Irritable bowel syndrome (IBS) and chronic constipation share several traits related to bowel movement and gastrointestinal (GI) symptomatology. The 2 conditions also may arise from similar pathophysiologic mechanisms involving dysregulation of communication and coordination between the brain and gut. Multiple neurotransmitters and hormones are involved in the regulation of GI function. In particular, serotonin may have a key role in the regulation and dysregulation of motility, sensitivity, and secretion. Brain imaging studies, including magnetic resonance imaging and positron emission tomography, have provided evidence of altered activity in specific brain regions of patients with IBS compared to non-IBS control groups. Certain types of peripheral alterations in the gut also may contribute to the evolution and progression of IBS. Low-grade immune activation has been associated with altered motility and afferent and epithelial function in patients with IBS. Biopsy-based studies have demonstrated elevated levels of various proinflammatory factors in the gut of patients with IBS. Interaction between physiologic and psychological factors also may contribute to the origin of at least some IBS cases. In all likelihood, IBS etiology involves a collaboration of factors that contribute to different stages of disease evolution.


**ABSTRACT**

Irritable bowel syndrome (IBS), specifically the constipation-predominant subtype, and chronic constipation share several traits related to bowel movement and gastrointestinal (GI) symptomatology. The 2 conditions also may arise from similar pathophysiologic mechanisms involving dysregulation of communication and coordination between the brain and gut. Multiple neurotransmitters and hormones are involved in the regulation of GI function. In particular, serotonin may have a key role in the regulation and dysregulation of motility, sensitivity, and secretion. Brain imaging studies, including magnetic resonance imaging and positron emission tomography, have provided evidence of altered activity in specific brain regions of patients with IBS compared to non-IBS control groups. Certain types of peripheral alterations in the gut also may contribute to the evolution and progression of IBS. Low-grade immune activation has been associated with altered motility and afferent and epithelial function in patients with IBS. Biopsy-based studies have demonstrated elevated levels of various proinflammatory factors in the gut of patients with IBS. Interaction between physiologic and psychological factors also may contribute to the origin of at least some IBS cases. In all likelihood, IBS etiology involves a collaboration of factors that contribute to different stages of disease evolution.

Brain-gut dysregulation is the key mechanism underlying IBS, although it also may apply to chronic constipation. Central factors play a role in enhanced perception of visceral events, leading to visceral hypersensitivity and altered motility. Brain-gut interactions are mediated by the autonomic nervous system, which is comprised of the extrinsic nervous system that includes the vagal and sacral parasympathetic systems and the sympathetic system. Within the bowel wall,
the enteric nervous system intrinsically influences secretion, motility, and possibly sensation (Figure 1).3,4

There are several neurotransmitters and hormones that play a role in regulating and modulating gastrointestinal (GI) function. These substances influence motility, visceral sensitivity, and secretory activities. Increasingly, the receptors of these neurotransmitters are targets for novel drug development aimed at more effective treatments for IBS and chronic constipation (Table).5-8

Among the many neurotransmitters involved in GI function, serotonin is a key contributor to normal function and to dysfunction. Recent studies have shown that alterations in serotonin levels and signaling mechanisms may affect GI physiology, including motility, sensitivity, and secretion. The altered GI physiology then leads to clinical symptoms of disorders, such as chronic constipation and IBS-C.9-11

Several pathophysiologic mechanisms have been identified in association with altered brain-gut interactions in IBS. Alterations in intestinal motility have been reported in IBS. For example, smooth muscle hyperreactivity leads to colonic hypercontractility, a characteristic of IBS-D. Other mechanisms include visceral hypersensitivity, sustained activation of the immune system after infection or inflammation, stress, and genetic factors.4,12 All of these factors are unlikely to play a significant role in every patient. Instead certain factors likely predominate in one individual but not another, which likely explains the heterogeneity within the population of patients with IBS.

