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Infections and Childhood Psychiatric Disorders: Tick-Borne Illness and Bipolar Disorder in Youth

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Abstract

Objective: To explore possible links between tick-borne illness (TBI) and pediatric bipolar disorder (PBD) in a retrospective series of youth from a Northeast U.S. psychiatric private practice.

Methods: PBD diagnosis in 27 youth (15 Bipolar I and 12 Bipolar II) was based on DSM-IV TR criteria following interviews with parents and children, questionnaires and school reports. Testing for *Borrelia burgdorferi* (Lyme disease), Babesia, Bartonella, *Mycoplasma pneumoniae*, Anaplasma and Ehrlichia occurred between February 2013 and July 2015. Lyme testing included an ELISA and Western Blot IgM/IgG and cultures; Babesia and Bartonella were ascertained by IgM/IgG antibody titers and fluorescent in-situ hybridization (FISH) tests. Other pathogen exposure was determined by IgM/IgG antibody titers. Testing was performed at LabCorp, Mayo Medical, IgeneX, Advanced Labs and/or Galaxy Diagnostics Laboratories. Clinical diagnoses were confirmed by physicians familiar with TBI. Data was summarized using descriptive statistics.

Results: Eighty-one percent of the sample was male and 19% was female. Mean age at PBD diagnosis was 7.3 years. Exposure to one or more pathogens was found in 24/27 (89%) of the patients. Frequency of positive serology included: Babesia (n=16), Mycoplasma pneumoniae (n=11), Bartonella (N=8), and Lyme (n=6). Twenty-two of these 24 agreed to clinical evaluation and 92% (20/22) were diagnosed with TBI.

Conclusion: The high rate of TBI in PBD patients presented here is provocative. If confirmed, this association may suggest gene-environment interactions and has implications for the prevention and treatment of PBD. Research evaluating TBI in bipolar cases vs. matched controls with other psychopathology and without psychiatric disease using standardized serological testing is needed.

Keywords: Pediatric bipolar disorder; *Borrelia burgdorferi*; Tick-borne infections

Introduction

Although the role of inflammation in psychiatric illness has been the focus of many recent studies, the search for initiating pathogens has been an unresolved issue in scientific literature for over a hundred years. This paper focuses on the possible association of tick-borne infections (TBI) and pediatric bipolar disorder (PBD).

As far back as 1896, Scientific American published an editorial entitled "Is Insanity Due to a Microbe?" [1] In this report, doctors found that transferring cerebrospinal fluid from mentally ill individuals into rabbits resulted in the latter getting ill, leading the physicians to conclude that "certain forms of insanity" "similar to typhoid, diphtheria and others" could be attributed to an infectious process.

Resurgence of interest in the role of microbes in mental illness has occurred in recent decades [2]. A number of studies have implicated the parasite *Toxoplasma gondii* in the development of bipolar disorder and schizophrenia in exposed and infected individuals [3-5]. In addition, a variety of viral infections including HIV, HSV-1, HSV-2, Epstein-Barr, Cytomegalovirus, Measles, Mumps and Influenza have been implicated in the development of psychiatric disturbances in adults [6].

The medical literature contains hundreds if not thousands of case reports of infectious agents playing a role in neuropsychiatric symptoms. The exact nature of this association, i.e., cause, effect, moderating component etc., is often still unclear. This type of interaction is consistent with the hypothesis put forth by Müller and Bechter viewing mental disorders as a "mild encephalitis" or an "encephalopathic" process [7,8].

Support for the role of infectious agents in childhood psychiatric disorders has come from research into both Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) [9-11]. The former is felt to be associated with a previous Group A Beta Hemolytic Streptococcal infection while the latter has a non-streptococcal trigger, whether infectious, environmental, or metabolic, that creates a misdirected immune response. The resulting cerebral inflammation is manifested through a variety of clinical symptoms. PANDAS criteria include the sudden onset of significant obsessions, compulsions and/or tics; while PANS refers to the abrupt onset of obsessive compulsive disorder (OCD) or severely restricted food intake, not better explained by a known neurologic or medical condition. Features shared between PANDAS/PANS and PBD are many [12,13]. Both groups of illnesses are associated with a variety of other manifestations including: anxiety, emotional lability, depression, irritability, severe aggression, oppositionalism, behavioral regression, sensory hypersensitivities, and sleep disturbances.

Results presented in this paper were obtained as part of a PANDAS/PANS screening panel looking for evidence of possible infectious

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triggers including infections caused by Group A Streptococci, *Mycoplasma pneumoniae* and tick-borne illnesses (e.g. Lyme disease), in youth presenting with symptoms of bipolar disorder, excessive anxiety, mood disturbance or heightened irritability.

Lyme disease (LD), the most frequent vector borne illness in the United States, has been associated with mood dysregulation in children and adults [14]. Studies indicate that a broad range of psychiatric reactions have been seen with Lyme disease including paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa and obsessive-compulsive disorder [15].

