New and Important Insights Into IBS: From Epidemiology to Treatment CME

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Introduction

Disorders of gastrointestinal dysfunction, including irritable bowel syndrome (IBS), continue to attract increasing attention as our understanding of them accelerates. At this year's meeting of the American College of Gastroenterology, a number of important new findings in IBS emerged regarding epidemiology, impact, diagnosis, prognosis, potential mechanisms, and treatment. This summary discusses this new knowledge and places it in appropriate clinical context.

Epidemiology

It is well known that IBS is highly prevalent in the general population, but national US data are limited and previous studies have often focused on self-reported diagnosis of IBS data rather than applying standard diagnostic criteria (eg, Rome).[1]

Hungin and colleagues[2] applied random-digit-dialing technology to conduct telephone interviews in more than 5000 subjects 18 years and older in the United States. Using a structured questionnaire to obtain information on IBS, they identified the overall prevalence of this disorder to be 14%, with a female-male ratio of approximately 2:1. More women than men had typical IBS symptoms, but overall only about one fourth had been formally diagnosed as having IBS; 34% had symptoms for more than 10 years, and 48% had symptoms for more than 5 years. Approximately 60% of subjects used over-the-counter medications, and 20% used nothing to treat their IBS. These investigators reported that abdominal pain was the major reason patients visited healthcare professionals. They also observed that there was a higher rate of cholecystectomy and hysterectomy among those with IBS in the population. These findings are consistent with other high-quality US epidemiologic studies.[3] Similar results have also been observed in Europe[4] and Australia.[5]

In another epidemiologic study of 1069 employees of the Veterans' Affairs Health Care System in Utah, Tuteja and colleagues[6] evaluated potential risk factors for IBS. They recruited a total of 723 subjects, obtaining a response rate of 72%, and observed that 9% had IBS, as expected. Adjusting for age and sex, IBS was not associated with smoking, aspirin use, alcohol consumption, or education level. However, unmarried patients and those taking acetaminophen were at a significantly higher risk for IBS. Being unmarried may be of relevance because there is a lack of social support and therefore a potential increased vulnerability to stress. On the other hand, acetaminophen use may reflect the need for this medication for abdominal pain or extraintestinal pain, although there is no evidence that acetaminophen effectively relieves pain in this condition.

Impairment of quality of life is considered by many to be an important prerequisite if a condition not associated with mortality is to be labeled a disease.[1,7] Hungin and associates[8] reported that despite substantial nonconsulting, IBS had a significant impact on patients' day-to-day life: 25% were working fewer hours and 20% had changed their work schedule because of the disease. Although IBS has a confirmed predominance among women, it is still not known whether there are sex-specific differences that predict health-related quality of life in IBS.[1] Sach and associates[9] evaluated this issue. They found that IBS in both women and men had a similar overall gastrointestinal symptom severity score. They also noted that IBS patients in this study had more impaired mental and physical quality of life and worse vital exhaustion scores than controls. It appeared that in women physical factors may predominately predict impaired quality of life, whereas in men cognitive factors appear to be stronger predictors of impaired quality of life.

Thus, sex differences do matter in IBS, as exemplified by the not-yet-explained superior efficacy of the new peripherally acting serotonin-modulating drugs in IBS, which appear to be more efficacious in women (although admittedly there are fewer data in men).[1,7] Additional work is required to interpret the sex-specific impact of IBS and explore the mechanisms underlying the sex-specific differences in this disease.

Diagnosis

Symptomatic Differentiation

There is increasing interest in evaluating the utility of symptoms for distinguishing IBS from other functional and organic diseases.[1] One of the major issues that often faces clinicians is the challenge of differentiating IBS with constipation from functional constipation due to slow colonic transit or pelvic floor dysfunction.

Crowell and colleagues[10] evaluated patients seen in a tertiary referral center who fulfilled the Rome I criteria for either IBS or functional constipation. They applied a standardized bowel symptom questionnaire to determine which symptoms might differentiate IBS from functional constipation. They observed significant symptom overlap for the 2 conditions. However, they were able, applying discriminate analysis, to correctly classify the majority of patients (73%), although the model appeared to lack clinical utility and requires prospective testing. At this stage, differentiating IBS from other functional bowel diseases based on symptoms is arbitrary; more work is needed to determine if meaningful groupings can be identified with more careful attention to specific symptoms and pathophysiologic abnormalities in constipated patients.

IBD and IBS: Common Link?

A key issue that continues to be controversial is whether IBS and inflammatory bowel disease (IBD) have a common link. A small increased risk of IBD among individuals with IBS has been identified in 1 prospective cohort study.[11] Furthermore, it is well recognized that typical IBS-like symptoms may occur in IBD in remission.[1] Therefore, it may be difficult to distinguish these diseases unless colonoscopy and biopsy are performed.