The IBS subtypes with diarrhea and constipation often are associated with specific patterns of physiologic dysregulation. In IBS-D, segmental, or nonpropulsive, contractions in the colon are decreased, whereas high-amplitude propagating (propulsive) contractions (HAPC) are increased. Additionally, postprandial rectal tone, rectal hypersensitivity, and gastrocolic response are increased. For the most part, the physiologic correlates are reversed in constipation. Segmental contractions may be increased, whereas HAPCs, postprandial rectal tone, and gastrocolic response are all decreased. Rectal hypersensitivity is present in the majority, but not all, of patients with IBS, but there is some debate about whether it is more predominant in the diarrhea or constipation subtypes.13

The pathophysiologic contribution of visceral hypersensitivity to IBS was illustrated over 25 years ago in a study that examined pain threshold in patients with IBS and a control group in response to rectosigmoid balloon distension. The study demonstrated that patients with IBS are more likely than control subjects to report pain or more intense pain in response to a given balloon volume or pressure.14 Enhanced visceral perception in IBS has been demonstrated in several subsequent studies conducted at various research centers.

Brain imaging studies have provided evidence of alterations in supraspinal processes in patients with IBS. In one representative study, patients with IBS and
healthy control subjects underwent functional magnetic resonance imaging (fMRI) during rectal distension. This study revealed altered patterns of regional brain activity in patients with IBS compared to control subjects. Specifically, patients with IBS exhibited greater thalamic and anterior cingulate cortex (ACC) activation in response to painful stimuli than control subjects.  

Positron emission tomography (PET) imaging studies have provided additional insight into the pathophysiology of IBS. The studies have shown increased activation of a more dorsal subregion of the ACC in response to pain or the anticipation of pain in patients with IBS. In addition, there are sex-related differences in brain activation patterns between men and women with IBS in response to rectosigmoid distension. Men with IBS are more likely to activate regions associated with cognitive processing of painful stimuli, whereas women with IBS activate limbic regions associated with the affective or emotional response to pain.  

**Immune Activation and Irritable Bowel Syndrome**

In addition to the central abnormalities associated with IBS, evidence suggests that peripheral alterations in the gut also exist in IBS. In particular, the role of mucosal immune markers has attracted considerable attention. Low-grade immune activation has a putative role in the altered motility and afferent and epithelial function of the gut in IBS. Between 7% and 30% of patients recovering from a GI infection develop IBS-like symptoms. As many as 17% of unselected patients with IBS report that the onset of their symptoms coincided with a bout of gastroenteritis. Studies involving colonic biopsies have demonstrated increased levels of proinflammatory immune markers in GI tissue specimens from patients with IBS. Increased levels of enteroeendocrine cells, T cells, and interleukin-1 β mRNA were found in colonic mucosal biopsies in postinfectious patients with IBS. Other studies have demonstrated increased levels of intraepithelial lymphocytes, T cells, and mast cells in the colonic mucosa of unselected patients with IBS. Mast cells in proximity to nerves have been reported to correlate with the frequency and severity of abdominal pain or discomfort. Low-grade infiltration of lymphocytes has been found in the myenteric plexus in full-thickness jejunal biopsies of patients with IBS but these patients had extremely severe IBS with evidence of neuropathic disease.  

Interaction between gastroenteritis and psychological factors also may play a role in an individual’s risk of developing postinfectious IBS. Comparison of individuals who developed IBS after infection and those who did not showed that those individuals who developed postinfectious IBS had significantly higher scores on assessments of anxiety, somatization, neuroticism, life events, and hypochondriasis.

One possible interpretation is that an acute visceral event may not be sufficient by itself to cause postinfectious IBS. Response to the event is in part centrally modulated, and current stress or psychological factors may alter central modulation of visceral events, increasing the vulnerability of developing postinfectious IBS. That conceptual framework underscores the significance of brain-gut interactions and the necessity for both components of the interaction to be healthy in order to avoid the onset or exacerbation of a functional GI disorder, such as IBS.

The pathophysiologic development of IBS likely involves a collaboration of factors at different stages of disease evolution. IBS is known to have a genetic component, which predisposes an individual to this condition. Then a confluence of risk factors, triggering factors, and perpetuating factors carry the evolutionary process to the expression of symptomatic IBS (Figure 2).

