ChronoBiology LETTER

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Articles in this edition

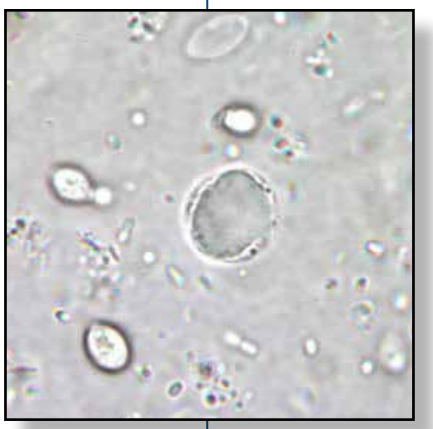
1 Blastocystis: *A Question of Pathogenicity*
3 *Diagnos-Techs Introduces—*
Matthew Stoner, PhD
Scott Buesing, ND
4 *The Therapy Corner: The Anxiety-Depression Spectrum*

GASTROINTESTINAL HEALTH PANEL

Blastocystis: A Question of Pathogenicity

Carrie C. McMillin, ND

With our growing knowledge of the intricacies of the gut microbiome, we are often faced with difficult questions regarding the clinical implications of this knowledge. Recent improvements in diagnostic methods allow us to more accurately identify which microbes are present; however, as clinicians we need to make the decision to treat or not to treat—a decision that is not always straightforward. Many organisms are not clearly classified as pathogenic or nonpathogenic, resulting in confusion around their clinical significance. One such group of organisms that has been widely disputed is *Blastocystis* spp. There has been considerable discussion regarding its status as a true pathogen and the legitimacy of a disease (blastocystosis) caused by this organism. A review of current literature, however, shows that accumulating evidence strongly suggests that *Blastocystis* is a potentially pathogenic organism.



***Blastocystis* cysts.** **www.cdc.gov/dpdx**

There are several confounding factors that make it difficult to clearly categorize *Blastocystis*. First of all, humans are host to many different genotypes of *Blastocystis*. The existence of various genotypes may be the reason for conflicting data,[1-3] as it is possible that only some isotypes are pathogenic.[4] In addition, it is difficult to differentiate among *Blastocystis* isotypes based on morphology. As a result, some studies have employed the use of polymerase chain reaction (PCR) testing to distinguish between various genotypes. In one of the most extensive studies conducted, it was found that among these genotypes, *Blastocystis* can be grouped into seven distinct subtypes,[5,6] although some sources propose more. It has also been shown that transmission can occur between animals and humans, illustrating that animals can serve as a large potential reservoir for human infections.[1]

Historically, there has also been much debate regarding the taxonomic classification of *Blastocystis*. Since its discovery, it has been classified as the cyst of a flagellate, vegetable, yeast, and fungus, only recently having been reclassified as a protist. Today *Blastocystis* is included as a stramenopile, a class of botanical protists such as brown algae that possess flagella with mastigonemes

Continued on page 2.

Blastocystis
continued from front cover.

(hair-like structures projecting from the flagellum). *Blastocystis*, however, is nonmotile and does not possess flagella. A new class for *Blastocystis* was therefore created—*Blastocystea*.[1,7]

As mentioned earlier, the various *Blastocystis* subtypes can be transmitted between animals and humans in addition to human-human transmission. This makes it difficult to assign *Blastocystis* species according to the host of origin. In fact, this may be one reason for conflicting reports regarding cell variations and pathogenesis in the past. It has been noted in epidemiological studies that subtype 3 is the most frequently isolated. As such, it is widely believed that this is the most likely genotype of human origin, formerly designated as *B. hominis*.[8-11] Because humans can be infected by numerous *Blastocystis* subtypes, and the various subtypes are indistinguishable from each other via microscopy, it is now recommended that laboratories report the presence of *Blastocystis* spp. instead of *Blastocystis hominis*. (Note: This is a change that you will soon see in the Diagnos-Techs microscopy reports.)

