REVIEW ARTICLE

NEW INSIGHTS INTO THE PATHOGENESIS OF IRRITABLE BOWEL SYNDROME

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Abstract: Irritable Bowel Syndrome is one of the most frequently seen functional bowel diseases. Despite its high prevalence, the etiology and pathogenesis of IBS could not still be explained completely and diagnosing is quite difficult in some cases. IBS, being a multisymptomatic functional gastrointestinal system disease, has a broad clinical spectrum and in general, the symptoms are associated with gastrointestinal dysmotility and visceral hypersensitivity. The true diagnosis is based on four key factors: medical history, physical examination, minimal laboratory tests and colonoscopy or other appropriate tests in some cases. However, a homogeneous pathophysiological pattern has not been defined for IBS and this situation, with a high degree of probability, reflects that IBS is a multifactorial disorder that involves abnormalities in brain-gut interactions, visceral hypersensitivity, intestinal motility and secretion, psychosocial factors, composition of the gut microbiota, disturbed intestinal permeability and low grade immune activity.

Key Words: Irritable, bowel, gastrointestinal, IBS

Irritable Bowel Syndrome is one of the most frequently seen functional bowel diseases characterized by recurrent abdominal pains and change in bowel habits (diarrhea/constipation). IBS is a long-term illness in which patients suffer from chronic or recurrent gastrointestinal symptoms despite the fact that routine clinical investigations are normal. Although regional variation exists, the prevalence of IBS ranges from 10–15% in population-based studies in North America and Europe. The prevalence of IBS is most common between 20 and 40 years of age with a significant female predominance (1). Irritable bowel syndrome is divided into four sub-groups by evaluation of the patient's stool according to BSFS (Bristol Stool Form Scale) as diarrhea-predominant, constipation predominant, mixed type and the ungroupable. Constipation predominant IBS diagnosis (IBS-C) is made if more than 25% of bowel movements are type 1 or type 2 and less than 25% is type 6 or 7. Whereas in the diarrhea-predominant IBS (IBS-D); while more than 25% of the bowel movements are type 6 or type 7, less than 25% are type 1 or type 2. In mixed-type IBS (IBS-M); in more than 25% of the bowel movements type 1 or type 2 and again in more than 25% type 6 or type 7 coexistence is seen. The patients that do not fall into any of these three categories are included to the unsubtyped group (IBS-U). And in time, inter-type transitions may be observed in 75% of these patients. IBS is associated with decreased quality of life,

impaired social function and loss of work productivity. Onset of symptoms is most common in young adults and IBS has a global prevalence of around 11% (2). Despite its high prevalence, the etiology and pathogenesis of IBS can still not be explained completely and diagnosing is quite difficult in some cases (3). IBS, being a multisymptomatic functional gastrointestinal system disease, has a broad clinical spectrum and in general, the symptoms are associated with gastrointestinal dysmotility and visceral hypersensitivity (4). In this compilation, we will mention the diagnosis and main pathophysiological bases of IBS.

Diagnostic criteria and clinical symptoms of IBS:

Since the pathophysiology of IBS could not be completely understood and the routine investigations show normal results, IBD diagnosis is based on the combination of altered bowel habits and abdominal pain according to the Rome IV criteria (5). According to that, IBS diagnosis can be made when a patient has recurrent abdominal pain complaint associated with 2 or more of the following criteria: (1) related with defecation; (2) associated with change in defecation frequency; (3) associated with change in appearance of stool. Because of the relationship with motility disorder, visceral hypersensitivity, change in mucosa function and immune function, bowel microbiota changes and the change appearing in the central nervous system (CNS) process, the Rome IV criteria were expanded according to this concept of these bowel-brain interaction disorders.

