Irritable Bowel Syndrome: Current Review on Pathophysiology and Diagnostic Aspects

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ABSTRACT

Until now, Irritable Bowel Syndrome (IBS) has been one of gastrointestinal disorders which have not been fully understood. Clinically, there are some findings that indicate the role of inflammatory process in pathogenesis of IBS; such as, the onset of IBS that occurs after an episode of gastroenteritis (post-infective IBS (PI-IBS)). Although there is less evidence supporting genetic factors in pathogenesis of IBS, there are some reports about serotonin release in the plasma correlated to predominant constipation symptom. In contrast, increased serotonin release in IBS cases correlated to predominant diarrhea symptom. The stress-mast cell axis is one of pathophysiologic pathway that is expected to be able to explain the correlation between stress and characteristics found in IBS symptoms. Psychosocial factor has been well-considered to have important role in pathogenesis of IBS.

Diagnosis of IBS is based on history of pain or abdominal discomfort that correlated to abnormal defecation pattern, without any obvious alarm sign. Nowadays, there is no specific laboratory test or physical or biochemical marker pathognomonic for IBS; therefore, clinical symptoms become the main modality in diagnosing IBS. This article will discuss the pathophysiology and diagnosis of IBS which will be helpful for clinicians in the management of IBS in daily practice.

Key words: irritable bowel syndrome, gastrointestinal disorder.

INTRODUCTION

Until now, Irritable Bowel Syndrome (IBS) has been one of gastrointestinal disorders which have not been fully understood. According to the classic concept, such syndrome is caused by visceral hypersensitivity resulting in abdominal pain or discomfort and gastrointestinal motor disorder which lead to alteration of defecation pattern, i.e. diarrhea or constipation. IBS is classified as one of functional gastrointestinal disorders. The term ‘functional’ refers to chronic and recurrent symptoms which cannot be explained by obvious structural or biochemical abnormalities.

Nowadays, such paradigm has been challenged by various evidences indicating organic abnormalities in patients who have fulfilled the Rome criteria for IBS. The changing paradigm has affected the use of ‘functional’ term for IBS, which is further considered as less relevant. However, such concept is still controversial. Better understanding on IBS pathophysiology hopefully will provide better diagnostic methods and treatment.

THE ROLE OF INFLAMMATION IN IBS PATHOGENESIS

Clinically, there are some findings that indicate the role of inflammatory process in IBS pathogenesis. The first is that IBS onset which occurs after an episode of gastroenteritis (post-infective IBS (PI-IBS)) in 7-31% patients and 4-26% patients with gastroenteritis caused by various microorganisms including parasites.

It is assumed that post-infective IBS represents about 6-17% total IBS cases. A study in Spain reported an increased relative risk of IBS up to eight fold in one year of post Salmonella gastroenteritis, while a study in Nottingham reported that 25% study subjects had persistent defecation disorder six months after infective gastroenteritis episode. It is concluded that the duration of diarrhea, young age and female sex would increase the risk while vomiting would reduce the risk. Other studies demonstrated increased cells in lamina propria and mucosa as well as increased lymphocytes.
infiltration which became persistent in the colon of IBS patients with such post-infective episodes.\textsuperscript{12,13}

The correlations found between persistent symptoms of gastrointestinal dysfunction and gastroenteritis severity and duration are not surprising. More severe disease episode correlated to deeper microorganism penetration, greater inflammation of mucosa, as well as greater damage on epithelial and sub-mucosal nerves; which need longer recovery period. A subgroup of patients with IBS demonstrated persistent increase of inflammatory cytokines level including interleukin-1 that inhibited water and sodium absorption leading to persistent diarrhea.\textsuperscript{14} Abnormalities of autonomic nervous system in gastrointestinal tract was assumed as precipitating factor for constipation and motor disorder. Such findings has given more emphasis on the role of inflammation against infection rather than microorganism as etiologic factor of infection which is important precipitating factors in physiological changes of colon and the development of IBS symptoms.\textsuperscript{8} It has not been known how frequent and how much does sub clinical condition of gastroenteritis contribute on IBS cases without any obvious history of previous gastroenteritis episode. Patient with post-infectious IBS obviously has better prognosis compared to idiopathic IBS as the symptoms will diminish within 5-6 year period.\textsuperscript{11} Other finding indicates that the role of inflammation in developing IBS-like symptoms in patients with IBD who had been in remission period, particularly in ulcerative colitis, is more frequent than it has been assumed previously. It is assumed that inflammation process during acute exacerbation of IBD precipitates persistent sensory and motor alteration in the colon during the remission period which has become the basic pathogenesis of IBS-like symptoms.\textsuperscript{8}