Although it can be found worldwide,[12,13] *Blastocystis* has a higher prevalence rate in developing countries. This has been linked to poor hygiene, contaminated food and water consumption, and exposure to animals.[14] Recent studies point to the classification of *Blastocystis* as pathogenic or opportunistic, concluding that it may be associated with a variety of disorders. It has also been suggested that immunocompromised patients are at greater risk for *Blastocystis*-associated disorders.[1,15-18]

Interestingly, several surveys have reported that *Blastocystis* was more frequently isolated in immunocompetent individuals suffering from intestinal disorders than similar patients without GI symptoms.[19-23] Another survey pointed out an increased prevalence of *Blastocystis* isolation in atopic patients.[24]

More recent research has focused on investigating whether the biology and pathogenicity of *Blastocystis* is related to genotype. Unfortunately, no conclusive data has been found. It has, however, been suggested that subtype 1 is associated with disease, while subtypes 2 and 3 appear to be nonpathogenic,[1] although more research is needed.

There is accumulating evidence of an association between* Blastocystis *and irritable bowel syndrome (IBS).

Blastocystis-associated illness is most commonly associated with abdominal pain and acute or chronic diarrhea, although it has also been linked to nausea, vomiting, bloating, flatulence, and anorexia.[1,25] Diagnosis is made by microscopic stool examination (O&P testing), ideally conducted on fecal samples from three separate days.[26] There is some evidence that the acute GI presentations are associated with an increased infection density, most commonly greater than five parasites per high power field.[1,16,19] Other signs and symptoms include eosinophilia,[27] fecal leukocytes,[28] and cutaneous rashes (with urticaria being most notable).[29] In general, *Blastocystis* is non-invasive,[30] with extraintestinal infections being a rare occurrence and only then when mediated by another pathogen. It has also been noted that mixed infections with *Blastocystis* and *Entamoeba histolytica* are not uncommon.[31] There is accumulating evidence of an association between *Blastocystis* and irritable bowel syndrome (IBS). Specifically, some studies have shown an increased prevalence of *Blastocystis* in patients with IBS compared to IBS-negative patients with GI symptoms.[32,33] It is not yet clear whether *Blastocystis* can be considered an etiological agent of IBS or IBS simply creates an environment in which *Blastocystis* can thrive.[34]

As with many other organisms, clinical outcomes of the presence of *Blastocystis* vary considerably based on numerous factors, making it is difficult to predict its pathogenic potential. Some studies have shown that treatment with metronidazole,[35] nitazoxanide,[36] and trimethoprim-sulfamethoxazole (TMP-SMX)[37] has resulted in eradication of the organism and resolution of GI symptoms. However, these drugs are all broad-spectrum antibiotics; therefore, it is difficult to ascertain if clinical cure was instead the result of treatment and eradication of a separate and unidentified pathogenic organism.

Some herbs that have been found to reduce or inhibit growth of *Blastocystis* spp. include *Coptis chinensis*, *Brucea javanica*, *Punica granatum*, *Picrorhiza scrophulariiflora*, and *Allium sativum*.[38-42] In one study, children treated with *Saccharomyces cerevisiae* had a higher cure rate than

those receiving metronidazole.[43] It has also been suggested that a high fiber, low lactose diet may be an important component to a *Blastocystis* treatment plan.

Despite considerable gaps in our understanding of this organism, it is worth noting that there are no studies to date that prove unequivocally that *Blastocystis* is nonpathogenic, and there is accumulating evidence around its pathogenic potential. Treatment should be considered for both acute and chronic cases in the presence of associated symptoms, appropriate clinical context, and the absence of other causative pathologies.

For references, please see Newsletter section of website (www.diagnostechs.com).

Upcoming Free Webinars:

April 10th, 2014 –
Clinical Update - Inflammatory Bowel Disease

May 15th, 2014 –
Clinical Update - Celiac Disease

Please visit **www.diagnostechs.com** for more information about our free webinars.

