Changing the Way We Think About Irritable Bowel Syndrome

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Irritable bowel syndrome has long been considered a functional gastrointestinal disorder. However, recent studies have suggested possible organic causes that can explain the multitude of symptoms in IBS.

Brief History

The irritable bowel syndrome has been thought of as a functional gastrointestinal disorder for many years. As long as three thousand years ago, Hippocrates described a triad of symptoms consisting of abdominal discomfort, irregular bowel movements and bloating. In 1817, William Powell reported a case with similar symptoms as Hippocrates. In 1849, Cumming described a syndrome of irregular bowel habits consisting of alternating diarrhea and constipation.[1] In 1928, Bockus and his colleagues described the syndrome as "neurogenic mucous colitis."[2] Bockus determined that this disease can only be diagnosed by exclusion which was the belief until the 1970's.

Epidemiology

Today IBS is one of the most common diagnosed medical problem affecting an estimated 4-35% of the population worldwide, with a prevalence of 9-22% in the United States.[1,3-5] Approximately 12% of office visits in the United States are due to IBS along with approximately 28% of gastroenterology referrals.[1,6-8] It is the 7th most common outpatient diagnosis. Irritable bowel syndrome is the second most common cause for absenteeism, trailing only the common cold. Disability rates are equal to or more severe than organic GI diseases. The prevalence rate is 2-3 times higher in women.[1] This appears to be the case worldwide except in India and Sri Lanka where there is no known gender differences.[9] Hispanics and Asians are less likely to have IBS. There have been conflicting studies on the prevalence differences for Caucasians versus African Americans. The onset usually is in the late teenage years and twenties. The prevalence peaks in the 3rd and 4th decades and begins to decline in the 6th and 7th decades.[1,3,4] After diagnosis, up to 75% of patients will remain symptomatic after 5 years.[10]

Economics

IBS patients miss three times as many work days as the average person. In the United States, the disease accounts for 3.5 million office visits, 2.2 million prescriptions and 35,000 hospitalizations per year. Patients with IBS use more medical resources than the non-IBS patient. These include physician visits, tests, unnecessary surgeries and medications. It is currently estimated that IBS costs the United States between 15-30 billion dollars per year.[11-13] This includes both direct medical costs as well as indirect costs.

Extraintestinal symptoms

Patients with IBS undergo more appendectomies and hysterectomies than non-IBS patients. The most common extraintestinal manifestations include genito-urinary symptoms such as dysmenorrhea, dyspareunia, impotence, urinary frequency, as well as feelings of incomplete bladder emptying. IBS also appears to affect the perception of sexual function. Eighty-three percent of IBS patients compared to 16% of non-IBS patients report impaired sexual functioning.

Diagnosis

The diagnosis of irritable bowel syndrome was originally made using the Manning criteria: pain eased with defecation, pain associated with change in frequency of bowel movements, pain associated with change in consistency of bowel movements, abdominal distention, tenesmus, and mucous in the stool.[14] In 1992, the Rome criteria for the diagnosis of irritable bowel syndrome was published. In 2000, the Rome II criteria was published (See Table 1)[14] In a study of 98 patients, confirmed to have IBS using a clinicians diagnosis as the gold standard, it was found that the Rome I criteria in the absence of red flags to be 65% sensitive, 100% specific and 100% positive predictive value. The cornerstone of the Rome Criteria is abdominal pain. Without abdominal pain, IBS can not be the diagnosis.[1]

Table 1. The ROME I Criteria for the diagnosis of IBS was developed in 1992

ROME I Criteria:	Rome 2 Criteria	Red Flags
Presence for at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that cannot be explained by structural or biochemical abnormalities and at least two of the following	2 or more of the following, at least 25% of occasions or days:	1. Documented weight loss 2. Nocturnal Symptoms
1. Pain relieved with defecation	1. Altered stool frequency	3. Blood mixed in the stool
2. Change in the frequency of bowel movements	2. Altered stool forms	4. Recent antibiotic use
3. Change in the form of the stool	3. Altered stool passage	5. Family history of colon cancer
	4. Bloating or feeling abdominal distention	6. Relevant abnormalities on physical exam (2)

