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Pathophysiology of the irritable bowel syndrome – Reflections of today

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ABSTRACT

Irritable bowel syndrome (IBS) is a chronic gastrointestinal symptom complex defined by abdominal pain and disturbed bowel habits over 3 months within a period of 6 months, in absence of any identifiable organic pathology. Over the years, speculations of the pathophysiology of IBS has moved from elusive central nervous symptoms impinging on psychosomatic disease, to objective signs of intestinal fermentation with abdominal bloating and intestinal dysmotility. The specific subgroup of post-infectious IBS is of special interest since it opens the possibility of dysbiosis as the pivotal point for development of IBS in association with traveler's diarrhea or antibiotic treatment with ensuing dysbiosis and abdominal symptoms that may resolve over decades. The undefined disease mechanisms that take place within the gut seem responsible for the gut-brain signaling leading to activation of brain centers that drive the clinical picture of IBS, further modulated by the patient's social background and previous lifetime events.

Introduction

The irritable bowel syndrome (IBS) is a multifaceted disease of unknown etiology. The paucity of a single etiology IBS makes it unlikely to cure, why the pathophysiology of this syndrome is an important factor fort the approach to the patient with an ultimate goal of controlling symptoms.

IBS is considered to be a biopsychosocial disorder with a key factor in altered brain-gut interactions that modulates the response of the patient to different challenges. Changes in the brain-gut communication are associated with gut motility disturbances, visceral hypersensitivity and disordered autonomic gastrointestinal (GI) responses. Many factors play an important role for the spectrum of IBS symptoms but some may be more prominent in certain individuals than in others. Stress, gender, genetics, previous GI infections stand out as specific hallmarks in the development of IBS, all being modulated by various psychosocial factors [1,2].

Gastrointestinal motility

Several studies show that patients with IBS have increased gut motility particularly following meals or under stressful conditions. A number of motility abnormalities including prolonged propagated contractions and high-amplitude propagating contractions are more frequently seen in IBS compared with healthy subjects. However, a consistent motility abnormality which could explain the symptoms in all IBS patients has not been defined, why motility recordings cannot readily be used as diagnostic tool for IBS. Nonetheless, in terms of motility patterns, IBS patients with diarrhea-predominant disease (IBS-D) display more rapid GI transit times than do normal subjects, while patients with constipation predominant IBS (IBS–C) have a normal or slower GI transit than normal [3,4]. The mixed-pattern of IBS (IBS-M), may have divergent transit times but have not been extensively studied.

Visceral hypersensitivity

Experimental evidence confirms that a variety of differences exist in IBS. Patients with IBS have increased sensitivity to balloon distension in both the upper and lower GI tract and are sensitive to intestinal contractions as compared to normal subjects. In line with this data show that IBS patients have rectal hypersensitivity in tandem with somatic hypersensitivity to thermal stimuli [5,6]. Two mechanisms have been forwarded as explanation for the visceral hypersensitivity in IBS; hypervigilance towards expected aversive events from the viscera, and hyperalgesia inducible by sustained noxious visceral stimulation [7].

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Central nervous modulation

Signaling from the brain to the GI tract is important to ensure optimal digestive functions, which has a bearing on mood. With an increasing number of functional neuroimaging techniques, evidence for central nervous modulation of the brain-gut axis has emerged. Application of functional brain-imaging techniques of positron emission tomography and functional magnetic resonance imaging can directly show the role of specific central networks in normal subjects and compare to an altered processing of visceral nervous signaling. In healthy subjects, brain regions such as the mid insula and anterior insula, anterior cingulated cortex (ACC), prefrontal cortex (PFC), thalamus, and the dorsal pens and periaqueductal gray of the pons are activated in response to visceral as well as somatic nociceptive stimuli [8]. In IBS, functional brain imaging show that altered visceral sensory, affective and motor responses are associated with differences in regional cerebral blood flow [9].

