Management of Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders. The prevalence rate is 10–20% and women have a higher prevalence. IBS adversely affects quality of life and is associated with health care use and costs. IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation. The consensus definition and criteria for IBS have been formalized in the “Rome II criteria”. Food, psychiatric disorders, and gastroenteritis are risk factors for developing IBS. The mechanism in IBS involves biopsychosocial disorders; psychosocial factors, altered motility, and heightened sensory function. Brain-gut interaction is the most important in understanding the pathophysiology of IBS. Effective management requires an effective physician-patient relationship. Dietary treatment, lifestyle therapy, behavioral therapy, and pharmacologic therapy play a major role in treating IBS. Calcium polycarbophil can benefit IBS patients with constipation or alternating diarrhea and constipation. (Internal Medicine 43: 353–359, 2004)

Key words: functional gastrointestinal disorder, brain-gut interaction, calcium polycarbophil, 5-HT (3) receptor antagonist, 5-HT (4) receptor agonist

Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (1). IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation (2). IBS adversely affects quality of life and is associated with health care use and costs. The pathophysiology of IBS is being explored, and the management of IBS remains unsatisfactory. In this article on the management of IBS, the focus is on the epidemiology, pathophysiology, diagnostic criteria and consideration of conventional and newer treatment of IBS.

Epidemiology

IBS is one of the most common clinical problems encountered by the generalists and gastroenterologist (1). It is now widely accepted that the prevalence of IBS is between 10% and 20% of the US population (3). In our study with a questionnaire given to employees of some companies, the prevalence of IBS was found to be 15.5% in Japan (4). IBS is the most prevalent digestive disease, representing 12% of visits to primary care physicians and 28% of referrals to gastroenterologists (5). It affects females more often than males. The annual incidence is probably 1–2%. The onset of symptoms is balanced by symptom loss, so the prevalence remains stable from year to year (6). The natural history of IBS is one in which symptoms appear, disappear, and change over time (7). The prevalence of gastrointestinal diseases was studied in two British national birth cohorts (8). There was a significantly higher proportion with IBS in the 1970 cohort compared with the 1958 cohort at age 30. The study suggests a period effect in IBS, possibly due to adult life exposure or variation in recognition and diagnosis of IBS.

Gender Differences

Female-to-male prevalence ratios for IBS vary from 1 : 1 to > 2 : 1 across a variety of studies, and women are more likely to develop IBS-like symptoms following an episode of infectious gastroenteritis (9). In population-based studies, there are no large differences in the prevalence of IBS symptoms between men and women or among the three major symptom subtypes of IBS (diarrhea- or constipation-predominant or alternating). However, the majority of persons with IBS-like symptoms do not seek care for these symptoms and, in those who do seek care; there is a 2-to-1 female-to-male predominance (10). Constipation-predominant IBS is more common in women. Although some of this sex-related bias has been attributed to differences in psychosocial factors and use of health care, considerable evi-
There is strong evidence that persons with moderate to severe IBS who seek care for their symptoms (consulters) show decreased HRQOL (10). The impact of IBS on HRQOL in non-consulters is less clear. Finally, a therapeutic response in IBS-related symptoms corresponds to an improvement in HRQOL. The scores of patients in IBS reference groups were significantly lower on several SF-36 domains than those of the US normative population (20). Scores on several SF-36 scales were also significantly lower in the IBS reference groups compared with the GERD, asthma, and migraine samples.

**Diagnosis**

IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disturbed defecation. The consensus definition and criteria for IBS have been formalized in the “Rome II criteria” (2). A committee consensus approach, including criticism from multinational expert reviews, was used to revise the diagnostic criteria and update diagnosis and treatment recommendations, based on research results. The 1998 Working Team assessed the terminology and results of relevant clinical research in order to revise the diagnostic criteria (Table 1).

The Rome criteria, which lacks the so-called “red flags”, has a very high predictive value for diagnosing irritable bowel syndrome (21). So-called “red flags” mean relevant abnormalities on physical examination, documented weight loss, nocturnal symptoms, blood in stool, history of antibiotic use, and family history of colon cancer. Red flags require consideration of another disorder.

**Causes**

Causes of IBS remain unclear, but food, psychiatric disorders, and gastroenteritis are risk factors for developing IBS. Food-related gastrointestinal symptoms, especially postprandial symptoms are common in patients with IBS (22). A majority of IBS patients consider their symptoms to be related to meals. Especially foods rich in carbohydrates and fat cause problems. Female sex and anxiety predict a high degree of food-related symptoms in IBS. Furthermore, different food items are made responsible for IBS symptoms (23). Patients with predominant diarrhea IBS have to be carefully questioned about consumption of different kinds of food (i.e., coffee, alcohol, chewing gum, soft drinks).

