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Microbial Induced Autoimmune Inflammation as a Cause of Mental Illness in Adolescents: A Case Series

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Daniel A. Kinderlehrer [α] & Nancy Brown [σ]

Abstract- The incidence of mental health disorders in adolescents continues to rise. The cause of the increase in mental illness is multifactorial, including both environmental and biological causes. To investigate the latter, ten adolescents at a psychiatric residential treatment center in Colorado with the DSM-5 diagnosis of major depressive disorder (MDD), of whom seven were additionally diagnosed with generalized anxiety disorder (GAD), were chosen at random for further serologic study. Testing revealed exposure to group A *Streptococcus* (GAS) in 3 of 10 (30%); *Borrelia burgdorferi sensu lato* (*Bbsl*) in 2 of 10 (20%); and *Bartonella* spp. in 3 of 10 (30%). In addition, 9 of 10 (90%) subjects had abnormal Cunningham Panels, which measures levels of antineuronal antibodies that have been associated with psychiatric disturbances. Given the degree of psychological dysfunction in these adolescents requiring intensive residential treatment, this case series lends support to the hypothesis that exposure to infectious agents may play a role, perhaps by autoimmune mechanisms, in the significant and ongoing rise in the rate of neuropsychiatric illness in adolescents. This preliminary report adds to this premise and requires further investigation.

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I. Introduction

Mental health problems among adolescents are increasing [1]. The most common mental health disorder in this age group is anxiety. Anxiety disorders occur in approximately 32% of adolescents 13 to 18 years of age, and 8.3% had severe impairment [2]. The number of adolescents who experienced major depressive disorder (MDD) was 21.48% in 2015 and increased by nearly a third from 2009/2010 to 2015 [1]; 13.3% of youth aged 12 to 17 report suffering from at least one major depressive episode in 2017 [3]. The suicide rate among persons aged 10 to 24 has increased 56% between 2007 and 2017; since 2014 suicide has replaced homicide as the second most common cause of death for teenagers ages 10 to 19 in the United States [4].

The cause of mental health disorders in adolescents is multifactorial, including both biological and environmental causes. Stress issues have been cited as a significant factor [5]. Common sources of stress in adolescence include social stress/peer pressure, academic pressure, isolation, dysfunctional home environment, physical or sexual abuse, bullying, low self-esteem and substance abuse. Compounding these issues, adolescents who spend more time on social media and electronic devices such as smartphones are more likely to report mental health issues, and an increase in screen time is associated with a decrease in in-person social interaction and an increase in depressive episodes [1].

It is clear that biological issues also have a significant role in mental health disorders. Neuropsychiatric symptoms can be caused by multiple organic issues including heavy metal toxicity [6], allergy to gluten [7], thyroid disorders [8], and autoimmune illness [9]. In addition, the medical literature is replete with the identification of neuropsychiatric disorders caused by infection [9,10].

Infections transmitted by ticks have been linked to a spectrum of mood and behavioral disorders. *Borrelia burgdorferi sensu lato (Bbsl),* the pathogen that causes Lyme disease, is responsible for a wide range of mental health disorders, including anxiety disorders, depression, schizoaffective disorders, bipolar disorder, eating disorders, addiction, suicide, violence, anhedonia, depersonalization and dissociative episodes [11-17].

Other tick-borne infections can also cause neuropsychiatric illness. Infections with *Bartonella* spp. have been associated with anxiety, panic disorder, depression, obsessive compulsive disorder (OCD), phobias, eating disorders, alcohol and drug abuse, psychosis and personality disorders [18-22]. *Bartonella henselae (B. henselae)* is also associated with a wide spectrum of autoimmune conditions [23-37], including pediatric acute-onset neuropsychiatric syndrome (PANS)[22].

Autoimmune mechanisms may underly the linkage between infection and neuropsychiatric disorders. In 1994, Swedo et.al. described mental health issues associated with group A *Streptococcus* (GAS) infections [38]. Based on the first fifty children who met the clinical description of neuropsychiatric disorders following streptococcal infections, Swedo outlined five diagnostic criteria for this diagnosis and coined the term pediatric autoimmune neuropsychiatric disorders

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associated with streptococcal infections (PANDAS) [39]. These criteria include OCD or tic disorder (as defined by DSM IV, American Psychiatric Association, 2000), prepubertal age of onset, an abrupt onset with relapsing or remitting course, neurological abnormalities during exacerbations (such as involuntary, choreiform movements or motor hyperactivity), and a temporal association between streptococcal infections and neuropsychiatric symptom exacerbations.

