

Review Article

Irritable Bowel Syndrome

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INTRODUCTION

Functional diseases of the digestive system show no evidence of organic alterations, but only the *function* of the organs is involved, usually being chronic illness. The Irritable Bowel Syndrome (IBS) is an example of functional disorder in which pain and / or abdominal discomfort are associated with alterations in bowel habits, with bloating and feeling of fullness often being of the clinical picture [1]. The very uncomfortable symptoms profile compromises the quality of life of patients. The prevalence of IBS varies from 3 to 20%, with a mean of 10% to 15%, decreasing after the age of 60 years [2,3].

The diagnosis is essentially clinical and are significant the presence of psychological comorbidities that may contribute to the development of IBS such as depression, anxiety, stress and insomnia. Depression in particular is quite common, occurring in up to 30% of patients (compared with 18% of the general population) [4]. A direct correlation between anxiety and depressive disorders and IBS severity can be observed.

Symptoms may vary or even disappear over time, i.e., the manifestations can be present for a certain period, then improve or even disappear partially or completely. Eventually, the disorder can also change into another digestive functional symptom, such as functional dyspepsia [5].

Pathophysiology

IBS is considered a condition resulting in a common group o heterogeneous symptom from multiple distinct pathologies. As such, there are some evidences of dysregulation of pathophysiological pathways presented in table 1.

The pathophysiology of IBS is complex and has aspects that need to be better defined, as there are variables involved at a greater or lesser degree, which may or may not act synergistically. The initial presentation of IBS and symptom exacerbations may be preceded by the presence of psychological or physical stressors,

Table 1: Pathophysiological pathways of IBS⁶.

IBS : Pathophysiology
Mast cell infiltration and degranulation
Altered serotonin biosynthesis and metabolism
Visceral hypersensitivity
Exagerated stress response
Post-infectious IBS: immune activation and bacterial infection
Microbiota alterations

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- Intestinal constipation

as well as alterations in intestinal motility and increased visceral sensitivity.

It is noteworthy the association between the syndrome symptoms and stress, depression and also the coexistence of psychiatric conditions [7]. In the United States for instance, the prevalence of psychiatric disorders in patients treated in tertiary care centers ranged from 40% to more than 90% [8,9].

The role of the intestinal microbiota has been highlighted in the pathogenesis of IBS as:

- Changes in fecal microbiota;
- Widespread use of probiotics by the population;
- Post-infection IBS;
- Recognition of the participation of intestinal microbiota in the immune system.

The interaction between the host and the gastrointestinal microbiota may be important in the pathogenesis of IBS. Thus, bacterial alterations have been observed such as a reduction of *Lactobacillus* and *Bifidobacteria* in fecal samples and the concentrations of species such as *Enterobacteriaceae*, *coliforms* and *Bacteroides spp.* It is not worthy the fact that the forms of IBS with diarrhea or constipation have different microbial populations [10].

As far as we know, the intestinal microbiota somehow participates in the etiopathogenesis of symptoms in this disease. Therefore, it is important to consider that up to approximately 30% of adult patients diagnosed with IBS reported that symptoms started after an episode of acute viral or bacterial intestinal infection, a situation in which the intestinal microbiota can be severely affected.

Evidence therefore suggests the involvement of the intestinal microbiota in at least one subgroup of IBS patients, constituting a target for specific therapeutic benefit. Thus, any prior occurrence of enterocolitis should always be investigated upon suspected diagnosis of the syndrome.

The inflammatory aspect must not be over looked, as IBS is characterized by a pro-inflammatory profile with involvement of IL-6 and IL-8 cytokines [11]. In patients with certain comorbidities, there is a further increase in IL-1 β and TNF- α levels [12]. In cases in which there is a predominance of diarrhea, the clinical manifestations are related to molecular alterations involving dysregulation of mast cells from the tight junctions of the jejunal mucosa [13].

