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PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME

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Resume The literature review is devoted to the study of factors that occupy an important place in the pathophysiology of irritable bowel syndrome, such as the relationship between the central and enteral nervous system, intestinal barrier function, gene polymorphism, low-level inflammation, imbalance of neurotransmitters and cytokines, as well as changes in the intestinal microbiome.

Keywords: irritable bowel syndrome, genes, inflammation, cytokines, microbiome, psychosomatics

Disturbances in the communication between the gut and the brain are common among gastrointestinal diseases (GD). Among these diseases, intestinal impaction syndrome (IBS) has a high percentage. IBS is a disorder of intestinal function characterized by abdominal pain and discomfort without obvious structural changes [1]. The etiology of IBS is not fully understood, but it can be caused by several factors. Studying the etiology and pathogenesis of IBS is very important for the development of pharmacotherapeutic drugs [2]. Pathogenesis of IBS includes alterations in gastrointestinal motility, post-infection reactivity, visceral hypersensitivity, brain-gut axis, changes in microbiota, bacterial overgrowth syndrome, food sensitivities, carbohydrate malabsorption, and intestinal inflammation. includes [2]. While there is no definitive cure for IBS, it can be managed with certain medications, stressors, and dietary changes. Therefore, the study of the brain-gut axis provides a basis for the development of new therapies [3].

IBS patients can be divided into a diarrhea-predominant type, a constipation-predominant type, a mixed type in which both occur together, and an unspecified type that transitions from one type to another [2]. The identification of intestinal symptoms in patients is the basis for making the diagnosis of ITS, but the presence of abdominal pain is the key to diagnosing this condition [2]. According to the Rome IV criteria, IBS is divided into four types: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed type (IBS-M) and unclassified type (IBS-U). Classification of patients into these types depends on time [4]. Conventional treatments for IBS focus on symptom relief. However, the multiplicity of its origins does not allow treatment with a single drug [3].

Population studies have shown a high incidence of IBS [2,5]. In a recent study involving 24 countries, using the Rome IV criteria for diagnosis, IBS was detected in 40% of the population, which led to a change in the quality of life and medical care of these patients [6]. In the West, patients with IBS are predominantly female, while in the East, it is believed that IBS are underdiagnosed [7].

IBS is thought to be caused by abdominal pain or discomfort, diarrhea or constipation as a result of visceral hypersensitivity and gastrointestinal motor dysfunction [2]. However, the pathophysiology of IBS is not fully understood. Genetic predisposition, food intolerance, brain-gut axis dysfunction, microbiota changes can trigger this disease. To date, it is not known which of these pathological factors cause or aggravate IBS, and the main reason for this is the individual manifestation of symptoms [8]. It can be noted that the treatment of IBS is focused on its clinical symptoms rather than its pathophysiology [9].

Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

A large number of studies show that genetic risk for the development of IBS exists in people with complex polygenic and atypical aberrations of one gene [10,11]. A mutation in SC5NA, a sodium ion channel gene, has been found to be associated with abdominal pain in patients with IBS [12]. Additionally, single nucleotide polymorphism studies have identified gene polymorphisms associated with ITS pathogenesis, including serotonin signaling [13], immune regulation, epithelial barrier function [14], bile acid synthesis [2], and cannabinoid include receptors [15]. Other studies have shown that KDELR2, the endoplasmic reticulum-retaining receptor KDEL, and the glutamine receptor-interacting factor GRID2IP are important in the development of IBS [16]. Because these studies did not include enough patients and did not find clear structural changes, the role of genetic factors in IBS remains unknown.

About 60 genes have been studied in order to confirm the connection of genetic factors with IBS, and only information about the TNFSF15 gene has been presented. Changes in this gene were identified in previous studies [2], and subsequent studies confirmed the previous ones [14,17,18]. Since the TNFSF15 gene is involved in inflammatory bowel diseases, it is important to study it thoroughly [19].

In addition, among the epigenetic factors, DNA methylation was found to be associated with ITS. In a study to compare DNA methylation, ChG was detected in the peripheral blood of patients with ITS compared to healthy individuals [20]. At the same time, such changes were also observed in the mucous membrane of the large intestine. An increase in DNA methylation was detected in stress-related genes - NR3C1, CRHR1 and brain neutrophil [21]. These data suggest that DNA methylation is important in the pathogenesis of IBS and warrants further investigation.

The pathogenesis of IBS is also associated with changes in the gut microbiota, affecting immunity and gut integrity and altering the brain-gut axis and gut neuromuscular junctions [2]. Normally, the intestinal mucosal epithelium stimulates homeostatic immune responses, maintains barrier integrity, and maintains tolerance to bacteria by restricting microbes from the intestinal surface or lumen. This process is important for the growth of bacteria in the intestine and for the proper functioning. Barrier disruption due to inflammatory factors, pathogens, deepens the immune response and causes inflammation. This inflammatory process affects the intestinal environment, leading to a change in the composition of the intestinal microbiota [2]. A number of studies have shown that the diversity of gut microbiota and its relationship with the severity of IBS have been reported [22,23]. However, the identification of changes in the microbiota by IBS species has hardly been carried out.