According to the most recent Center for Disease Control and Prevention statistics, an estimated 300,000 people in the United States are diagnosed with LD each year [16]. Twenty-five percent of the cases occur in children, with the highest rates in boys between the ages of 5 to 9. The bacteria Borrelia burgdorferi, which is carried by the *Ixodes scapularis* tick, causes LD. These ticks can carry multiple pathogens and are able to transmit a variety of infections at one attachment. The infectious agents may include any combination of the following: Borrelia, Bartonella, Babesia, Ehrlichia, Anaplasma and various Mycoplasma species.

This retrospective patient review explores possible links between exposure to tick-borne pathogens and the presence of PBD in a case series of 27 youth from a single Northeast US practice located in New Jersey, a Lyme endemic area.

Materials and Methods

A retrospective case review of 27 bipolar youth from a single New Jersey practice was used to examine rates of exposure to tick-borne pathogens. The sample (Table 1) consisted of 81% males (22/27) and 19% (5/27) females with a mean age at BPD diagnosis of 7.3 years (range 5-12). Bipolar diagnoses were based on DSM-IV TR [17] criteria using information from parent questionnaires, clinical interviews with parents and children, and school reports. Fifteen youth (2 girls and 13 boys) met the criteria for Bipolar I, and twelve (3 girls and 9 boys) met the criteria for Bipolar II. PANDAS and PANS diagnoses were given using the criteria proposed by Swedo et al. [10]. Patients provided specimens between February 2013 and July 2015 for evidence of exposure to tick-borne pathogens, including *Borrelia burgdorferi*, Babesia, Bartonella, *Mycoplasma pneumoniae* (MP), Anaplasma, and Ehrlichia. Lyme testing was performed using Immunofluorescent Antibody Testing (IFA), enzyme-linked immunosorbent assay (ELISA), Western Blot Immunoglobulins M and G (IgM and IgG) and culture; Babesia and Bartonella were ascertained by IgM/IgG antibody titers and fluorescent *in situ* hybridization (FISH) tests; other pathogens were tested for using IgM/IgG antibody titers. Testing was performed at one or more of the following laboratories: LabCorp, Mayo Medical, IGeneX Laboratories, Advanced Labs and Galaxy Diagnostics. Serologic confirmation of Lyme was based on the sample meeting CDC criteria or having a positive culture for *Borrelia burgdorferi*. Lyme Western Blot IgM or IgG that was positive by IGeneX Lab criteria only was not counted in the final data collection. The presence of MP infections was considered positive if the IgM antibody titer was elevated, as the IgG antibody titer was considered representative of past infections. Final diagnosis of a TBI was based on evaluation of symptoms, physical examination, and review of laboratory results by a clinician that specializes in this area. Descriptive statistics were used to summarize the de-identified data that was obtained during clinical care.

Number	Sex	Age in years at bipolar diagnosis	Bipolar type
1	Male	7	II
2	Male	9	II
3	Female	6	II
4	Male	5	II
5	Male	5	I
6	Female	8	II
7	Male	10	I
8	Male	5	II
9	Male	12	I
10	Male	5	I
11	Male	5	I
12	Male	12	I
13	Male	8	II
14	Male	8	I
15	Female	5	I
16	Male	7	II
17	Male	6	I
18	Male	9	II
19	Male	8	I
20	Male	5	I
21	Female	7	II
22	Female	9	I
23	Male	8	II
24	Male	4	I
25	Male	10	I
26	Male	6	II
27	Male	8	I

Table 1: Characteristics of sample.

Results

Table 2 shows the results of serologic testing. The most common tick-borne organisms were: Babesia (N=16), *Mycoplasma pneumoniae* (N=11), Bartonella (N=8), Lyme (N=6), Anaplasma (N=1) and Ehrlichia (N=1). CDC testing criteria for LD was used to make the LD diagnosis in this sample but if more flexible testing guidelines were used (i.e. IgeneX) that number would be increased to 9. Twenty-four of 27 or 89% of the patients had positive serological evidence of exposure to one or more potentially tick-borne pathogen. Twenty-two of these twenty-four or 92% youth with positive serology complied with the recommendation for a clinical assessment by a specialist in TBI. Of those that did, 20/22 or 92% were diagnosed with at least one TBI. Of note, in addition to the presence of the different tick-borne pathogens, 4 of the 27 patients in the sample or 23.5% were positive for PANDAS. Patient number 15 was diagnosed and treated for PANS secondary to *Mycoplasma pneumoniae*.

Discussion

There are over 250 peer-reviewed scientific articles addressing the causal association between tick-borne disease and mental illness, with LD being the most studied so far [18]. TBIs can spread to the central nervous system within weeks of contact, but lay dormant and not produce symptoms for years, with the potential to have a profound effect on a youngster's physical and psychological development [19].