Diagnos-Techs Introduces—

Matthew Stoner, PhD

Director of Research and Development

Dr. Stoner completed his PhD in Toxicology at Texas A&M University, where he studied estrogen receptor-modulated gene expression in breast cancer and endometrial cancer. He subsequently completed postdoctoral training in Molecular Toxicology at the Pennsylvania State University. Dr. Stoner then was appointed Research Assistant Professor in the College of Pharmacy at the University of Rhode Island, where he established a research laboratory supported by the Rhode Island IDeA Network of Biomedical Research Excellence. Additionally, while at the University of Rhode Island, he lectured in the areas of endocrinology and laboratory techniques in molecular biology and trained and mentored junior scientists. Most recently, Dr. Stoner was Senior Research Scientist at CertiChem, Inc., where he optimized sensitive bioassays for the detection of endocrine-active chemicals that leach from consumer products. He has more than 20 peer-reviewed publications in journals that cover diverse areas of cell and molecular biology and toxicology. As the Director of Research and Development at Diagnos-Techs, Dr. Stoner investigates and incorporates into production new technologies and methodologies to expand our clinical diagnostic test offerings.

Scott Buesing, ND

Medical Support

After receiving a Bachelor's degree in Electrical Engineering from Iowa State University, Dr. Buesing went on to acquire a Doctorate in Naturopathic Medicine from Bastyr University in 2004. While in school, Dr. Buesing received an NIH research training grant to study the in-vitro effects of an alternative cancer treatment from the 1930s. Upon graduation, he collaborated on several research studies at Bastyr University including benefits of creatine and diets high in legumes. In 2008, after several years in private practice, he joined a multidisciplinary team in a partial hospitalization program for patients suffering with mental health conditions, focusing on integrative treatment. Dr. Buesing utilized treatments including dietary and lifestyle changes, oral and intravenous nutrient therapies, botanical medicine, biofeedback, mind-body techniques, and meditation. While in practice, he taught patient-oriented classes in meditation and nutrition. In addition to clinical practice, Dr. Buesing has worked as a consultant, providing synopses of current medical research on numerous health topics including vitamin D and healthy dietary strategies.

The Therapy Corner

The Anxiety-Depression Spectrum

Brandy Webb, ND

Anxiety disorders make up the largest category of psychiatric conditions in the United States, with depressive mood disorders following second (with lifetime prevalence rates of 28% and 16%, respectively).[1] A growing number of patients present to the doctor's office in search of treatment for generalized anxiety as they discover they are unable to manage the incessant worry, insomnia, and accompanying physical symptoms they experience on a near-daily basis. Individuals with known psychiatric disorders are not the only ones affected—one in three individuals will suffer a panic attack at some point in his or her lifetime.[2] Depressive symptoms may be less common, but they are no less pernicious to a patient's quality of life; this is particularly true of the persistent thoughts of worthlessness, apathy, and debilitating fatigue. What's more, over 70% of individuals with either anxiety or depression meet the diagnostic criteria for both conditions; thus, it is very likely that you will encounter patients suffering from anxiety and depression simultaneously.[3]

Clinical Features & Diagnosis

Generalized anxiety disorder (GAD), the most common anxiety disorder, is characterized by excessive worrying that causes significant impairment and occurs on more days than not for at least six months. When screening for GAD, the single best question to ask is, "Do you worry excessively about minor matters?" The World Health Organization's ICD-10 description calls this "free-floating" anxiety. Generalized anxiety disorder is diagnosed through careful psychiatric assessment and only after other psychiatric conditions (such as ADHD, depression, and bipolar disorder) and organic diseases have been ruled out. The psychiatric evaluation should include questions about possible substance abuse, personal history of trauma (emotional, physical, or sexual), and family psychiatric history. Anxiety symptoms can be related to underlying conditions like thyroid disease, anemia, and cardiac conditions. In patients with clinical features that may suggest these or other organic diseases, the minimum work-up should include a physical exam as well as a CBC, chemistry panel, thyroid panel, circadian cortisol assessment (such as the TAP or ASI available through Diagnos-Techs), and ECG. If drug abuse is suspected, toxicology testing should be performed as well. Additional factors to consider include caffeine intake, nicotine use, and prescription medications.