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Gender and Hormones

Hormones appear to play a role in IBS. The symptoms appear to be worse in women during menstruation.[15] Women on hormone replacement therapy tend to be more symptomatic than women not on therapy.[16] One study found that men with IBS are more likely to have lower testosterone and luteinizing hormone than unaffected men.[17] Other studies have found that men with IBS have more nurturing traits and reduction in the male-trait score.[18,19]

Psychological Factor and Abuse

A history of abuse predisposes patients to IBS. In addition to having a history of abuse of varying types; emotional, sexual, or physical and/or a history of stressful life events, social stress or anxiety and having a maladaptive coping style, affect the severity and clinical course of IBS.[20] There is a strong association between IBS and having a concurrent psychological disturbance. Various studies have demonstrated a 40-90 percent association rate with IBS. Psychological disorders associated with IBS include personality disorders, psychological distress, altered health beliefs and coping styles.[20]

Infection

Researchers have suggested that IBS can be explained by bacterial overgrowth in the small intestines. The theory stems from the finding that regardless of the predominant symptom of IBS, 92% of the patients complain of abdominal bloating.[21] The bloating is usually postprandial. Numerous imaging studies show increased intestinal gas in IBS patients. Total hydrogen gas excretion and the maximal rate of gas excretion following lactulose ingestion was higher in IBS patients.[22] The gases produced are hydrogen and methane which demonstrates that this abnormal gas production following lactulose intake in IBS patients cannot be explained by simply a disaccharide intolerance.

Normally, it is uncommon for bacteria to grow in the proximal small intestine. It has been theorized that there is a proximal spread of bacteria along the small intestines. New bacterial growth in the proximal small intestine may be the cause of the increased gas production in IBS patients.[23] Nucera et al24 found that out of 200 patients with IBS, 75 percent had abnormal lactulose-glucose breath tests. This is consistent with bacterial overgrowth of the small intestine.

Another study found that 78% of IBS patients had an abnormal breath test. This suggested that a small intestine bacterial overgrowth may be present. The study consisted of 202 IBS patients who had met the Rome I Criteria. They were treated with antibiotics with successful eradication of the bacteria being measured by a normal breath test. After eradication, half of the patients no longer met the Rome I Criteria.[25] This study was followed with a double-blind randomized control trial. This follow-up study consisted of 111 patients with IBS. Thirty-seven percent of those with IBS had normalization of global symptoms within one week compared to just 11% in placebo-treated patients. Of the patients who bacterial eradication was considered complete, 75 percent achieved normalization of global symptoms.[26] Another study proved that metronidazole is superior to placebo in alleviating symptoms in IBS.[27] This is further evidence of bacterial overgrowth as the potential etiology in at least some IBS patients.

In recent years, studies have shown that a high percentage of people with infectious gastroenteritis develop IBS. This was demonstrated in two control studies. The first study followed 318 subjects with gastroenteritis and compared them to a population database of 584,308 controls for one year to see if a diagnosis of IBS was made. They found that 4% of the post-infectious patients had developed IBS within 12 months compared to 0.3% of the general population.[28] A second study[29] followed post-infectious gastroenteritis subjects and controls for 6 months and found that 17% had developed IBS compared to only 1.9% of the controls. The odds ratio was 10 (95% confidence interval, 3-31). This study used the Rome II criteria for diagnosis of IBS.[30] Overall, the incidence of post-infectious onset IBS has been shown to be between 4-30%.[31]