Balloon distension of the distal colon, demonstrate differences in regional brain activation in patients with IBS as compared with healthy controls. The dorsal region of the ACC is consistently more activated in patients with lBS compared to controls. This region is responsible for cognitive processing of sensory input, including response attention and selection. Furthermore, dorsal ACC activation correlates with subjective unpleasantness of visceral and somatic pain. Accumulating evidence suggests that IBS patients have altered activation of brain regions involved with attentional processes and response selection in the ACC and anterior midcingulate cortex, emotional and autonomic responses to stimuli in the ventromedial PFC, perigenual ACC, infragenual cingulate cortex and subcortical regions receiving cortical projections from the subcortical regions as well as afferent signals from the visceral organs in response to actual or anticipated colorectal distension [10]. Such findings are consistent with enhanced anxiety responses and hypervigilance [11]. It is hypothesized that patients with IBS may fail to recruit central nervous down-regulating mechanisms in response to incoming or anticipated visceral pain with altered activation or deactivation of brain areas involved in the emotional or cognitive processing of visceral stimuli, resulting in amplification of pain perception. Supporting the significant influence of central nervous factors on IBS symptomatology, it has been demonstrated that alterations in brain activation patterns are affected by treatment [12]. Furthermore, in IBS patients treated with the $5HT_3$ receptor antagonist alosetron for IBD-D, there is a decrease in the regional cerebral blood flow in brain regions including the ventromedial PFC, infragenual cingulate cortex and amygdala in association with improvement of IBS symptoms and mood ratings [13,14]. Furthermore, treatment of women with IBS with amitryptiline is associated with reduced pain related to cerebral activations in the perigenual ACC and left posterior parietal cortex during auditory stress [15]. These findings support a clinically important contribution of a central nervous modulation of visceral pain in IBS. In support of this, IBS treatment can significantly affect brain activation in key regions for visceral pain sensations and correlate with symptom improvement.

Autonomic nervous system

The autonomic nervous system with its sympathetic, parasympathetic and enteric branches mediate brain-gut communication. In this way, GI motility, secretion, and immune function is coordinated and modulated. An increased sympathetic nervous activity and decreased parasympathetic activity are important for a response to stress. Resulting changes in GI function may provide the mechanism linking stressful life events to IBS symptoms. Studies investigating the autonomic nervous function in IBS patients show inconsistent results, as explained by differences in patient sample characteristics, assessment parameters, and experimental conditions under which measurements were done, i.e. fed or fasting conditions, gender, bowel habits and IBS symptom severity. However, as might be expected from a model that emphasizes an increased stress response, increased sympathetic activity and decreased parasympathetic nervous activity are the most frequently noted differences in IBS patients as studied with cardioautonomic reflexes [16,17].

Neuroendocrine responses

IBS postulates stress-induced alterations in brain neuronal circuits, referred to as the emotional motor system, as the principal effector system for emotional and motivated behavior. In IBS, there are inadequate antinociceptive responses, and altered sympathetic nervous activity and hypothalamic-pituitary-adrenal (HPA) axis responses. There is data evaluating HPA axis responses at baseline, to hormone challenge and to experimental stress in IBS patients. At baseline, increased HPA axis hormone levels (adrenocorticotropin, glucocorticosteroids) have been reported in patients with IBS compared to healthy individuals. Two studies reported divergent results with regard to corticotrophin releasing factor (CRF)-stimulated HPA. One study found increased adrenocorticotropin hormone, but normal cortisol levels, while the other demonstrated both a blunted adrenocorticotropin response with low cortisol levels when analyzing both IBS and functional dyspepsia patients with concurrent psychological co-morbidity [18,19].

Administration of CRF has also been shown to increase colonic motility to a significantly greater degree in IBS patients compared to control s in a study by Fukudo et al. [19]. In a subsequent study by the same group, administration of a non-specific peripheral CRF receptor antagonist was shown to significantly suppress the enhanced motility induced by electrical stimulation in the rectum. Hence, data support a pathophysiological role of stress and CRF in IBS [20].

