of the nuclei, detection of a large number of euchromatin in them, expansion of the nuclear pores, an increase in the number of mitochondria and ribosomes. At this time, a sharp increase in the cytoplasm of the number and size of secretory granules filled with catecholamines was recorded [37, 38].

As a result of our experiments, it has been established that the concentration in the blood plasma of the main hormone of the rat adrenal cortex, corticosterone, also has clear circadian characteristics. But its diurnal dynamics have different characteristics than circadian chronorhythms of catecholamines. Thus, the maximum plasma concentration of control animals was observed in the morning period of the day and at 8 a.m. was equal to 119.2 ± 9.70 nmol / l. The rhythm batiphase occurred at 8 p.m. (42.3 ± 3.84 nmol / l). The amplitude of corticosterone secretion was 43.5 ± 3.17%.

A single intragastric administration to rats of the experimental group of cadmium chloride solution in all studied time intervals led to the activation of the secretory activity of adrenal medulla cells, accompanied by an increase in the release of catecholamines into the blood.

The acrophase concentration of adrenaline in the blood plasma was recorded, as in the group of intact animals, at 12 a.m. (23.4 ± 0.65 nmol / l, $p<0.001$), the batiphase at 8 p.m. (11.1 ± 0.20 nmol / l, $p<0.001$). The maximum value of norepinephrine was also recorded at 12 a.m. - 74.7 ± 1.12 nmol / l, $p<0.001$; the minimum is in the evening hours (28.6 ± 0.88 nmol / l, $p<0.01$).

The amplitude of the rhythm of adrenaline secretion in rats of the experimental group decreased from 17.5% to 14.6%, and norepinephrine from 43.1% to 38.8%. Although such changes did not have a reliable character, they are evidence of a certain functional depletion of cells responsible for the secretion of catecholamines.

Cadmium poisoning in animals caused an

increase in plasma corticosterone concentration during the day. At the same time, the architectonics of the rhythm of this indicator in rats of the experimental group did not differ from the intact ones - the acrophase accounted for 8 a.m., the batiphase at 8 p.m. At 8 a.m. the concentration of corticosterone in the blood plasma was 184.3 ± 6.33 nmol / l ($p<0.001$). At 8 p.m. this indicator in experimental animals significantly decreased and was 78.2 ± 4.32 nmol / l ($p <0.001$). The amplitude of corticosterone secretion decreased from 43.5% to 32.3%, which indicates the stressful functioning of the corresponding adrenal tissue under conditions of cadmium poisoning.

As a result of the research, it was also found that the indicators of the amount of antibodies that were studied in intact rats periodically change during the day.

Thus, the maximum value of the content of immunoglobulins of classes IgA and IgM in serum was recorded at 12 a.m. (in this time interval it reached 0.58 ± 0.031 and 1.36 ± 0.101 g / l, respectively), and the amount of IgG at 4 p.m. (3.81 ± 0.151 g / l). The batiphases of chronorhythms of antibodies, both IgA and IgG, occurred at 4 a.m. and amounted to 0.47 ± 0.044 and 3.14 ± 0.142 g / l, respectively, and IgM at 12 p.m. (1.18 ± 0.124 g / l).

The mezor of circadian rhythms IgA reached 0.53 ± 0.020 g / l with an amplitude of 10.5%, IgM - 1.29 ± 0.036 g / l (7.3%), IgG - 3.51 ± 0.092 g / l (7 9%).

The dynamic equilibrium of the immune system may be disturbed as a result of the direct or indirect influence of stress factors. Their effects on various parts of the immune system can manifest themselves as immunosuppressive and immunostimulating effects [37, 38].

The reaction of the immune system in response to various stress reactions is often accompanied by an increase in the concentration of immunoglobulins in the plasma (mainly classes G and A) due to their release from the depot. Large surgeries that give a strong stress reaction, on the contrary, lead to a decrease in the levels of immunoglobulins of all classes due to their sorption on cells and damaged tissues. Such shifts disappear relatively quickly [28, 31].

More constant are the changes in the ratio of immunoglobulins during the reaction of the immune system to foreign bodies. When the inflammatory reaction associated with the initial contact of the body with this antigen, in the early stages of inflammation increases the content of lgM, and then the level of lgG increases. Levels of lgG and lgA increase with repeated contact with this antigen, even in the early stages of the development of the inflammatory reaction (29, 30).

It is known that the effect of various forms of stress on rats is accompanied by the occurrence of oxidative stress in the tissues of their organs, a manifestation of which is the accumulation of lipid peroxidation products and carbonylated proteins in them. An important role in the stimulation of free radical oxidation of lipids and proteins in rats when exposed to harmful environmental factors acquire shifts from the activity of first-line enzymes of antioxidant protection, increased sensitivity to the action of prooxidants, as well as changes in the state of redox processes in mitochondria [39].

We have found that cadmium poisoning causes disturbances in the chronorhythm organization of the content of all the studied classes of antibodies with signs of desynchronosis in the studied animals.

In particular, the acrophases of the amount of immunoglobulins IgA and IgM have moved from daytime to nighttime. At 12 p.m. the mentioned indicators were respectively 0.38 ± 0.022 and 0.56 ± 0.088 g / l. The smallest amount of these antibodies was recorded: IgA - at 4 p.m. (0.28 ± 0.041 g / l), IgM - at 8 p.m. (0.35 ± 0.112 g / l).

The average daily levels of these immunity parameters reached the following values: IgA - 0.31 ± 0.022 g / l ($p<0.001$ compared with a group of intact rats), the amplitude of oscillation - 16.3%; IgM - 0.44 ± 0.088 g / l ($p<0.001$), amplitude - 23.4%.

The highest level of IgG in cadmium poisoning was found at 12 p.m. - 3.65 ± 0.112 g / l, the batiphase moved to 12 a.m. and amounted to 2.95 ± 0.092 g / l. The mezor of daily variations in the amount of these antibodies reached 3.19 ± 0.084 g / l ($p<0.05$ compared with the control), the amplitude - 21.8%.

Thus, the analysis of the chronorhythms of rat erythrocyte pro- and antioxidant systems, adrenal

hormones in their blood plasma and humoral immunity indices in blood serum under conditions of cadmium intoxication revealed activation of the LPO on the background of AOD deficiency, as well as disruptions of the endocrine and immune status of animals, accompanied by signs of desynchronosis. This gives reason to argue about the imbalance of the above mentioned systems, which leads to a decrease in the adaptive-compensatory capabilities of the organism.

Conclusions. 1. Indicators of the oxidative antioxidant state of white rats, the level of adrenal hormones and the immunological reactivity of the organism under the conditions of the physiological norm have a circadian pattern.

2. The impact on the body of cadmium chloride at a dose of 5 mg / kg disrupts the structure of the chronorhythms of the indicators of the pro-and antioxidant systems of white rats, is a consequence of the adaptive-compensatory and decompensatory reactions of the body to environmentally harmful load.

3. Cadmium poisoning leads to a disruption of the hormonal activity of the adrenal glands and the development of desynchronosis of their activity.

4. Analysis of circadian chronorhythms of rats' immune status indicators revealed an immunosuppressive effect of cadmium chloride, accompanied by signs of desynchronosis.

5. The degree of imbalance in the circadian dynamics of the studied parameters depends on the time of day.

Prospects for further research. The study of circadian chronorhythms of free radical homeostasis, adrenal hormones and indicators of humoral immunity under the influence of other xenobiotics on the body will be continued.

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DDC-UDC UDC: 611.212.5.013:612.63.025.2 DOI:10.19221/201923

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TOPOGRAPHIC-ANATOMICAL PECULIARITIES OF THE NASAL SEPTUM RUDIMENT DURING THE EMBRYONIC PERIOD OF HUMAN ONTOGENESIS

Abstract. *12 specimens of the nasal portion during the embryonic period of human ontogenesis were examined by means of micro- and macrodissection and morphometry as well as regularities of its development, formation and morphological transformations of the human nasal portion. At the end of the embryonic period the primary nasal cavity was found to be formed separated by the primary palate from the primary oral cavity. The nasal septum is formed by means of joining median nasal processes. The permanent palate begins to emerge in the form of the palatine projection (in the right).*
Key words: *nasal cavity, embryo, intrauterine period, ontogenesis.*

Introduction. Review of the scientific literature is indicative of a number of studies dealing with investigation of the structural organization of the nasal walls and the structures adjacent with them [1, 2]. At the same time, there is a lack of information concerning topographic-anatomical peculiarities of the structure and changeability of the nasal structures at different age periods. The nose, as a topographic-anatomical object of the face, is one of its most important elements and considerably forms general perception of a man [3].

The questions concerning the sources of origin, terms of anlage, mechanisms of development and peculiarities of the nasal cavity structure at different age periods remain disputable [4]. Investigation of its age morphology is an important issue for clinicians, since during the period of organ formation their interrelations with the adjacent structures of the facial portion change rather quickly. It requires a special approach to understanding pathological process, its spread, and selection of the most rational and effective methods of treatment and prevention of possible complications of the adjacent portions [5].

Development of new methods in operative surgery requires their anatomical substantiation. Therefore, development of microsurgical anatomy as an anatomical base in the development of microsurgery is absolutely logical. Microsurgical anatomy is a direction of clinical anatomy dealing with the study of structure and topography of small anatomical structures of the organs and parts of the body in the norm and pathology concerning microsurgery requirements [6].

Objective: to study spatial-temporal dynamics of the formation of the constituent elements of the nasal cavity during the embryonic period of human ontogenesis.

Materials and methods. 12 specimens of the nasal cavities of human embryos from 5,0 mm to 13,0 mm of PCL were examined. A complex of up-to-date methods of morphological examination was applied including micro- and macroscopy, anthropometry, morphometry and statistical analysis.

Results and discussion. Examination of 10 series of histological specimens found that on the 4th week of the intrauterine development (embryos with 5,0 – 5,5 mm of the parietal-coccygeal length (PCL)) the oral fossa is determined surrounded superiorly by the unpaired frontal process, inferiorly – by the cardiac projection, and laterally – by the maxillary processes. Its posterior border is formed by the mandibular arch.

The nasal cavity as it is does not exist yet. Though, downward and from the sides of the frontal tuber the epithelial cells are densely located, forming two thickened laminae represented by 4-5-rows of the columnar epithelium. The nuclei of its cells are spherical or elongated in shape, they occupy a central position. On the periphery of the laminae the epithelial cells extend above the ectodermal layer forming an elevation.

In the area of the middle part of the above

thickened portions of the epithelium in the embryos with 6,0 mm of PCL inconsiderable protrusion of the epithelium occurs into the underlying mesenchyme – it is the primary stage of the olfactory placode rudiment located in the cranial-caudal direction. They are 118 ±1,0 mcm long, and 64 ±0,5 mcm wide. The epithelium of the olfactory placodes is 20 ±0,3 mcm thick, in some places – 24 ±0,3 mcm. The distance between their medial borders is 1,1 ±0,1 mm.

The second epithelial thickness is located a little dorsally and laterally from the olfactory placodes. It consists of cylindrical cells which nuclei form 5-6 lines. This thickening extends into the underlying mesenchyme and is the rudiment of the lens placodes located at the distance of 330 ±10,0 mcm from the nasal placode.

The maxillary processes are located lower from the nasal placodes. They grow in the direction to the medium line. At this stage of development the distance between them is 880 ±10,0 mcm. Their lateral border is 160 ±6,0 mcm high, and the free medial border is not higher than 88 ±2 mcm.

Examination of histological sections of the embryos 7,0-7,5 mm long (the fifth week of the intrauterine development) found that epithelial protrusion of the nasal placodes becomes more pronounced, and depressions are formed on the free surface of the placodes – it is the primary stage of the olfactory fossa formation. The walls of the latter are formed by 4-6-row cylindrical epithelium 36 ±2,0 mcm thick with oval dark stained nuclei. The number of nuclei rows gradually decreases to 1-2 to the periphery. The nasal placodes are 60 ±2,0 mcm deep in the embryos 7,1 mm long, and 188 ±10,0 mcm long – in the embryos 7,5 mm long. The distance between the medial borders of the middle nasal processes is 1,1 ±0,1 mm.

Inconsiderable conglomeration of the blood corpuscles are found in the mesenchyme layer – the islets of the internal organ blood formation. In some places they are separated from the surrounding mesenchyme by one layer of the elongated cells, which should be considered as the primary stage of formation of the vascular endothelial lining. In addition to the above, fine conglomerations are found in the form of 3-5 cells, and even separate cells of the erythroblast type.

At this stage of development the sizes of the nasal processes enlarge. These processes grow in the caudal direction and hang over the primary oral cavity.

The olfactory fossae are lined with the cylindrical epithelium 36 ±2,0 mcm thick. Its nuclei are arranged in 4-6 rows. The nasal/olfactory fossae are 96 ±5,0 mcm deep, 180 ±6 mcm high and – 96 ±4,0 mcm wide. The distance between them is 1,2 mm.

The transverse size of the median nasal processes in embryos 8,8 mm is 264 ±10,0 mcm, the vertical one – 286 ±10,0 mcm; in the lateral nasal processes they are 220 ±3,0 mcm and 242 ±8,0 mcm respectively. The median nasal processes come closer together gradually. The distance between them in embryos 8,8 mm becomes shorter to 1,08 mm.

The maxillary processes are located downward and laterally from the nasal processes. The maxillary processes grow medially and forward. They come closer to the lateral nasal processes, but at this stage of development they are not connected yet. They are separated by a small slit passing to the eye rudiment.

An intensive growth of the nasal fossae and adjacent structures occur in embryos 9,5-10,0 mm long. Due to their intensive growth and epithelial protrusion into the underlying mesenchyme they are transformed into the nasal chambers or cells growing in a dorsal direction and a little caudally (in the direction to the primary oral cavity), but they are not connected yet. The nasal cells are lined with the high stratified cylindrical epithelium with unchanged thickness.

The islets of the internal organs formation of a various shape are detected in the mesenchyme. Some of them are located in the form of a chain resembling capillaries. A small concentration of the islets is seen from the side of the epithelial protrusion and in the area of the median nasal processes.

On histological sections the nasal cells are semilunar in shape open into the side of an opposite cell. Their caudal extremities are located closer one to another than the cranial ones, as they have been before. The nasal cells are 540 ±20,0 mcm deep. They are located at the distance of 150 ±6,0 mcm from the primary oral cavity and separated from the latter by the mesenchyme layer 100 ±5,0 mcm thick, placed between the epithelium lining the nasal cells and the epithelium

lining the primary oral cavity. The height and width of the nasal cells do not change practically: they are 200 ±10,0 mcm high (in embryos 8,0 mm long – 180 ±5,0 mcm) and 100 ±10,0 mcm wide (in embryos 8,0 mm long – 9,6 mm). The internal surface of the nasal cells is smooth.

The anterior-posterior axis of the nasal cells is oblique. Their primary (anterior) portions are located one from another at the distance of 1,2 mm, and their blind (posterior) extremities – at 1,1 mm.

At this stage of development the nasal processes enlarge considerably, especially the median ones. Their transverse size is 660±20,0 mcm, the vertical one – 750±25,0 mcm. The sizes of the lateral nasal processes are 440±10,0 mcm and 418±10,0 mcm respectively. At the earlier stages the nasal processes of embryos are presented by the mesenchyme covered with the external layer of the epithelial cells with the nuclei placed in 1-2 rows.