The frequency of depression, anxiety, and other major psychiatric disorders is high in patients with IBS. Indeed, up to 60% of patients with IBS have been reported to have a psychiatric disorder, which was considerably higher than the rate of psychiatric disorders in organic disease or healthy controls, suggesting a causal association. However, in a cohort of young adults with IBS from New Zealand, IBS appears to not be related to psychiatric disorders (24).

A small but significant subgroup of patients with IBS reports a sudden onset of their IBS symptoms after a bout of...
gastroenteritis. Population-based surveys show that although a history of neurotic and psychologic disorders, pain-related diseases, and gastroenteritis are all risk factors for developing IBS, gastroenteritis is the most prominent (25). The normal response to infection, such as vomiting and diarrhea, is protective and beneficial. However, in about 10% of patients these protective changes persist and may contribute to the development of post-infective or post-infectious IBS (PI-IBS) which may persist for many years (26). PI-IBS is associated with modest increases in mucosal T Lymphocytes and serotonin-containing enteroendocrine cells (25). Animal models and some preliminary human data suggest that this leads to excessive serotonin release from the mucosa. A prospective community-based, case-control study supports the existence of PI-IBS in some individuals (27). Symptoms consistent with IBS and functional diarrhea occur more frequently in people after bacterial gastroenteritis compared with controls, even after careful exclusion of people with pre-existing functional gastrointestinal disorders (FGIDs).

Pathophysiology

IBS is considered a biopsychosocial disorder resulting from a combination of 3 interacting mechanisms: psychosocial factors, altered motility and transit, which may reflect severity of bowel dysfunction, and increased sensitivity of the intestine or colon. In other words, mechanism in IBS is biopsychosocial disorders; psychosocial factors, altered motility, and heightened sensory function (Fig. 1). Understanding the brain-gut axis is the key to the eventual development of effective therapies for IBS (11).

Visceral hypersensitivity was detected in patients with functional gastrointestinal disorders and has been proposed as a biological marker of IBS. Lowered rectal pain threshold is a hallmark of IBS patients. Rectal barostat testing is useful to confirm the diagnosis of IBS and to discriminate IBS from other causes of abdominal pain (Fig. 2) (28). However visceral hypersensitivity is one of the mechanisms of IBS, but it does not explain the entire symptomatology. Repetitive distension of the distal sigmoid colon below the sensory threshold induces oral exaggerated motility of the colon in IBS patients. The distension inhibits motility of the small intestine in healthy subjects, but this inhibition is blunted in IBS patients. IBS patients may have not only visceral hypersensitivity, but also an abdominal intestinal reflex (29).

Regional brain activity in response to rectal balloon distension in patients with IBS and healthy controls was compared. Positron emission tomography scans (PET) were obtained during rectal balloon distension (30). Statistical parametric mapping and region of interest analysis were performed to identify and compare differences in regional cerebral blood flow (CBF) for each distension pressure within and between the groups of interest. IBS patients with a history of sexual or physical abuse were compared to the patients without abuse. The observations on the effect of abuse

Table 1. Diagnostic Criteria in ROME II

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<th>DIAGNOSTIC CRITERIA</th>
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<td>At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features:</td>
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<td>(1) Relieved with defecation; and/or</td>
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<td>(2) Onset associated with a change in frequency of stool; and/or</td>
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<tr>
<td>(3) Onset associated with a change in form (appearance) of stool.</td>
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The following symptoms cumulatively support the diagnosis of IBS:

- abnormal stool frequency (for research purpose “abnormal” may be defined as >3/day and <3/week);
- abnormal stool form (lumpy/hard or loose/watery stool);
- abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- passage of mucus
- Bloating or feeling of abdominal distension.

These symptoms can be used to subclassify patients with predominant diarrhea or constipation for entry into clinical trials.
suggest a possible modulating role of abuse history on this brain response.

Transient rectal pain was induced by inflating a latex balloon in patients and the functional responses of the brain was assessed by means of functional magnetic resonance (f-MRI) imaging (31). A strong variability of the individual responses to rectal pain was found in patients with IBS. Group analysis revealed significant deactivations within the right insula, the right amygdala, and the right striatum. These findings suggested that the central nervous system plays a significant role in the pathophysiology of this syndrome.

Recently, f-MRI offers an opportunity to study whether activation of the cingulate cortex, an area involved with the affect and pain intensity coding, might be linked to poorer clinical status with IBS (32). A 16-year-old woman with a history of sexual abuse, psychosocial distress, and functional GI complaints was reported. Psychosocial, clinical, and fMRI assessment was performed when the patient experienced severe symptoms and again 8 months later when clinically improved. Activation of the midcingulate cortex (MCC) and related areas involved with visceral pain encoding are associated with poor clinical status in patients with severe IBS and psychosocial distress and appear to be responsive to clinical improvement.