Gut mucosal immune system

Studies report that 7–30% of patients with a recent history of proven bacterial gastroenteritis develop IBS-like symptoms, what is considered as "post-infectious IBS" (PI-IBS) [21]. Additional observations verify mucosal abnormalities in the colon of patients with PI-IBS [22]. Patients with a history of a previous *Campylobacter* infection and PI-IBS were found to have an increased number of intraepithelial lymphocytes and enterochromaffin cells together with increased intestinal permeability, even after one year compared to controls. A subsequent study was performed to prospectively determine the relative importance of both psychological and histological factors for the development of PI-IBS after a *Campylobacter* infection. PI-IBS, predominantly of the IBS-D subtype, occurred in 103 of 747 (13.8%) of those infected. Enterochromaffin cell counts were higher in patients with PI-IBS compared with patient controls and healthy volunteers. Mucosal T lymphocytes of the lamina propria were significantly higher in patients with PI-IBS and patient controls in contrast to healthy volunteers. Anxiety, depression and fatigue were significantly increased in patients with PI-IBS compared with patient controls [22,23]. Increased numbers of enterochromaffin cells and depression were equally important independent predictors of developing PI-IBS [23]. Another study found that patients with PI-IBS have greater mRNA expression of the inflammatory mediator, interleukin-1β [24].

There is strong evidence of increased mucosal immune markers

in unselected IBS patients. Increased numbers of intraepithelial lymphocytes, T cells, and mast cells have been observed (**22**). Approximately 40% of patients with IBS diagnosed by the Rome criteria were found to have evidence of a non-specific microscopic colitis on colonic tissue biopsies [25]. A recent study by Barbara et al. [26] found that 77% of IBS patients showed an increased area of mucosa occupied by mast cells as compared with controls. In addition, in IBS there was a 1.5-fold increase in the number of degranulating mast cells, and an increased mucosal content as well as release of tryptase and histamine. Specifically, mast cells in close proximity to nerves were significantly correlated with the severity and frequency of abdominal pain and discomfort. Although the release of tryptase and histamine did not correlate with abdominal pain and discomfort, mast cells release various biologically active substances that can sensitize primary afferent neurons.

Serotonin and serotonergic mechanisms

The extracellular space is the serotonin reuptake transporter (SERT). SERT is present in both the brain and the gut. The amount of serotonin (5HT) reuptake that occurs from the extracellular space is genetically determined and is based on the presence of long (l/l), short (s/s) or heterozygous (l/s) polymorphisms in the promoter for synthesis of SERT. The homozygous short and heterozygous variant reduces reuptake of serotonin. SERT activity is important in influencing the availability of serotonin to stimulate serotonin receptors, and influence the response to other serotonergic medications such as selective serotonin reuptake inhibitors, being used in the treatment of depression, as well as the novel newer prokinetic agents with serotonergic actions in IBS, such as prucalopride and velusetrag. There is now evidence suggesting that SERT polymorphisms may influence a patient's response to treatment. A small study with 15 patients of either sex with IBS-D where alosetron, one mg orally twice daily for six weeks was given, and intestinal transit measured. Twenty-three subjects submitted blood samples for analysis and SERT polymorphisms were identified. When colonic transit was measured, patients with the [l/l] polymorphism and high serotonin reuptake, resulting in less serotonin available for stimulation of gut peristalsis, had more outspoken slowing of intestinal transit with alosetron than the heterozygotic patients. The importance of SERT and its effect on colonic transit with alosetron as regards its clinical efficacy is interesting upcoming serotonergic drugs that may be used for treatment of IBS [27]. Other studies report conflicting results on the association of specific SERT polymorphisms and associated clinical characteristics, such as bowel habit predominance in IBS, differences that are likely to be due to ethnic variants in genotype of the polymorphisms [28].