On the medial surface of each median nasal processes there is well marked projection. Therefore, the above processes gradually come closer together. Though, the distance between them remains considerable – 880±20,0 mcm. The median and lateral nasal processes outline the primary nostrils by means of the surfaces turned one to another. The primary nostrils still remain open-ended downward, since the maxillary processes growing to the median line and forward are not yet connected with the nasal processes.

In embryos 11,0-12,0 mm long the nasal cells grow further – dorsally and a little caudally in the direction to the primary oral cavity. Though, at this stage of development they are not connected yet. During the above stages the nasal cells close blindly. They are located at the distance of 80±3,0 mcm from the primary oral cavity. They are 580 ±20,0 mcm deep, and 220±10,0 mcm high.

The superior, inferior and lateral walls of the nasal cells are smooth. Depressions (Jacobson's organ rudiment) appear on the medial wall, in its middle portion.

The median nasal processes are directed downward and laterally. Their transverse size in the embryo 12,0 mcm long is 920±30,0 mcm, and they are 780 ±20,0 mm wide. The lateral nasal processes are 850±20,0 mcm long and 600±10,0 mcm wide. They are directed downward and medially. The distance between the median nasal processes turned one to another is 850±20,0 mcm.

The maxillary processes continue to grow. Their anterior-posterior size increases to 1,5 mm and their height – to 750±10,0 mcm. At this stage of development they are connected with the lateral nasal processes, and their free border is located near the inferior extremity of the median process.

At the end of the embryonic period (embryos with 13,0-13,5 mm of PCL) the nasal cells penetrate into the primary oral cavity. Due to this fact the primary nasal cavity, oral cavity and pharynx are connected. It should be noted that penetration of the nasal cells into the primary oral cavity occurs in the embryos 11,5 mcm long of the intrauterine development.

The study of the nasal portion of the embryos with 13,5 mm of PCL demonstrated that both halves of the primary nasal cavity are of a bent shape - first directed dorsally, later – a little caudally (in the direction of the primary oral cavity), and they open near its lateral walls. The anterior-posterior size of the primary nasal cavity is 690±20,0 mcm.

If in embryos with 10,0 mm of PCL the difference between the superior and inferior extremities of the nasal cells is not considerable, in embryos with 13,0 mm of PCL the superior extremities of both halves of the primary nasal cavity are separated one from another more than the inferior ones. The distance between the former is 1,3 mm, and the latter – 990±20,0 mcm. The height of the primary nasal cavity is no more than 660±10,0 mcm, and the width – 180 ±5,0 mcm. Every half of the primary nasal cavity begins with the opening in front (primary nostril), which is limited laterally by the lateral nasal process 770±10,0 mcm long and 550 ±10,0 mcm wide, and medially – by the anterior border of the nasal septum formed due to connection of the median nasal processes. The vertical size of the nasal septum is 660±10,0 mcm, the transverse one – 880±15,0 mcm and the anterior-posterior one – 484±10,0 mcm.

In the area of the primary nostrils the transition of the ectodermal epithelial cells, with the nuclei located in 1-2 rows, into the high stratified cylindrical epithelium lining the primary nasal cavity with the nuclei located in 5-6 rows is well marked. Externally from the epithelium there is a layer of mesenchyme cells containing practically

continuous chain of islets of the internal organ blood formation. A part of them is separated from the surrounding mesenchyme by one row of cells of an elongated shape of an endothelial type.

In the dorsal direction the vertical size of the primary nasal cavity decreases gradually, and in the places of protrusion into the primary oral cavity the primary choanas (posterior nostrils) of a spherical or elongated in the vertical direction shape are formed. Their sizes are 200 x 200, or 220 x 230 mcm. The distance between the primary choanas is no longer than 880±10,0 mcm.

The anterior-posterior axes of the both halves of the primary nasal cavity are located in an oblique direction.

The primary nasal cavity is separated from the primary oral cavity by the primary palate 286±8,0 mcm thick, 1,1 mm wide and 280±6,0 mcm long.

At this stage of development a small projection appears in the right of the lateral wall of the primary oral cavity – the rudiment of the palatine process.

The projection looks like an inconsiderable protrusion into the primary oral cavity of the maxillary process mesenchyme covered with 3-4 rows of the epithelium. On the frontal sections it looks like a cone with its apex directed to the tongue and located on the level of its inferior border.

The palatine process is 200±5,0 mcm high, its anterior-posterior size is 420±7,0 mcm, its free extremity penetrates 100±4,0 mcm into the primary oral cavity.

All the walls of the primary nasal cavity are smooth. The maxillary processes have already connected with the lateral nasal processes, though they are not completely closed.

Conclusions. 1. At the end of the embryonic period the primary nasal cavity is formed separated from the primary oral cavity by the primary palate. 2. The nasal septum is formed by means of junction of the median nasal processes, and the permanent palate begins to form in the shape of the palatine projection (in the right).

Prospects of further studies: to investigate peculiarities of the development of the nasal portion structures and nasal septum during the pre-fetal period of human ontogenesis.

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DDC-UDC 616.24-002.5-036.1-073.75:577.124.5 DOI:10.19221/201924

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THE IMPACT OF X-RAY SEVERITY AND MICOBACTERIA EXCRETION ON GLUCOSE METABOLISM DISORDERS IN NEWLY DIAGNOSED PULMONARY TUBERCULOSIS PATIENTS

Abstract. *Aim. The present study was performed to detect the glucose metabolism disorders in newly diagnosed pulmonary tuberculosis patients and to evaluate the relation of the disorders to the X-ray severity and the presence of mycobacteria excretion. Materials and methods. We examined 78 patients with newly diagnosed pulmonary tuberculosis. Oral glucose tolerance test, fasting insulin level were measured, the insulin resistance index (HOMA-IR) and the body mass index were calculated. For statistical data processing, the general-purpose data processing software package Statistica for Windows version 13.2 was used. Results. Our study found an increase in glycosylated hemoglobin level, which correlated positively with the volume of pulmonary lesion. Oral glucose tolerance test demonstrated statistically significant increase of the median of 2 hour blood glucose level in the group of patients with mycobacteria excretion. The median of the fasting plasma insulin level was 3.8 times higher in patients with newly diagnosed pulmonary tuberculosis, compared to the control group. Conclusions. Our findings suggest that pulmonary tuberculosis is associated with glucose metabolism disorders. Mycobacteria excretion and bilateral pulmonary lesions were accompanied by the impaired glucose tolerance and increase of glycosylated hemoglobin levels, that allows consider these indicators as markers of unfavorable course of pulmonary tuberculosis.*

Key words: *pulmonary tuberculosis, oral glucose tolerance test, insulin, Homeostatic Model Assessment of Insulin Resistance.*

Introduction. About 1.7 billion people, 23% of the world's population, are estimated to have a latent tuberculosis (TB) infection, and are thus at risk of developing active TB disease during their lifetime [1]. The lifetime risk of active TB is significantly increased among those who have predisposing factors like comorbid diseases or pathological conditions that can lead to immune defense weakness. According to WHO experts, the top five most significant risk factors for TB are poor nutrition, Human Immunodeficiency Virus (HIV) infection, Diabetes Mellitus (DM) and harmful habits (tobacco and alcohol abuse). Individual risk of TB in patients with DM is significantly lower than the risk of HIV-positive patients, but in countries with high TB-DM burden, it plays a key role in TB morbidity control [2].

TB-DM comorbidity has become a major public health problem in Ukraine. According to the Public Health Center of the Ministry of Health of Ukraine, in 2016, the incidence of TB-DM comorbidity in Ukraine reached 2.5 per 100 thousand population (1044 cases were detected), this is about 3.1% of the total TB cases. For comparison: in 2015 this indicator was 2.7%. The percentage of comorbidities among patients with multidrug-resistant tuberculosis (MDR-TB) also had raise from 3.7% in 2015 to 4.2% in 2016.

It is known, that clinical course of patients with TB-DM tends to be more severe due to immunosuppression and interaction of anti-TB and DM drugs. TB-DM patients have higher treatment failure rate, compared to non-diabetic TB patients (4.8% vs. 1.5%). In addition, the number of TB relapses is statistically significantly higher among DM patients if to compare with non-DM (20% vs. 5.3%).

Recent studies have shown a high prevalence of newly diagnosed type 2 diabetes and pre-diabetes among TB patients [3-5].

Aim. The present study was performed to detect the glucose metabolism disorders in newly diagnosed pulmonary tuberculosis patients and to

evaluate the relation of the disorders to the X-ray severity and the presence of mycobacteria excretion.

Material and methods. We examined 78 newly diagnosed pulmonary TB patients. All of them were treated in Kharkiv Regional TB Dispensary No. 1 from 2016 to 2017. We excluded from the study patients who had HIV/TB co-infection, TB/DM comorbidity, pregnant women, children and elderly patients. Depending on the mycobacteria excretion, which was confirmed by culture, microscopic smear and molecular methods of diagnosis of tuberculosis, patients were divided into groups. The control group included 20 healthy persons, which were correlated with the comparison groups by gender and age. All patients were examined according to the order of the Ministry of Health of Ukraine No. 620 of 14. 09. 2014. Additionally oral glucose tolerance test (OGTT) was performed and fasting insulin level was measured. HOMA-IR and Body Mass Index were calculated.

Statistical processing of the obtained results was carried out by analyzing the contingency tables using the StatisticaBasicAcademic 13 for Windows software package. We used the median (Me) interquartile range (Lower - lower quartile, Upper - upper quartile) and sample size (min - minimum, max - maximum value). The difference between groups was determined by non-parametric statistics using the Kolmogorov-Smirnov test and Mann-Whitney (CMW) test criteria. To study the independent variables, we used the non-parametric Kruskal-Wallis (CKW) test criteria and the median test.

The work was performed according to the requirements for researches with the participation of people: Statute of the Ukrainian Association for Bioethics and the GCP norms (1992), requirements and norms of ICH GLP (2002), typical ethics provisions of the Ministry of Public Health of Ukraine 66 dated February 13, 2006.

Results. Group I consisted of 19 newly diagnosed pulmonary TB patients who had no mycobacteria excretion (24.4 %). Group II included 59 newly diagnosed pulmonary TB patients who had mycobacteria excretion (75.6 %). Age and sex distribution were nearly the same in both groups. Age ranged from 20 to 57. Men prevailed in both groups: 10 (52.6 %) and 44 (7.6 %) respectively. The overwhelming majority of Group I patients were hospitalized to the TB hospital in satisfactory condition. Clinical course of the Group II patients was aggravated. They were often complained of fatigue - (44.1%), fever - (37.3%), night sweats - (16.9%) and coughing that lasts three or more weeks - (50.8%).

In most patients of both groups the BMI was within normal ranges, though 6 patients from Group II (10.2%) had expressed underweight (BMI < 16.0).

When comparing medians of the carbohydrate profile indicators of TB patients and healthy controls, we found statistically significant difference ($p<0.01$, CMW) in fasting insulin levels (16.15 mcU/ml vs. 4. 78 mcU/ml) and 2-hour glucose levels (4.95 mmol/L vs 3.92 mmol/L). HOMA-IR was statistically significantly higher among TB patients (3.19 vs. 0.82). But we didn't find statistically significant differences in fasting blood glucose levels (4.28 mmol/L vs.3.92) and glycosylated hemoglobin levels (5.67% vs. 5.77%) between groups respectively ($p>0.01$, CMW).

X-ray examination reviled that in most cases patients of both groups had infiltrative changes in their lungs (Group I – 94.8%, Group II – 96.6 %). For Group I patients, there were mainly pathologic changes within one lobe (63.2%), while in Group II we observed huge infiltrative changes in both lungs (79.7%). Cavitation was present in 31.6% patients in Group I and in 77.9% of Group II patients. It should be noted, that in Group I patients prevailed single cavities up to 1.0 cm in diameter (83.3%), on the contrary, in Group II, multiple decay cavities of various sizes were prevailed (63%).

Depending on the increase in the volume of infiltrative changes, there was a monotonous statistically significant ($p=0.0409$, CKW) increase in the median level of glycosylated hemoglobin from 4.8% (pathological changes within the lobe of the lung) to 6% (total lesion of one lung) with a maximum of 7.1% with bilateral lung injury. Thus, when both lungs were involved in the pathological process, the level of glycosylated hemoglobin was increased by almost one and a half times as compared with limited lung changes. The OGTT showed a statistically significant ($p= 0.023384$, CMW) increase in the median of 2-hour glucose level in pulmonary TB patients who had mycobacteria excretion 5.8 mmol/L compared to those, who had no mycobacteria excretion (4.7 mmol/L).

Discussion. *Mycobacterium tuberculosis*, the etiological agent of Tuberculosis can induce

Reactive Oxygen Species (ROS) production by activating phagocytes which are important part of host defense mechanism against Mycobacterium. ROS production is enhanced by the host cells to clear out mycobacterial infection. However, this can become damaging to the host cell itself. Such damage is controlled by the induction of antioxidant defense mechanisms. Excessive ROS production may promote tissue injury and inflammation in affected individuals. Imbalance between the free ROS and the antioxidant mechanisms usually leads to oxidative stress (OS) [6]. In the lung, there is a higher risk of OS compared to other organs. Many studies demonstrated that increased oxidative stress is associated with insulin resistance pathogenesis by insulin signals inhibition and adipokines dysregulation. Research in this area has revealed that there is a strong correlation between the state of oxidative stress in the body and the incidence of insulin resistance and even late stage diabetes cases [7,8].

In our study we found the presence of insulin resistance in patients with newly diagnosed pulmonary tuberculosis that is confirm the results of previous researchers. We did not find statistically significant differences between glycosylated hemoglobin levels and fasting blood glucose levels in pulmonary tuberculosis patients compared to healthy controls. It allows us to suppose, that such routine research methods like glycosylated hemoglobin and fasting blood glucose test have low sensitivity when detecting carbohydrate metabolism disorders in patients with pulmonary tuberculosis.

But, we found a statistically significant increase in glycosylated hemoglobin level of pulmonary tuberculosis patients that positively correlated with the volume of pathological changes in the lungs which is indicate to deeper glucose metabolism disorders in tuberculosis patients who had bilateral injury of pulmonary tissue, compared to those, who had limited pathological changes. We also identified, at a statistically significant level, glucose metabolism disorders in the form of impaired glucose tolerance in patients with newly diagnosed pulmonary tuberculosis who had mycobacteria excretion.

Conclusions. According to our results, patients with newly diagnosed pulmonary tuberculosis develop insulin resistance - condition that is a precursor to developing of type 2 diabetes. Mycobacteria excretion and bilateral injury of lung tissue leads to expressed carbohydrate metabolism disorders. Fasting blood glucose level is low sensitivity index when detecting carbohydrate metabolism disorders, while glycosylated hemoglobin and oral glucose tolerance test can be considered as markers of impaired glucose metabolism in patients with pulmonary tuberculosis.