**Dietary and Psychological Treatment**

Currently, there is little convincing scientific evidence from well-designed trials to support the role of dietary modification or exclusions in IBS (33). Similarly, there is an absence of conclusive data linking any dietary components directly to the pathogenesis of IBS. The role of diet, as a single modality, is unlikely to play a major role in treating IBS. Dietary modifications should be viewed as a valuable part of a multicomponent management approach in combination with other strategies such as lifestyle, behavioral, and pharmacologic therapy.

Cognitive-behavioral therapy (CBT) was compared with education (EDU) with respect to clinical efficacy and safety in female patients with moderate to severe IBS. The efficacy and safety of an antidepressant, desipramine (DES) against placebo (PLA) was also assessed (34). Clinical, physiologic, and psychosocial assessments were performed before and at the end of treatment. For female patients with moderate to severe IBS, CBT is effective and DES may be effective when it is taken adequately.

Although CBT and relaxation therapy have both been promising in IBS patients, these therapies seem not to be superior to standard care alone (35). A randomized controlled trial with three arms (standard care for all groups plus either CBT or relaxation) for 8 weeks was conducted, in which blinded outcome assessments were performed using validated measures with 1 year of follow-up. There were no significant differences among the three treatment conditions. All three arms showed similar improvement.

Psychotherapy and antidepressants are effective in patients with severe IBS, but the cost-effectiveness of either treatment in routine practice has not been established (36).
Patients with severe IBS were randomly allocated to receive 8 sessions of individual psychotherapy, 20 mg daily of the specific serotonin reuptake inhibitor (SSRI) antidepressant, paroxetine, or routine care by a gastroenterologist and general practitioner. Both psychotherapy and paroxetine were superior to treatment as usual in improving the physical aspects of HRQOL, but there was no difference in the psychological component. During the follow-up year, psychotherapy but not paroxetine was associated with a significant reduction in health care costs compared with treatment as usual. For patients with severe IBS, both psychotherapy and paroxetine improve HRQOL at no additional cost.

**Pharmacotherapy**

**Conventional therapies**

Dietary fiber and laxative are frequently recommended for patients with constipation-predominant IBS. Anti-diarrheal agents, including loperamide, may help patients with diarrhea-predominant IBS. Antispasmodics and anti-cholinergic agents are best used for patients with pain-predominant IBS and diarrhea-predominant IBS on an as-needed basis in clinical practice (Table 2) (2).

Calcium polycarbophil was compared with placebo in a six-month, randomized double-blind crossover study (37). Polycarbophil was rated better than placebo in monthly global responses to therapy. Patient diary entries showed statistically significant improvement for ease of passage with polycarbophil. Polycarbophil was rated better than placebo for relief of nausea, pain, and bloating. The data suggest that calcium polycarbophil can benefit IBS patients with constipation or alternating diarrhea and constipation, moreover, it may be particularly useful in patients with bloating as a major complaint.

**Novel therapies**

Prokinetic effects were studied in IBS patients with intestinal gas retention (38). In patients with abdominal bloating, gas evacuation and perception of jejunal gas infusion were measured. The effects of intravenous neostigmine vs. intravenous saline were tested in patients with intestinal gas retention; pharmacological stimulation of intestinal propulsion improved gas transit, abdominal symptoms, and distension.

Local rectal anesthesia reverses visceral and cutaneous hyperalgesia in IBS patients (39). Women with IBS rated pain intensity and unpleasantness to distension of the rectum and thermal stimulation of the foot before and after rectal administration of either lidocaine jelly or saline jelly in a double-blind crossover design. Local anesthetic blockade of peripheral impulse input from the rectum/colon reduces both visceral and cutaneous secondary hyperalgesia in IBS patients. Thus rectal administration of lidocaine jelly may also be a safe and effective means of reducing pain symptoms in IBS patients.

Users of oral steroids are at reduced risk of developing IBS. In a cohort study in the UK (40), a nested case-control analysis was performed to estimate adjusted relative risk (RR). Current users of steroids presented an RR of 0.6 compared to non-users. Daily doses greater than 10 mg of prednisolone daily were associated with an RR of 0.4. The reduced risk of IBS was greater among females than males. Oral steroids can reduce the risk of a diagnosis of IBS. On the other hand, it was reported that steroids do not improve the symptoms of post-infectious IBS. Post-infectious IBS is associated with increased serotonin-containing enterochromaffin cells and lymphocytes in rectal biopsy. Patients with post-infectious IBS underwent a randomized, double-blind, placebo-controlled trial of 3 weeks of oral prednisolone, 30 mg/day. Prednisolone does not appear to reduce the number of enterochromaffin cells or cause an improvement in symptoms in post infectious IBS (41).

