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CASE REPORT

Anorexia Nervosa Caused by Polymicrobial Tick-Borne Infections: A Case Study

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Abstract: The etiology of anorexia nervosa (AN) is multifactorial, and infections may play a contributory and possibly a prominent role. A case is presented which is indicative of a causal association between tick-borne infections and AN. This adolescent female was diagnosed with AN at an eating disorder clinic after excessive food restriction and an irrational fear of weight gain necessitating nasogastric tube feeding. Her history was consistent with systemic infections and she tested serologically positive to *Borrelia burgdorferi, Babesia microti*, and *Mycoplasma pneumoniae*; in addition, her clinical presentation was consistent with a *Bartonella* infection. After treatment with oral and intravenous antimicrobials, she stopped food restriction and no longer had body image concerns. Physicians should be aware of the possibility that tick-borne infections could underly a diagnosis of AN. The role of tick-borne infections in the etiology of AN warrants further study.

Keywords: anorexia nervosa, infection, lyme borreliosis, babesia, mycoplasma, bartonella

Introduction

Anorexia nervosa (AN) is an eating disorder in which patients with an abnormally low body weight have a distorted body image accompanied by an intense fear of gaining weight. People with AN usually severely restrict the quantity of food they eat. They sometimes control calorie intake by vomiting, abusing laxatives, diet aids, diuretics, enemas, or excessive exercise. The fear of weight gain continues regardless of how much weight is lost.

Eating disorders are a major cause of morbidity and mortality. It is estimated that 9% of the world population suffers from an eating disorder[1,2] and 9% of the US population or 28.8 million Americans will have an eating disorder in their lifetime.[3] It is estimated that 26% of people with eating disorders attempt suicide and 10% of people with eating disorders lose their lives as a result of their condition;[4,5] AN has the highest mortality rate of any mental disorder.[4] Eating disorders in children are on the rise—between 1999 and 2006 there was a 119% increase in hospitalizations related to eating disorders in children less than twelve years of age.[6–8]

AN is considered to be a combination of genetic and environmental factors. Family and twin studies as well as molecular genetic analysis suggest an inheritable vulnerability.[9–13] Environmental influences include dysfunctional home circumstances and a history of trauma,[14,15] as well as modern Western culture's emphasis on thinness.[16,17] However, infections may also play a role in the genesis of AN.[18] Favaro et al found an association of in utero exposure to viral infections, both varicella and rubella, with the development of AN in offspring.[19] Raevuori et al

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described an association of AN and other eating disorders with patients who had previously been on antibiotic, antiviral, and antifungal medications,[20] leaving open the question of whether the increase in eating disorders was related to infection, inflammation or pharmaceuticals. Park et al described four patients who experienced the onset of AN following viral infections,[21] and Simon described four young children who developed anorexia due to an Epstein-Barr virus infection.[22] Breithaupt et al studied a nationwide prospective cohort of 525,643 girls in Denmark over 27 years, and correlated the data with hospital admissions for infections and prescribed antimicrobials for infections. They found that hospital treated patients with infections as well as less severe infections treated with antimicrobial agents were associated with an increased risk of AN, bulimia nervosa, and eating disorders that were not otherwise specified.[23]

In 1994, Swedo et al described mental health issues associated with Group A *Streptococcus* (GAS) infection and coined the condition Pediatric Autoimmune Neuropsychiatric Infections Associated with Streptococcal Infections (PANDAS).[24,25] Sokol and Gray described the first cases of AN temporally associated with a GAS infection,[26] and this report was followed by additional case reports of children with PANDAS-like syndromes following GAS infection who developed AN.[27–29] When it became clear that in addition to GAS, multiple microbes could trigger a PANDAS-like syndrome, the syndrome's nomenclature was updated to Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), of which PANDAS is a subset. Criteria were developed at the First PANS Consensus Conference in 2013, and the primary criteria include obsessive-compulsive disorder (OCD) or severely restricted food intake with no known neurological or medical condition that would account for these symptoms.[30]

