Irritable bowel syndrome and intestinal parasites: a view from South America

Síndrome de intestino irritable y parasitosis intestinal: una visión desde Sud-América

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ABSTRACT
Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder of uncertain etiology. Several studies have proposed the possible role of intestinal parasites in the pathogenesis of IBS. We aimed to summarize the epidemiological studies that describe a possible link between intestinal parasites and IBS, with special interest in endemic areas for intestinal parasitism such as South America. A comprehensive review of the literature was conducted by using the keywords: irritable bowel syndrome, intestinal parasites, protozoan infection, soil-transmitted helminths and South America. *Giardia lamblia* may cause IBS symptoms that can persist several years after effective treatment. *Dientamoeba fragilis* can cause IBS-like symptoms, but low sensitive parasitological techniques may fail to detect it. *Entamoeba histolytica* can cause a chronic non-dysenteric colitis, but several studies have failed to find an association with IBS. The role of *Blastocystis hominis* in IBS remains controversial. In addition, epidemiological studies evaluating the effect of soil-transmitted helminths in IBS are scant. Symptoms elicited by intestinal parasites may resemble to those in IBS, especially in endemic areas such as South America, where both the prevalence of IBS and intestinal parasitism are high. Whether these organisms are the cause or contributing factors in IBS remains a subject of study. Routine parasitological examination of stools in individuals who full-fit the criteria for IBS should be included upon initial assessment in endemic countries.
Key words: *Irritable bowel syndrome; Intestinal diseases, parasitic; Protozoan infections; Helminthiasis; South America (source: MeSH NLM).*

RESUMEN
El Síndrome de intestino irritable (SII) es un desorden gastrointestinal funcional de etiología incierta. Muchos estudios han propuesto que los parásitos intestinales pueden tener un rol en la patogénesis del SII. Se sintetizó estudios epidemiológicos que describen una relación posible entre el parasitismo intestinal y el SII, con especial interés en aquellos estudios que fueron realizados en zonas endémicas para dichos organismos. Se realizó una revisión extensa de la literatura por medio de las siguientes palabras clave: síndrome de intestino irritable; parásitos intestinales; protozoarios; helmintos y Sud-América. *Giardia lamblia* puede causar síntomas similares al SII que pueden persistir por muchos años, después de tratamiento efectivo. *Dientamoeba fragilis* puede causar un cuadro similar al SII, pero al emplearse técnicas de baja sensibilidad, se puede fallar en detectar su presencia. *Entamoeba histolytica* puede causar un cuadro de colitis no disentérica, pero varios estudios no han podido encontrar una relacion con el SII. El rol del *Blastocystis hominis* en el SII sigue siendo controversial. Adicionalmente, los estudios epidemiológicos evaluando el efecto de los helmintos en el SII son escazos. Los parásitos intestinales pueden causar síntomas que pueden parecerse a los que se encuentran en pacientes con SII. Ésta observación merece especial atención en regiones como Sud-América, donde las prevalencias del SII y del parasitismo intestinal han sido estimadas como altas. Si es que éstos organismos son la causa o un factor contributor en el SII, aún es materia de estudio. En la evaluación inicial de un probable caso de SII, los estudios parasitológicos pueden ser necesarios, especialmente en áreas endémicas.
Palabras clave: *Síndrome del colon irritable; Parasitosis intestinales; Infecciones por protozoos; Helmintiasis; América del Sur (fuente: DeCS BIREME).*

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by chronic abdominal pain associated with constipation, diarrhea or bloating [(1)]. Traditionally, an altered brain-gut axis has been accepted as a main pathogenic mechanism of IBS [(2)]. Nonetheless, recent studies propose that gut microbiome alterations [(3)] and intestinal inflammation are important features related to this condition. This theory is supported by the evidence that a subgroup of IBS patients may report the onset of their symptoms after an episode of acute gastroenteritis; known as post-infectious IBS (PI-IBS) [(4)]. Thus, the role of intestinal infections and the resulting microbiome disturbance is currently an area of special interest in IBS.

