ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Insights on Disorders of Gut-Brain Interaction

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G&H What conditions fall into the category of disorders of gut-brain interaction, and how does irritable bowel syndrome fit into this category?

GS Disorders of gut-brain interaction are a group of conditions that were formerly referred to as functional gastrointestinal (GI) disorders—a term that clinicians may be more familiar with because it is what these conditions were historically called. They are now referred to as disorders of gut-brain interaction because a dysfunction within the so-called gut-brain axis is at the core of most of these disorders. As a corollary to this, the primary symptom in most of these disorders is a perceptive abnormality. The main complaint is pain. Disorders of gut-brain interaction are thought of as pain-central or pain-predominant disorders, although patients can experience other perceptive symptoms or abdominal symptoms such as bloating or nausea.

Disorders of gut-brain interaction are associated with a constellation of abdominal-perceptive symptoms. Irritable bowel syndrome (IBS) is the most common prototypical disorder of gut-brain interaction, affecting somewhere in the order of 5% to 10% of adults worldwide. Because IBS is defined by the presence of abdominal pain in association with changes in stool frequency and form, abdominal pain as well as bowel symptoms need to be present to establish an IBS diagnosis.

G&H What is the role of glutamatergic signaling in the gut-brain axis and disorders of gut-brain interaction?

GS Glutamate is a very intriguing neurotransmitter in terms of its role in disorders of gut-brain interaction. Neurotransmitters are at the core of GI tract function, and exploration of their role in gut-brain dynamics is one of the newer areas of interest within the field.

Historically, attention was focused on serotonin and adrenergic neurotransmitters such as norepinephrine, but glutamate has received increasing attention in recent years. Glutamate is a nonessential amino acid that has a role in sensory function at the level of the GI tract. Glutamate has central activity as well, so it has an important role in pain perception at the level of the spinal cord and brain. It also has a role in memory. Understanding of glutamatergic signaling may pull together understanding of disorders of gut-brain interaction. With repeated experiences of abdominal discomfort or pain, attention and memory are modified, potentially leading to contextualizing and conditioning toward future experiences.

Another reason glutamatergic signaling is interesting and unique is that its understanding can potentially lead to treating disorders of gut-brain interaction through dietary intervention via modulation of the gut microbiota. This awareness is leading to an evolution in the field beyond gut-brain interaction to microbiota-gut-brain interaction and is bringing the role of the intestinal microbiota into the picture.

There was a time when symptoms such as those seen in IBS were thought to be driven by anxiety and depression. It is now more commonly acknowledged that there likely are multiple different pathways leading to a common expression of symptoms that defines IBS or a related disorder of gut-brain interaction such as

functional dyspepsia. These patients can potentially be subcategorized according to whether glutamate signaling or the serotonergic system or another mechanism underlies the primary deficit or defect.

G&H What clinical factors need to be considered to efficiently diagnose a disorder of gut-brain interaction?

GS The most important element in the diagnosis of IBS or a related disorder of gut-brain interaction is to make certain that the symptoms align with the diagnosis. It is not uncommon for a patient who simply presents with diarrheal symptoms to be given a diagnosis of IBS. Such a diagnosis is inappropriate because the patient is missing one of the cardinal symptoms that defines the disorder, namely abdominal pain. The clinician needs to explore differential diagnoses and focus on different aspects of the symptom experience if the patient does not have the full constellation of symptoms that defines the disorder.

Another important aspect in making a diagnosis is to review red-flag symptoms that should alert the clinician to pursue a more immediate evaluation or endoscopic examination. Conditions and findings that fall into this category would be, for example, anemia, blood in the stool, weight loss, or awakening at night with pain or diarrhea. Family history, such as a history of inflammatory bowel disease or GI malignancy, also can raise concerns. These factors should be reviewed for every patient to make certain that early detection of a disorder is not being overlooked.

Regarding treatment, the severity of the symptoms is the first point of focus and refers to the degree of abdominal pain or discomfort and symptom frequency. Assessment of the impact of symptoms on quality of life and function is very important as well. It is also essential to understand and address which symptoms are most bothersome to the individual patient. This will dictate the initial approach to treatment selection options.

G&H What patient-specific factors need to be considered when diagnosing a disorder of gut-brain interaction and formulating a treatment plan?