The identification of PANS as including anorexic pathology has illuminated the role of infection induced autoimmunity in the genesis of some patients with eating disorders. Zerwas et al performed a nationwide, population-based study of all children and adolescents born in Denmark between 1989 and 2006, and managed until 2012. The study population included 930,977 individuals. They found a significantly higher risk of eating disorders in both children and adolescents with autoimmune illness —36% higher risk for AN, 73% for bulimia nervosa, and 72% for unspecified eating disorders.[31] In children and adolescents with PANS, it appears that "an infection can cause a cascade of immunological, psychological, and physical symptoms that can lead to an abrupt restriction and/or avoidance of food."[32]

Molecular mimicry has been proposed in the autoimmune etiology of PANS-like syndromes—antibodies to microbes cross the blood-brain barrier and provoke psychiatric and neurologic symptoms.[33] Early attention implicated autoantibodies against α-melanocyte stimulating hormone (alpha-MSH), which is involved in the regulation of appetite, body weight, behavior, and mood.[34] Elevated levels of autoantibodies to neuronal proteins have been identified in PANS/PANDAS patients including against dopamine receptors,[35–37] lysoganglioside,[38] and tubulin.[39] These autoantibodies have been associated with activation of calcium calmodulin-dependent protein kinase II (CaMKII), a multifunctional enzyme highly concentrated in the brain that mediates many different learning, memory, and developmental cell pathways, as well as altering dopamine transmission that can lead to neuropsychiatric symptoms.[38,40,41]

While anorexia is a common symptom in patients with both acute and chronic infection,[42] a literature search could find only one case report of AN associated with a tick-borne infection, Lyme borreliosis.[43] The patient described in the present case history was diagnosed with multiple tick-borne infections: Lyme borreliosis, babesiosis, mycoplasmosis, and bartonellosis. Neuroborreliosis has been linked to multiple neuropsychiatric syndromes including depression, anxiety disorders, bipolar disorder, anhedonia, addictions, suicide, depersonalization and dissociative episodes.[44–50] Babesiosis has been associated with neuropsychiatric disorders as well, particularly anxiety and depression, although the reports of this association have been in the context of *Babesia* co-infections in patients who also have Lyme disease.[44–47]

Mycoplasma pneumoniae (*M. pneumoniae*) is best known as a respiratory pathogen, but it can also be tick-borne[51] and result in significant systemic inflammation.[52,53] *Mycoplasma* spp. can invade the central nervous system and can trigger autoimmune inflammation in organs throughout the body, including vasculitis, arthritis, meningitis and encephalitis.[54–59] Infection with *M. pneumoniae* can cause neuropsychiatric symptoms including acute psychosis,[60,61] OCD,[62] and mania.[63] In addition, *M. pneumoniae* has been identified as a PANS trigger.[32,64,65]

Bartonella spp. are transmitted to humans via cat scratches, animal bites, and sand fleas.[66] In addition, *Bartonella* can be transmitted via tick vectors,[66–68] and may be a common co-infection with Lyme borreliosis.[69–71]

Bartonella spp. are responsible for a wide spectrum of clinical syndromes in humans, including both neurological and psychiatric illness.[72–75] The latter category includes depression, anxiety disorder, panic disorder, OCD, phobias, alcohol and drug abuse, psychosis, and personality disorders.[75–77] In addition, *Bartonella* is associated with a wide spectrum of autoimmune conditions.[77–92] Breitschwerdt et al have described a child with PANS that was triggered by *Bartonella henselae* (*B. henselae*) infection.[77]

Methods

A case is presented of an immunocompetent adolescent female diagnosed with AN who was serologically positive for *Borrelia burgdorferi* (*B. burgdorferi), Babesia microti* (*B. microti*), and *M. pneumoniae*, and clinically diagnosed with *Bartonella* infection, who responded to antimicrobial treatment to these infections and has remained in sustained remission from her eating disorder.

Informed consent was obtained from the parents of this patient to publish this history as well as the photograph in Figure 1. Institutional review was not required to publish the case details.

Figure 1 Striae on medial aspect of left thigh.

