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Is Irritable Bowel Syndrome a Low-Grade Inflammatory Bowel Disease?

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The influence of the immune system on gastrointestinal (GI) function has long been recognized. The work has focused mainly on the effect of overt inflammation on GI motility. Studies in patients with inflammatory bowel disease (IBD) have shown that colonic inflammation reduces basal contractile activity in the distal colon, which, under physiologic conditions, slows fecal stream [1]. Other studies have reported that intestinal inflammation alters responsiveness of the colonic motor system to a meal [2] and to pharmacologic stimulation [3]. Altered motor patterns seem to improve during remissions of IBD [1], suggesting that colonic dysfunction is dependent on the degree of the inflammation. A study in patients with inactive Crohn's disease, however, has shown persistently abnormal small intestinal motility compared with healthy controls, suggesting long-lasting effects of inflammation [4]. Thus, these studies suggest that immune activation and mucosal inflammation alter motility in humans.

The immune system may alter gut function by targeting intestinal smooth muscle cells, nerves, or the pacemaker system (interstitial cells of Cajal). Surgical specimens from the inflamed small intestine of patients with Crohn's disease have demonstrated increased muscle contractility upon carbachol stimulation attributable to changes at the receptor level [5]. In contrast, colonic muscle contractility has been reported to be decreased in patients with ulcerative colitis [6]. Also, gut inflammation has been shown to decrease the response of circular and longitudinal muscle to endogenous tachykinins [7].

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Structural changes in the enteric nervous system (ENS), such as increased number of ganglion cells [8] or axonal degeneration [9], have been documented extensively in IBD. The presence of an inflammatory cell infiltrate [10] and expression of major histocompatibility complex class II molecules in the ENS of IBD patients [11] suggest that these abnormalities involve immune activation. COX-2 expression in neural cells of the myenteric plexus was found in patients with active IBD but not in healthy controls [12], and thus increased prostaglandin synthesis may be one of the mechanisms leading to gut dysfunction. Other studies reported increased substance P content and its receptor in patients with Crohn's disease [13,14]. A recent study in patients with ulcerative colitis described ENS remodeling with a shift from mainly cholinergic to substance P (SP)-positive innervation [15]. Finally, the number of interstitial cells of Cajal (ICCs) has been shown to be reduced in patients with Crohn's disease [16]. In addition to motility disorders, one of the possible mechanisms leading to symptom generation in inflammatory disorders of the GI tract is visceral hypersensitivity. Reports on visceral hyperalgesia in IBD, however, are controversial. Patients with active ulcerative colitis show decreased thresholds for painful and non-painful stimuli when compared with healthy controls or patients with colitis in remission [17,18]. Conversely, an increased threshold for rectal distension has been found in patients with isolated ileal Crohn's disease compared with controls or patients with diarrhea-predominant IBS [19]. A recent study in patients with ulcerative colitis showed that discomfort thresholds during rectal distension are correlated inversely with the activity of the disease. Patients with colitis, however, had higher thresholds to visceral perception than healthy controls and irritable bowel syndrome (IBS) patients [20]. The presence of visceral hyperalgesia in IBD likely depends on disease activity, whether acute or chronic inflammation predominates, and the region involved. Intuitively, different immune or inflammatory cell infiltrates will impose different effects on sensory nerve function—a concept supported by recent preliminary reports in animals [21,22].

Taken together, these studies suggest that in patients with IBD severe inflammation affects all parts of the neuromuscular apparatus, resulting in significantly altered gut function that may persist even during periods of remission.

Irritable bowel syndrome symptoms in inflammatory bowel disease

There is considerable overlap between symptoms in patients with IBS and IBD, and they include abdominal pain and diarrhea. The presence of endoscopically verified colitis, fever, GI bleeding, serologic markers of inflammation, and overt inflammation in biopsies is diagnostic for IBD. In a proportion of patients later diagnosed with IBD, however, initial symptoms may be attributed to a functional gut disorder. A recent study