In recognition of the finding that multiple microbes in addition to GAS can trigger autoimmune encephalitis and autoimmune encephalopathies or PANDAS-like syndromes, this condition is now referred to as pediatric acute-onset neuropsychiatric syndrome (PANS), and criteria have been developed for this diagnosis. Children must have the abrupt onset of OCD or severely restricted food intake; there must be no known neurologic or medical disorder that would account for the symptoms; and include at least two of the following seven conditions: anxiety, emotional lability and/or depression; irritability, aggression, and/or severe oppositional behaviors; behavioral (developmental) regression; sudden deterioration in school performance; motor or sensory abnormalities; somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency [40]. Multiple microbes have been documented as triggering PANS including herpes simplex virus, influenza A virus, varicella zoster virus, Epstein-Barr virus, HIV, recurrent sinusitis, the common cold, *Mycoplasma pneumonia* and *B. henselae* [22,41,42].

Immune cross-reactivity between microbes and host tissues has been well documented and is attributed to molecular mimicry [43,44]. Children with PANS-like conditions exhibit elevated levels of antineuronal antibodies against dopamine receptors [45-47], lysoganglioside [48], and tubulin [49]. Antineuronal antibodies crossing the blood-brain barrier can activate calcium calmodulin-dependent protein kinase II (CaMKII), a multifunctional enzyme highly concentrated in the brain, which mediates many different learning, memory, and developmental cell pathways. CaMKII alters dopamine neurotransmission, leading to neuropsychiatric symptoms of OCD as well as tics, and youths with OCD and tics have elevations in CaMKII activity [50].The Cunningham Panel was developed to assess patients with PANS-like syndromes, and includes levels of these antibodies as well as CaMKII activity.

This exploratory study has two aims. First, to examine whether adolescents with serious mental health disorders have a higher rate of exposure to GAS, *Bbsl*, and *Bartonella* spp. than the general population. Secondly, to evaluate whether adolescents with significant mental health disorders have elevations in antineuronal antibody levels, consistent with autoimmune induced neuroinflammation as a possible cause of their disorders.

II. Methods

Subjects were randomly selected patients at a residential adolescent treatment center. The severity of their mental health issues prevented them from living at home and attending school. All were suffering from depression, and some also suffered from anxiety. Informed consent was reviewed and approved by the Western Institutional Review Board (WIRB). Consent was obtained from all subjects and their guardians.

Serum testing included Lyme ImmunoBlot IgM and IgG for evidence of exposure to *Bbsl; Bartonella* Multi-species Western Blot IgM and IgG for evidence of exposure to *Bartonella* spp.; Anti-DNase B (ADB) for evidence of exposure to GAS; and the Cunningham Panel for evidence of autoimmune neuroinflammation. The Cunningham Panel includes five assays performed on serum that measure human IgG levels by enzyme-linked immunosorbent assay (ELISA) directed against the Dopamine D1 Receptor, Dopamine D2L Receptor, Lysoganglioside-GM1, and Tubulin, as well as a cell stimulation assay which measures the ability of a person's serum IgG to stimulate CaMKII activity in human neuronal cells.

III. Results

The subjects ranged from fourteen to seventeen years of age. There were six females and four males. All ten satisfied DSM-5 criteria for MDD, and seven additionally satisfied DSM-5 criteria for GAD. Three of the subjects were diagnosed with Attention Deficit Disorder (ADD), three subjects had made serious suicide attempts, four subjects had behavior associated with non-suicidal self-injury disorder (NSSID) in the form of cutting, and one had tics. One subject had previously been diagnosed with celiac disease, but the remaining nine had no known medical disorder. See Table 1.

Table 1: Diagnoses of Subjects

Subject	Age	Gender	MDD	GAD	Suicide attempt	Eating Disorder	NSSID (Cutting)	Tics	Medical Disorder
1	16	M	+	+	+				Celiac
2	16	F	+		+		+		
3	14	M	+	+					
4	15	F	+	+		+	+	+	
5	15	F	+	+					
6	16	F	+	+					
7	15	M	+	+					
8	17	F	+	+	+		+		
9	17	M	+						
10	15	F	+				+		

MDD, Major depressive disorder
GAD, Generalized anxiety disorder
NSSID, Non-suicidal self-injury disorder

Three of ten subjects (30%) had elevated levels of ADB. See Table 2.

Table 2: Results of Anti-DNase B testing

Subject	Anti-DNase B (RR:0-170)
1	**286**
2	125
3	<78
4	<78
5	**324**
6	113
7	<78
8	**238**
9	163
10	<78

Elevated levels are highlighted and in bold

Table 3 summarizes the results of the Lyme ImmunoBlot IgM and IgG testing. Two of ten subject (20%) had antibodies to IgG specific bands P23, P34 and P39.

