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Review Article

The role of *Blastocystis* sp. as an etiology of irritable bowel syndrome

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ABSTRACT

Introduction: *Blastocystis* is a common intestinal protozoan of humans and animals. The role of this organism as a pathogen is still controversial. The *Blastocystis* infection could be asymptomatic or could include nausea, anorexia, abdominal pain, flatulence, and/or diarrhea. An association between *Blastocystis* infection and acute chronic digestive disorders such as irritable bowel syndrome (IBS) have also been suggested.

Aim: In this article, the evidence concerning *Blastocystis* infection causing IBS will be discussed, with regard to the subtypes of the parasite.

Discussion: An association between the parasite and IBS has been suggested in the recent literature. The explanations of pathogenicity include an intra-subtype difference (ST4 and ST7) with regard to protease activity during infection with *Blastocystis*.

Conclusions: It is most likely that the presence of *Blastocystis* in the human intestine plays a significant role in IBS. On the other hand, it is still not known if *Blastocystis* is the etiological agent responsible for this type of gut dysfunction. There are many reports in the literature which are mutually exclusive. More studies are needed to confirm this hypothesis.

1. Introduction

1.1. *The prevalence and classification of* Blastocystis

Blastocystis is an unusual unicellular enteric protozoan parasite present in humans throughout the world.[1] In a healthy population, the prevalence has been reported to be between 30%–50% and 1.5%–10.0%, in developing and developed countries, respectively.[2] People in the age range of 30–50 years are mostly infected by *Blastocystis*.[3–5] In immune-compromised individuals, the prevalence of *Blastocystis* is about 30%–40% in developed countries.[6–8]

Originally, the parasite was considered to be an innocuous yeast until the 1970s when evidence was presented that *Blastocystis* is actually a protozoan. Based on molecular studies, the parasite has been placed within an informal group known as ''Stramenopiles.''[9] The taxonomy of the species is still unresolved. Until recently, it was based on the host from which it was isolated (i.e. *Blastocystis hominis* from humans,

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Blastocystis ratti from rats). Modern phylogenic studies have noticed human to animal, and animal to human transmission; therefore, it has been proposed to summarize the assorted names into one ''*Blastocystis* species.''[10,11]

Based on small subunit rDNA (SSU rDNA) analysis, at least 17 subtypes (STs) of *Blastocystis* were detected, which colonize a wide range of hosts including humans, other mammals, birds, reptiles, and insects.[12,13] Humans are colonized mainly by ST1 to ST4 (named *B. hominis*). However, this is dependent on regions and countries, and infection by ST5 to ST9 is also observed.[14–16] Till date ST10 to ST17 have not been found in humans.[15]

1.2. *The life cycle and pathogenicity of* Blastocystis

The life cycle and transmission of *Blastocystis* is still under investigation. There are two types of life cycles described, sexual by autogamy to form primary cysts and asexual by binary fission.[7] The cysts are the only transmissible forms of *Blastocystis* and are transmitted by the fecal-oral route, where the thick-walled parasite is the resistant form, responsible for external transmission, and the thin-walled cyst is responsible for autoinfection.[10] The cysts infect epithelial cells and develop into the vacuolar form, then further to multivacuolar or amoeboid form, which plays a more active role in the development of clinical manifestations. *Blastocystis* exhibits a strong tropism to the intestine and is a strict anaerobe. It is a common inhabitant of the human gastrointestinal tract.[17]

The pathogenic potential of *Blastocystis* is still controversial.[18,19] For many years it has been suggested that *Blastocystis* is a commensal organism of the human intestine.[10] Recent epidemiological data demonstrate the association of *Blastocystis* with a variety of disorders, including diarrhea, abdominal pain, fatigue, constipation, flatulence, and irritable bowel syndrome (IBS),[1] as well as extra-intestinal manifestations such as skin rash or urticaria.[20] However, *Blastocystis* has been found both in patients with gastrointestinal symptoms and asymptomatic individuals.[8,21]

2. Aim

In this article the direct and indirect evidence of *Blastocystis* infection in causing IBS will be discussed, with regard to the subtypes and the protease activity of the parasite.

