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Pathophysiology of Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a large bowel functional disorder characterized by abdominal pain or discomfort and is associated with bowel habit changes without organic disorder. IBS is affected by many factors and is suspected of involving central and peripheral mechanisms, such as gastrointestinal dysmotility, bowel visceral/mucosal hypersensitivity, increased bowel permeability and interaction among the luminal factors including food and bowel microbiota changes, bowel epithelial barrier, mucosa immunity, genetic factor and biopsychosocial and brain gut axis which are suspected to affect IBS pathophysiology. Understanding the various factors and mechanisms underlying IBS helps in the consideration of management and repair of patients' prognosis.

1 INTRODUCTION

Irritable bowel syndrome (IBS) is a functional abnormality of the large bowel characterized by abdominal pain or discomfort and is associated with bowel habit changes without organic abnormalities. IBS patients' various complaints and the absence of certain diagnostic markers make clinical presentation crucial in establishing IBS diagnosis (Owyang, 2009).

Worldwide, IBS occurs in 3.6% - 21.8% of the population with an average of 11%. In the United States, the incidence of IBS reaches 15% of the population, in Asia the prevalence is between 2.9% - 15.6% of the population, while in Indonesia there is no documentation of the number of IBS incidents. Women are known to have more IBS than men with the ratio of 3:1 (Sperber, 2010; Mearin et al., 2012; Manan, 2014).

IBS can occur at various ages, but its prevalence decreases with age. At least 50% of IBS patients experience early symptoms before the age of 35 and it rarely occurs at the age of above 60 years where more organic abnormalities are found (Mach, 2004). IBS has a high social impact in the community and is influential in decreasing the quality of life. In the United States, IBS is the most common digestive disease with an average of 10.6 visits per year and requires high health costs. About 2 million prescriptions are given out by doctors to IBS patients and spend approximately $742 per year (Owyang 2009; Sperber, 2010).

The pathophysiology of IBS remains unknown for certain to date. Genetic factors, intestinal microbiota, intestinal dysmotility, particularly lactose intolerance, visceral hypersensitivity, mild inflammation, and abnormalities of brain-gut interaction are suspected to underlie IBS complaints (Park et al., 2010; El-Salhy, 2012). Understanding the various factors and mechanisms underlying IBS helps in the consideration of the management and repair of patients' prognosis.

2 LARGE BOWEL ANATOMY

The large bowel is a part of the lower gastrointestinal tract, with the length of about 1.5 m and diameter of 6 - 7 cm. It consists of cecum, colon, rectum, and anus. The ileocecal valve lies at the upper limit of the cecum and prevents the return of the fecal matter from the cecum into the small intestine. The appendix is located around 2.5 cm from the ileocecal valve. The colon consists of ascending, transverse, and descending colon. The

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anal canal is between the two medial borders of the levator ani muscle. The sphincter muscle is able to withstand the occurrence of incontinence. The large bowel has two main functions serving as a reservoir of residual digestion products and water absorbance and electrolytes in the process of digestion (Porth, 2011).

3 ENTERIC AND AUTONOMIC NERVOUS SYSTEM

The intramural nerves in the gastrointestinal wall consist of 2 plexuses, i.e. the myenteric/Auucach plexus and the submucosal/Meissner plexus. Both plexuses are connected to ganglion cells along the gastrointestinal wall. The myenteric plexus lies between the muscles of the circular and the longitudinal muscles, while the submucosal plexus is between the mucosal layer and the circular muscles.

The activity of neurons is governed by local stimuli, inputs from the autonomic nervous system, and transmitter fibers connecting the two plexuses. The myenteric plexus consists of a linear chain of connecting neurons located along the gastrointestinal tract and has the biggest role in gastrointestinal motility. Meanwhile, the submucosal plexus works to regulate segmental function in the gastrointestinal tract by integrating signals from the mucosal lining to regulate intestinal motility, intestinal secretion, and nutrient absorption (Porth, 2011; Wood et al., 2012).