While there may be some overlap with anxiety, patients experiencing depressive disorders primarily suffer from hopelessness, depressed mood, and apathy toward activities that previously brought joy. The hallmark for depression is that these symptoms last a minimum of 2-4 weeks and cause significant distress to the patient. As with anxiety, depressed patients should receive psychiatric screening, a medication review, and laboratory testing to rule out organic disease (CBC, ferritin, chemistry panel, circadian cortisol assessment, thyroid panel, inflammatory markers, and infectious disease testing are all worth considering). Zinc and folate status should be considered in patients presenting with depression or anxiety, as well, due to an apparent association between deficiency in zinc or folate and the development of mood disorders.[4]

Once alternative psychiatric diseases and organic diseases are ruled out, treatment targeting the anxiety or depression (or both) may be pursued.

Conventional Treatment

Cognitive behavioral therapy (CBT) and pharmacologic agents are the mainstays of treating anxiety and depression conventionally. Cognitive behavioral therapy is best facilitated by well-trained professionals, usually a certified mental health counselor or psychiatrist, although many primary care and holistic practitioners incorporate some degree of CBT into their practices. This type of therapy involves a combination of identifying and modifying destructive thought patterns, emotions, and behaviors that contribute to specific psychiatric states like anxiety or depression. Therapists play an active role guiding patients through self-reflection and cognitive/behavioral exercises that attempt to change certain automatic processes that predispose to anxiety or depression. For example, a cognitive behavioral therapist might help an anxious patient prone to

irrational fears recognize that when she feels her heart beating hard in her chest, she should refrain from concluding that she is having a heart attack. Cognitive behavioral therapy has demonstrated reduced relapse rates after a course of treatment compared to drug therapy.[5,6] Nonetheless, for a variety of reasons, many patients are managed with drug interventions.

The choice of pharmacotherapy depends on the particular presenting complaints and the severity of symptoms. The drug therapies employed for moderate-to-severe anxiety and depression are generally the same. For mild depression or anxiety, drug therapy is typically not recommended (instead, cognitive behavioral therapy is considered the best conventional approach). For moderate anxiety or depression, CBT and drug therapy are often recommended concomitantly. A psychiatric referral is common at this stage, since these practitioners can facilitate both pharmacotherapy and cognitive behavioral therapy. Initial drug therapy usually involves selective serotonin reuptake inhibitors (SSRIs). This class contains drugs like escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). The comparative efficacy of the various SSRIs has been shown to be about the same, although it is worth noting that neither fluoxetine nor sertraline is approved for generalized anxiety disorder (though both are approved for other anxiety disorders and are frequently prescribed for the off-label treatment of GAD).[7] Thus, choosing which SSRI to use should be guided by factors such as other medications the patient may be taking (due to risk of known interactions), cost, and potential side effects. For example, escitalopram is less associated with sexual dysfunction compared to other SSRIs, paroxetine is associated with more weight gain compared to other SSRIs, and fluoxetine and sertraline are more associated with sleep disturbances compared to other SSRIs.[8] Sample adult SSRI initial dosing regimens include the following (for pediatric dosing, please see manufacturer recommendations for each drug):[7]

- Escitalopram (Lexapro) 10mg QD, or
- Paroxetine (Paxil) 20mg QD, or
- Sertraline (Zoloft) 50mg QD

Other classes of psychotropics that are frequently used for initial treatment include serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, atypical antidepressants, and benzodiazepines. Alternatives like tricyclic antidepressants, monoamine oxidase inhibitors, and antipsychotics are generally not used for initial treatment due to potential side effects and safety concerns. If initial SSRI treatment fails, first switch to a different SSRI. If the patient still does not respond, consider the following:[7]

- Duloxetine (Cymbalta) 30mg QD, or
- Buproprion (Wellbutrin) 150mg QD (for use in depression but not anxiety)
- L-methylfolate (Deplin) 7.5 or 15mg QD (off-label usage as monotherapy or adjunctive therapy)[9]

For some patients, the pharmacologic approach can be effective at reducing their symptoms of anxiety or depression. For others, however, pharmacotherapy proves ineffective or is associated with significant side effects prompting discontinuation. For these patients, natural approaches to mood stabilization may be a viable alternative to drug therapy.