Case Presentation

This female patient initially presented at seventeen years of age having been diagnosed with anorexia nervosa. She lived in upstate New York from two until sixteen years of age. As a young child in upstate New York, she had several tick attachments but no observed rash and no known infections. She had a healthy infancy and normal developmental milestones but at two years of age began screaming and pulling out her hair for no accountable reason (trichotillomania). By four years of age, she experienced social anxiety and gradually developed generalized anxiety and irritability. At twelve years of age, she began complaining of fatigue and frequent sore throats with anterior cervical adenopathy. At fourteen years of age, this patient had yet another tick attachment which led to a two-centimeter erythematous tender rash but no other immediate sequelae, and she was not treated. However, over the next year her fatigue worsened, and she experienced impaired cognition, postural lightheadedness, sleep disturbances, and worsening anxiety and irritability as well as depression.

At fifteen years of age, the patient began restricting her food intake and purging after meals with forced vomiting leading to an admission to an eating disorder unit at age sixteen; she was diagnosed with AN at that time. Separate trials on sertraline and fluoxetine led to suicidal ideation, but aripiprazole afforded some benefit. She was discharged after two weeks and entered an intensive outpatient program for two months, but was readmitted to an inpatient program due to refusal to eat and suicidal thought with intent. Nasogastric tube feeding was commenced at that time. She was again discharged but readmitted after two weeks because of suicidal thought with intent. She continued to receive tube feedings intermittently when she refused food intake, and was readmitted three months later with suicidal intent and was placed on desvenlafaxine. She was readmitted after another month refusing to eat. She was fed through a dobhoff tube and discharged but after another month needed to be readmitted after pulling out her tube and refusing to eat. This cycle repeated itself one more time, and at the time I initially evaluated her, she was attending an outpatient eating disorder program. Despite intensive interventions with inpatient and outpatient psychotherapy, behavioral interventions, and psychotropic medication, she continued to refuse oral food intake.

At the time of her initial visit the patient was taking desvenlafaxine and aripiprazole as well as lorazepam and

melatonin at bedtime. She had the nasogastric tube in place and stated that she was otherwise refusing to eat. She maintained that she still had an overweight issue and had to stay on a restricted diet. She continued to describe anxiety, depression, and irritability as well as fatigue, impaired cognition with poor concentration, errors in speech, non-restorative sleep with early morning awakening, postural lightheadedness, and frequent sore throats with enlarged cervical nodes. In addition, she complained of numbness and paresthesias in her hands and toes, neck and hip pain, and muscle twitching. Physical examination revealed she was 66 inches in height and weight was 58 kg; sitting blood pressure was 130/80 mmHg with a pulse of 80 beats per minute (bpm) and blood pressure was 118/60 mmHg with a pulse of 100 bpm standing. The remainder of the examination was unremarkable with the exception of her skin. There were prominent erythematous striae on her breasts, hips, and thighs. The patient described these striations as stretch marks and indicative of her overweight issue. A picture of these striae on her left medial thigh is in Figure 1.

Laboratory evaluation revealed normal routine blood counts and chemistries as well as quantitative immunoglobulins. She had negative antinuclear antibodies (ANA) and GAD-65 autoantibody. Testing for tick-borne infections revealed the following:

- Lyme Western blot IgM positive at 18, 39, 41, 66 and 83–93 kDa bands.
- Lyme Western blot IgG positive at 28 and 41 kDa bands.
- *B. microti* serum immunofluorescent antibody (IFA) IgM = 40 (reference range [RR]: <20).
- *B. microti* IFA IgG <40 (RR: <40).
- Human monocytic ehrlichia (HME) IgM <20 (RR: <20).
- HME IgG <40 (RR: <40).
- Human granulocytic anaplasma (HGA) IgM <20 (RR: <20).
- HGA IgG <40 (RR: <40).
- *Bartonella henselae* (*B. henselae*) IgM<20 (RR: <20).
- *B. henselae* IgG <40 (RR: <40).
- *M. pneumoniae* IgM = 3581 (RR<20).
- *M. pneumoniae* IgG = 2010 (RR<40).