The gastrointestinal tract is also innervated by the autonomic nervous system by both the sympathetic and parasympathetic nerves. The parasympathetic nerve innervates the abdomen, small bowel, cecum, ascending colon, and transverse colon through the vagus nerve. The descending colon is innervated by the parasympathetic nerves derived from the sacral segments of the spinal cord. The parasympathetic preganglionic fibers will affect the intramural plexus and work directly on the intestinal smooth muscle. Most of the parasympathetic fibers are excitatory components (Porth, 2011).

In addition, gastrointestinal sympathetic innervation travels through the thoracic ganglia, celiac, superior mesenteric, and inferior mesenteric. Sympathetic control is largely mediated through changes in neuronal activity in the intramural plexus. The sympathetic nervous system acts to control mucosal secretions by mucosal glands, reducing motility by inhibiting intramural pyelid neuron activity, improving sphincter function, and improving smooth muscle tone of the gastrointestinal tract. The sympathetic fibers supply the lower esophagus, the pylorus, and the internal and external anal sphincters. Most are excitatory nerves, but their role in controlling sphincters is poorly understood (Porth, 2011; Wood et al., 2012).

4 CONCEPT OF BOWEL PHYSIOLOGY

There were two aspects of bowel physiology that are most relevant to explain the functional digestive disorders, i.e. sensation and motility aspects. Bowel mobility includes myoelectric activity, contraction, tone, regularity of movement, and transit periods governed by reflex mechanisms and is strongly associated with intestinal sensitivity (Browning and Travagli, 2014).

4.1 Bowel Sensation Aspect

Gastrointestinal function is controlled by the enteric nervous system located in the gastrointestinal wall and the sympathetic-parasympathetic nerves of the autonomic nervous system. The concept of sensation in the digestive system refers to the perceptual awareness of intestinal stimuli as well as afferent input on the gastrointestinal sensory pathway, both related to perception and reflex response. The activation of the vagal nerve afferent is known to modulate viscera pain. The stimulus of neurons from the afferent spine fibers and received directly by the spinal dorsal horn will be delivered to the supraspinal to the cortical regions where the perception of consciousness is generated. In addition, wobble viscera is also innervated by a group of spherical sensitive splanchnic afferent fibers (Kellow et al., 2006).

4.2 Bowel Motility Aspect

Bowel motility functions include propulsion along the gut, mixing bowel contents with digestive enzymes, directing the digestive product to the absorption surface area, preventing retrograde movement of intestinal contents, as well as removing the digestive residue. Motility is controlled by reflexes, both central and peripheral reflexes, as well as brain-gut axis. Gastrointestinal contractions can be classified by duration, such as

phasic contractions/short duration and tonic/continuous contractions.

Phasic contractions play a role in the movement of digestive products while tonic contractions are beneficial in food-storing function such as in the proximal abdomen, large bowel, and sphincter areas. Communication between the various intestinal areas is facilitated by the transmission of myogenic and neurogenic longitudinal signals throughout the gut (Kellow et al., 2006; Browning and Travagli, 2014).

Motility of the gastrointestinal tract moves rhythmically continuously to encourage food products to move in the gastrointestinal tract. The smooth muscle provides contraction strength except on the pharynx and the upper third of the esophagus. Gastrointestinal motility is stimulated by incoming food or resulting from gastrocolic reflexes and gastrointestinal hormones. Impulses are generated by smooth muscle and are conducted from one fiber to another (Porth, 2011; Yan, 2015).

The colon's storage function causes its movement to differ from that of the small intestine. There are two types of colon movement, i.e. mixing motion and pushing motion. Mixing motion of each segment is called haustration movement because the movement occurs in segmented pockets or haustra. The haustration movement is a digging-type movement that results in all gastrointestinal materials interacting with the gastrointestinal mucosa. Another colonic movement is mass propulsion movements where most of the colon segments contract to produce this movement. Mass motion occurs for about 30 seconds, followed by a relaxation period of 2-3 minutes and the next contraction. The series of mass propulsion movements occur for only 10-30 minutes and only a few times a day. The normal defect process is initiated from the mass propulsion movement (Porth, 2011; Yan, 2015).

