Simmering innards: Does irritable bowel syndrome have an immunological basis?

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Not so long ago, physicians construed the irritable bowel syndrome (IBS) as being a neurotic trait: it was all in the head. Today most clinicians believe that the main abnormality lies in the brain (and spinal cord), which reacts abnormally to stimuli from the gut. Recent studies are identifying a basis for these neural changes – low grade inflammation in the gut – which may play a key role in IBS.

IBS is not a disease of our modern times, having been evident in the 19th century. Over the past few decades it has become recognized as a common gastrointestinal (GI) syndrome characterized by chronic abdominal pain and altered bowel habits. The prevalence of IBS in North America, estimated from population-based studies, reaches 10% to 15% (1). Of those with symptoms, only about one-third of patients will consult a family physician; one-fifth is then referred to a gastroenterologist or other specialist. IBS carries with it a low quality of life and increased use of our dwindling health care resources. Despite it being such a common problem, much remains unknown about the syndrome and its pathogenesis.

As a 'functional disorder' without morphological features, the diagnosis of IBS is defined on patient symptoms, in the absence of any organic pathology. The Rome II criteria (2) stratify patients with IBS into those with diarrhea predominance, constipation predominance or alternating symptoms. Such a high variability of symptoms makes it likely that IBS is a group of heterogeneous etiologies with a common end point of pain and altered bowel function.

At least three interrelated factors appear to affect symptoms to varying degrees; namely, psychosocial factors, altered gut motility and secretion, and visceral hypersensitivity (3). Research has suggested that the latter plays a pivotal role in the intestinal motor abnormalities and abdominal pain described by a large proportion of patients with IBS (3-8).

Several putative mechanisms may elicit the visceral hypersensitivity in IBS, affecting both the central and peripheral nervous systems. At a central level, these mechanisms may no longer properly modulate (eg, inhibit) the response to afferent sensory signals rising from the gut. Peripherally, sensitization of sensory neural endings occurs at the end-organ level and then sends signals through the overly excited spinal cord (dorsal motor nucleus) to the brain.

Animal models of intestinal inflammation reveal the development of visceral hypersensitivity and symptom generation (9,10). In humans, a good deal of the information on inflammation has come from the literature on postinfectious IBS (PI-IBS) and acute inflammatory states. Persistent IBS symptoms develop in approximately 20% to 30% of patients following acute bacterial infections of the GI tract (11-15).

Tissue damage in the gut causes recruitment of circulating neutrophils, lymphocytes and monocytes, which in turn secrete chemical and inflammatory mediators, which cause further tissue damage (16). These mediators (such as potassium, hydrogen ions, ATP, bradykinins and prostaglandin E_2) can directly activate nerve endings and ultimately sensitize the afferent nerve terminals, resulting in an increased response to painful stimuli (17). Additionally, further inflammatory cascades involving substance P, histamine and 5-hydroxytryptamine can elicit increased firing of nearby nociceptive sensory afferents and recruit other local, previously silent, nociceptive nerves (18). Chronic irritation may then lead to altered afferent input and the release of neuroactive chemicals in the dorsal horn of the spinal cord.

As the acute inflammatory event resolves, nerve remodelling during the healing process can trigger chronic hypersensitivity in the gut tissue to mechanical and chemical stimuli (19). This process is also seen after other types of tissue damage, such as dental abscess (20), and pediatric urinary tract (21) and pulmonary infections (22). In the GI tract, it is also commonly seen in patients with quiescent inflammatory bowel disease and in some patients after a bout of diverticulitis (16).

Even when the peripheral irritation ceases, synaptic changes in the neurons located in the dorsal horn can persist, affecting 'pain memory' and central excitability. Such an excitable state may then lead to hyperalgesia (severe pain evoked by modest discomfort) mediated via central projections to the thalamus and cortex. Persistent central excitability may subsequently result in allodynia, in which rather innocuous stimuli produce pain (19,23).

There also may be a lessening of the normal central inhibition on the ascending painful stimuli. Thus, the basis for abnormal colonic and small intestinal sensations can reside at any level; increased sensory input into the dorsal horn of the spinal cord and/or central modulation of these sensations, including psychological influences that affect the interpretation of the sensations.

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But is the persistent visceral hypersensitivity just due to altered sensory nerves? It now appears that, at least in a subset of patients, continued low-grade inflammation may play a role. Increased lymphocytes have been found in the mucosal biopsies of PI-IBS patients compared with controls (24,25), as have enteroendocrine cells (24,26). Low-grade infiltration of lymphocytes and neuronal degeneration have been reported in the myenteric plexus in patients with severe IBS who underwent full-thickness jejunal biopsies (27).

Mucosal mast cells also appear to be increased in patients with IBS, both in diarrhea-predominant patients (28) and in mixed groups of constipation- and diarrhea-predominant patients (29-31). Mast cells are known to lie close to enteric nerves (32,33), and can influence enteric nerve function and muscle contractility (34,35). There may be greater amounts of mast cell tryptase and histamine in addition to increased mast cells in the colonic mucosa of patients with IBS than in controls (30). Both of these inflammatory mediators are known to be released from mast cells (36) and can activate enteric nerves via protein-activated receptor-2 (37) and histamine (38,39) receptors, respectively. Indeed, the severity of the abdominal pain and discomfort in IBS correlates with the proximity of the mast cells to nerve endings (30). Overall, mast cells likely play a role in the visceral hypersensitivity that is an inherent part of IBS.

T cells have also been found in elevated numbers in patients with IBS. Elevated mucosal T lymphocytes (determined by CD3+ staining) were identified in both PI-IBS patients and IBS patients without a discrete time of onset of symptoms (24,26,31). In one of these studies (31), T lymphocytes stained for the interleukin (IL)-2 receptor (CD25), suggesting activation of these T cells.

These findings suggest that an initial insult (such as an enteric infection in PI-IBS patients or inflammatory bowel disease that goes into remission but leaves symptoms of IBS) can evolve into the symptom complex of IBS. IBS therefore may begin as an inciting event injuring the bowel followed by an inability to down-regulate the subsequent inflammation. The reason for this ongoing inflammation is not clear, but interestingly, patients with IBS are less likely to have high-producer IL-10 gene alleles (40), similar to patients with inflammatory bowel disease. IL-10 plays a significant anti-inflammatory role; if IL-10 were produced in low levels, mild inflammation could persist.

Other potential causes of continued low-level inflammation in the GI tract include food allergies and changes in bacterial microflora. Allergic reactions can evoke inflammatory cell infiltration in the GI tract (41), but the prevalence of food allergies in IBS is unclear (42). Gut microflora may be altered in patients with IBS (43); some findings suggest that IBS patients may have intestinal bacterial overgrowth (44) and increased colonic fermentation (45). Further information is needed to elucidate the role of these environmental factors in promoting and perpetuating the putative low-grade inflammatory process.

Much remains unknown about the potential causes of IBS. There may not be a unifying hypothesis to link all the aspects of this diverse syndrome. Nevertheless, markers of low-grade inflammation, which were initially found in diarrhea-predominant and postinfectious cases of IBS, are increasingly being found in constipation-predominant patients as well. Thus, inflammation may figure as an underlying factor in visceral hypersensitivity in more cases of IBS than previously was suspected. These intriguing inroads may be the key to our understanding of the basis for the IBS and may yield exciting therapeutic possibilities.

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