Normal diversity in the gut microbiota is essential not only for a healthy gut, but also for the normal physiological functioning of important organs such as the brain. The occurrence of dysbacteriosis in children and the elderly affects brain activity. This indicates that the brain needs the products produced by the metabolism of intestinal microbes [24,25].

The brain-gut axis includes the enteric nervous system (ENS), the central nervous system (CNS), the gut devoir in the periphery, and the hypothalamic-pituitary-adrenal axis. The relationship between the intestine and CNS is bidirectional and is carried out through neural, endocrine and neuroimmune pathways [2]. At the physiological level, GIT sends signals that affect the brain, causing changes in the immune system, secretion, and motility [25]. This axis is considered the node that connects food intake, digestion and defecation management. Structural abnormalities in the brain-gut axis can lead to alterations in reflex and perceptual responses of the nervous system, leading to ITS-like gastrointestinal disorders [2].

Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

The vagus nerve contains thousands of nerve endings, 80% of which are afferent and transmit impulses to the CNS and brain. The vagus nerve is the main communication pathway between the brain and the microbiota. Pathways involved in this coupling similarly convey efferent signals from the CNS to the gut wall [26]. The vagus nerve is considered the main part of the VNS, and the sympathoadrenomedullary axis is considered a special part of the VNS and participates in the process of acute stress. The sympathoadrenal and GGB axis are among the main stress response systems in vertebrates [27]. Many mental disorders, anxiety, increased sensitivity to pain and stress are caused by changes in these systems [2].

Eliminating imbalances between CNS and VNS is important for ENS prevention. Abnormalities in the VNT, manifested by decreased parasympathetic nervous system activity and increased sympathetic nervous system activity, lead to impaired autonomic reflexes in patients with IBS, which in turn causes intestinal and extraintestinal symptoms [2]. One study examined the relationship between resting brain activity in vitro. Intestinal barrier function tests were performed in healthy women and women with IBS, taking into account IBS severity levels. At the end of the study, it was found that the indicators of women with moderate and severe IBS and healthy women are statistically different, and this difference is manifested in epithelial permeability, as well as structural and functional characteristics of the brain. was Women with IBS diagnosed with low intestinal permeability have been found to have more severe clinical symptoms. Research results have shown that interactions between gut permeability and the brain play an important role in the development of clinical symptoms of IBS [28].

Corticotropin-releasing factor (CRF) is an endogenous neuropeptide consisting of 41 amino acids, produced by endocrine cells of the hypothalamic paraventricular nucleus. CRF is the main activator of the GGB axis. CRF acts both centrally and peripherally, controls the body's response to stress and participates in the manifestation of IBS clinical symptoms [2]. Given that CRF and IBS receptors (CRFR1 and CRFR2) influence immunity and gut motility through the brain-gut axis, relative insights into the pathophysiology of IBS may emerge in the future [29]. Animal models can help with this. In a study in hypo-anxious mice, administration of CRO induced colonic hypersensitivity, a symptom that was ameliorated after administration of a CRFR1 antagonist. CRF and IBS receptors influence smooth muscle contractility, mucosal transport, mucosal permeability, and visceral pain perception, and are characterized by the origin of IBS in the colon [2].

GGB hyperreactivity is observed in patients with IBS, and gender may play an important role [30]. One study examined the GGB axis, colonic motility, and autonomic response. Changes in brain activity were studied in patients with IBS after administration of CRF, increased intestinal motility was observed in the group of men with IBS, and decreased sympathovagal and basal parasympathetic tone was noted in the control group of women. A study has shown that the administration of centrally acting medical treatments can help relieve the clinical symptoms of stress-induced IBS [31].

Psychological stress is considered to be a major trigger of IBS and may be a major factor affecting the brain-gut axis [32]. Stress affects gut motility and permeability, visceral hypersensitivity, immune responses, and gut microbiota [33]. The importance of the stress factor in IBS is related to the secretion of pro-inflammatory cytokines, which activate the GGB axis and VNS, stimulate the production of CRF, adrenocorticotropic hormone, and cortisol, affecting intestinal homeostasis [34].

A number of animal models have been developed to elucidate the pathophysiology of IBS. These models are based on the use of chemical or mechanical substances and have been used to induce psychological or physiological stress (drugs, separation from the mother, washing the stomach with cold water, electric

Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
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shock to the legs...) [35]. None of these models are perfect, but they allow us to think about the brain-gut axis in the development of IBS.