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DDC-UDC 616.24-002.5-008.811.9-036-085.281.015.8 DOI:10.19221/201925

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DYNAMICS OF PULMONARY TISSUE DESTRUCTION MARKERS IN PATIENTS WITH NEW CASES OF TUBERCULOSIS WITH DIFFERENT SUSCEPTIBILITY OF THE PATHOGEN DURING TREATMENT

Abstract. *The study was designed to investigate the difference in the dynamics of levels of pulmonary tissue destruction markers in patients with new tuberculosis cases with different sensitivity of the pathogen on the background of treatment. Materials and methods. 124 patients with pulmonary tuberculosis (TB) were divided into 2 groups: group 1 (n = 84) - patients with MDR-TB; Group 2 (n = 40) - patients with pulmonary tuberculosis susceptible to antimicrobial treatment. The levels of free hydroxyproline (FH), protein-bound hydroxyproline (PBH), matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), and aldosterone (A) were investigated at the beginning of treatment and after 2 and 3 months from the start of treatment. Results. Under the influence of 1st line drugs, in the 3rd months of treatment, there was a decrease in the activity of the macrophage system on the background of sputum conversion and lower levels of MMP-9, PBH and A, indicating the inhibition of degradation processes on the background of low fibrotic activity. Under the influence of therapy with second-line drugs for 3 months, the activity of fibrosis formation was higher in Group 1 than in Group 2. It was accompanied by a decrease in the level of PBH and a decrease in the level of FH, indicating inhibition of destructive changes. The slowed conversion of sputum smear in Group 1 on the background of therapy with second-line drugs was accompanied by a deceleration in the decrease of MMP-9 / TIMP-1 ratio. Moreover, the reduction of MMP-9 / TIMP-1 ratio for 2 months of treatment is associated with the growth of TIMP-1, and for 3 months it is associated with further growth of the MMP-9 level, that is, the activity of the destruction processes remains significantly higher. The less pronounced dynamics of decrease in A level and growth of TIMP-1 promotes more active fibrosis formation in Group 2. That is, on the background of treatment with the 1st line drugs, there was a decrease in the activity of the processes of fibrosis, which reduces the amount of residual changes. Conclusions. On the background of treatment with the first-line drugs, patients showed less activity of destruction and less subsequent fibrotic changes, compared with patients treated with second-line drugs.*

Key words: *multi-drug-resistant tuberculosis, aldosterone, protein-bound hydroxyproline, free hydroxyproline.*

Introduction. To overcome the epidemic of Multi-drug-resistant tuberculosis (MDR-TB) in the world, World Health Organization (WHO) recommends to achieve 75% level of treatment

effectiveness [1].

Treatment effectiveness is controlled by sputum bacterial conversion and healing of pulmonary destructions at the end of treatment.

It is known that the formation of destruction cavities involves the destruction of the extracellular matrix, which contains collagen fibers that support the pulmonary structure. In the lungs, collagen fibers are destructed by Matrix metalloproteinase (MMP), which can affect all components of the extracellular matrix [2]. One of the products of the collagen fibers destruction in pulmonary tissue is hydroxyproline and its fractions. The process of MMP synthesis is regulated by Tissue inhibitors of metalloproteinase (TIMP), which play an important role in the processes of fibrosis [3]. However, not only the level of MMP is important, but also its ratio to TIMP, which approaches 1 in the absence of pathology [4].

Recent studies indicate the role of A in the processes of fibrosis It is able to activate blood monocytes, induce inflammation, lead to impaired fibrinolysis, strengthen and accumulate collagen. [5] Thus, the destruction of the extracellular matrix is one of the most important pathological events in the formation of residual changes in the pulmonary tissue during tuberculous inflammation [6, 7].

Aim. The study was designed to investigate the difference in the dynamics of levels of pulmonary tissue destruction markers in patients with new tuberculosis cases with different sensitivity of the pathogen on the background of treatment.

Materials and methods. 124 patients with new cases of pulmonary Tuberculosis (TB) were examined. Patients were divided into Group 1 (n = 84) - MDR-TB, and Group 2 (n = 40) - pulmonary TB with preserved sensitivity of the pathogen to anti-tuberculosis drugs.

The patients were aged from 18 to 55 years, the average age was 35.6 ± 3.1 years; men - 72.5%, women - 27.5% ($p < 0.05$).

In Group 1, all patients had destruction of the pulmonary tissue and bacterial excretion.

Patients with HIV, diabetes, Hepatitis B / C, COPD, cardiovascular disease were excluded from the study.

Clinical, biochemical, microbiological and instrumental studies were performed in all patients at the beginning of treatment, as well as after 2 and 3 months from the start of treatment. The levels of free hydroxyproline (FH), protein-bound hydroxyproline (PBH), MMP-9, TIMP-1, and aldosterone (A) were studied.

Statistical data processing was carried out using non-parametric statistics by STATISTICA application software package. To compare the values on 3 stages of the dynamic study within the combined group, as well as within the Groups 1 and 2, the Friedman nonparametric method was used, followed by pairwise comparison of groups using the Wilcoxon criterion. To compare Groups 1 and 2 at different stages of dynamic treatment, the Mann-Whitney test was used. To present the results, the median, interquartile range (Lower - lower quartile, Upper - upper quartile) and sample size (min - minimum, max - maximum value) were used. To establish functional relationships between the parameters, the Spearman correlation coefficient R was calculated, with statistical significance at $p < 0.05$.

Results. The dynamics of the levels of pulmonary tissue destruction factors was studied in patients with TB in the course of treatment with standard chemotherapy regimens.

According to sputum microscopy data, bacterial excretion at the beginning of treatment was observed in 85.7 ± 3.8% of cases in Group I and in 100% of Group 2; after 2 months of treatment, bacterial excretion was observed in 40.5 ± 5.4% of cases in Group 1 and in 17.5 ± 6% of cases in Group 2 ($p < 0.05$); at the 3rd month of treatment, bacterial excretion was observed in 11.9 ± 3.5% of cases in Group 1, while in group II sputum smear conversion was recorded in 100% of cases, which was accompanied by 100% positive x-ray dynamics in the form of partial resorption of infiltrations and reduction of destructions, whereas in Group 1, positive radiological dynamics was observed in 60.7% of cases only.

The difference in the dynamics of indicators of tissue destruction factors, A and collagen metabolism products in patients in Groups 1 and 2 was analyzed.

It was found that within 3 months of treatment, the level of FH in Group 1 was significantly higher than in Group 2 (by 11.3%, 6.7%, 10.2%, respectively, at the beginning of treatment, after

2 and 3 months of treatment (p <0.05 for all cases)).

The level of PBH was higher in Group 2, and it significantly increased in Group 1 by 8.9% during treatment, in contrast to the dynamics in Group 2, where we observed a significant decrease in its level by 53.2% (p <0.05).

The initial level of TIMP-1 was higher in Group I, and it increased within 3 months of treatment in both groups. The intensity of TIMP-1 level increase in Group 2 was significantly higher (by 39.2%) compared with an increase (by 27.4%) in Group 1 (p <0.05)).

The initial level of A in Group 1 was lower by 6.5% (p <0.05). During treatment, there was a decrease in its level in both groups: in Group 1 by 34.3% and in Group 2 by 59.6% (p <0.05). The intensity of the decrease in the level of aldosterone was significantly more pronounced in Group 2 (by 34.5%, (p <0.05)).

The initial levels of MMP-9 and its dynamics during treatment in the groups did not have a significant difference. There was a trend of an increase in the level of MMP-9 in both groups.

To assess the balance of the processes of destruction and repair of tissues, the ratio of MMP-9 / TIMP-1 was applied, which approaches 1 in the absence of pathology. In both study groups, this parameter was increased to 2.7 and 2.9 in groups 1 and 2 respectively, indicating an active inflammatory process with a predominance of destruction. In the course of treatment, a more intensive dynamics of ratio decrease was observed in Group 2 with a significant decrease by 25% in contrast to 16.6% in Group 1 (p <0.05). Also, a higher ratio of MMP-9 / TIMP-1 in patients from Group 1 in the third month of treatment was observed in the absence of sputum conversion in 11.9 ± 3.5% of cases.

As is known, the production of MMP-9 stimulates macrophages activated by the Mycobacterium tuberculosis (MTB). This is confirmed by the correlation links in Group 1 (between MMP-9 and monocytes (r = 0.56, p = 0.003), TIMP-1 and monocytes (r = 0.89, p = 0.00001) and FH and monocytes (r = 0.82, p = 0.00001)), and correlations in Group 2 (between MMP-9 and monocytes (r = 0.65, p = 0.001), TIMP-1 and monocytes (r = 0, 74, p = 0.00005), FH and monocytes (r = 0.92, p = 0.00001) and PBH and monocytes (r = 0.82, p = 0.00001).

An increase in the level of TIMP-1 was accompanied by an increase in the level of MMP-9 in dynamics during treatment. This is indicated by the correlation relationships between them at the 2nd month of treatment in Group 1 (r = 0.79, p = 0.00001) and at the 3rd month of treatment in Group 1 (r = 0.8, p = 0, 00001) and in Group 2 (r = 0.64, p = 0.005).

High levels of FH in Group 1 are associated with higher activity of MMP-9 in this group and are confirmed by the dynamics of these parameters and correlations in Group 1 obtained during the 2nd month of treatment (r = 0.37, p = 0.00005). In Group 2, the increase in the level of FH on the 2nd month of treatment was associated with an increase in the level of MMP-9 (r = 0.8, p = 0.00001).

The decrease in the level of PBH in Group 2 is accompanied by a decrease in the induction of collagen by aldosterone, as indicated by direct correlations that appeared at the 2nd month of treatment (r = 0.33, p = 0.043) and intensified at the 3rd month of treatment (r = 0, 55, p = 0.0001).

Discussion. The obtained dynamics of tissue destruction markers indicates a more favorable effect of the 1st line drugs compared with the 2nd line drugs on the reparation processes.

The decrease in the level of FH in both groups on the 3rd month of treatment is associated with the subsequent activation of TIMP-1, but in Group 2 this dynamics is more pronounced, which indicates inhibition of destructive processes.

The decrease in the level of PBH in Group 2 is accompanied by a decrease in the induction of collagen by aldosterone. In Group 1, the slower dynamics of A decrease and the increase in MMP-9 reflect the preservation of high activity of the processes of fibrosis and the formation of fibrotic changes, as indicated by an increase in the level of PBH and a slower X-ray dynamics.

Thus, under the influence of 1st line drugs, on the 3rd month of treatment, there was a decrease in the activity of the macrophage system on the background of sputum conversion and a decrease in the levels of MMP-9, PBH and A, which indicates the suppression of destruction processes on the background of low fibrotic activity.

Under the influence of treatment with second-line drugs, at the 3rd month of treatment,

fibrosing activity was higher in Group 1 than in Group 2, which was accompanied by a decrease in PBH and a decrease in FH level, which indicates inhibition of destructive changes. Slow sputum smear conversion in Group 1 during the treatment with second-line drugs was accompanied by a slower decrease in the ratio MMP-9 / TIMP-1. Moreover, the decrease of the ratio MMP-9 / TIMP-1 in the 2nd month of treatment is associated with an increase in the level of TIMP-1, and in the 3rd month it is associated with a further increase in the level of MMP-9, that is, the activity of the destruction processes remains significantly high. A less pronounced decrease in A level and growth of TIMP-1 promotes active fibrosis formation in Group 2. That is, during treatment with 1st-line drugs, there was less activity of fibrosing processes, which reduces the amount of residual changes.

Obtained data reflect an important role of free hydroxyproline, protein-bound hydroxyproline and aldosterone as well as the role of the matrix-metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 in regulation of fibrotic and reparation processes in pulmonary tissue. It means that these markers can predict the processes of destruction healing in pulmonary tissue.

Comparison of these parameters in patients treated with first- and second-line drugs showed less activity of destruction and less subsequent fibrotic changes in patients treated with first-line drugs, compared with patients treated with second-line drugs.

Conclusions

Under the influence of 1st line drugs, on the 3rd month of treatment, there was a decrease in the activity of the macrophage system on the background of sputum conversion and a decrease in the level of MMP-9, PBH and A, which indicates the suppression of destruction processes on the background of low fibrotic activity. Under the influence of treatment with second-line drugs, at the 3rd month of treatment, the activity of fibrosis was higher and was accompanied by an increase in the level of PBH and a decrease in the level of FH. Slow sputum conversion during therapy with second-line drugs was accompanied by a slowdown (8.2%) in a decrease of MMP-9 / TIMP-1 ratio due to the further increase in the level of MMP-9 and a significantly high activity of the destruction processes. That is, against the background of treatment with 1st line drugs, there was less activity of the processes of fibrosis, which reduces the amount of residual changes.

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DDC-UDC 616.31+615.212+572.77 DOI:10.19221/201926

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CORRELATION OF THE STATE OF THE ORAL CAVITY MUCOUS MEMBRANE AND THE DYNAMICS OF THE ANALGESIA-NOCICEPTION INDEX IN PATIENTS UNDER THE CONDITIONS OF THE DENTITIONS CORRECTION

Abstract. *The article represents the results of the study of the correlation of the state of the oral cavity mucous membrane (SOCMM) and the dynamics of the analgesic-nociception index (ANI) with the use of ANI-Monitor in patients in the dentition correction conditions. It was determined that the SOCMM state correlates with the data of the analgesia/nociception index. Indicator can be used as a predictor of dental pain, which allows to assess the probability of pain sensations formation in the preclinical stages of the development of trophic changes in the conditions of dentition correction.*
Keywords: *index of analgesia/nociception, heart rate variability, correction of dentitions, oral mucous membrane, physiological adaptation to dentures.*

Introduction. Physiological adaptation of patients to partial or complete loss of dentition and their correction remains topical for the physiology of the maxillofacial area. The prosthesis is an irritant that causes excitation in the cerebral cortex. The duration of habituation is influenced by the dental status and the degree of nociception. There are the following phases of adaptation to dentures: 1st – irritation, 2nd – partial brake action, 3rd – complete brake action [3]. Qualitative analgesia can significantly affect the course of these phases. It should be noted that dentures have an effect on the tissues of the prosthetic bed (are in direct contact with the prosthesis). For removable dentures, the tissues of exposure are the mucous membrane of the alveolar process, hard palate.

Material and methods of the study. To achieve the aim, there were examined 85 patients aged 25-80 years without concomitant pathology, who were divided into the following groups: 1st (n=11) – with intact dentitions (control group); 2nd – with the partial loss of teeth: 2nd-a (n=9) – without correction of dentitions, 2nd-b (n=12) – with the correction of dental bridges, 2nd-c (n=10) – with the correction of partial removable laminar prostheses (primary prosthetics), 2nd-d (n=11) – with the correction of partial removable laminar dentures (re- prosthetics), 3rd (n=12) – with the complete loss of dentitions: 3rd-a (n=5) – without correction of dentitions, 3rd-b (n=13) – with the correction using complete removable laminar dentures (primary prosthetics), 3rd-c (n=14) – with the correction using complete removable laminar dentures (re- prosthetics). Defect of dentition was classified according to Kennedy [2]. The condition of the mucous membrane of the oral cavity in patients of the 3rd experimental group was characterized according to Suple classification for the toothless jaws [4]. Examination of the patients was performed in a stationary dentist's office in the first half of the day using a standard set of dental instruments. To characterize the dental status, the index of caries intensity in constant bite was used. The evaluation of the condition of periodontal tissues was performed on the basis of clinical data, Schiller-Pisarev's test, periodontal indices: papillary-marginal-alveolar (PMA) and CPI index. To evaluate the gum inflammation, a simplified OHI-S oral cavity hygiene index and Sillness-Loe gingival index (GI) were determined [1]. Patients with dental correction were tested on the day of dentures' fixation, as well as during the 7th, 14th and 30th day after the dentures' correction. The assessment of the balance of nociception/anti-nociception was performed using ANI-Monitor apparatus (MetroDolores, France) with the calculation of the original index of analgesia/nociception ANI (Analgesia Nociception Index) [5]. Digital data is statistically processed using Microsoft Exel and Statistica 5.5 computer software.

