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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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