showed that the prodrome period in patients with Crohn's disease and ulcerative colitis was 7.7 and 1.2 years, respectively. Most of the patients presented with abdominal bloating, diarrhea, excessive gas production, and stomach pain. When Rome I criteria were applied, patients with Crohn's disease who presented with IBS symptoms had a prodromal period of 6.8 years, while patients with ulcerative colitis had a prodromal interval of 2.7 years [23]. Similarly, during periods of remission, IBD patients may present with symptoms resembling IBS, including constipation and bloating. A substantial number of patients with ulcerative colitis in remission reported bowel symptoms highly suggestive of IBS despite no signs of active inflammation [24]. A recent study demonstrated that 57% of patients with Crohn's disease and 33% of patients with ulcerative colitis in long-standing remission, as assessed by laboratory, clinical, and endoscopical parameters, have IBS-like symptoms. Patients with Crohn's disease reported more GI symptoms and reduced well-being than patients with ulcerative colitis. IBS symptoms seemed not to be affected by age, treatment, or extent of the disease but correlated with the duration of the disease [25]. Based on Rome II criteria, another study confirmed a several-fold higher proportion of IBS symptoms in patients with colitis in remission. IBS symptoms were present in 41.7% and 31.5% of patients with Crohn's disease and ulcerative colitis, respectively, but only in 7.6% of healthy controls [26].

These findings are consistent with the hypotheses that subclinical inflammation and immune activation that precede the expression of IBD result in symptoms of IBS and that previous immune activation and inflammation are followed by gut dysfunction and the generation of IBS symptoms.

Degree of inflammation, gut function, and symptom generation

Diagnosis of active IBD requires the presence of macroscopic inflammation, polymorphonuclear and mononuclear cells, and epithelial damage in biopsies. The severity of the disease, however, does not always correlate with the severity of symptoms reported by patients [27]. Abdominal pain and diarrhea are also frequent symptoms in microscopic colitis, which is characterized by only a mild increase in intraepithelial lymphocytes and monocytes.

The question arises, what degree of gut inflammation is necessary to affect gut function? Gut function may be altered by low numbers of inflammatory cells positioned at strategic locations such as in proximity of enteric nerves. It is beginning to be recognized that an intact epithelium in the absence of mucosal inflammation does not exclude the presence of inflammation in deeper layers of the gut that can result in altered gut function [28].

The availability of more sensitive techniques to assess inflammation such as immunohistochemistry or molecular methods may result in a new definition of inflammation in the gut. The transition between mild immune

activation and gut inflammation is a continuum, and setting an arbitrary threshold between these two entities may be artifactual and eventually misleading.

Low-grade inflammation and irritable bowel syndrome

There is growing evidence that previous infection and persistent low-grade inflammation play an important role in the pathogenesis of gut functional diseases. A large epidemiological study has identified infectious gastroenteritis as the most significant environmental risk factor for the development of IBS [29]. IBS symptoms have been reported to develop in a significant proportion of subjects with documented *Campylobacter*, *Salmonella*, *Escherichia coli*, *Shigella* infections and viral infection [30–33]. Although rates differ among these studies, the estimates range from 7% to 31% of infected subjects. Several risk factors for subsequent IBS development have been identified, the strongest being the duration of diarrhea during enteritis [34], which could reflect the severity of the initial inflammation.

Results of several studies suggest that symptoms in postinfective IBS are generated or maintained by immune mechanisms. Increased intraepithelial lymphocytes (IEL) and lamina propria lymphocytes, together with elevated numbers of enteroendocrine cells, were found in patients with postinfectious IBS, following documented infectious enteritis. These changes in mucosa persisted for at least 1 year and were accompanied by increased mucosal permeability [35]. A small but significant increase in lamina propria lymphocytes, compared with healthy controls, also was observed in patients with postinfectious IBS 3 months after infection [36].

Interleukin (IL)-1β mRNA expression was higher in rectal biopsies in patients with enteritis who subsequently developed IBS, than from those patients whose bowel normalized thereafter. Levels of IL-1β further increased 3 months after infection in patients with IBS, while asymptomatic subjects had similar levels to healthy controls [31]. As IL-1β is a proinflammatory cytokine, these findings are consistent with the hypothesis that subjects who subsequently develop IBS after infection inefficiently downregulate acute inflammatory responses. Support for this concept of impaired control of cytokine production in subsets of IBS patients has gained support from recent genetic studies in IBS. A recent study confirmed increased IL-1β levels, structural changes in enteric nerves, and increased mast cell counts in biopsies from patients with postinfectious IBS [32]. Patients with postinfectious IBS also may exhibit a cytokine imbalance favoring proinflammatory cytokine IL-12 versus counterinflammatory cytokines IL-10 and transforming growth factor (TGF)-β [37].