Results of the research and their discussion. In the structure of the morbidity of periodontal tissues in the younger age gingivitis predominated, in some cases the generalized periodontitis of varying degrees of severity. With age, periodontosis was often found. In patients who use dentures, signs of injury of the mucous membrane of the prosthetic bed were observed. Such examined persons complained of chewing and tactile discomfort, frequent damage of the mucous membrane of the oral cavity (SOCMM). In some cases, allergic reactions that were manifested by hyperemia, edema, hemorrhage, paresthesia of SOCMM and tongue have been determined.

As a result of the study according to the Kennedy dentitions defects classification, the 3rd class dominated in patients of the 2nd-a group, the 3rd and 4th classes dominated in the 2nd-b group, 1st and 2nd classes dominated in the 2nd-c and 2nd-d groups. In general, the differences of defects in dentitions, mainly, depended on age. The effect of the prosthesis on the SOCMM (3rd experimental group) depended on the age, gender, state of the masticatory apparatus, the patient's occupational activity and physical status. The 1st class of the SOCMM according to Suple prevailed in persons under 50 years of age, in the persons from the age of 50 to 70 years – it was the 2nd one, at the age of 70 and older – the 3rd and 4th classes alternated. In patients with the 1st class of SOCMM, a well-characterized alveolar process and alveolar part were observed, that were coated with a slightly moving mucous membrane. Hard palate was covered with a uniform layer of mucous membrane that is moderately mobile in its posterior tertiary part. Anatomical folds of the mucous membrane on both jaws are located at a distance from the apex of the alveolar process. In such patients, favorable conditions for orthopedic treatment of complete absence of teeth are created in the oral cavity. In patients with 2nd class, the mucous membrane was atrophied and with a thin tensed layer covered the alveolar process or part, the hard palate. The places of folds' fastening were placed somewhat closer to the top of the alveolar process. Patients with a 3rd class the alveolar process or its part and the back third of the hard palate were covered with a loose mucous membrane. This condition of SOCMM was often detected in the case of atrophy of the alveolar process. In the examined patients of the 4th class, the alveolar process and the alveolar part were covered with moving mucous membranes teniae that were placed along and easily displaced during insignificant loads. The teniae were found more often on the lower jaw in the complete atrophy of the alveolar part. It should be noted that the teniae could be clamped and then the use of prosthetics becomes impossible. It is therefore of interest to early detect the changes of SOCMM in order to prevent its structural disorders.

It is known that the autonomic nervous system (ANS) is sensitive to homeostasis disorders. Attention is drawn to the study of the ANS reaction to the nociceptive signaling. The sympathetic-vagal balance adequately reflects the registering the heart rate variability (HRV). In recent years, an express method has been offered based on the analysis of purely parasympathetic tone using the ANI-Monitor apparatus [5]. On the basis of the indicated data, using the mathematical calculations, the ANI index, displayed on the device screen, is calculated. The analysis process takes a few seconds and gives an objective assessment of pain sensations in real time. The advantage of this technique is in the simplified method for registering and analyzing the respiratory patterns of HRV, which prompted us to try to apply it in dentistry.

The analysis of ANI data in the examined persons reflects mainly the state of comfort in patients of the control group. Its values significantly increase (at 23-56%, $p<0.05$) in the case of trophic disorders. The data of index are important in terms of dentition correction in dynamics. Thus, at the time of dentures' fixation, the index acquired maximum values. The day after the fixation of the prosthesis, the ANI values decreased in patients of the 2nd-b subgroup at 5-8% ($p<0.05$), 2nd-c subgroup – at 11-18% ($p<0.05$), 2nd-d – at 9-13% ($p<0.05$), 3rd-b – at 18-22% ($p<0.05$) and 3rd-c – at 9-11% ($p<0.05$) relative to the original values. During the 7th day after the dentures' fixation in the examined patients of the 2nd-b subgroup, the ANI data were not significantly different from the control. In patients of the 2nd-b and 2nd-c the index decreased at 7 and 5%, respectively ($p<0.05$), 3rd-b and 3rd-c – at 10 and 5% ($p<0.05$), respectively, regarding the data during the 2nd day. This index achieved the baseline level in these groups only during the 30th day after the prosthetics, which may reflect the complete adaptation of patients (in particular, SOCMM) to dentures. The rather high values of the ANI were an indication for a better correction

of the prosthesis and its fitting to the prosthetic bed.

Conclusion. The state of the SOCMM correlates with the data of the analgesia/nociception index. Index could be used as a predictor of dental pain, which allows us to assess the likelihood of pain sensation formation in the dentitions correction. The data of the autonomous regulation balance allow us to more broadly assess the condition of the mucous membrane, including pre-clinical stages of the development of the atrophic processes in the tissues of the prosthetic bed. Using an ANI-monitor in dentistry will prevent possible negative reactions of SOCMM on the removable dentures, and may also be effective in the planning of the stages of orthopedic rehabilitation.

Prospects for further research. To evaluate and compare the data of the analgesia/nociception index with patients' self-assessment of pain, to determine the specificity and sensitivity of the index in patients with different types of higher nervous activity and the efficacy of its use in certain dental pathologies.

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DDC-UDC 611.087.1:572.512]-055.62:618.3-008.9-092.9 DOI:10.19221/201927

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DYNAMICS OF THE MASS-GROWTH INDEXES OF RATS, GOT FROM MOTHERS WITH EXPERIMENTAL METABOLIC SYNDROME

Abstract. *According to experts, about 1,5 billion inhabitants of our planet are overweight, and about 300 million are suffering from obesity. But a particular concern is the increase in the prevalence of obesity among children, which is doubling every three decades. Therefore, the purpose of our work is to determine the dynamics of mass-growth rates of rats received from mothers with an experimental metabolic syndrome depending on the dietary ration. For this purpose, 120 white laboratory rats on the 1st, 7th, 14th, 21st, 30th, 60th, 90th and 120th days of postnatal life were examined. It was found that rats receiving high-calorie diet throughout the experiment had a significantly higher body mass compared to control. Taking into account this, conclusions were drawn about the influence of dietary foods on body weight.*

Key words: *rat, metabolic syndrome, body weight, body mass index, Lee index.*

Introduction. Today, there is no doubt that the roots of metabolic disorders are in child's and juvenile age [1,2]. The rapid increase of the distribution of the obesity, especially in developed countries, leads to a substantial increase of amont of children and teenagers that have signs of metabolic violations [3]. Given the data, that specify about the presence of metabolic syndrome (MS) in overweight and obese children [4,5,6,7]. The risk of developing MS with the surplus body weight is about 20%, then at obesity this index exceeds 50%.

23,8 % boys and 22,6% girls have excessive body weight in the developed countries [8]. According to WHO, the number of patients with MS in the world ranges from 14% to 24%, in Europe - approximately 40-60 million person. Therefore, in opinion of WHO experts, MS is a new pandemic of the XXI century, which is becoming a scale of demographic catastrophe for developed countries. Consider, that MC in two times is anymore widespread, than diabetes mellitus [9].

As obesity during pregnancy is the substantial factor of development of metabolic violations for descendants in adult age, this problem acquires a large value. Despite the high significance of the metabolic syndrome, as a pathogenetic basis for the development of a number of diseases, the dynamics of mass-growth rates occurring in the offspring, depending on the conditions of their feeding in the postnatal period, is not sufficiently studied.

Objective: to determine the dynamics of the mass-growth indices of rats obtained from mothers with an experimental metabolic syndrome.

Materials and methods: the object of the study is the offspring of 120 white laboratory rats at the 1st, 7th, 14th, 21th, 30th, 60th, 90th and 120th days of postnatal life. The animals were retained in the conditions of vivarium. During work with animals followed requirements and recommendations of the European Union Directive 2010/10/63 EU on experiments on laboratory animals, the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1961). The rats offspring were divided into 3 groups: I - the experimental group MS_1: rats were obtained from females with a simulated metabolic syndrome, these animals after a birth received a high-calorie diet until the 120th day inclusive. II group - an experimental group of MS_2: rats were obtained from females with a simulated metabolic syndrome, who received a standard diet after birth. III group is a control group of rats - with a standard diet and water regime ad libitum. Since the time from birth to the 21st day of the postnatal life in rats is a period of breastfeeding, therefore the division of the experimental groups MS_1 and MS_2 began from the 30th day of observation.

Morphometric parameters were determined

in rats: mass and body length were measured (naso-anal length). Based on the data obtained, mass-growth rates were calculated, namely: body mass index (BMI) is the ratio of body weight (g) to a square of body length (cm^2) and the Lee Index (the ratio of the cubic root mass in grams to body length in centimeters). The results of the study were statistically processed using Student's test. The compared results considered such, that for certain differ at $p<0,05$.

Results. In the newborn rats of the control group, the body weight was 5365,42 ± 227,54 mg, BMI was 0,45 ± 0,02, and the Lee index was 0,5 ± 0,01, respectively (table 1). The body weight of the offspring of the experimental group on the 1st day of life was statistically significantly higher (6278,84 ± 318,32 mg) compared to the control. As for mass-growth indicators, their values were also higher (BMI 0,55 ± 0,02 and Lee index – 0,55 ± 0,01 respectively).

At the 7th day of postnatal life of offspring of control animals, body mass index increases compared to the previous observation period and is 8545,48 ± 365,74 mg. In animals, obtained from females with metabolic syndrome, body mass was significantly higher – 11485,23 ± 545,24 mg. Correspondingly, BMI indicators increased (0,65 ± 0,01 in experimental animals and 0,53 ± 0,02 in control animals). The index of Lee index in both study groups did not have significant differences (0,47 ± 0,01 and 0,42 ± 0,01 respectively). The progeny of the control animals at the 14th day of life continues to tend to increase body mass index and mass-growth indices. A similar pattern can be observed in the offspring of animals with a simulated metabolic syndrome, but the above indicators are significantly higher compared to the control group (18785,76 ± 1519,81 mg and 13245,44 ± 1307,45 mg, respectively). BMI in the offspring of experimental animals is statistically significantly higher than in the control group – 0,56 ± 0,02 vs. 0,43 ± 0,01. As for the Lee index, there was no significant difference between the studied groups.

In the offspring of animals in the experimental group, for the 21st day of observation, the body mass is 32348,26 ± 3174,26 mg, while in animals of the control group, the similar indicator is significantly lower - 21856,61 ± 2348,85 mg. BMI growth in both groups was observed, but in the offspring of animals derived from females with metabolic syndrome, BMI rates were significantly higher in comparison with control animals (0,62 ± 0,02 and 0,53 ± 0,01 respectively).

At the end of the first month of life, animals move to self-catering. Therefore, the experimental animals were divided into two groups: the first group (hereinafter MS_1) - animals, starting from the 21st day of life, received a high-calorie diet until the 120th day inclusive. Animals of the second group (hereinafter - MS_2), in the similar terms received a standard diet.

At the 30th day of postnatal life in the offspring of control animals, the body mass index was 29785,64 ± 5324,49 mg, and in animals of the experimental group MS_2 34865,43 ± 5271,32 mg (table 2). The offspring of animals that received a high calorie diet showed a significantly higher body mass index than control ones 44756,73 ± 6028,49 mg. Similar changes are observed in BMI in all studied groups of animals. Regarding changes in the Lee index, there were no significant differences between the values of the control group and the MC_2 group.

At the end of the second month of life in the offspring of control animals, an increase in body

Table 1

Comparative characteristics of mass-growth indices of offspring of rats from the 1st to the 21st day of life, (M ± m); * - the results are considered to be valid at p <0,05.

Day of life	Experiment	Body weight, mg	BMI	Lee Index
1	Control	5365,42 ± 327,54	0,45 ± 0,02	0,5 ± 0,01
	Metabolic syndrome	6278,84 ± 418,32*	0,55 ± 0,02*	0,55 ± 0,01*
7	Control	8545,48 ± 365,74	0,53 ± 0,02	0,42 ± 0,01
	Metabolic syndrome	11485,23 ± 545,24*	0,65 ± 0,01*	0,47 ± 0,01*
14	Control	13245,44 ± 1307,45	0,43 ± 0,01	0,42 ± 0,01
	Metabolic syndrome	18785,76 ± 1519,81*	0,56 ± 0,02*	0,47 ± 0,01*
21	Control	21856,61 ± 2348,85	0,53 ± 0,01	0,44 ± 0,01
	Metabolic syndrome	32348,26 ± 3174,26*	0,62 ± 0,02*	0,49 ± 0,01*

Table 2

Comparative characteristics of mass-growth indices in rats from the 30th to the 120th day of life, (M ± m); * - the results are considered to be valid at p <0,05.

Day of life	Experiment	Body weight, mg	BMI	Lee Index
30	Control	29785,64 ± 5324,49	0,44 ± 0,01	0,38 ± 0,01
	Metabolic syndrome, group 1	44756,73 ± 6028,49*	0,6 ± 0,01*	0,41 ± 0,01*
	Metabolic syndrome, group 2	34865,43 ± 5271,32	0,52 ± 0,01*	0,39 ± 0,01
60	Control	65385,64 ± 7465,26	0,58 ± 0,01	0,38 ± 0,01
	Metabolic syndrome, group 1	87915,43 ± 9468,64*	0,8 ± 0,02*	0,42 ± 0,01*
	Metabolic syndrome, group 2	72164,41 ± 8665,23	0,65 ± 0,01*	0,39 ± 0,01
90	Control	104586,23 ± 14346,34	0,64 ± 0,01	0,37 ± 0,01
	Metabolic syndrome, group 1	129865,52 ± 12648,37*	0,82 ± 0,02*	0,4 ± 0,01*
	Metabolic syndrome, group 2	108465,26 ± 9796,65	0,67 ± 0,01	0,38 ± 0,01
120	Control	157625,48 ± 20486,15	0,74 ± 0,01	0,37 ± 0,01
	Metabolic syndrome, group 1	185563,48 ± 21456,96*	0,87 ± 0,02*	0,4 ± 0,01*
	Metabolic syndrome, group 2	160456,35 ± 15018,73	0,75 ± 0,01	0,37 ± 0,01

mass index is observed to 65385,64 ± 7465,26 mg, respectively. In the group of experimental animals with a standard diet, the body weight reached 72164,41 ± 8665,23 mg. Animals of the MS_1 group exhibited a statistically significantly higher body weight than control animals (87915,43 ± 9468,64 respectively).

During the third and fourth months of life in the control animals, the tendency to increase body weight with an increase in the observation period persists. At the 120th day of life, the weight of the body of control animals is 157625,48 ± 20486,15 mg, the mass-growth rates also increase (BMI is 0,74 ± 0,01, Lee index – 0,37 ± 0,01). Regarding the dynamics of body mass of animals receiving high-calorie diet, the changes of the above indicators are more pronounced (185563,48 ± 21456,96 mg, 0,87 ± 0,02 and 0,4 ± 0,01 respectively). In the offspring of experimental animals of the MS_2 group, at the end of the observation period, the mass-growth indices are leveled and not significantly different from the values of the control group.

