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Different Pathophysiological Mechanisms of Irritable Bowel Syndrome

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Abstract

Introduction: Irritable bowel syndrome (IBS), which is the most frequently diagnosed gastrointestinal condition, is a symptom-based condition defined by the presence of abdominal pain or syndrome accompanying altered bowel habits, in the absence of another disease that may cause such symptoms. The pathphysiology of IBS is unknown, however, the prevailing hypothesis relates to gut-brain interaction disorder which occurs due to various relevant factors, alone or in combination. These factors include visceral hypersensitivity, abnormal gastrointestinal motor function, altered gastrointestinal mucosal and immune function, abnormalities in the gut microenvironment and alterations in the functioning of the central nervous system.

Method: The present paper is a review study focusing on different pathphysiological mechanisms that may cause IBS.

Results: As a result of the examination, we observed that ileocecal valve dysfunction, abdomino-phrenic dyssynergia, gastro paresis, pancreatic exocrine insufficiency, biliary dyskinesia and gut-brain axis play a role in the path physiology of IBS. Some of those contribute the direct development of IBS, whereas some others worsen IBS symptoms.

Conclusion: There exist different pathphysiological mechanisms that play a role in the development of IBS. Having knowledge about these mechanisms may provide insight into future clinical studies to be conducted. In addition making right interventions to these mechanisms can prominently reduce the economic burden of IBS on states.

Keywords: irritabl bowel syndrome; osteopathy; psychoneuroimmunology; complementary medicine

Introduction

Irritable bowel syndrome (IBS), which is the most frequently diagnosed gastrointestinal condition, is a symptom-based condition defined by the presence of abdominal pain or syndrome accompanying altered bowel habits, in the absence of another disease that may cause such symptoms (Chey et al., 2015) . Population-based prevalence estimates of IBS vary globally, in part related to differences in study populations, diagnostic criteria, and study methodology. The

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population prevalence of IBS in North America is approximately 12%. IBS is most common in South America (21%), and it is least common in Southeast Asia (7%). In the United States, Canada and Israel, the symptoms of IBS are seen 1.5 to 2 times more frequent in women than men. While women frequently report abdominal pain and constipation, men report diarrhea (Lovell & Ford, 2012b, 2012a) (figure 1).

The pathophysiology of IBS is unknown, however, the prevailing hypothesis relates to gut-brain interaction disorder which occurs due to various relevant factors, alone or in combination. These factors include visceral hypersensitivity, abnormal gastrointestinal motor function, altered gastrointestinal mucosal and immune function, abnormalities in the gut microenvironment and alterations in the functioning of the central nervous system (Aziz & Simrén, 2020).
IBS usually occurs in people between the ages of 20 and 40. It accounts for almost one-third of all gastroenterology cases seen in primary care, and one-third of these are referred to secondary care for further evaluation (Aziz & Simrén, 2020). According to the estimations made in the US, the economic burden of IBS is quite high(Everhart & Ruhl, 2009). Plannings that are made to reduce expenses include making early diagnosis and minimizing inappropriate and repetitive situations (Lacy et al., 2018).

There exist different pathophysiological mechanisms that play a role in the development of IBS. Having knowledge about these mechanisms may provide insight into future clinical studies to be conducted. In addition making right interventions to these mechanisms can prominently reduce the economic burden of IBS on states. This clinical review focuses on the different pathophysiological causes of IBS.

