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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.