Discussion of the results. So, from the moment of birth up to the 120th day, including in the offspring of animals of all the studied groups, there was a gradual increase in body weight with an increase in the observation period. However, in the offspring of experimental animals that received a high calorie diet from the 21st day of life, significantly higher body mass indexes were observed until the end of the observation period compared to control animals (185563,48 ± 21456,96 and 157625,48 ± 20486,15 in accordance). A similar trend can be traced in the dynamics of mass-growth indicators. The revealed changes are confirmed by clinical data on cases of fetal macrosomia and organomegaly born from women with gestational diabetes and obesity. Gestational diabetes is also a risk factor for the development of kidney abnormalities [10,11].

In the offspring of animals that received a standard diet from the 21st day of life, there was also a gradual, statistically significant increase in body weight from birth during four months of life compared to control posterity. However, at the end of the observation period, body mass index and mass-growth indices are offset and almost do not differ from the control group.

The determination of obesity throughout the experiment was carried out using the Lee index for each rat [12]. BMI was used as an integral indicator for monitoring the reproduction of alimentary obesity. In experimental groups, both indicators were significantly higher in the period from the 30th to the 120th day of life compared with the control group. However, while comparing the BMI of the Lee index between the two experimental groups, the changes were more pronounced in the rats receiving a high-calorie diet.

Conclusions. 1. In the offspring of rats from the 1st to 21st day of observation, there was a significant increase in body weight compared to the control group (MS: 32348,26 ± 3174,26 and

control group: 21856,61 ± 2348,85).

2. Starting from the 30th day of life until the 120th day, in the offspring of experimental animals receiving a high calorie diet, a statistically significant increase in body mass index was observed (MS_1: 185563,48 ± 21456,96 and control group: 157625,48 ± 20486,15).

3. In animals that received a standard diet from the 21st day of life, body weight was significantly higher than the control, but at the end of the observation period, the mass-growth rates in animals in this group are leveled.

4. Taking into account the dynamics of BMI and Lee index throughout the experiment, when comparing experimental and control rats, it can be argued that the diet has a significant effect on the dynamics of these mass-growth rates.

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DDC-UDC 616.12-005.2:616.155.194]-036.1-071 DOI:10.19221/201928

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ERYTHROCYTE AT COMORBID COURSE OF CHRONIC HEART FAILURE AND ANEMIA: POSSIBILITIES OF LASER POLARIMETRY

Abstract *The article deals with the possibility of application of the methods of correlation optics and laser polarimetry for objectification of the structural changes of the erythrocyte membranes at combined course of chronic heart failure, diabetes mellitus type 2 and anemia. In patients with chronic heart failure and diabetes mellitus type 2 increasing of the anisotropic component of erythrocyte membranes was detected, which indicated conformational changes of proteins of the erythrocyte membrane structures as a result of chronic hyperglycemia. More expressed such transformations are observed during the investigation of probability and coordinate distribution of the intensity of the Fourier spectrum of laser image of the erythrocyte suspension layers at complication of the underlying disease by anemia of different degrees of severity, which serves as the basis of heterogeneity of the erythrocyte membranes structure. Quantitatively such transformation of the Fourier spectrum, caused by the change in optical anisotropy of the erythrocytes, are illustrated by the ranges of set of the statistical moments, which objectively characterize the structure of the changes of the corresponding histogram intensity. Correlation analysis revealed statistically significant direct relationship between the level of basal glycemia and the degree of anisotropy of the suspension of erythrocytes in the investigated patients, whereas the level of hemoglobin was negatively associated with the values of asymmetry and access.*

Keywords: *chronic heart failure, diabetes mellitus type 2, anemia, laser polarimetry, Fourier spectrum, erythrocyte, biological tissue.*

Introduction. Laser radiation during interaction with biological tissue (BT) can be absorbed and dissipated. Each of these processes has some information on micro- and macrostructure of the biological environment [3, 6]. Nowadays the development of the relevant methods of research of the scattered radiation by the optically active biological structures is of great topicality for obtaining new information about their structure.

The most common and sufficiently tested are spectrophotometric methods based on the analysis of the spatial changes of the intensity of the field of scattered laser radiation by the optically heterogeneous biological environments. The set of the tools and analytical methods of the polarimetric studies of the morphological structure of BT was called "laser polarimetry" [7].

Intensive development of the vector approach to the investigation of the morphological structure and physiological status of the various BT created a foundation for the development of model representations of their structure. The modeling structure of the BT [8] is based upon the idea that it is a two-component structure that consists of:

✓ optical-anisotropic component – the matrix predominantly formed by the fibrous tissue components (collagen fibers, proteins, fibrin fibers, etc.). This component is able to

change the main parameters of the laser radiation during its passage through the layer of BT;

✓ amorphous component – the components of BT, which has no fibrous structure. The latter is optically neutral, i.e. one that does not change the basic characteristics of the beam of laser radiation while passing through BT.

Such spatial structure of the biological tissue is similar to the "frozen" optically-uniaxial liquid crystals.

The possibility of usage of the laser polarimetry methods for objective assessment of the erythrocytes' membranes is caused by the presence in their architecture the significant part of the specific protein structures, which, in its turn, are anisotropic from the optical point of view, that is, they are able to change the properties of the laser radiation during its passage through BT. Protein components of the erythrocyte membrane, unlike lipid, have the clear complicated hierarchical structure due to their complex level of organization. It is known that spectrin has penta- or hexagonal structure [1], which is formed by the tetramers of its molecules, that are linked to short actin microfilaments on the both ends [5]. The last acts as the connecting elements for the formation of a hexagonal mesh. The spectrin cytoskeleton of the erythrocyte maintains the definite form of the cell, therefore structural change in the ordering of the molecules can serve as a prerequisite change of the morphological structure of the erythrocyte membrane and the resulting disorder of its functional properties. Methods of the optical physics reveal and objectify the above-mentioned changes, which to our mind can expand the arsenal of the diagnostic methods of the diagnosis of the morpho-functional characteristics of the membranes of red blood cells due to various pathological conditions.

Aim of the investigation: To investigate the possible structural changes of the erythrocytes membranes in patients with chronic heart failure (CHF), diabetes mellitus (DM) type 2 and anemia of different degrees of severity by means of laser polarimetry methods.

Study design. With the help of the modern instrumental non-invasive methods of investigation a comprehensive survey of 120 patients with CHF, DM type 2 and anemia, who were hospitalized to the cardiological department of the Chernivtsi Regional Hospital for War Veterans, was conducted. The average age was 76,04±1,84 years. All examined patients according to their comorbidities were randomized into the following subgroups: I – CHF patients with comorbid DM type 2 (n=12), II – patients with CHF with comorbid anemia of different degrees of severity (n=32), III – patients with CHF, complicated by comorbid anemia and DM type 2 (n=76). The control group for comparative studies comprised 12 patients with CHF without comorbid anemic syndrome (AS) and DM type 2, whose age was not statistically significantly different from the average age of the patients of the experimental groups.

Patients of the IInd experimental group had the following distribution depending on the severity of AS: IIA subgroup – the patients with CHF with mild anemia (hemoglobin more than 91 g/L) – 16,66% of all examined patients of the experimental group) IIB subgroup – the patients with CHF with comorbid moderate anemia (hemoglobin – 71-90 g/L) – 10,00% correspondently. The patients of the III experimental group were also randomized into subgroups due to the level of hemoglobin: IIIA – 38 patients (31,67%) with CHF, DM type 2 and mild AS, IIIB – the patients with CHF, DM type 2 and moderate AS – 38 individuals (31,67%).

For the objective assessment of the functional state of erythrocytes membrane laser polarimetry of the red cell suspension smear was applied. Scheme of the optical laser polarimeter is presented on Fig. 1. Irradiation was conducted by the beam (Ø=104 mkm) of the He-Ne laser (1) with a wavelength λ=0,6328 mm. With the help of the polarizing film (quarter-wave plate and polarizer) different states of polarization of the illuminating beam were formed. Polarization images of the layers of the erythrocyte suspension (6) were formed in the plane of the light-sensitive pad (800x600) of the CCD camera (10) through the object glass (7), the resolution of which was sufficient for the measurements in the size range of structural laser images of the erythrocytes suspension (2-2000 microns).

The investigation of the optical properties of erythrocyte suspension layers was based upon the following methods:

1. Polarization imaging of the optical-anisotropic layer of the blood cells components obtained in the crossed planes of the polarizer and analyzer and statistical analysis of the received laser images.

2. Phase analysis of the polarization rendered laser image by determining the intensity of the coordinate distribution of Fourier spectrum of the red cell suspension layer.

To assess coordinate distributions of random variables their histograms were used; and we calculated set of statistical points of the 1st to the 4th grades (Fig. 2).

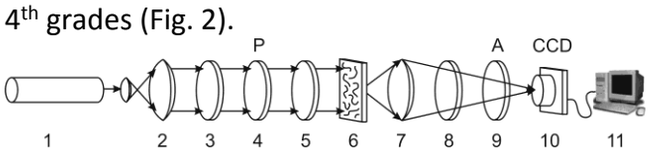

Fig. 1. Optical laser polarimeter

where: 1 – He-Ne laser; 2 – collimator; 3, 5, 8 – quarter-wave plates; 4 – polarizer; 6 – object of investigation; 7 – object glass; 9 – parser; 10 – CCD camera; 11 – personal computer

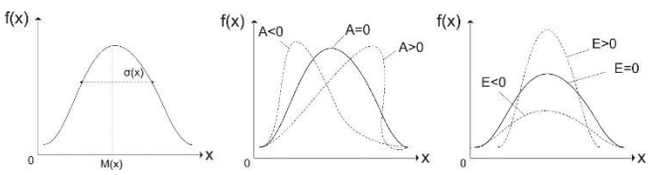

Fig. 2. Statistical points of the 1st – 4th grades (medium, variance, asymmetry, kurtosis)

Results of the investigation. Fig. 3 illustrates the coordinate (1) and probability (2) intensity distributions of Fourier spectrum of the erythrocyte suspension laser image of the patients of control group. Received results show that the intensity distribution of the histogram of Fourier spectrum has symmetrical "bell-like" distribution.

Another picture is observed during analysis of the structure of Fourier spectrum of the erythrocyte suspension laser image of the patients with CHF and DM type 2 (Fig. 4). Apparently the intensity distribution is uneven (fragment 1), and the histogram is transformed into an asymmetric dependence (fragment 2). Revealed fact indicates the growth of the anisotropic component of the red blood cells membrane, conditioned primarily by the conformational changes of the protein structure of erythrocyte membranes compared to the control group. We assume that the above-mentioned changes reflect complex disorders of the peculiarities of the erythrocyte membranes due to chronic hyperglycemia (activation of the peroxic oxidation of the biopolymers and lipids, increased production of reactive oxygen compounds, protein molecules glycolization, and, as a result, change of the conformational and spatial orientation of the protein fibrils, including integrated, of the erythrocyte membrane) [4], accompanied by worsening of the morphological features of the red blood cells membrane.

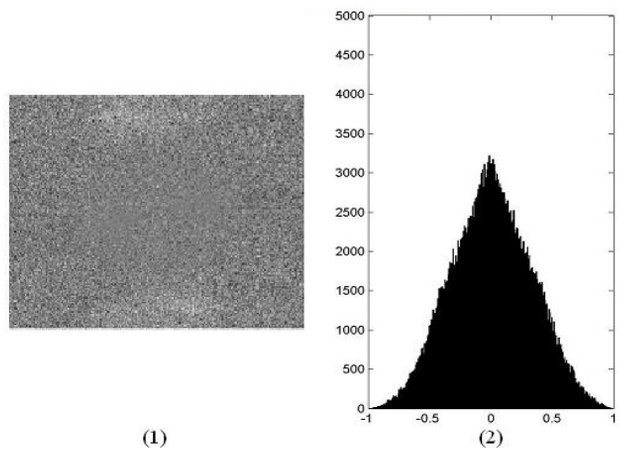

Fig. 3. Fourier-phase investigation of the erythrocyte suspension of the control group

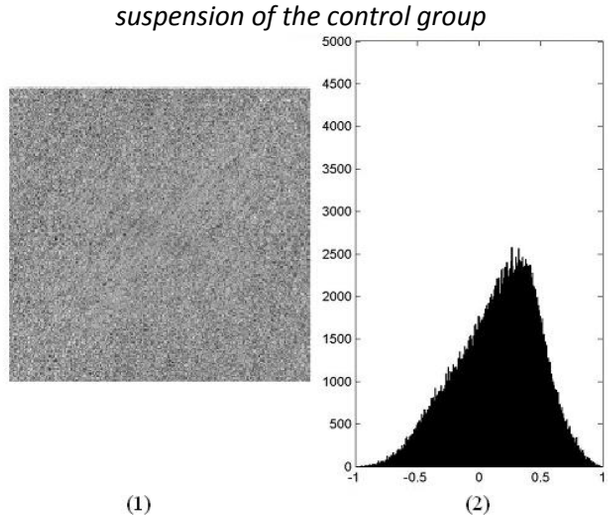

Fig. 4 Fourier-phase investigation of the erythrocyte suspension of the patients with CHF and DM type 2

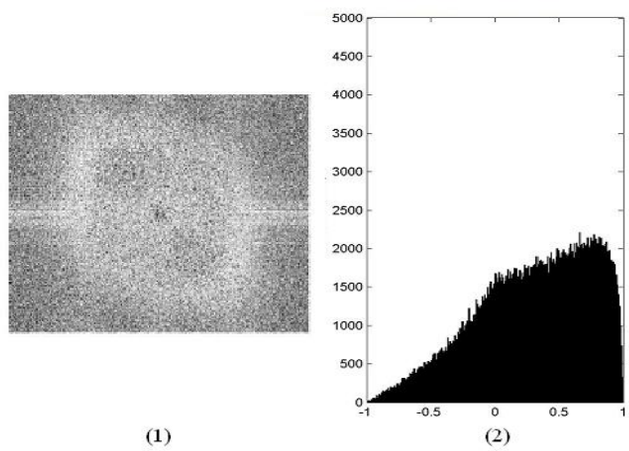

Fig. 5. Fourier-phase investigation of the erythrocyte suspension of the patients with CHF and mild anemia

More clearly such transformations are observed at the investigation of the probability and coordinate distribution of the Fourier spectrum intensity of the red cell suspension laser image of the patients of the other studied groups (Fig.5 – Fig.8). This, in our opinion, serves as the basis of heterogeneity of the erythrocyte membranes structure due to investigated comorbidity.