Inflammation

Several studies have shown the presence of increased inflammatory cell levels in patients with IBS.[20] These findings include increased mast cells in the muscularis externa of the colon and ileum, increased cellularity of the colonic and ileal mucosa, lymphocytic infiltrates in the myenteric plexus and increased nitrous oxide synthetase.[32-37] The findings of inflammation occur usually within three months of infectious gastroenteritis. During this time period, IBS patients have a higher lymphocyte count in the rectal mucosa. The count is not high enough to meet the criteria for lymphocytic colitis.[38] A small study of patients with severe IBS have shown that on full thickness biopsy, a low grade ganglionitis existed. Two of the ten IBS patients with the low grade ganglionitis had post-infectious IBS.[39] There is also evidence that low grade inflammation of the small intestine such as the inflammation following Campylobacter infection could cause bile acid malabsorption.[38] This in turn could cause the symptoms of post-infectious IBS.

Enteric nervous system

One of the earliest studies to show that the nervous system played an important role in IBS involved the difference in perception of pain in patients with IBS compared to controls. Ritchie[40] found that patients with IBS experienced rectal pain when a balloon was inflated in the rectum at lower volumes than non-IBS patients. In this study, fewer than 10% of non-IBS subjects reported pain at a distending volume of about 60 ml compared to greater than 50% of IBS patients reporting pain at the same distending volume.

The enteric nervous system (ENS) is a complex system that rivals the spinal cord and brain in the number of nerves and neurotransmitters involved. It can work both in conjunction with the CNS as

well as on its own as demonstrated in pig intestines in vitro.[41] Intrinsic primary afferent neurons(IPAN) are analogous to dorsal root ganglia of the CNS. They are the peripheral sensors that feed information to the ENS in order to allow autonomous regulation of the gut by the ENS. Drugs that activate IPANs stimulate diarrhea and drugs that inhibit their action cause constipation. One clinical trial used 5-Hydroxyindalpin to stimulate the IPANs and the result was diarrhea.[42] It has been theorized, however, that a drug that targets the distal terminal of IPANs may lead to better control of gut motility.[41] When stimulated by 5HT-4, IPANs cause the release of acetylcholine and calcitonin g related peptide.[41] These neurotransmitters induce gut motility. 5HT-4 also causes the increase release of 5HT-4 at neuromuscular junctions and nerve-nerve synapses in the myenteric plexus.[43-45] The combination of these factors is the reason that Tegaserod, a 5HT-4 receptor agonist, stimulates gut motility. Tegaserod has been shown to provide relief of IBS-c (constipation type) over placebo in several trials.41 5HT-3 is the signal used by the CNS to interpret the intestinal tract environment. Like 5HT-4, 5HT-3 is part of the prokinetic pathway. Antagonizing 5HT-3 is useful in the treatment of hypermotility states such as IBS-D (diarrhea type). Alosetron and Cilansetron, 5HT-3 antagonists, have been effective in the treatment of IBS-D.[46-48]

Celiac Disease

Celiac disease and irritable bowel syndrome share many common gastrointestinal symptoms. It was found that patients with irritable bowel syndrome as diagnosed by ROME II criteria have a higher association with also having celiac disease as compared to normal controls. One study tested for the presence of celiac disease by the presence of serum IgA antigliadin, IgG antigliadin, and endomysial antibodies in 300 patients diagnosed with IBS. Positive antibody tests were followed by biopsy for confirmation of the diagnosis. The results were compared to 300 patients who did not carry the diagnosis of IBS. They found that 14 patients with IBS also had celiac disease compared to just 2 of the non-IBS controls (p=0.004, odds ratio = 7.0 [95% CI 1.7-28]). According to this study, it may be prudent to refer patients with IBS for Celiac disease testing.[49]

Another smaller study comparing 34 subjects with dyspepsia, 50 subjects with IBS, and 78 asymptomatic healthy controls did not show a statistically significant difference in the association with celiac disease.[50] However, in this study celiac disease was diagnosed solely by serology. Whether there is an actual association between the diseases or merely celiac patients falsely being labeled with IBS remains to be seen. Future studies should look into the results of treating the celiac disease to see if the IBS symptoms remain.