Tricyclic antidepressants at a low dose may be more efficacious in IBS than placebo. Selective serotonin reuptake inhibitors (SSRIs) have only been subject to a few placebo-controlled studies, and adequate data are lacking. Short-term administration of antidepressants alters intestinal transit, but the selective 5-hydroxytryptamine re-uptake inhibitor, paroxetine, has different effects compared to the tricyclic drug. These effects on transit precede any effects on mood.
Although there is a high prevalence of affective disorder in IBS clinic patients, these drugs may have additional therapeutic actions on the gut. These actions might be taken into account when prescribing antidepressants in IBS (42).

The novel nonpeptide corticotropin-releasing hormone (CRH) type-1 receptor (CRH-R1) antagonist, antalarmin, produced the pronounced anti-ulcer effect and additionally suppressed the stress-induced colonic hypermotility, mucin depletion, autonomic hyperarousal and struggling behavior in rats. Brain CRH-R1 and vagal pathways are essential for gastric ulceration to occur in response to stress and peripheral CRH-R1 mediates colonic hypermotility and mucin depletion in this model. Nonpeptide CRH-R1 antagonists may therefore be prophylactic against stress ulcer in the critically ill and therapeutic for other pathogenetically related gastrointestinal disorders such as peptic ulcer disease and IBS (43).

Serotonergic agents

The gut contains large amounts of serotonin (5-HT) and this neurotransmitter is now known to be intricately involved in the control of gastrointestinal physiological function via a number of receptor subtypes. 5-HT (3) and 5-HT (4) receptors are currently the focus of much attention with respect to the therapy of IBS by the use of either agonists or antagonists (44).

5-HT (3) antagonist: Recently, alosetron, a 5-HT (3) receptor antagonist has been introduced in the treatment of female IBS patients. However, it should be reserved for the treatment of diarrhea-predominant IBS in females who have failed to respond to conventional therapy, and it should be started at a low dose (45). At present, alosetron is not available in Japan. Women with diarrhea-predominant IBS are satisfied with alosetron 1 mg b.i.d. treatment overall and also with respect to specific attributes of IBS medication, which they consider the most important (46).

A placebo-controlled functional brain imaging study was performed to assess the effect of alosetron on IBS, regional brain activation by rectosigmoid distension and associated perceptual and emotional responses (47). Rectosigmoid stimulation was performed with a computer-controlled barostat (Fig. 2). Changes in regional cerebral blood flow were assessed using positron emission tomography (PET). Stimulus ratings and changes in gastrointestinal symptoms were assessed using verbal descriptor scales. In nonconstipated irritable bowel syndrome patients, 3 weeks of treatment with alosetron decreases brain activity in response to unanticipated, anticipated and delivered aversive rectal stimuli in structures of the emotional motor system, and this is associated with a decrease in gastrointestinal symptoms. The most frequent adverse event associated with the use of alosetron is constipation and in some rare cases, the development of colonic mucosal ischemia (48). On the other hand, another study reported that alosetron users did not differ from IBS patients not using alosetron in the incidence of bowel surgery or hospitalized complications of constipation; there were no cases of colonic ischemia (49). The statistical upper limit of colonic ischemia rates in alosetron users was 2.28/1,000 person-year.

5-HT undergoes reuptake by the transporter protein, SERT. Polymorphisms in the promoter for synthesis of SERT (SERT-P) influence the response to serotonergic medications in depression. Genetic polymorphisms at the SERT promoter influence the response to alosetron in IBS and may influence the benefit-risk ratio with this class of compounds (50).

5-HT (4) agonist: The novel 5-HT4 receptor agonist, tegaserod, is currently available in the United State and in other countries for constipated IBS patients (44), but it is not available in Japan. The physiologic actions of tegaserod are related to its ability to stimulate gastric and intestinal motility. In clinical trials, tegaserod was associated with significantly better scores on the subject’s global assessment of relief as compared with placebo (51). The absolute efficacy of tegaserod compared with placebo varied between trials and averaged 10% to 12%. Tegaserod had a good safety profile; diarrhea was the only adverse effect that occurred more often in tegaserod recipients than in placebo recipients. The recommended dosage for patients with constipation-predominant IBS is 6 mg b.i.d. before meals for 4 to 6 weeks, with an additional 4 to 6 weeks of treatment if the initial therapy is only partially effective. The addition of tegaserod to the arsenal may be helpful in patients with constipation-predominant IBS.

Conclusion

Management of IBS involves positive diagnosis and limited exclusion of organic disease. Brain-gut interaction is the most important in understanding the pathophysiology of IBS. Understanding of the brain-gut axis is the key to the eventual development of effective therapies for IBS. Effective management requires an effective physician-patient relationship. In the future, development of optimal therapies will be necessary.

References

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