ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

Insights Into Conditions That Overlap With Irritable Bowel Syndrome

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G&H What underlying disease mechanisms play a role in the pathophysiology of irritable bowel syndrome?

GH Irritable bowel syndrome (IBS) is an example of disorders of gut-brain interaction (DGBIs). These conditions are now defined by the Rome criteria and characterized by specific symptoms in the absence of structural abnormalities that can be identified utilizing routine clinical testing. The exact cause of IBS is unknown; however, it is likely that a variety of factors collectively or in isolation contribute to the manifestation of IBS. Although for many years there was a belief that motility abnormalities played a key role, it has been increasingly recognized that an increase in sensitivity of the gastrointestinal (GI) tract plays an important role and other factors include low-grade or minimal mucosal inflammation. Many studies also suggest that a composition of the stool microbiome plays a role, but it is possible that this is just a reflection of changes of colonic transit or diet. Thus, an altered central processing of afferents from the gut in combination with gut factors, such as minimal inflammation, is likely to cause IBS.

G&H How frequent is the overlap of functional dyspepsia and IBS, and what are the implications of this?

GH The proportion of patients who simultaneously have IBS and functional dyspepsia (FD) depends on the overall impairment patients have. Patients severely affected by a condition are much more likely to have an overlap. In populations who are seen at specialized centers, more than two-thirds of all patients report an overlap of symptoms, whereas in population-based samples who are not seeking medical attention, overlap is rare. My colleagues and I have conducted a systematic review and meta-analysis in which we reviewed all available data on overlap and then compared population-based samples of primary, secondary, and tertiary care to see what factors are associated with overlap. It is clear from these data that severely affected participants have overlap. Participants in the population-based group who happened to have some symptoms but were unlikely to seek medical attention for them had just a single symptom. This is a problem for researchers conducting clinical trials because frequently the inclusion criteria require that participants are only affected by, for example, IBS and nothing else. However, the patients with IBS alone are not representative of severely affected patients or the ones in most need of medical care.

G&H Does the frequency of overlap between DGBIs and gastroesophageal reflux disease indicate they may not be separate conditions?

GH It has been fascinating for decades that symptom intensity in patients with gastroesophageal reflux disease (GERD) is not linked to the severity of lesions. It is frequently observed in clinical practice that patients without endoscopic esophageal lesions who experience typical and often severe GERD symptoms but do not appropriately respond to the acid-lowering therapies have concomitant

IBS or FD. Therefore, patients who have minimal or no endoscopic lesions and very severe GERD symptoms also are likely to have overlap. However, this disconnect between severity of lesions and symptoms occurs in other organic diseases. In duodenal ulcer disease, for example, some patients present with the typical symptoms; if they fast, they have pain, and endoscopy may show a tiny duodenal ulcer. However, other patients will have no symptoms whatsoever until they manifest with a life-threatening GI bleed and have a deep ulcer somewhere in the duodenum. Obviously, the severity of GI symptoms is not only determined by the severity of structural abnormalities (eg, size of a duodenal ulcer or erosion) but by the processing of information arising from the gut in the brain. If a patient has a sensitive gut or a DGBI, it appears reasonable to expect that the processing of information from more than one organ is affected. Thus, it is likely that FD and IBS occur simultaneously.

G&H What is your take on persistent IBS symptoms in patients with quiescent inflammatory bowel disease?

GH With inflammatory bowel disease (IBD), there is the same disconnect between severity of mucosal lesions and symptoms. This is why, for example, the Crohn's Disease Activity Index does not simply rely on mucosal lesions, but also includes stool frequency and symptoms to measure how quality of life is impaired. There are patients who had an episode of a flare and have ongoing symptoms, and results of endoscopy and appropriate testing show that all the inflammatory activities are under control. Having said this, inflammation can aggravate the perception of symptoms.