The patient was diagnosed clinically and serologically with Lyme borreliosis, babesiosis, and mycoplasmosis, and initially treated with oral azithromycin 250 mg twice daily to treat infections with *B. burgdorferi* and *M. pneumoniae*, and artemisinin 100mg every other day to treat *Babesia*. In addition, the patient was clinically diagnosed with bartonellosis, and began sulfamethoxazole/trimethoprim (SXT) at 800 mg/160 mg twice daily. The introduction of SXT triggered an increase in her hip pain, and she was more adamant in her refusal to eat, leading to discontinuation of the SXT. The patient was then started on intravenous ceftriaxone 2 gm daily administered through a peripherally inserted central catheter (PICC), after which she began improving. Artemisinin dose was progressed to 200 mg twice daily four days out of seven, and SXT was restarted at 400 mg/80 mg, both of which were well tolerated. Postural lightheadedness continued to be problematic and repeat vital signs revealed BP=96/60 mmHg with pulse 80 bpm sitting and BP=86/66 mmHg with pulse 132 bpm standing accompanied by symptoms of near-syncope. The patient was diagnosed with postural orthostatic tachycardia syndrome (POTS) and started on midodrine 5 mg twice daily with resolution of her lightheaded symptoms.

At this point, she was consuming a normal caloric intake and no longer required the nasogastric tube. When SXT was increased to 800 mg/160 mg twice daily the patient again had thoughts of not eating; these thoughts stopped when she decreased the dose. This response was interpreted as a Jarisch-Herxheimer reaction (JHR), which is a flare in symptoms coincident with the introduction of antimicrobial agents. After one week the decision was made to increase her dose of SXT gradually. She increased the dose of SXT to 800 mg/160 mg in the morning and 400 mg/80 mg in the evening, and one week later increased to 800 mg/160 mg twice daily and it was tolerated well without a JHR.

Intravenous ceftriaxone was discontinued after three months and the patient began cefdinir 300 mg twice daily. The patient was maintained on cefdinir, and continued the azithromycin and SXT for a total of one year, during which her eating disorder stayed in remission and her other symptoms gradually resolved. She continued to take desvenlafaxine but she no longer complained of depression, and anxiety was minimal. By that time her energy, sleep, and cognition were good, and she no longer complained of neck or hip pains, sore throats or swollen cervical nodes. The striae were no longer erythematous. Two years since discontinuing antibiotics, these symptoms have remained in remission.

Discussion

This patient presented with multiple symptoms, a clinical diagnosis of AN, and positive serologies to *B. burgdorferi, B. microti*, and *M. pneumoniae*. (The patient's Lyme IgM Western blot was CDC positive for Lyme disease; it is noteworthy that persistent IgM positivity to *B. burgdorferi* is consistent with chronic infection.[93,94]) In addition, she was clinically diagnosed with bartonellosis.

The clinical evidence for the diagnosis of bartonellosis in this patient is supported by the presence of dermatological striae that were not in the normal skin plains seen with *striae distensae*, ie, stretch marks. Nor did she ever experience abnormal weight gain, rapid or otherwise, that would account for *striae distensae*; nor was there evidence of hypercortisolism. Rather, these striae have been described in patients with *Bartonella* infections, and are a result of neovascularization that is stimulated by this microbe.[95] Breitschwerdt et al described 29 patients who had serological and/or PCR evidence of *Bartonella* infection, 24 of whom described the onset of cutaneous lesions since the onset of neuropsychiatric symptoms.[96] The majority of those lesions were similar to the striae that this patient manifested on presentation. *Bartonella* immunoreactivity has been detected in skin-tissue biopsies in these lesions.[97] Further evidence of *Bartonella* infection in this patient is the provocation of Jarisch-Herxheimer reactions when she was started on SXT, or the dose of SXT was increased; when SXT was introduced, she experienced an increase in hip pain and was more adamant in her refusal to eat, and SXT has anti-*Bartonella* activity.[98]

Bartonella is a common co-infection of Lyme borreliosis. In a survey of *Ixodes* ticks in northern New Jersey, Adelson et al found that 35% harbored *B. burgdorferi* while 34% were colonized with *Bartonella* spp.[69] Additional studies of *Ixodes* ticks have also found a high incidence of *Bartonella* spp.,[70,71] and case studies have documented *Bartonella* seropositivity and the presence of *Bartonella* DNA in the serum of patients with *B. burgdorferi* infection of the nervous system.[72,73] This patient was seronegative for *B. henselae*, but false negative serological results are frequent.[99] *Bartonella* spp. other than *B. henselae* have caused infection in humans,[100] which may account for false negative serologies when testing for only *B. henselae.*

As noted above, *Bartonella* infection is associated with a wide range of neuropsychiatric symptoms and autoimmune conditions, including PANS,[75–92] although a literature review did not disclose a case of anorexia nervosa. This patient's JHR in response to SXT, which resulted in increased resistance to oral food intake, suggests the possible role of *Bartonella* infection in the pathogenesis of her eating disorder.