I. IBS and intestinal parasites: epidemiology and clinical presentation

IBS occurs in all age groups and about half of the patients with IBS may present with abdominal symptoms before the age of 35 years [(5)]. Furthermore, there is a female predominance described in several studies [(6)]. A

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Table 1. Rome III criteria for IBS diagnosis.

Abdominal pain that is present at least 3 days per month in the previous 3 months, along with two or more of the following symptoms:
• Improvement with defecation.
• An onset associated with a change in the frequency of bowel movements.
• An onset associated with a change in the appearance of stools.
Onset of symptoms must have started at least 6 months before diagnosis.

recent meta-analysis showed that the estimated global prevalence of IBS was 11.2% (95% CI, 9.8-12.8%) [7]. Most of this data is based on large community surveys from Europe, Southeast Asia, and North America [5,6,8] whereas the prevalence estimations in South America are limited to small cross sectional studies [9-12]. In spite of this heterogeneity, the region of South America had the highest prevalence of IBS (21%).

IBS is defined on the basis of clinical grounds by meeting the Rome III criteria (Table 1). Further classification includes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed pattern IBS (IBS-M) and unclassified IBS (IBS-U). Thus, given the broad definition and the lack of diagnostic markers [13], it is possible that other conditions can present with symptoms similar to IBS and meet the Rome III criteria. For example, intestinal parasitic infections can present with a wide array of GI symptoms similar to those reported by IBS patients [14] and may full-fit the Rome III criteria [15].

The chronic nature of some of intestinal parasitic infections along with the lack of adequate screening programs in tropical areas may contribute to their wide distribution [16-19]. Hence, in a region where intestinal parasitism and IBS rates are both high such as in South America, the diagnosis of IBS may be a challenge.

II. Intestinal protozoans and IBS

Parasitic infections affect millions of people in both urban and rural areas around the world (20). Protozoan infection is a major public health problem in the developing countries where poor sanitation and suboptimal quality of water are commonly present (21). Table 2 shows the association studies that have assessed the role of intestinal protozoans in patients with IBS.

1. *Giardia lamblia*

G. lamblia is a multi-flagellated protozoan, spread by fecal-oral route with a global distribution. It is highly infective; only 10 cysts are needed to infect an individual and cause GI complaints. Approximately 50% of those infected individuals clear the organism without any symptoms. Another 5-15% shed cysts asymptomatically and the other 35% develop an acute or chronic infection. Non-specific abdominal symptoms such as abdominal pain, diarrhea, constipation, and bloating can largely overlap to those presented by patients with functional GI disorders such as dyspepsia and IBS [22]. Although the prevalence of this agent in IBS patients is low [22-24], no symptom elicited by this parasite could reliably discriminate those IBS patients with giardiasis from those uninfected by this parasite [22].

Prospective studies have shown that after an infective gastroenteritis by *G. lamblia*, a subgroup may persist with abdominal symptoms consistent with IBS. Furthermore, diarrhea- predominant IBS (IBS-D) has been reported to be the most common presentation in these cases [25]. Along with IBS, another long term complications such as chronic fatigue syndrome (CF) have been described up to 3 years after the initial infection and suggests an overlap between both conditions [26]. On the other hand, case-control studies have failed to find an association between G. lamblia and IBS [23,24].

2. *Dientamoeba fragilis*

The first time it was recognized in 1909, *D. fragilis* was thought to be a harmless commensal. Nonetheless, *D. fragilis* causes acute and chronic GI disease in humans [27,28]. Whether it causes the symptoms as a single agent or in association with other parasites (e.g. *Enterobius vermicularis*) [29] remains uncertain. Over the past four decades the global incidence of *D. fragilis* has ranged from 0.4% to 42% [28]. This variation may be explained by the increasing use of adequate culture techniques and DNA-based testing such as PCR.

D. fragilis has been found in symptomatic and asymptomatic individuals. In 2010, a study in Pakistan reported that the prevalence of *D. fragilis* by using PCR analysis in patients with IBS-D was 4% in comparison with 0% in the control group [15]. However, in Mexico, *D. fragilis* was found to be more frequent in the control group (26.6%) rather than the infected group (2.2%) ($p = 0.002$) [30]. Likewise, in 2015 a study in Denmark found a positive association between *D. fragilis* and IBS' controls (34.8% vs 23.4%, $p=0.03$) [23].