In an attempt to determine whether enteric serotonin signaling is defective in IBS, Coates and colleagues measured mucosal serotonin, tryptophan hydroxylase-1 mRNA, the serotonin transporter mRNA and serotonin transporter immunoreactivity in patients with IBS, patients with ulcerative colitis, and healthy controls [29]. These outcome measures were all significantly reduced in UC, IBS-C, and IBS-D as compared to controls. When the serotonin release was investigated under basal conditions and mechanical stimulation, no changes were detected in any of the groups relative to healthy controls. Hence, a conclusion was made that IBS and UC are associated with similar molecular changes in serotonergic signaling mechanisms. While UC and IBS have distinct pathophysiological properties, these data suggest that shared defects in serotonin signaling may underlie the altered motility, secretion, and sensation in both disorders. Although this study is intriguing and demonstrates significant molecular alterations specific to the gut in IBS patients further investigation is needed to more completely understand serotonergic mechanisms in IBS.

Altered brain-gut interactions in IBS

Stress is widely believed to play a major role in the pathophysiology and clinical presentation of IBS and may induce these altered physiologic responses via effects on brain-gut communication and interactions. In genetically predisposed individuals, the permanent experience of stress enhances responsiveness of the central nervous circuits which should increase their vulnerability in developing functional and affective disorders such as IBS [30,31].

Stress may be central (e.g., psychological distress) or peripheral (e.g., infection, surgery) in origin. Studies indicate that patients with IBS report more lifetime and daily stressful events, including IBS, compared with patients presenting organic GI conditions or healthy individuals [32]. Stress in IBS patients is also strongly associated with symptom onset, exacerbation and severity. Despite the fact that the effects of stress on gut function are universal, patients with IBS appear to have a greater reactivity to stress compared with healthy individuals.

Psychosocial factors in patients with IBS and similar functional GI disorders display concurrent psychological disturbances, particularly those with severe symptoms. A number of psychosocial factors have been recognized to modify the illness experience and influence health care utilization and treatment outcomes. These factors may be a history of emotional, sexual abuse, physical abuse, stressful life events, chronic social stress, anxiety disorders, or maladaptive coping with life itself. A current conceptual model regarding the role of psychosocial factors and stress in IBS suggests that adverse, past as well as present, life experiences influence stress responsiveness, physiologic responses, and susceptibility to developing and exacerbating symptoms via amplification of brain-gut interactions. The characterization of psychosocial factors is of outmost importance in IBS, because of their potential of modulating lifetime experiences and influence patterns of pain reporting and medical health care utilization, psychosocial interview may reveal associated symptoms and concerns that the patient may not have previously expressed and can contribute to the severity of the disorder and its outcome.

There is increasing evidence for *sex and gender effects*, not only in prevalence, but also in clinical presentation, pathophysiology and treatment response in IBS [33,34]. Although there exists a gender bias in diagnostic criteria and rates of general healthcare utilization, IBS appears to occur in females at about twice the rate of men, with an even higher ratio in tertiary care referral centers. In general, while rates of abdominal pain are similar, women with IBS report more constipation, bloating, and extraintestinal visceral and somatosensory symptoms and pain disorders. Both IBS and non-IBS symptoms appear to be influenced by the menstrual cycle with higher symptom ratings at onset of menses, presumably through ovarian hormones affecting central and peripheral sensitization mechanisms [35]. Female sex hormones appear to have an influential role on gut motility and pain perception supported by changes during different phases of the menstrual cycle and pregnancy as well as findings in animal studies. In contrast, the role of male sex hormones in IBS is completely uncovered. Female gender is a predisposing factor for the development of post-infectious IBS [36]. Although there is evidence that gender differences in treatment response ma y exist, large clinical trials with sufficient numbers of men and women with IBS are needed to determine if these differences for a specific treatment truly exist.

Relatively few data are currently available that demonstrate consistent physiological differences in visceral sensory thresholds or motor patterns in females compared to males. Women with IBS appear to have enhanced recto-sigmoid perception compared to men [34]. This may in part be due to sex-related differences in the central processing of aversive information originating from the

colon. Naliboff et al. [34] found that men with IBS had greater activation in brain regions associated with the *cognitive* processing of painful sensations including the insula and midcingulate cortex, while women with IBS showed greater activation in limbic regions including the amygdala and infragenual cingulate cortex which are associated with the *emotional* processing of visceral stimuli. Gender-related differences in sympathetic nervous system responses to recto-sigmoid consistently with men with IBS having a greater sympathetic activation response than women. Further studies with larger sample sizes of men and women with control of menstrual cycle are needed to more completely understand how sex differences in biological factors play a role in the greater vulnerability of women to develop chronic pain disorders such as IBS and the differences in symptom presentation and physiologic responses in IBS.