In another study, we evaluated patients with IBD in remission who were being treated long term with anti–tumor necrosis factor-α (TNFα) therapy. Before and after their anti-TNFα treatment in randomized order, each patient underwent brain magnetic resonance imaging (MRI) while undertaking a cognitive task and completed a nutrient challenge to assess visceral sensory function. For this simple test, the participants consumed 200 mL of a liquid meal, consisting of a standardized enteral feeding solution, every 5 minutes up to a total volume of 600 mL. After each liquid meal, they rated their GI symptoms (using a visual analogue scale). The total score of symptoms reported during this test meal is a sensory measure. In patients with FD, for example, the symptom score is much higher compared with that in controls. Interestingly, if we study patients with IBD who achieved clinical and endoscopic remission while treated with biologics, the symptom response to a standardized test meal is augmented when the test meal is administered before the scheduled next dose of the biologic as compared with 2 or 3 days after the biologic. At the same time, MRI studies revealed that the administration of the biologic altered the function of prefrontal, amygdala, posterior cingulate, and visual regions when the subjects had to perform cognitive tasks in the MRI scanner. All this suggests that an inflammatory process alters brain function and augments perception of visceral sensory function. In a subgroup of patients with IBS or FD, a very subtle inflammatory process can be found based upon circulating gut-homing T cells or increased counts of inflammatory cells in, for example, the duodenal mucosa. This minimal inflammatory process appears to be linked to symptoms in patients with IBS but equally may play a role in patients with IBD who continue to experience symptoms after complete healing of mucosal lesions.

G&H Can IBS or FD develop after an acute gastroenteritis?

GH In addition to the link between IBS or FD and minimal inflammation, there is good evidence that an acute episode of infectious enteritis can precede the manifestation of FD or IBS. A landmark study from Canada provided compelling evidence that GI infections caused by bacterial contamination of the water supply of a village were subsequently linked to an increased incidence of IBS. A significant proportion of these affected individuals became ill with infectious diarrhea, and then were suffering from postinfectious IBS and other functional GI disorders. Interestingly, in animal studies we have been able to demonstrate that after an acute colonic mucosal inflammation (by application of a chemical agent, trinitrobenzoic acid), which completely healed within weeks, visceral sensory function was still augmented months after mucosal healing. In this context, it is fascinating to see that there are profound strain differences. Although the acute inflammation changes the GI sensory function in Sprague-Dawley rats, in other strains (eg, Fischer rats), no changes occurred. This could provide an explanation why some people develop long-lasting symptoms after an acute GI infection while others do not experience any long-term effects. There is most likely a genetic factor that determines the susceptibility to develop IBS and other conditions after the acute infection.

G&H Is the clinical phenotype for overlap patients the same for patients without overlap?

GH The concept of overlap, which manifests mainly in patients with severe manifestations or patients who need therapy, is a bit of a paradigm shift because it challenges the current strict delineation of the various DGBIs but

is well aligned with the key pathophysiologic concepts of these disorders. In real-life clinical practice, overlap is frequently observed and requires appropriate therapeutic approaches. The diagnosis requires a much more systemic approach. Symptoms are often not focused on a single organ like the colon or the gastroduodenum, and patients who are severely affected are more likely to have multisystem complaints (GI and extraintestinal) with an increased prevalence of depression and anxiety disorders. Our recent systematic review and meta-analysis clearly showed that patients who have overlap are much more severely affected with reduced quality of life. Thus, this is typical of patients with IBS who are seen in the tertiary care setting or specialized centers.

G&H What are the most common non-GI conditions that overlap with IBS?

GH What is striking is that approximately two-thirds of patients with complex DGBIs have either depression or an anxiety disorder. The presence of one of these conditions is a hallmark of a complex DGBI. On top of this, there are a multitude of other symptoms like back pain, chronic fatigue, and similar somatic complaints.

G&H Are non-GI conditions in IBS coincidence or shared pathophysiology?