3. Discussion

3.1. *Irritable bowel syndrome (IBS)*

IBS is a chronic disorder of the gastrointestinal tract manifesting with complex symptoms of abdominal pain associated with constipation or diarrhea, or both, and bloating with irregular defecation.[21–23] Physicians diagnose IBS by using symptom-based criteria known as Rome criteria (developed in 1988).[22] The prevalence of IBS is between 5%–24% and 35%–43% in developed and developing countries, respectively.[24,25] It is suggested that the prevalence of IBS is highest in women, since the female gender is a frequently reported risk factor for developing post-infected IBS (PI-IBS),[26] as well as in children and the elderly.[27]

The pathophysiology of IBS remains elusive. There are most likely several interconnected factors which occur in patients that account for the clinical symptoms of IBS such as altered gut reactivity in response to luminal or psychological stimuli, visceral afferent hypersensitivity and a hypersensitive gut with enhanced visceral perception and pain.[23] In addition, hereditary, environmental and dietary factors, emotional stress, abdominal surgery, food intolerance and enteric infections may also play a significant role.[21] Recent studies have described a possible role of protozoan parasites such as *Blastocystis* sp., *Giardia intestinalis*, *Dientamoeba fragilis*, and *Entamoeba histolytica* in the etiology of IBS.[19,23,24,28] In some studies *Blastocystis* was detected more frequently in patients with IBS (38%–46%) than in the control group (7%–11%),[19] whereas in other studies there was no association between the occurrence of *Blastocystis* and IBS.[29–32]

3.2. *Genetic diversity of* Blastocystis *in connection with IBS*

In the recent literature, the pathogenic potential of *Blastocystis* in humans has focused on subtyping.[22] Consequently, Kaneda et al.[33] indicated that ST1, ST2 and ST4 may be responsible for gastrointestinal symptoms. Yan et al.[34] presented only ST1 in a group of symptomatic patients, which was later confirmed by Hussein et al.[35] and El Safadi et al.[28] demonstrating that ST1 was associated with an elevated pathogenicity. Also, the pathogenicity of ST4 was hypothesized by Stensvold et al.[36] Some authors speculated that certain subtypes (e.g. ST3) might contribute to the pathogenic potential of *Blastocystis* only when the amoeboid form is present.[34] Poirier et al.[24] suggested that ST7 is correlated with IBS. Studies on the IBS population showed a higher prevalence of ST1, ST3 and ST4 isolates of *B. hominis*.[11,37,38]

The pathogenicity explanations may include intra-subtype differences in *Blastocystis* protease activity,[39] which has already been reported. The cysteine proteases produced by *Blastocystis* ST4 and ST7[40,41] were shown to be able to cleave human IgA in vitro, and this was suggested as a mechanism for parasite survival and colonization in the gut.[42] Enzymes can also modulate inflammatory IL-8 production[43] and are able to increase the permeability of intestinal epithelial cells.[44]

3.3. *The possible role of* Blastocystis *in the etiopathogenesis of IBS*

Blastocystis is speculated to be a direct or indirect cause of IBS, but variation in its relative presence between case and control groups has led to further confusion.[29,37,45] The proposed mechanism which might play a role in IBS is a low grade inflammation due to ongoing immune activation caused by carrying or being infected with *Blastocystis*, which provides a persistent antigenic exposure.[23,46] Hussain et al.[47] showed that IgG antibody levels to *Blastocystis* in patients with IBS were significantly higher compared with asymptomatic controls. Udkow and Markell[31] have speculated that the increased incidence of *Blastocystis* is rather an indicator of intestinal dysfunction and is not a cause of IBS.