D. fragilis has been found in symptomatic and asymptomatic individuals. In 2002, Borody et al. [31] reported 21 patients who presented chronic IBS- like symptoms including abdominal cramping, bloating, constipation and diarrhea (2-15 bowel motions per day). After receiving treatment with iodoquinol and doxycycline it was noted that all the participants eradicated the parasite and 67% of them resolved their symptoms. Nonetheless, Engsbro et al. [32] reported that after a course of metronidazole, only 7 (32%) IBS participants resolved their symptoms and there was no association between symptoms

resolution and the eradication of this parasite. Additional studies are needed to determine the association of *D. fragilis* with IBS.

3. *Entamoeba histolytica*

Among the six known species of Entamoeba, only *E. histolytica* has been recognized to be a pathogen [33]. *E. histolytica* is an invasive pathogen and the causative agent of amebiasis with approximately 500 million cases of symptomatic disease annually [34], usually acquired in developing countries. Invasive disease (colitis) is characterized by abdominal pain, tenderness and intense diarrhea along to ulcerative changes on histopathology. Infrequently, it may also present as chronic non-dysenteric diarrhea, weight loss and abdominal pain that can last for years.

There are discordant results about the role of *E. histolytica* in IBS. A study conducted in 130 individuals suggested that *E. hystolitica* may be implicated in this condition [35] by causing PI-IBS. Nonetheless, in India Anand et al. [36] did not find significant differences between IBS cases and the control group in terms of stool positivity, serological results, colonoscopy abnormalities or histopathological findings. Likewise, Sinha et al. [37] failed to find any improvement in the IBS symptoms score after receiving effective antiparasitic treatment in a leprosy rehabilitation center. Discordance on these findings may be explained by the different study population, study design and the variable intestinal mucosal lesion produced by this parasite. Furthermore, patients with invasive amoebic dysentery may report more symptoms whereas chronic carriers of amoebic cysts may not [38].

Although the prevalence of *E. histolytica* in IBS patients is low, intestinal amebiasis may form part of the differential diagnosis of patients with IBS, especially in those with an acute presentation or acute exacerbations of IBS symptoms [14]. Thus, a careful travel history along to parasitological examination may be needed.

4. *Blastocystis hominis*

Blastocystis is the most frequent protozoan reported in human fecal samples [39,40]. It is widely distributed, with prevalence rates range from 1.5% to 50% in developed and developing countries, respectively [41]. The pathogenic role of Blastocystis remains controversial [42-47]. Endoscopy and biopsy results have usually revealed that *Blastocystis* does not invade the colonic mucosa in human patients, although some edema and inflammation may be noted. Nonetheless, some reports have also described colonic ulcerations in patients infected by *Blastocystis* as the single agent [48]. Symptoms that have been attributed to *Blastocystis* are nonspecific and include diarrhea, abdominal pain, cramps, bloating, fatigue, anorexia, and nausea [49].

The pathogenic role of *Blastocystis* in IBS has received major attention in the last decades. It was first described in Italy that *Blastocystis* was more frequent in subjects with IBS (defined by Rome I criteria) compared to the controls ($p = 0.006$) [42]. Likewise, a study in Pakistan including 95 IBS' cases from the outpatient clinic and 55 controls'(Rome II criteria) demonstrated that the prevalence of *Blastocystis* was higher in cases rather that in controls (46% vs. 7%; $p<0.001$) [43]. Nonetheless, another study conducted in the same country whose study population was healthy individuals did not find any association (13.6% vs. 12%; $p=0.8$) [45]. In Mexico and Denmark several studies have been conducted with discordant results as well [23,30,50].