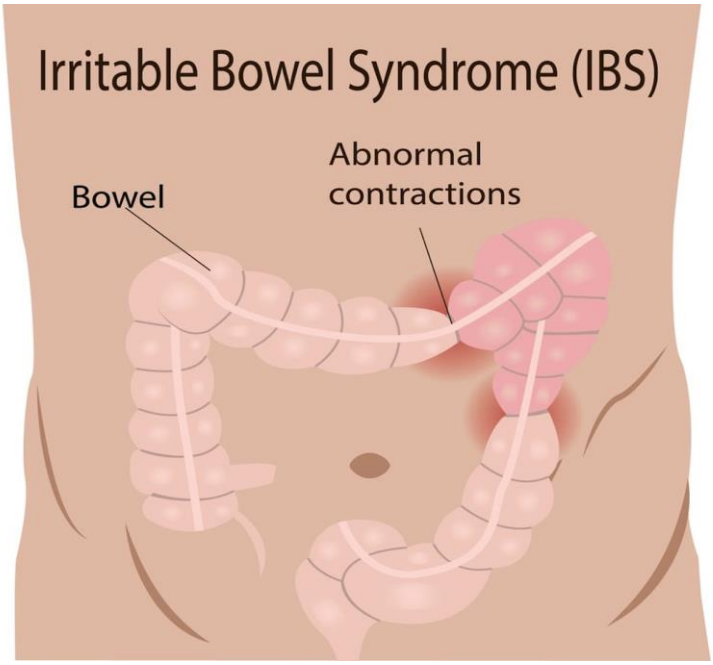

Figure 1: Irritable bowel syndrome

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Ileocecal Valve Dysfunction

The ileocecal valve (ICV), also defined as the ileocecal junction, is a sphincter valve that separates the small intestine from the large intestine and regulates the passage of chyme under the influence of hormones and nerve fibers. The removal of the ICV can lead to the migration of bacteria from the colon to the ileum and, under certain circumstances, may result in a severe intestinal bacterial overgrowth (SIBO) syndrome characterized by a change in the number of bacteria in the upper gastrointestinal tract. SIBO usually involves symptoms such as abdominal discomfort, bloating, and diarrhea, but sometimes it can lead to severe malabsorption, malnutrition, and vitamin B12 deficiency (Germani et al., 2021) (figure 2).

The role of the ICV, a relatively unexplored sphincter in the gastrointestinal tract, in health and disease is largely unknown. It has been reported that the ICV protected the small intestine against excessive bacterial growth by preventing reflux of colonic contents into the small intestine. The ICV pressure has been found to be low in the patients diagnosed with SIBO (Roland et al., 2014, 2017). SIBO has been attributed as a pathophysiological factor contributing to IBS symptoms (Ford et al., 2009; Pimentel et al., 2006, 2011; Sachdeva et al., 2011).

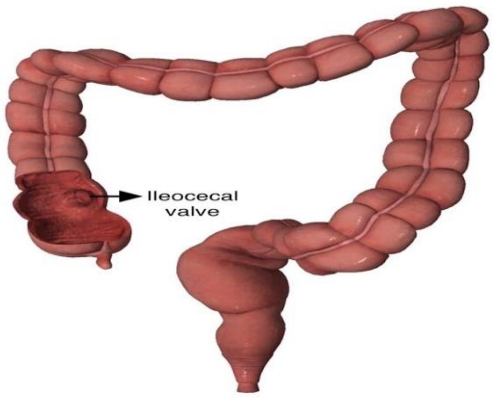

Figure 2: Ileocecal valve

Abdomino-Phrenic Dyssynergia

Abdominal bloating has been reported as one of the most common complaints in various functional bowel disorders, but, despite its clinical significance, its pathophysiology and management are still not fully understood. When described as the subjective sensation of abdominal distention, bloating is associated with a true increase in abdominal girth. However, the term is also defined as “sensation of increased abdominal pressure”, and it is commonly seen particularly in patients with diarrhea-dominant irritable bowel syndrome (Villoria et al., 2011). The volume of the abdominal cavity shows physiological differences, and a recent study has indicated that it actively adapted to the contents of the abdominal wall. An increase in intra-

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abdominal volume, modeled by colonic gas infusion, caused an increase in circumference, which was measured independently of body posture, by altering muscle activity of the anterior abdominal wall and diaphragm. The volume-response relationship is not affected by the gas infusion rate (Villoria et al., 2008).

The internal oblique muscle in the upright position exerts anti-gravity activity. It contracts to withstand gravitational forces and support the abdominal contents (Tremolaterra et al., 2006; Villoria et al., 2008). In this position, the colonic gas infusion occurs as a result of postural activity. It is associated with the contraction of anterior abdominal wall muscle that was not previously contracted. This muscular response of the anterior abdominal wall to the extra load probably represents a compensatory contraction to control the girth increase and prevent excessive abdominal distension.

