Aswan University Medical Journal, volume 4 / No.2/ September 2024 (55-61) Online ISSN: **2735-3117**

Review article

Blastocystis and Irritable Bowel Syndrome: The Mysterious Link

Shimaa Refaey Mohamed Abd-Elal*, Hanaa Ahmed El-Hady, Amal Mostafa Ahmed, Asmaa Kamal Abd Ellah

Department of Medical Parasitology, Faculty of Medicine, Sohag University

ABSTRACT

Keyword: IBS, *Blastocystis*, Dysbiosis

***Corresponding author:** Shimaa Refaey Mohamed Abd-Elal

Email: Shimaa.refaee@med.sohag.edu.eg.

Phone: 01004920534

Irritable bowel syndrome (IBS) is classified under the category of the functional gastrointestinal disorders that characterized by with abdominal discomfort or pain with irregular bowel movement in the form of diarrhea or constipation without a known organic cause. Post-infectious IBS (PI-IBS) refers to developing IBS after enteric infection. Various parasites, including Blastocystis have been implicated as potential causes for PI-IBS. Blastocystis spp. is a unicellular parasite colonizing the intestinal tract of different mammals, including man. Several factors such as subtype, parasite load, and host-related factors may influence the outcome of Blastocystis infection. Several studies have suggested a relation between the presence of Blastocystis spp. and IBS as it is frequently found in IBS patients. While some studies linked certain subtypes of Blastocystis like Blastocystis ST-1 and Blastocystis ST-3 to IBS, most studies have not been able to establish a clear association between IBS and specific subtypes. Inflammation, dysbiosis, and disruption of gut homeostasis are the major suggested mechanisms by which Blastocystis spp. may cause IBS.

INTRODUCTION

A brief look at IBS

IBS is a functional gastrointestinal disorder manifested by recurrent abdominal discomfort or pain, along with changes in the consistency or frequency of feces without any identifiable organic cause".[1] Post-infectious IBS (PI-IBS) refers to IBS development after enteric infection.[2] Various parasites like *Blastocystis* spp., *Giardia lamblia* and *Entamoeba histolytica* have been implicated as potential causes for PI-IBS, although the connection is not entirely clear. [3,4]

It is a common disease with a 10-20% global prevalence.[5] Interestingly, females are 1.5-3 times more likely than males to develop IBS. It affects individuals of all ages, although it is more commonly experienced by those under the age of 35. The incidence of IBS tends to decrease among individuals over the age of 50.[6]

The manifestations of IBS exhibit variability between individuals. They may include irregular bowel habits in the form of either constipation or diarrhea, flatulence, and abdominal discomfort. It is important to recognize that IBS is a syndrome with multiple different forms rather than a single disease with a specific diagnosis.[7]

Unfortunately, most pharmacological drugs are unable to significantly improve the quality of life of

IBS patients. [8] Therefore, it is critical to understand the underlying factors contributing to IBS symptoms.[9]

Factors involved in the pathogenesis of IBS

The pathophysiology of IBS is complex, as it is believed to be multifactorial, with the main important abnormalities including mucosal inflammation, visceral hypersensitivity, dysbiosis (alterations in the gut microbiota), and dysfunction of the autonomous nervous system.[10] according to research, enteric infections, stress, and genetic criteria, are important factors that increase the susceptibility to developing IBS.[8]