As noted earlier in this paper, being infected by LD in adulthood has been associated with a variety of psychiatric conditions. Although research into the effects in children and adolescents is limited, one study by Tager et al. looking at 20 children ages 8-16 found that the majority of these youth experienced irritability, depression, insomnia and problems with distractibility [20]. Additional literature supports the observation that cognitive and behavioral difficulties in Lyme and

Number	Known tick bite	Lyme	Babesia	Bartonella	Mycoplasma pneumoniae (mp) igm	Pandas/pans (not mp)	Other
1	Age 3or 4	+	+				
2			+				
3				+	+		
4		+		+	+		
5				+			
6			+		+	+	
7				+		+	
8	Age 3		+		+	+	
9	Age 16		+				
10		IgeneX igg		+			
11			+		+		
12			+		+		
13				+	+		
14			+				
15		IgeneX igg			+		**DX'd only as PANS due to MP**
16		IgeneX igg					
17		+		+	+	+	
18		+	+				
19			+				
20			+		+		
21		+					**Anaplasma ehrlichia**
22		+					
23			+				
24			+				
25			+				
26			+				
27			+	+	+		

+: positive on testing by at least one laboratory

Table 2: Results of serological testing.

other TBIs are similar to those observed in affective, oppositional defiant, and attention deficit disorders [19]. Of note, Borrelia infection can cause an exacerbation of pre-existing mental illness.

The increasing awareness of the importance of the immune system and inflammation in both the development and perpetuation of infectious diseases and mental disorders is relevant when one thinks of TBI. In addition, bacterial infections and chronic inflammation are recognized to be associated with many autoimmune diseases [21]. LD has been associated with a variety of proinflammatory cytokines and chemokines as well as increased proinflammatory lipoproteins. Lyme surface antigens through the mechanism of molecular mimicry may play a role in the physical and psychiatric manifestations of the disease and warrant further study [21,22].

There is no question that the high rate of tick-borne illness found in this case series of PBD patients is provocative. Seventy-four percent or 20/27 youth with PBD were positive for TBI by both laboratory testing and clinician assessment. These results are surprising in two ways: 1.The majority of these patients did not have a known tick bite and 2. The presence of TBI in this population is much greater than chance and raises the issue of the nature of the relationship of TBI to PBD, although conclusions about temporal or causal relationships cannot be made at this point. Of note, a number of parents indicated that they felt the child was born with difficulties and were surprised that tick exposure had occurred; could the relationships be due to greater exposure (attractants, e.g. pheromones) or increased susceptibility to certain infections (possible immune dysfunction) in bipolar youth? It is known that the number of ticks carrying *Borrelia burgdorferi* and other bacteria have increased significantly in the U.S. and the rates of childhood mental illness have also increased in recent years [16,23]. This potential relationship requires much more intensive exploration before any conclusion can be reached.

Co-infections complicate the clinical picture further as humans are exposed to Bartonella and other pathogens through contact with a variety of other vectors, e.g. body lice, fleas, sand flies [24] etc., that are carried by domestic animals and rodents.

The true prevalence of TBI in the general population in the area where the study was done is unknown, and this data is crucial to interpretation of the results reported here. Each pathogen genus (e.g. Borrelia, Bartonella, Babesia, Mycoplasma, etc.) consists of a variety of different species, only some of which are known to affect humans, while others have different hosts. Cross reactivity of species may interfere with results of intra-genus testing. For example, there are different types of Mycoplasmas, e.g. *Mycoplasma pneumoniae*, *Mycoplasma fermentans*, *Mycoplasma hominis*, *Mycoplasma genitalium*, etc., some of which are carried by Ixodes ticks [25] and have the potential to interfere with serologic testing. Although MP is a leading cause of respiratory infections, it can also result in extra-pulmonary problems including gastrointestinal, cardiovascular, musculoskeletal, renal and neurologic symptoms (manifestations of encephalitis) [26,27]. The recent rise of macrolide resistant strains of Mycoplasma in the United States adds to concern about this pathogen, especially as it is a tick-borne co-infection [28].

The presence of infection with PANDAS/PANS in addition to the TBIs is high in this study. Again, this may indicate some level of heightened susceptibility or weakened immunity in these individuals. It may well be that individuals with a heightened genetic predisposition are more sensitive to environmental insults (infections, trauma, environmental toxins, etc.) which lead to inflammatory and immunologic changes which may themselves result in increased vulnerability or decreased immune reactions (e.g. more infections) that in the end result in emotional, behavioral and physical symptoms.

Results presented in this study require replication in broader populations and geographic regions. The research should be extended to include those with TBI in bipolar cases vs. matched controls with other psychopathology as well as those without psychiatric disease using standardized serological testing. It may be that the presenting manifestations of TBI in some youth are more in the behavioral/emotional realm, than in physical manifestations (e.g. rash, joint pain, headaches, etc.). In addition, the initial psychiatric presentations may include signs of diverse childhood mental disorders (e.g. OCD, Attention-deficit Hyperactivity Disorder) and not just bipolarity. Prospective data will ultimately be needed to establish causality and identify potential mechanisms. Further work in this area may yield novel and more effective treatment in youth with some forms of mental illness.

Conclusion

Tick-borne infections are among the many possibilities that should be considered when psychiatric symptoms appear resistant or only partially responsive to treatment. As clinicians, it is important to be aware that what may present as treatment resistant mood and/or anxiety disorders, may in fact be due to our present inability to identify all responsible infectious agents, and associated inflammatory and immunologic factors.

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