As there are no characteristic motor abnormalities of IBS, it is difficult to interpret the nature of the clinical manifestations of diarrhea, constipation or the alternating occurrence of both. Changes in gastrointestinal motility and the balance between absorption and secretion may constitute the basis of intestinal habits [1], being partly mediated by the dysregulation of intestinal serotonin signaling. The important interrelations between the enteric system and the smooth muscle fibers of the digestive tract are probably related to motor hyper reactivity, which is triggered by different stimuli. The exaggerated gastrocolic reflex is a good example of motor hyperactivity triggered by feeding: the urge to defecate occurs, in this case, immediately after food intake.

The subject is intriguing, as although the number of mast cells, macrophages, T cells and λ FLC-positive mast cells are reduced in IBS patients when compared to normal subjects, these findings are not associated with the presence of visceral hypersensitivity or abnormal response to stress. Recent data have questioned the role of microscopic inflammation as the underlying mechanism of visceral hypersensitivity, suggesting there is a disruption in the mucosal immune system in these patients. On the other hand, an increased innate immune activity in the intestinal mucosa and in blood is found in subpopulations of IBS patients. Mast cells and monocytes seems to be particularly important as well as an activated adaptive immune response. Increased epithelial barrier permeability and abnormal gut flora might lead to increased activation of the intestinal immune system [14].

A heritable component of IBS is suggested by the study in families and twins, but genetic investigations have so far failed to provide strong evidence for specific markers of susceptibility. However recent studies have indicated that genetic alterations of immune function may contribute to IBS pathogenesis: the risk of IBS and the constipation-predominant subtype is influenced by polymorphism in the *TNFSF* gen, which is particularly involved in the regulation of immune and inflammatory responses [15].

As mentioned, IBS is a multifactorial functional intestinal disorder, involving different and interrelated physiopathological aspects. Is it valid to assume that, given the different physiopathological alternatives, a certain degree of synergism must occur between factors responsible for the disease. The increased visceral perception to pain and discomfort that often occurs in these cases can also contribute to the symptoms.

Diagnosis

The "Rome III criteria", which basically propose a diagnosis of inclusion, are shown in Chart 1 [16]. It is important to carefully consider the Rome III criteria, as they constitute the basis upon which it may be possible to characterize the diagnosis of inclusion, provided that some routine diagnostic standards are met, as shown below. On the other hand, recent studies have

Chart 1: Irritable Bowel Syndrome Diagnosis Roma III Criteria (16)

- Abdominal pain or discomfort at least 3 times / month in the last 3 months associated with 2 or more of the following findings:
 - improves after bowel movement
 - onset associated with changes in frequency of bowel movements
 - onset associated with changes in form (appearance) of stool
- Symptoms onset must have occurred at least 6 months before diagnosis

questioned the diagnostic criteria of IBS, even using the Rome III criteria, suggesting little difference between the diagnostic accuracy of IBS and the organic disease [17].

Even though there is no biological marker for IBS diagnosis, it is important to consider that the Rome criteria represent a contribution with satisfactory sensitivity and diagnostic relevance, even in primary care units [18].

Subgroups of IBS

IBS has the following subgroups according to intestinal habits [16]:

IBS with diarrhea: More common in males, it occurs in up to 1/3 of cases. It alternates between soft (> 25%) and hard stools (<25%).

IBS with constipation: More common in females, it occurs in up to 1/3 of cases. It alternates between hard (> 25%) and soft stools (<25%).

IBS with mixed habit or cyclic pattern: Present in 1/3 to 1/4 of the cases. Hard and soft stools in more than 25% of the time.

IBS is usually diagnosed through the medical history carefully aiming to meet the Roma III criteria, recalling that their accuracy is not always the ideal [14]. A careful physical examination is performed and supplementary tests are not usually necessary. Routine tests may eventually be performed, which do not include colonoscopy (Chart 4), after excluding alarm symptoms, as shown in Chart 2 [5].

The inclusion diagnosis is established after the differential diagnosis is made with other morbidities with similar clinical features. The main diseases that are part of the differential diagnosis are shown in Chart 3. It should be recalled that IBS must be differentiated from other functional possibilities such as functional abdominal pain syndrome, functional constipation and chronic functional diarrhea.

