Internal Medicine: Open Access

Barbuti et al., Intern Med 2014, 4:3
DOI: 10.4172/2165-8048.1000150

Review Article Open Access

Functional Diseases of the Digestive System: Irritable Bowel Syndrome

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Received date: February 20, 2014, **Accepted date:** April 22, 2014, **Published date:** May 04, 2014

Abstract

Irritable bowel syndrome (IBS) is a very prevalent and high incident disease. As the great majority of functional diseases, it is female predominant and leads to serious damage to the quality of life. Its pathophysiology is complex, which pushes the specialists to study it even more deeply, in order to find the most suitable way to diagnose and treat it. Depending of the clinical presentation, different drugs can be used, although we are still missing the magic bullet to relieve our patient's complaints. This paper reviews the newest insights regarding IBS, covering its diagnosis, epidemiology and treatments, focusing specially the clinical practice.

Keywords: Irritable bowel syndrome; Diarrhea; Constipation; Dysbiosis

Introduction

Diseases of the digestive system are divided into two broad categories: organic and functional diseases.

Organic diseases are characterized by anatomical or structural, chemical, biochemical or infectious alterations, resulting in symptoms or malfunction of a certain organ. On the other hand, a functional disease which is much more prevalent and has increasing incidence is characterized by the lack of a known organic substrate that can explain the understanding of symptoms [1].

In an attempt to standardize the diagnosis and management of functional diseases and regulate research in this area, researchers periodically meet in Rome to review the so-called "Rome criteria". The latest revision of these standards has been adopted: the "Rome III criteria". It is noteworthy that the Rome III criteria were vouched for by researchers from Europe and the United States, which does not always reflect the overall characteristics of patients from other regions of the world [2]. Among the functional disorders, Irritable Bowel Syndrome (IBS) is a common and frequent problem in which bowel habits are altered in association with abdominal pain or discomfort [2].

Epidemiology

The Irritable Bowel Syndrome (IBS) is a common functional disorder probably affecting 10-15% of the population in developed countries, being 2-3-fold more common in females [3,4]. IBS accounts for 10-15% of all visits to the general practitioner and 25-50% of visits to the gastroenterologist, with an estimated 2.6 million office visits and 3.5 million consultations, including hospital visits [5]. It is worth mentioning that, despite the high frequency, only a fraction of patients with complaints effectively seeks medical assistance.

Diagnosis

The Rome III criteria should be used to characterize the disease: recurrent abdominal pain and/or discomfort for at least 3 days a month in the last 3 months associated with 2 or more of the following: improvement with defecation and/or altered bowel movement frequency and/or altered stool form.

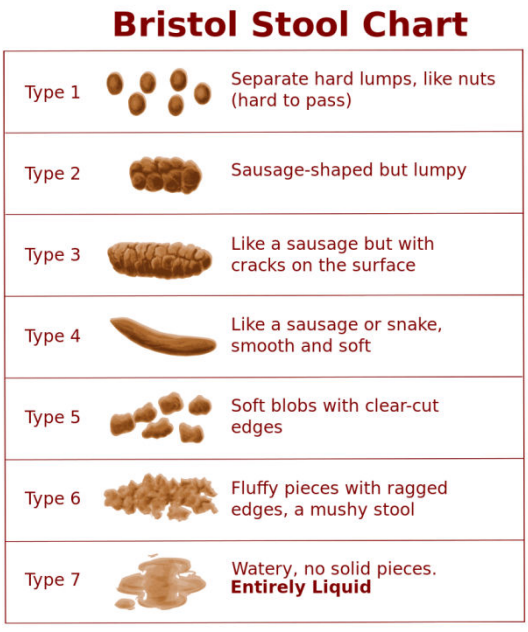

Figure 1: Bristol Stool Chart

The predominant forms of IBS presentation are [6,7]:

1. Constipation-predominant IBS (IBS-C): hardened, dry or lumpy stools (coprolith) in ≥ 25% and soft or pasty stool in <25% of evacuations;