**GENETIC FACTORS**

Little evidence has been known supporting positive genetic factors in IBS pathogenesis. One study demonstrated that part of IBS patients had genotype profile that was similar in IBD patients, i.e. anti-inflammatory cytokines, interleukin-10 (IL-10) secretor and lower level of *transforming growth factor β* (TGF-\(\beta\)) (*low secretor*).\textsuperscript{15} In addition, other study demonstrated that patients with IBS and post acute gastroenteritis episode had higher mRNA IL-1β expression compared to the patients with acute gastroenteritis but did not experience IBS.\textsuperscript{16} However, more detailed studies are required; the study indicated that increased acute inflammatory response is assumed to be a determinant factor in developing post-infectious IBS. Therefore, it raises an assumption that such determinant factor may be genetically inherited, and gastroenteritis may become one of precipitating factors in developing inflammatory-based IBS in susceptible individual.

**SEROTONIN DYSREGULATION**

Serotonin released by enterochromafine cells as a response to stimulus in gastrointestinal tract is the main regulator of peristaltic reflexes and transmitting enteric sensory signal.\textsuperscript{17,18} The enterochromafine cells activate Intrinsic Primary Afferent Neurons (IPANs) and Extrinsic (sensoric) Primary Afferent Neurons. Submucosal IPANs secreting acetylcholine and calcitonin gene-related peptide (CGRP) are activated through 5-HT1P receptors and it will initiate the peristaltic and secretory reflexes. Neurotransmitter release is triggered by 5-HT4 receptors which act in prokinetic pathway. Serotonergic impulse transmission in the mucosa and enteric nervous system is terminated by the trans-membrane transporter 5-HT, SERT (serotonin reuptake transporter). Mucosal SERT and expression of tryptophan hydroxylase-1 are reduced in experimental inflammation, IBS-C, IBS-D, and ulcerative colitis. Enhanced serotonin receptors due to reduced SERT have a role in developing diarrhea symptoms and abdominal discomfort in IBS-D, while receptor desensitization may cause constipation. An experiment showed that similar symptoms were developed in transgenic mice without SERT. This finding supported the role of mucosal SERT in IBS pathogenesis.\textsuperscript{19}

![Figure 1. Enterochromafine cells activated by pressure or chemical stimuli in gut lumen which will release 5-HT to stimulate 5-HT receptors in submucosal IPANs and lead to initiation of peristaltic and secretory reflexes.](image)
IPANs are activated by 5-HT\textsubscript{1p} and possibly are also activated by 5-HT\textsubscript{4} receptors. The cells utilize Ach and CGRP as co-neurotransmitters. Neurotransmitter released from IPANs is facilitated by 5-HT\textsubscript{4} receptors. Extrinsic sensory nerves that innervate the mucosa of gastrointestinal tract are located on vagus and spinal nerves.

Other evidence supporting abnormal serotonin dysregulation is reduced plasma serotonin level in IBS patients with predominant symptoms of constipation; while in contrast, there is increased serotonin release in diarrhea-predominant IBS cases.\textsuperscript{21} A study comparing rectal biopsy specimen in patients with IBS, ulcerative colitis and control demonstrated that there was a defect on serotonin signaling in IBS cases and ulcerative colitis with reduced serotonin on mucosa and reduced immunoreactivity of serotonin transporter. This fact supported significant molecular defect in IBS which possibly occurs after an episode of infection.

The Role of Stress-Mast Cells axis in Pathogenesis of IBS with Predominant Diarrhea Symptoms

Clinical and epidemiological studies have demonstrated that the intensity and duration of symptoms in diarrhea-predominant IBS patients is obviously affected by chronic stress as the comorbid factor.\textsuperscript{3} However, a clear correlation pathway between stress and pathophysiology of IBS disorder and symptoms has not been well-plotted.