In the upright position, the diaphragm domes are located in the upper part of the abdominal cavity without the gravity load, and in healthy individuals, intra-abdominal volume increase triggers inhibition of diaphragmatic activity (Villoria et al., 2008). Abdominal computed tomography (CT) imaging has shown that the inhibition of diaphragm activity reflected an adaptive relaxation that allowed cranial expansion of the abdominal cavity to accommodate the extra volume load. As the domes move, diaphragm columns and the gap, from which electromyographic activity is measured, can be sensed on a set of adjacent electrodes spaced 15 mm intervals and are fixed with no translocation. These data on abdomino-phrenic coordination occurring during abdominal accommodation revealed the possibility that abdominal distension may be connected with abnormal activity of the abdominal wall (Villoria et al., 2008). In the same experimental model, it has been shown that patients complaining of abdominal distension developed a paradoxical relaxation of the anterior wall in response to colonic gas infusion, and with the same volume loads, the increases in their circumference were significantly larger than those of healthy subjects (Tremolaterra et al., 2006). These results have asserted that abdominal distension was associated with abnormal control of the anterior abdominal wall.

Patients with functional bloating characteristically report that bloating sensation fluctuates. A study in which an original technique for morpho-volumetric analysis of the abdomen (Perez et al., 2007) was used, has compared abdominal CT scans taken at basal conditions with scans taken during an episode of spontaneous bloating with no or mild sensation of bloating (Accarino et al., 2009). As compared to basal conditions, anterior wall protrusion during bloating was associated with significant diaphragmatic descent. In another study, the electromyographic activity of the anterior abdominal muscles and the diaphragm has been measured while increasing the volume of the abdominal cavity by colonic gas load in 20 patients complaining of abdominal bloating and 15 healthy subjects. In healthy subjects, the column gas load enlarged the circumference, relaxed the diaphragm, and increased anterior wall tone. With the same gas load, the patients developed significantly more abdominal distension. This was found to be related to paradoxical contraction of the diaphragm and relaxation of the internal oblique muscle (Villoria et al., 2011).

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These results show that abnormal diaphragm activity plays a key role in the occurrence of abdominal distension in patients with functional bowel disorders.

Gastroparesis

Gastroparesis is a syndrome that occurs with symptoms of gastric retention, together with documented delayed gastric emptying in the absence of luminal obstruction (Jung et al., 2009). The regulation of gastric emptying is achieved by the complex coordination of smooth muscle contraction, the enteric nervous system (ENS) and central nervous system (CNS). Parasympathetic control is mediated by the vagus, while sympathetic control is mediated by the celiac ganglion (T5-T10) (Nguyen et al., 2020). Sensory and motor neurons with a predominance of sensory afferent C fibers constitute 60-80% of the vagus. Parasympathetic activity increases secretions and motility and modulates sensation, while sympathetic activity decreases secretions and motility. The autonomic nervous system (ANS) is responsible for integrating the external environment and maintaining homeostasis, through a complex reflex response system to alterations in organ function. Autonomic dysfunction can lead to changes in homeostasis and ultimately the dysfunction of the target organ (Campbell et al., 1977). In a cohort of patients with confirmed autonomic dysfunction, gastric emptying scintigraphy revealed both rapid and delayed gastric emptying (Lawal et al., 2007) (figure 3).

Gastroparesis is manifested by a number of symptoms that refer to the stomach, but it also has extragastric manifestations. Nausea is the most prevalent symptom reported by about 95% of patients (Hasler et al., 2013). Upper abdominal pain and discomfort are also common, and predominant in 21% of patients (Cherian et al., 2010). Bloating, as one of the main symptoms, is seen in 7% of cases (Hasler et al., 2013). Many gastroparetic patients also experience various intestinal symptoms, including discomfort, constipation and diarrhea (23). In a published report, it was stated that 65% of patients with idiopathic gastroparesis met the criteria for irritable bowel syndrome (IBS) (Parkman et al., 2011).