When compared with the Rome III (6) criteria, two changes in IBS diagnostic criteria stand out in Rome IV. First of these is exclusion of abdominal discomfort from the scope of identification criteria and this means that abdominal pain is not a prerequisite for IBS diagnosis anymore. The basis underlying this amendment was the vague nature of the term ‘’discomfort’’ and the word ‘’discomfort’’ not existing in every language or expressing different meanings in different languages. Besides that, it is not clear whether the discrimination between discomfort and pain is qualitative or quantitative, the knowledge about the meaning of the word discomfort significantly varies among individuals and it is thought to cover too many symptoms. The other major amendment contained the modification made on the symptom frequency threshold. Compared to the period indicated as minimum 3 days in a month in Rome III, in Rome IV, occurrence of abdominal pain at least 1 day in a week on average during the previous month is regarded necessary. It is possible for both amendments to decrease the IBS prevalence in population-based studies; however, since most of the IBS patients recognize pain as one of the main symptoms (7) and appearance of the symptoms in most of the IBS patients in clinical samplings in a frequency higher than once a week (8), neither of these amendments will significantly affect the IBS prevalence in clinical populations. Besides that, with the aim of emphasizing that a significant proportion of IBS patients actually report worsening in pain with defecation and/or stool frequency and/or change in stool form, since it was regarded necessary for abdominal pain to be described with the wording ‘’…*related with* defecation…’’ (Rome IV) instead of ‘’….*recovering* with defecation….’’ (Rome III), a minor amendment made on the definition of the main IBS criteria was also included to Rome IV.

In clinical practice, there are limited aspects in respect of use of Rome Criteria. These criteria may leave the patients who can be treated successfully however who do not meet the criteria out of scope. The subject patients’ remaining out of scope may be originating from the symptom duration being shorter than 6 months, symptoms appearing in frequency lower than 1 in a week or inability of meeting

2 of the 3 criteria. Besides that, some patients may have two or even more FGIDs and these concurrent symptoms are not included in the scope of Rome IV Criteria (9).

Premonitory symptoms suggest existence of an organic disease; however, some authors believe that the accuracy level provided by these remains insufficient (10). The IBS patients' complaining also of various other gastrointestinal (for example dyspepsia) symptoms and nongastrointestinal symptoms like migraine, fibromyalgia, chronic fatigue, chronic pelvic pain, sexual dysfunction, eating disorders, food intolerances and other disorders that provide additional support to diagnosis is a situation worthy of notice.

Some diseases such as inflammatory bowel disease (IBD), microscopic colitis, celiac disease, lactulose and fructose intolerance, colon cancer, enteric infections, food allergy and intolerance as well as neuroendocrine tumors may show similarity to IBS and therefore some diagnostic tests may be needed for diagnosis. It can be seen that a series of various diagnostic methods including manometry, colonoscopy and enteroclysis (11,12) along with stool cultures and blood tests provide benefit in respect of excluding the organic disease. Routine laboratory analyses like complete blood count and blood enzyme panels are normal tests in IBS. Diagnostic evaluation depends on whether the predominant symptom is diarrhea or constipation. The tests suggested for the patients who report symptoms with unclear etiology are: faecal calprotectin or lactoferrin in stool, celiac disease serology, inflammatory disease markers (ESR, CRP, peripheral blood smear), thyroid function tests and selective malabsorption markers (i.e. albumin, ferritin). In special cases, gastroscopy and/or colonoscopy is needed. It is recommended to exclude microscopic colitis or another low-grade chronic inflammation in patients mainly with diarrhea and even in patients with normal mucosa biopsies (13).

Faecal calprotectin is a non-invasive screening method for intestinal mucosal inflammation and it is seen to be more effective than the standard test application such as C-reactive protein (14). It is accepted that IBS patients are under risk in respect of concurrent celiac disease existence. It is estimated that celiac disease may develop in a proportion reaching 4.7% of the patients meeting IBS criteria (15).

Stool analysis may prove to be useful in respect of diarrhea symptom especially in developing countries. When presence of warning symptoms or premonitory symptoms do not exist, colonoscopy for screening purposes should be made if the patient is over the age of 50 . The correlation between IBS and small intestinal bacterial overgrowth (SIBO) has been validated in many researches. This validation has been made mostly by using breath tests, however in about 60% of the patients with IBS and diarrhea, quantitative microbiological assessment of the duodenal aspirate that confirmed SIBO was also used. Hydrogen glucose breath test is the most common non-invasive SIBO diagnostic method (16).