4.3 Hormones in the Gastrointestinal System

The digestive tract is the largest endocrine organ in the body. The digestive tract produces a hormone that passes through the portal circulation to the general circulation, then returns to the gastrointestinal tract and begins to work. Hormones produced by the digestive tract include gastrin, secretin, and cholecystokinin. These hormones affect the motility and secretion of electrolytes, enzymes, and other hormones (Porth, 2011; Kellow et al., 2006).

4.4 Anus and Defecation Process

Under normal conditions, the anus is in a closed position. The anal closure is governed by the Kohlrausch valve, the puborectal muscles, the internal and external anal sphincter muscles, and the anal vein. Both types of sphincter muscles will have tonic contraction. The internal sphincter muscle is intrinsically stimulated by the sympathetic nerves (L1, L2) through the adrenoceptor signal, whereas the external sphincter muscle (a striated muscle) is stimulated by the pudendal nerve. The process of defecation begins with rectal ampulla excision with digestible material and stimulates rectum stretching, causing internal sphincter reflex relaxation, external sphincter constriction, and sensation for defecation.

Continuous defecation sensation results in shortened rectum, external puborectal sphincter and anal relaxation, an annular contraction of the descending colonic circle muscles, the sigmoid colon, and the rectum via the S2-S4 parasympathetic stimulus. It is then followed by mechanical support in the form of increased abdominal pressure to push the feces out. The normal frequency of defecation is about 3 times a day-3 times/week and is affected by the fiber intake composition. The average adult excretes 60-80 g of feces/day and increases more than 200 g/day during diarrhea (Yan, 2015).

4.5 Irritable Bowel Syndrome (IBS)

IBS is a gastrointestinal disorder characterized by changes in bowel habit with discomfort or abdominal pain without structural and biochemical abnormalities (Saha, 2014). There are no certain pathognomonic specific lab tests or physical examinations for IBS. Thus, clinical symptoms are very important in the diagnosis of IBS (Bellini and Gambaccini, 2014).

In 1978, Manning et al. set six simple criteria and had a separate interpretation to diagnose IBS (appendix 1). Manning criteria are known to have a sensitivity of 58% and a specificity of 74% (El-Salhy 2012; Manan, 2014).

In addition to Manning criteria, there are ROME criteria with higher sensitivity and specificity. The criteria of ROME III in 2006 are said to have a positive predictive value of 98% with a sensitivity of 71% and specificity of 88% (Mach, 2004; Jung, 2011; El-Salhy 2012). According to ROME III criteria, IBS was confirmed when there was no

organic abnormality that accompanied the complaints such as abdominal pain or discomfort in the abdomen recurring for at least 3 days/months in at least 3 months followed by 2 or more symptoms:

1. Improvement of symptoms after defecation
2. Changes in frequency of defecation
3. Changes in the consistency of feces

In addition, we found other symptoms that support IBS, such as abnormal defecation frequency (< 3 times per week or > 3x per day), fecal consistency stability, straining, incomplete feeling after defecation, feces mixed with mucus and bloating (Videlock and Chang, 2007).

The four subgroups are IBS-C (constipation dominance), IBS-D (diarrhea dominance), IBS-M (mixture of constipation and diarrhea), and IBS-U (unsubtype).

However, due to the instability of frequent symptoms, subclassification changes from time to time may be possible (Manan, 2014).

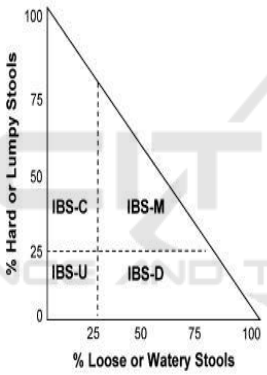

Figure 1: Hardness of Lumpy Stools

IBS-D is the most common type. This subgroup reflects low transit capacity of the colon. On the contrary, IBS-C reflects a long transit period of the colon. IBS-M (mixed) is where a patient has complaints of diarrhea episodes and constipation that alternate. The classification of IBS-U is unsubtyped if the patient's complaints are not sufficient to meet the criteria of other subtypes (Videlock and Chang, 2007; El-Salhy 2012).