Continued on page 6.

Anxiety-Depression
continued from page 5.

Natural Treatments

Many patients present to holistic practitioners seeking alternatives to drug therapies for a variety of reasons, such as failure to respond, side effects, or concerns for long term safety. Potential treatments include diet and lifestyle modification, breathing exercises, nutrient therapies, and herbal medicine.

Breathing Exercises

One often-overlooked contributor to anxiety is disordered breathing patterns. It is not always clear why patients develop disordered breathing, although chronic stress may be one contributing factor.[10] Patients affected by this condition often develop chronic hyperventilation syndrome, which is characterized by reduced carbon dioxide levels in the blood. Generally, disordered breathing is not evident to the patient or providers, although one clue is frequent sighing or yawning. In some cases, labs reveal low-normal or depressed serum CO_2; however, capnometry (measuring CO_2 in exhaled air) is the best way to definitively diagnose disordered breathing patterns. Along with a feeling of anxiousness, acute hyperventilation episodes can be associated with palpitations, numbness, tingling of the extremities, lightheadedness, dizziness, and what patients might describe as "air hunger". Hyperventilation syndrome is more common in females and often becomes worse premenstrually and during pregnancy.[11] Blood sugar fluctuations may trigger disordered breathing, as well.[12]

One effective way to treat anxiety is by correcting disordered breathing patterns through breathing exercises. There are numerous breathing exercise techniques, one of which is called the Chaitow technique. This technique involves a 2-3 second inhalation through the nose, followed by a 1-second pause, and ending with a 6-7 second exhalation through lightly pursed lips.[10] Patients should work up to 30 cycles (about five minute's worth) and perform a full set in the morning, evening, and at times of acute anxiety.

Check out the archived webinar titled "A Neuroendocrine Approach to Anxiety and Depression".

Dietary Modification

As mentioned, blood sugar fluctuations can trigger disordered breathing, which may predispose to anxiety states. Altered blood sugar metabolism can also play a role in depressive symptoms. A diet comprised primarily of foods with lower glycemic indices, when accompanied by abundant intake of healthy fats, lean protein, and fiber, can lead to improved blood sugar regulation. This can be a key factor in mood stabilization, regardless of where patients fall on the mood spectrum. Often times the challenge is simply getting patients to eat regularly. Reduced appetite is a common symptom in anxiety and depression, and patients may have a tendency to skip meals altogether. Encouraging patients to identify ways to consume consistent, healthful meals can be a simple, effective intervention in treating these conditions.

Exercise

Another lifestyle modification that can support proper mood balance is physical activity. While not all studies agree, there are promising results suggesting that exercise is beneficial for depression and anxiety in sedentary patients.[13,14] In fact, exercise recommendations are incorporated into the formal practice guidelines of numerous medical authorities, including the National Institutes of Health and the American Psychiatric Association. Exercise recommendations vary, but a typical regimen consists of 3-5 sessions per week, each session lasting 45-60 minutes, comprised of both aerobic activity and resistance training. Aerobic activity intensity should fall in the 50-85% of maximum heart rate range, while resistance training should consist of, for each targeted muscle group, three sets of eight reps at 80% maximum weight.[15,16]

Sleep

Anxiety and depression are frequently characterized by sleep disturbances, although it may be difficult to identify clearly which occurred first—the disordered mood or the disordered sleep. Regardless, the association between sleep and mood is well established. Insomnia amplifies the tendency to mistake benign stimuli as threatening, as experienced in anxiety states, and it also can predispose to feelings of hopelessness, as seen in depression.[17,18] One way to address anxiety and depression is to guide your patients toward improved quality and quantity of sleep, while

also ruling out conditions that might interfere with sleep, such as restless leg syndrome or sleep apnea. The ideal sleep pattern for most individuals consists of eight hours of uninterrupted sleep adhering as much as possible to the natural circadian rhythm (10pm-6am).