Different IBS biomarkers have been defined and tested; however none of these is a practical indicator of the subject disease that can be commonly used. A short while ago, promising results for faecal volatile organic metabolites (VOM) and colonic mucosal markers were obtained. It has been shown that in IBS patients, nerve growth factor, IFN-*g*, toll-like receptor 4 (TLR4), pre-haptoglobin 2 expression increased seriously compared to the control group and was specifically low compared to the ulcerative colitis patients (17).

In conclusion, the true diagnosis is based on four key factors: medical history, physical examination, minimal laboratory tests and colonoscopy or other appropriate tests in some cases.

The pathogenesis of irritable bowel syndrome

However, a homogeneous pathophysiological pattern has not been defined for IBS and this situation, with a high degree of probability, reflects that IBS is a multifactorial disorder that involves abnormalities in brain-gut interactions (18), visceral hypersensitivity (19), intestinal motility and secretion (20), psychosocial factors (21), composition of the gut microbiota (22), disturbed intestinal permeability (23) and low grade immune activity (24).

Disruption of the bidirectional brain-gut communication which determines the changes in digestive secretion and motility and leads to visceral hypersensitivity is one of most important elements of IBS etiology (25). Another factor in FGID pathogenesis is the change in the intestinal epithelial barrier which plays a critical role in preserving the intestinal homeostasis. The permeability of this epithelium may increase depending on genetic factors, disturbances in gut microbiota, diet, stress, infection and inflammation.

The Rome IV criteria and the publications about these criteria, although the emphasis on the term ‘’functional’’ used in their naming has been reduced, reflect a logical change made in conceptualization of the GI disorders family they cover. In recent years, the opinion that many specific pathophysiological processes, altered immune function, increased intestinal permeability and the imbalance between different types of gut bacteria included, play a role gradually receives broader acceptance. Besides that, it is also accepted that the neural and hormonal interaction between brain and gut carries importance in respect of formation and regulation of the symptoms that appear in the disorders.

Brain-gut axis

The brain-gut axis defines the bidirectional information exchange that happens between these two organs. This neuroanatomic substrate is a complex integrated circuit that transmits the information it receives from the cognitive and emotional centers to the gastrointestinal system and provides data transmission at the opposite direction as well (26). In our day, IBS is thought to be a regulation disorder in the system named as the brain-gut axis where abnormal function in the enteric, autonomic and/or central nervous systems plays a role along with peripheral abnormalities that are probably predominant in some patients and that disturb processing of the signals coming from periphery at the center in the other patients (4). The gastrointestinal system is intensely innervated to provide information regarding the lumen contents, the processes that regulate digestion and absorption and the potential threats. The gastrointestinal afferent sensory fibers that terminate at the bowel wall express a series of membrane receptors and ion channels that receive the information about disruption of mucosal epithelium and lumen contents. These neurons, besides activating local responses, transmit the sensory information to the spinal cord or the brain stem through vagus nerve and spinal afferents for its advanced processing and integration. However, it should be overemphasized that during normal digestion lots of information coming from afferent ends are mostly not perceived and is used in reflexes that control motility, secretion and blood flow (27).

The signals that come from the bowel and ascend upwards, reach the brain from the spinal cord through anterolateral and dorsal column pathways and here they are transmitted to the ventral nuclei of the thalamus and to primary and secondary somatosensory cortex regions for localization, intensity and pain duration and finally to the limbic regions for the

emotional component of pain response.

The immune system plays the role of an important intermediary in the function of brain-gut axis. As a result of injury, inflammation or ischemia, leukocytes, lymphocytes, thrombocytes, mast cells, macrophages, fibroblasts and the mediators released from blood vessels change the activities of the sensory nerves and increase their sensitivity by affecting them directly or indirectly. Therefore, the abnormal inflammatory response given to different events (stress, infection, food, etc.) can be responsible for presence of pathological cellularity and inflammatory cytokines in the colons of some IBS patients (27).

The neuroendocrine system that potentially plays a role in IBS pathogenesis consists of two constituents: 14 types of endocrine cell spread on the intestinal mucosa and ENS nerve fibers. This system, like serotonin, peptide YY(PYY), GIP, somatostatin, CCK, ghrelin and other transmitters, changes motility, secretion, absorption and intestinal microcirculation by production of transmitter substances that relay signal to the neighbouring cells (paracrine) through the vascular system (endocrine) or the intrinsic/extrinsic nerves (28). Besides that, IBS is characterized by the abnormal synthesis, transport and inactivation of the peptides and amines which affect motility, secretion, absorption in intestinal mucosa and the sensation in the organ (29). In different IBS types, there are also changes in the intensity of ileal serotonin, PYY, GIP and somatostatin cells (30).

