Pennsylvania Testimony: Lyme and Associated Diseases

Robert Bransfield, MD, DLFAPA

We have an opportunity to improve the health and productivity of residents of Pennsylvania by becoming more effective in preventing, diagnosing and treating Lyme and associated tick-borne disease. We first must ask, how extensive is the problem, what is impeding forward progress and how can we move forward?

How extensive is the problem?

Lyme and associated diseases are a chronic, persistent infectious process that causes autism and other developmental impairments, a broad spectrum of impairments resulting in decreased productivity, mental illnesses, suicide, violence and homicide, an epidemic of opioid and other substance abuse, auto accidents and dementia and other degenerative neurological impairments. There are over 700 journal articles supporting this statement at http://www.ilads.org/ilads_news/2017/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/ More recently I did a study on Lyme and associated diseases and suicide. Based upon the calculations in the article and current CDC statistics, there are 410 suicides in Pennsylvania per year as a result of Lyme and associated diseases. Now I am performing a study on homicide and homicidality and Lyme and associated diseases. I am identifying more homicides associated with Lyme disease in Pennsylvania than in any other state. Another part of this epidemic is an epidemic of opioid abuse. Many Lyme patients who are being inadequately diagnosed and treated go on to develop chronic illnesses which can include chronic pain. The problem is further compounded when the medically necessary non-addictive medications are denied by Pennsylvania insurance companies while the so called "preferred drugs" covered by the plan are the generic addictive opioid medications. This can and does result in an epidemic of drug abuse resulting in overdose and auto accident deaths.

What impedes forward progress?

We always want a gold standard for diagnosing a medical condition. Unfortunately, the two-tiered testing that many use is instead a fool's gold standard for diagnosing Lyme and tick-borne diseases. Animals are receiving better care than humans. The Cornell Multiplex testing for horses for chronic Lyme with OspF testing and epidemiological statistics for dogs (www.DogsandTicks.com) are more reliable in many geographical areas than CDC collection methods. When diagnosing every other condition, the comprehensive clinical exam is the gold standard of diagnosis, why is the diagnosis of Lyme disease reduced to a lesser standard? The highly lucrative and commonly used two-tiered testing is conceptually flawed since it is an immune based test to test for an organism that is known to suppress and evade the immune system and is no more accurate than a coin toss. In contrast, HIV testing is 500 times more sensitive than the two-tiered Lyme testing. Policies need to be implemented to discourage excessive reliance upon the two-tiered testing and to encourage greater reliance upon the comprehensive clinical exam and for the diagnosis of Lyme disease with greater awareness of the possible late stage manifestations.

In 1682 Dr Thomas Wynne, my ancestor who was William Penn's physician, treated an epidemic of smallpox on the *Welcome* as it sailed to what is now Philadelphia. Now we are dealing with a different, but also threatening epidemic. Your efforts can help protect the viability of the healthcare system created by Dr Wynne and the health and productivity of Pennsylvania.

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September 1, 2017

Senator Sue Serino, Chair Senate Task Force on Lyme and Tick-Borne Diseases
Senator Kemp Hannon, Chair Senate Standing Committee on Health

Re: Association between the opioid crisis and the Lyme epidemic

Greeting Senators Serino and Hanson,

As a follow up to the meeting on Tuesday, I would like to add something that was not in my advanced written testimony.

In the hearing, there were references by committee members to the opioid crisis. As a psychiatrist, I deal with this problem as well as Lyme disease. I don't think the link between the opioid crisis and the Lyme disease epidemic was apparent to the committee members.

I shall describe a representative case history describing something I have seen far too many times.

A young patient acquires Lyme/tick-borne diseases and the diagnosis is missed, dismissed and/or they are undertreated. The symptoms progress over a period of years to include psychiatric symptoms, chronic pain and other symptoms. Eventually they are prescribed pain medications and/or other controlled substances or they acquire these medications through other means. Their use of pain medications (opioids) and other controlled substances increases and becomes an addiction. They may then turn to multiple physicians, multiple pharmacies, illegitimate sources of drugs and/or turn to illegal activity. They attempt to overcome their addiction, have a period of sobriety, then have some triggering event, relapse and take the dose of opioid they had previously used. However, the period of sobriety altered their tolerance to the drug and that same dose is now a lethal dose. They are discovered deceased and everyone is surprised, puzzled and grief stricken.

The point I would like to make to the Committee is that inadequately diagnosed and inadequately treated Lyme/Tick-Borne Diseases as well as inadequately treated mental illnesses are contributing to the opioid epidemic. Clearly not all opioid deaths are associated with Lyme or mental illnesses, but many are and better attention to both of these problems can contribute to reducing the severity of the opioid crisis.

Sincerely,

Robert C. Bransfield MD, DLFAPA

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ORIGINAL RESEARCH

Suicide and Lyme and associated diseases

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Purpose: The aim of this paper is to investigate the association between suicide and Lyme and associated diseases (LAD). No journal article has previously performed a comprehensive assessment of this subject.

Introduction: Multiple case reports and other references demonstrate a causal association between suicidal risk and LAD. Suicide risk is greater in outdoor workers and veterans, both with greater LAD exposure. Multiple studies demonstrate many infections and the associated proinflammatory cytokines, inflammatory-mediated metabolic changes, and quinolinic acid and glutamate changes alter neural circuits which increase suicidality. A similar pathophysiology occurs in LAD.

Method: A retrospective chart review and epidemiological calculations were performed.

Results: LAD contributed to suicidality, and sometimes homicidality, in individuals who were not suicidal before infection. A higher level of risk to self and others is associated with multiple symptoms developing after acquiring LAD, in particular, explosive anger, intrusive images, sudden mood swings, paranoia, dissociative episodes, hallucinations, disinhibition, panic disorder, rapid cycling bipolar, depersonalization, social anxiety disorder, substance abuse, hypervigilance, generalized anxiety disorder, genital–urinary symptoms, chronic pain, anhedonia, depression, low frustration tolerance, and posttraumatic stress disorder. Negative attitudes about LAD from family, friends, doctors, and the health care system may also contribute to suicide risk. By indirect calculations, it is estimated there are possibly over 1,200 LAD suicides in the US per year.

Conclusion: Suicidality seen in LAD contributes to causing a significant number of previously unexplained suicides and is associated with immune-mediated and metabolic changes resulting in psychiatric and other symptoms which are possibly intensified by negative attitudes about LAD from others. Some LAD suicides are associated with being overwhelmed by multiple debilitating symptoms, and others are impulsive, bizarre, and unpredictable. Greater understanding and a direct method of acquiring LAD suicide statistics is needed. It is suggested that medical examiners, the Centers for Disease Control and Prevention, and other epidemiological organizations proactively evaluate the association between LAD and suicide.

Keywords: depression, tick-borne, immune, homicidal, epidemiology, psychoimmunology

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use:

http://youtu.be/hcHgil0d89g

Plain language summary

Currently, there are over 40,000 well-documented and many more undocumented suicides in the US each year, and many are unexplained. A number of infectious diseases, and in particular chronic infectious diseases, have also been associated with suicide. This article analyzes the association between suicide and Lyme and associated diseases (LAD). Based upon the medical literature demonstrating the physiology associated with suicide, a chart review, and epidemiological calculations, it was demonstrated there is a causal relationship between LAD and suicide, and the pathophysiology of LAD can be explained and it causes a significant number of suicides. LAD causes immune effects, biochemical changes, and a number of psychiatric symptoms that contribute to suicidal risk. By indirect calculations, it is estimated there are possibly over

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http://dx.doi.org/10.2147/NDT.S136337

1,200 LAD suicides in the US per year. Greater understanding and a direct method of acquiring LAD suicide statistics is needed.

Introduction

Contributors and deterrents of suicide

Suicide is a major and potentially preventable health problem needing greater attention. It is the result of an interaction of multiple known and unknown contributors, deterrents, and acute triggers. Some of the well-recognized contributors to suicide include anhedonia, depression, psychosis, substance abuse, bipolar illness, panic attacks, posttraumatic stress disorder, obsessiveness, anxiety, agitation, impulsivity, aggressiveness, depersonalization, rigidity, narcissism, borderline personality, feelings of helplessness, hopelessness, repression, lack of outlets for frustration, sexual issues, boundary issues, other mental conditions, chronic pain, disability, neurological impairments, chronic medical problems, infections, immune reactions, genetic vulnerabilities, social isolation, adverse life events, abusive relationship(s), family dysfunction, family substance abuse, family mental illness, separation or divorce, exposure to trauma, abusive development (ie, child abuse or neglect), family history of mental illness or suicide, incarceration, legal problems, financial distress, prior suicide attempts, high crime rates and other broader community conditions, limited access to health and social services, and easy access by persons at risk to lethal means (ie, 90-day supplies of medication or unlocked firearm).[1,2] Acute triggering events can include window of fear, exposure to the suicidal behavior of others, acute sleep deprivation, alcohol and/or drug intoxication or withdrawal, recent rejection, loss, embarrassment or failure, "intimate partner problems, physical health conditions, financial challenges, and legal problems".[3] Deterrents to suicide include mental fitness, frustration tolerance, cognitive abilities, coping skills, parenthood, supportive relationships, community and other social connections, purpose, ethical and religious beliefs, good medical and neurological health, and access to social services and psychiatric and medical care.[4]

Understanding suicidality requires a very complex formula and is associated with many different sequential events, contributors, deterrents, and acute triggers which are both known and unknown. While acknowledging the significance of all of these other components to suicidality, the scope of this article shall specifically focus upon suicide and (LAD).