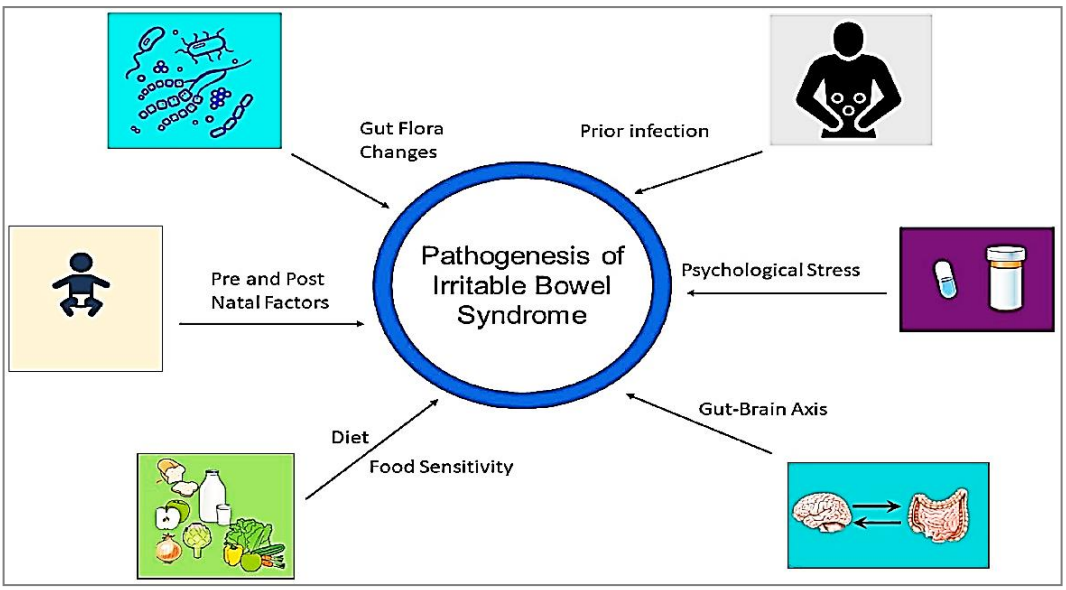

Figure 1. Elements in the Pathophysiology of IBS.[11]

A brief look at *Blastocystis* spp.

Blastocystis spp. is anaerobic protozoal parasite colonizing the gastrointestinal tract of different mammals including man. It is now considered one of the widespread enteric parasites, particularly in developing countries where low socioeconomic status, poor hygiene, frequent contact with birds and animals, and ingestion of contaminated food and water are major risk factors.[12] It is transmitted fecal-orally, with transmission occurring either from human to human or from animal to human.[13] Research has revealed that *Blastocystis* has extensive genetic diversity, with at least 40 different subtypes (STs 1-21 and STs 23-44) found according to the variations in the small subunit ribosomal ribonucleic acid (SSU-rRNA) gene. These subtypes are found in different hosts, involving man, rodents, birds, primates, and other mammals. Only 16 subtypes (STs1-10, ST12, ST14, ST16, ST23, ST35 and ST41) were isolated from humans [14]; *Blastocystis* STs 1-4 are considered the most prevalent in man with prevalence about 90 %, with *Blastocystis* ST-1 being the most pathogenic. [15] Previously thought to be a commensal parasite with no pathogenic role, new research has linked it to numerous gastrointestinal manifestations in addition to cutaneous manifestations. The association with conditions such as inflammatory bowel disease (IBD) and IBS increased the surge of worldwide interest and study in *Blastocystis* spp. [16]

There is still much debate about the pathogenicity of *Blastocystis* spp., mainly due to its existence in both asymptomatic and symptomatic individuals. The most accepted explanation for the pathogenicity of *Blastocystis* spp. was the association between virulence and *Blastocystis* subtype. Recently, it has been noted that there are variations in pathogenicity even within the same subtype, indicating that not all strains within a subtype are pathogenic. These findings suggest that predicting

pathogenicity based on subtyping alone is not feasible. The main phenotypic differences observed in pathogenic strains are the presence of amoeboid forms and the secretion of proteases and other hydrolases.[17] These hydrolytic enzymes are the key in the pathogenesis of *Blastocystis* spp. They induce the mucosal cells to produce interleukin-8, leading to intestinal inflammation. Additionally, these enzymes trigger epithelial apoptosis, resulting in increased in the intestinal permeability. Furthermore, the enzymes destroy the secretory immunoglobulin A, which is the main mucosal immunoglobulin defence, aiding in immune evasion and survival of the parasite.[18] Several factors such as parasite load, and host-related factors, along with the subtype, may influence the outcome of *Blastocystis* infection.[19]

The relation between IBS and *Blastocystis* spp. infection:

In the last few years, several hypotheses and a rising number of research have linked *Blastocystis* infection to the incidence of IBS. The similarity of symptoms caused by *Blastocystis* spp. to those of IBS, such as nausea, abdominal pain and diarrhea, supports the proposal of this relation.[18]

As *Blastocystis* spp. is commonly present in IBS patients, many researches hypothesized a relation between IBS and carrying this protozoan. [20] It is still not fully understood whether *Blastocystis* spp. causes IBS/IBS-like symptoms or IBS-related changes in the intestinal environment favor *Blastocystis* spp. colonization.[18]

Yakoob et al. [21] conducted one of the initial studies to explore the potential link between a parasite and IBS. Their findings revealed a significantly higher occurrence of *Blastocystis* spp. along with higher levels of IgG antibodies against *Blastocystis* spp. in patients with IBS compared to the control non-IBS group.