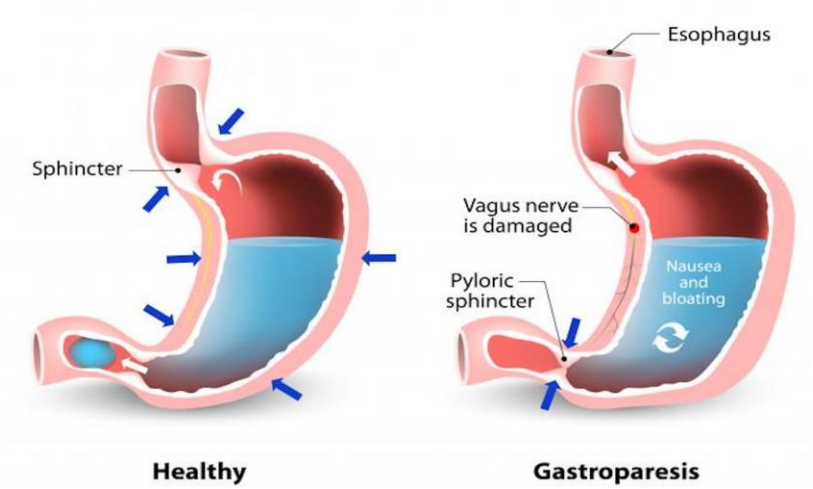

Figure 3: Effect of vagus nerve in gastroparesis.

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Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency (PEI) can be defined as a reduction in pancreatic enzyme activity in the intestinal lumen below the threshold required to maintain normal digestion. Pancreatic enzymes play a significant role in the digestion and absorption of nutrients. Its secretion is stimulated to up to a certain extent in the cephalic and gastric phases, but the most important stimulus occurs in the intestinal phase, where chyme enters the duodenum (Lindkvist, 2013). The presence of fatty acids, amino acids and stomach acid in the duodenum is the most powerful stimulator of exocrine pancreatic secretion (Watanabe et al., 1986). Vagal and neural reflexes stimulate pancreatic secretion in the cephalic and gastric phases (Lindkvist, 2013). During the intestinal phase, cells in the duodenal mucosa secrete cholecystokinin (CCK) (Pandol, 2003) which stimulates the secretion of pancreatic enzymes from acinar cells and secretin (Schaffalitzky de Muckadell et al., 1981), which ensures the secretion of water and bicarbonate from ductal cells.

The pancreatic enzyme content consists of bicarbonate and water secreted by ductal cells, and several enzymes that are secreted by acinar cells and have a specific capacity to digest proteins, carbohydrates and fats. In cases where the exocrine pancreatic function is reduced, the decrease in fat digestibility is the determining factor causing significant symptoms and clinical complications; because lipase, the main lipolytic enzyme of pancreatic juice, is the pancreatic digestive enzyme having the lowest stability in the gastrointestinal tract (DiMagno et al., 1977). Pancreatic enzyme deficiency leads to maldigestion and malabsorption of nutrients and is one of the well-known causes of malabsorption syndrome. In addition, diarrhea, abdominal distention, cramps, gas and weight loss are frequently observed in pancreatic exocrine insufficiency (Dominguez-Muñoz, 2019).

A single-center prospective study covering more than 300 patients with suspected IBS has reported a prevalence of 6% of pancreatic exocrine insufficiency (based on the fact that pancreatic fecal elastase concentration is $\leq$ 100 µg/g), and pancreatic enzyme supplements prominently improved the symptoms (Leeds et al., 2010). Consequently, pancreatic exocrine insufficiency should be considered as a cause of IBS symptoms.

Biliary Dyskinesia

Biliary Dyskinesia is a functional gastrointestinal disorder that can cause severe abdominal pain. In addition to gallbladder dyskinesia, functional biliary disorders include acalculous biliary pain, biliary dysmotility, sphincter of Oddi dysfunction, ampullary stenosis, and postcholecystectomy syndrome(Clark,2019).