Epidemiological statistics

Suicide is a major public health concern; however, suicide statistics are significantly underreported. Suicidality statistics include those with suicidal thoughts, suicidal plans, suicidal attempts, self-harm injuries, and completed suicides. The 2014 US statistics show 9.3 million (3.9%) have suicidal thoughts, 2.7 million (1.1%) made a plan, 1.3 million (0.6%) attempted suicide, 494,169 visited a hospital for self-harm injuries, and 42,773 completed suicide.[5] A number of ratios are established which include 13/100,000 commit suicide per year, there are 25 attempts for every completed suicide, 12 people harm themselves for every completed suicide, and 0.3% of those with suicidal thoughts commit suicide per year.[5]

Based upon the CDC research, there are at least 329,000 cases of Lyme disease diagnosed per year, mostly in children and middle-age adults, but only 25,000–40,000 per year meet their Surveillance Case Definition.[6] According to the CDC, "Surveillance Case Definitions establish uniform criteria for disease reporting and should not be used as the sole criteria for establishing clinical diagnoses."[7]

Diagnosing LAD

Any diagnosis is based upon a thorough clinical examination combined with physician judgment, and Lyme disease is no exception. Clinical practice guidelines may provide additional assistance. The US Agency for Healthcare Research and Quality maintains the National Guideline Clearinghouse and works closely with the Institute of Medicine to maintain standards for trustworthy evidence-based clinical practice guidelines which can assist with diagnosis.[8] In the National Guideline Clearinghouse, the only guidelines specifically addressing Lyme disease are the ILADS Guidelines (2014), but the American Psychiatric Association Practice Guidelines for the Psychiatric Evaluation of Adults (2016) are also listed.[8–10] These guidelines recognize the value of a thorough clinical exam, mental status exam, pattern recognition, and clinical judgment, and the ILADS guidelines discuss laboratory assessment in determining the diagnosis.[9,10]

Although not currently recognized in the National Guideline Clearinghouse, many turn to the Infectious Diseases Society of America (IDSA) Lyme disease guidelines (2006) for guidance in diagnosing Lyme disease.[11] The IDSA guidelines also recognize the value of a thorough clinical, laboratory assessment and physician judgment. They have a disclosure stating guidelines "are not intended to supplement physician judgment"; adherence to them are voluntary and their application is to be determined by the physician while recognizing "each patient's individual circumstances".[11]

For diagnosis, there are many similarities between the ILADS and IDSA guidelines, and a comprehensive clinical assessment is essential.

In addition to *Borrelia burgdorferi*, a number of other tick-borne coinfections, and secondary opportunistic infections, may also be diagnosed, which explains using the term "and associated diseases".[9,11] *B. burgdorferi* may be diagnosed as a persistent infection with immune suppressant and evasive capabilities,[12] or there may be a postinfectious process. In either case, the psychiatric symptoms are associated with an immune-mediated process.[13–17]

Citations addressing suicide and LAD

Currently, there are over 340 peer-reviewed international journal articles documenting psychiatric symptoms associated with LAD.[18] Although some patients may have no, or minimal, symptoms following a tick bite, others develop significant symptoms over time, including a broad spectrum of psychiatric impairments, such as the development of suicidal risk.[19] Combined homicide and suicide have also occurred.[20] In a prior presentation, homicidal tendencies occurred in about 15% of late-stage Lyme/tick-borne disease patients, and most of these patients also had suicidal tendencies.[21] No journal article has ever before performed a comprehensive assessment of the association between LAD and suicide.

Fourteen case reports in the international literature describe patients who became suicidal after acquiring LAD.[22–35] Fourteen additional citations recognize the causal association between suicide and LAD.[15,16,36–47] One article reviewed the clinical course of 57 patients diagnosed with Lyme disease and documented four suicide attempts in the 57 patients.[48] Five articles recognized that suicidality associated with LAD has an immune-mediated pathophysiology.[13,15,28,31,40]

Suicide as well as depression, anxiety, brain fog, paranoia, loss of mental capacities, and other mental symptoms were also reported to be associated with the Lyme vaccine clinical trial. The Adverse Event Reporting System described a 43-year-old man who committed suicide seven months after receiving the vaccine who described severe pain and an inability "to get relief from 14 different doctors he had seen".[29,49]

Depression is a well-recognized contributor towards suicidal risk. In the general population, there is a 16.2% lifetime prevalence and a 6.6% prior 12-month prevalence.[50] Although depression is not prevalent in the early stages of LAD in patients who are diagnosed and treated early and effectively,[51] in the later stages of LAD, the prevalence of depression is significantly higher with findings of 37%,[52] 37%,[53] 50%,[54] 51%,[55] 64%,[56] 47% (mood swings),[57] and 80% (with intrusive symptoms).[28] Intrusive symptoms can also contribute to causing suicide and violence, and 34% of patients with a history of LAD acquire intrusive symptoms.[28] Among these patients, 69% become suicidal, while 31% develop homicidal tendencies.[28]

A survey of a patient support group concluded hopelessness by lack of educated doctors, isolation, debilitating symptoms, depression caused by Lyme disease, feeling like a burden, and watching our friends die contributed to suicidal feeling in patients with LAD.[58]

Environmental exposure and suicide

Suicide risk is greater in outdoor workers, in particular forestry workers, and veterans.[59–63] Recent studies demonstrated the rate of suicide was highest among persons working in the farming, fishing, and forestry group (84.5/100,000), while the lowest rate was found in the education, training, and library occupational group (7.5/100,000).[64,65] While tick-borne disease exposure could be a contributor to those working in farming and forestry, it might not explain the high rate in fisherman.[66] Veterans can be at risk for tick-borne diseases from exposure during basic training and deployment; however, other causes of suicidality must also be considered, such as family disruption from deployment, being trained to kill, toxic exposure, and trauma.[67]

Infections increasing suicidality

Sickness syndrome is a well-recognized response to infection and is associated with anhedonia and depression, both of which are associated with suicidal risk.[68] A number of infections have been associated with suicide including influenza, coronaviruses, cytomegalovirus, HIV/AIDS, *Toxoplasma gondii*, and hepatitis C. Latent infection with *T. gondii* is a prevalent condition that has been linked in humans to suicide and suicide attempts. *T. gondii* titers may quantify a proneness to suicidal behavior. In a sample of 20 European nations, the prevalence of *T. gondii* was positively associated with national suicide rates, and *T. gondii* seropositivity was associated with a sevenfold greater risk of self-directed violence.[69–74]

The Danish nationwide register studies demonstrate a strong correlation between infections requiring hospitalization and suicide. In one study, hospitalization for COPD was associated with a significantly increased risk for

suicide.[75] Another study looked at all infections requiring hospitalization and demonstrated an increased risk of dying by suicide was found among people with hospital contacts with infections. The relative risk of suicide was increased among individuals with any hospitalization with infections by 42% compared with individuals without prior infection; the greater the number of hospital contacts for infections and days spent in treatment, the greater the risk of death by suicide. The authors said "The highest risks of suicide were found among individuals with hepatitis infection and HIV/AIDS infection" and "It will be important to understand how milder and long-term infections contribute to depression and suicidality. Such infections often go untreated and remain latent in the body for years."[76]

Psychoimmunology of suicide

The infectious disease and suicide association is mediated by cytokine and other immune effects. Infections impact CNS functioning by provoking cytokines that "can modulate the concentration of monoaminergic neurotransmitters and their metabolites in various regions of the CNS".[77] There is a significant body of research demonstrating a strong association between inflammation, brain inflammation, elevated cytokine levels, and suicide.[78–80] "Most suicide attempters, or subjects with suicidal ideation, show an imbalance in the immune system."[81] Interferon treatment for hepatitis C has been a clinical model demonstrating the significance of inflammation-mediated mental symptoms including suicide.[82] Cytokine activation has been associated with both suicide and self-harm behavior.[83] "IL-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity."[84] The brains of suicide victims had significantly increased microgliosis, which demonstrates the presence of brain inflammation, compared to subjects who died from other causes.[85] "Increased levels of IL-1β, IL-6 and TNF-α were shown in the anterior prefrontal cortex of teenage suicide victims."[86] "Suicidal ideation was significantly associated with an elevated inflammatory index of C-reactive protein, IL-6, IL-10 and TNF-α, in patients with depression."[87] A meta-analysis on inflammation in suicidal patients demonstrated "there are aberrant cytokine levels in blood, cerebrospinal fluid (CSF) and postmortem brain samples from suicidal patients. The levels of IL-1β and IL-6 were most robustly associated with suicidality, and these cytokines may help distinguish suicidal from non-suicidal patients."[88] In summary, conditions that cause brain inflammation can contribute significantly to suicidality. Lyme disease has been associated with the same proinflammatory cytokines TNF-α, IL-1β, and IL-6 that are associated with suicide.[89]