Diagnosis

Until recently, the diagnosis of IBS was a diagnosis of exclusion which required a lengthy battery of tests. With the advent of the Rome criteria, physicians have been able to make the diagnosis of IBS on the basis of symptoms in the absence of red flags. Several studies examined the pre-test probability and prevalence of organic disease in patients with IBS. Using flexible sigmoidoscopy, colonoscopy, and barium enema, between 0-1.3% of patients were found to have organic disease. Other studies using abdominal ultrasonography and rectal biopsy failed to identify organic disease in IBS patients. Laboratory studies such as a complete blood count, chemistry panel and fecal occult blood testing similarly found organic disease in only 0 to 1.3% of IBS patients. TSH was abnormal in 0.6 to 6% of patients. Several studies have shown that IBS patients have abnormal breath tests for lactose intolerance in 22-26% of cases. However, one study found the presence of an abnormal breath test in 78% of IBS patients.[13] In addition, Celiac disease was found to be more prevalent in IBS patients, 5% compared to 1% of the general population.[49,50]

The alarms or red flags (see Table 1)[14] used in the Rome criteria such as hematochezia, anemia, weight loss, chronic severe diarrhea and family history of colon cancer, all lead to a high pre-test probability of organic disease and therefore justify initiating a targeted work-up. The Rome I criteria was found to be 65% sensitive, 100 % specific with a 100% predictive value for IBS.[1]

Treatment

The etiology of IBS is complex with overlapping etiologies contributing to the symptoms. (See Figure 1) It has been proposed that small bowel bacterial overgrowth, post-infectious states, inflammatory states as well as psychological factors, all contribute to the vast symptoms of IBS. For this reason, the treatment must be tailored to each IBS patient. Patients with predominant psychological etiology may do well with antidepressants and behavioral therapy. Several studies have looked into treating patients with antibiotics when bacterial overgrowth is the suspected etiology. Other therapies are used to control symptoms such as antispasmodics, bulking agents, and serotonin receptor agonists and antagonists.

Antispasmodics

There are two antispasmodics available in the United States, dicyclomine and hyoscyamine. These drugs are thought to work by decreasing the spontaneous activity of the intestinal smooth muscles. Atropine-like adverse effects often lead to intolerance and the relaxation of the smooth muscle can worsen constipation. Currently there is only a grade B recommendation for the use of anti-spasmodic agents for IBS management.[20] Five smooth muscle relaxants were found to have greater efficacy than placebo. These include cimetropium bromide, pinaverium bromide, octylonium bromide, trimebutine, and mebeverine.[51]

Bulking agents

Several bulking agents have been studied including wheat, bran, corn, fiber, calcium, polycarbophil, ispaghula husk and psyllium. Bulking agents were effective in improving stool bulk and stool frequency but they were not found to be more effective than placebo. Adverse effects of bloating and abdominal discomfort were worsened by those agents.[20]

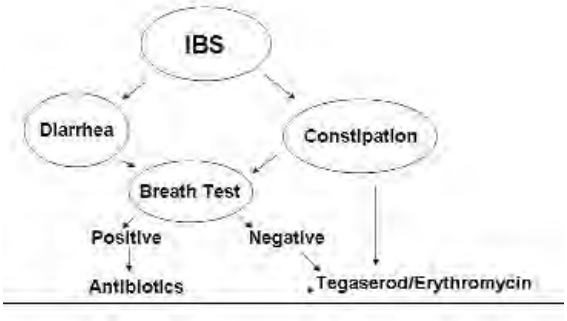

Figure 1: Diagram demonstrating the proposed overlapping etiologies of IBS.