The pathophysiology of biliary dyskinesia is not able to be fully understood. It is usually caused by narrowing due to inflammation and fibrosis and eventually the obstruction of gallbladder emptying. In other conditions, it is observed to be caused by an intrinsic functional motility disorder of the gallbladder wall smooth muscle or cystic duct (Morgan & Adams, 2019).

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In biliary dyskinesia, the pain is located in the right upper quadrant or epigastrium, is colic in nature, produces satiety, and is typically associated with nausea or bloating. In addition, the patient may report loss of appetite and weight loss (Behar et al., 2006).

It has been associated with other gastrointestinal motility disorders, including biliary dyskinesia, irritable bowel syndrome, colonic inertia, and gastroparesis (Morgan & Adams, 2019).

Gut-Brain Axis

The results from preclinical studies published in the past decade strongly support the notion of bidirectional brain-gut-microbiome interactions. The changes in these interactions play a role in the pathogenesis and pathophysiology of classical brain-intestinal disorders such as IBS and other functional gastrointestinal disorders (Mayer, 2011; Rhee et al., 2009).

The human intestinal tract is home to about 100 trillion microorganisms, mostly of bacterial origin. Studies have found that gut bacteria were of critical importance to health and disease and presented strong evidence that they could affect emotion processing and coping with stress. The microbiota-gut-brain axis connects the nervous system with gut, metabolic, neuroendocrine and immune functions (Moser et al., 2018). A disruption of the gut-brain axis, plays a role in the pathophysiology of gastrointestinal disorders, such as IBS and inflammatory bowel disease, which are biopsychosocial diseases (Oświęcimska et al., 2017). The vagus nerve, the main component of the parasympathetic nervous system, is considered to be the sixth sense due to its role in interoceptive awareness (Zagon, 2001). It can sense the microbiota, transfer gut information to the central nervous system with which it is integrated, and then generate an adapted or inappropriate response. In addition, it may perpetuate a pathological state of the digestive tract or promote neurodegenerative disorders (Eisenstein, 2016; Tse, 2017).

Dysbiosis exists in patients with IBS. In terms of this axis, however, the real question is whether dysbiosis is a cause or a consequence of abnormal gut-brain processing. Interoceptive or exteroceptive stress involves in the pathophysiology of IBS and can alter the gut microbiota (O'Mahony et al., 2009). Stress inhibits the vagus nerve, while stimulating the sympathetic nervous system (Sahar et al., 2001). The vagus, a mixed nerve with anti-inflammatory properties via both afferent and efferent fibers, is at the interface of the gut-brain axis. An abnormal vagal tone has been defined in IBS (Bonaz et al., 2016a). Neuroactive compounds such as γ-aminobutyric acid (GABA), serotonin, dopamine, acetylcholine (ACh) are released by bacteria and mainly move locally on the enteric nervous system, the gut brain. Some of these compounds arrive at the large brain via blood and peripheral organs or the vagus (Bonaz et al., 2018). In this section, we will focus on the effect of the vagus existing at the interface of the microbiota-gut-brain axis (figure 4).

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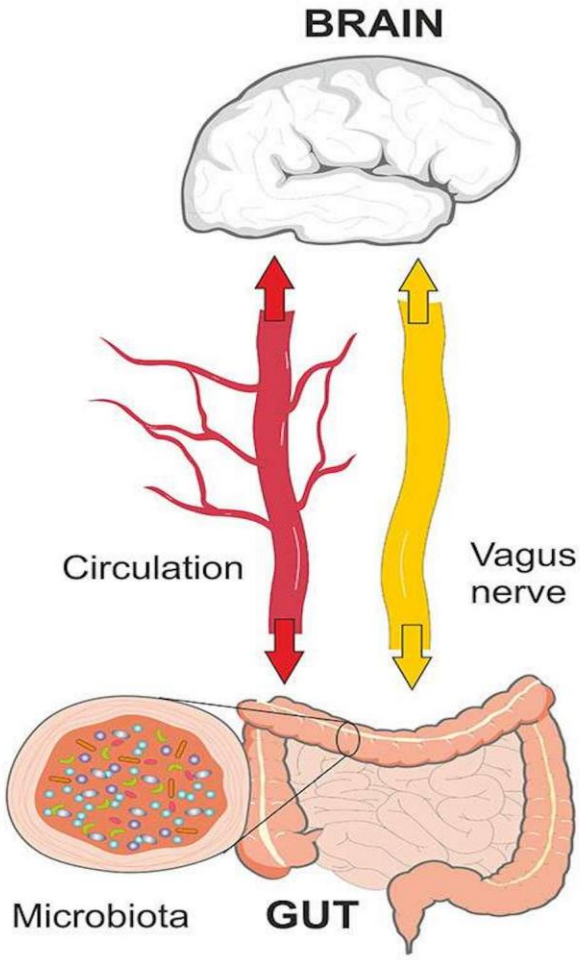