LAD psychoimmunology and suicide

There are multiple known and unknown mechanisms by which *B. burgdorferi* causes immune-mediated neuronal dysfunction resulting in clinical symptoms. Although some symptoms may be associated with infection within the brain or in the brain vasculature, infection in the periphery can also provoke significant immune activity that crosses the blood–brain barrier.[13] These immune-mediated effects include activation of proinflammatory cytokines and increases in TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-17, IL-18, interferon-gamma, neopterin, C-reactive protein, surface lipoprotein E, and the chemokines CXCL12 and CXCL13, release of proinflammatory lipoproteins from the outer coat of *B. burgdorferi*, immune effects from the flagella of *B. burgdorferi*, immune effects from outer surface protein A of *B. burgdorferi* inducing apoptosis and astrogliosis, autoimmune effects, direct cytotoxicity by proximity of *B. burgdorferi* to neurons and adherence to and invasion of neurons, interactions with Schwann and glial cells producing nitric oxide, the spirochetes locally inducing cytokines such as IL-6 or TNF-α in glial cells, the secretion of cytotoxic substances by leucocytes and glial cells contributing to damage of oligodendrocytes that are vital for the functioning and survival of neurons, and other immune effects from the other known and unknown coinfections and opportunistic infections.[13,17] In addition, metabolic pathophysiological changes are also associated with altered tryptophan metabolism, increases in quinolinic acid, oxidative stress, excitotoxicity, and changes in homocysteine metabolism.[13,17,90]

Inflammatory-mediated changes in tryptophan metabolism, quinolinic acid, and glutamate

The effects of inflammation on mood and behavior could partially be mediated by the effects upon tryptophan metabolism, kynurenine pathway metabolites, and glutamate neurotransmission. Inflammation increases indoleamine 2,3-dioxygenase which shifts tryptophan metabolism away from serotonin and melatonin towards an increase of quinolinic acid. Quinolinic acid correlates significantly with guilt, and the ratio of quinolinic acid/3-hydroxykynurenine correlates significantly with guilt and psychomotor agitation.[91] Quinolinic acid levels also correlate with increased suicidal risk.[92] High cerebrospinal fluid quinolinic acid levels correlate with high suicidal intent.[93] Quinolinic acid levels have

been demonstrated to be continuously elevated in the patients who had suicide attempts, and the levels were highest in close proximity to the attempt.[94] Quinolinic acid is an NMDA receptor agonist which leads to an excess of calcium influx into neurons. Quinolinic acid levels are increased, while kynurenic acid, an NMDA receptor antagonist, is decreased in suicidal patients which supports a role for a glutamatergic mechanism in suicidality. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus and the anterior midcingulate cortex compared to controls.[95] Quinolinic acid in cerebrospinal fluid is increased in a number of chronic infections including *B. burgdorferi* infections and correlates with "symptom severity" and "pathological potential".[96,97]

Altered neural circuits increasing suicidality

Decreased structural and functional connectivity in the amygdala–prefrontal neural system impairs emotional regulation and is associated with increased suicide risk.[98] The cingulate cortex is known to recruit other brain regions in response to conflict.[99] Brain regions and circuits associated with impulsive aggressiveness and self-directed aggressiveness involve an interaction between the orbital frontal cortex, the anterior cingulate cortex, and the amygdala. The orbital frontal cortex is significant in restraining impulsive outbursts, while the anterior cingulate cortex coordinates other brain regions in response to conflict. The amygdala is involved in fear response and other aversive emotions. In impulse-prone individuals, there is decreased activity in the orbital frontal cortex and/or anterior cingulate combined with normal or increased activity of the amygdala which demonstrates how these two restraining brain regions are not adequately counteracting the fear response when something is perceived and threatening and this can result in explosive and impulsive behavior.[100] It has been found that decreased white matter integrity and density in the superior longitudinal fasciculus is associated with intermittent explosive disorder.[101] LAD has been associated with a predominately white matter encephalopathy with white matter-processing impairments.[102]

Methods

A pilot study was performed to review clinical data. This consisted of a retrospective review of randomly selected inactive charts of patients with LAD from the author's practice with their identity protected. These patients were evaluated with a comprehensive assessment including premorbid assessment, history of tick exposure, history of the presence of erythema migrans rash, early tick-borne disease symptoms, symptoms in the course of illness, and current status with a comprehensive neuropsychiatric and general medical assessment and review of systems using the 280-item Neuropsychiatric Lyme Assessment with pattern recognition and a review of laboratory assessment, which may include enzyme-linked immune assay, immunofluorescent assay, Western blot, DNA-based testing, coinfection testing, single-photon emission tomography, magnetic resonance imaging, or other diagnostic testing to determine the diagnosis.[8–11,103,104] Only testing from laboratories validated by the Clinical Laboratory Improvement Amendments of the US Department of Health and Human Services Centers for Medicare and Medicaid Services was considered valid. Charts in which the diagnosis of Lyme disease was unclear were excluded from the study. The 253 charts that met the criteria were divided into four groups based upon symptoms – suicidal and homicidal, suicidal not homicidal, experiencing explosive anger not suicidal or homicidal, and not suicidal, homicidal, or experiencing explosive anger. The patients who were both suicidal and homicidal were considered to be the most severe cases, while the patients who were least severe were the patients who were not homicidal, suicidal, or experiencing explosive anger. Names were converted to an identifier before entering findings into a database of individual participant data. Clinical findings most relevant to the diagnosis and suicidal risk were analyzed. All 29 of the suicidal and homicidal charts were reviewed, and a representative sample of 20 charts from the suicidal group was pulled at random from the suicidal but not homicidal group and 20 charts were pulled at random from the not suicidal, homicidal, or experiencing explosive anger group. A comparison of individual participant data is made by comparing the findings for all patients suicidal and homicidal (N=29) to the findings for those suicidal and not homicidal (N=20) and not homicidal or suicidal or experiencing explosive anger (N=20). The premorbid health status is the control for each group and is shown in parentheses in Figure 1. Symptoms associated with risk were ranked by comparing the prevalence of different findings among the three different groups. Two representative cases of suicidal LAD patients are described. In the case reviews, identifying information was removed to conceal identities. In the nonfatal case, written consent was obtained for publication. In the fatal case, written consent from the next of kin was obtained for publication.

Since there are no databases of LAD suicides, the prevalence can only be estimated indirectly by using CDC statistics of Lyme disease, calculating the percent with

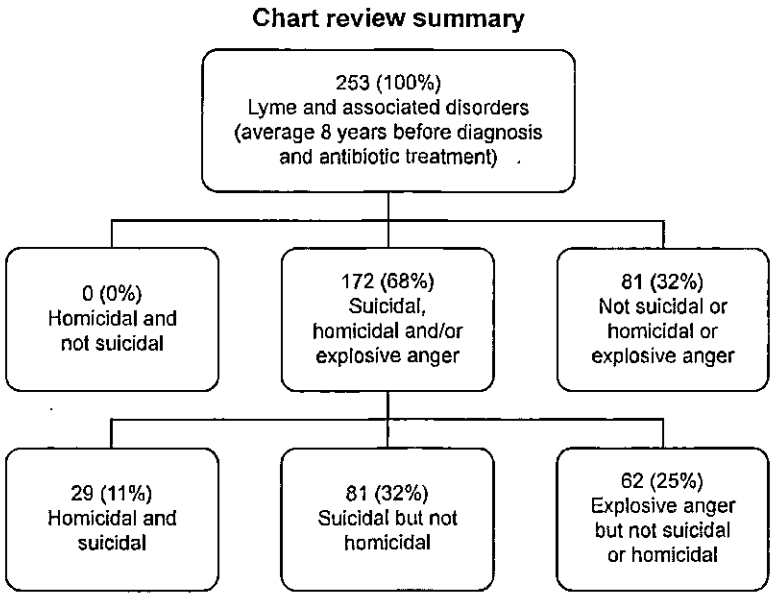

Figure 1 Chart review flowsheet.

persistent symptoms that occur each year, multiplying this number by the duration based on the medical literature, and multiplying this by the percent of patients with suicidal thoughts to determine the number of patients with Lyme disease and suicidal thoughts. The CDC statistics of the ratios of patients with suicidal thoughts to those who completed suicides were used to calculate the estimated number of patients with LAD and suicidal thoughts who completed suicide per year in the US.

The Meridian Health Institutional Review Board, Neptune, NJ, USA, approved this study (IRB # 201704192J), as exempted. Patient consent to review their medical records was not required as there was minimal risk to subjects, no subject identifiers or links to identifiers were used or collected, and it was a retrospective chart review of already existing data. In the case reports, the next of kin of the deceased patient signed a consent to publish the case, and the patient who survived signed a consent to publish the case.

Results

Chart review

A review of 253 inactive charts of patients with LAD (58% female, 42% male, age 8–64 years, average age 39 years) from the investigator's practice demonstrated an average of 8 years before diagnosis and initiating treatment for LAD. All of these patients met the clinical criteria for the diagnosis of LAD. Many had a history of erythema migrans rashes; all had objective clinical findings; most had laboratory confirmation and were tested positive for *B. burgdorferi*; some had findings demonstrated by single photon emission tomography, magnetic resonance imaging, and/or spinal taps, and most tested positive for a number of coinfections which included *Babesia, Bartonella, Anaplasma, Ehrlichia chaffeensis, Rickettsia rickettsii*, Epstein–Barr virus, cytomegalovirus, human herpesvirus-2, *Mycoplasma pneumonia, Chlamydophila pneumoniae*, and hepatitis C virus. The laboratory assessment of these patients was often performed before referral to the investigator.

