REVIEW ARTICLE

Irritable Bowel Syndrome: A Clinical Review

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Abstract

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain and altered bowel habits in the absence of any organic cause. The prevalence varies from country to country ranging from 10 to 15 percent and younger women are more sufferer. Many factors have been proposed among which disorder in gastric motility, visceral hypersensitivity, intestinal inflammation and infection, alteration in gut flora, food sensitivity, genetic predisposition and psychosocial dysfunction are remarkable. Rome IV criteria is commonly used for diagnosis of IBS. Subtypes of IBS are recognized based on the patient's reported predominant bowel habit. Investigations are done to exclude other differentials. Treatment includes lifestyle modification, dietary restrictions of certain foods, adjunctive pharmacological therapy with antispasmodics, antidepressants, antibiotics, probiotics and behavior modifications.

Keywords: Irritable bowel syndrome, Bristol Stool Form Scale, Rome IV criteria, diarrhoea, constipation, abdominal pain.

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Introduction:

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain and altered bowel habits in the absence of any organic cause.[1] The main cause of IBS is not entirely understood as various factors play a key role in its pathophysiology. There is no specific diagnostic test and it is diagnosed through some criteria and exclusion of other diseases. It negatively affects quality of life and work productivity. So accurate diagnosis of IBS is important to minimize unnecessary invasive investigations and to reduce social and economic effects of the disease.

This clinical review covers the epidemiology, pathophysiology, diagnosis and management of IBS.

Methods:

Evidence to support this review was obtained from searches from MEDLINE, PUBMED, Google scholar, Science direct, Cochrane databases for the terms *pathophysiology, etiology, pathogenesis, diagnosis, irritable bowel syndrome* and *IBS* from January 2000 to December 2019. The range was expanded from January 1978 to December 2019 for *IBS, diet, treatment, therapy*. A total 168 articles were found among which 36 articles were selected for inclusion.

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Epidemiology

Prevalence -

The prevalence of IBS varies among countries ranging from 10 to 15 percent. The prevalence is 25 percent higher in those aged less than 50 years as compared with those who were older. Women are more sufferer and likely to have constipation predominant IBS as compared with men.[2]

Associated conditions -

IBS is associated with other conditions including chronic fatigue syndrome, fibromyalgia, non-cardiac chest pain, gastroesophageal reflux disease, functional dyspepsia, and psychiatric disorders including anxiety, somatization and major depression.[3]

Pathophysiology

The pathophysiology of IBS is unclear though multiple factors has been proposed -

Gastrointestinal motility-

Some sort of motor abnormalities are observed in some IBS patients including increased frequency and irregularity of luminal contractions, prolonged transit time in

constipation-predominant IBS, and an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS.[4]

Visceral hypersensitivity-

Visceral hypersensitivity is observed frequently in IBS patients which may result from stimulation of various gut wall receptors triggered by bowel distention or bloating. These receptors transmit signals via afferent neural pathways to the dorsal horn of the spinal cord and ultimately to the brain. It is not clear whether this heightened sensitivity is mediated by the local GI nervous system, by central modulation from the brain, or by combination of the two.[5]

Intestinal inflammation-

Immunohistologic investigation has revealed mucosal immune system activation characterized by alterations in particular immune cells and markers in some patients with IBS. Release of chemical mediators (nitric oxide, histamine and proteases) by increased colonic infiltration with lymphocytes and mast cells stimulating the enteric nervous system lead to abnormal motor and visceral responses within the intestine.[5]

Post infectious-

Some patients give a history of an acute diarrheal illness (bacterial, protozoan, helminth infections, and viral infections) preceding the onset of irritable bowel symptoms.[6] Risk factors for post infectious IBS included young age, prolonged fever, longer duration, anxiety, and depression. Several theories have been proposed for bowel symptoms following acute infection, e.g., bile acid malabsorption, increase in serotonin-containing enteroendocrine cells and use of antibiotics.[7,8]