Figure 4: Gut-brain axis (communication between the central and the enteric nervous system)

The vagus contains 80% and 20% of afferent and efferent fibers, respectively, and innervates up to the left colonic flexure. In both cases, an interaction is also possible between the vagus fibers and the microbiota-rich colonic mucosa (Bonaz et al., 2018). Vagal afferent fibers are distributed throughout all layers of the digestive wall, but do not cross the epithelial layer (Powley et al., 2011), thus not in direct contact with the intestinal luminal microbiota. As a result, these fibers can sense microbiota signals only indirectly, either through the diffusion of bacterial compounds or metabolites, or by means of other cells in the epithelium that transmit luminal signals. Interactions between intestinal endocrine cells and vagal afferents occur at the interface of intestinal chemosensing (Raybould, 2010). The effect of stress on the gastrointestinal tract is well known (Taché & Bonaz, 2007). Stress, through its neuromediators, corticotropin-releasing factor and related peptide urocortins, increases intestinal permeability by acting on G protein-coupled corticotropin-releasing factor (CRF 1 and 2) receptors located in the brain and

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gastrointestinal tract (Tache et al., 2018); these two factors play a role in the pathophysiology of IBS. CRF2 receptors are involved in the disruption of intestinal permeability (Ducarouge et al., 2017). The CRF and urocortin are released by mastocytes of the lamina propria, which have CRF1-2 receptors that release cytokines and other pro-inflammatory mediators (Theoharides & Cochrane, 2004). The CRF also increases intestinal permeability through mast cell release of tumor necrosis factor (TNF)-α and proteases (Overman et al., 2012).

Targeting CRF receptors for the inhibition of mast cell activation by selective antagonists is a treatment option for the chronic inflammatory disorders exacerbated by stress. Chronic early life stress increases intestinal permeability, which would subsequently render adult rats visceral hypersensitive and causes dysbiosis (Moussaoui et al., 2017). Stress inhibits the vagus as per normal and stimulates the dorsal motor nucleus of the vagus and spinal cord sympathetic preganglionic neurons through autonomously related projection neurons of the paraventricular hypothalamus (PVH) (Wood & Woods, 2007). The vagus possesses anti-inflammatory properties via its afferent and efferent fibers 45. Stress, on the other hand, exhibits a pro-inflammatory effect. Being exposed to multiple repetitive stressors promotes an allostatic load by preventing recovery of parasympathetic tone 56, thus weakening the anti-inflammatory regulatory effect of the vagus. Stress disrupts the overall protective effect of the vagus on the epithelial barrier, thus promoting dysbiosis by altering epithelial homeostasis.

Conclusion

In patients presenting with IBS type symptoms, the presence of other functional gastrointestinal problems should be searched after excluding organic pathological causes. Ileocecal valve dysfunction, abdomino-phrenic dyssynergia, gastroparesis, pancreatic exocrine insufficiency, biliary dyskinesia and stress-induced vagal tone change may trigger IBS symptoms or play a role in the pathophysiology of IBS. A better understanding of the pathophysiology of IBS would also bring about new non-pharmacological and pharmacological treatments. For now, it is important for health professionals to understand the role of diet, lifestyle, and stress management whether or not there are medical treatments for IBS.

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