Therefore, the multifactorial patho-physiology of IBS and FGID involves a series of different factors that may contribute to the change of motility and symptom perception :psychosocial factors (also includes sexual abuse in childhood associated with higher IBS incidence in childhood); visceral hypersensitivity; gastrointestinal infection, inflammation or mucosal irritation; genetics; mast cell involvement that suggests low grade immune activation; food intolerance and changes in bacterial flora and luminal antigen(4).

Intestinal barrier

The intestinal barrier which protects us against the threats originating from the intestinal lumen, plays a critical role in preservation of the intestinal homeostasis. Referring to animal researches, various factors that lead to intestinal barrier dysfunction have been defined. These factors include the genetic and epigenetic changes, decrease in glutamine synthetase activity, a fall in proteolytic activity caused by the pancreatic enzymes that appear in the intestinal lumen or bacterial proteases and stress-induced mast cell activation. In humans, the factor that leads to intestinal barrier dysfunction can be one of these mechanisms. In animal studies, it has been shown that psychological stress has indirectly activated the mast cells through corticotropin-releasing hormone (CRH) secreted by eosinophils (31). Increase of the intestinal permeability and the consequent antigenic material translocation in epithelium enables the stimulation of the intestinal immune system by production of inflammatory mediators that can maintain permeability and create abnormal neuron responses (32).

The effect of psychosomatic disorders

The close relationship of IBS with mental disorders is a quite established deep rooted belief in clinical practice. One of the most common psychiatric disorders associated with IBS is depression which appears in a great proportion like 30% of IBS patients. The relationship between depression and IBS may both originate from the IBS probability of IBS being higher in patients with depression history and may be linked to development of secondary

depression in patients who had been diagnosed FGID previously. It has been shown that depressive syndrome, sleep disorders or sexual dysfunctions may emerge in IBS patients with long lasting disease progress (33). Anxiety often accompanies IBS (16% compared to the ratio which is 6% in the control group) and may worsen the IBS symptoms (34).

In conclusion, although it is known that there is a connection between mental disorders and IBS, it should be emphasized that the etiology of these is multifactorial and complex and has not gained complete clarity. Psychological stress is an important risk factor in respect of development of several diseases and when it is present, it may aggravate their symptoms. However, psychological stress may develop as a consequence of IBS also (35).

Genetic susceptibility

Emergence of IBS more frequently in monozygotic twins compared to dizygotic twins (33% compared to 13.3%, respectively) shows that genetic predispositions play a role in development of this disease. Compared to the 2% of the individuals in the control group, in a proportion greater than 33% of the patients, IBS family history is discovered. As shown in a recently made research, IBS may involve genetically determined changes in serotonergic transmission in the gastrointestinal system (36). A large portion of the intestinal serotonin is stored in the enterochromaffin cells (EC) found in the intestinal mucosa. It has been determined that the number of these cells and consequently the 5-HT level on the intestinal wall is higher in IBS-D patients whereas it decreases in IBS-C patients (37).

On the surface of the enterocytes, serotonin reuptake transporters (SERT) are found. These inhibit the serotonergic transmission and accelerate the motility of the gastrointestinal system by reducing the reuptake of this amine (34). It has been shown that in IBS patients the SERT gene expression has decreased and this decrease may be responsible for appearance of diarrheic symptoms originating from the increased 5-HT level on the intestinal wall (37). The findings of Colucci et al.(38) have not validated this situation. In the study made by these researchers, it is reported that lower SERT expression and decreased 5-HT intake activity originates from 5HTTLPR (5-HT transporter long polymorphic region) polymorphism in the human SERT gene. The examined gene has dominant –short (S) and recessive – long (L) alleles. Presence of allele S is associated with a lower SERT expression and decrease of 5-HT reception activity. Although the severity of IBS symptoms in patients with LS/SS genotype was meaningfully higher compared to the LL genotype, generally in IBS patients and in case of stratification, the frequency of 5HTTLPR genotypes in C-IBS and D-IBS patients has not shown a meaningful difference compared to the healthy control subjects. Thus, it is seen that 5HTTLPR polymorphism affects the course of the disease however it does not affect its emergence or clinical picture in respect of the predominant bowel habit (38).