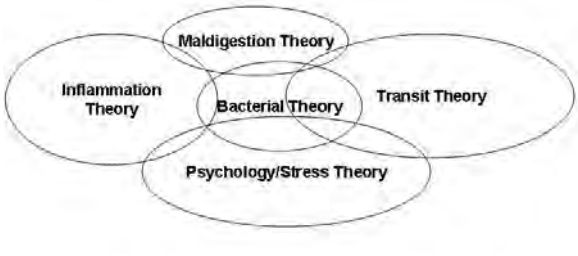

Figure 2: Algorithm for evaluation and treatment of IBS

Anti-diarrheal agents

Diarrhea can be controlled with many over the counter agents such as Loperamide which includes Immodium and Kaopectate II among others. This agent works by slowing gut transit and up regulating water and electrolyte absorption.[52] Prescription Lomotil can be used if the over the counter agents fail to provide relief.

Serotonin receptor agonist (5HT4)

Serotonin receptor activation stimulates peristalsis thereby increasing intestinal and colonic transit time and also reduces visceral sensitivity. Tegaserod is the only 5HT4 currently available. Several well-designed, randomized, controlled trials using the ROME criteria for diagnosis have demonstrated significant improvement of constipation symptoms. The recommended dosage is 6mg twice daily and the trials duration extended over 12 weeks. Significant reduction of bloating, abdominal discomfort and improvement of bowel-habit satisfaction were reported but the magnitude of these improvements were not consistent among those trials. This is likely secondary to different methodology used to evaluate the symptoms. 9-10% of patients reported diarrhea as the most frequent adverse effects compared to 4-5% in the placebo group.[41] Another recent study looking at the efficacy of Tegaserod for repeated therapy using 2660 patients found that Tegaserod was superior to placebo in both initial use and repeated therapy.[53] It should be kept in mind that the FDA approved regimen is only for short duration in females whose primary symptom is constipation. The role of Tegaserod is not clearly defined in patients with alternating constipation with diarrhea. No recommendation exists for males.

Serotonin receptor antagonist 5HT3

5HT3 antagonism slows colonic transit and improves discomfort. Alosetron is the first FDA-approved 5HT3 receptor antagonist for the treatment of IBS with diarrhea. Because of reported cases of ischemic colitis, its use was stopped in November 2000. The FDA allowed the marketing of the drug again in June 2002 at the dose of 1mg twice daily. Four trials resulted in statistically significant improvement in abdominal pain and fecal urgency though the magnitude of the improvements were different across the trials. Alosetron has a grade A recommendation by the ACG for IBS with diarrhea. The most commonly reported adverse effect is constipation occurring in 22-39% of patients vs 3-14% controls. Unfortunately, ischemic colitis is unpredictable. Physicians are advised to adhere the FDA guideline of using Alosetron for "women with severe, diarrhea-predominant IBS who failed to respond to conventional IBS therapy" in view of the potentially serious adverse effects.[46-48]

Behavioral and psychotropic therapy

Because of the frequent findings of psychological disorders in IBS, especially depression and anxiety disorders, behavioral therapies have been tried for treatment. There have been at least 16 randomized controlled trials. Presence of a psychological disorder was found in 80% of patients. Unfortunately, these trials contained flaws in the methodology. Behavioral therapy seems to improve both the IBS symptoms and the psychological manifestations although the evidence fails to be unequivocal. Currently, only behavioral therapy has Grade A recommendation for the treatment of IBS.[20]

The use of antidepressants has been helpful in some patients. Those with abdominal pain, bloating and diarrhea seem to be most susceptible to the benefits of tricyclic antidepressants.[54] The mechanism of action is two-fold. First, they appear to effect motility and visceral sensitivity as well as central pain perception.[55] They also have anticholinergic effects which can help with diarrhea. More recent studies have found SSRIs to be somewhat helpful in alleviating symptoms and improving mood.[20]

Hypnotherapy

Several studies have evaluated the benefit of hypnotherapy in reducing symptoms of IBS in both the short and long-term. One study consisted of IBS patients receiving weekly 1-hour session of gut-directed hypnotherapy for a total of 12 weeks. They found that the patients improved in the long-term follow-ups.[56] Another study followed 204 patients using questionnaires for 6 years. They

found that initially 71% of the patients had symptom improvement. After 5 years, only 19% of the patients who initially responded had regressed. Measures of quality of life, anxiety, and depression all were statistically significantly improved.[57]