Many patients fulfilled CDC Surveillance Case Definition, while in other patients, Surveillance Case Definition was not used as the sole criteria for establishing the clinical diagnosis.[7] It is recognized Lyme disease Surveillance Case Definition based upon immune-based two-tier testing has a very low sensitivity (46%)[105] and "generated over 500 times false-negative results than two stage HIV testing".[106] The limitations of this testing are understandable since two-tier Lyme testing is an immune-based test for a highly adaptive spirochete that is well known to suppress and evade the immune system.[12,107,108] This also explains the disparity between the number of CDC Surveillance Case Definition cases and the actual cases of Lyme disease each year.[6,7] Comparing these two groups was not the purpose of this study; however, the only distinction that could be seen between these two groups in the clinical presentation was a higher prevalence of periostitis in the patients fulfilling CDC Surveillance Case Definition.

Of the 253 patients, 68% (N=172) were suicidal, homicidal, and/or had explosive anger, while 32% (N=81) were nether suicidal and homicidal nor had explosive anger. On looking at the 172 patients in greater detail, 43% of the 253 (N=110) were suicidal, 32% (N=81) were suicidal but not homicidal, and 11% (N=29) were both suicidal and homicidal. Moreover, none of the 253 patients were homicidal without also being suicidal, and 25% of the 253 (N=62) had explosive anger but were neither suicidal nor homicidal (Figure 1).

Among the 109 patients who were suicidal, 26% (N=29) were also homicidal. A review of patients who were both suicidal and homicidal demonstrated an average of 8.4 years before diagnosis and initiating LAD treatment. Of all the patients, 10% had preexisting depression. After infection, 97% of this group had depression. One patient (4%) had preexisting suicidal and homicidal tendencies, but the date of onset of the infection was unclear in this patient and may have preceded the onset of these symptoms.

In the chart review of LAD patients, a higher level of risk to self and others in the order of significance was associated with the presence of explosive anger, intrusive images, sudden mood swings, paranoia, dissociative episodes, hallucinations, disinhibition, panic disorder, rapid cycling bipolar, depersonalization, social anxiety disorder, substance abuse, hypervigilance, generalized anxiety disorder, genital–urinary symptoms, chronic pain, anhedonia, depression, low frustration tolerance, posttraumatic stress disorder, obsessive compulsive disorder, cardiac symptoms, cognitive symptoms, musculoskeletal symptoms, and fatigue, but not gastrointestinal symptoms, vegetative symptoms, pulmonary/upper respiratory symptoms, or neurological symptoms (Table 1). Very few of these conditions were present in these patients before they were infected with LAD (Table 2).

Table 1 Higher-risk vs lower-risk groups

Clinical finding	Suicidal and homicidal	Suicidal	Not suicidal, homicidal, or aggressive
Hallucinations	45% (0%)	25% (0%)	0% (0%)
Explosive anger	83% (4%)	60% (0%)	0% (0%)
Dissociative episodes	18% (4%)	5% (0%)	0% (0%)
Paranoia	76% (0%)	25% (0%)	10% (0%)
Disinhibition	80% (0%)	35% (0%)	20% (0%)
Intrusive images	48% (0%)	0% (0%)	5% (0%)
Rapid cycling bipolar	21% (0%)	20% (0%)	5% (0%)
Sudden mood swings	93% (0%)	85% (0%)	15% (0%)
Panic disorder	80% (4%)	50% (0%)	35% (5%)
Depersonalization	76% (4%)	55% (0%)	40% (0%)
Substance abuse	28% (8%)	5% (0%)	10% (5%)
Social anxiety	55% (0%)	65% (10%)	20% (0%)
Hypervigilance	72% (0%)	55% (5%)	35% (0%)
Generalized anxiety	90% (4%)	65% (0%)	50% (5%)
Anhedonia	72% (4%)	85% (0%)	59% (5%)
Genital–urinary symptoms	59% (5%)	80% (5%)	45% (0%)
Chronic pain	57% (0%)	65% (0%)	35% (0%)
Depression	97% (10%)	100% (15%)	80% (5%)
Low frustration tolerance	100% (0%)	90% (0%)	80% (0%)
Posttraumatic stress disorder	24% (17%)	15% (0%)	15% (15%)
Obsessive compulsive disorder	48% (0%)	30% (10%)	35% (0%)
Cardiac symptoms	63% (8%)	50% (0%)	50% (0%)
Cognitive symptoms	100% (4%)	100% (0%)	85% (0%)
Gastrointestinal symptoms	71% (4%)	85% (0%)	75% (5%)
Musculoskeletal symptoms	100% (0%)	90% (0%)	90% (0%)
Fatigue	97% (0%)	85% (0%)	85% (0%)
Vegetative symptoms	100% (0%)	95% (0%)	100% (0%)
Pulmonary/upper respiratory	66% (8%)	70% (0%)	70% (5%)
Neurological symptoms	86% (0%)	95% (0%)	90% (0%)

Note: Data in parentheses report the findings before infection.

Case reviews

A patient who committed suicide

The patient was infected 10 years before being diagnosed with Lyme disease with coinfections with clinical symptoms and laboratory confirmation. Before diagnosis, there was a progressively increasing onset of multiple symptoms that included attention span impairments, executive dysfunction, sensory hyperacusis, memory impairments, slow processing, depersonalization, derealization, aggressive intrusive thoughts and images, dissociative episodes, illusions, hallucinations, decreased frustration tolerance, feeling overwhelmed, sudden abrupt mood swings, agitation, hypervigilance, paranoia, disinhibition, explosive anger, suicidal thoughts, guilt, substance abuse, crying spells, depression, anhedonia, apathy, panic attacks, agoraphobia, social anxiety, generalized anxiety, posttraumatic stress disorder, non-restorative sleep, anorexia, decreased libido, night sweats, headaches, cranial nerve symptoms, neuropathy, burning hands and feet, fatigue, weakness, tremors, twitching, myoclonic jerks, musculoskeletal symptoms, racing pulse, irritable gut, and spastic bladder. The patient had limited response to psychiatric treatments, and antibiotics resulted in extreme Jarisch–Herxheimer reactions with increased severity of symptoms.

Table 2 Findings in the groups before infection

Clinical finding	Suicidal and homicidal	Suicidal	Not suicidal, homicidal, or aggressive
Hallucinations	0%	0%	0%
Explosive anger	4%	0%	0%
Dissociative episodes	4%	0%	0%
Paranoia	0%	0%	0%
Disinhibition	0%	0%	0%
Intrusive images	0%	0%	0%
Rapid cycling bipolar	0%	0%	0%
Sudden mood swings	0%	0%	0%
Panic disorder	4%	0%	5%
Depersonalization	4%	0%	0%
Substance abuse	8%	0%	5%
Social anxiety	0%	10%	0%
Hypervigilance	0%	5%	0%
Generalized anxiety	4%	0%	5%
Anhedonia	4%	0%	5%
Genital–urinary symptoms	5%	5%	0%
Chronic pain	0%	0%	0%
Depression	10%	15%	5%
Low frustration tolerance	0%	0%	0%
Posttraumatic stress disorder	17%	0%	15%
Obsessive compulsive disorder	0%	10%	0%
Cardiac symptoms	8%	0%	0%
Cognitive symptoms	4%	0%	0%
Gastrointestinal symptoms	4%	0%	5%
Musculoskeletal symptoms	0%	0%	0%
Fatigue	0%	0%	0%
Vegetative symptoms	0%	0%	0%
Pulmonary/upper respiratory	8%	0%	5%
Neurological symptoms	0%	0%	0%

Some treatments were denied by the insurance company, and disability coverage was denied. The patient became increasingly disabled and demoralized. After three failed attempts, a suicide plan that had been in place for an extended period of time was implemented.

A veteran who almost committed suicide

In the words of the patient,

> I woke up on a beach out of the country with a bottle of scotch in one hand and my handgun in the other. I did not remember driving there. My doctor said I was in a psychogenic fugue state. My life was being destroyed by Lyme disease and no one had a clue. At work, I had been highly awarded throughout my career but it became a real struggle and I did not understand why. When I went to work that morning, I was tired, frustrated and in a state of dread and fear and I drove 100 miles past the base. I only drank a small amount of the scotch; the bottle was still nearly full. I have never been a big drinker and as a result I fell asleep on the beach. I woke up the next day wondering how I got there and why and drove back to the base and turned myself in for Away Without Leave (AWOL). After being diagnosed, treated and having recovered, I can relate to other veterans living with undiagnosed and untreated Lyme disease.