Regarding *Mycoplasma*, Toufexis et al described four children with PANS and eating restrictions who had positive IgG titers to *M. pneumoniae*, but only one of whom also had an elevation in her IgM antibodies.[32] Their report does not cite the actual titers of IgG and IgM antibodies. It is not clear whether *M. pneumoniae* was playing a role in the subjects with PANS since there is a high background of IgG prevalence in control populations,[101,102] and IgM false positivity occurs in the setting of other infections due to cross-reactivity.[103] Similarly, Piras et al described a case of PANS with "a positive test for Mycoplasma pneumoniae", in which the subject responded to clarithromycin; neither the IgM nor the IgG titers were reported.[64] On the other hand, Frankovich et al, in their series of five cases with PANS, describe one subject who had significant elevations in both IgM and IgG titers to *M. pneumoniae*.[65] The patient in this current report had high levels of both IgM and IgG antibodies to *M. pneumoniae*, thus confirming active infection with this microbe.

Babesiosis can result in anorexia,[104] but there are no case reports in the medical literature connecting *Babesia* infection with PANS, AN or other eating disorders. *Babesia* infection is a well-documented cause of autoimmune hemolytic anemia, particularly in its acute stage, but it has not been linked to other autoimmune conditions.[104]

Neuroinflammation occurs in both acute and persistent infection with Lyme borreliosis.[105,106] Persistent infection with *B. burgdorferi* can induce chronic autoimmune disease,[107] and anti-neuronal antibodies are present in many patients with persistent symptoms following treatment for Lyme borreliosis.[108] As yet there are no reports of *B. burgdorferi* as a trigger for PANS. Neuropsychiatric symptoms associated with Lyme borreliosis are similar to those with PANS, including anxiety, depression, OCD and tics.[44–50,109]

Review articles cite the occurrence of eating disorders and, specifically, AN in patients with Lyme borreliosis,[44–47] but a review of the medical literature revealed only one case history of AN associated with Lyme disease. Pachner et al described a twelve-year-old boy who initially presented with intermittent swelling of his right knee. He was serologically positive for Lyme disease and was treated with doxycycline 100 mg twice daily for thirty days with resolution of his knee swelling.

Two months later he became depressed, withdrawn, restricted his food intake, exercised compulsively, and lost 14 kg. Immunoblotting of his serum revealed antibodies to outer surface protein (Osp) A and Osp B. He was treated with intravenous penicillin 20 million U/day for 14 days and within weeks he increased his food intake, gained weight, and was no longer depressed.[43]

Similarly, this patient responded well to an antimicrobial regimen directed at her polymicrobial tick-borne infections, and two years since the cessation of her antibiotics she has remained asymptomatic and free of her prior symptoms of an eating disorder. This patient may indeed have suffered from a PANS-like syndrome starting at the age of two when she exhibited trichotillomania followed by the development of a generalized anxiety disorder. While she did not exhibit OCD, trichotillomania has similarities to OCD, although there are differences between the two disorders as well.[110] The eating disorder appeared to occur after another tick attachment when she was 14-years-old that exposed her to a reinfection or to additional tick-borne pathogens. All four of the tick-borne pathogens with which she was infected are associated with autoimmunity, and three of them are linked to neuroinflammation—*B. burgdorferi, M. pneumoniae*, and *B. henselae*. Any one or all these infections could have contributed to this patient's eating disorder.

Conclusion

There is increasing support for the role of infections in the genesis of AN in some patients. The data suggest that autoimmunity is playing a prominent role in the pathogenesis of microbial-induced AN, and that role has been elucidated in children and adolescents with PANS. This is the first documented case of Lyme borreliosis complicated by three co-infections triggering AN. This adds to the existing literature that infections can play a more prominent role in AN. The corollary is that physicians should become aware of this association in the evaluation of patients with AN, as it may provide a treatment option for this serious and sometimes fatal condition. The possibility that tick-borne infections could underlie the diagnosis of AN warrants further study.

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The author reported no conflicts of interest for this work.

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