Future therapy

There is overwhelming evidence that small bowel bacterial overgrowth is prevalent in a much higher percentage of patients with IBS compared to the healthy population. There is current research looking into an algorithm for treating IBS according to this data. The algorithm calls for a lactulose breath test at the time of initial patient presentation. If the breath test is positive, treatment with Cipro/Flagyl have been successful in eradicating bacterial overgrowth, resulting in a negative breath test.[25,26] Following bacterial eradication, patients can then be started on traditional therapy for IBS up to and including the 5HTa agonists and antagonists. We are currently studying the efficacy of Xifaxan 400 mg TID and comparing it to Cipro or Flagyl for use in bacterial eradication in the small bowel. It is our opinion that small bowel bacterial overgrowth is not the only etiology of IBS but one of many triggers. ■

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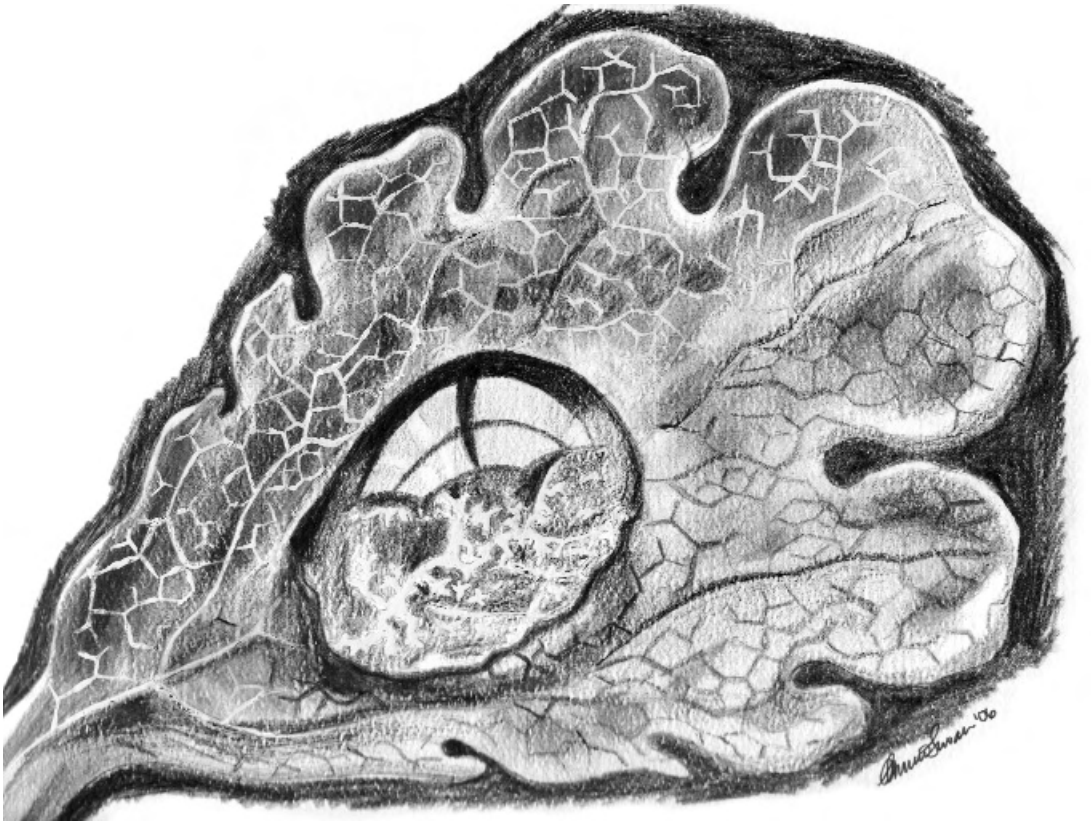

Forgotten Perspectives

Drawing courtesy of Shruti Tewari, MD