IBS also causes extraintestinal symptoms such as headache (23%-45%), back pain (27%-81%), fatigue (36%-63%), myalgia (29%-36%), dyspareunia (9%-42%), and urinary frequency disorders (21%-61%). IBS patients with psychosomatic comorbids have more severe symptoms and are less responsive to treatment (Videlock and Chang, 2007).

5 Pathophysiology of IBS and the Underlying Factors

Despite the high prevalence of IBS, the pathophysiology of IBS has not been fully known until recently. IBS is based on many factors and is suspected to involve central and peripheral mechanisms (Bellini and Gambaccini, 2014; Soares, 2014). The factors affecting the occurrence of IBS include dysmotilities, visceral hypersensitivity, post infection, food intake, changes in intestinal microbiota, genetics, and psychosomatic factors. The mechanism of IBS occurrence through these factors is simply presented in Appendix 2 (Kellow et al., 2006).

5.1 Dysmotility

Motility disorders in IBS include increased frequency, irregular luminal contractions, prolongation of transit time, and excessive motor responsiveness to food consumption. Motility disorders can be related to patients' complaints (Soares, 2014). Serotonin has a role in intestinal motility, including regulation of gastrointestinal motility, secretion and sensation. Serotonin is an important signaling molecule in the gut and acts on enterocytes, smooth muscles and enteric nerves.

Most serotonin is produced in enterochromaffin cells. Serotonin activates both intrinsic and extrinsic primary afferent neurons to initiate peristaltic reflexes and secretions and transmit signals to the central nervous system. Some studies showed that in gastrointestinal functional abnormalities including IBS, there are abnormalities in the serotonergic enteric signals and result in hyperalgesia.

Serotonin signal changes occur and cause enteric and extra-enteric symptoms. In diarrhea-predominant IBS (IBS-D) there is decreased reuptake of serotonin, whereas in constipation-predominant IBS (IBS-C) there is a disruption of serotonin signal output. Thus, the use of exogenous serotonin therapy agents to provide optimal serotonin signals may be considered in IBS therapy (Binienda et al., 2017; Soares, 2014).

5.2 Visceral Hypersensitivity

Visceral receptor hypersensitivity occurs in various stimuli in the intestinal wall of the intestinal visceral intestinal nerve and is triggered by bowel distention. Rectal distension in patients with IBS is also associated with an increase in excessive

cerebral cortex activity. In addition, visceral hyperalgesia is also a result of certain GI mediators (serotonin, linins) or increased spinal nerve stimulation due to activation of N-methyl-D-aspartate (NMDA) receptors (Soares, 2014).

5.3 Food Effects

One study found that about 64-89% of IBS patients reported complaints after eating certain foods. Approximately 93% of IBS patients feel the complaints 3 hours after eating, and 28% of patients feel the complaints 15 minutes after eating. Another study mentioned that some patients experience postprandial complaint worsening, especially after consuming wheat/grains, vegetables, dairy products, fatty foods, spicy foods, coffee, and alcohol. Lactose intolerance, fructose, and gluten are also said to aggravate IBS complaints (El-Salhy 2012; Rajilić-Stojanović et al., 2015; Stanley et al., 2016).

The reaction of IBS patients to certain foods is also associated with the intake of short-chain carbohydrates that are difficult to absorb. Short-chain carbohydrates can increase osmotic pressure and provide a substrate for bacterial fermentation, thus increasing gas production, colon distention, and causing uncomfortable sensations. In addition, excessive fiber administration can also provide complaints because it increases the substrate solving digestive products by the intestinal flora and produce gas. Intestinal supplements such as probiotics, prebiotics, synbiotics, and synthetic fibers are still undergoing research efforts to determine the possible benefits of IBS therapy (El-Salhy 2012; Rajilić-Stojanović et al., 2015).