The stress-mast cells axis is one of pathophysiology pathway that hopefully could explain the correlation between stress and some characteristics found in IBS symptoms. Mast cell has a role in regulation of gastrointestinal motility, increasing visceral perception, reactivating mucosal inflammation and disturbing the function of epithelial barrier either in experimental animal model or human.\textsuperscript{23} Both acute and chronic stress may induce activation of gastrointestinal mast cells. Anatomical contact between mast cells and enteric nerve fibers has been clearly demonstrated in the human gastrointestinal tract and such contact is getting more secure during the inflammation.\textsuperscript{24}

Increased number of mast cell and its product in distal gastrointestinal tract (terminal ileum, proximal and distal colon) has been well-known to be related with the onset and severity of IBS symptoms.\textsuperscript{25-27} Interaction of mast cell and enteric nerve fibers provides physical substrates for developing a correlation or communication between central nerve system and the gastrointestinal tract; therefore, stress may affect the physiology of gastrointestinal tract.\textsuperscript{21} An epidemiological study also demonstrated that dyspepsia was frequently complained by diarrhea-predominant IBS patients; therefore a study was conducted to recognize further about infiltration and activation of mast cell in the more proximal gut segment, in this case, the jejunum.

Such study concluded that majority (70%) diarrhea-predominant IBS patients that participated as the subjects had also experienced functional dyspepsia. The subjects also had higher basal stress level compared to the control and 30% among them experienced an onset of IBS symptoms with preceding episode of acute gastroenteritis. Immunohistochemical analysis on biopsy specimens of jejunum indicated significant increase of mast cells (CD117+) on jejunum mucosa in IBS patients compared to the control (34.0 vs 15.3 mast cells/HPF). All patients with IBS demonstrated jejunal mastocytosis (>20 mast cells/HPF). The triptase serum level in both groups was still within the normal limit; however, the luminal triptase level (jejunal aspiration) was significantly higher in the subject group (0.45 vs 0.09 µg/l) indicating positive local activation of mast cells. No positive correlation was found between the basal stress level and the amount of mucosal mast cells or luminal triptase level. Furthermore, there was also no significant difference for the amount of mucosal mast cells between patients with and without dyspepsia complaint.

Tryptase is a specific neutral protease produced by human mast cell. Although mast cell is the only source of significant trypase, it appears that no correlation found
between the amount of mast cell and luminal triptase level. Possible explanation for such fact is activation of mast cells and triptase secondary release are not continuous process. Release of specific mediator occurs gradually and triptase release to the lumen will increase only under certain circumstances. Therefore, it can be concluded that mast cell hyperplasia and triptase release are commonly occur and they are important findings in diarrhea-predominant IBS patient who has not received any treatment. Validity for both of them to be biological marker of IBS and their potential benefit in the management strategy of IBS should be studied further.

CENTRAL DYSREGULATION

Psychosocial factor has been well-considered as important factor in IBS pathogenesis. Anxiety and depression are commonly found in IBS patients compared to normal population. Some concepts regard IBS as one of somatization disorder, but evidences of organic pathophysiology had contravened the concept. There is a study that observed different brain responses in IBS patient. Measurement of regional brain perfusion during rectal distension demonstrated that IBS patients experienced greater activation of the anterior cingulate cortex, amigdala nucleus and dorsomedial frontal cortex in contrast either to the control subjects or patients with ulcerative colitis. It is assumed that the brain of individual without IBS has greater ability in activating the inhibition area of endogen pain. This may be a genetic predisposition. Amitriptyline, an antidepressant, has been proven to reduce rectal pain and correlates to activation of dextra prefrontal cortex area, dextra incula, and anterior cingulate cortex. Such central process may explain the potential benefit of antidepressant in IBS.