2. Diarrhea-predominant IBS (IBS-D): loose or pasty stool in ≥ 25% and hardened, dry or lumpy stools (coprolith) in <25% of evacuations;

3. Mixed IBS (IBS-M): hardened stools in ≥ 25% and loose or soft stools in ≥ 25%;

4. Undetermined IBS: Insufficient abnormality in stool consistency to be allocated in one of the above subtypes.

Aiming to characterize the group the patient belongs to, in addition to being important in the assessment of clinical response to treatment, the Bristol Scale [8] depicted in Figure 1 can be used.

In the majority of cases of IBS no additional tests or examinations are required: that according to the Rome III definition, there is no need for tests to establish the diagnosis of IBS, as long as warning signs and symptoms are taken into account (Table 1), of which presence require a more detailed investigation. However, even the existence of these signs and symptoms is not necessarily indicative of an organic lesion, i.e., their presence induces the physician to perform more detailed examination for organic diseases, but these are not necessarily present and when identified, they are usually benign.

Fecal blood loss
Anemia
Weight loss
Fever
Jaundice
Family history of colon cancer
Symptom onset after 50 years of age
Recent alteration in symptom pattern
Palpable mass

Table 1: Warning signals

A careful systematic review published in 2006 showed that the positive predictive value of warning signs and/or symptoms for the diagnosis of organic diseases is less than 10% [9]. It is important to consider that the presence of Rome III criteria and absence of warning signs and/or symptoms gives a positive predictive value of 98%, with a sensitivity of 63% for the diagnosis of IBS [10]. It is worth to recall that due to the high prevalence of IBS, it is not unusual to observe its association with other organic and functional disorders, which also makes its differential diagnosis a quite broad one (Table 2). Noteworthy epidemiological information is the coexistence of multiple functional disorders or even the "migration" of a functional disease to another, considering the same patient [11-13].

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

Table 2: Differential diagnosis of Irritable Bowel Syndrome

The need for specific tests, however, may vary from region to region, depending on the most commonly found diseases and obviously the family history of that specific patient. This is the case for instance, of parasite stool testing in countries with high rates of intestinal parasitic diseases or the antigen domysial antibody test in diarrheal IBS in countries with high prevalence or a family history of celiac disease. The same applies to colonoscopy with serial biopsies and upper digestive endoscopy with biopsies of the second portion of the duodenum in patients with a history of inflammatory bowel disease or celiac disease. There is evidence that also in cases of chronic diarrhea and normal colonoscopy, the incidence of microscopic colitis is not negligible [14].

Fecal calprotectin levels may be useful in the differential diagnosis [15], although there are only a few laboratories that perform the test.

It is of utmost importance for the clinician to be aware of these possible associations and other organic diseases more frequently observed together with IBS, such as lactose intolerance and bacterial overgrowth syndrome [16,17]. Screening for celiac disease, lactose intolerance and bacterial overgrowth is recommended specifically in diarrheal IBS.

Other pathologies should be considered as differential diagnosis such as malabsorption syndromes, food intolerance, food allergy, inflammatory bowel disease, neoplasias, functional diarrhea, functional constipation, functional bloating, psychiatric diseases and of course, as mentioned before, parasites, lactose intolerance, small bowel bacterial overgrowth and celiac disease [9,12].

It is imperative for the clinician to be aware of the chronic nature of this disease, which leads to severe quality of life impairment, increased absenteeism, as well as often leading to unnecessary surgeries, thus, eventually making IBS a public health problem [18,19].

Pathophysiology

The physiopathology of IBS is complex, involving several aspects such as altered processing of visceral pain through altered processes in peripheral afferent pathways, cortical pain processing and descending control of pain perception, visceral nociception, autonomic dysfunction and even genetic mechanisms, which may also vary from individual to individual [3].