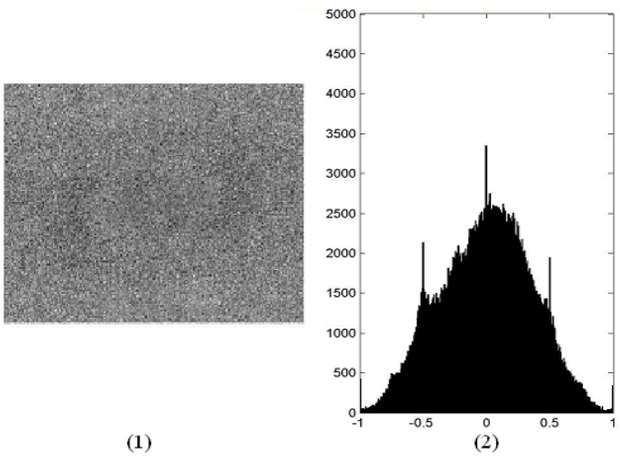

Fig. 6. Fourier-phase investigation of the erythrocyte suspension of the patients with CHF and moderate anemia

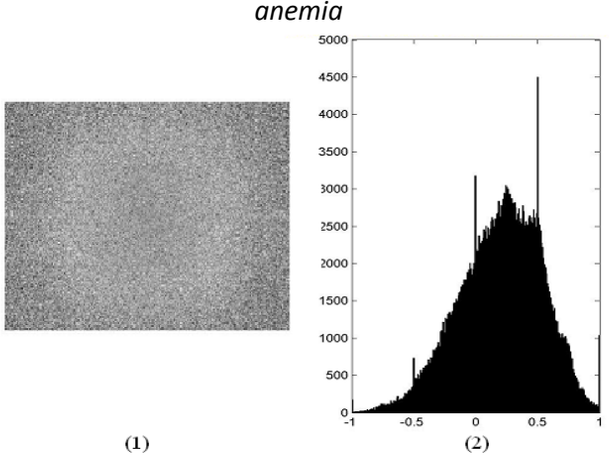

Fig. 7. Fourier-phase investigation of the erythrocyte suspension of the patients with CHF, DM and mild anemia

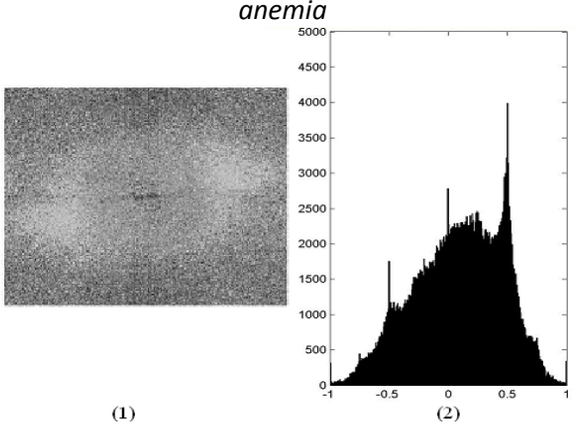

Fig. 8. Fourier-phase investigation of the erythrocyte suspension of the patients with CHF, DM and moderate anemia

The degree of anisotropy remained high in all patients of another research groups. We explained this as a progressive worsening of the morphological and functional properties of the erythrocyte membranes (primarily due to the progression of conformational changes of the protein component structure) due to comorbidity, that can not be objectified by means of traditional metods.

Additional agents that can contribute to the changes of the modification of the proteins of the red blood cells cytoskeleton and lead to the increasing of the degree of red cell suspension anisotropy is ATP and ions of Ca^{2+}, which affect the connections between the erythrocyte cytoskeleton proteins by the phosphorylation of the spectrin molecules [2]. Changes of the conformational structure of the proteins of the red blood cells cytoskeleton lead to the formation of transmembrane defects resulting in the loss of cell metabolites and ions. Destruction of only few connections in the actin-spectrin grid can cause the formation of spicules on the surface of the red blood cell. Oxidative denaturation of the protein components of the red cell membrane makes the erythrocyte sensitive to the impact of the endogenous proteases.

Quantitatively such transformations of Fourier spectrum, caused by the change of the optical anisotropy of the red blood cells, may be illustrated by the values and range changes of the set of statistical moments M; σ; A; E, which objectively characterize the structure of the changes of the corresponding intensity histograms (Table 1). Correlation analysis showed direct relationship between the level of fasting glucose and anisotropy degree of the red blood cells suspension of patients with coronary artery disease, diabetes mellitus type 2 and anemia, while the level of hemoglobin was negatively associated with the values of asymmetry and kurtosis, which, in its turn, characterize the degree of worsening of the morphological and functional properties of red blood cells of patients of this group (Table 2).

Conclusions.

1. All statistical points are sensitive to changes of the morphological and functional properties of red cell suspensions of the patients with chronic heart failure, diabetes mellitus type 2 and anemia

Table 1

Statistical points 1st - 4th degree of the coordinate intensity distribution of Fourier spectrum of the erythrocyte suspension laser image

Statistical point	Control group (n=12)	CAD + DM (n=12)	CAD + mild anemia (n=20)	CAD + moderate anemia (n=12)	CAD + DM + mild anemia (n=38)	CAD + DM + moderate anemia (n=38)
M medium	0,07 ± 0,009	0,11 ± 0,014	0,105 ± 0,012	0,16 ± 0,021	0,19 ± 0,032	0,31 ± 0,018 *¤ §
σ variance	0,16 ± 0,025	0,19 ± 0,024	0,24 ± 0,013	0,27 ± 0,016	0,29 ± 0,045 *	0,35 ± 0,031 * § #
A asymmetry	0,08 ± 0,100	0,63 ± 0,014 ¤	1,84 ± 0,120 * § ¤	2,62 ± 0,381 * § ¤	5,43 ± 0,290 * § #	8,13 ± 0,235 * § # ¤
E kurtosis	0,07 ± 0,016	0,29 ± 0,035	1,79 ± 0,295	6,18 ± 0,820 ¤	15,83 ± 1,980 * § #	27,18 ± 2,110 * § # ¤

*Note: * – difference is valid against control group, p<0,05; § – difference is valid against group CHF+DM, p<0,05; # – difference is valid against group CHF+mild anemia, p<0,05; ¤ – difference is valid against group CHF+DM+mild anemia, p<0,05*

Table 2

The correlation coefficients between the degree of red blood cells anisotropy and some laboratory parameters in patients with chronic heart failure, diabetes mellitus type 2 and anemia

Parameter	*A* asymmetry	*E* kurtosis
Hemoglobin, G/L	-0,63 *	-0,74 *
Fasting glucose, mmol/L	0,57 *	0,69 *

*Note: * – correlation coefficient is statistically valid (p<0,05)*

compared to the patients of the control group.

2. The most sensitive were changes of the statistical points of the 3rd and 4th grade (asymmetry A grew from 8 to 70 times; kurtosis E grew from 2,5 to 100 times)

3. Methods of the laser poliarimetry of the red blood cells smear with the following analysis of the statistical points of the 1st-4th grade might be used for early diagnosis of the structural and functional changes of the erythrocytes in patients with comorbid course of chronic heart failure, diabetes mellitus type 2 and anemic syndrome.

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DDC-UDC 612.172.2:796.012.6:233-852.5]-056.257 DOI:10.19221/201919

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INFLUENCE OF THE REGULAR YOGA PRACTICE ON THE HEART RATE VARIABILITY OF THE OVERWEIGHT INDIVIDUALS

Abstract. *Purpose of the work was to investigate the influence of the regular Yoga practice to the heart rate variability of the persons with overweight. Materials and methods: 32 overweight previously non-yoga practitioners were investigated during 24 weeks since beginning of regular Yoga practice. Main anthropometric, hemodynamic and heart rate variability parameters were analyzed trice (Week 0, 12 and 24), and received data were compared with parameters of 16 normal weight persons. Heart rate variability investigation was provided on the cardiac monitor "Diacard" AO "Solveig" (Ukraine). Results: We found out the significant reduction of the time and spectrum heart rate variability parameters of parasympathetic heart function regulation in overweight subjects before beginning of the regular Yoga practice. Dynamic control discovered progressive positive influence of Yoga to autonomic cardiac regulation with significant growth of parasympathetic activity and normalization of sympathetic/ parasympathetic balance with strong tendency to decreasing of resting heart rate, systolic and diastolic blood pressure, body weight, body mass index and waist circumference. Correlation analyze detected negative dependence between waist circumference and reduction of parasympathetic influence to the heart activity. Conclusions: The regular Yoga practice prominently improves the balance of autonomic regulation because of significant growth of parasympathetic influences and reduction of sympathetic stimulations of the heart function of overweight persons.*
Key words: *Yoga practice, obesity, overweight, heart rate variability.*

Introduction. The overweight and obesity was accepted by WHO as the major public health problem and the global pandemic in 1997 [17]. In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. High body mass index (BMI) accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to BMI were due to cardiovascular disease [5, 10, 16].

Many factors play a role in the relationship between overweight and cardio-vascular diseases (CVD), such as insulin resistance, hypertension, and reduced high-density lipoprotein. However, an imbalance in autonomic regulation of the cardiac function might be the mechanism for the increased prevalence of CVD in obesity [9]. Because the autonomic nervous system controls a significant part of the internal functions of the body, fat disequilibrium in obesity is an important negative factor [14, 18].

Heart rate variability (HRV) is a simple non-invasive instrumental method for the detection and investigation of cardiac autonomic dysfunction in different medical conditions, including obesity [3]. Low HRV is an established predictor of CV morbidity and mortality [11, 13].

Major health organizations, such as the International Association for the Study of Obesity (IASO) and the American College of Sports Medicine (ACSM), consistently support the need for more than 150–250 min/week of moderate-intensity physical activity to prevent weight gain. However, there is currently a lack of guidance for obese individuals on feasible strategies for weight loss and prevention of weight regain [12]. Yoga is an ancient system of practices based on the scientific principles of exercise, breathing and meditation, and philosophical beliefs concerning

life and thinking. The origin of yoga has been ascribed to the Indus Valley Civilization (2600-1900 BCE) although some researchers suggest more ancient origins. Participation in yoga has increased dramatically throughout the world in recent decades. Many styles of yoga have been tested in the clinical setting and most involve the performance of physical postures (*asanas*), breathing exercises (*pranayama*) and meditation [4, 6].

A growing number of research studies have shown that the practice of Yoga can improve strength and flexibility, and may help control such physiological variables as blood pressure, respiration and heart rate, and metabolic rate to improve overall exercise capacity [7, 8, 15]. Investigations suggest that Yoga practice is effective for decrease of the general stress, awareness on satiety, positive influence for over eating and weight reduction [2].

However, the chronic effects of Yoga training on HRV in obese persons and its correlation with anthropometric characteristics improvement remain inconclusive and need to be investigated.

The purpose of the work was to investigate the influence of the regular Yoga practice to the heart rate variability of the persons with overweight.

Materials and methods. 32 overweight previously non-yoga practitioners were investigated during 24 weeks since beginning of regular Yoga practice. There were 18 female and 14 male persons with BMI >25 kg/m^2 and from 25 to 47 years of age (40,3±2,4 y.o.). All investigated persons have agreed to participate in an experiment. Comparative analyses of HRV parameters was conducted with data of 16 non-obese subjects with the same age/gender characteristics. Informed written consent was taken from all the subjects and they were screened for any history of drugs/alcohol intake, familial history of hypertension and cardiac diseases, or presence of any medical illness likely to affect the HRV parameters based on clinical history and physical examination. Yoga training was conducted three times in a week; every class lasted 90 min and consisted of asanas, pranayama and meditation under the supervision of the experienced Yoga master. HRV investigation was provided trice (beginning of Yoga practice and after 12 and 24 weeks) in comfortable conditions. The blood pressure of each subject was measured in supine position. Analysis of HRV was performed based on 5 min ECG recorded at rest in the supine position. Recordings were taken during 08:00 am – 11:00 am to avoid any hemodynamic effect on HRV on the cardiac monitor “Diacard" AO “Solveig" (Ukraine). HRV analyses and results estimation were based on the classic approach for analysis of variability of heart rate that is recommended by the European society of cardiology and North American society of pacing and electrophysiology [1]. The parameters of autonomic regulation of heart rate and results of spectral analysis were registered; and received data were calculated via support of statistical program «Kubios HRV”. Statistical analysis was performed with Statistical Package for the Social Sciences software for Windows (version 21). Differences in variables were tested using Mann–Whitney U test for the data having nonparametric distribution and Student’s t-test for the data with parametric distribution. The results were presented as mean ± standard deviation (SD). Pearson’s correlation was used to correlate the HRV measures and the obesity indices. Statistical significance was considered to be $p<0.05$.

Results. The anthropometric characteristics of the investigated subjects present in the Table 1. It shows comparable age of overweight and non-overweight subjects with prominent differences in the body weight (BW), BMI and waist circumference (WC) between groups.

The time domain, frequency domain variables of HRV of both the groups were calculated and are presented comparatively in Table 2. Among the time domain measures, SDNN, RMSSD, and pNN50% were calculated. All these time domain variables were significantly less ($p<0.05$) in the overweight group as compared to the normal weight group. Spectral parameters – high-

Table 1

Baseline characteristics of overweight and non-overweight subjects

Characteristic	Control group (n=16)	Total cohort (*n* = 32)	Male (*n* = 14)	Female (*n* = 18)
Age (y)	41,.2±3,5	40,3±2,4	38,2±10,1	42,3±11,4
Body weight (kg)	76,8±6,3	95,5±16,3	89,4±12,2	97,3±14,2
BMI (kg/m^2)	23,4±2,1	30,5±4,2	29,9±5,1	30,9±3,3
Obese (BMI 30+) (n; %)	0; 0%	11; 34%	5; 36%	6; 33%
Waist circumference (cm)	81,3±8,4	94,7±14,7	93,9±14,5	95,3±15,1

frequency component of the spectrum, HF (ms^2), low frequency component of the spectrum – LF (ms^2) also were significantly reduced in overweight subjects. However, the LF/HF ratio as an indicator of the balance of sympathetic and parasympathetic autonomic regulation and one of the indirect sympathetic marker in overweight subjects exceeded the same one from the non-obese persons.

Next HRV investigations on the Week 12 and Week 24 of the regular Yoga practice we conducted to detect possible influence of that exercise complex to the autonomic regulation of the cardiac functions. Received data are presented in the Table 3 and suggest significant (p<0.05) growth of the main time and spectrum characteristics of HRV in overweight persons during continuous Yoga practice.

Dynamic investigation of the resting heart rate (RHR), systolic (SBP) and diastolic blood pressure (DBP), BW and BMI (Table 4) revealed tendency of the positive influence of the regular Yoga training to investigated characteristics of overweight persons. We concluded that all investigated parameters progressively decreased partially coming into normal ranges in some subjects. BW and BMI normalized in 4 obese (36%) and 6 overweight persons (29%).

Table 2

Comparison of HRV measures between overweight and normal weight groups

Variables	Overweight subjects (n=32)	Control group (n=16
SDNN (ms)	32,4±8,7	44,5±7,6 *
RMSSD (ms)	26,5±4,5	42.7±9,8 *
PNN50%	5,8±1,5	21,6±6,4 *
LF ms^2	252,9 ±28.3	456,7±56,9 *
HF ms^2	165,5±38,7	530,5±112,7 *
LF/HF	1.2±0.95	0.67±0,8 *

*Note: * - p < 0,05, comparing with the control group*

Table 3

Dynamics of HRV characteristics of the overweight subjects during investigation

Variables	**Week 0**	**Week 12**	**Week 24**
SDNN, ms	32,4±2,7	37,5±3,4	41,4±4,7 *
RMSSD, ms	26,5±4,5	32,6±6,3	38,7±5,9 *
pNN50, %	5,8±1,5	12,4±3,5	15,8±5,2 *
LF, ms^2	252,9 ±28.3	354,4±46,8	398,5± 56,8 *
HF, ms^2	195,5±38,7	365,7± 82,7	464,3±91,7 *
LF/HF ratio	1,2±0.95	0.97 ± 0.95	0.86 ± 0.95 *

*Note: * - p < 0,05, comparing between week 0 and week 24*

Table 4

Changes of hemodynamic and anthropometric characteristics during investigation (n=32)

Parameters	**Week 0**	**Week 12**	**Week 24**
Resting heart rate (bpm)	78,3±8,5	73,9±6,3	67,4±9,1
Systolic blood pressure (mmHg)	134,3±5,6	130,5±6,3	126,8±8,1
Diastolic blood pressure (mmHg)	85,7±5,9	82,5±6,7	77,1±5,4
Body weight (kg)	95,5±16,3	93,7±11,5	89,8±9,9
Body mass index (BMI) (kg/m^2)	30,5±4,2	28,8±5,3	26,4±3,7

Correlation indexes were calculated to reveal possible dependence between HRV data and anthropometric and hemodynamic parameters of the investigated subjects. Moderate negative correlation was detected between WC and HF (r=-0,412), WC and RMSSD (r=-0,324), WC and SDNN (r=-0, 432), BMI and DBP (r=-0,375), RHR and SDNN (r=-0,356), RHR and HF (r=-0,432). However, positive correlation was revealed between LF and WC (r=0,441), LF/HF and WC (r=0,318). Other HRV parameters were not significantly correlated with anthropometric and hemodynamic characteristics of the observed individuals.