KothandaRaman and colleagues[12] evaluated the pain experienced by patients with IBS compared with that experienced by patients who had Crohn's disease. They studied 12 patients with IBS and 22 with Crohn's disease, all of whom completed the McGill Pain Questionnaire, the Pain Disability Index, the Pain Catastrophizing scale, the Multi-Dimensional Pain Inventory, and a quality-of-life measure (the 36-Item Short-Form Health Survey [SF-36]). Pain descriptors were similar in both groups, although the patients with Crohn's disease had a more helpless attitude and a lower overall quality of life. Therefore, it appears that the pain experience is similar in IBS and Crohn's disease and that using pain descriptors to differentiate IBS from IBD is unlikely to be effective.

Zaman and associates[13] evaluated symptoms in patients with Crohn's disease (n = 30) and left-sided ulcerative colitis (n = 25) or IBS (n = 21). In patients with IBS compared with active IBD, the symptoms were remarkably similar, suggesting that it can be difficult to differentiate IBD based on gastrointestinal symptoms alone. The precise utility of the Rome II criteria in IBD remains poorly defined, but these criteria are likely to be insufficient on their own. Alternatively, alarm symptoms, such as rectal bleeding or weight loss, in combination with typical IBS symptoms may be considerably more helpful in differentiating active IBD from IBS, as may be the use of inflammatory markers, such as a sensitive assay for C-reactive protein or calprotectins.[1]

Sugar Intolerance

Another condition that can be confused with IBS is sugar intolerance; however, the role of fructose and sorbitol in the etiology of symptoms typical of IBS remains controversial. A high prevalence of sugar malabsorption has been observed in patients with IBS, although the benefits of restricting intake of the problematic sugars has been highly variable.[14,15]

Gagliardi and colleagues[16] noted that the mean fructose intake in the United States is at least 37 g/d. They studied 15 healthy adult patients who consumed both 25 g and 50 g of fructose on separate days. Breath hydrogen testing was then conducted. The study authors observed that 50% of patients had hydrogen peak levels above 20 ppm with the 25-g dose of fructose, whereas 75% taking the 50-g dose had an abnormal hydrogen peak. This finding suggests that in the normal population a large number of individuals have fructose malabsorption. Furthermore, symptom scores were greater after both doses of fructose, although the higher dose did not increase the scores.

Choi and associates[17] specifically assessed fructose intolerance in the setting of IBS. They studied

209 patients with unexplained bloating, altered bowel habit, and pain who were given either a 25-g or 50-g fructose challenge. It was observed that in patients receiving the higher fructose load, symptom scores were higher for diarrhea but not for other gastrointestinal symptoms. Overall, one third of patients with suspected IBS in this tertiary referral center appeared to have fructose intolerance. However, avoidance of fructose and symptom relief were not evaluated. Clinicians may wisely wish to consider prescribing a low-fructose diet as part of their initial management of IBS with diarrhea, but the benefits even among patients with coexistent fructose intolerance are as yet not established.

Prognosis

Durability of Diagnosis

Traditionally, IBS is considered to be a "safe" diagnosis.[1] Adeniji and colleagues[18] studied a well-characterized cohort of patients to confirm the safety (durability) of a diagnosis of IBS. They reviewed a cohort of patients who were diagnosed with IBS between 1989 and 1992 and who fulfilled the Rome I criteria for the diagnosis. The study population was reinterviewed for IBS symptoms 10-13 years after the initial diagnosis. In 75 patients, the mean time to the second interview was 11.8 years, and none had the diagnosis refuted. There were other gastrointestinal diagnoses noted in small numbers among patients in this cohort, including 5 cases of diverticulitis and 3 of gallbladder disease. Many patients (46%) had undergone a second, but arguably unnecessary, structural evaluation that ultimately produced negative results (no change in diagnosis). Of particular interest was the finding that only 43% of patients continued to meet the Rome I criteria for IBS, implying that some symptoms in IBS will often fluctuate. This finding suggests that the current symptom criteria for IBS may require reconsideration to include subthreshold cases.

Postenteritis IBS

Currently, another area of major interest in IBS is the prognosis of postenteritis IBS.[19] It is now well recognized that up to 1 in 5 cases of IBS will occur after infection, and a low-grade inflammatory process has been documented in some of these cases, although histologically the colonic mucosa is normal.[1,19]

In a study by Spears and colleagues,[20] patients with acute infectious enteritis were administered standardized questionnaires 3 months after infection as part of a repeat evaluation. Although a small study, the investigators observed that 2 patients with IBS 3 months after infection also had depression. In contrast, the remaining 9 patients who did not develop postenteritis IBS were negative for depression on the patient health questionnaire. These results are consistent with the literature, which suggests that psychological factors may identify a vulnerability to the development of postinfectious IBS.[1] The latter may in turn reflect disturbed central down-regulation of visceral afferent signals from the gut that may be genetically determined.

Pathophysiology

Altered Serotonin Signaling?