Alteration in fecal microflora-

It has been found that the fecal microbiota in individuals with IBS differ from healthy controls and vary with the predominant symptom. This theory is supported by improvement of symptoms with probiotics in some diarrhea-predominant IBS patients.[9]

Bacterial Overgrowth-

There are some conflicting data reporting an association between IBS and small intestinal bacterial overgrowth (SIBO). Some studies demonstrated improvement in symptoms after eradication of the overgrowth evidenced by reduction in abnormal breath hydrogen levels.[10] In addition, constipation predominant IBS patients exhibited increased methane production, a gas by product of intestinal bacteria.[11]

Food Sensitivity -

Multiple factors have been considered to contribute to food sensitivity in patients with IBS:

Food allergy - IBS patients show increased number of positive food skin-prick tests compared with controls.[12]

Carbohydrate malabsorption - Fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) in patients with IBS produce symptoms and increase intestinal permeability and possibly inflammation after they are fermented in the distal small and large bowel.[13]

Fructose and lactose intolerance may cause gastrointestinal (GI) symptoms such as flatus, pain, bloating, belching and altered bowel habits. Dietary restriction of fructose and lactose have shown some benefit in alleviation of these symptoms.[14]

Gluten sensitivity - Several studies suggest some overlap between celiac disease and IBS.[15] So steps should be taken to confirm the absence of celiac disease prior to making a diagnosis of IBS.

Genetics -

Some genetic predisposition may play a role in some patients with IBS.[16]

Psychosocial Dysfunction -

Psychosocial factors may influence the expression of IBS.[17] Studies showed increased stress, anxiety, depression, phobias, somatization and history of abuse in patients with IBS compared to control.

Clinical manifestations

Chronic abdominal pain -

The pain is usually described as a cramping sensation in abdomen with variable intensity and periodic exacerbations with wide variety in location and character. Defecation may improve or worsen the pain.[18] Some patients report abdominal bloating and increased gas production in the form of flatulence or belching. Psychological stress and some meals may exacerbate the pain.

Altered bowel habits -

It includes diarrhea, constipation, alternating diarrhea and constipation, or normal bowel habits alternating with either diarrhea and/or constipation.

Diarrhea - Diarrhea is usually characterized by frequent loose stools of small to moderate volume occurring during waking hours, most often in the morning or after meals. It may be preceded by cramping abdominal pain, urgency with a sense of incomplete evacuation or tenesmus. About 50% of all patients complain of discharge of mucus with stools.[19]

Constipation — Stools are often hard and pellet-shaped. Patients may experience tenesmus even in empty rectum.

Diagnosis

Diagnostic criteria - The most widely used diagnostic criteria are the Rome IV criteria.

- **Rome IV criteria for IBS** – According to the Rome IV criteria, IBS is defined as recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria:[18]
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form (appearance)
- **IBS subtypes** – Subtypes of IBS are recognized based on the patient's reported predominant bowel habit on days with abnormal bowel movements. The Bristol stool form scale (BSFS) should be used to record stool consistency.

IBS subtypes are defined for clinical practice as follows:

- **IBS with predominant constipation(IBS-C)** - Patient reports that abnormal bowel movements are usually constipation (type 1 and 2 in the BSFS)
- **IBS with predominant diarrhea (IBS-D)** - Patient reports that abnormal bowel movements are usually diarrhea (type 6 and 7 in the BSFS)
- **IBS with mixed bowel habits (IBS-M)** - Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea)
- **IBS unclassified (IBS-U)** - Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes
- **Other criteria** - The Manning criteria include relief of pain with bowel movements, looser and more frequent stools with onset of pain, passage of mucus, and a sense of incomplete emptying.[19] No symptom-based criteria have ideal accuracy for diagnosing IBS.