5.4 Intestinal Flora/Intestinal Microbiota

From several studies it is known that IBS patients have fewer amounts of Lactobacillus and Bifidobacterium spp compared to those without IBS. Intestinal flora attaches to epithelial cells and prevents bacterial pathogenic association with the epithelial cell wall, thus increasing the defense against pathogenic bacteria including Clostridia spp (El-Salhy, 2012).

Small intestinal bacterial overgrowth (SIBO) is known to be associated with an increase in the amount and type of digestive tract bacteria. Several studies show controversy regarding the relationship between IBS and SIBO. Studies showing the association between IBS and SIBO are evidenced by the abnormalities of the hydrogen number of IBS patients after receiving a number of carbohydrates (lactulose breath testing). Administration of antibiotics may cause changes in the amount of normal intestinal flora, resulting in the enteric effects of pathogenic bacteria and potential immunogenic effects. Some preliminary data suggest an improvement in IBS symptoms such as abdominal distension and flatulence symptoms in patients receiving probiotic preparations. However, these data still require further research (Kellow et al., 2006; Soares, 2014).

A study found a decrease in the amount of intestinal lactobacillus in stressed mice. Several other studies also support the theory that the intestinal microbiota affect the brain-gut axis. The fetal microbiota in a person with IBS are different from those without IBS and vary according to the dominating symptoms (El-Salhy 2012; Kellow et al., 2006; Soares, 2014).

5.5 Enteric Infection/Inflammation

IBS symptoms can be triggered by enteric infection and can persist for weeks, months, and years. The prevalence of IBS in post-acute gastrointestinal infection patients is about 10%-30%. IBS is also known to occur in 32%-46% of patients with ulcerative colitis and as much as 42%-60% in patients with Crohn's disease in remission.

Fecal calprotectin increases significantly in these conditions. As many as 25% of postoperative IBS patients show symptoms corresponding to the IBS-D classification that occurred about 6 months after the onset of acute infection of virus, bacteria, protozoa, and worms.

Significant factors affecting the occurrence of postinfectious IBS include female sex (4-23%), previous infectious diseases, prolonged healing periods, and history of anxiety, depression, somatization, and neurosis. However immune activation may occur in non-IBS where chronic inflammation affects cell histology such as inflammatory bowel disease, celiac disease, or ulcerative colitis (Kellow et al., 2006; Stanley et al., 2016).

Several studies have shown that inflammation and immune cells have an effect on the intestinal nervous system that regulates gastro intestinal motility and intestinal sensitivity. The occurrence of increased bowel permeability during episodes of acute gastroenteritis leads to inflammation and changes in intestinal microbiota, as well as bowel barrier dysfunction. In addition, idiopathic bile acid malabsorption can occur and an increase in

enteroendocrine cells containing serotonin and T lymphocytes.

The lymphocyte cells release the mediator (nitric oxide, histamine and protease) and stimulate the enteric nervous system. One study showed a correlation between the symptoms of abdominal spasm in IBS in the presence of mast cells that are activated in the terminal ileum and colon. The association of mast cells with enteric nerves through tryptase activation of specific protease receptors on the sensory nerves stimulates visceral hypersensitivity (Soares, 2014; Stanley et al., 2016).

Inflammatory responses especially after infection show an increase in CD-3 and CD-8 lymphocytes as well as calprotectin macrophages. This change will rapidly decrease, but in a few patients the symptoms persist. Persistent symptoms were found to increase the number of serotonin cells. Serotonin secretion by enterochromaffin cells will increase as a result of immune cell secretion products such as CD4 T cells. Furthermore, serotonin will enhance the immune response. Enterochromaffin cells will be associated with CD3, CD20, and some serotonergic receptors expressed by lymphocytes, monocytes, macrophages, and dendritic cells. In addition, immune cells in the small intestine and colon have receptors of intestinal vasoactive polypeptide (El-Salhy, 2012).