Abdominal pain or its equivalent, the abdominal discomfort, must be present to establish the diagnosis [16]. The pain is not generally very intense but, together with other manifestations, may impair patient quality of life.

The clinical presentation must disclose what the predominant feature is, diarrhea, constipation or both, remembering that the occurrence of other abdominal symptoms such as bloating, distension, borborygmus and flatulence are not unusual.

Although it has not been demonstrated that psychological factors can cause or trigger the syndrome or its maintenance, they should always be investigated, including: anxiety, depression, somatization, symptom-related fears [1]. Therefore, when

Chart 2: Alarm symptoms

- Rectal blood loss
- Anemia
- Weight loss
- Fever
- Family history of colon cancer
- Symptom onset after 50 years of age
- Recent alteration in symptom pattern

Chart 3: Differential diagnosis of Irritable Bowel Syndrome.

- Malabsorption syndrome
- Lactose intolerance
- Intolerance to foods
- Inflammatory Bowel Disease
- Neoplasia
- Celiac Disease
- Functional diarrhea and pain syndrome
- Psychiatric Disorders

Chart 4: Routine laboratory tests in Irritable Bowel Syndrome.

- CBC and erythrocyte sedimentation rate
- Thyroid function (TSH / free T4)
- Glycemia
- Stool (parasites, occult blood)

managing patients with suspected IBS, psychological factors must be carefully analyzed, considering the direct association between IBS symptoms and stress and possible coexisting psychological or psychiatric conditions [6]. It is necessary; however, to pay careful attention to these findings, as their generalization to all cases of IBS is not prudent.

Physical examination is generally normal or show mild and uncharacteristic findings, such as tenderness in the left iliac fossa on the palpable sigmoid colon. Rectal examination is advisable in some cases, aiming to rule out rectal disease and abnormal function of the anorectal sphincter, which may contribute to constipation symptom.

Supplementary tests are generally unnecessary in young patients in good overall health condition. When requested, they aim to assess the patient overall status and the main components that may be altered when establishing the differential diagnosis, but these tests do not help in the diagnosis of IBS itself. Therefore, there is no mandatory sequence of tests to be performed, and an overall evaluation is suggested in Chart 4. More elaborate tests should only be performed when it is necessary to establish the differential diagnosis with other clinical entities. In these cases, colonoscopy may be requested, as well as antiendomysial antibody and lactose absorption test, among others.

Treatment

As with any proposed treatment, it is essential to establish an effective physician-patient relationship. It is important to identify patients' concerns, listen to and reassure them, such as explaining that the symptoms have nothing to do with cancer or other severe bowel disease [19]. These patients' complaints should be taken into account by the physician as a *real situation* and not just as an illusory manifestation of "anxiety" and consequent somatization.

It is important to assure patients that IBS is a benign process that has a chronic and recurrent course.

In general, IBS cases can be considered mild, moderate and severe and therapeutic measures should be in accordance with the clinical picture intensity.

Treatment strategy depends on several factors, such as symptom type and intensity, as well as the predominance (diarrhea, constipation, pain, bloating). The diagnosis of psychological comorbidities (anxiety, depression, stress) should also be considered and the negative impact on quality of life that accompanies the disease.

Treatment is usually symptomatic (aimed at normalization of bowel habits and abdominal pain reduction) and brings relief to patients with milder symptoms, such as those seen in basic health units or offices of general practitioners. The treatment of patients with more severe symptoms remains somewhat a challenge, as diagnosis is often contested and treatment response can be more time-consuming and sometimes uncertain.

The patient's lifestyle and eating habits should be evaluated, such as lack of physical activity, poor diet, lack (or excess) of fiber intake. When there is a predominance of constipation, it is also important to investigate the lack of adequate time for evacuation. In this case, in addition to the behavioral aspect related to evacuation, the increase in fiber intake and regular physical exercise are usually beneficial. Excessive intake of coffee (caffeine), indigestible carbohydrates and high lactose intake can aggravate the symptoms of patients with predominant diarrhea [19].

