ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Changing Paradigms in Functional Gastrointestinal Disorders

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G&H How are functional gastrointestinal disorders defined?

NT Functional gastrointestinal disorders (FGIDs), which are also referred to as disorders of gut-brain interactions, are common, affecting 1 in 5 Americans. Patients present with chronic, unexplained gastrointestinal (GI) symptoms. Examination findings are normal, including endoscopy findings, so the condition is therefore classified as "functional." Because there is no obvious structural explanation, it is presumed that a disturbance of function is at work. For example, a sensory disorder, a motor disorder, or perhaps a disorder of central processing of gut-brain signaling may be present. However, in my view, this is an old, outmoded paradigm.

Researchers have been intensely searching to find possible structural changes in patients with FGIDs. Recent studies of intestinal tissue have demonstrated that, at least in a subset of patients, subtle gut pathology is present with immune activation and is likely important in the etiopathogenesis of the disease. This is an exciting time because new answers are finally emerging. Novel treatments that will revolutionize this field can be expected to follow. Rather than simply symptom suppression, which is the current approach, a cure (complete symptom control) may be possible in some cases.

G&H What anatomic characteristics and immunologic mechanisms link FGIDs and atopy?

NT The first point is that the pathology seen in FGIDs is different from the usual GI pathology in organic diseases such as Crohn's disease. FGID pathology is characterized by an alteration in gut homeostasis, often with an increase in eosinophils and/or mast cells in localized sections of the intestinal tract in subsets of patients. The site of disease involvement correlates to some extent with symptom patterns. Both abnormal tissue and systemic immune response are characteristic of FGIDs. Cytokine changes have been observed, although studies have been inconsistent in terms of the exact circulating signatures. Most striking has been the finding of circulating homing small-intestinal T cells, which signal an active inflammatory process in the small intestinal tract. These T cells are elevated in both irritable bowel syndrome (IBS) and functional dyspepsia, the 2 main types of FGIDs.

Increased permeability in the small intestinal tract has been observed in FGIDs, both in IBS and functional dyspepsia (leaky gut), potentially allowing foreign antigens, including microbial and food antigens, into the mucosa that can initiate an inflammatory response. Further, food antigens may induce acute changes and may explain the strong association of IBS and functional dyspepsia with

postprandial complaints. In IBS for example, directly presenting food products onto the duodenum has been directly observed to induce an acute reversible inflammatory process with eosinophil recruitment and disruption of the intestinal barrier in real time. These new insights are exciting because eliminating relevant food antigens could be a way to more effectively manage these diseases in the future.

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It is important to note that most people with FGIDs do not experience immunoglobulin E–mediated food allergic responses. Referral to an allergist is usually not helpful. Although not indicative of food allergy in the traditional sense, patients with FGIDs perhaps can be considered to have an atypical food allergy manifestation in many instances.

The extraintestinal manifestations of these disorders, such as asthma or anxiety, could well be driven by the gut pathology and associated immune response. Epidemiologic studies demonstrate that asthma, for example, is increased in patients who have FGIDs. Conversely, asthmatics are more likely to have IBS. The explanation for this overlap has been elusive, but abnormal intestinal immune responses and tissue eosinophilia in subsets of patients may implicate common pathways in these patients.

The microbiome remains an active area of exploration in FGIDs. Bacterial signatures in the large and small intestines have been reported in intestinal biopsies, and although these signatures vary across studies, the findings suggest that there are microbial markers for some of these disorders. Changes in the gut microbiome and lung microbiome also may be at play in patients with disease overlap. Both microbiomes are altered in asthma, for example. The exact links remain to be elucidated, and more research is needed.

Other common environmental risk factors for both lung disease and FGIDs also may be shared. A recent study found that cigarette smoking is a risk factor for functional dyspepsia and IBS-predominant diarrhea. Smoking is also a risk factor for chronic obstructive lung disease, which may be confused with asthma.

We have observed that duodenal eosinophilia, seen in functional dyspepsia, is a risk factor for new onset of anxiety 10 years later, suggesting that gut pathology may be a trigger for psychological distress in some cases, not the other way around.

G&H What are the roles of genetics and epigenetics in the pathophysiology of comorbid FGIDs and atopy?

NT Some genes appear to be associated with IBS, although less is known regarding genetic predisposition and functional dyspepsia. Whether genetic changes have anything to do with predisposition to extraintestinal manifestations of IBS and functional dyspepsia is not known. The finding that patients with FGIDs have an increased risk of also experiencing asthma, atopic conditions, and autoimmune disease fits best with the immune-activation hypothesis for FGIDs previously described.

Very little is known about epigenetics and FGIDs. If environmental factors are driving these diseases—which almost certainly seems to be the case—then epigenetic factors will likely be relevant. This area needs to be better studied.

G&H What is the association between immunotherapy and eosinophilic GI disorders?

NT Immunotherapy does not appear to aggravate or induce FGIDs. Recently, there has been great interest in targeting eosinophils and mast cells as well as blocking the activation or products of those immune cells, such as with histamine blockade, as treatment for FGIDs. There are promising emerging data for histamine 1 blocker therapy in IBS and functional dyspepsia.