The importance of the other polymorphisms is also accepted. Presence of these is related with the increase of proinflammatory cytokine TNF-α expression and decrease of the anti-inflammatory cytokines IL-10 ve TGF-β expression (33).

Some data at limited level are also available about the role of epigenetics in IBS pathology. – In recent researches, the importance of the stress which causes the epigenome to be reshaped in the stress which causes visceral pain has been shown (39).

Stress

Chronic stress can create susceptibility for

IBS development by increasing the disorders in gastrointestinal system motility, gut microbiota, visceral sensation and mucosa function and also cause exacerbation of its symptoms (40).

Stress activates the hypothalamic, pituitary, adrenal (HPA) axis and this may disrupt the bidirectional communication between brain and gut (41). It is also asserted that chronic stress and increased glucocorticoid levels can cause a permanent increase in sensitivity against visceral stimuli by affecting the amygdala which is an important limbic structure and anxiety-like behaviour as well.

Excessive catecholamine release that reduces the amount of acidic mucopolysaccharide in the intestinal mucosa and the mucin production shows a negative effect on the mucosal barrier. Under stress conditions, IgA production which prevents adhesion of pathogens to intestinal epithelium decreases. These processes can lead to disorders in gut microbiota and increase the permeability of the intestinal wall against bacterial antigens and toxins (37).

The role of gut microbiota in IBS

The gut microbiota contains 1000-1150 species of bacteria (10^{13}–10^{14}) (42) and plays an important role in intestinal development, processing and digestion of food, immune system function, resistance against pathogens, numerous metabolic pathways as well as in modulation of neurotransmitters, hormone production and secretion. The changes in the count and composition of bacteria are defined as dysbiosis. In dysbiosis, many factors such as drugs (antibiotics, nonsteroidal anti-inflammatory drugs), high carbohydrate containing diets, chronic mental or physical stress, history of a past illness, climate changes or air pollution play a role. Humans live in a condition of close symbiosis with our intestinal microbiota which shows effect both directly and through its metabolites. Although it is determined that more than 1200 different microbes exist in the GI system (43), these microbes are found in only a small ratio in every healthy individual (44). The firm relationship between the host and intestinal microbiota is being explained by showing the role of the naturally found, non-pathogenic commensal microbiota in intestine physiology, development of energy metabolism (45) and mucosal immune system education (46) as example.

In the experimental researches and observational studies made over the past decade, it was shown that the microbial composition in the Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) patients can change compared to the healthy individuals. In the recent years it has been determined that the dysbiosis in the microbiota related with lumen and mucosa is associated with IBS (47). However, although it has been shown that changes in gut microbiota appear in these disorders, the importance that the microbial dysbiosis detected in IBD and IBS carries has to be determined and the role of nutrition, therapeutic and environmental factors in preservation of the gut microbiota and its role in disruption of gut microbiota composition in these disorders should be specified. Finally, the potential of the altered intestinal microbiota for curing and preventing GI disorders like IBD and IBS has not yet gained clarity. It has been shown that bacterial diversity decreased both in the lumen and the mucosa specimens taken from IBS patients (47-49). It has been reported that there was a decrease in *Lactobacillus* and *Bifidobacterium* spp in IBS-D and even they did not exist at all and the pathogenic species like *Enterobacter* have increased (50). In IBS-C patients, it was determined that the *Veillonella* species was predominant (40).

Post-infectious IBS

Although the individuals in whom IBS develops after a gastroenteritis disease (post-infectious IBS) constitutes only a subgroup of the IBS cases, the increase of the risk of IBS development after a previous GI infection seven times more strengthens the hypothesis that the abnormalities in the immune interactions between the microbe and host is related with IBS pathophysiology (51). Potentially, an altered microbiota composition is associated with disruption of the microbe recognition property in IBS and this may lead to a change in the capability of eradicating the microbial invaders. Therefore, indication of that the Toll-like receptor expression change (52) in the mucosa and the increase in serum antibody levels formed against flagellla which is a bacteria component (53) in IBS patients has been shown attracts attention. Besides that, the intestinal microbiota can affect the other factors that are asserted to be in the scope of IBS pathophysiology, also; for example, intestinal permeability (54), brain function (55), enteric nervous system (56) as well as intestinal motility (57) and visceral pain (58). Moreover, it can create the key symptoms like bloating and gas in IBS patients through lumen microbiota carbohydrate fermentation and gas production (59).