A proposed mechanism of disease suggests that persistent exposure to *Blastocystis* antigens may cause a low grade inflammation in the intestinal mucosa, which can lead to IBS symptoms [51]. Furthermore, the immune activation driven by *Blastocystis* in patients with IBS is more prominent than in asymptomatic individuals [52]. Clinical manifestations elicited by this parasite vary among the 10 subtypes identified [41], and may explain in part its different pathogenic potential. For example, in one study conducted in Pakistan, an analysis of the genotypes of *Blastocystis* among 158 individuals with IBS-D and 157 healthy controls, revealed that *Blastocystis* type 1 was present in 86% of IBS-D patients compared to 14% of the controls ($p<0.001$) while type 3 was present in 47% of the individuals with IBS-D compared to 53% in the control group ($p<0.001$) [44].

Although several studies support a positive role for *Blastocystis* in IBS, it is striking that *Blastocystis* is more frequently found in asymptomatic individuals rather than in those with an inflammatory GI condition such as IBS or IBD. New studies have proposed that *Blastocystis* may be part of a diverse microbiota, more resistant to intestinal disturbs. Nevertheless, additional studies including subtyping of *Blastocystis* are warranted to evaluate its true pathogenic role.

III. Helminths

Soil-transmitted helminths (STH) cause chronic abdominal complains as well as nutritional deficit and anemia, albeit specific clinical manifestations may vary individually. For example, large numbers of adult Ascaris worms in the small intestine can cause abdominal distention and pain in addition to lactose intolerance and malabsorption. Trichuriasis (whipworm) is preferentially located in the cecum and mucosal lesions produced at the site of attachment may resemble an inflammatory bowel disease (IBD) [53]. Moreover, hookworm infection may cause invasion and attachment to the intestinal mucosa and submucosa, producing iron-deficiency anemia and nutritional impairment. In addition, *Strongyloides stercoralis* preferentially colonizes the proximal portions of the GI tract and cause chronic diarrhea, abdominal discomfort and bloating, especially if malabsorption is present. During hyperinfection and dissemination, complete disruption of the mucosal patterns, ulceration and paralytic ileus can be seen [54]. Chronic infection

by these parasites has been suggested to play a role in inflammatory conditions such as IBS or IBD [55].

In general, little is known about the impact of helminths in the development of IBS. In Nicaragua, where the prevalence of STH is non-negligible, there was no difference between IBS' cases and controls in terms of parasite carriage or STH infection. Nonetheless, this finding may be limited in part to the low sensitivity diagnostic methods used [24]. No other studies have reported a high prevalence of STH in IBS participants.

STH infection has been demonstrated to modulate the inflammatory response towards the Th2 branch, leading to an increase in IL-5, IL- 13 and IL- 10 levels (anti-inflammatory cytokine), which prevent the development of robust inflammatory conditions such as IBD in animal models [56]. As IBS is characterized by a chronic low-grade intestinal inflammation, it is possible that helminth infection may prevent the intense immune response from other conditions and result in milder GI symptoms that resemble IBS.

Given the high prevalence of STH in South America [57] and their ability to cause chronic GI symptoms and alter the immune response (with different clinical implications), it is questionable if the current Rome III criteria is applicable. High IBS rates could be related to the wide distribution of intestinal parasites, which is largely unexplored in this region to date. Thus, well-designed population- based studies are needed to assess a possible

Table 2. Summary of studies reporting the association of intestinal parasites and IBS included in this review.

