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New Mechanisms of Formation of Irritable Bowel Syndrome in Children

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Abstract: The review article is devoted to the analysis of foreign and domestic studies on irritable bowel syndrome in children. The author considers neuro-immuno-endocrine mechanisms of functional pathology formation, studies new pathogenetic mechanisms, systematizes the data of leading scientists aimed at improving the methods of diagnosis and timely prevention of irritable bowel syndrome in children.

Keywords: children, irritable bowel syndrome, functional disorders, immunity, pathogenesis.

The prevalence of IBS in most countries of the world averages 20%, varying from 9 to 48% in different populations. IBS is more common in young women (from 64 to 69%) and is often combined with other functional pathology. In Russia, about 10% of patients seek medical help with IBS symptoms, while 5% of patients go to doctors of other specialties – most often to surgeons, endocrinologists and gynecologists [6].

In practical work, a pediatrician often has to deal with abdominal pain, which is quite naturally observed in seemingly practically healthy children from 6 weeks to 3-4 months of age. This condition is commonly referred to in pediatrics as intestinal colic. Clinically, it is manifested by the sudden anxiety of the child, crying, twitching legs, bloating, which usually decreases or passes after the discharge of feces and gases. Classical intestinal colic is characterized by the so-called "rule of three": crying for 3 or more hours a day, at least 3 times a week, for 3 consecutive weeks. Despite the fact that colic attacks are repeated quite often, the general condition of the child remains quite satisfactory, in the period between attacks the child is calm, he has a good appetite and he normally adds body weight; psychomotor development also corresponds to normal indicators. When a child reaches the age of 4-6 months, colic, as a rule, stops on its own [1].

Functional bowel diseases (FZK) are part of a large group of diseases related to functional pathology of the gastrointestinal tract (GI tract), and are very widespread throughout the world. These disorders affect all segments of society, regardless of gender, age, race, religion, skin color or socio-economic status. The relevance of the active process of studying these nosological forms, which has not stopped over the past decades, is dictated not only by a significant decrease in the quality of life of patients, but also by significant damage to the global health system due to direct and indirect costs of their treatment. The achievements of fundamental and clinical science over the past 10 years in the study of epidemiology, etiology, pathophysiology, diagnosis and therapy of FPC have necessitated the revision of the Rome Criteria III that existed since 2006. In May 2016 The world gastroenterological community at the American Gastroenterological Week got acquainted with the Roman Criteria IV, the main provisions of the consensus have already been published. It should be noted with regret that the hopes pinned on a significant scientific breakthrough in understanding the essence of functional pathology of the gastrointestinal tract have not been fully justified and

practicing gastroenterologists of the world still do not have universal tools in their hands for the curation of such patients. Nevertheless, with the publication of updated criteria, internists have modern, non-stop adapting clinical recommendations that determine the vector of clinical thinking in cases of both diagnosis and choice of therapy methods [5].

Transferred intestinal infections lead to neuroimmune damage and are one of the causes of the formation of IBS. It was found that 24-32% of patients developed a syndrome similar to IBS 3 months after acute intestinal infection. It was shown that IBS often developed after a bacterial intestinal infection (Salmonella spp., Shigella spp., Campylobacter spp.), the occurrence of IBS after acute viral gastroenteritis caused by noroviruses was also noted. Studies of intestinal microbiota disorders have become a new step in the knowledge of IBS. A close relationship has been established between the microbiota and intestinal motility: changes in the microbiota have a pronounced effect on the development of sensory-motor dysfunction of the intestine. It has been proven that the microbiota is able to "control" intestinal motility: Bifidobacterium bifidum and Lactobacillus acidophilus enhance propulsive motility, and Escherichia spp. she's being oppressed. The mechanisms of the microbiota's influence on intestinal motor function have been established through the isolation of metabolites or fermentation products of bacteria, changes in neuroendocrine function and endogenous production of mediators within the framework of the intestinal immune response. The achievement of recent years is the proof that the intestinal microbiota, through metabolites and mediators, is able to control the emotional state and stress reactions of the body [8].

The role of vitamin D as an important regulator of the permeability of the intestinal barrier, suppressing microbial invasion into the intestinal epithelium by increasing the synthesis of proteins of intercellular compounds – occludin, claudine, vinculin, zonulin, in addition, the ability of vitamin D to influence the healing process of the intestinal mucosa was found. Due to the effect on the Th1/Th2 balance towards the Th2 response, inhibition of IL-12 production, vitamin D is able to reduce the activity of the inflammatory process in autoimmune diseases, including IBD [4].

The key to the emergence of IBS is considered to be a violation in the "gut–brain" axis system. The development of visceral hypersensitivity in IBS in a child is often associated with intestinal infections (post-infectious IBS), food allergies, operations and traumatic manipulations at an early age, childhood psychological stress (anxiety, depression, impulsivity, emotional problems) and social maladaptation. But, apparently, the pathogenesis of IBS is much more complicated. Today, a lot of research is devoted to the formation and development of the "gut–brain" axis, the study of a wide range of factors that can affect this process. The gut–brain axis is a complex two-way system connecting the emotional and cognitive centers of the brain and the intestine through neuroendocrine and immunological influences. This axis includes the central nervous system (brain and spinal cord), the autonomic and enteral nervous system, and the hypothalamic-pituitary-adrenal axis. Understanding the points of influence on the gastrointestinal tract from the outside can provide additional opportunities for therapy and prevention of abdominal pain disorders in childhood [2].