In conclusion, still a deficiency in the information regarding what kind of a role intestinal microbiota plays in IBS pathophysiology is in question. Therefore, to study the connection between microbiota and IBS pathophysiology in detail, researches that consider the heterogeneity of IBS symptoms and the components of IBS pathophysiology other than the microbiota and evaluate the microbiota composition in time should be made.

Nutrition

The relationship between nutrients and the functional gastrointestinal symptoms can be explained with the abnormal modulatory mechanisms that arise as a response to various stimuli that nutrients mediate (31). In gastrointestinal system nutrient presence modulates gastrointestinal motility, barrier function (secretion, absorption), sensitivity and the intestinal microbiota. Some intestinal receptors are nutrient-specific and the stimulation of these lead to activation of the neurohumoral pathways that are related to the composition of the meal. The strongest component of nutrients that affect motility, sensitivity and intestinal barrier is fat; however, carbohydrates in low amounts and the wheat proteins such as gliadin or gluten are also important (27).

Hypersensitivity to some nutrients may lead to disruption of intestinal mucosa, low-grade inflammation in the gastrointestinal system, increase of intestinal epithelial permeability and visceral hypersensitivity (28). Although well-defined food allergies are not common in IBS patients, it has been observed that IBS symptoms intensify due to fructose malabsorption (60). Chemicals which have potential bioactivity such as salicylates, amines and glutamates may also cause abdominal pain, bloating or diarrhea and these are associated with IBS (61).

In IBS patients, most of their symptoms are related with consumption of a specific type of meals and 63% of the patients know the products that must be avoided (62). It has been proved that in fermentation process excessive gas production and osmotic hypertension may increase the IBS symptoms and this occurs through insufficiently absorbed nutrients that are defined as FODMAP (fermentable oligosaccharides, disaccharides, monosaccha-rides and polyols). The aforesaid substances include the short chain carbohydrates such as fructose, lactose, sugar alcohols which are found in milk products, some vegetables and fruits (for example: onion, garlic, leek, cabbage, Brussels sprouts, corn, apple, peach,

watermelon, plum, dried fruits), cereal products (wheat, rye) and honey (63).

There is fructose malabsorption and dietary fructose intolerance in about one third of the patients with IBS suspicion. Lactase activity has decreased also in nearly 70% of the adult population (64). In individuals who have lactase deficiency, lactose is not absorbed by being hydrolyzed in the small bowel, but passes through the gastrointestinal tract to the colon where gas that causes luminal distension as a result of bacterial fermentation and generates the gastrointestinal symptoms and the short-chain fatty acids are produced (65).

Dietary fiber deficiency is an important factor for IBS-C symptoms; however some patients may paradoxically complain of the intensification of their symptoms after consumption of greater amount of water soluble fiber. The gas produced during the decomposition of the water soluble fiber and FODMAPs by the intestinal bacteria causes intestinal gas and discomfort. This process depends on the composition of the intestinal microflora (36).

In summary, abnormality of the fermentation of the substances taken by nutrition in the colon may lead to the development of GI symptoms. The fructose containing FODMAP diet mostly constitutes a part of these arguments due to the present supportive evidence that shows meaningful recovery of IBS symptoms. However, since this kind of dietary changes may cause and aggravate microbial dysbiosis, in order to determine the long-term effectiveness and reliability, future studies that evaluate the long-term effects shown by dietary changes on the microbiota composition are needed.