Table 3: Results of Lyme ImmunoBlot testing

Subject		P93	P66	P58	P45	P41	P39	P34	P31	P30	P28	P23	P18	Results
1	IgG					++							+	NEG
	IgM													NEG
2	IgG					+							+	NEG
	IgM					-								NEG
3	IgG			+		+		+						POS
	IgM													NEG
4	IgG			+	+	+								NEG
	IgM					+								NEG
5	IgG					+				++			+	NEG
	IgM					+								NEG

6	IgG					+	+					++		Pos
	IgM													NEG
7	IgG			+		+								NEG
	IgM													NEG
8	IgG													NEG
	IgM													NEG
9	IgG					+								NEG
	IgM													NEG
10	IgG													NEG
	IgM											+		NEG

IgG, Immunoglobulin G
IgM, Immunoglobulin M

Three of ten subjects (30%) had antibodies to either *B. henselae, Bartonella elizabethae (B. elizabethae) or Bartonella vinsonii (B. vinsonii).* See Table 4.

Table 4: Results of the Bartonella Multi-species Western Blot IgG and IgM

Subject	Bartonella Western blots	
	IgG	IgM
1	NEG	NEG
2	NEG	NEG
3	POS B. elizabethae	NEG
4	NEG	NEG
5	NEG	NEG
6	POS B. vinsonii	NEG
7	NEG	NEG
8	NEG	NEG
9	POS B. henselae	NEG
10	NEG	NEG

IgG, Immunoglobulin G
IgM, Immunoglobulin M
B. elizabethiae, Bartonella elizabethiae
B. vinsonii, Bartonella vinsonii
B. heneslae, Bartonella henselae

Nine of ten subjects (90%) had abnormalities in the Cunningham Panel with elevations in anti-neuronal antibodies and five of ten (50%) subjects with elevations in CaMKII activity. See Table 5.

Table 5: Results of the Cunningham Panels

Subject	Anti-Dopamine D1 RR:500-2000	Anti-Dopamine D2L RR:2000-8000	Anti-Lysoganglioside RR:80-320	Anti-Tubulin RR:250-1000	CaMKII Activity RR:53-130
1	**1:8000**	1:8000	1:80	**1:2000**	125
2	**1:4000**	1:8000	1:160	**1:4000**	**137**
3	**1:4000**	1:8000	1:160	**1:4000**	**133**
4	**1:4000**	1:8000	1:160	**1:8000**	**159**
5	**1:4000**	1:8000	1:160	**1:4000**	**130**
6	1:2000	1:4000	1:80	**1:2000**	121
7	**1:4000**	1:2000	1:40	**1:2000**	123
8	**1:16000**	**1:16000**	1:320	**1:4000**	**134**
9	1:2000	1:4000	1:80	1:1000	113
10	**1:4000**	1:8000	1:80	**1:4000**	118

Abnormal results are highlighted and in bold

CaMKII, Calcium calmodulin-dependent protein kinase II

Table 6 depicts the positive results of all the assays in the ten subjects.

Table 6: Summary of Positive Results

Subject	Anti-DNase B positive	Bbsl ImmunoBlot positive	Bartonella spp. Western Blot positive	Cunningham Panel positive
1	+			+
2				+
3		+	+	+
4				+
5	+			+
6		+	+	+
7				+
8	+			+
9			+	
10				+

Bbsl, Borrelia burgdorferi sensuolato

IV. Discussion

In this case series, three of ten subjects (30%) had positive titers to ADB consistent with exposure to GAS. ADB titers become positive one week to one month after streptococcal infection and usually stay positive for months. However, in some individuals ADB titers stay positive longer than one year, including in some with streptococcal carrier states [51,52]. ADB titers are positive in the majority of patients with streptococcal induced autoimmune illnesses including rheumatic fever and post-streptococcal glomerulonephritis, as well as in patients with PANDAS [51-53]. Fujikawa et. al. found that only 8% of a non-carrier control population had elevations in ADB titers [52]. The finding that 30% of the subjects in this study had elevations in ADB levels suggests the possibility that GAS may have played a role in their mental health issues.

