TREATMENT OF PATIENTS WITH IRRITABLE BOWEL SYNDROME

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The disease significantly worsens the quality of life, reduces the social activity of patients, and requires significant material costs for their examination and treatment. In the event that the diagnosis of IBS is established only on the basis of patient complaints, the absence of anxiety symptoms and a minimum number of laboratory and instrumental studies, as recommended in the Rome III criteria, the probability of an incorrect diagnosis remains quite high (up to 25%). The effectiveness of most recommended drugs and regimens in the treatment of IBS does not exceed 38%, which indicates insufficient study of the pathogenesis of the disease. Approaches to the treatment of combined functional gastrointestinal disorders (for example, IBS and functional dyspepsia syndrome (FDS)) have not been developed. In recent years, based on the studies, data have been obtained that in addition to the emotional component, structural changes contribute to the formation of IBS symptoms. The role of increased permeability of the intestinal wall due to impaired synthesis of proteins that form tight junctions between epithelial cells is discussed ; changes in the expression of signaling receptors that interact with the host organism and bacterial cells; disturbances in the cytokine profile towards an increase in proinflammatory cytokines; the presence of nonspecific inflammation in the intestinal wall; as well as changes in the qualitative and quantitative composition of the intestinal microflora. However, the relationship between the above changes and with the formation of disease symptoms remains insufficiently studied. A more in-depth study of the structure of functional diseases seems relevant; assessment of the feasibility of performing a set of laboratory and instrumental examinations to make a diagnosis; determination of optimal treatment regimens for such patients depending on the effect of drugs on the main mechanisms of symptom formation. Irritable bowel syndrome (IBS) is one of the most common gastrointestinal diseases, the main manifestations of which are abdominal pain, flatulence, and changes in the consistency and frequency of stool. According to various authors, the prevalence of IBS in the world ranges from 4 to 30%. The disease significantly worsens the quality of life of patients and requires significant material costs for the treatment and examination of patients. Despite the fact that the history of studying functional disorders has been going on for more than 100 years, many questions regarding the etiology, pathogenesis and treatment tactics have not been answered unambiguously to this day. Initially, the cause of symptoms in IBS was considered to be motor and sensitivity disorders that occur in the absence of structural, organic or known biochemical pathology, in genetically predisposed individuals under the influence of unfavorable environmental factors against the background of psychoemotional stress or intestinal infection. However, already at the end of the last century, this point of view was

criticized. Thus, D.S. in 2018 D.S. Sarkisov wrote that the diagnosis of "irritable bowel syndrome" is not purely functional, but has its own structural equivalent, a morphological basis. From today's perspective, the understanding of the pathogenesis of IBS has undergone significant changes. Much attention is paid to possible changes in the structure and function of the enteric nervous system. The enteric nervous system, which coordinates the motility and secretion of the gastrointestinal tract, contains more than 100 million nerve cells grouped into the myenteric plexus of Auerbach and submucous plexuses. Neurons of the myenteric plexus mainly regulate motility, and neurons of the submucous plexus participate in maintaining homeostasis. Almost all known mediators are present in the enteric nervous system. Such a complexly organized system can ensure the functioning of the gastrointestinal tract independently, responding to the slightest changes in the intestinal microflora, cytokine profile, etc. However, to ensure optimal functioning of the gastrointestinal tract, the regulatory influence of the central nervous system is necessary.

In patients suffering from IBS, changes are determined that can lead to dysfunction of the enteric nervous system: disruption of the qualitative and quantitative composition of the intestinal microflora, inflammatory changes in the intestinal wall, which leads to a change in the state of the receptor apparatus of the pain pathways. The identified changes are interconnected with each other and form a logical chain, the end of which is the development of symptoms of the disease. However, it remains unclear whether the above-described disorders determine their severity and nature, since the influence of structural and morphological elements in patients with functional diseases is often superimposed by psychological and mental components, which often overlap the primary organ symptoms. In recent years, the problem of qualitative and quantitative changes in the composition of intestinal microflora in patients suffering from IBS has been widely discussed. The syndrome of excessive bacterial growth (SIBO) occurs in such patients 6 times more often than in healthy individuals. It is suggested that the presence of SIBO leads to an increase and persistence of symptoms of the disease, is associated with a lower level of expression of the anti-inflammatory cytokine IL-10 in the blood serum; in addition, a positive correlation is determined between the duration of the IBS history and the presence of SIBO. According to E. Pyleris et al ., in patients with a confirmed diagnosis of IBS and SIBO, when examining an aspirate of the contents of the descending part of the duodenum in an amount greater than 10, the following microorganisms were determined: Escherichia coli (12.7%), Enterococcus spp (10.9%); other enterobacteria (18.2%); in the control group: Escherichia coli (3.1%), Enterococcus spp (6.1%). However, the problem of the combination of IBS and SIBO is also considered from another point of view. It is discussed that SIBO manifests itself with symptoms similar to those in IBS, but does not at all serve as a manifestation of this functional disease. Thus, with a combination of IBS and SIBO, there is an increase in the main complaints,