THE ROLE OF CORTICOTROPIN-RELEASING HORMONE (CRH) IN PATHOGENESIS OF IBS

CRH is the main mediator of stress response in brain-gut axis. In IBS, any disorder of such axis is assumed to be related with over response against stressor. A study showed that administration of peripheral CRH would increase sensory and neural function of visceral organ as such thing may also trigger ACTH response in IBS patient. Electrical stimulation on rectum significantly provided more trigger on colon motility in IBS patients compared to the control. Furthermore, the study evaluated the impact of giving alpha-helical CRH, a non-selective CRH-receptors antagonist, to IBS patients and control. After administration of alpha-helical CRH, the colon motility response was significantly reduced in IBS patients compared to the control. Alpha-helical CRH reduced the severity of abdominal pain and anxiety induced by electrical stimulation in IBS patients. The plasma level of ACTH and cortisol usually are not suppressed by alpha-helical CRH.

An experiment in rats indicated that administration of specific CRH-1 receptor antagonist apparently inhibited sensitization of visceral perception induced by colorectal distension. There have been more evidences developed supporting the concept that peripheral CRH and CRH-1 receptor have become important in sensitization of gut-brain axis. CRH has been proven to produce depolarization response associated with
increased excitability of mienteric and mucosal neurons. On the other hand, injection of peripheral CRH has been reported to induce secretory effect, motor function and permeability. There are functional differences between CRH-1 and CRH-2 receptors. Activation of CRH-1 will cause pro-inflammatory response and pro-nociceptive effect on visceral pain; while stimulation of CRH-2 will produce opposing response, i.e. anti-inflammatory and anti-nociceptive responses.

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Throughout these years SIBO has been assumed as a condition that frequently found in IBS patients and intestinal motility disorder has been regarded as its predisposition factor. A study that aimed to discover the prevalence of SIBO has conducted intestinal manometry and culture of intestinal aspirates of IBS patients and control group. Furthermore, the study has evaluated its correlation to intestinal motility and IBS symptoms. Investigator in the study has used two definition for alteration of intestinal flora, i.e. the standard SIBO definition (≥ 10^9 colonic type bacteria/ml) and the other definition, i.e. slight increase of intestinal bacterial growth (≥ percentile in the control group).

The study indicated that SIBO (standard definition) only occurred in 4% of both subject groups (IBS and control). The signs of gastrointestinal motility disorder were found in 86% patients and 39% control (p=0.02). Patients with SIBO have fewer Major Migrating Complex (MMC) phase III (activity fronts) (p=0.08) compared to patients without SIBO; however, there was no difference in other motility parameters. Slight increase of intestinal bacterial growth (≥ 5 x 10^3/ml) was frequently found in patients compared to the control (43% vs 12 %, p=0.002), but there was no correlation to intestinal motility. No correlation was found between the alteration of bacterial amount and the pattern of IBS symptom. According to the clinical definition that is frequently used, the study is not able to prove the important role of SIBO in pathogenesis of IBS. Alteration of intestinal motility also cannot be the basis to assume the development of changing intestinal bacterial growth. Nevertheless, slight increase of intestinal bacterial is apparently more frequent in IBS patients, and this should be studied further.

DIAGNOSIS OF IBS

Diagnosis of IBS is based on history of pain or abdominal discomfort correlated to abnormal defecation pattern, without any alarm sign. Until now, no specific laboratory test or physical or biochemical marker has been found pathognomonic for IBS; therefore, clinical symptoms has become the main modality in diagnosing IBS.

Diagnostic criteria of IBS have been rapidly developed. In 1978, Manning et al applied six criteria to differentiate IBS from organic gastrointestinal disease. Talley et al showed that Manning criteria had 58% sensitivity and 74% specificity.

More concern on functional gastrointestinal disorder has encouraged the Rome working group in 1988 and for the first time they presented the IBS criteria. Later, the criteria developed into a classification system for functional gastrointestinal disorder which has been covered in the Rome Criteria (Rome I) and it was published as a book in 1994. The criteria have been widely used and it was revised in 2000 as the Rome II criteria, and its final revision on April 2006 was known as the Roma III criteria.
or both combinations are only available as simple classification related to the fecal consistency. However, classification of diarrhea-predominant IBS (IBS-D) and constipation-predominant IBS (IBS-C) subtypes may still be used.  

Rome III criteria of irritable bowel syndrome:  

- Persistence for at least three months or more  
- Pain or abdominal discomfort for at least 3 days per month which:  
  - Relief on defecation  
  - Associated with a change in form (appearance) of stool  
  - Associated with a change in defecation frequency.