Studies	Country	Diagnostic method	Organisms studied	Criteria (b)	IBS patients [Parasite prevalence N (%)]	Control group [Parasite prevalence N (%)]	Population	Publishing year
Sinha P et al. [37]	India	Microscopy Serology Culture	*E. hystolitica*	Manning	22/81 (27.2)	45/81 (55.6)	GD	1997
Anand et al. [36]	India	Microscopy Serology Colonoscopy	*E. hystolitica*	Consensus	61/144 (42)	41/100 (41)	Healthy Primary care	1997
Giacometti et al. [42] (a)	Italy	Trichrome Stain	*B. hominis*	Rome	15/81 (18.5)	23/307 (7.5)	GD	1999
Yakoob et al. [43] (a)	Pakistan	Culture	*B. hominis*	Rome II	44/95 (46.3)	4/55 (7)	GD	2004
Tungtrongchitr et al. [45]	Thailand	Culture	*B. hominis*	Rome II	8/59 (13.6)	3/25 (12)	Healthy	2004
Yakoob et al. [44] (a)	Pakistan	Culture	*B. hominis*	Rome III	95/158 (71)	38/157 (38)	GD	2010
Droguman-Al et al. [47] (a)	Turkey	Lugol Stain	*B. hominis*	Rome III	8/21 (38)	5/43 (11.6)	Healthy	2010
Ramirez- Miranda et al. [50]	Mexico	Flotation Method	*B. hominis* *G. lamblia* *E. histolytica*	Rome III	n.a/115 (15.7) n.a/115 (1.7) n.a/115 (2.6)	n.a/209 (12) n.a/209 (1.4) n.a/209 (2.9)	GD	2010
Yakoob et al. [15] (a)	Pakistan	Culture PCR	*B. hominis* *D. fragilis*	Rome III	90/171 (53) 7/171 (4)	25/159 (16) 2/159 (1.3)	GD	2010
Surangsrirat [15] (a)	Thailand	Culture	*B. hominis*	Rome II	11/66 (16.7)	6/60	GD	2010
Yakoob et al. [15]	Pakistan	Microscopy Culture/PCR	*B. hominis* *D. fragilis*	Rome III	75/171 (44) 6/171 (4)	33/159 (21) 4/159 (2)	GD	2010
Jimenez- Gonzales et al. [30] (a)	Mexico	Flotation Method	*B. hominis* *D. fragilis*	Rome III	14/45 (31.1) 1/45 (2)	6/45 (13.3) 12/45 (27)	GD	2011
Cekin et al. [46]	Turkey	Lugol Stain	*B. hominis*	Rome III	51/877 (5.82)	6/192 (3.12)	GD	2012
Douglas Morgan et al. [24]	Mexico	Formalin Ethyl/Iron staining	*B. hominis* *G. lamblia* *E. histolytica*	Rome II	13/163 (7) 5/163 (3) 18/163 (11)	20/194 (10) 7/194 (3) 26/194 (13)	Healthy	2012
Wensaas et al. [26] (a)	Norway	n.a	*G. lamblia*	Rome III	376/817 (46.1)	1571128 (14)	GD	2012
Mumcuoğlu et al. [32]	Turkey	Culture	*B. hominis* *D. fragilis*	Rome III	n.a/55 0/55	n.a/50 0/50	GD	2013
Krogsgaard et al. [23] (a)	Denmark	Microscopy Culture/PCR	*D. fragilis* *B. hominis* *E.histolytica* *G. intestinalis*	Rome III	71/204 (34.8) 45/204 (22.1) 0 1/204 (0.5)	29/124 (23.4) 18/124 (14.5) 1/124 (0.8) 0	Healthy	2015

[a] Studies that present a positive association between a specific parasite and IBS cases.
[b] Criteria used for IBS diagnosis.
[c] N.A: Non- available. GD: Gastrointestinal Department

association between the diagnosis of intestinal parasites and IBS in endemic areas such as South America.

Conclusion

There are a number of challenges to determine the real prevalence of IBS in endemic areas for intestinal parasitism. Most of the criteria used for the diagnosis of IBS include symptoms that may be present in protozoan and helminthic infections. Additional studies are needed to determine the real prevalence of IBS after the exclusion of well-known parasitic pathogens in highly endemic populations. Even after the exclusion of an active infection, it would be challenging to confirm whether the IBS symptoms were the result of a previous parasitic infection or purely related to IBS. The need for highly sensitive parasitological techniques to rule out the presence of ova and parasites seems to be recommended as a priority in this setting. In regions where intestinal parasitism is less prevalent, large high-quality case-control or cohort studies are needed to confirm previous suggested associations between specific parasitic infections and different types of IBS. Finally, the understanding of the brain-gut-microbiome axis and better diagnostic methods to objectively asses its abnormalities will be of paramount importance for confirmation of IBS as well as to uncover the role of intestinal parasites. Although the diagnosis of IBS relies on clinical grounds, stool examinations may rule out an intestinal parasite as a confounding factor and may be helpful in regions such as South America.

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