GS Several different pharmacotherapeutic options need to be discussed with the patient as well as an increasing number of nonpharmacologic options such as dietary approaches. Psychological approaches also need to be presented to the patient. Such approaches, including cognitive behavioral therapy and even hypnotherapy, can be as effective or more effective than medication.

Some patients do not want to be on a daily medication for symptom management and prefer a trial of dietary approaches or lifestyle modifications, such as factoring in exercise and better sleep hygiene, which are known to be of benefit in patients with disorders of gut-brain interaction.

Of course, treatments may be layered, combining pharmacotherapy with dietary approaches and lifestyle modification.

G&H How do central neuromodulators such as tricyclic antidepressants and selective serotonin reuptake inhibitors impact the gut and disorders such as IBS?

GS It has long been known that neuromodulators have the potential to ameliorate abdominal symptoms that typify IBS and related disorders. It is also well known that a high percentage of patients with gut-brain disorders will have overlapping symptoms outside the GI tract. For example, a fair percentage of patients will have symptoms that align with a diagnosis of fibromyalgia, or they may have chronic headaches or pelvic pain or have a diagnosis of dyspareunia or interstitial cystitis.

However, it is important for clinicians to recognize that factors other than a patient's reported pain severity score impact treatment response. For example, a neuromodulator may be prescribed to improve abdominal pain in a patient reporting a 7 out of 10 on a pain severity scale, yet that same patient may present several months later reporting abdominal pain in the same scoring range despite acknowledging overall improvement in symptoms with treatment. It is important to move beyond objective measures such as pain scale scores and more qualitatively understand the impact of treatment on the patient as a whole. Deeper probing into the patient's experience may reveal that, although maximal pain intensities continue to be reported in a similar range, overall function, quality of life, and well-being are reported as substantially improved. Often, with treatment IBS patients realize that although they still rate their pain as a 7 out of 10 in severity, they may have pain less frequently (perhaps only a day or two a week instead of every day), and the pain may not last as long as it once did; thus, there is not as much of an impact on their quality of life and activities, such as their social life and ability to work.

G&H What research and applications are currently underway regarding neuromodulation in the management of these disorders?

GS Regarding neuromodulators specifically, again, the number of options is growing. Focus had been on

tricyclic antidepressants for a long time, but these agents are associated with adverse effects. The team at Washington University, led by my mentors the late Dr Ray Clouse, who was a professor of medicine and psychiatry, and Dr C. Prakash Gyawali, showed that 30% to 50% of patients can have intolerable adverse effects largely owing to the anticholinergic-receptor and antihistaminergic-receptor effects of the medications when given a trial of one of these medications. Overcoming this challenge led to an interest in neuromodulators other than tricyclic antidepressants.

Attention has turned in recent years to selective serotonin reuptake inhibitors (SSRIs). A number of smaller studies have looked at these agents, which appeared to have a greater benefit than placebo when reviewed collectively in a meta-analysis. However, observations of physicians in clinical practice suggest that, although SSRIs are better tolerated than tricyclic antidepressants, they tend to not be quite as effective in alleviating abdominal pain symptoms.

The adrenergic effects—specifically the norepinephrine effect—of certain antidepressants may be of benefit regarding abdominal symptoms. This has led to interest in serotonin/norepinephrine reuptake inhibitors (SNRIs). Such agents include duloxetine and venlafaxine, which have a positive effect on that norepinephrine-receptor system. Several open-label studies that have been conducted to date show a positive benefit. More published data on the value of SNRIs in disorders of gut-brain interaction will likely be forthcoming, and there is eagerness in the field to see clinical trial data on the use of these agents in the management of IBS and related disorders.

There is also a growing body of literature on alpha-2-delta ligands such as pregabalin and gabapentin. These medications have been shown to be beneficial in other, non–GI-related pain disorders and are thought to block some of the afferent pain signaling from the end organs, such as the gut, to the spinal cord, where ultimately that pain is transmitted up to the brain and perceived. These medications may be useful nonantidepressant options to consider and may have good potential as adjunctive therapy.

It is an exciting time for growth of gut-brain therapeutics because the field is starting to put all of the pieces together. There is now room for optimism for patients who have not yet found satisfactory treatment for alleviation of their symptoms. An ever-growing portfolio of options means greater opportunities for symptom improvement in the majority of patients.

Disclosures

Dr Sayuk is a speaker and consultant for Salix, AbbVie, Ironwood, and Alnylam and a speaker for GI Health Foundation.

Suggested Reading

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