A complexly organized multilayered intestinal barrier – the intestinal epithelium covered with a mucin layer in combination with microsocialities of the parietal and lumen microbiota, components of innate and adaptive immunity – interacts environmental factors with the gastrointestinal tract (GIT). The development and activity of each of the components of the intestinal barrier is largely genetically determined. And the impact of many external factors, primarily microbial pathogens and food antigens, leads to the emergence of immunological tolerance or the development of inflammation – perhaps the first universal link in the pathogenesis of a whole range of diseases. The surface areas of the mucin layer covering the epithelial cells are a matrix for the microsociety of the parietal intestinal microbiota, which is in close dynamic competitive interaction with the luminal microbiota and pathogenic microorganisms. The inner layers of mucin are less densely populated, but they are immunologically highly active due to the work of various factors of innate and adaptive immunity at this level – membrane Toll receptors, antimicrobial peptides, sIgA and short-chain fatty acids, dendritic cells. The most studied endogenous factor – short–chain fatty acids (FFA) – acetate, propionate, butyrate - are produced by the intestinal microbiota during the fermentation of dietary fibers and perform a number of important functions: trophic (energy substrate, stimulation of growth

and proliferation of enterocytes); regulatory (regulator of motility, intestinal blood flow, as well as the activity of mucin production by goblet cells); anti-inflammatory; immunotropic; carcinoprotective [3].

The modern concept of epigenetics is closely related to the activity of FGC — the ability to regulate the activity of individual genes, preventing the realization of predisposition to various polygenic diseases, through the interaction in the intestine of the intestinal microbiota (CMB) and its active metabolites – FGC, biotin, folic acid with food components, vitamins [10,14].

The microbiome is a complex collective of microorganisms living on human tissues that communicate with the external environment. The emergence and introduction into daily practice of modern molecular genetic laboratory research methods has overturned the established ideas about the ierrachic structure and the role of the human microbiome. New young sciences – metabolomics, genomics, proteomics, epigenetics – study and structure a huge pool of new knowledge about the microbiome, its multifaceted functions. Functional metagenomics explains the possibilities of gene interaction between the intestinal microbiota (CMB) – a genetic bank of microbial, plasmid and chromosomal genes – and human cells through gene-metabolic networks. The positions of the microbiome as the primary immune barrier, its modulating role in the onset and course of a number of different somatic and infectious diseases and conditions are extremely interesting [12].

The positions of the biologically active substance, the prohormone vitamin D, are largely overestimated today: its functions are systemic and much broader than the concept of "bone metabolism". Cholecalciferol formed in the skin under the action of UV irradiation/coming from animal food or from plant food - ergocalciferol must undergo hydroxylation twice – in the liver (to calcidiol) and kidneys (to calcitriol) to convert into an active hormone [48]. In addition to bone effects – bone mineralization due to increased absorption of calcium in the intestine and its reabsorption from urine – calcitriol is characterized by a wide arsenal of extra-bone effects: cardiovascular, immunotropic, neuroprotective, as well as the growth and differentiation of a number of cells, keratinocytes, lung cells, breast, prostate and intestines [49]. To date, vitamin D receptors have been found on the surface of almost all immune cells – CD4+ and CD8+ lymphocytes, B-lymphocytes, neutrophils, antigen-presenting cells, including macrophages and dendritic cells, which makes them susceptible to vitamin D-mediated modulation. The role of vitamin D deficiency has been proven in the pathogenesis of many somatic diseases – arterial hypertension, colorectal cancer, breast and prostate cancer, rickets and osteoporosis, as well as inflammatory bowel diseases (IBD) [7,9,11,13].

Conclusion.

Thus, visceral hypersensitivity, motor disorders, visceral hyperalgesia, changes in the regulation of the gastrointestinal tract by the central nervous system, vegetative disorders, genetic and environmental factors, intestinal microbiota disorders, the consequences of intestinal infections and psychological problems of varying severity contribute to the pathogenesis of IBS. It is obvious that patients with IBS are characterized by comorbidity of somatic, visceral and psychiatric forms of pathology. Taking into account the above, the statement is formulated in a generalized form that IBS is not a specific form of pathology of the gastrointestinal tract, central nervous system or psyche, but, perhaps, it is a new bioneuropsychosocial state of a modern person. It was determined that genetic and epigenetic, immune and inflammatory, neurological and psychological factors, changes in the intestinal microbiota in combination with environmental influences complement the manifestations of visceral hypersensitivity and intestinal motility disorders in the clinical picture of IBS, which, in turn, depends on the complex interaction between the intestine and the nervous system in the regulation of the digestive system of a growing organism.

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