The findings of many studies have revealed that the incidence of *Blastocystis* spp. in the control group is nearly similar to its incidence in the IBS group. Moreover, some authors found higher rate of *Blastocystis* spp. in the control group than IBS group. This has made it challenging to definitively link the infection with this protozoan to the development of IBS. [19,22,23] Furthermore, the relation between the existence of certain subtypes of *Blastocystis* and having IBS has been investigated. While some authors have proposed a relation between IBS and specific subtypes like *Blastocystis* ST-1 and *Blastocystis* ST-3, other authors have not been able to establish a clear association between IBS and specific subtypes.[20] The explanation for these disparities in reporting may be resulting from the small studied sample size of IBS cases. The multifactorial etiology of IBS may also explain these differences. [24]

The potential link between *Blastocystis* & IBS pathophysiology mechanisms

The mechanism by which *Blastocystis* spp. may cause IBS is still not clear, but many hypotheses were proposed **(Figure 2)**.

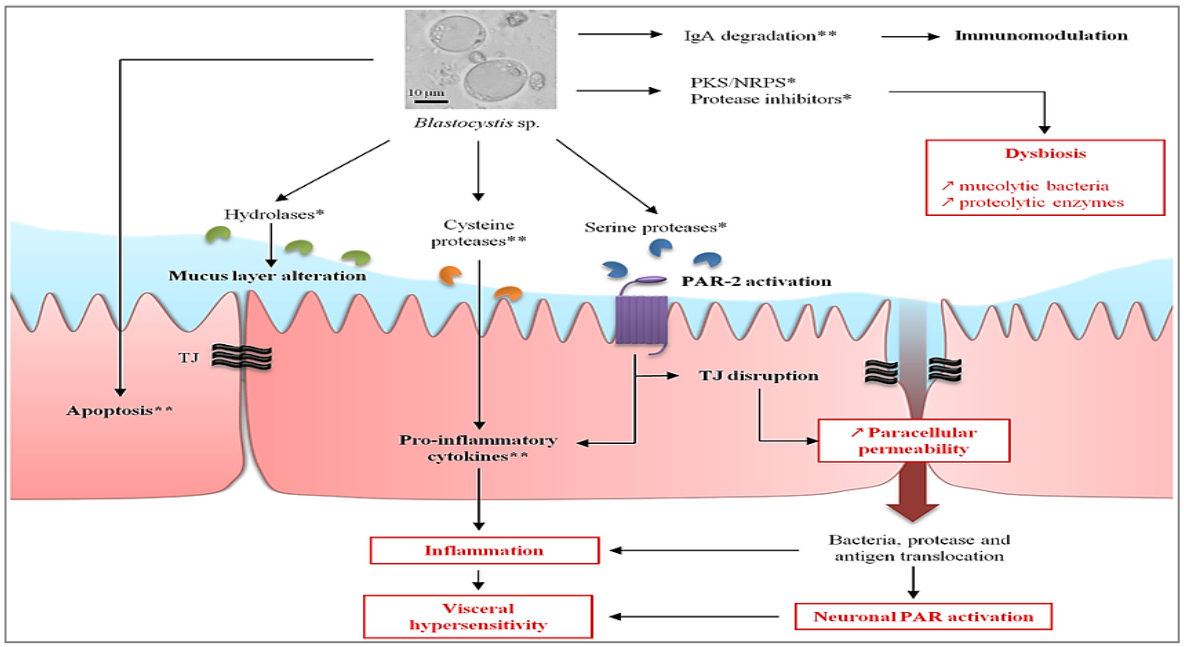

Figure 2. The potential link between *Blastocystis* & IBS pathophysiology mechanisms (in red).[24]

i. Inflammation:

Firstly, it has been suggested that persistent exposure to antigens in chronic *Blastocystis* infection may lead to low-grade inflammation, which could potentially explain the IBS-like symptoms.[25]

ii. Disruption of gut homeostasis

Although the association between IBS and carrying particular *Blastocystis* subtypes has not proved yet, considerable variations in proteases activity between the different *Blastocystis* subtypes have been reported.[26] Notably, the proteases secreted by *Blastocystis* are able to damage the actin filaments and mucosal barrier, leading to increased intestinal permeability, and subsequently development of symptoms resembling IBS. [27] Furthermore, it was reported that *Blastocystis* ST-3 is able to regulate microRNAs levels which are essential for maintaining claudin-7 in addition to the integrity of gut barrier. [28] Claudin-7, a key tight junction protein, which is important for decreasing the permeability of the gut. [29]

iii. Genetic polymorphism

The presence of variations in the genes responsible for producing inflammatory cytokines has been suggested to be a factor in the etiology of IBS. Olivo-Diaz et al., [30] reported that certain single nucleotide polymorphisms (SNPs) in interleukins 8 & 10 may influence the susceptibility to developing IBS in *Blastocystis*-infected persons. While the genetic variations in the IBS-related regions of interleukins 6, 8 &10 may have varying effects on different ethnic groups, these SNPs may heighten the susceptibility to IBS. [31] Recent research has also investigated the potential association between IBS and *Blastocystis*, with a focus on the role of interleukins 8 & 10 gene variations. There is recent study found significantly increased levels of tumor necrotic factor-α, interferon-γ, interleukins 6, 8 &10 in the serum of IBS cases infected by *Blastocystis* spp., suggesting the crucial impacts of *Blastocystis* spp. in developing IBS through modulating IBS-related cytokines. [32]

iv. Altered gut microbiota (Dysbiosis):

Gut microbiome refers to the wide range of enteric microbes that coexist in the gut, performing specific functions such as metabolism of food and medications, immunomodulation, intestinal mucosal maintenance and defence against opportunistic or external pathogens. The alteration in the gut microbiome is called "dysbiosis" and caused by loss or overgrowth of certain agent, decrease in microbial diversity or gene mutations. [10]

Recent studies have been found a relation between IBS and dysbiosis, suggesting that *Blastocystis* spp. could potentially contribute to IBS by disrupting the gut microbiota.[33] In another word, dysbiosis may be the missing ring in the relation between *Blastocystis* and IBS.

Dysbiosis can trigger many immunologic and inflammatory responses that may impair the gut barrier integrity and lead to increased intestinal permeability. Consequently, this disruption can disturb the gastrointestinal homeostasis in addition to dysregulation of the brain-gut nociceptive pathways, resulting in increased gastrointestinal pain sensation or visceral hypersensitivity, which are commonly observed in IBS.[11]

Conclusion

The infection with *Blastocystis* spp. is considered a risk factor for developing IBS, particularly the IBS-D. The mechanism through which *Blastocystis* spp. can develop IBS is not clearly defined. It is believed that the proteases released by *Blastocystis* spp. disrupt gut permeability, inducing the development of IBS. Additionally, *Blastocystis* spp. could potentially contribute to IBS by disrupting gut microbiota.

REFERENCES:

1. **Sorouri M, Pourhoseingholi MA, Vahedi M, Safaee A, Moghimidehkordi B, Pourhoseingholi A, *et al* (2010).** Functional bowel disorders in Iranian population using Rome III criteria. *Saudi J Gastroenterol,* 16: 154-160. https://doi.org/10.4103/1319-3767.65183
2. **Thabane M. and Marshall, I. (2009).** Post-infectious irritable bowel syndrome. *World J Gastroentrol,* 15: 3591-3596. https://doi.org/10.3748/wjg.15.3591
3. **Spiller R, and Garsed K. (2009).** Post-infectious irritable bowel syndrome. *Gastroenterol,* 136: 1979-1988. https://doi.org/10.1053/j.gastro.2009.02.074
4. **Wensaas K, Langeland N and Hanevik K. (2012).** Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. *Gut,* 61: 214-219. https://doi.org/10.1136/gutjnl-2011-300220
5. **Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearjn F and Spiller RC. (2006).** Functional bowel disorders. *Gastroenterol,* 130: 1480-1491. https://doi.org/10.1053/ j.gastro. 2005.11.061
6. **Canavan C, West J and Card T. (2014).** The epidemiology of irritable bowel syndrome. *Clin Epidemiol,* 6:71 https://doi.org/10.2147/CLEP.S40245
7. **Salonen A, De Vos WM, and Palva A. (2010).** Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. *Microbiol*, 156: 3205-3215. https://doi.org/10.1099 /mic.0.043257-0
8. **Khan S and Chang L. (2010).** Diagnosis and management of IBS. *Nat Rev Gastroenterol Hepatol,* 7: 565-581. https://doi.org/10.1038/nrgastro.2010.137
9. **Thompson DG. (2005).** IBS-the irritation of inflammation. Gastroenterol, 129: 378-380. https://doi.org/10.1053/j.gastro.2005.05.040