Discussion. In present work, we investigated influence of the 24-weeks Yoga practice to HRV variables of 32 overweight person. Comparative analyses was conducted with normal-weight subjects comparable in terms of their age and general health characteristics. However, obese persons had significantly higher BW, BMI, and WC than normal weight controls. The resting heart rate was significantly higher in the overweight

subjects in comparing to the normal-weight group, which corresponds to several studies about finding of tachycardia in obese people as risk factor of the CVD [5].

The HRV variables SDNN, RMSSD, pNN50, HF indices that reflect the cardiac parasympathetic nerve activity [13] were significantly lower in overweight than in normal weight persons. Besides that, the sympathetic marker LF/HF ratio significantly exceeded in obese subjects in comparison to normal weight controls. According to studies, obese and overweight persons suffer from an increased mortality risk supposedly due to CVD related to either continuously lowered parasympathetic or heightened sympathetic activation [11, 14].

Moreover, correlation analysis showed that the HRV parasympathetic variables, like SDNN, RMSSD, HF ms^2, were negatively dependent from WC, while RHR had moderate positive relation with LF and LF/HF ratio. Based on absence of any significant dependence between HRV parameters and BMI, we can suggest that WC is the more important predictor of CVD in overweight subjects, which should be carefully controlled and corrected by physical exertions.

Taking for attention, that Yoga practice tends to be very popular all over the world, it was important to analyze it`s positive effects for reduction of the CVD risks including dysregulation of the sympathetic-parasympathetic balance. Although the mechanism by which yoga influences autonomic activity is not well investigated, regular Yoga practice appears to directly stimulate the vagal nerve and enhance parasympathetic output leading to parasympathetic dominance and normalization of the cardiac function, mood, and energy states, as well as stimulation of neuroendocrine, metabolic, cognitive, and immune responses.

Our work shows not only progressive positive anthropometric (reduce of BMI, WC, BW) effects from the regular Yoga training of the overweight persons, but also sufficient hemodynamic (decrease RHR, SBP, DBP) results and significant positive influence to HRV parameters with tendency to normalization of the main time and spectrum variables (SDNN, RMSSD, pNN50, LF, HF, LF/HF ratio). 24 weeks` Yoga practice realized adequate stimulation of the parasympathetic regulation of heart function in overweight subjects leading to reduction of cardio-vascular risks. During the period of supervision, BMI, WC, BW and HRV variables had strong tendency to normalization, but did not fully came into normal ranges. According to that, continuation of regular Yoga training is strongly recommended for this category of persons.

Conclusions. Time (SDNN, RMSSD, pNN50) and spectrum (HF, LF/HF ratio) HRV parameters of parasympathetic part of cardiac function regulation in overweight persons were significantly ($p<0,05$) reduced in comparing with normal-weight subjects, suggesting about complex negative influence of obesity as a predictor of cardiac problems. Negative moderate correlation between parasympathetic variables of HRV and WC, also positive moderate correlation between sympathetic spectrum variables (LF, LF/HF) and WC without strong relationship between HRV parameters and BMI recognize the abdominal type of overweight as more important negative factor of vegetative dysregulation.

The regular Yoga practice helps in balancing of autonomic regulation because of significant growth of parasympathetic influences and reduction of sympathetic stimulations of the heart function, which was confirmed by HRV monitoring and dynamic analyzes of hemodynamic parameters (resting heart rate, systolic and diastolic blood pressure) of overweight persons.

Heart rate variability test is a modern, non-invasive adequate method of estimation of the heart function`s autonomic regulation in overweight subjects and may be used not only for evaluation of the predictors of cardiac problems but also as an objective reflection of positive changes of health during physical training.

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DDC-UDC 378.147:001.891-057.87:061.22 DOI:10.19221/2019210

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FORMS OF STUDENT SCIENTIFIC GROUP WORK WITHIN THE SYSTEM OF PROBLEM-BASED LEARNING

Abstract. *In the present article we discuss the role of problem-based learning, namely games in out-of-class student scientific research. The authors analyze means and methods of conducting this type of scientific research within the framework of scientific society of Internal Medicine, Clinical Pharmacology and Occupational Diseases department. Thus students get assistance with broadening their concept of the world, developing skills to apply theoretical knowledge and modern scientific research methods in practical context, which are of great importance for acquiring professional skills and further scientific research of students after University graduation.*
Keywords: *games, problem-based learning, scientific-research work, student scientific society, student.*

World Health Organization defines a modern doctor as a person who helps, makes decisions, communicates, manages and takes into consideration interests and needs of the society. As a future specialist graduating from higher educational establishment has to be highly competitive on the market, the main aim of scientific, scientific-technological and innovative policy of the educational system is to provide training for specialists, scientific and scientific-pedagogical staff to use their educational, scientific and creative potential in full to benefit the economy.

Medical students graduating from University must possess necessary knowledge and be able to acquire new scientific awareness and skills to diagnose. But what is more important to have a logical and quick methodology for finding necessary information, thus, introducing a new and unique “way of functioning”. Due to the doubling of knowledge in the world every 12 months it is no longer useful to simply memorize. Modern speed of life, information flows and scientific integration require constant learning. This process is formed by a doctor himself after he gets necessary skills in college. These skills are based on the idea of competitiveness and changing demands of nowadays. One of the main approaches in teaching-learning process that ensures all skills mentioned above is problem-based learning (PBL) (Beylefeld A. & Struwig M., 2007, p. 933). As any other method it has its pros and cons and is not always appropriate. Self-education, practical skills acquiring, content instead of facts, team work are all advantages that teachers have to use in classrooms. Among disadvantages one should mention greater time span needed, certain level of expertise and motivation required. PBL is much spoken about in scientific papers and methodology works. Today we would like to discuss our experience in problem-based learning within the framework of student scientific research work.

One component of qualitative education formation and professional development of a doctor in all higher educational establishments in Ukraine as well as in medical institutions is scientific research work (SRW) of students. SRW includes systematic participation in research activities, teaching students methodology and methods of research, acquiring necessary skills and technologies, modeling creative approach to solving certain scientific problems (Sirenko Yu.I., 2015, p. 594). In Ukraine students’ SRW is based on a certain legislative basis namely the Law of Ukraine “About Scientific and Scientific-

Technological Activity" (2014) and the Law "About the Higher Education" (2014). SRW includes two tightly connected aspect: 1) teaching elements of research activities, organization and methods of such activities; 2) carrying out research activities by students under the supervision of professors and teachers.

Another subdivision of SRW is based on time of these activities: inclass activities that are incorporated into the teaching-learning process and activities that students carry out outside the classroom. Inclass SRW includes such kinds as a) students' groups and societies functioning within departments; b) participation in scientific-research work within department research areas; c) presentations of reports on scientific conferences in higher educational establishments; d) participation in institutional, interinstitutional, regional and national Olympiads and conferences (Sirenko Yu.I., 2015, p. 594). The most consistent and thus profitable kind of SRW activities is students' groups and societies.

Student Scientific Group (SSG) is an organizational formation at the department, the participants of which constitute a wide range of students of the university, and which is formed taking into account scientific activities of the department and in accordance with the thematic plans of the department (Beylefeld A. & Struwig M., 2007, p. 933). SSG functioning is guided by the Constitution of Ukraine, current legislation and the Regulations of the Student Scientific Society of Higher Educational Institution. Scientific societies at the university departments are created with the purpose of realization of creative scientific potential of students and their participation in research works and programs worked on at the University, as well as for the purpose of fulfilling scientific, educational and creative professional activities.

The aims of student scientific societies and groups are:

1. Finding the most potential and talented students capable of carrying out the research work;
2. Broaden the research activities of the department with students' work;
3. Developing students' skills of carrying scientific research work;
4. Attracting talented students to scientific activities.

The major tasks of students' scientific societies and groups are:

1. Attracting students interested in scientific and research work to participate in department research;
2. Organizing scientific-research work of students;
3. In-depth studying of the chosen subject by students.

Thus, SRW allows scientists to find and guide those students who have talents and motivation for raising their professional and medical skills, to develop their methodological and organizational talents. SRW offers students various methods of developing the above-mentioned qualities, namely, regular clinical trials with experienced instructors, night shifts in the clinic, participation in competitions and in multidisciplinary conferences, presentations, travelling to other cities and countries for study.

Authors' experience in SRW was formed after many years of practice and allows to share some main principles. First of all, the main direction of the society is defined by the chair of the department and is agreed by the staff, individual students are managed by a teacher/professor in charge of SSG. SSG is formed by the students of different specializations, such as "General Medicine", "Pediatrics", "Medical Psychology" etc. Society meetings are held twice a month, with each subsequent meeting held by another lecturer/teacher. Interesting and crucial topics of meetings are chosen by teachers, which allow students to listen, study, get the most up-to-date information on this subject. Therefore, before the beginning of the academic year, an annual plan of the work of the SSG is drawn up, in which all topics, mentors of the meeting (they should be teachers having a Ph.D. or Doctor of Medical Science degree), and forms of student work are specified. As to the forms we mainly differentiate between seminars, scientific debates, workshops, individual work in the clinic, etc.

This is just a short extract to understand the way SSG is organized. Traditional methods are not ignored in the schedule, allowing students and mentors to practice more usual forms like debates, mini-lectures, presentations etc.

As to the preparation the materials of meetings

are created by mentors and are guided by the principle of the unity of theory and practice. At the beginning of the meeting a mentor gives a mini-lecture, thus introducing students to a chosen topic, articulating the aim and plan of the meeting, and briefly highlighting current scientific aspects of the topic (Bistrova Yu.V., 2015). Subsequently one or two students (who previously received the task to independently work out the most significant achievements in diagnostics or treatment of a given illness) in the form of a presentation or abstract share their knowledge on this topic. A student, who prepares a speech for a society meeting, spends his own time and is responsible for the quality of information he presents. This enables the student to develop important qualities for a future doctor-researcher – creative thinking, responsibility and ability to defend one's point of view. This prior preparation allows students to participate in a lively discussion at each meeting to analyze modern aspects of pathogenesis and differential diagnostics, students eagerly share issues of clinical pharmacology, pharmacotherapy and differentiated treatment of diseases of internal organs. But society's aim is not limited to forming theoretical basis for students. It is also recommended to use clinic patients' cases to deepen theoretical knowledge, work out the skills of collecting a medical history, clinical examination, conducting and analyzing the results of instrumental research methods, mastering the methodology of choosing optimal medicine and conditions for its rational use for each individual patient. This practice is provided by night shifts, medical cards processing, examining patients etc. As an important step the post analysis is carried out by students together with their mentors. This analysis includes perspective and retrospective perspective discussion of medical appointments from medical cards of patients, assessment of the quality of pharmacotherapy from the point of view of rationality, compliance with the protocols of medical care for patients with various diseases, interactions, completeness of appointments, detection or prediction of probable side effects of drugs, errors in the appointment of combination therapy, suggestion of ways to correct them, and work with scientific literature.

One of the most beneficial forms of SRW is workshops. Speaking about Internal Medicine department workshops are usually held on topics of cardiology, pulmonology, gastroenterology and hematology. Mentors who organize these workshops conduct them together with practical doctors of clinics. Thus, workshops on pulmonology are carried out in the office of functional diagnostics of a clinic, which gives an opportunity to show the method of spirography, pneumothachometry. While having a workshop on cardiology students are able to conduct electrocardiography and interpret it. Department of Fetal and Blood Transfusion of the Emergency Hospital allows students of Scientific Society to master the basics of transfusion medicine in practice. Gastroenterological workshops are based on students' solving clinical problems of liver diseases in the form of simulation games.

Unusual format of conducting, the opportunity to independently establish a diagnosis, make a plan and suggest a treatment scheme motivate students to work hard and go beyond textbooks and lectures. Additional laboratory and instrumental means (mentors are to provide students with all necessary data upon request) help to embody theoretical knowledge into practical skills, promote increased urge to study.

A game is a method often used within the scientific society program scope. A game can be defined as an activity with entertaining aspect directed by strict rules united by certain strategies for one or more members cooperating or competing with each other using their skills and knowledge to attain a set goal (Denina R.V., 2015, p. 282).

Games can be used successfully at different stages of teaching process: starting with material presentation up to acquiring more complex skills and their further synthesis as well as evaluation and application. The answer to the question why games are successful lies in the regression to earlier stages of personality development when learning and acquisition are natural for human beings. Students mentally are taken back to their childhood where they are free from stereotypes and restrictions, free from fear to make mistakes. They are immersed into environment of unstressed trying, low responsibility, necessary cooperation and friendly support. Simultaneously games are dynamic and diverse, thus suggesting

high motivation and enthusiasm level.

Here are some cases of games used within the scope of SSG schedule.

Case #1.

Scientific Society Meeting

Topic: 'Peculiarities of Examining and Treating Patients with Chest Pain'

Format: consultation with medical experts

Number of Students: 12

Aim: to acquire skills of diagnosing and choosing correct treatment

Preliminary Stage: Students are given lists of illnesses that may cause chest pain. Illnesses are studied at earlier courses. Every student is also given a diagnosis for which they have to a) make a list of complains, b) develop analyses results, c) prepare additional information like anamnesis etc.

Main Stage: In turns students play roles of patients consulting with a group of medical experts revealing the story of the illness. His colleagues join their efforts to diagnose a patient and choose the best treatment. Correct answers, involvement, asking related questions and ability to follow the procedure are all keys to success.

Evaluation: Evaluation takes place after all students get their diagnoses and treatment. It is the responsibility of a teacher not only to evaluate, but also to discuss the activity with all members, point out strong and weak issues of each participant.

Quest game is another case we would like to present within the society program. During this type of activity theoretical knowledge and information easily transform to practical skills, associations necessary for forming a future professional are formed. The process of this game includes a system of clues and tasks connected with topic under discussion (Chornovol-Tkachenko O.O., 2009, p. 123). They are hidden in different clinical departments of the hospital, when deciphering or solving one task leads to a new place for getting another clinical problem to solve. Evaluation is on the teacher and correct answers as well as promptness in problem solving are taken into consideration. The final stage of the quest is discussion with participants and evaluation. Below an example of quest game used at the scientific society is given.

Case # 2

Scientific Society Meeting

Topic: 'Treatment of Patients with Chest Pain'

Format: quest game

Number of Students: 10-12

Aim: after getting all pieces of information about complaints, symptoms and examination results to diagnose and appoint a correct treatment

Preliminary Stage: Before the game starts pieces of clinical task are placed in different departments and wards (Cardiac Department, X-ray, USD department etc) All students from two teams.

Main stage: Each group is given a clue (a format can be a riddle, a word etc.) which points to a place with the first task. If the task is not solved within a certain period of time a teacher supplies an easier clue. After completing a task a group is given another one to solve or find a place. All pieces of solved tasks are brought together to form a clinical picture of the case.