Altered gastrointestinal reactivity (secretion and motility):

Secretory and motility alterations are directly related to the symptoms reported in IBS. Colonic transit time and activity vary according to the type of clinical presentation of the disease, so that in diarrheal IBS accelerated colonic transit can be observed as well as decelerated, secondary to changes in the myoelectric activity of the small intestine. Patients with IBS and constipation with abdominal distension usually have a tendency to slow intestinal transit when compared to healthy subjects or those with constipation, but no abdominal distension [20].

Visceral hypersensitivity

Presence of hyperalgesia is common in patients with IBS, although it is not present in all patients. It can be mediated by alterations in afferent visceral impulses, in their central processing or even a combination of them [21,22].

Central nervous system processing

The central processing of afferent impulses can be altered in IBS and they can be mediated by several receptors, such as N-methyl-D-aspartate (NMDA), serotonin, calcitonin gene related peptide (CGRP), substance P, bradykinin, tachykinins and neurotrophins [21].

There is no characteristic inflammatory process in IBS, at least from the macroscopic point of view, as it can be confirmed by the typically low levels of fecal calprotectin. However, more recent evidence may show an increase in inflammatory cells in the colon and small intestine, especially in cases of post-infectious IBS [20].

Post-infectious IBS

IBS may develop in approximately 25% after cases of more intense acute gastroenterocolitis. It is true that certain patients are unable to resolve the post-infectious inflammatory process, a mechanism that seems to be influenced by genetic characteristics or even by the degree of mucosal invasion by the infectious agent and consequent neural injury.

Another interesting theoretical proposal would be the development of malabsorption of bile salts in some cases, as certain patients seem to respond well to treatment with cholestyramine [23].

Dysbiosis

Recently, several groups have investigated the association between intestinal microbiota and IBS using techniques that do not depend on cultures, since the vast majority of our microbiota is not cultivable. When compared to healthy individuals, patients with IBS seem to have a different microbiota, both adults and in children.

Difference scan occur even between different IBS subtypes, which still lack scientific confirmation. The presence of dysbiosis greatly modifies the mucosal barrier, decreasing mucus and defensin secretion by the intestinal wall, thus reducing the effectiveness of tight junctions. Thus, antigen presentation is modified, altering the local and systemic immune response; intestinal motor and secretory abnormalities as well as direct interference on intestinal cell trophic condition and visceral sensitivity are promoted. This would perpetuate mucosal inflammation, mainly observed in cases of post-infectious IBS [3,24-26].

Genetics

Several intestinal receptors are involved in the physiopathology of IBS. Their affinity and density can be modulated by specific genes, many of them also associated with certain conditions that tend to be found in IBS patients, such as depression. This is observed regarding serotonin receptors: serotonin receptor (5-HT2A, HTR3a, b, c, d, e), serotonin transporter 5-HTTLPR, neuropeptide S1 (NPSR1), adrenergic alpha-2-O catechol methyl transferase, cannabinoid (CB1, CB2) [25].

The most convincing evidence, however, is the TNFSF15 gene, which could be observed in independent cohorts [27,28]. Genes may influence neural and barrier function, mast-cell or immune activity, colonic transit and secretion. Thus, in the future, studies focusing on genetic abnormalities in IBS may direct treatment to alterations related to each of the involved genes [25].

Treatment

The initial approach involves a methodical doctor-patient relationship, in which the clinician should explain the nature of the syndrome, its chronicity and emphasize its benign nature.

Foods have a strong influence on gastrointestinal motility and secretion through specific receptors or simply by changing volume or pH of the gastrointestinal lumen through neural, endocrine and paracrine mechanisms. The different types of specific receptors are able to recognize the major nutrient categories. Moreover, the gastrointestinal mucosa has taste receptors from the T1R and T2R family and several members of the transient receptor potential family of ion channels, with all of them being involved the detection of any substance that stimulates specific gustatory sensory cells [29].