Gluten is a factor well known to affect the permeability of the intestinal barrier, to create low-grade inflammation and to stimulate the visceral and autonomic nervous system (28). In individuals with celiac disease, symptoms suggesting IBS may develop while gluten intolerance may also be seen in IBS patients. The role of gluten in IBS pathogenesis has not been clearly proved. NCGS (Non-Celiac Gluten Sensitivity) is a syndrome that has intestinal and extra-intestinal symptoms related to the ingestion of gluten containing food. This is a disease entity different from celiac disease or wheat allergy. Due to the similarity of the intestinal symptoms of NCGS to IBS symptoms, many patients who have NCGS complaint are misdiagnosed as IBS. In NCGS patients, extra-intestinal symptoms arise more frequently compared to IBS: fatigue, headache, anxiety, numbness, myalgia, weight loss and even autism or hallucinations (66).

Infections

Especially being IBS-D, diagnosis in some patients can be associated with an acute gastrointestinal infection story in the past. This disorder is defined as post-infectious irritable bowel syndrome (PI-IBS). The factors that cause PI-IBS are protosoal (*Trichinella* sp.), parasitic (*Giardia intestinalis*) or viral (norovirus, Norwalk virus) infections as well as the bacterial infections (*Salmonella* sp., *Shigella* sp., *Campylobacter jejuni*, *Escherichia coli* – ETEC, EAggEC, O157:H7) (33).

It is thought that PI-IBS probability shows correlation with the severity of the symptoms and the course of infection. This disease can be seen even 6 years after acute enteritis (67). PI-IBS mostly appears in young individuals whereas the risk decreases in the individuals over 60 years of age (68).

PI-IBS is also characterized by the increase of T cell, neutrophil and mast cell counts in the colonic mucosa, hyperplasia of EC cells. Stimulation of the immune system causes chronic low-grade inflammatory state in the gastrointestinal mucosa that leads to PI-IBS (50).

Low-grade inflammation

Based on the recent studies, it has been asserted that the visceral hypersensitivity in IBS could be secondary to the activation of immune cells and development of low-grade inflammation. In IBS patients, increase in incidence of mucosal hyperplasia, lymphocyte aggregation and increased count of EC cell, eosinophil and mast cell develops compared to the healthy control subjects and this validates that low-grade inflammation arises in intestines which have IBS (37).

In some IBS patients, the serum levels of the proinflammatory factors such as IL-1*b*, IL-6, IL-8, IL-12, TNF-*α*, T and B cells and macrophages increase (69). The severity of the symptoms shows correlation with the levels of inflammatory markers (40).

There is an overlap in the clinical symptoms that are present in functional disorders (such as IBS) and in chronic inflammatory bowel disorders (such as Crohn's colitis). It has even been asserted that IBS may be an inflammatory disorder type where low-grade non-specific intestinal inflammation is found (70). For example, it has been shown that mucosal pro-inflammatory cytokine levels have increased in many IBS patients, and especially in post-infectious IBS (71). Functional disorders may also constitute the cause for the symptoms to persist or for clinical exacerbations in validated IBD patients. Determination of the faecal calprotectin concentration is accepted as the best non-invasive screening method for intestinal mucosal inflammation in these patients (72).

In conclusion; IBS is a disease that has complex etiological factors; where there are unanswered questions despite many studies made on its definition, pathophysiology, diagnostic criteria and management. As recommended in the Rome IV criteria also, when making a diagnosis in IBS patients, the age, characteristics of the primary symptom and other clinical and laboratory findings of the patient should be evaluated altogether. Despite all the effort spent in forming the diagnostic criteria concerning IBS, the present criteria remain incapable in daily practice.

While IBS symptoms have traditionally been found associated with disturbed gastrointestinal motility, visceral hypersensitivity and psychological stress in general, in the recently made studies now the role of the changes in intestinal and colonic flora is also emphasized. It has been shown both in experimental and observational studies that in IBS patients, not only intestinal microbial dysbiosis occurred, but at the same time bacterial diversity has decreased, too. The potential of the gut microbiota to affect the brain-gut axis is spoken of. It is still not clarified which mediators and pathways are at the forefront in the patients who have visceral hypersensitivity. It has been shown in observational studies that especially infectious gastroenteritis cause risk increase in IBS development. Therefore, research should continue on gut microbiota, intestinal barrier permeability, neuroimmune functions and psychological stress and on their interaction with each other. In further studies, by revealing these pathophysiological mechanisms, efficient treatment plans can be formed.

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