It is worth mentioning that there is scarce scientific evidence to support the life style recommendations, as well as conclusions endorsed by Evidence-Based Medicine, but clinical observation has shown that the behavioral aspect of treatment may contribute to good therapeutic results.

Physical activity may be a relevant recommendation as a primary treatment modality in IBS: physically active patients will face less symptom deterioration compared with those physically inactive.

DRUG THERAPY

The response rate to placebo in IBS is high, as in all functional disorders, ranging from 33% to 88%. The implications of this fact must be recalled when considering the benefits of certain drugs and how they should be appreciated. The efficacy of this or that medication assessed through therapeutic test depends on the response rate to placebo, which in turn depends on the expectations of both the patient and the physician [20].

The pharmacological therapy is aimed at relieving the predominant symptom or complaint and consists in a symptomatic treatment, as the exact mechanism for the development of IBS, as seen above, has yet to be definitively established.

The main therapeutic resources according to the predominant symptom are presented below.

Diarrhea

As mentioned, there are no available studies that meet the

requirements for levels of evidence and recommendations of Evidence-Based Medicine, but clinical experience suggests that antidiarrheal agents are generally effective.

Loperamide: Loperamide is an effective agent for the treatment of diarrhea, improving bowel movement frequency and stool consistency, but it is not more effective than placebo in reducing pain [20]. A synthetic opioid agonist, it has no effects on the central nervous system or other adverse effects at low doses. Concomitant administration of intestinal motility inhibitors allows a better dose adjustment. Recommended dose: 2 mg – 1-2x/day [21].

Alosetron, cilansetron and tegaserod: All effective in the treatment of IBS. A meta-analysis has showed that serious adverse events are rare in the eligible randomized clinical trials included in the systematic review [22].

Constipation

It is essential to include the patient into a broader program of bowel retraining, such as the one proposed for treatment of functional constipation, which includes abundant water intake, physical activity, high-fiber content diet, regular evacuation habit after a meal, etc.

Osmotic laxatives: Osmotic laxatives such as magnesium salts are relatively safe and generally useful in the treatment of constipation, despite the lack of clinical studies specifically directed to the IBS. The non-absorbable sugars (lactulose, sorbitol, mannitol) tend to induce flatulence and distension, and moreover, they should not be used as a long-term treatment [2,21].

Fibers: Fibers and other bulking agents (agar-agar, *Plantago ovata*, calcium polycarboxylate) have been used as the initial therapy for constipation. In this case, of the total amount of ingested fibers, approximately two-thirds should be insoluble and one-third soluble. To follow this recommendation, products made with refined flour should be replaced by whole grain products (bread and cereals) [23,24].

Linacotide: Linacotide a 14-amino acid synthetic peptide, is a promising new first-in-class guanylatecyclase C agonist with a novel, dual mechanism of action. An interesting meta-analysis showed that, unlike more well established agents, can relieve abdominal pain, bloating and constipation associated with IBS-constipation and has a low propensity for systemic side effects [25,26].

Artificial juices should be replaced by natural products and meat (as a source of protein) replaced by vegetables [27,28]. One should pay attention to the fact that dietary fiber promotes improvement in intestinal transit and the liquid content of the stools, but has no effect on other associated symptoms of IBS, such as abdominal pain and discomfort. Fibers can also sometimes aggravate flatulence and bloating [24].

Prokinetic agents (domperidone, bromopride, metoclopramide): Prokinetic agents have been used in clinical practice as an aid in the treatment of IBS with constipation, but there is no specific indication for that. Their use is based on the reduction of intestinal transit time. They have no effect on abdominal pain.

Abdominal pain

Antispasmodic agents: A meta-analysis of clinical trials with antispasmodic agents shows clinical benefits with the use of pinaverium, hyoscine, mebeverine, otilonium and others, but there have been few clinical trials that assessed long-term use of antispasmodic agents in patients with diarrhea-predominant IBS. However, clinical experience has shown that some of them are usually effective [23,24].