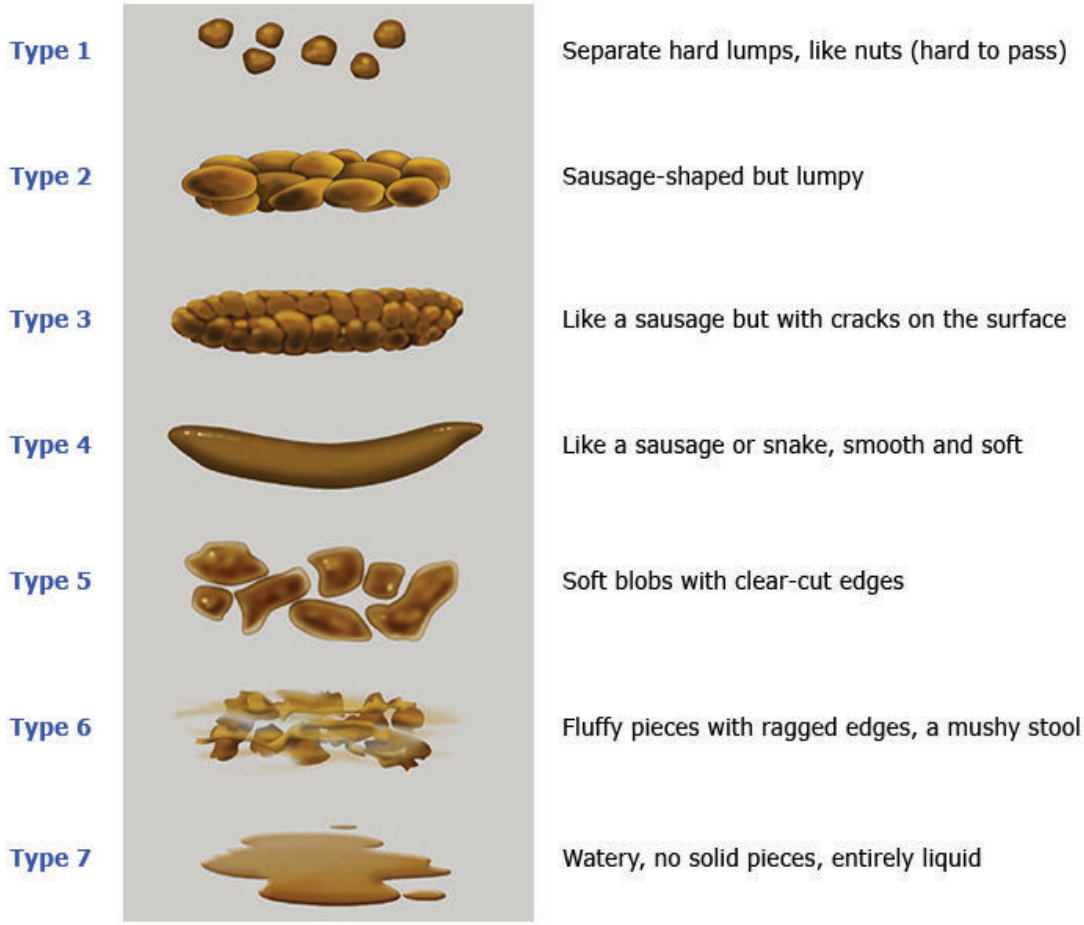

Fig.-1: *The Bristol stool form scale (BSFS)*

Initial evaluation

History and physical examination — Thorough history including past medical, medication and family history is required to exclude other disorders that may produce similar symptoms. The physical examination is usually normal in patients with IBS.

Laboratory investigation — There is no definitive diagnostic laboratory investigation for IBS. The purpose of investigating is primarily to exclude an alternative diagnosis. A complete blood count is performed in all patients. In patients with diarrhea, fecal calprotectin or lactoferrin, stool testing for giardia and serologic testing for celiac disease should be done.[20] If fecal calprotectin and fecal lactoferrin cannot be performed, C-reactive protein levels should be checked. Other tests are guided by the clinical presentation; such as age-appropriate colorectal cancer screening in all patients, abdominal radiograph to assess for stool accumulation in IBS patients with constipation, etc. Anorectal manometry and balloon expulsion testing should be done to rule out dyssynergic defecation in patients with severe constipation that is refractory to management with dietary changes and osmotic laxative therapy.