10. **Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P and Yong VC. (2019).** The microbiome and irritable bowel syndrome—A review on the pathophysiology, current research and future therapy. *Front Microbiol,* 10: 1136. https://doi.org/10.3389/fmicb.2019.01136
11. **Shaikh SD, Sun N, Canakis A, Park WY, and Weber HC. (2023).** Irritable Bowel Syndrome and the Gut Microbiome: A Comprehensive Review. *J Clin Med,* 28: 2558. https://doi.org/10.3390/jcm12072558
12. **Alfellani MA, Stensvold CR, Vidal-Lapiedra A, Onuoha ES, Fagbenro-Beyioku AF and Clarck CG. (2013).** Variable geographic distribution of *Blastocystis* subtypes and its potential implications. *Acta Trop,* 126: 11-18. https://doi.org/10.1016/j.actatropica.2012.12.011
13. **Tasić N, Milenković T, Bujić V, Zdravković D and Tasić A. (2016).** *Blastocystis hominis*: a Mysterious and Commonly Disregarded Parasite. *Med Biol,* 18: 39-47 https://doi.org/10.22190/FUMB161027001T
14. **Boutahar M, Belaouni M, Ibrahimi A, Eljaoudi R, Aanniz T and Er-Rami M. (2023).** Prevalence of *Blastocystis* sp. in Morocco: Comparative assessment of three diagnostic methods and characterization of parasite forms in Jones' culture medium. Parasite, 30: 64. https://doi.org/10.1051/parasite/2023065
15. **Li WC, Wang K and Gu Y. (2018).** Occurrence of *Blastocystis hominis* and *Pentatrichomonas hominis* in sheep and goats in China. *Parasites Vectors,*11: 1-7. https://doi.org/10.1186/s13071-018-2671-5
16. **Rostami A, Riahi SM, Haghighi A, Saber V, Armon B and Seyyed tabaei SJ. (2017):** The role of *Blastocystis* sp. and *Dientamoeba fragilis* in irritable bowel syndrome: a systematic review and meta-analysis. *Parasitol Res,*116: 2361-2371. https://doi.org/10.1007/s00436-017-5535-6
17. **Sekar U. and Shanthi M. (2015).** Recent insights into the genetic diversity, epidemiology and clinical relevance of *Blastocystis* species. *JMR,* 1: 33-39. http://doi.org/10.31254/jmr. 2015.1110
18. **Roberts T, Stark D, Harkness J and Ellis J. (2014).** Update on the pathogenic potential and treatment options for *Blastocystis* sp. *Gut Pathog,* 6: 1-9. https://doi.org/10.1186/1757-4749-6-17
19. **Salvador F, Lobo B, Goterris L, Alonso-Cotoner C, Santos J, Sulleiro E, *et al.* (2021).** *Blastocystis* sp. carriage and irritable bowel syndrome: is the association already established? *Biology,* 10:340. https://doi.org:10.3390/biology10040340
20. **Olyaiee A, Sadeghi A, Yadegar A, Mirsamadi ES and Mirjalali H. (2022).** Gut Microbiota Shifting in Irritable Bowel Syndrome: The Mysterious Role of *Blastocystis* sp. *Front Med,* 9: 890127. https://doi.org/10.3389/fmed.2022.890127
21. **Yakoob J, Jafri W, Jafri N, Khan R, Islam M, Beg MA and Zaman V. (2004).** Irritable bowel syndrome: in search of an etiology: role of *Blastocystis* hominis. *Am J Trop Med Hyg,* 70: 383-385. https://doi.org/10.4269/ajtmh.2004.70.383
22. **Krogsgaard LR, Engsbro AL, Stensvold CR, Nielsen HV, Bytzer P. (2015).** The prevalence of intestinal parasites is not greater among individuals with irritable bowel syndrome: a population-based case-control study. *Clin Gastroenterol Hepatol,*13:507-13. https://doi.org:10.1016/j.cgh.2014.07.065
23. **Khademvatan S, Masjedizadeh R, Rahim F, Mahbodfar H, Salehi R, Yousefi-Razin E, *et al.* (2017).** *Blastocystis* and irritable bowel syndrome: frequency and subtypes from Iranian patients. *Parasitol Int,* 66:142-5. https://doi.org:10.1016/j.parint.2017.01.005
24. **Poirier P, Wawrzyniak I, Vivare`s CP, Delbac F and El Alaoui H. (2012).** New insights into *Blastocystis* spp.: a potential link with irritable bowel syndrome. *PLoS Pathog,* 8: e1002545. https://doi.org/10.1371/journal.ppat.1002545
25. **Stark D, van Hal S, Marriott D, Ellis J, & Harkness J. (2007)**. Irritable bowel syndrome: A review on the role of intestinal protozoa and the importance of their detection and diagnosis. *Int J Parasitol.*, 37(1):11-20. https://doi.org/10.1016/j.parint.2016.05.015