Another illustration of brain-gut interactions came from a study that compared visceral responses of patients with IBS and healthy volunteers without IBS exposed to 2 sessions with an auditory stimulus in

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**Figure 2. Stressors and IBS Symptoms**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Trigger Factors</th>
<th>Perpetuating Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological stress</td>
<td>Psychosocial stressors</td>
<td>Symptom-related anxiety</td>
</tr>
<tr>
<td>Early life experience</td>
<td>Infection surgery antibiotics</td>
<td>Patient with IBS</td>
</tr>
</tbody>
</table>

IBS = irritable bowel syndrome.
which the order was counterbalanced. During 1 session, subjects listened to conflicting sounds (auditory stress) while undergoing rectal distension. The subjects then rated the intensity and unpleasantness of the visceral sensations. During the other session, subjects were exposed to relaxing nature sounds. Patients with IBS rated the intensity and unpleasantness of the visceral sensations significantly higher during stress than did the control group. Patients with IBS also reported higher levels of stress, anger, and anxiety during the auditory stress condition. The patients with IBS and the control group did not differ in their sensory ratings to rectal distension while listening to the relaxing sounds.28

FUNCTIONAL CAUSES OF CONSTIPATION

As previously stated, the functional causes, subtypes, of constipation are normal-transit constipation, slow-transit constipation, and defecatory disorders, such as pelvic floor dysfunction, rectoanalgic and pelvic floor muscles to facilitate defecation. These patients respond to anorectal biofeedback training. Slow-transit constipation results from absent or a decreased number of pacemaker cells (ie, interstitial cells of Cajal) and enteric neurons, leading to decreased colonic motility and frequency of mass movements.29 These patients are typically treated with laxatives and prokinetic agents.

CONCLUSIONS

Altered brain-gut interaction is the key mechanism in IBS and is associated with physiologic alterations affecting GI motility, autonomic responses, visceral perception, neuroimmune and neuroendocrine responses, and brain activation patterns. The principal subtypes of chronic constipation are normal-transit constipation, slow-transit constipation, and pelvic floor dysfunction. Determining the underlying mechanisms of constipation is a necessary component of evaluating patients with IBS and chronic constipation, as the findings may affect treatment and outcome.

DISCUSSION

Dr Kalloo: I found the MRI study fascinating. When you treat these patients, does the imaging change?

Dr Chang: There are 2 studies that have been published in IBS with pharmacologic therapy. One is the alosetron/PET imaging study that showed that patients on alosetron versus placebo had a decreased activation of some of the limbic regions, such as the amygdala and ventral striatum, and these changes correlated with a positive symptom response. Howard Mertz just published a study of the effect of amitriptyline on brain activation patterns in female patients with IBS with and without stress. It was only under the stressful condition that amitriptyline decreased anterior cingulate activation in female patients with IBS, but not during the relaxation condition.

Dr Kalloo: Although cost is a factor, do you ever see these studies as a routine part of diagnostic testing in patients?

Dr Chang: No. I think they are currently used more in proof-of-concept studies.

Dr Kalloo: Stress is clearly a factor in some patients. When do you recommend psychological testing in patients with IBS?

Dr Lembo: I recommend it with patients who are refractory to treatment.

Dr Harris: If I feel that there is a significant comorbid psychological component, and I’m worried about missing something, such as a bipolar condition, or more psychopathology than I have time to get to within the time that I interview a patient, then I’ll refer that patient for psychological testing. If I feel that the patient may just have a significant anxiety component, and I may be using a psychoactive medication to treat the patient anyway, then I may just try that medication first without referring the patient. Thus, I think it’s also in the more severe patients.

Dr Chang: Most of the time, but I see a more refractory, severe group of patients. Most of them are seeing a psychotherapist already, but if there are psychosocial factors of chronic stress that I think impact their condition, I will make sure that they receive counseling or see a therapist. However, I only suggest it when I think a patient is open to it.

Dr Talley: I’m not convinced psychologists help, unless you specifically intervene with therapy, such as cognitive behavioral therapy or hypnotherapy if you have it available, or something else. I don’t see much value for my patients in referral for an assessment that will come back and tell me that they’ve got psychosocial disturbances. All my patients are psychosocially disturbed in some way or other, whether it’s organic or functional disease I’m seeing them for. I’m not even
sure sometimes whether it’s cart or horse. Are they disturbed because they are miserable from their symp-
toms, or are they disturbed and they have miserable symptoms? You often can’t tell that. Usually major
depression is pretty obvious, thus I do screen for that.

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