Puthia et al.[43] studies have shown that in rat epithelial cells, *Blastocystis* ST4 can induce apoptosis in a contact-independent manner, increasing epithelial permeability. *Blastocystis* ST7 is likely to use hydrolases to attack host tissues for its nutrient supply.[24] The parasite may participate in this process by degrading host glycoproteins that constitute the mucus and can use them as a carbohydrate and protein source to survive within the intestinal environment. In addition, cysteine and serine proteases could also degrade mucins.[24,40,41] They are known to be involved in paracellular permeability, inflammation and hypersensitivity.[48] The impairment of the mucus may initiate an inflammatory and allergic response caused by chronic exposure to luminal antigens. Then, the proteases from *Blastocystis* and gut bacteria could also target receptors at the intestinal cell surface: protease-activated receptor type 2 (PAR-2) inducing inflammation and tight junctions disruption are frequently seen in IBS and are responsible for hypersensitivity in IBS patients.[48]

4. Conclusion

Blastocystis affects both immunocompetent and immunocompromised individuals. The non-specific symptoms of *Blastocystis* infection are IBS-like which include diarrhea or constipation, abdominal pain, and nausea. IBS is a functional gastrointestinal disorder and gut inflammation is one of the many proposed mechanisms of pathogenesis. Intestinal barrier function disturbances may contribute to the diarrhea observed in *Blastocystis* patients. Moreover, *Blastocystis* has the ability to produce a cysteine protease that breaks up IgA antibody allowing colonization of *Blastocystis* in the human gut. The role of this parasite as an etiological agent of IBS is inconclusive due to the controversial nature of *Blastocystis* as a human pathogen. On the other hand, it is possible that there is a subgroup of *Blastocystis* that could be pathogenic in some patients (ST4 and ST7 produce proteolytic enzymes). There are many reports in the literature which are mutually exclusive. More studies are needed to confirm this hypothesis.

Conflict of interest

None declared.