Evaluation: A teacher carries out evaluation. All aspects of work are taken into consideration. Quest games are followed up by a discussion.

We would like to point out from our experience that this method allows students to experience active learning and is a method for creativity and attention development. Quest games are good for effective forming and reinforcing skills of medical students. They also include other methods for expanding their teaching possibilities.

In addition one should also bear in mind the possibilities provided by methods used while playing quest games. Among them brainstorming should be mentioned. It allows students to feel free while expressing their ideas, thus ensuring formation of skills like concentration, self-assurance, responsibility for your decision and ability to prove one's point of view.

As the outcome of student's work during the year in SSG we offer student's participation in Annual International Medical and Pharmaceutical Congress of Students and Young Scientists. Also students share their scientific achievements at conferences, congresses and congresses in Ukraine and other European countries. This, in turn, forms oratory skills, the ability to independently think and make decisions, participate in discussions, answer the questions, defend their views on the problem. The results of

scientific research are reflected in the publications in various journals, collections of scientific works of students and young scientists. Conferences and congresses are perfect means of getting future doctors see and accept various approaches and develop tolerant attitude. This is another aspect that should be taken into consideration while mentoring CIS: mentors within pedagogical ethics have to encourage students to form their professionalism, humanity, justice, mutual respect and personal dignity.

Students work on understanding the main deontological principles of the medical profession, having a sympathetic attitude to the patient and his relatives. Mentors emphasize that a benevolent attitude towards the patient, a sedative word of a doctor or psychologist, encouraging information are powerful means of mobilizing the protective forces of the patient's body to recover.

Thus, we would like to conclude the following:

1. Problem-based learning applied in Student Scientific Group helps to develop critical, creative and analytical thinking, develop the ability to apply theoretical knowledge and modern methods in practical activity.

2. Experience in SSC participation helps to acquire skills in independent scientific research work and improve quality of Internal Medicine studying.

3. Students taking part in SSC get possibility to master the chosen specialty, acquire necessary research skills to proceed with scientific research work after graduation.

4. Games being a part of PBL are successful and beneficial method that can be used for out-of-class SSG meetings.

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DDC-UDC 616.-07-08:576 DOI:10.19221/2019211

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LYME-BORELIOUS IN UKRAINE (LITERATURE REVIEW)

Abstract. *The article deals with the analisis of recent literature on Lyme disease (tick-borne borreliosis). It is proved that this zoonotic disease affects the skin, nervous, musculoskeletal and cardiovascular systems and also the statistical date on the number of registered cases of infection with this disease are presented here.*
Keywords: *Lyme disease, borellosis, antigenic structure, symptoms, course of the disease, statistics.*

In recent years there has been an intensification of natural foci of zoonoses that are especially dangerous to humans, such as tick-borne encephalitis, Lyme disease (tick-borne borreliosis), and a significant increase in the incidence of the diseases in Ukraine, as well as other countries worldwide.

Environmental changes (first of all, global warming) are among the causes of this phenomenon contributing to the increase of ticks as vectors of infections and the exposure of the population to them while visiting endemic areas.

Nowadays, Lyme disease is a serious medical-biological and medical-social problem due to the predisposition to chronicity and development of lesions of the central nervous system, musculoskeletal system, cardiovascular system leading to adverse consequences - long-term disability and incapacity of people of any age and sex. Every year, the study of such pathology in medical practice becomes more relevant. Much attention is paid to detecting lesions of the musculoskeletal system among non-erythematous forms, which are difficult to diagnose and most of which are able to simulate various diseases. In general, Lyme disease or tick-borne borreliosis is a bomb with a clock mechanism that can destroy human health.

Lyme Disease (La Maladie De Lyme in French, Die Lyme-Krankheit in German) is an infectious transmissible naturally focal disease caused by spirochetes transmitted by Ixodes and is characterized by propensity to the prolonged and chronic course of disease predominantly with lesions of the skin, nervous, musculoskeletal and cardiovascular systems.

The causative agents of borreliosis are spirochetes of the genus Borrelia, which belong to gram-negative microorganisms. They contain two main protein components – specific flagellin and non-specific HSP60. By the structure, they are labile spirochetes resembling a spiral helix of 20-30 microns long and 0.2-3.0 microns thick.

A distinctive feature of the Borrelia is the absence of mitochondria in them. A significant antigenic polymorphism is specific to pathogens of Lyme disease. Genomic differences can have a clinical significance since they determine the antigenic structure of pathogens. The symptom complex of the disease depends on it to a certain extent. In Europe and the United States of America, there are some differences in the prevalence of different strains of the pathogen. Thus, the *B.garinii* and *B.afzelii* genotypes are prevalent mostly in the European part of the post-Soviet area. In the United States, strains of pathogenic Borrelia belong to one genotype - *B.burgdorferi sensu stricto*, which has arthrogenic properties. In Europe, the most pathogenic genotypes of Borrelia are known, which lead to the development of arthritis, meningoradiculitis, and acrodermatitis:

1. B.burgdorferi (causing arthritis).
2. B.garinii (causing meningoradiculitis).
3. B.afzelii (causing acrodermatitis).

These gram-negative spirochetes growing in a culture medium that contains amino acids, vitamins, and animal serum. They consist of 2 main protein components – specific flagellin and HSP60 protein. The antigenic structure of the Borrelia is represented by:

- surface proteins Osp (A, B, C, D, E, F);
- flagellar antigen;

- cytoplasmic antigen.

Within the genotype, there is also variability in the composition of superficial proteins OspA and OspC. Most of the antigenic determinants of the outer membrane are similar to the antigenic determinants of other Borrelia species and even some bacteria, which explains the possibility of cross-immunological reactions.

Borrelia, isolated in different geographical zones, differ in morphology and protein composition (this is typical for Eurasia). Different genetic species have a different DNA nucleotide sequence. It has been found that it is possible to detect Borrelia belonging to two different genotypes in a single tick. Cases of simultaneous infection with borreliosis and tick-borne encephalitis virus are known in medical practice. The main transmission of infection is vector-borne one, that is, through the bite of Dermacentor marginatus tick of the Ixodes genus.

The pathogen enters the human body with tick saliva. The primary lesion develops in the place of penetration, which is clinically manifested by the development of erythema. Hematogenous dissemination begins after the penetration of the Borrelia through the dermis and into the vessels, characterized by spirochetemia of short duration with a small number of spirochetes. The pathogen enters the viscera, joints, central nervous system through the hematogenous and lymphogenous way. In dissemination, the Borrelia penetrate into macrophages, endothelial cells of various organs and systems, which is clinically manifested by the development of multiple organ dysfunction. The ability of the pathogen to intracellular parasitism provides the possibility of a chronic course of the disease with late relapses and prolonged persistence of Borrelia in the body (over 10 years). When the Borrelia die, they excrete endotoxin, which causes an immunopathological cascade.

The vast majority (81.7%) of new cases of borreliosis is recorded in May-September, that is, it occurs in the spring-summer-autumn period.

Symptoms in Lyme disease

The clinical picture of Lyme disease is characterized by polymorphism of manifestations: lesions of skin, musculoskeletal, nervous, and cardiovascular systems, general intoxication. In clinical practice, the development of the disease is divided into 4 stages:

- localized (the stage of the primary lesion);
- disseminated (generalized);
- persistent (chronic);
- residual (post-treatment Lyme disease syndrome).

Often the course of the disease becomes chronic and relapsing. The acute course (from a few weeks to 6 months) involves two successive stages - early localized and disseminated. The chronic form of the disease may last be lifelong with periods of exacerbation and remission.

Stages of the disease (may overlap or appear simultaneously, all of the symptoms do not usually appear together):

1. Early limited stage:

1) flu-like symptoms;

2) erythema migrans - usually occurs in ≈7 (3-30) days from the tick bite; first reddish spot or papule rapidly enlarges in diameter, diameter >5 cm, ring-shaped with enlightenment in the center (could be monochromatic), the contours are clearly delineated, remains at the skin level being painless and not itchy;

3) rarely lymphocytic lymphoma of the skin - painless, reddish-blue node, most often on the auricle, nipple or scrotum. Erythema migrans and systemic symptoms disappear within 4-12 weeks in patients untreated with antibiotics; less intense symptoms may persist in some patients for several years or chronic symptoms of the late stage develop (there may be the first and only symptom of borreliosis, even a few years after infection, such as arthritis).

2. Early disseminated stage (organ) - can develop from several weeks to several months after infection:

1) arthritis – most often mono-, sometimes oligoarthritis of large joints (knee, ankle, elbow), typically without an intensive systemic inflammatory reaction, despite the predominantly significant effusion in the joint capsule, periodic exacerbations (from several days to several weeks) eventually occurring less often, becoming shorter and milder; arthritis may become chronic if left untreated;

2) myocarditis (≈5% of patients) – sudden AV blockade or other conduction and rhythm disturbances; usually, articular and neurological symptoms are present at the same time;

3) nervous system lesions (neuroborreliosis) – simultaneous or gradual lesions of the central and

peripheral nervous systems at different levels: lymphocytic meningitis (usually mild, headache may be the only symptom) and neuritis of the cranial nerves (paresis or paralysis, most often of the facial nerve, which may be bilateral).

3. Late stage:

1) chronic erythematous erythroderma of the extremities – reddish-blue, usually asymmetric changes of the skin of the distal limbs, appear several years after infection; at first, inflammatory edema, then dominated by atrophy (thin depilous skin with a purple shade), the pain of adjacent joints and paresthesia are often present;

2) chronic arthritis, the prolonged lesion is less common; light myositis, bursitis or tendonitis;

3) chronic neuroborreliosis (very rare) – inflammation of the nerve roots and peripheral nerves, peripheral polyneuropathy, chronic encephalitis, and myelitis.

The main clinical manifestations of Lyme disease, depending on the stage of the disease, are given in Table 1.

Table 1.

Clinical manifestations of Lyme disease at different stages of the infectious process (according to L.M. Vovk, 2011)

Lesions of organs and systems	Early localized infection	Early disseminated infection	Chronic infection
General detoxification manifestations	Flu-like syndrome	Pronounced general weakness	Syndrome of chronic fatigue
Lymphatic system	Regional lymphadenitis	Generalized lymphadenopathy	-
Skin	Erythema migrans	Secondary erythema and exanthema	Benign lymphocytoma of skin, chronic erythematous erythroderma
Cardiovascular system	-	Atrioventricular blockade, myocarditis	-
Nervous system	-	Meningitis, neuritis of the cranial nerves, meningoencephalitis, radiculoneuritis, Bannwarth syndrome	Encephalomyelitis, radiculopathy, vasculitis
Musculoskeletal system	Myalgia	Erratic pain in bones, joints, muscles, first arthritis attacks	Chronic polyarthritis

There are five variants of common lesions of organs and systems in Lyme disease: 1) skin; 2) nervous system; 3) bone and joint system; 4) cardiovascular system; 5) mixed variant.

The incubation period of the disease lasts from 1 to 50 days from the time the pathogen enters the body, accounting for an average of 10 - 12 days.

During the course of the disease, there are 3 periods:

The first period lasts up to 7 days. It is characterized by skin lesions and infectious manifestations: headaches, nausea, drowsiness, rapid fatigability, weakness, myalgia, and arthralgia.

The main symptom of this disease is the presence of erythema at the site of the tick bite in the form of a red spot or papule, which may reach the size of 10-60 cm gradually increasing. There are often unpleasant sensations in the field of erythema, itching, moderate pain.

Skin redness is often accompanied by weakness, chills, heat, fever to 39 - 40° C, headache, and muscle ache. Sometimes nausea and vomiting, dry cough, runny nose, rarely itchy throat are noted.

The second period lasts 2-6 weeks. Characteristic neurological and cardiac complications, marked neurological symptoms are usually manifested after erythema disappears by the following: serous meningitis, encephalitis, neuritis of the cranial nerves, lesions to the peripheral nervous tissue, manifested in 10-25% of the infected patients.

The most common neurological disorder in Lyme disease is Bannwarth syndrome, which includes serous meningitis with lesions of the spinal nerves of the cervical and thoracic spine. A month later,

neurological disorders resolve, but they can recur, becoming chronic. Moreover, the following symptoms and syndromes with CNS lesions will occur:

1) mono-, polyneuritis;
2) lymphocytic meningitis;
3) chorioretinitis;
4) meningoradiculoneuritis;
5) myelitic paraplegia;
6) myeloradiculoneuritis;
7) focal or common meningitis;
8) paroxysmal disturbances of consciousness;
9) epileptic seizures;
10) cerebral vasculitis with cerebral infarctions;
11) progressive encephalomyelitis.

The development of cardiac disturbances is possible on the fifth week of the disease: disturbances of heart contractions, cardiac pain, pericarditis, myocarditis, heart failure, cardiac conduction disorder. The duration of symptoms is up to 6 weeks. Erratic pain in the muscles, joints, bones, weakness remain in patients with borreliosis during the second period.

The third period lasts from 2 months up to 2 years. Lesions of large joints are specific to this period. The disease then becomes chronic, which is represented by the alternation of recurrence and remission periods or resembles a continuous relapse. Chronic Lyme disease is manifested by arthritis, osteoporosis, thinning of cartilage, degenerative changes.

Typical symptoms of the late stage of the disease are:

1. Chronic acrodermatitis;
2. Neuroborreliosis (a combination of progressive chronic encephalomyelitis and polyneuropathy).
3. Benign lymphoma.

Outbreaks of Lyme disease in the Chernivtsi region

2015 – 10 cases registered;

2016 – 13 cases registered (three children aged 1 y. 10 m., 4 years and 5 years among the infected patients);

2017 – 4 patients registered.

In the Lviv region for the period from 2010 to 2017, 461 cases of Lyme borreliosis were registered. If 9 cases were registered in 2010, then in 2011 – 28, 2012 – 53, 2013 – 48, 2014 – 44, 2015 – 126, 2016 – 153, 2017 – 169 cases.

Consequently, the Ixodes are the main vectors of the pathogen of Lyme disease, as well as the reservoir of the pathogen at the same time. The ticks are aggressive towards humans. Migratory birds can carry Ixode tick-borne borreliosis to other continents.

Therefore, tick-bite victims should certainly consult an infectious disease physician who is obliged to prescribe a preventive treatment to the patient, regardless of whether the tick is infected, or not. After all, the risk of becoming infected with Lyme disease is real, even though it is small considering there are only 4 out of 5 ticks are the vectors.

Conclusions. Timely antimicrobial therapy is important to prevent dissemination of infection and the development of organ lesions. Therefore, specific serological studies should be conducted for patients with an unknown cause of the disease in the presence of medical history data confirming tick bite.

Significant prevalence of the disease in Ukraine (on studying ticks, their infection with Borrelia was detected in 18.3%, that is, every fifth tick is a vector of Borrelia).

In particular, during the period from 2000 to 2010, the incidence of Lyme borreliosis in Ukraine has increased by 21.9 times from 58 to 1,275 cases (0.12 to 2.77 rate per 100,000 population). The total number of officially registered cases for this period has been 4,596. The trend for further growth is predicted. This is evidenced by the fact that 13,061 cases were registered in Ukraine for the period from 2011 to 2017, that is, the incidence has increased dramatically for a shorter period.

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Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet athttp://dnb.dnb.de

№ 2/2019 – 10
Passed in press in September 2019


Berlin