The pathogenesis of IBS remains obscure, and in particular, an explanation for alternating diarrhea and constipation has been elusive. In arguably one of the most important papers presented during this year's meeting, Moses and colleagues[21] studied potential deregulation of the gut's serotonin transporter in IBS.

It is known that serotonin (5-hydroxytryptamine or 5HT) is released from enteroendocrine (or enterochromaffin) cells in response to either chemical or mechanical stimulation of the gut mucosa. Serotonin in turn initiates peristalsis, and then the serotonin released is taken up in health by a highly selective serotonin transporter (SERT). One potential mechanism that could explain altered bowel function in IBS is an abnormality in the serotonin transporter itself. The study authors evaluated this hypothesis in patients with IBS with constipation and IBS with diarrhea compared with patients with ulcerative colitis and healthy controls. They were able to convincing show on blinded review that SERT immunoreactivity was less intense in patients with IBS with constipation and patients with ulcerative colitis.

If these findings are indeed correct, they represent a landmark observation. The findings suggest that patients with constipation and IBS may have a reduced capacity to reuptake serotonin, leading to excess free serotonin and then desensitization of these receptors, thus reducing motor function. In contrast, in the setting of diarrhea, serotonin uptake was normal. If the underlying abnormality in serotonin transporter function alternated, then this would in turn explain alternating constipation and diarrhea.

These data strongly suggest that IBS is a "real" gut disease and a potential diagnostic disease marker. They also suggest that it is valid to subdivide IBS into constipation and diarrhea symptom subgroups. This study also provides additional rationale for the use of serotonin-modulating agents in IBS and provides a new target for drug modulation. Confirmation of these very exciting initial findings in larger patient samples is awaited with great interest.

Therapy

Tegaserod

Tegaserod is a partial serotonin type 4 agonist (at least in the guinea pig ileum) and is a prokinetic agent that also promotes fluid secretion.[7] Recent randomized, controlled trials have shown that this drug is effective in IBS with constipation, with significant global improvement and improvement in constipation symptoms and abdominal pain.[22] One issue to be resolved is whether the benefits of tegaserod are purely due to its prokinetic action relieving constipation. Animal data suggest that tegaserod has some visceral analgesic actions, although the relevance of this to humans is not yet established.[7]

Dunger-Baldauf and colleagues[23] aimed to evaluate the relevance of the improvement in constipation by performing a meta-analysis of the available tegaserod phase 3 clinical trials. They compared the time course of daily abdominal pain and discomfort and daily bowel movements and failed to show any temporal relationship between these symptoms. The study authors concluded that any benefit to abdominal pain was independent of the drug's prokinetic action. However, a proof-of-concept study comparing standard osmotic laxatives with tegaserod is warranted to validate this finding.

An important issue for clinicians is the safety of tegaserod. Ruegg and colleagues[24] evaluated the combination of antidepressant drugs with tegaserod in the phase 3 tegaserod clinical trials. They showed that tegaserod in combination with antidepressants appeared to be well tolerated and that there were no increased adverse events in this setting. This finding is reassuring because combination therapy is likely to be used by clinicians for IBS in difficult cases.

Tegaserod is a prokinetic, and hence diarrhea would be expected with its use. However, this appears not to be a major issue according to data reported by Earnest and associates.[25] The study authors found that when diarrhea was reported, it occurred early in treatment and that the majority of patients (71%) had only 1 episode. The safety of tegaserod, even in IBS with diarrhea, has been described elsewhere recently.[26] Therefore, although 1 in 10 patients will experience diarrhea, this appears to be a mild and transient issue that typically requires no additional therapy. There are 5-hydroxytryptamine type 4 or 5HT4 receptors on the atria in the heart, but other data support the safety of tegaserod in terms of an absence of electrocardiographic effects.[27]

Probiotics

Probiotics are gaining increasing attention as potential therapies for IBS.[28] Uncontrolled studies have been encouraging, as evidenced by presentations during this year's scientific sessions. Positive results were reported by Bazzocchi and coworkers[29] in an open, uncontrolled trial. Similarly, in a retrospective study, Faber[30] reported significant improvement in symptoms and quality of life from baseline with probiotic therapy. However, Kim and colleagues[31] conducted a randomized, double-blind, placebo-controlled trial and found more sobering and likely more accurate results. They found no overall symptomatic improvement associated with the probiotic they administered (although bloating did improve), and they also found no change in colonic transit.

Only high-quality randomized controlled trials will address the issue of whether probiotics have a place in the treatment of IBS. Furthermore, any benefit will need a mechanistic explanation, which at present is lacking.

Conclusion

This year's annual meeting of the American College of Gastroenterology has provided a forum for the presentation of new and important insights into IBS. Some truly exciting developments have emerged that will hopefully translate into improved patient outcomes as we begin to unravel this increasingly better understood disease entity.

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