Summarizing case review results

There are many patterns of suicide seen in LAD patients, and the cases described represent the two most common patterns of suicide that have been observed. These cases demonstrate not all patients follow the same pattern in the development of suicidal risk. In the first case, the suicide risk evolved and increased over an extended period of time and was well planned with an overwhelming severity of multiple symptoms including all of the symptoms associated with suicidality that were demonstrated in the chart review. This case had similarities to the suicide case described in the Lyme vaccine trials. The second case was unpredictable with no advanced planning, and these cases are often bizarre and senseless. In this case, there appeared to be an acute trigger, possibly sleep deprivation, which is a recognized trigger for suicidal behavior in the presence of other psychiatric risks for suicide.[109]

Lyme disease statistics relevant to suicide

It has been calculated that 28% of Lyme patients progress to develop chronic symptoms,[110,111] nearly half of the patients had Lyme disease for more than 10 years before their initial diagnosis,[112] once depression occurs it tends to persist,[113] and psychiatric symptoms associated with LAD often persist in spite of antibiotic treatment.[114,115] A prior study demonstrated 41% of children who had been diagnosed with Lyme disease had suicidal thoughts and 11% had made suicidal gestures,[116] another study demonstrated 33% of late-stage Lyme disease patients were suicidal,[21] and another study demonstrated 18% of posttreatment Lyme disease patients hade suicidal ideations,[117] while another study demonstrated 69% of Lyme/tick-borne disease patients with intrusive symptoms had suicidal thoughts.[28]

Possible prevalence of suicidality associated with LAD

There are no direct records of the number of LAD patients who commit suicide. Therefore, an indirect method is implemented to estimate the possible prevalence of suicidality

associated with LAD. Using the statistics previously stated in this article and the CDC statistic of at least 329,000 cases per year of Lyme disease and recognizing that initial infections occur mostly in children and middle-age adults, it has previously been calculated that 28% of Lyme patients progress to develop chronic symptoms which would mean at least 92,120 per year go on to develop chronic symptoms.[6,108] Of the total number of patients, 48% go 10 or more years before their initial diagnosis, and symptoms (including psychiatric symptoms) often persist when there has been a significant delay in initiating antibiotic treatment.[112] Since many are relatively young with significant longevity, it is estimated the average duration of illness is at least 25 years which calculates to 2,303,000 having chronic symptoms. Studies previously discussed demonstrated persistent suicidal ideations were present in 33%, 69% (with intrusive symptoms), 18% and 43% in the chart review in this article.[21,28,117] I shall use the most restrictive number of 18% of posttreatment Lyme disease patients having suicidal ideations which calculates to 414,540 LAD patients with suicidal ideations.[117] When using this number with the suicidality ratio of 0.3% with suicidal ideations of committing suicide per year and other ratios, it calculates to 1,244 suicides, 14,928 self-harm events, 31,100 suicide attempts, and 414,540 patients with suicidal ideations in the US per year from LAD, based on indirect calculations.[5] This number would be higher when adding undiagnosed and untreated cases with persistent symptoms and when adding those attributed to the coinfections and other associated diseases that may be seen in patients with Lyme disease.

Conclusion

LAD contributes to causing suicidal tendencies, suicide, and combined suicidal and homicidal tendencies in individuals who did not show these tendencies before being infected. Suicide risk is greater in veterans and outdoor workers, both of whom have greater exposure to LAD. Multiple case reports and other journal articles recognize a causal association between suicidal risk and LAD. LAD has been associated with an increased risk of depression in a number of different studies and has also been associated with intrusive symptoms, both of which are associated with an increased risk of suicide. A suicide was reported in the Lyme vaccine clinical trial.

Multiple studies link infections, in particular chronic infections, and the associated proinflammatory cytokines, and metabolic changes and neural circuit dysfunction with increased risk of suicidal behavior. It appears that suicide with infectious diseases and LAD share common immune, quinolinic acid, glutamate, and neural dysfunction-mediated pathophysiology resulting in a broad spectrum of psychiatric and other symptoms that can be associated with increased suicidal risk. Tick-borne and other coinfections may further contribute to increasing symptoms (Figure 2).

Lyme and associated diseases infection→
Persistent proinflammatory cytokines→
Dysregulation of tryptophan metabolism→
Quinolinic acid→NMDA receptor agonism→
Glutamate dysregulation→
Neural circuit dysfunction→
Psychiatric dysfunction→
Suicidal, sometimes also homicidal

Figure 2 The death formula.
Abbreviation: NMDA, N-methyl-D-aspartate.

The chart review of 253 patients generally reflects the findings in the medical literature. In the chart review, the patients were infected an average of 8 years before diagnosis and antibiotic treatment, and 43% had suicidal tendencies. In addition, 26% of these suicidal patients were also homicidal, but there were no patients who were homicidal without also being suicidal.

A higher level of risk of harm is associated with the presence of a number of conditions acquired as part of LAD and include explosive anger, intrusive images, sudden mood swings, paranoia, dissociative episodes, hallucinations, disinhibition, panic disorder, rapid cycling bipolar, depersonalization, social anxiety disorder, substance abuse, hypervigilance, generalized anxiety disorder, genital–urinary symptoms, chronic pain, anhedonia, depression, low frustration tolerance, posttraumatic stress disorder, obsessive compulsive disorder, cardiac symptoms, cognitive symptoms, musculoskeletal symptoms, and fatigue, but not gastrointestinal symptoms, vegetative symptoms, pulmonary/upper respiratory symptoms, or neurological symptoms.

Some LAD suicides are associated with being overwhelmed by severe, multiple neuropsychiatric, and general medical symptoms.

Other LAD suicides are impulsive, bizarre, senseless, and difficult to predict. It is possible that disabling symptoms, feeling like a burden, and negative attitudes about Lyme disease from family, friends, doctors, and/or the health care system may also contribute to suicidal risk.

The prevalence of LAD suicides calculated by an indirect method is estimated to be possibly 1,244 suicides and 414,540 patients with suicidal ideations in the US per year from LAD.

A means of acquiring accurate direct statistics of suicide and LAD is needed. It is suggested medical examiners, the

CDC, and other epidemiological organizations proactively evaluate the association between LAD and suicide. Better recognition of the significance of LAD, earlier diagnosis and treatment, better understanding of the pathophysiology of suicide, and screening for suicide risk in LAD patients are also needed.

Abbreviations

CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America; IL, interleukin; ILADS, International Lyme and Associated Diseases Society; LAD, Lyme and associated diseases; NMDA, N-methyl-D-aspartate; TNF-α, tumor necrosis factor-alpha.

Acknowledgments

The author expresses his appreciation to Lorraine Johnson, JD, MBA, Andy Kogelnik, MD, PhD, Douglas Bransfield, MBA, JD, and Barbara Rosenthal for their assistance. He would like to acknowledge the memory of many fine individuals whose lives were lost by suicide and the challenge of those currently affected by suicidal thoughts.

Disclosure

The author has been an expert witness in cases involving suicide and in cases involving Lyme disease. He reports no other conflicts of interest in this work.

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Medical Hypotheses xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Divergent opinions of proper Lyme disease diagnosis and implications for children co-morbid with autism spectrum disorder

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ARTICLE INFO

Article history:
Received 1 February 2014
Accepted 6 June 2014
Available online xxxx

ABSTRACT

This paper proposes that some children with an autism spectrum disorder (ASD) in the United States have undiagnosed Lyme disease and different testing criteria used by commercial laboratories may be producing false negative results. Two testing protocols will be evaluated; first, the Centers for Disease Control (CDC) and Infectious Disease Society of America (IDSA) approved two-tiered Enzyme Immunoassay (EIA) or Immunofluorescence Assay (IFA) followed by an IgM and/or IgG Western Blot test. Second, a clinical diagnosis (flu like symptoms, joint pain, fatigue, neurological symptoms, etc.) possibly followed by a Western Blot with a broader criteria for positive bands [1]. The hypothesis proposes that the former criteria may be producing false negative results for some individuals diagnosed with an ASD. Through an online survey parents of 48 children who have a diagnosis of an ASD and have been diagnosed with Lyme disease were asked to fill out the Autism Treatment Evaluation Checklist (ATEC) before they started antibiotic therapy and after treatment. Of the 48 parents surveyed 45 of them (94%) indicated their child initially tested negative using the two-tiered CDC/IDSA approved test. The parents sought a second physician who diagnosed their child with Lyme disease using the wider range of Western Blot bands. The children were treated with antibiotics and their scores on the ATEC improved. Anecdotal data indicated that some of the children achieved previously unattained developmental milestones after antibiotic therapy began. Protein bands OSP-A and/or OSP-B (Western Blot band 31) and (Western Blot band 34) were found in 44 of 48 patients. These two bands are so specific to *Borrelia burgdorferi* that they were targeted for use in vaccine trials, yet are not included in the IDSA interpretation of the Western Blot.

Autism

Autism is a developmental disorder that appears in the first 3 years of life. It is a physical impairment linked to abnormal biology and chemistry that affects typical development of social and communication skills [2]. Over the last twenty years the reported prevalence of autism has increased over 600% [3]. The increased awareness has led to a classification of Autism Spectrum Disorders [ASDs]. ASDs are a group of developmental disorders including, Autism Disorder, Asperger Syndrome, and Pervasive Developmental Disorder – Not Otherwise Specified [PDD-NOS] [4,5]. The latest data from the CDC indicates 1 in every 68 children will be diagnosed with an ASD [4].