Eosinophilic duodenitis is relevant in some patients with FGIDs, particularly patients with unexplained upper GI symptoms (of whom more than 50% also have IBS symptoms). Data are emerging that proton pump inhibitors (PPIs) suppress duodenal eosinophils and tighten up mucosal permeability. Thus, a hypothesis has been presented that PPIs may be effective in treating dyspepsia in many patients, not because of suppression of acid but because of suppression of intestinal inflammation associated with eosinophilia. On the other hand, PPIs can change the microbiome, so there is a theoretical concern that PPIs may possibly aggravate symptoms in other patients.

G&H What characteristics of the microbiome do patients with FGIDs and atopy share?

NT An adult microbiome, or at least a reasonably stable microbiome, is established at approximately age 3 years, but diet rapidly alters it. Both dietary factors and microbiome factors may underlie FGIDs. Microbial breakdown of food may release food antigens that drive the disease grouping currently mistermed as FGIDs. Research is being directed at that interaction between diet and the microbiome and at understanding likely triggers. Once all of this is understood, dietary interventions could be prescribed that support a healthy microbiome, and these interventions could be applied to at-risk patients to even prevent FGIDs.

If such intervention becomes a reality, it is possible that improvement in disorders such as anxiety may be possible, along with improvement in gut disorders, because, as mentioned, subtle gut pathology may drive anxiety in some patients with FGIDs.

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G&H What can be done to ameliorate risk?

NT Not enough is known about risk yet. People who have had psychological trauma are potentially at risk, so stress-related factors need to be examined. Cigarette smoking is now known to be a likely risk factor. Diet also is likely relevant, although it remains unclear which dietary intervention is optimal. There is evidence that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is of benefit in patients with IBS, and likely in those with functional dyspepsia as well, but this benefit is only temporary (as relapse is rapid if foods are reintroduced). The role of probiotics is also uncertain.

How to prevent disease is unclear. As understanding of the triggers expands, prevention will become a reality. Evidence exists, for example, that wheat antigens can be a trigger. A German study showed that wheat was a factor that drove acute eosinophilia and permeability changes in the duodenum in IBS. This does not mean that all people with FGIDs should consider a low-wheat diet, however. There are several possible antigens in wheat that might drive disease, and this is an area of active research.

G&H Should patients with FGIDs be screened for allergic asthma and other atopic conditions, and vice versa?

NT The answer is unclear. Routine screening is not performed. It would not be unreasonable for a clinician to ask a patient with allergic asthma about GI symptoms, and ask a patient with chronic GI symptoms about asthma and other atopic conditions. Doing so does not change treatment much, although the clinician would want to know if the patient is on anti-eosinophil therapy (eg, for eosinophilic asthma). That would arguably be an important piece of clinical information when considering next treatment steps for the patient based on the emerging evidence for duodenal eosinophilia in FGIDs.

Because it is rare for an allergist to find a patient with an immunoglobulin E–mediated food allergy that accounts for his or her IBS, screening with routine food allergy testing is of little or no value. In addition, an allergist's findings of positive food allergy prick test results in a patient with gut disease will likely not be that helpful to the gastroenterologist, as false-positive results are common. The clinician could more simply try a standard 6-food elimination diet also used for eosinophilic esophagitis in an affected patient. The same paradigm may apply for a subset of patients with FGIDs. Unless the gastroenterologist strongly suspects a food allergy, angioedema, or so on, referral to an allergist is not needed.

G&H What are the most forward-thinking treatment options that are available for patients with a FGID and a comorbid atopic disorder?

NT Treatment is evolving to focus on therapies targeting pathophysiology as opposed to the current approach of controlling symptoms. One target is small intestinal bacterial overgrowth (SIBO); however, it should be pointed out that tests for SIBO measure a small component of the intestinal microbiome and miss most of the bacteria present. Breath tests also often produce many false-positive results. That being said, rifaximin (Xifaxan, Salix) has been widely used, but is nonspecific. The hope for the future is using nonabsorbable antibiotic–like therapy that targets very specific gut microbes.

The inflammatory process and increased gut permeability are other targets. An interesting small study has shown that glutamine may improve small intestinal permeability and, in turn, IBS symptoms. An approach

that promotes the small intestine to heal, resolving any permeability abnormality, may well be a very effective strategy because the antigens that are inducing the disease presumably are blocked.

Directly targeting mast cells and eosinophils is possible. Current mast cell–targeted therapies, such as disodium cromoglycate, are largely ineffective, but specific biologics that can target activation of these cells are under study. Preliminary evidence is showing their value. In primary eosinophilic gastrointestinal disorders (EGIDs), there is evidence that certain biologics reduce eosinophils and symptoms, and those patients have symptoms that are virtually identical to those of patients with FGIDs. In fact, it is very difficult to distinguish the 2 groups. EGIDs and FGIDs may be part of the same disease spectrum.

Dietary approaches need further work. Dietary therapies that are simple for the patient to adhere to and very effective are needed. Current dietary approaches are far from simple (eg, the low-FODMAP diet), and adherence is a major issue.

Disclosures

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Suggested Reading

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