REFERENCES

1. Tan KS. New insights on classification, identification and clinical relevance of *Blastocystis* spp. *Clin Microbiol Rev*. 2008;21(4):639–665.
2. Bálint A, Dóczi I, Bereczki L, et al. Do not forget the stool examination!-cutaneous and gastrointestinal manifestations of *Blastocystis* sp. infection. *Parasitol Res*. 2014;113(4):1585–1590.
3. Doyle PW, Helgason MM, Mathias RG, Proctor EM. Epidemiology and pathogenicity of *Blastocystis hominis*. *J Clin Microbiol*. 1990;28(1):116–121.
4. Lu CTL, Sung YJ. Epidemiology of *Blastocystis hominis* and other intestinal parasites among the immigrant population in northeastern Taiwan by routine physical examination for resistance approval. *J Microbiol Immunol Infect*. 2009;42(6):505–509.
5. Zaglool DAM, Khodari YAW, Farooq MU. *Blastocystis hominis* and allergic skin diseases; a single centre experience. *J Health Sci*. 2012;2(1):66–69.
6. Sanchez-Aguillon F, Lopez-Escamilla E, Velez-Perez F, et al. Parasitic infections in a Mexican HIV/AIDS cohort. *J Infect Dev Ctries*. 2013;7(10):763–766.
7. Basak S, Rajurkar MN, Mallick SK. Detection of *Blastocystis hominis*: a controversial human pathogen. *Parasitol Res*. 2014;113(1):261–265.
8. Roberts T, Stark D, Harkness J, Ellis J. Update on the pathogenic potential and treatment options for *Blastocystis* sp.. *Gut Pathogens*. 2012;6:17–25.
9. Silberman JD, Sogin ML, Leipe DD, Clark CG. Human parasite finds taxonomic home. *Nature*. 1996;380(6573):398.
10. Parija SC, Jeremiah SS. *Blastocystis*: taxonomy, biology and virulence. *Trop Parasitol*. 2013;3(1):17–25.
11. Lee LI, Chye TT, Karmacharya BM, Govind SK. *Blastocystis* sp.: waterborne zoonotic organism, a possibility? *Parasites Vectors*. 2012;5:130–134.
12. Alfellani MA, Taner-Mulla D, Jacob AS, et al. Genetic diversity of *Blastocystis* in Livestock and Zoo animals. *Protist*. 2013;164(4):497–509.
13. Stensvold CR, Alfellani M, Clark CG. Levels of genetic diversity vary dramatically between *Blastocystis* subtypes. *Infect Genet Evol*. 2012;12(2):263–273.
14. Alfellani MA, Stensvold CR, Vidal-Lapiedra A, Onuoha ES, Faqbenro-Beyioku AF, Clark CG. Variable geographic distribution of *Blastocystis* subtypes and its potential implications. *Acta Trop*. 2013;126(1):11–18.
15. Stensvold CR, Suresh GK, Tan KS, et al. Terminology for *Blastocystis* subtypes – a consensus. *Trends Parasitol*. 2007;23(3):93–96.
16. Scicluna SM, Tawari B, Clark CG. DNA barcoding of *Blastocystis*. *Protist*. 2006;157(1):77–85.
17. Fayer R, Elsasser T, Gould R, Solano G, Urban Jr J, Santin M. *Blastocystis* tropism in the pig intestine. *Parasitol Res*. 2014;113(4):1465–1472.
18. Moosavi A, Haghighi A, Mojarad EN, et al. Genetic variability of *Blastocystis* sp. isolated from symptomatic and asymptomatic individuals in Iran. *Parasitol Res*. 2012;111(6):2311–2315.
19. Yakoob J, Jafri W, Jafri N, et al. Irritable bowel syndrome: in search of an etiology: role of *Blastocystis hominis*. *Am J Trop Med Hyg*. 2004;70(4):383–385.
20. Katsarou-Katsari A, Vassalos CM, Tzanetou K, Spanakos G, Papadopoulou C, Vakalis N. Acute urticaria associated with amoeboid forms of *Blastocystis* sp. subtype 3. *Acta Derm Venereol*. 2007;88(1):80–81.
21. Giacometti A, Cirioni O, Fiorentini A, Fortuna M, Scalise G. Irritable bowel syndrome in patients with *Blastocystis hominis* infection. *Eur J Clinl Microbiol Infect Dis*. 1999;18(6):436–439.
22. Fouad SA, Basyoni MMA, Fahmy RA, Kobaisi MH. The pathogenic role of different *Blastocystis hominis* genotypes isolated from patients with irritable bowel syndrome. *Arab J Gastroenterol*. 2011;12(4):194–200.
23. Stark D, van Hal S, Marriott D, Ellis J, Harkness J. Irritable bowel syndrome: a review on the role of intestinal protozoa and the importance of their detection and diagnosis. *Int J Parasitol*. 2007;37(1):11–20.
24. Poirier P, Wawrzyniak I, Vivarès CP, Delbac F, El Alaoui H. New insights into *Blastocystis* spp.: a potential link with irritable bowel syndrome. *PLoS Pathog*. 2012;8(3):e1002545.
25. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480–1491.