Lyme disease

Lyme disease is a multisystemic illness caused by the spirochete bacteria *Borrelia burgdorferi* [Bb]; it is the most common vector born disease in the United States [6]. The most common mode of transmission of Lyme disease is through the bite of an infected Ixodes Scapularis tick (also known as a deer tick) [6]. Misdiagnosis of initial symptoms of Lyme disease and delayed treatment can lead to debilitating chronic illnesses with musculoskeletal, cognitive, and neuropsychiatric impairments [7]. Children who have been undiagnosed and later found to have Lyme disease have displayed decreased reading comprehension and handwriting skills, impaired speech fluency, attention deficit behavior, hyperactivity, withdrawal from activities with peers, inability to perform at grade level, obsessive compulsive behavior, anxiety, mood swings, dyslexic-like behaviors, sensitivity to light and sound, and inability to manage frustration [8]. Lyme disease has been called "The Great Imitator" because

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http://dx.doi.org/10.1016/j.mehy.2014.06.005
0306-9877/

Please cite this article in press as: Kuhn M, Bransfield R. Divergent opinions of proper Lyme disease diagnosis and implications for children co-morbid with autism spectrum disorder. Med Hypotheses (2014), http://dx.doi.org/10.1016/j.mehy.2014.06.005

infected individuals often present neurological and physical symptoms that are similar to other disorders [9].

Diagnosing lyme disease

There is a division of opinions between physicians on how to properly diagnose Lyme disease. Some physicians follow guidelines published by the Infectious Disease Society of America (IDSA), while others follow guidelines published by International Lyme and Associated Disease Society (ILADS). Both guidelines are peer reviewed and evidence based [10]. The IDSA guidelines are recommended to physicians by both the CDC and the Food and Drug Administration (FDA).

According to the CDC the proper way to diagnose Lyme is:

> Signs and symptoms (flu like symptoms, joint pain, fatigue, neurological symptoms) and a history of possible exposure to infected blacklegged ticks
> Laboratory blood tests are helpful if used correctly and performed with validated methods. Laboratory tests are not recommended for patients who do not have symptoms typical of Lyme disease. Just as it is important to correctly diagnose Lyme disease when a patient has it, it is important to avoid misdiagnosis and treatment of Lyme disease when the true cause of the illness is something else [6].

The CDC recommends the following protocol for laboratory testing:

> The first required test is the Enzyme Immunoassay (EIA) or Immunofluorescence Assay (IFA). If this test yields negative results, the provider should consider an alternative diagnosis; or in cases where the patient with has had symptoms for less than or equal to 30 days, the provider may treat the patient and follow up with a convalescent serum. If the first test yields positive or equivocal results, two options are available: (1) If the patient has had symptoms for less than or equal to 30 days, an IgM Western Blot is performed; (2) if the patient has had symptoms for more than 30 days, the IgG Western Blot is performed. The IgM should not be used if the patient has been ill for more than 30 days [6].

Physicians who follow ILADS guidelines use a clinical diagnosis of neurological symptoms, exposure to an area endemic for ticks, joint pain, inflamed lymph nodes and family history of Lyme or autoimmune disorders [11]. ILADS physicians also use laboratory testing, but do not always determine a patient negative for Lyme if the first-tier test comes back negative (EIA or IFA) [11]. Many times a Western Blot is performed and a broader view of the results are evaluated. There are nine known Bb species specific Western Blot antibodies (bands): 18, 23, 31, 34, 37, 39, 83 and 93 [12]. Only one of these Bb genus specific bands is needed to confirm that there is lab evidence of exposure to the Bb spirochete and can confirm a clinical diagnosis of Lyme disease [11]. CDC Western Blot IgG surveillance criteria include 18, 23, 30, 37, 39 and 93 and exclude bands 31, 34 and 83, even though bands 31 and 34 are so specific to Bb they were targeted for use in Lyme vaccine trials [13].

Controversy with laboratory testing

The CDC cautions against using unapproved testing:

> CDC and the Food and Drug Administration (FDA) have become aware of commercial laboratories that conduct testing for Lyme disease by using assays whose accuracy and clinical usefulness have not been adequately established. Health-care providers are reminded that a diagnosis of Lyme disease should be made after evaluation of a patient's clinical presentation and risk for exposure to infected ticks, and, if indicated, after the use of validated laboratory tests [14].

The CDC also states

> Surveillance case definitions establish uniform criteria for disease reporting and should not be used as the sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement [15].

However many use the CDC surveillance criteria as a diagnostic criteria.

The two-tiered testing model is the only laboratory testing approved by the CDC and FDA, but the sensitivity of the test has been scrutinized. The sensitivity of the two-tier test system has been estimated to be 44%–56% when standard commercial Lyme testing was evaluated in clinical practice [1,10,16–22]. In a molecular diagnostic study, the sensitivity of this testing approach may be as low as 7.5% [23]. Some reasons for the false negative test result include: specimen improperly handled; test run too soon (antibodies to Bb have not formed); Western Blot does not test for all antigens; immune suppression by recent antibiotics; lab tests are standardized for early, not late stage Lyme disease; antibodies may decline over time; antibodies are bound up in immune complexes (tests detect only free antibodies); spirochetes may be hidden or dormant in a cell deficient wall [13].

The outcomes of the two-tiered testing has raised concerns with physicians about its validity. Recently Virginia and Maine (United States) passed bills which require all doctors in their state to inform their patients that a negative outcome on the two-tiered test does not conclusively rule out infection of Bb [24,25].

Lyme/Autism connection

A study of was conducted by Dr. Garth Nicolson in 2003 where 20% of the children ($n = 48$) diagnosed with an ASD came back positive for Lyme disease [26]. A similar study was conducted by Dr. Aristo Vojdani [27] and 22% of the ASD patients ($n = 54$) he tested came back positive. Kuhn et al. [19] evaluated five children diagnosed with an ASD and Lyme disease before and after they were treated with antibiotic therapy. All five children in the study showed improvement on the ASD evaluation tool used to assess them after they completed treatment [19]. In all of the published studies the children were considered positive using a clinical diagnosis and a broader interpretation of the Western Blot [26,19,27]. In a personal interview with an assistant of Dr. Charles Ray Jones, a pediatric physician who exclusively treats Lyme disease, it was claimed that 50% of his patients who have been diagnosed with an ASD have come back positive for Lyme disease. He also claimed that all of his patients' symptoms improve with antibiotic therapy. In a recent study Ajamian et al. [28] evaluated 120 children, 70 with ASD and 50 healthy controls for Lyme using the two-tiered Lyme test. Using the CDC approved two-tiered testing protocol 0/120 children tested positive.

Hypothesis

Shortly after the Ajamian et al. study was published numerous medical media websites and publications reported headlines akin to: "Lyme/Autism theory debunked." The mentioned study followed CDC and FDA approved laboratory guidelines for Lyme

Please cite this article in press as: Kuhn M, Bransfield R. Divergent opinions of proper Lyme disease diagnosis and implications for children co-morbid with autism spectrum disorder. Med Hypotheses (2014), http://dx.doi.org/10.1016/j.mehy.2014.06.005

disease testing and it was conducted with an appropriate control sample [28]. We believe it is inappropriate to make a definitive statement about the connection between Lyme disease and Autism without using clinical criteria and other diagnostic tests. Our hypothesis is that some patients with an ASD who test negative using the two-tiered laboratory Lyme test are actually receiving a false-negative and their autistic symptoms will improve with proper antibiotic treatment. To test this we sent an online survey to parents of 48 children who claimed to have a child with a diagnosis of Lyme disease and an ASD. To be considered for the survey the parents had to submit the child's official diagnosis of an ASD from a licensed psychologist and a laboratory test showing some sign of Bb infection. In the initial questionnaire we asked if their child met the CDC two-tiered guidelines (6% [3/48] responses reported that they met the criteria). The parents of the other 45 children took their child to another physician who diagnosed them with Lyme disease using the broader interpretation of the Western Blot and clinical criteria like neurological symptoms, fatigue, relapse of flu like symptoms, and sensitivity to light and sound.

To determine if the treatment did alleviate any autistic symptoms the parents filled out the Autism Treatment Evaluation Checklist (ATEC) twice. First, they completed the ATEC describing their child's symptoms before they started antibiotic therapy and second after treatment finished.

The ATEC was developed in 1999 to help researchers evaluate the effectiveness of various treatments for children with autism and adults and to help parents determine if their children benefit from a specific treatment. It is a one-page form designed to be completed by parents, teachers, or caretakers. It consists of 4 subtests: I. Speech/Language Communication (14 items); II. Sociability

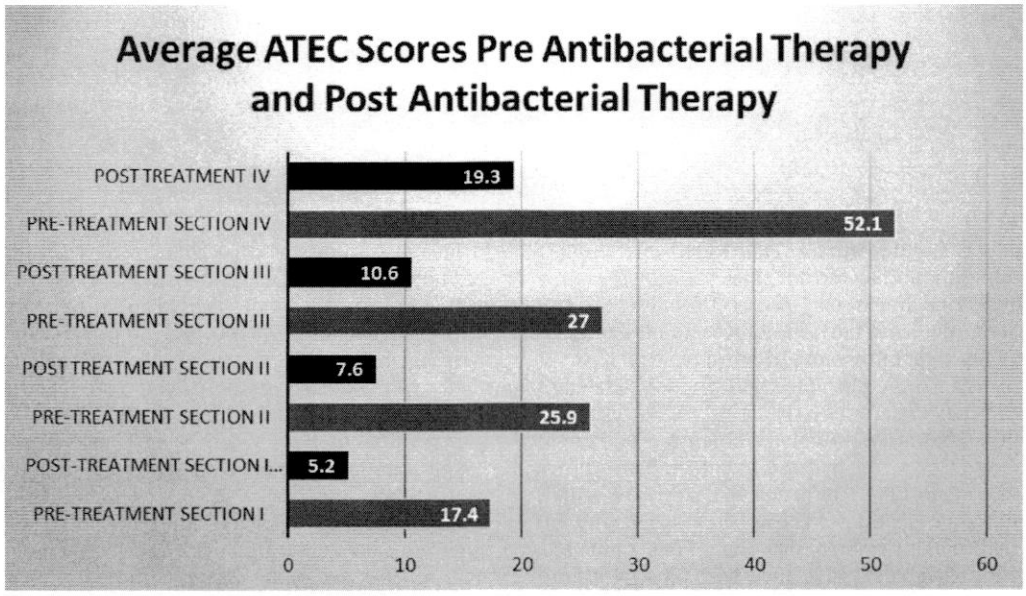

Fig. 1. Pre and post ATEC scores reported by the parents in the study. The subsets of the ATEC are: Section I – Speech/Language/communication, Section II – Sociability, Section III – Sensory/Cognitive Awareness, Section IV –Health/Physical/Behavior.