Evidence of *genetic factors* in IBS is supported by several studies. There is an increased frequency of IBS in adults with an affected first degree relative, which suggests that familial aggregation of IBS occurs, supporting a genetic or intrafamilial environment component, but this may be explained in part by familial aggregation of somatization [37]. Levy and colleagues [38] tried to assess the relative contribution of genetic and social learning influences on the development of IBS by comparing concordance rates in monozygotic and dizygotic twins to concordance between mothers and their children. Questionnaires soliciting information on the occurrence of more than 80 health problems, including IBS, in self and other family members were sent to both members of 11,986 twin pairs. Concordance for IBS was significantly greater in monozygotic (17.2%) than in dizygotic (8.4%) twins, supporting a genetic contribution to lBS. However, the proportion of dizygotic twins with IBS who have mothers with IBS (15.2%) was significantly greater than the proportion of dizygotic twins with IBS who had co-twins with IBS (6.7%). In addition, having a mother with IBS and a father with IBS were independent predictors of IBS status; both were stronger predictors than having a twin with IBS. This study lends further support that heredity contributes to development of IBS, but social learning has an equal influence.

Prior infectious gastroenteritis is a hallmark of the IBS. It has been noted that a large subset of patients with IBS can trace the development of their symptoms to an episode of infectious diarrhea, primarily bacterial or amoebic and possibly even viral. Risk factors for PI-IBS include duration of acute diarrheal illness, female sex, and the presence of significant life stressors occurring around the time of infection [39,40]. It is not clear why acute GI infections are a predisposing or etiological factor for development of IBS. Overall, the defect is probably related to an inability to down-regulate the initial inflammatory stimulus efficiently. This may manifest itself as maintenance of increased mucosal serotonin-producing enterochromaffin cells, T-lymphocytes, macrophages, mast cells and pro-inflammatory cytokines which conceivably interact with the sensorimotor regulation of the gut resulting in changes in gut function [23].

Dysbiosis

Accumulating evidence indicate that perturbation of the gut microbiota composition and diversity may play an important role in the development of IBS [41]. The basic concept for a disturbance of the GI ecosystem, vaguely termed '*dysbiosis*', is that about 10% of those who once have had a bacterial intestinal infection later develop post-infectious IBS [42]. Another alternative is that antibiotic treatment may cause long-standing dysbiosis with ensuing symptoms of IBS. Under such circumstances, luminally-acting antibiotics such as rifaximin may have a positive, but usually transient therapeutic effect [43], whereas broad-spectrum antibiotics may further increase the risk of microbial perturbation and development of IBS [44]. Experience from recurrent *C. difficile* infection CDI, which is generally accepted as a cause of dysbiosis, fecal microbiota transplantation has been used remarkable therapeutic results [45]. In a research setting, patients fulfilling the Rome III criteria of IBS have been studied using an anaerobic cultivated human intestinal microbiota (ACHIM), aiming to rectify GI dysbiosis diversity, while simultaneously assessing IBS symptoms. An initial feasibility study using historical controls suggests that the ACHIM microbiota is able to reduce, and in a few instances even cure, the IBS (Fig. 1). However, the effect is unforeseeable as the IBS problem is multifactorial with a myriad of bacteria in the IBS gut, from which we know very little. Bold attempts have been made to outline a typical IBS microbiota where *Prevotella* and *Clostridiales* stand out as possibly overrepresented, where *Clostridiales* were associated with a methanogenic flora [46], supposedly involved with IBS typical of the constipation subtype [47]. The theoretical challenge with microbiota transplantation falls back on the composition of the microbiota, both within the gut lumen, at the lining of the inner mucosal layer or at the epithelial border, and the given microbiota composition. Today much effort is spent on the finding of a "super-donor" as outlined by past medical history, biometrics and fecal microbiological spectrum. Just as important may a "super-receiver" be carrying the right components of the microbiota that should match the donated microbiota in order to normalize gut function and hence, quality of life.