Dietary factors have been increasingly considered to be important, and more recently, especially the diets poor in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) [26,30]. Among FODMAPs is the lactose, of which restriction is especially important in cases of proven intolerance. The decrease in gluten ingestion may be beneficial, even in individuals without celiac disease, as well as of galactans (consisting of repeating galactose units obtained through the hydrolysis of lactose), fructans (fructose polysaccharides), disaccharides (lactose, sucrose, maltose) and monosaccharides (fructose, sorbitol, mannitol and xylitol), which may also be related to the syndrome in intolerant patients [30,31].

Some patients may also respond to specific dietary restrictions, greatly benefiting from the so-called "food diary", in which patients report their diets and their feelings of wellbeing or not, trying to correlate the ingestion of certain foods or food groups to specific symptoms [32].

The pharmacological treatment (Table 3) is directed to the patient's clinical presentation of the disease. Antispasmodics are very important, as abdominal pain and/or discomfort is part of the syndrome by definition. Among them are usually prescribed mebeverine (200 mg b.i.d.), pinaverium bromide (100 mg b.i.d.), otilonium bromide (up to 40mg t.i.d.), *Menthapiperita* (200 mg - 1-2 cpt.i.d.) and Trimebutine (200 mg t.i.d.). Therapeutic results with these drugs are not always immediate; a 30-day treatment is frequently needed for the patient to show improvement. Antispasmodics can be used in both forms of IBS presentation: both diarrhea and constipation, in IBS-D and IBS-C [33,34].

IBS-C (Constipation)	IBS-D (diarrhea)
Antispasmodics (trimebutine, otilonium bromide, mebeverine, pinaverium bromide, Mentha piperita)	Antispasmodic agents
Probiotics	Probiotics
Antibiotics (rifaximin, metronidazole, quinolones, cephalosporin, etc.)	Antibiotics
	alosetron

	Bile salt adsorbent (cholestyramine, colesevelam)
Antidepressants (serotonergic agents)	Antidepressants (tricyclic)
Visceral analgesics (pregabalin)	Visceralanalgesics
	Mesalamine
	Ketotifen, disodium cromoglycate
	Loperamide
Alternative therapies	Alternative therapies

Table 3: Pharmacological treatment of irritable bowel syndrome (IBS) according to predominant symptom

IBS is basically a visceral hypersensitivity disorder and thus, the use of visceral analgesics such as antidepressants either tricyclic or serotoninergic ones is justified, due to their activity on pain modulation and perception. The choice of antidepressant drug will depend on the type of IBS (e.g., imipramine for diarrhea, paroxetine for constipation) and the patient's age and weight. Antidepressants interfere with intestinal motility and visceral sensitivity and may also be related to altered sleep and appetite patterns. Therefore, their use should be individualized. Cases of evident psychiatric disorders should be referred to a specialist [35,36].

The presence of bacterial overgrowth in IBS patients has been increasingly studied. Treatment includes antibiotics, often broad-spectrum types. Drugs such as metronidazole, ciprofloxacin, tetracyclines and cephalosporins are commonly used. However, the best option would be the use of drugs with little or no absorption, to prevent the occurrence of undesirable side effects. Rifaximin seems to be the ideal drug, although it is not available yet in some centers. The use of antibiotics is important in any of the syndrome's presentation [37,38].

Dysbiosis (intestinal flora imbalance) has been demonstrated in IBS and in this sense, probiotics seem an interesting option. The choice of probiotic will depend on the type of clinical presentation of the syndrome. Most studies involve the use of *Lactobacillus* and *Bifidobacterium* strains. Well-designed studies are still necessary for definitive conclusions to be drawn on the effective importance of probiotics in the treatment of IBS.

However it is worth mentioning that such microorganisms offer the potential to actually be effective. They inhibit the coupling of pathogen strains to their intestinal receptors, increase effectiveness of the mucosal barrier, act directly on intestinal and systemic immunity, interfere on motility and act on visceral sensitivity. It is important to recall that the effect is strain-specific and it is therefore essential for the clinician to become familiarized with the clinical studies carried out with each strain, in order to decide what the best option is. The probiotic effect lasts as long as the strains are ingested and thus, chronic supplementation is required [4,24].