26. Spiller R, Garsed K. Infection, inflammation, and the irritable bowel syndrome. *Dig Liver Dis*. 2009;41(12):844–849.
27. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut*. 1999;45:1160–1168.
28. El Safadi D, Meloni D, Poirier P, et al. Molecular epidemiology of *Blastocystis* in Lebanon and correlation between subtype 1 and gastrointestinal symptoms. *Am J Trop Med Hyg*. 2013;88 (6):1203–1206.
29. Scanlan PD. *Blastocystis*: past pitfalls and future perspectives. *Trends Parasitol*. 2012;28(8):327–334.
30. Dogruman-Al F, Simsek Z, Boorom K, et al. Comparison of methods for detection of *Blastocystis* infection in routinely submitted stool samples, and also in IBS/IBD patients in Ankara, Turkey. *PLoS ONE*. 2010;5(11):e15484. http://dx.doi.org/10.1371/journal.pone.0015484.
31. Udkow MP, Markell EK. *Blastocystis hominis*: prevalence in asymptomatic versus symptomatic hosts. *J Infect Dis*. 1993;168(1):242–244.
32. Cekin AH, Cekin Y, Adakan Y, Tasdemir E, Koclar F, Yolcular B. Blastocystosis in patients with gastrointestinal symptoms: a case-control study. *BMC Gastroenterol*. 2012;12:122–127.
33. Kaneda Y, Horiki N, Cheng XJ, Fujita Y, Maruyama M, Tachibana H. Ribodemes of *Blastocystis hominis* isolated in Japan. *Am J Trop Med Hyg*. 2001;65(4):393–396.
34. Yan Y, Su S, Lai R, et al. Genetic variability of *Blastocystis hominis* isolates in China. *Parasitol Res*. 2006;99(5):597–601.
35. Hussein EM, Hussein AM, Eida MM, Atwa MM. Pathophysiological variability of different genotypes of human *Blastocystis hominis* Egyptian isolates in experimentally infected rats. *Parasitol Res*. 2008;102(5): 853–860.
36. Stensvold CR, Christiansen DB, Olsen KE, Nielsen HV. *Blastocystis* sp. subtype 4 is common in Danish *Blastocystis*-positive patients presenting with acute diarrhea. *Am J Trop Med Hyg*. 2011;84(6):883–885.
37. Yakoob J, Jafri W, Beg MA, et al. Irritable bowel syndrome: is it associated with genotypes of *Blastocystis hominis*. *Parasitol Res*. 2010;106(5):1033–1038.
38. Wawrzyniak I, Poirier P, Viscogliosi E, et al. *Blastocystis*, an unrecognized parasite: an overview of pathogenesis and diagnosis. *Ther Adv Infect Dis*. 2013;167–178. http://dx.doi.org/10.1177/2049936113504754.
39. Abdel-Hameed DM, Hassanin OM. Protease activity of *Blastocystis hominis* subtype 3 in symptomatic and asymptomatic patients. *Parasitol Res*. 2011;109(2):321–327.
40. Mirza H, Tan KSW. *Blastocystis* exhibits inter- and intra-subtype variation in cysteine protease activity. *Parasitol Res*. 2009;104(2):355–361.
41. Sio SWS, Puthia MK, Lee ASY, Lu J, Tan KS. Protease activity of *Blastocystis hominis*. *Parasitol Res*. 2006;99(2):126–130.
42. Puthia MK, Vaithilingam A, Lu J, Tan KS. Degradation of human secretory immunoglobulin A by *Blastocystis*. *Parasitol Res*. 2005;97(5):386–389.
43. Puthia MK, Lu J, Tan KS. *Blastocystis ratti* contains cysteine proteases that mediate interleukin-8 response from human intestinal epithelial cells In an NF-kappaB-dependent manner. *Eukaryotic cell*. 2008;7(3):435–443.
44. Wawrzyniak I, Texier C, Poirier P, et al. Characterization of two cysteine proteases secrete by *Blastocystis* ST7, a human intestinal parasite. *Parasitol Int*. 2012;61(3):437–442.
45. Boorom KF, Smith H, Nimri L, et al. Oh my aching gut: irritable bowel syndrome, *Blastocystis*, and asymptomatic infection. *Parasit Vectors*. 2008;1:40–55.
46. Coyle C, Varughese J, Weiss L, Tanowitz H. *Blastocystis*: to treat or not to treat. *Clin Infect Dis*. 2012;54(1):105–110.
47. Hussain R, Jaferi W, Zuberi S, et al. Significantly increased IgG2 subclass antibody levels to *Blastocystis hominis* to patients with irritable bowel syndrome. *Am J Trop Med Hyg*. 1997;56(3):301–306.
48. Streck N, Mueller K, Schemann M, Haller D. Bacterial proteases in IBD and IBS. *Gut*. 2012;61(11):1610–1618.