26. **Karamati SA, Mirjalali H, Niyyati M, Yadegar A, Asadzadeh Aghdaei H, Haghighi A, *et al.* (2021).** Association of *Blastocystis* ST6 with higher protease activity among symptomatic subjects. *BMC Microbiol,* 21: 285. https://doi.org/10.1186/s12866-021-02341-9
27. **Mirza H, Wu Z, Teo J and Tan K. (2012).** Statin pleiotropy prevents rho kinase-mediated intestinal epithelial barrier compromise induced by *Blastocystis* cysteine proteases. *Cell Microbiol,* 14: 1474-1484. https://doi.org/10.1111/j.1462-5822.2012.01814.x
28. **Mohammad Rahimi RH, Yadegar A, Asadzadeh AH, Mirjalali H and Zali MR. (2022).** Modulation of microRNAs and claudin-7 in Caco-2 cell line treated with *Blastocystis* sp., subtype 3 soluble total antigen. *BMC Microbiol,* 22: 111. https://doi.org/10.1186/s12866-022-02528-8
29. **Kozieł MJ, Ziaja M and Piastowska-Ciesielska AW. (2021).** Intestinal barrier, claudins and mycotoxins. *Toxins,* 13: 758. https://doi.org/10.3390/toxins13110758
30. **Olivo-Diaz A, Romero-Valdovinos M, Gudino-Ramirez A, Reyes-Gordillo J, Jimenez-Gonzalez DE, Ramirez-Miranda ME, *et al.* (2012).** Findings related to IL-8 and IL-10 gene polymorphisms in a Mexican patient population with irritable bowel syndrome infected with *Blastocystis*. *Parasitol Res*, 111: 487-491. https://doi.org/10.1007/s00436-012-2830-0
31. **Xiao QY, Fang XC, Li XQ and Fei GJ. (2020).** Ethnic differences in genetic polymorphism associated with irritable bowel syndrome. *World J Gastroenterol,* 26: 2049-2063. https://doi.org/10.3748/wjg.v26.i17.2049
32. **Ismail MH, Molan AL and Abbas SK, (2022).** Serological levels of cytokines in irritable bowel syndrome (IBS) patients and non-IBS subjects with and without *Blastocystis* spp. infection. *Annal Parasitol,* 68: 77-85. https://doi.org/10.17420/ap6801.411
33. **Yason JA, Liang YR, Png CW, Zhang Y and Tan KSW. (2019).** Interactions between a pathogenic *Blastocystis* subtype and gut microbiota: *in vitro* and *in vivo* studies. *Microbiome,* 7: 30. https://doi.org/10.1186/s40168-019-0644-3