Calcium channel antagonists: Intestinal selectivity is attributed to the low absorption and rapid hepatic metabolism. This kind of agents has no systemic antimuscarinic actions. Examples are pinaverium, mebeverine. Otilonium bromide has the chemical structure of quaternary ammonium salt, thus acting as alocal antispasmodic agent with low systemic absorption [21].

Antimuscarinic agents (e.g., atropine, hyoscine, dicyclomine): Antimuscarinic agents can sometimes result in significant adverse effects such as sedation, tachycardia, dry mouth, urinary retention (elderly) and so can be used with restrictions [19,21].

Trime butine: Trime butane is a synthetic anticholinergic agent with tertiary amine structure and gastrointestinal motility regulator that acts by antagonizing acetylcholine at muscarinic receptors with a low frequency of adverse effects, such as skin rash and drowsiness [23].

Antidepressants: Antidepressants have been employed in the treatment of IBS-related abdominal pain due to their effect in pain perception modulation and for the treatment of the psychiatric disorder that may also be present. A recent meta-analysis on the role of antidepressants in IBS showed superiority of the active drug (tricyclic drugs and selective serotonin reuptake inhibitors) compared to placebo in relieving abdominal pain. Both agents appear to be equally effective. Data on safety and tolerability are limited [20,29].

The available information on the therapeutic efficacy of antidepressants based on clinical trials of adequate methodological design or meta-analyses are still recent and limited. Nevertheless, as reported for the tricyclic antidepressants, they often have good results in pain relief when used at low doses, acting as anti-nociceptive agents through central and peripheral neuromodulatory effect, regardless of anticholinergic, spasmolytic or antidepressant actions [29].

Studies have demonstrated that administration of imipramine prolongs intestinal transit time in patients with IBS and diarrhea, which makes the drug an interesting option for this subgroup of patients, particularly when abdominal pain is present. In contrast, paroxetine accelerates intestinal transit. Serotonin reuptake inhibitors usually have a less severe side-effect profile than tricyclic antidepressants and should therefore be considered for the treatment of IBS when there are coexisting psychological symptoms or pain syndromes, or in patients that did not respond to laxatives and antispasmodics. In these cases, the clinical response to antidepressants occurs only after 2 to 4 weeks of treatment and, if they are effective, especially in abdominal pain relief, they should be maintained for at least 6 months [20].

THERAPEUTIC ALTERNATIVES

Probiotics

Probiotics are living organisms found in food and dietary supplements, constituting a new therapeutic class that has attained importance in the treatment of several gastrointestinal disorders, such as inflammatory bowel disease [28,30-32]. These agents can be beneficial in IBS, although the physiopathological mechanisms are still hypothetical, such as their binding to the intestinal epithelium in the production of substances with antibiotic properties that could inhibit the invasion of pathogenic organisms.

Probiotics can modulate gastrointestinal immunity through changes in cytokine and cell environment from a proinflammatory to an anti-inflammatory state. They could also convert undigested fatty acids to short-chain carbohydrates, which would act as nutrients for colon cells and there by alter colonic motility [30].

The number of randomized controlled trials to validate the effectiveness of probiotics in IBS studies is still limited, but there are indications of several different probiotic strains with different combinations of latter, with some having been shown to be more effective than others. The following strains are examples of satisfactory performance: *Bifidobacterium* (particularly *B.infantis*), *Lactobacillus*, *Streptococcus salivarius*, with effects such as reduction in bloating and flatulence. Others have also been studied with satisfactory results, such as *Propionibacterium freudenreichii* [30]. In a recent meta-analysis, *B. infantis* 35624 has shown efficacy for improvement of IBS symptoms [32]. It can be said that the observations on probiotics are still preliminary, but it is likely that, in the future, other probiotics will also show benefits in the treatment of IBS. The indication of this new class in IBS has expanded due to the observation that many patients reported improvement after their use.