5.6 Impaired Intestinal Enteric Bowel System

The intestinal enteric nervous system consists of two parts: endocrine cells scattered among the mucosal epithelial cells of the intestinal lumen, and peptidergic, serotonergic cells, and nitric oxide-containing nerve cells from the enteric nervous system of the bowel wall. IBS patients exhibit a ghrelin-immunoreactive cell density in intestinal mucosa significantly lower in IBS-C patients and higher in IBS-D patients compared with someone without IBS. We also found a decrease in the number of neuropeptide cell expression inhibitors in gastric and somatostatin in patients with IBS-C and IBS-D.

Cell secretion of secretin and cholecystokinin (CCK) decreases in IBS-D but is normal patients in IBS-C. Ghrelin itself is an amino-28 peptide hormone found only in the abdominal tissues. Ghrelin is largely derived from endocrine cells in the abdominal mucosa-oxyntic and in small amounts in the small intestine, large intestine, and in the hypothalamus nucleus.

Ghrelin has several functions, including a role in the regulation of growth hormone (GH) derived from the pituitary gland and acting synergistically with GH-releasing hormone. Ghrelin hormone is known to accelerate gastric emptying, small and large bowel motility, and has anti-inflammatory effects and protects the intestines (El-Salhy, 2012).

5.7 Genetic Factor

Researchers have begun to develop the possibility of molecular mechanisms in the process of IBS. Several studies have shown that the risk of IBS in monozygotic twins is 2x higher than that of dizygotic twins. The genetic quantities of polymorphism and gen-environment interactions are suspected to be related to IBS although most occur independently (Soares, 2014).

The genetic factors involved in the pathogenesis of IBS are presumed to be due to the role of polymorphic gene coding for serotonin (SERT), cholecystokinin (CCK) receptor 1, anti-inflammatory and pro-inflammatory interleukins, and alpha 2 adrenergic receptors (Bellini, et al., 2014). The serotonin transporter (SERT) encodes the SERT protein located on chromosome 17q11.1-q12. Functional polymorphism is a site of insertion or deletion of 44 gene pairs in the SERT-gene-linked polymorphic region. Another study showed the relationship of functional polymorphism in SERT and IBS-D genes. In addition to the SERT polymorphism alleged to play a role in the mechanism of IBS occurrence, it turns out that the gene polymorphism of the CCK1 receptor CCKAR gene is also suspected to play a role in it (El-Salhy, 2012).

5.8 Psychosomatic

The whole process comes from the dysregulation of a two-way interaction between the intestine and the enteric nervous system (brain-gut axis), modulated by several psychosocial factors, and environmental factors such as infection and inflammation. Some neurotransmitters are found in the brain and intestines that regulate gastro-intestinal activity, including 5-hydroxytryptamine (serotonin) and its receptors (Mach, 2004).

Chronic stress significantly and consistently affects symptom onset and IBS exacerbation through sensorimotor dysfunction. A study conducted on rats found that psychological stress resulted in changes in the intestinal mucosal defense system to luminal bacteria and increased permeability of the intestinal

mucosal wall due to a cholinergic mechanism followed by presentation of mucus gastric mast cells. In addition, norepinephrine and corticotropin releasing factor (CRF) are also increased. The two types of CRF receptors are CRF-1 receptors that mediate an increase in colon contractility and CRF-2 mediating gastric hypomotilities when high stress occurs (Kellow et al., 2006).

6 CONCLUSION

Irritable bowel syndrome (IBS) is a functional abnormality of the large bowel characterized by abdominal pain or discomfort and is associated with bowel habit changes without organic abnormalities. There were two aspects of bowel physiology that are most relevant to explain the functional digestive disorders, i.e. sensation and motility aspects. The factors affecting the occurrence of IBS include dysmotilities, visceral hypersensitivity, post infection, food intake, changes in intestinal microbiota, genetics, and psychosomatic factors.

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