IBS with constipation

One option in cases of IBS with constipation would be some drugs that were unfortunately withdrawn from the market due to the occurrence of major cardiovascular events, such as cisapride and tegaserode, nonspecific 5HT4 agonists [39,40]. The latter has been approved for market release in some countries, but its use is restricted to young women with no history or evidence of heart disease [41,42]. Prucalopride is also a 5HT4 agonist, 150 to 250 times more specific than cisapride and tegaserode, which has no adverse cardiovascular effects. Its use has been approved for use only in cases of chronic constipation, with no evidence yet to support its use in cases of IBS with constipation [43].

More recently, linaclotide, a cGMP agonist, has been approved for market release in the USA, at a dose of 145-290 mcg, 1x/day [44]. With a similar mechanism of action, lubiprostone, acts by directly activating the intestinal chloride channels at a dose of 24 mcg b.i.d. [45,46].

IBS with diarrhea

The use of alosetron (0.5 mg QD), a 5HT3 antagonist, is important for use in women with difficult to treat forms of IBS-D. The 5HT3 receptors are distributed in enteric motor and peripheral afferent neurons and the central nervous system. The antagonism of these receptors greatly reduces visceral pain, colonic transit and intestinal secretion in the small bowel, making this drug highly effective in the treatment of the syndrome.

Cases of ischemic colitis caused this drug to be withdrawn from the U.S. market, being subsequently reintroduced [47]. Another drug that can be used in IBS-D is loperamide, a synthetic opioid agonist (2-4 mg PO up to 4x/day). It effectively reduces intestinal transit without significant analgesic effect, slightly limiting its use in IBS [47].

As previously mentioned, IBS can be triggered by acute gastroenterocolitis, with most patients developing the diarrheal form of the disease. These cases can also be related to chronic mucosal inflammation eventually found in IBS, supporting the use of anti-inflammatory topical drugs such as mesalamine (1.5 to 2.4 g POb.i.d.), sodium cromoglycate (250 mg PO q.i.d.) and ketotifen [47-51].

Approximately 25-33% of patients with functional diarrhea and IBS with diarrhea have bile salt malabsorption, which can usually be confirmed by therapeutic trial with bile salt adsorbents such as cholestyramine (4 g, b.i.d.) or colesevelam (1875 mg b.i.d.) [47,52].

Future trends

In cases of IBS with diarrhea, promising new drugs may soon be part of the therapeutic arsenal. This is the case of serotonin synthesis inhibitors, such as LX-1031, 5HT3 antagonists such as ramosetron, spherical carbon adsorbent such as AST-120, benzodiazepine receptor modulators such as dextofisopam and peripheral κ-opioid agonists, such as asimadoline [47].

New drugs are also being developed for the treatment of IBS with constipation-C. The most promising one, mentioned earlier and now available for the treatment of chronic constipation is prucalopride. Other 5HT-4 agonists are being developed, such as velusetrag [53]. New cGMP agonists are also being developed, such as plecanatide.

Antagonists of neurokinin are also promising, as well as DNK333 and antagonists of N-methyl-D-aspartate (NMDA) [54].

New visceral analgesics may also be used in IBS in all its presentations, as the presence of pain and/or discomfort is part of the syndrome diagnosis. One example is pregabalin, which is often used for chronic pain treatment [54].

Complementary Medicine such as psychotherapy, relaxation techniques, acupuncture or hypnotherapy has proved to be useful in many cases of IBS and may be indicated by the clinician [55]. Of acupuncture-related techniques, moxibustion or moxa, is frequently used in conjunction with acupuncture needling [55]. More recently another alternative, cognitive-behavioural therapy (CBT), has gained attention showing promise results. This approach is effective in alleviating the physical and psychological symptoms of IBS.

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