Rifaximin

Rifaximin is a semi-synthetic derivative of rifamycin, with an additional benzimidazole ring that prevents its systemic absorption. A recent meta-analysis showed that rifaximin proved more effective than placebo for global symptoms and bloating IBS patients. The modest therapeutic gain was similar to that yielded by other currently available therapies for IBS [33].

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Alternative medicine

Alternative Medicine usually refers to practices not typically employed in conventional allopathic Medicine and which are used *in its place*. What is considered Alternative Medicine is subject to constant change, as new treatments are submitted to rigorous scrutiny of Evidence-based Medicine, which may or may not prove to be effective.

Complementary medicine

Complementary medicine on the other hand refers to treatments used *in addition to* conventional treatments. Examples of complementary and alternative Medicine treatments include: hypnosis, acupuncture, homeopathy, meditation, yoga, dietary supplements, herbs, massage, energy therapies, etc.

Considering the increasing importance given to these therapeutic modalities, the U.S. government established a National Center for Complementary and Alternative Medicine (www.nccam.nih.gov), with the goal of helping the public regarding the choices of complementary and alternative treatments. It is noteworthy to remember that, as many Complementary and Alternative Medicine treatments have not been tested through controlled clinical trials, the efficacy may actually reflect, in some cases, the high placebo response that occurs in functional disorders such as IBS [34,35].

Herbs and natural products

Peppermint oil (*Mentha piperita*) has been frequently used, especially in Europe, with significant improvement in IBS symptoms [24,36]. It has antispasmodic action, probably acting as a calcium channel antagonist. Adverse effects are uncommon (rash, headache, heartburn, muscle tremor and ataxia) and are usually associated with over dosage.

Some Chinese and Tibetan herbs have been used for many decades and although larger studies are still lacking, a careful review identified several well-conducted trials demonstrating satisfactory results [21]. There are no reports of the national experience.

Acupuncture

After centuries of use as a therapeutic measure in traditional Chinese Medicine, acupuncture has lately earned substantial attention in Western Medicine. Unfortunately, most clinical trials involving acupuncture have methodological problems, the biggest of which being the lack of a system that could work as a placebo. A meta-analysis of the studies on acupuncture, showed that sham-controlled randomized clinical trials have found no benefits of acupuncture relative to a credible sham acupuncture control in IBS symptom severity or IBS-related quality of life. However in comparative effectiveness Chinese trials, patients reported greater benefits from acupuncture than from pharmacological therapies [34]. Symptom improvement has been demonstrated in patients with IBS, but further randomized studies are required, which can effectively evaluate the role of acupuncture in this syndrome [35].

Homeopathy

Some studies relatively well conducted according to Evidence-based Medicine criteria suggest that this form of treatment can be effective in IBS, concluding that the results of homeopathic treatment cannot be fully referred to as the result of a placebo effect. The initial data are thus thought-provoking, although evidence based on stringent, good-quality trials are still limited [35].

Hypnosis

There is quite conclusive evidence of hypnosis use in the treatment of IBS, with potentially positive long-term results and with clinical experience suggesting that some patients are more hypnotizable than others [30,37].

SUMMARY

Irritable Bowel Syndrome (IBS) is a frequent functional

disorder characterized by chronically recurring abdominal pain or discomfort and altered bowel habits. IBS is clinically diagnosed through careful anamnesis in patients who have symptoms that meet the Rome III criteria (abdominal pain/ discomfort for at least 3 days/months associated with alterations in the bowel habits and change in the aspect of the stools for the last three months). IBS has a multifactorial pathophysiology (visceral hypersensitivity, alterations in GI motility, alterations in intestinal microbiota, previous intestinal infections, psychological/psychiatric disorders). The treatment is aimed at normalizing bowel habits or/and decrease abdominal pain and or discomfort. It is based on pharmacological approach and use of probiotics in addition to the help to the psychological aspects when needed. The possibilities of Alternative and Complementary Medicine are commented.

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