The presence of some diagnostic criteria has apparently affected the IBS prevalence. An epidemiological study indicated that the IBS prevalence using Rome II Criteria was lower compared to Rome I criteria and Manning 2 (at least meet 2 of Manning criteria) or Manning 3 (at least meet 3 of Manning criteria). The prevalence found based on Manning 2, Manning 3, Rome I and Rome II criteria are 16.2%, 9.7%, 5.6%, and 5.1% respectively. About 97% subjects who met the Rome II criteria also met the Manning 2 criteria; however, in the subgroup that met the Rome II criteria there were more severe abdominal symptoms, more abundant psychosocial disorder and they need more frequent health services. Similar results have also been demonstrated by a community study in 8 European countries. The overall prevalence of IBS is 11.5% (6.2-12%); 2.9%, 4.2% and 6.5% according to Rome II, Rome I or Manning criteria respectively. The Rome III criteria are relatively new; therefore, its predictive value compared to previous criteria can not be concluded yet.

Patient with suspected IBS symptoms possibly has other organic disorder such as IBD, microscopic colitis, gastrointestinal infection, lactose intolerance, malabsorption syndrome, endocrine disorder and colorectal cancer, which still should be excluded. Therefore, it needs several laboratory examination, stool analysis, barium enema, flexible sigmoidoscopy or colonoscopy. Of course, such examination series would be costly. Some studies have tried to evaluate the effectiveness of such examination particularly compared to the expended cost.

Hamm studied the endoscopic results of 306 patients who met the Rome Criteria of IBS. He found that only 7 patients had abnormal colon. Three of them had IBD, 1 patient had intestinal obstruction, and 3 patients had colon polyp. Recently, alarm sign has become more important in diagnosis of IBS. A study suggested the alarm sign criteria (age, sex, sign of gastrointestinal bleeding, and severe pain) as the most important diagnostic factors with 93% sensitivity. Vanner also reported that in some cases without any alarm sign such as weight loss, nocturnal symptoms, bloody stool, recent antibiotic usage, history of colon cancer in the family or other disorders that are relevant to the physical examination, the Rome Criteria have 65% sensitivity and 100% specificity. Some other studies showed that the sensitivity for such symptoms ranged
between 42-94%, with specificity ranged between 55-94%. In Indonesia, the data of Endoscopy Center in Gastroenterology Division of Cipto Mangunkusumo Hospital, Jakarta, between 1998-2005 period indicated that diagnosis of IBS was cumulatively established on 449 out of 1947 patients (18.7%) based on colonoscopy results.42

A study41 in the United States showed that the cost for endoscopy procedures such as sigmoidoscopy and colonoscopy is about 50-75% of total diagnostic cost for IBS. Considering the risk and benefit ratio of such procedures, current review2 does not recommend such examination including the routine blood examination, stool analysis, breath air test (uji udara pernapasan), and gastrointestinal radiographic examination in establishing the diagnosis of IBS for the case with obvious positive symptoms without any alarm sign. Negative colonoscopy result also has not been proven to increase the patient’s quality of life.

In addition to endoscopy, the other thing that has become controversial, especially in overseas countries, is the celiac sprue which may have IBS-like symptoms without weight loss or other symptoms. According to a study,43 serologic examination for celiac sprue (using tissue transglutaminase) is quite effective in cost-effectiveness analysis, with assumption that the prevalence of celiac sprue is more than 8% IBS patients in the area of study conducted.

The classical concept that IBS is an exclusion diagnosis has been gradually left behind. Symptom-based criteria facilitate diagnosis establishment through specific symptom identification, exclusion of alarm sign and no abnormalities found on physical examination. Alarm sign or persistent condition that has no response to symptomatic therapy should be evaluated in more detailed fashion in keeping with the most predominant symptom.

CONCLUSION

Various novel developments in IBS pathophysiology have been promising for developing new diagnostic method. However, as long as there have not been no clear understanding on pathophysiology of IBS yet and no specific and sensitive biological marker for IBS diagnosis found, history taking and careful physical examination is still reliable in establishing the diagnosis.

REFERENCES