The most common difficulty scientists face in understanding the pathogenesis of IBS syndrome is IBS heterogeneity. In clinical biology, blood, urine, saliva and tissues are used to discover biomarkers using the mass spectrometry method [36]. In a study of the proteome in the urine of women with IBS, each case was classified according to the predominance of markers. The mass spectrometry method showed differences in urine proteome levels depending on subclasses. Among the proteins that showed changes, those related to homeostasis of intestinal activity and inflammatory reactions indicate that in the future, the detection of protein markers in the urine of patients with IBS can be evaluated as the main criterion for diagnosis [2] .

The treatment of IBS is one of the most serious problems of modern medicine, which ends with partial reduction of clinical symptoms or ineffectiveness of treatment [37]. The use of pharmacogenetics is recommended to improve treatment methods, which includes characteristics such as the genetic response of patients to drugs [82].

Pharmacogenetics modulates response through pharmacokinetics and pharmacodynamics in the treatment of IBS [38]. Cytochrome P-450 (CYP450) enzymes - CYP2C19 and CYP2D6 are important in the metabolism of drugs used in IBS, the main of which are antidepressants. CYP2D6 is an enzyme with more than 100 genetic variants, highly polymorphic, and CYP2D genes are involved in the metabolism of nontriptyline [2].

The pharmacological part of pharmacogenetics is currently focused on serotonin receptors involved in IBS. Serotonin (5-XT) is considered one of the important neurotransmitters and is involved in many functions of the intestine [39]. There is a growing need for serotonin receptors in the analysis of IBS. For example, 5-HT3 receptor antagonists are more commonly used. 5-HT3 gene receptors are considered polymorphic, and this type shows a response to treatment [40].

Tryptophan hydroxylase 1 (TXP1) is a limiting enzyme involved in the production of 5-HT and is characterized by polymorphism. TXP1 genotypes are more frequently identified among patients with IBS and are affected by the 5-HT3R antagonist, ramosetron [41]. This finding allows identification of subgroups of patients with IBS who are sensitive to ramosterone. Similarly, the study of TXP1 gene polymorphism allows us to determine the role of serotonin as an IBS marker.

Another field in the study of IBS is metabolomics. Metabolomics research can be done from two main technologies:

1) Mass spectrometry
2) Nuclear magnit resonance spectroscopy [42].

A comparative study using samples from healthy and non-healthy patients identified unique metabolites that may serve as diagnostic and prognostic biomarkers. A number of metabolites can change with food intake, and these changes can be used to identify disturbances in metabolic pathways and distinguish between a normal/healthy gut and a dysfunctional/unhealthy gut. Studying the relationship between gut microbiota and microbial metabolites and the host organism can provide important information about the pathophysiology of IBS [42]. In the future, researchers and clinicians should focus on the concentration of microbe-specific metabolites that influence the clinical signs and severity of IBS without relying on clinical symptoms [43].

Based on the pathophysiology of IBS, igloo therapy is also used in the treatment of patients. Iglootherapy is an effective method in the treatment of functional diseases of the gastrointestinal system [44]. Studies

Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

have shown that in patients with IBS, more positive results were recorded in igloo therapy than pinoveria bromide and lactulose. Importantly, this study observed improvement in clinical symptoms, long-term positive outcomes, fewer withdrawals, and fewer side effects [45]. However, since these studies were single-centered and included small numbers of patients, multicenter, high-quality, controlled studies were conducted to confirm their results. This study included 531 patients and compared the results of 4000 TB of pinoverium bromide and needle therapy. In this case, a 6-week treatment course and 12-week follow-up in patients who received igloo therapy showed that the patients had reduced clinical symptoms and improved quality of life indicators, and no side effects were observed [46]. Based on the above, it can be said that igloo therapy is highly effective in the treatment of IBS and may serve as one of the main treatment methods in the future. Despite the positive effects of iglootherapy, IBS main mechanism has not been fully explored. However, there is evidence for the involvement of neurotransmitters. Serotonin reverse transporter (SERT) gene polymorphism is involved in gastrointestinal disturbances in IBS. The SERT gene is involved in controlling the synaptic concentration of 5-XT. Based on research, the effectiveness of igloo therapy and IBS genetic role in the development of IBS have been studied. The effectiveness of iglootherapy in relieving the clinical symptoms of IBS may be related to SERT gene polymorphism in patients [47].

Because our knowledge of the pathophysiology of IBS is insufficient, treatment methods for this disease are focused on managing clinical symptoms rather than modifying it. This strategy includes lifestyle and dietary changes, psychological treatment, and pharmacological agents [48]. But for patients with IBS, this method of treatment is considered unsatisfactory, and the occurrence of side effects is related to pharmacological drugs. This, in turn, leads to stopping the course of treatment. Therefore, the demand for new alternative herbal remedies is increasing day by day. Microbiota management is an effective method in the treatment of IBS [2]. A meta-analysis showed that patients receiving probiotics had a positive change in IBS clinical symptoms [49-57]. However, the disadvantage of this method is that the quality of the studies conducted is low, they were conducted in a small population, and also recorded different results in different organisms.

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Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
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Volume: 3 Issue: 6 | Jun –2024 ISSN: 2720-6866
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