The immune system also may play a role in generating symptoms in patients with IBS and no history of GI infection. Chadwick et al found that most patients with insidious onset of IBS symptoms showed signs of immune activation as assessed by immunohistochemistry. From these

patients, 49% had normal conventional histology, and 40% had only microscopic inflammation, consisting of increased lamina propria cellularity, often accompanied by focal neutrophil infiltration. By using immunohistochemistry, a twofold increase in IEL and CD3 + cells and a sixfold increase in CD25 + cells were demonstrated. A subgroup of patients also had elevated numbers of neutrophils and mast cells [38]. This is in accordance with another study in IBS patients with or without history of previous gastroenteritis where increased numbers of lamina propria lymphocytes and mast cells were found [39].

Immune activation or inflammation in the mucosa also may affect the deeper layers of the gut. A study on full-thickness biopsies from patients with severe IBS revealed intra- and peri-ganglionic infiltration by lymphocytes at the region of the myenteric plexus [28]. Less than half of the patients had concomitant elevation of intra-epithelial lymphocytes, however, suggesting compartmentalization of the gut for immune processes. Almost all patients exhibited a thickening of the longitudinal muscle layer, and half of the patients displayed abnormal numbers or morphology of ICCs. This suggests that significant inflammation can be present in the deeper layers of the gut with apparently normal mucosa and that this inflammatory process can affect all the elements of the neuromuscular apparatus.

A recent study investigated the role of mast cells in IBS. The authors found that most of the patients had increased areas of mucosa occupied by mast cells, higher numbers of degranulating mast cells, and increased release of histamine and tryptase from biopsies than healthy controls. Furthermore, the abdominal pain or discomfort correlated with the number of mast cells located in close proximity to the enteric nerves [40]. Mast cells could be among the effector cells responsible for immediate-onset symptoms. This would suggest that luminal antigen plays a role in maintaining symptoms in IBS.

The data from these studies suggest that infectious gastroenteritis is an important trigger in at least a subset of patients with IBS. The authors propose that an activated immune system is responsible for maintaining symptoms. There is also evidence that immune mechanisms may be implicated in the pathogenesis of patients without history of gastroenteritis. Lymphocytes and mast cells are candidate effector cells involved in symptom generation.

Increased susceptibility to inflammation in irritable bowel syndrome and inflammatory bowel disorder

This article has mentioned that IBS and recent-onset of IBD may share some clinical similarities. Is there any evidence for a common pathogenetic pathway? There are reports suggesting that a common genetic background for IBD and IBS exists based on abnormalities within the immune system.

IL-10 is a pleiotropic cytokine with counterinflammatory properties. It has been shown that mice deficient in IL-10 develop spontaneous enterocolitis [41]. A recent study suggested that patients with IBS may be genetically predisposed to produce lower amounts of this anti-inflammatory cytokine [42]. This is similar to what has been described in patients with IBD [43]. In another study investigating the cytokine pattern in patients with post-infectious IBS, a higher frequency of tumor necrosis factor (TNF)-α intermediate phenotype with increased production of this proinflammatory cytokine was found [44]. TNF-α polymorphism also has been found in patients with IBD [45,46]. These studies suggest that patients with IBS and IBD may have a genetic predisposition to mount an increased proinflammatory response to luminal stimuli and have a decreased ability to down-regulate already existing inflammatory processes. It is possible that the degree of this alteration determines in part the clinical outcome.

Psychosocial factors in irritable bowel syndrome and inflammatory bowel disease: effects through the immune system

Psychosocial factors contribute to the predisposition, precipitation, and perpetuation of IBS symptoms [47]. Comorbidity of psychiatric conditions is high and occurs in up to 94% of patients [48]. Research in the field of psychosomatic medicine showed an association between depression and activation of the immune system [49] as recently documented by elevated C-reactive protein levels in patients with depression [50,51]. Depression also was found to be important predictor for developing postinfectious IBS [36]. Psychiatric conditions and IBD often coexist [52], and it has been suggested that depression and anxiety precede onset of IBD [53]. Recent prospective studies showed a significant correlation between depression and total number of relapses of colitis [54] or disease activity in IBD patients [55]. These data suggest that psychological factors play an important role in the expression of IBS and IBD. Activation of the immune system may be the common pathway mediating behavioral-induced changes in these conditions.