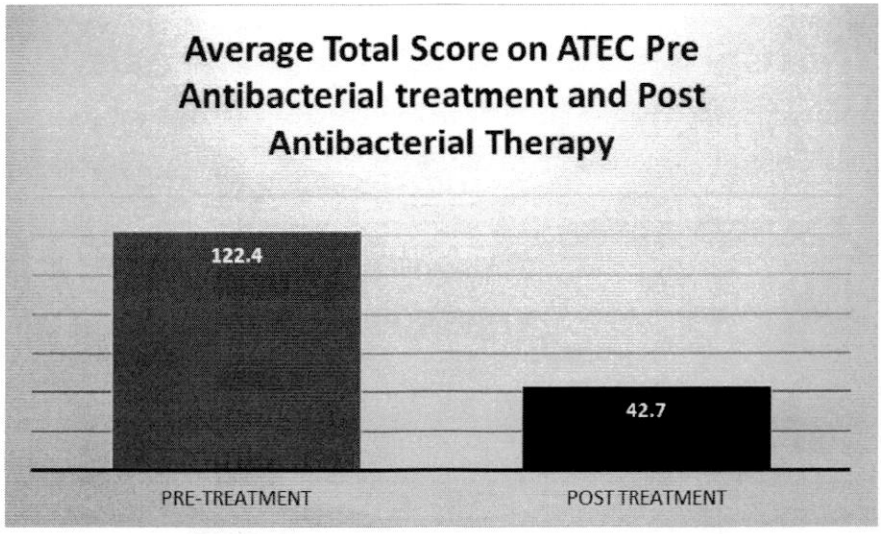

Fig. 2. Total pre and post ATEC scores reported by the parents in the study. A score of 104–180 is considered in the severe range. A score of 30 or below is considered mild.

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(20 items); III. Sensory/Cognitive Awareness (18 items); and IV. Health/Physical/Behavior (25 items).

When the parents complete the ATEC they select a zero if the phrase is not true, a one if it is sometimes true, and a two if it is very true; the lower the score the less severe the autistic symptoms. When the subset ratings are added a total score of 180 is possible. Scores closer to 180 would indicate a severe case of autism symptoms and a score less than 30 indicates a mild case of autistic symptoms. The ATEC is not copyrighted and may be used free of charge by any researcher [29]. The Autism Research Institute examined the reliability of the ATEC by conducting a split-half reliability test on over 1300 completed ATECs. The internal consistency reliability was high (.94 for the Total score) [29].

Empirical data

All 48 of the children's scores on the ATEC survey improved with antibiotic therapy (see Fig. 1). The overall mean score of the children moved from a classification of severe-autism to close to mild-autism (Fig. 2). Parents were also given the opportunity to explain in greater detail any changes they observed during treatment, some responded with anecdotal data (Fig. 3). The parents of the children in the study indicated that no other educational or biomedical therapies were changed during the period they treated their child's Lyme disease infection.

Consequence of the hypothesis and discussion

A large majority of the children in the survey would not have received antibiotic therapy if their physician followed the two-tiered IDSA/CDC recommended testing [93.8% (45/48)]. The CDC's Morbidity and Mortality Weekly Report (MMWR) claimed: "We do not recommend skipping the first test and just doing the Western Blot. Doing so will increase the frequency of false-positive results and may lead to misdiagnosis and improper treatment [14]." Yet, the physicians who treated the children in the survey

"Regained the ability to speak"
"Spoke first word three weeks after we started antibiotics."
"Reduced anxiety in public. Better sleep. Increased playtime with other kids. Social gains. Increased language."
Was completely non-verbal, now can speak in full sentences
"Before we started treatment my child needed round the clock supervision at school with a full time aid. Now he is in a regular education classroom with his peers almost the entire day with no assistance."
"My child use to self-injure himself (slap himself in the face, hit his head against the wall). All of those behaviors stopped once we treated his Lyme."

Fig. 3. A few examples of anecdotal data collected from the survey. Above are responses to the question: Did your child achieve any significant developmental milestones during treatment? Six out of forty eight participants (12.5%) responded "No.".

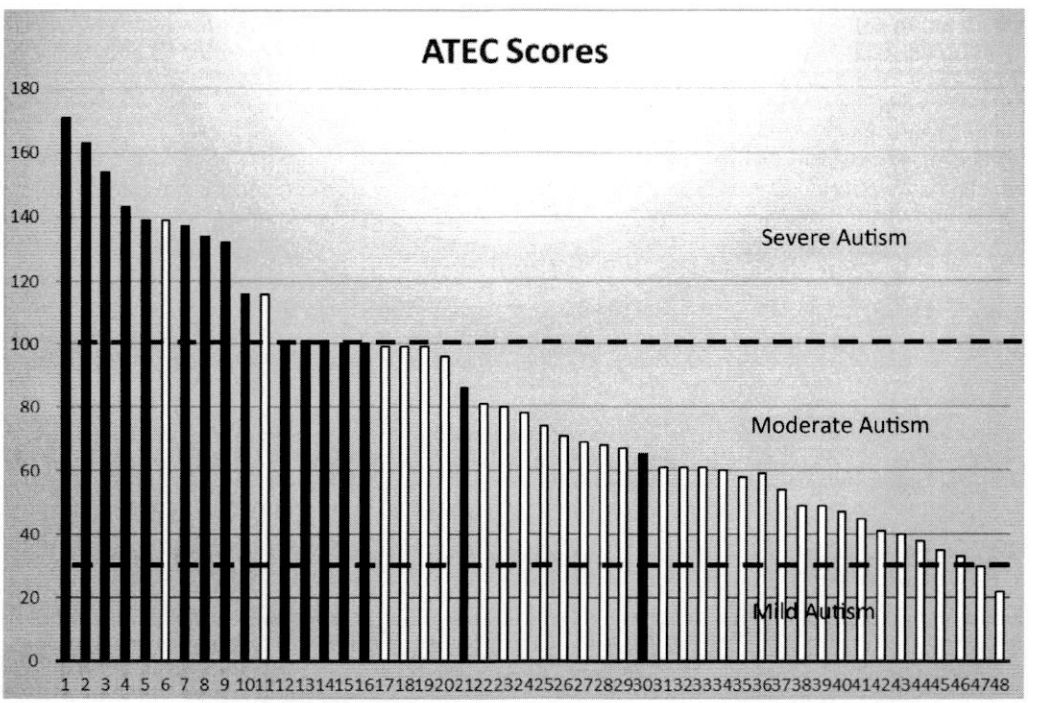

Fig. 4. The pre-treatment ATEC scores of all 48 children in the study. The scores in black indicated a positive result for OSP B. The scores in white had other positive bands on their Western Blot but not OSP B.

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did exactly what the MMWR warned against and the benefit to their patients was evident in the ATEC scores and the anecdotal data. The results of the study raise questions about the validity of the commercially approved IDSA/CDC Lyme disease test. If the parents of the children in the study had not pursued a second opinion from a physician who followed ILADS guidelines their child would have not received a Lyme disease diagnosis and they would have not received antibiotic therapy. The improved ATEC scores clearly indicate that the antibiotics had a positive impact on the welfare of the patients. These antibiotics would not have been prescribed if the treating physician followed CDC/IDSA guidelines. It is fair to questing if the prescribed antibiotics provided an assuaging effect on the patient's autistic symptoms due to an unidentified pathogen. But, the presence of multiple Bb specific protein bands in the patient's Western Blot suggest the patients improved health was due to the treatment of their Lyme disease. In the Ajamian et al. study none of the 70 children with autism in the study were treated with antibiotics, so it is not possible to determine if antibiotics would have been beneficial to them. This is not to suggest that antibiotics should be given to children with Autism who show no signs of Lyme disease, instead a deeper look at the diagnostic criteria should be considered to rule out infection.

Further evaluation of the data acquired from the survey indicated the presence of OSP-A and OSP-B in the children's Western Blot was prevalent. Of the 48 surveys collected 44 (91%) received a positive indication of said bands. These two bands are so specific to Bb that they were targeted for use in vaccine trials, yet are not included in the CDC interpretation of the Western Blot [29,13]. None of the parents in the survey indicated that anyone in their family had received a Lyme vaccine. In the Ajamian et al. [28] study only 5 of the 70 children were tested using the Western Blot and OSP-A and OSP-B were not included in the evaluation.