Additional evaluation based on the presence of alarm features —

- **Alarm features** – Alarm features include:[21]
  - Age of onset e 50 years
  - Melena or hematochezia
  - Nocturnal diarrhea
  - Progressive abdominal pain
  - Unexplained weight loss
  - Laboratory abnormalities, e.g., iron deficiency anemia, elevated C-reactive protein or positive fecal calprotectin or lactoferrin
  - Family history of IBD or colorectal cancer
- **Patients without alarm features** – Additional investigations are not required beyond the initial evaluation in patients meeting diagnostic criteria for IBS having no alarm features.
- **Patients with alarm features** – In patients with alarm features, additional evaluation are required to exclude other causes of similar symptoms. The evaluation is based on the clinical presentation and usually includes endoscopic evaluation in all patients and imaging in selected cases. In patients with diarrhea, colonoscopy is done to evaluate for the presence of IBD and perform biopsies to exclude microscopic colitis.[22] Abdominal ultrasonography or computed tomography scan is done if there is a clinical suspicion for a structural lesion.

Disease course

Most patients with IBS have chronic symptoms that vary in severity over time. In a systematic review, 2 to 5 percent of patients were diagnosed with an alternate gastrointestinal disease over a course of long term follow up. Some patients may experience a change in IBS subtype over time.

Treatment

Initial therapy

Lifestyle modification: In patients with mild and intermittent symptoms that do not impair quality of life.

Education and reassurance: Patients should be counseled about the chronicity of IBS and no additional risk of malignancy. The clinician should establish realistic therapeutic limitations with expectations and involve the patient in treatment decisions.

Dietary modification: A careful dietary history may reveal patterns of symptoms related to specific foods. Some patients with IBS may benefit from exclusion of gas-producing foods (eg, beans, onions, celery, carrots, raisins, bananas, apricots, prunes, Brussels sprouts, wheat germ, pretzels, and bagels, alcohol, and caffeine);[23] a diet low in FODMAPs; and in selected cases, lactose and gluten avoidance.

Both a low FODMAP diet and a strict traditional IBS diet (regular meal pattern; avoidance of large meals; reduced intake of fat, insoluble fibers, caffeine, and gas-producing foods such as beans, cabbage, and onions) improve IBS symptoms.[24]

Lactose avoidance — Patients with known lactose intolerance should be placed on a lactose-restricted diet. An empiric trial of a lactose-free diet in patients who complain of persistent abdominal bloating despite exclusion of gas-producing foods may be tried.

Gluten avoidance — Gluten has been demonstrated to alter bowel barrier functions in patients with IBS-D, but evidence to support gluten avoidance in patients with IBS has been conflicting.[25]

Fiber — The role of fiber in patients with IBS is controversial, but given the absence of serious side effects and potential benefit, psyllium/ispaghula should be considered in patients with IBS whose predominant symptom is constipation.[26]

***Physical activity* —** Physical activity may improve symptoms in some IBS patients and should be advised.[27]

Adjunctive pharmacologic therapy

Patients having impaired quality of life due to moderate to severe symptoms of IBS are treated with pharmacologic agents. Treatment should be based on the predominant symptom and subtype.

Constipation — Polyethylene glycol (PEG) is suggested in patients with IBS-C who have failed a trial of soluble fiber (eg, psyllium/ispaghula). If the patient still remains constipated, lubiprostone, linaclotide, or plecanatide can be tried. In women under the age of 65 who fail these agents, a trial with tegaserod is an alternative. Tegaserod reduces abdominal pain in IBS as well as improves constipation. Dyspepsia overlaps with IBS, and tegaserod may provide symptom benefit for dyspepsia.[28]

Diarrhea — In diarrhea-prone patients with IBS, the stools are characteristically loose and frequent but of normal total daily volume. In patients with diarrhea-predominant symptoms, antidiarrheals (eg, loperamide)[21,29]are used as initial treatment and bile acid sequestrants (eg, cholestyramine, colestipol, colesevelam)[30] as second-line therapy.