GH As I mentioned, there is an increased prevalence of extraintestinal complaints in patients with DGBIs. This includes symptoms such as headache or musculoskeletal complaints. It is speculated that alterations in the processing of somatosensory input from, for example, the musculoskeletal apparatus are responsible for these symptoms. Recent epidemiologic research indicates that asthma and allergies may be positively associated with functional GI conditions. Again, this points toward the role of inflammation and immune processes in the pathophysiology of DGBIs and concomitant non-GI disorders.

G&H What should future research on this topic focus on?

GH The greatest need is for a better understanding of gut-brain interactions and how to reset them or modulate them if they are contributing to the manifestation of DGBIs. From a clinical perspective, intervention targeting the brain such as cognitive behavioral therapy, hypnotherapy, or specific drugs might be important. Recent work also emphasized the role of the mucosa-associated microbiome in the small intestine. This microbiome is linked to alterations of gastric emptying or visceral sensory function. This suggests that there are opportunities to selectively alter sensory and/or motor function by targeting the mucosa-associated microbiome. Interestingly, the bacteria that colonize the small intestine are determined during the first 12 months of life. Thus, childhood factors may play a role. Conceptually, researchers need to keep in mind that the small intestine is one of the largest surfaces in contact with our environment. The microbes that colonize the intestine constantly interact with the human body and shape immune functions. Therefore, an unhealthy microbiome, or small intestinal dysbiosis, may have implications for our health. Research that elucidates the interdependencies between gut microbiome—more specifically mucosa-associated microbiome in the small intestine—and visceral sensory function, diet, and the manifestation or severity of a DGBI is an exciting area of study with significant clinical implications.

Disclosures

Dr Holtmann has received unrestricted educational support from Bayer Pty Ltd and the Falk Foundation. He has received research support via the Princess Alexandra Hospital in Brisbane from GI Therapies Pty Ltd, Takeda Development Center Asia Pte Ltd, Eli Lilly Australia Pty Ltd, F. Hoffmann-La Roche Ltd, MedImmune Ltd, Celgene Pty Ltd, Celgene International II Sarl, Gilead Sciences Pty Ltd, Quintiles Pty Ltd, Vital Food Processors Ltd, Datapharm Australia Pty Ltd, Commonwealth Serum Laboratories Pty Ltd, Prometheus Laboratories, Falk GmbH & Co KG, Nestle Pty Ltd, and Mylan. He is a patent holder for a device to take aseptic biopsies (US 20150320407 A1).

Suggested Reading

Ford AC. Overlap between irritable bowel syndrome and inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2020;16(4):211-213.

Gray MA, Chao CY, Staudacher HM, Kolosky NA, Talley NJ, Holtmann G. Anti-TNFα therapy in IBD alters brain activity reflecting visceral sensory function and cognitive-affective biases. *PLoS One*. 2018;13(3):e0193542.

Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol*. 2016;1(2):133-146.

Jones MP, Shah A, Walker MM, Koloski NA, Holtmann G, Talley NJ. Overlap of heartburn, functional dyspepsia, and irritable bowel syndrome in a population sample: prevalence, temporal stability, and associated comorbidities. *Neurogastroenterol Motil*. 2022;34(9):e14349.

Marshall JK, Thabane M, Garg AX, Clark WF, Salvadori M, Collins SM; Walkerton Health Study Investigators. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. *Gastroenterology*. 2006;131(2):445-450.

Shah A, Gurusamy SR, Hansen T, et al. Concomitant irritable bowel syndrome does not influence the response to antimicrobial therapy in patients with functional dyspepsia. *Dig Dis Sci*. 2022;67(6):2299-2309.

Shanahan ER, Kang S, Staudacher H, et al. Alterations to the duodenal microbiota are linked to gastric emptying and symptoms in functional dyspepsia. *Gut*. 2023;72(5):929-938.

von Wulffen M, Talley NJ, Hammer J, et al. Overlap of irritable bowel syndrome and functional dyspepsia in the clinical setting: prevalence and risk factors. *Dig Dis Sci*. 2019;64(2):480-486.