but no new ones arise. Therefore, antibiotics prescribed for the treatment of SIBO in IBS are less effective, leading to a decrease in the intensity of symptoms than, for example, in the case of a combination of SIBO with diseases such as rosacea and scleroderma, when they are completely eliminated. The results of studies on the qualitative composition of microflora are contradictory, due to the lack of wide availability of adequate methods for its study. However, despite the inconsistency of the data provided, there is no doubt about the presence of significant differences in the intestinal microflora in patients with IBS and healthy volunteers. Inflammatory changes in the intestinal wall. Representatives of opportunistic and pathogenic microflora possessing adhesion factors and penetrating into lymphoid follicles trigger a cascade of immune reactions leading to the development of inflammation in the intestinal wall. Recent publications provide data on an increase in the level of mast cells, intraepithelial lymphocytes and plasma cells in the intestinal mucosa of patients suffering from IBS. Mast cells carry receptors for β-E on their surface and, during degranulation , release a large number of biologically active substances such as heparin, leukotrienes , proteases, which leads to the activation of naive T cells and their differentiation into functional effector cells: CD8+ cytotoxic T cells, CD4+ T- helper cells (TH), CD4+ T12 and regulatory T13 cells, as well as a change in the cytokine profile. The overwhelming majority of studies provide data on an increase in the expression of proinflammatory and a decrease in the expression of anti-inflammatory cytokines in intestinal wall biopsies in such patients , which may be responsible for the persistence of inflammatory changes in it. At the same time, the cytokine profile of peripheral blood in patients with IBS is assessed quite contradictorily. For example, data are provided on both increased and normal expression of TNF-a. In addition, both increased and normal levels of the anti-inflammatory cytokine IL-10 were found in the blood serum of patients with IBS. The inconsistency of the obtained results can most likely be explained mainly by the paracrine effect of cytokines and the lack of correlation between their expression in the intestinal wall and peripheral blood. Thus, it can be assumed that changes in intestinal microbiota, increased expression of signaling receptors, decreased expression of tight junction proteins, and disruption of the cytokine profile lead to the formation of inflammatory changes in the intestinal wall in patients with IBS. Data on the presence of inflammatory changes are contained in publications over the past fifteen years.

Changes in pain sensitivity. Formation of central and peripheral sensitization . Information about the presence of inflammation is transformed into an electrical signal, which is conducted along the sensory nerve fibers to the spinal ganglion, from where the central axons are directed through the posterior roots to the posterior horn of the spinal cord. The basis of sensitization The long-term depolarizing effect of glutamate and cytokines released from the endings of afferent nerve fibers due to intense constant impulses coming from the zone of altered intestinal tissue serves as the main mechanism of stimulation of nociceptive neurons of the

posterior horns of the spinal cord. With prolonged and intense stimulation, neurons of the spinal ganglion and the posterior horn of the spinal cord become hyperexcitable , and areas of abnormal activity appear in them. The resulting processes lead to the appearance of antidromic stimulation, i.e. stimulation directed from the spinal cord to the periphery, which is enhanced and maintained by the release of substance P in the nerve endings, which functions as a neurotransmitter , and calcitonin gene-related peptide (CGRP), forming visceral hypersensitivity. To level the above changes, the most optimal seems to be the effect on peripheral opioid receptors. Since stimulation of opioid receptors results in approximately equal changes in the expression of both excitatory and inhibitory neurotransmitters , the resulting effect of such influence will depend on the initial expression and ratio of these mediators, and will be modulating (antispasmodic with an initial predominance of excitatory, and prokinetic with an initial predominance of inhibitory neurotransmitters). In addition to sensitization nociceptive neurons of the posterior horn, tissue damage initiates an increase in the excitability of nociceptive neurons in higher centers, including the nuclei of the thalamus and the somatosensory cortex of the cerebral hemispheres.

Emotional disturbances. As early as the end of the 19th century, Wiliam Osler noted that many patients suffering from "mucous colitis" are hysterical, egocentric and hypochondriacal [172]. According to data cited in modern literature, concomitant anxiety, depressive, hypochondriacal disorders are observed in 81% of patients with IBS. Stressful events experienced in childhood (verbal, sexual or physical abuse), in adulthood (divorce, loss of loved ones), lack of social support can predispose patients to the development of the above conditions . However, the literature also provides opposite data that the prevalence of anxiety, paranoid ideas, depression, obsessive- compulsive disorders in patients with IBS only slightly exceeds that in the population of people not suffering from IBS.

Possible causes of emotional disorders. A study published in 2012 provides data that long-term intestinal disorders themselves can increase the level of anxiety and depression; in addition, according to Maddock C. et al. (2004), increased expression of proinflammatory cytokines can contribute to the development of depression. In patients with diagnosed depression, increased expression of proinflammatory cytokines IL-1, IL-2, IL-6, TNF-a and the ratio of INF - y/ IL-4 in the blood serum are determined. In addition, changes in the intestinal microbiota have been described in individuals with emotional disorders.

It is also known that with stress-induced increase in glucocorticoid production, dysfunction of the intestinal barrier increases, which is accompanied by migration of bacteria with pro-inflammatory properties, increased inflammation in the intestinal wall, and increased expression of pro-inflammatory cytokines through an immunogenic response. Cytokines damage the integrity of the blood-brain barrier and open access to the brain for potentially pathogenic and pro-inflammatory elements [196], which can lead to the development and/or

aggravation of emotional disorders. At the same time, as a result of prolonged emotional stress, with an already existing depressive and/or anxiety disorder, glucocorticoid inhibition of the expression of pro-inflammatory cytokines is suppressed, which leads to activation of peripheral pro-inflammatory processes.

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