In this case series, 2 of 10 (20%) subjects showed evidence of exposure to or current infection with *Bbsl*. The Lyme immunoblot assay, which utilizes pure recombinant proteins as test antigens, is more sensitive and specific than the Lyme ELISA and the Lyme Western Blot [54-56]. While cross-reactivity of some *Borrelia* proteins with antigens from other bacteria and viruses is well known [40], the presence of IgG antibodies at 23-kdA (outer surface protein [Osp]C), 34-kdA (OspB) and at 39-kdA are considered specific and therefore diagnostic for *B. burgdorferi* [57-60]. Subjects 3 and 6 demonstrated IgG reactivity at Bands 23, 34 and/or 39. While these results do not meet the Centers for Disease Control and Prevention (CDC) criteria for reporting Lyme disease, the CDC criteria were established for surveillance purposes only, not for clinical diagnosis [61,62].

While neuroinflammation has been documented in both acute and persistent infection with *Bbsl* [63-65], this pathogen has not as yet been documented as a singular cause of PANS. Cross et.al. described the case of a pre-pubescent female who developed PANS with a positive Cunningham Panel, was serologically positive for *Streptococcus* but also for several tick-borne infections including *Bbsl, B. henselae,* and *Babesia*

duncani, and responded to broad spectrum antimicrobial therapy [66]. Many of the neuropsychiatric symptoms of neuroborreliosis parallel or overlap with those of PANS, including anxiety disorders, depression, OCD and tics[11-17,67].

Some of the chronic symptoms in patients with post-treatment Lyme disease syndrome (PTLDS) are attributed to autoimmunity [68,69], and Chandra et. al. found anti-neuronal antibody levels 41 of 83 (49.4%) PTLDS patients who continued to suffer from chronic symptoms of pain, fatigue, and impaired cognition; antibodies against *Bbsl* cross-reacted with several neural proteins[63]. Likewise, Fallon et.al. found higher levels of antibodies against Lysoganglioside-GM1, Tubulin, and Dopamine D1-Receptor as well as well as elevated activity of CaMKII in patients with a prior history of Lyme borreliosis but not in those without that history[70]. Osp A has a protein sequence similar to GAS [71], and OspA is associated with autoimmune reactivity[69]. It is not unlikely that *Bbsl* is yet another microbe that can trigger PANS-like syndromes. The finding that 20% of subjects in this case series had evidence of exposure to *Bbsl* raises the possibility that this microbe is playing a role in their mental health issues.

In this case series, 3 of 10 (30%) subjects showed evidence of exposure to or current infection with *Bartonella* spp. *B. henselae,* an intracellular gram-negative pleomorphic bacillus, is the causative agent of cat scratch disease (CSD) transmitted via the cat flea. In addition to transmission via fleas, sandflies and lice, *B. henselae* can be transmitted via the Ixodes tick [72,73]. Co-occurrence of Bartonella spp. with known tick-borne pathogens such as *Bbsl* is not uncommon. A survey by Adelson et. al. of Ixodes ticks in northern New Jersey found *B. burgdorferi* present in 35% while 34% harbored Bartonella spp. [74]. Additional surveys have confirmed the high incidence of Bartonella spp. in Ixodes ticks [75,76]. The *Bartonella* bacillus is difficult to grow; therefore, culture is not recommended [77]. While polymerase chain reaction (PCR) in serum or tissue specimens is the most definitive way to diagnose infection with *Bartonella,* PCR detection lacks sensitivity (43–76%) [78]. ELISA and Indirect immunoflourescence assays (IFA) are the standard tools to diagnose bartonellosis, however increased sensitivity is associated with decreased specificity with both these antibody assays [79,80]. There is preliminary evidence that Western blot testing for *Bartonella* as performed in this case series is both more sensitive and specific than either IFA or ELISA testing [81].

B. henselae causes a wide spectrum of clinical illness in humans, including autoimmune and psychiatric illness as noted above. There is an abundance of data on infections in animals with *B. vinsonii* and *B. elizabethae,* but in humans it is limited. There are reports that both species can cause infective endocarditis [82-84], and *B. vinsonii* has additionally been reported to cause neurological abnormalities[85,86]. There are no reports of neuropsychiatric complications with these two *Bartonella* species. However, these infections need to be considered emerging illnesses at this time; few laboratories are equipped to identify these potential pathogens and correlate them with clinical syndromes. There is also the possibility of cross-reactivity among different species of *Bartonella* [87]. The relevance of positive *Bartonella* spp. IgG in three adolescents in this study is unclear.