Nutrient Therapy & Botanical Medicine

One well established, effective nutrient that can be used in the treatment of both anxiety and depression is 5-hydroxytryptophan (5-HTP). This derivative of the amino acid L-tryptophan is a precursor to serotonin and can be useful for increasing central serotonin levels and thus stabilizing mood. Dosing 5-HTP with L-tyrosine, another amino acid, can result in even greater antidepressant effects.[19] It is important to rule out bipolar disorder and suicide ideation, however, as 5-HTP should be avoided in these patients due to evidence of increased suicide attempts when these individuals take 5-HTP.[20] For maximum benefit, 5-HTP should be dosed around 50-100mg TID. Caution is advised when combining with other antidepressants that potentiate serotonin levels (such as SSRIs), as this may result in elevated serotonin levels (a potentially life-threatening condition called serotonin syndrome characterized by blood pressure changes, agitation, and diarrhea).[21]

Piper methysticum (kava) and *Hypericum perforatum* (St. John's wort) are two of the most powerful herbs to treat anxiety and depression, respectively. In fact, although we primarily think of using *Piper methysticum* to treat anxiety, it can be used for depression as well. Compounds in this herb are thought to bind GABA receptors within the amygdala and hippocampus, which is likely responsible for its mood benefits; at the same time, these compounds appear to inhibit calcium channels, providing skeletal and smooth muscle relaxation.[22,23] A typical dosing regimen of *Piper methysticum* for anxiety is 70mg TID of a standardized extract (30% kavalactone content). Current evidence suggests that *Hypericum perforatum* targets depression primarily by acting on GABA and benzodiazepine receptors, although it also affects serotonin, norepinephrine, and dopamine pathways.[24,25] Dosing generally falls within the range of 300mg BID-TID of a standardized extract (0.3% hypericin content). As with 5-HTP, caution should be taken with patients already taking antidepressant drugs, due to the potential for serotonin syndrome with concomitant dosing of *Hypericum perforatum*.[26]

The following is a summary of the potential natural therapies discussed:

- Chaitow breathing exercises 5 minutes BID
- Low glycemic diet with ample healthful fats, protein, and fiber
- Exercise 3-5 times per week, 45-60 minutes per session
- 8 hours uninterrupted sleep (ideally 10pm-6am)
- For anxiety—*Piper methysticum* 70mg TID standardized extract
- For depression—*Hypericum perforatum* 300mg BID-TID standardized extract
- For anxiety or depression—5-Hydroxytryptophan 50-100mg TID (for depression, may use in combination with L-tyrosine up to 500-1000mg QD divided dosing)

For more details on natural treatments, please check out the archived Diagnos-Techs webinar titled "A Neuroendocrine Approach to Anxiety and Depression" from January 2014 located at our website (www.diagnostechs.com). In addition to targeting mood disorders directly, it may be important to identify contributing factors pertaining to adrenal function, GI status, and sex hormone levels. Natural therapies to regulate cortisol output, balance gut microbiota, or optimize sex hormones can be beneficial in patients presenting with anxiety or depression, since symptoms may be exacerbated by these other conditions. Thus, treatment plans for patients presenting with mood disorders may include things like fish oil, anti-inflammatory herbs, liver supportive herbs, B-vitamins, zinc, folate, and magnesium. By approaching anxious or depressed patients from a holistic, systems-based approach, practitioners are ensured the greatest likelihood of clinical success.

For references, please see Newsletter section of website (www.diagnostechs.com).

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