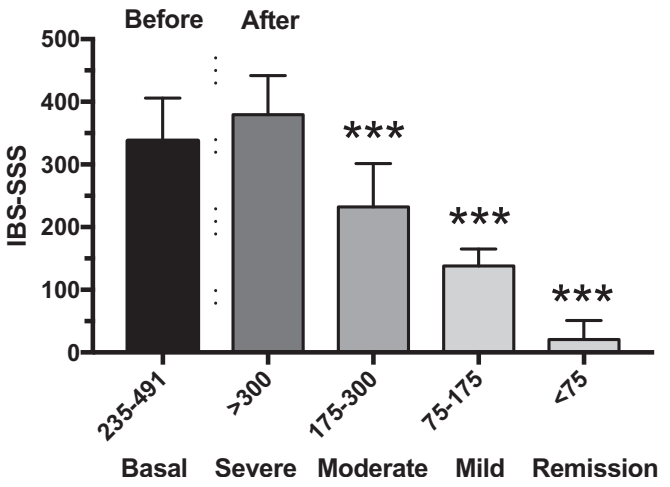

Fig. 1. Results of fecal microbiota transplantation in 50 subjects. The IBS category is shown on the horizontal axis and the IBS-SSS on the vertical axis. Eleven IBS patients remained in severe condition, 21 were relieved to moderate IBS-SSS, 14 to mild IBS-SSS and 4 went into remission until 1 month follow-up. ***$p < 0.001$. Adapted from Benno et al., this issue.

Summary

IBS is conceptualized as a deviated gut-brain communication with altered GI function, modulated by internal and external factors including stress, food intake, and post-infectious GI conditions. Visceral hypersensitivity is one of the hallmark features of IBS. This hypersensitivity is experimentally measured by balloon distension of the colon or rectum, with an increased perception of bowel distension and discomfort during normal bowel activity. Functional brain imaging studies during visceral distension suggest gut-brain alterations in IBS. In IBS, regional brain activation differs from that of healthy controls, suggesting central nervous and autonomic processing of pain. These processes are susceptible to modulation by psychological symptoms, stress and previous life events. It has

been postulated that in genetically predisposed individuals, sustained stress can result in permanently increased stress responsiveness of central stress circuits with vulnerability to develop functional and affective disorders. Stress is strongly associated with symptom onset and patients with IBS appear to have greater responsiveness to stress as compared to healthy individuals. Peripheral factors, such as previous GI infection, appear to be capable of inducing chronic changes that lead to IBS symptoms with a greater tendency to occur in women. There is also evidence of increased inflammatory or immune markers in colonic mucosa in unselected IBS patients. Altered serotonin signaling mechanisms has been shown to be altered in IBS which may contribute to the clinical presentation and altered gut function observed in IBS. Recent data show that a fecal transplant can relieve symptom in certain IBS patients, which seems to be a way forward in order to tackle IBS.

Practice points

- *Irritable bowel syndrome is a common chronic gastrointestinal symptom complex defined by subjective symptoms*
- *Various functional abnormalities in the gastrointestinal tract and in the brain occur as a consequence of disease development*
- *In the multitude of possible causes of IBS, dysbiosis stand out as one probable cause of disease*
- *Fecal microbiota transplantation can rectify dysbiosis, thereby relieving post-infectious IBS*

Research agenda

- *The root of pain in IBS through mechanistic studies of peripheral innervation pathways.*
- *The influence of sex hormones on IBS sensitivity and pain*
- *Studies on fecal microbiota therapy are necessary to define the right super-donor and super-receiver for future matching of microbiota therapy*

Conflicts of interest

None.

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