Experimental models of functional gut disorders

Animal models are valuable for investigating the role of intestinal inflammation in gut dysfunction. NIH Swiss mice infected with the nematode *Trichinella spiralis* developed muscle hypercontractility in vitro, which persisted long after parasite eviction [56]. This process was initiated by mucosal Th2 cytokines and maintained by COX-2 [57] and TGF-β [58] in the muscle layer. Previously infected mice displayed abnormal small bowel motility in vivo, with increased retroperistalsis and heightened visceral sensitivity [59]. Although conventional histology and myeloperoxidase were

normal in the postinfective state, increased numbers of CD3 + cells were found in the gut. It should be pointed out, however, that the mucosal compartment was otherwise unremarkable in its appearance. Abnormal muscle contractility normalized when the previously infected mice were fed probiotic bacteria, which also decreased COX-2 and regulated on activation, normal T expressed an secreted expression in the intestine [60].

Abnormal stomach function including delayed gastric emptying, impaired sensitivity to distension with up-regulated SP and calcitonin-gene related peptide-containing nerves, and abnormal feeding behavior developed in mice chronically infected with *Helicobacter pylori* [60,61]. Most of these changes persisted for at least 2 months following bacterial eradication. The degree of neuromuscular impairment, evidenced by acetylcholine release upon EFS, correlated with the degree of mononuclear cell infiltration.

Altered gut function also was observed in rat models of colitis showing abnormal motility, even in the uninflamed segment [62], and increased visceral sensitivity. Postinflammatory hyperalgesia can be observed as long as 17 weeks after induction of the trinitrobenzene sulfonic acid colitis [63]. These studies show that experimental inflammation can induce abnormal gut function, including dysmotility and visceral hyperalgesia, which can be long-lasting.

What drives immune activation and inflammation in functional bowel disorders?

Most patients with GI infection recover without any long-term consequences, restoring their bowel function after few weeks of the initial infection. A small proportion of patients continues to experience chronic problems, however, and the question arises what drives their symptoms that can sometimes persist for up to 6 years after infection [64]? A genetic predisposition to increased susceptibility to inflammatory stimuli may underlie some cases. Environmental factors also should be considered. The gut is exposed continuously to a variety of bacterial and dietary antigens. Immune tolerance toward these antigens assures normal functioning of the gut. During gut infection and inflammation, tolerance is abrogated, and the mucosal immune system may be sensitized toward one or more antigens related to the offending agent. As some patients with IBS have increased intestinal permeability [35], it is likely these patients are exposed to a broader array of luminal antigens, which through molecular mimicry could maintain immune activation. To test this hypothesis, the authors repeatedly administered crude *Trichinella spiralis* antigen to mice that had recovered from this nematode infection. Antigen-fed mice maintained abnormal gut motility and colonic hyperalgesia for 2 months after infection, while mice receiving placebo normalized gut function [59]. Similarly, mice

previously infected with *H. pylori* had slower gastric emptying when gavaged with *H. pylori* antigen compared with placebo-fed controls [61]. In both experiments, the abnormal gut function was accompanied by mild but significant increase in CD3 + cells in the gut wall. These results provide proof of concept that symptoms in patients with IBS could be maintained by the exposure of the gut to the relevant bacterial or viral antigens, or even to dietary antigens, which cross-react with the epitopes of the infectious agent.

Is irritable bowel syndrome a mild form of irritable bowel disease?

The authors believe that IBD and at least a subset of IBS patients exist at two ends of the same spectrum of pathophysiology, which involves immune activation and inflammation. This is prompted by the observation that IBS symptoms may precede IBD, which reflects gut dysfunction generated by subclinical inflammation. It also has been observed that IBS occurs in patients in remission from IBD. This concept is underpinned by results of basic scientific studies in animal models showing that immune activation and inflammation restricted to the mucosal compartment result in profound changes in neuromuscular function that may persist after recovery of the mucosa. Emerging evidence shows similarities in genotype between IBD and a subset of IBS patients; polymorphisms of genes that encode cytokine secretion may result in an imbalance of pro- and counter-inflammatory signals. This in turn would lead to inefficient down-regulation of inflammatory responses and promote low-grade inflammation. It is a matter of the severity of inflammation that separates IBD and this IBS subset, and this may reflect additional genetic abnormalities or greater exposure to environmental factors in the case of IBD. This prompts the question as to whether IBD is more common in patients with IBS, and there is some evidence to support this [65]. Clearly in IBD the brunt of immune-mediated injury is borne by the mucosal compartment, whereas in IBS, the mucosal compartment may play a role in initiating events, but the brunt of injury is taken by the deeper neuromuscular tissues. Further work is required to elucidate differences in the regulation of immune activity between these compartments to better understand the relationship of IBD and IBS.

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