Eluxadoline, an agent that combines a mu-opioid receptor agonist and a delta-opioid receptor antagonist, has also been approved for treatment of IBS-D.[31]

Alosetron, a 5-hydroxytryptamine-3 receptor (5HT-3) antagonist, is approved for the treatment of severe diarrhea-predominant IBS in female patients whose symptoms have lasted for six months and who have failed to respond to all other conventional treatment.

Abdominal pain and bloating —

***Antispasmodics* —** In patients with abdominal pain due to IBS, antispasmodics (eg, mebeverine and pinaverine, dicyclomine and hyoscyamine) are used on an as-needed basis. In patients with IBS-C, antispasmodics are initiated only if the abdominal pain persists despite treatment of constipation. The selective inhibition of gastrointestinal smooth muscle by antispasmodics and peppermint oil reduce stimulated colonic motor activity and may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency.[32,33]

***Antidepressants* —** Antidepressants have analgesic properties along with their mood improving effects.[21,32] Tricyclic antidepressants (TCAs), via their anticholinergic properties, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS,[32] hence should be used cautiously in patients with constipation. Antidepressants should be started at a low dose for the treatment of abdominal pain in IBS. At least three to four weeks of therapy should be attempted before increasing the dose because of their delayed onset of action. Amitriptyline, nortriptyline, and imipramine can be started at a dose of 10 to 25 mg at bedtime. If the patient is intolerant of one TCA, another can be tried.

As there are lack of consistent high-quality evidence demonstrating an improvement in symptoms, SSRIs/SNRIs are not used for the treatment of IBS unless depression acts as a cofactor.

***Antibiotics* —** While antibiotics should not be routinely recommended in all patients with IBS, in patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies (eg, a diet low in FODMAPs, antispasmodics, and TCAs), a two-week trial of rifaximin is suggested.[34]

***Probiotics* —** Probiotics are not routinely recommended in patients with IBS. Although they have been associated with an improvement in symptoms, the magnitude of benefit and the most effective species and strain are uncertain.[35]

Refractory symptoms

A small subset of patients with irritable bowel syndrome (IBS) has refractory symptoms. Patients with continued symptoms despite adjunctive pharmacologic therapy should be carefully reassessed, paying specific attention to the type of ongoing symptoms, the degree to which symptoms have changed, compliance with medications, and the presence of alarm features that should prompt further evaluation.

Behavior modification — Patients with unrelenting symptoms that are associated with psychiatric impairment may benefit from behavioral modification in conjunction with antidepressants.

Anxiolytics — The use of anxiolytic agents in patients with IBS should be limited to short-term (less than two weeks) reduction of acute situational anxiety that may be contributing to symptoms. Side effects of anxiolytics include the risk of habituation, rebound withdrawal, and drug interactions. Furthermore, benzodiazepines may lower pain thresholds by stimulating gamma aminobutyric acid (GABA) receptors, thereby decreasing brain serotonin.

Other therapies — Other therapies have been evaluated in patients with IBS (eg, herbs, acupuncture, enzyme supplementation, fecal microbiota transplantation, antihistamines (Ebastine) and mast cell stabilizers (Ketotifen) but their role in the treatment of IBS remains uncertain.[36]

Conclusion:

IBS remains a significant cause of distress, morbidity and to some extent, disability among people of all ages around the world. As there is no specific investigation to diagnose IBS, it is hoped that novel biomarkers will be invented to aid in accurate diagnosis. The physicians should understand the pathophysiology well and take into mind about the role of dietary, lifestyle and behavioral modifications with or without pharmacological interventions for effective treatment of IBS. The management should be individualized for each patient for an effective result.

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