In this case series, 9 of 10 (90%) subjects demonstrated the presence of anti-neuronal antibodies and 5 of 10 (50%) had CaMKII activation. The utility of the Cunningham Panel has been demonstrated in the assessment of PANDAS/PANS by Shimasaki et. al. They evaluated 58 patients meeting the diagnostic criteria for PANDAS/PANS who were tested pre-and post-treatment. Patients were categorized as “Improved/Resolved” (n=34) or “Not-Improved/Worsened” (n=24). The changes in assays of the Cunningham Panel paralleled changes in patient symptoms following treatment with an accuracy of 90%, a sensitivity of 88% and a specificity of 92% [88]. Chain et.al. compared 35 acute onset PANDAS patients with 28 healthy controls and found that 32 sera (91.4%) in the PANDAS group were positive for one or more of the antineuronal autoantibodies compared with 9 of 28 healthy controls (32.1%) [89]. Likewise, Connery et.al. found that the Cunningham Panel accurately predicted significant responses in aberrant behavior and social responsiveness in children with autism [90]. Multiple other studies have found an association between autoimmune neuropsychiatric disorders such as PANDAS/PANS and the biomarkers included in the Cunningham Panel [45-50, 91-96]. Antineuronal antibodies crossing the blood brain barrier and activating CaMKII may underlie the serious mental health issues in the subjects in this case series.

Hesselmark and Bejerot have challenged the utility of using the Cunningham panel to diagnose PANS [97].Their study found both low sensitivity and specificity of the Cunningham panel, and did not find a statistical difference between patients with PANS and healthy controls. But their findings have been challenged because, among other issues, they used invalid serum collection tubes—they used gold top tubes that contain both a clot activator and a serum gel separator rather than glass red top tubes that have no additives [98].

The rates of infections with GAS [99,100] and tick-borne pathogens [101] are increasing, and perhaps molecular mimicry resulting in immune cross-reactivity underlies the rise in autoimmune illnesses [102]. Non-microbial factors that underlie the development of autoimmunity are also increasing, including occupational exposures such as pesticides [103,104], dietary changes and their impact on the microbiome

[105,106], and stress-related disorders such as post-traumatic stress disorder (PTSD) [107,108]. Indeed, all these factors can alter epigenetics [109-114], and epigenetics is crucial to the development of autoimmunity [115]. Therefore, it is possible that multiple factors are contributing to autoimmunity and are cumulative in succeeding generations.

V. Conclusion

The increasing incidence of mental health disorders in adolescents is multifactorial. Stress issues and an increase in screen time on electronic devices has appropriately received attention, but less attention has been given to the role of organic disorders. This case series documented exposure to *GAS, Bbsl* and *Bartonella* spp. in 5 of 10 (50%) subjects, raising the possibility that these microbes may be playing a causative role in the subjects' mental illness. In addition, 9 of 10 (90%) subjects had evidence of autoimmune neuroinflammation as evidenced by their positive Cunningham Panels. The high percentage incidence of antineuronal antibodies and CaMKII activation in this group of ten subjects may not necessarily be indicative of all patients in this facility due to the small sample size, but it is possible that neuroinflammation is an important contributor to the increasingly high incidence of mental health disorders in the adolescent population.

Given the serious and increasing morbidity and mortality of mental illness in the adolescent population, the implications are significant for promoting future research. Further studies in a larger cohort of patients compared with a healthy control population that would help elucidate the roles of *GAS, Bbsl* and *Bartonella* along with autoimmune neuroinflammation in the etiology of mental health issues in the adolescent population is warranted.

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Author contributions

D.A.K. conceived the premise of this research and secured IRB approval. N.B. secured approval from subjects and their guardians and implemented the collection of data. N.B. performed the analysis of the data. D.A.K. authored the manuscript.

Conflicts of interest
The authors cite no conflict of interest.

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Acronyms used:
DSM – Diagnostic and Statistical Manual of Mental Disorders
MDD – major depressive disorder
GAD – generalized anxiety disorder
GAS – group A Streptococcus
Bbsl – Borrelia burgdorferi sensu lato
OCD – obsessive compulsive disorder
B. henselae – Bartonella henselae
CSD – cat scratch disease
PANDAS – pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections
PANS – pediatric autoimmune neurospsychiatric syndrome
CaMKII– calcium calmodulin-dependent protein kinase II
IgM – immunoglobulin M
IgG – immunoglobulin G
WIRB – Western Institutional Review Board
ADB – Anti-DNase B
ADD – attention deficit disorder
NSSID – non-suicidal self-injury disorder
Osp – outer surface protein
B. elizabethae – Bartonella elizabethae
B. vinsonii – B. vinsonii
CDC – Centers for Disease Control and Prevention
PTLDS – post-treatment Lyme disease syndrome
IFA – immunoflouresence antibody
ELISA – enzyme-linked immunosorbent assay
PTSD – post-traumatic stress disorder

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