Further dissemination of the data revealed that nearly all of the children who received an ATEC score of severe-autism had band OSP-B present on their Western Blot (Fig. 4). According to the results of the survey, 16 of the 48 children had a score of severe-autism. Of those 16 children 14 (88%) tested positive for OSP-B. Of the remaining 33 children who's scores were in the moderate to mild range only 2 children (6%) tested positive for OSP-B. This data could be significant because, as indicated earlier, OSP-B is not typically tested for in commercially available Lyme disease tests. The OSP-B band could be a vital point of interest for future researchers investigating the Lyme/Autism connection. Physicians who have a patient with an ASD that who are considering a Lyme disease diagnosis should find a laboratory that tests for OSP-B before ruling out the infection.

If this small scale study is any indication of what may be causing or exacerbating the children's autistic symptoms it could mean a percentage of the autism community is actually suffering from Lyme disease and some of those symptoms could be alleviated with proper testing and treatment. We believe it is advantageous for parents who have a child diagnosed with an ASD to seek out a physician who does not strictly follow the two-tiered laboratory criteria to diagnose Lyme disease.

Dr. Bransfield has testified as an expert in cases involving Lyme disease.

Limitations of this study include no physical interaction or observation of the children and only using the parents survey results in the study. The parents did not indicate what type of antibiotics or antibacterial therapy was used to treat their child was used or the duration of its use.

Conflict of interest statement

None.

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1821 words

Lyme/Tick-Borne Diseases and Autism Spectrum Disorders

Robert C Bransfield, MD, DLFAPA

Understanding the cause of autism is not a simple process. Autistic patients have a large range of symptoms that are considered to be on a spectrum and these conditions are called have spectrum disorders (ASD). There are multiple genetic and environmental contributors, multiple processes causing disease and a wide range of symptoms occurring in different individuals. The disease processes are mostly associated with abnormal functioning of the immune system. Normally the immune system responds to threat first with inflammation which ends and is then replaced by antibody production (adaptive immunity). With ASD there are abnormalities in the functioning of the immune system. Inflammation instead may persist and antibodies may be formed that harm the developing nervous system (autoimmunity). The persistence of inflammation is stressful to cells by causing a process called oxidative stress, there can be abnormalities of the energy source within the cell, the mitochondria, and other associated biochemical abnormalities may also occur. Environmental contributors provoking these immune abnormalities include environmental toxic exposures and infectious diseases.

The same infectious and immune process can have a very different effects at different ages—embryonic development, a developing fetus at different developmental stages, the neonate, an infant, a child, an adolescent, an adult and in late life.

Other variables relevant to ASD include which of the 24 infections and coinfections associated with ASD are contributory (Bransfield 2009); whether the infection was previously present or persistent, whether the infection is just in the mother, in the mother and fetus or just in the infant; whether or not there is infection within the central nervous system; whether there were direct effects of the infection vs. immune effects provoked by the infection or both; whether the disease process is caused by inflammation or autoimmunity or both; the presence of toxins; the presence of deficiencies; treatments and response to treatment. Understanding the association between Lyme/tick-borne diseases (LY/TBD) and ASD requires an approach from multiple perspectives. One approach is to compare the similarities between ASD and LY/TBD.

Epidemiology

The 15 states most prevalent for autism show a correlation with the 15 states most prevalent for Lyme disease (DeNunzio). Of the twenty states that reported the highest occurrence of Autistic Disorder per 10,000 people; fifteen reported a higher than average number of Lyme disease cases. Conversely, of the twenty states that reported the lowest incidence of Autistic Disorder per 10,000 people; zero reported a higher than average number of Lyme disease cases. (Kuhn et al. 2012). Autism prevalence in California, Oregon and Washington counties is positively associated with precipitation (Waldman M et al. 2008) and precipitation has a positive correlation with tick survival (Nieto NC et al. 2010) which impacts the prevalence of tick-borne diseases.

Evaluating Lyme Disease/Tick-Borne Disease Patients for Autism Spectrum Disorders

Although clinicians have previously noted the association between Lyme disease and ASD (Bransfield et al. 1998) the first study was a comprehensive case history review on the charts of 102 gestational LYD/TBD cases which revealed 9% had been diagnosed with autism and most were diagnosed with a broad spectrum of developmental disabilities. As a control, 66 mothers with Lyme disease who were treated with antibiotics prior to conception and during the entire pregnancy; all gave birth to normal healthy infants (Jones et al. 2005).

Testing Autism Spectrum Disorder Patients for Lyme Disease/Tick-Borne Disease

Most studies demonstrate about 25% of ASD are infected with *Borrelia burgdorferi* (Vojdani 22%, Lyme Induced Autism Foundation 26%, Nicholson 20-30%, Levin 100% in a Lyme epidemic area of Connecticut), however other infections are also present and may be more prevalent than *Borrelia burgdorferi* and include *Mycoplasma species* 56%, with 70% of these especially *M. fermentans*, *Human Herpes Virus-6* (HHV-6) 29%, *C. pneumoniae* 8%, and also coinfections with *Bartonella, Ehrlichia*, and *Babesia* (Nicholson 2007).

Biochemical Similarities between Lyme Disease/Tick-Borne Disease and Autism Spectrum Disorders

LYD/TBD and ASD have biochemical similarities in regard to how the body utilizes oxygen and sulfur. More technically, both have alterations of the oxidoreductive system and homocysteine/methionine metabolism. Both have increases of superoxide dismutase, malondialdehyde and glutathione peroxidase activity. Both have decreased glutathione (Bransfield et al. 2008).

Brain Imaging Similarities between Lyme Disease/Tick-Borne Disease and Autism Spectrum Disorders

LYD/TBD and ASD both include a predominance of white matter findings and significant temporal lobe dysfunction. In ASD the temporal lobe, hippocampal, and amygdala impairments are associated with memory impairments and nonverbal social impairments. Both LYD/TBD and ASD patients demonstrate an excessive sensitivity to light, sound and other stimulation. This clinical observation is supported by brain imaging of patients with LYD/TBD that demonstrates increased thalamus activity (a brain region that gates sensory input) and associated increased activity in auditory and visual areas of cortex (Bransfield et al. 2008).

Immune Similarities between Lyme Disease/Tick-Borne Disease and Autism Spectrum Disorders

LYD/TBD and ASD both have been associated with a combination of inflammatory and autoimmune processes. Both are associated with a persistent inflammation with an elevation of the same components of the immune system (Tumor Necrosis Factor Alpha and Interleukin-6). With both this persistent inflammation is also associated with activation of immune cells within the central nervous system (microglia) and antibodies against brain tissue. Both LYD/TBD and ASD patients are more likely to have the same genetic risk factor, the HLA-DR4 genotype (Bransfield et al. 2008).

Treatment with Antibiotics

Treatment of LYD/TBD during pregnancy can prevent the development of autism and other developmental disabilities associated with LYD/TBD (Jones et al. 2005). Another study has objectively demonstrated that antibiotic treatment can reduce ASD symptoms associated with LYD/TBD (Kuhn et al. 2012).

Economic Cost of Autism Spectrum Disorders Associated with Lyme and Tick-Borne Diseases

Since about 25% of ASD is associated with *Borrelia burgdorferi* and since well over 50% of ASD is associated with other persistent infections (Nicholson G. 2007) and 673,000 US children have ASD (11 per 1000) with an estimated life-time healthcare cost of $16 million for each person with autism (Kogan MD, 2009), LYD/TBD and other persistent infections appear to be associated with many trillions of dollars in societal costs plus the massive human cost that cannot be converted to dollars.

Summary

ASD results from multiple causes with both genetic and environmental contributors, including LYD/TBD. Acute infections in the mother, fetus and/or newborn may cause acute immune reactions and chronic infections in the mother, fetus and/or newborn may cause persistent immune reactions and these immune reactions may adversely affect fetal brain development causing autism spectrum disorder. The recognition that LYD/TBD can be a contributor in a significant number of ASD cases has a significant impact upon prevention and treatment options which can help save life, quality of life and economic viability. When LYD/TBD is present, the antimicrobial treatment of women intending to become pregnant, pregnant women, newborns and autistic spectrum disorder patients can prevent and treat some cases of ASD. ASD associated with LYD/TBD warrants significant attention, research, diagnostic and treatment awareness and advocacy efforts.

Future Directions in Research

Clinically relevant research is needed to better understand this very complex issue. It is necessary to acquire better epidemiological statistics; to better understand the disease contributors (infectious and otherwise) and the interaction of disease contributors, disease deterrents, the multiple pathophysiological processes, the pathophysiology associated with different symptoms and treatment options and effectiveness.

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Medical Hypotheses (2007) xxx, xxx–xxx

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The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders

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Received 18 August 2007; accepted 7 September 2007

Summary Chronic infectious diseases, including tick-borne infections such as *Borrelia burgdorferi* may have direct effects, promote other infections and create a weakened, sensitized and immunologically vulnerable state during fetal development and infancy leading to increased vulnerability for developing autism spectrum disorders. A dysfunctional synergism with other predisposing and contributing factors may contribute to autism spectrum disorders by provoking innate and adaptive immune reactions to cause and perpetuate effects in susceptible individuals that result in inflammation, molecular mimicry, kynurenine pathway changes, increased quinolinic acid and decreased serotonin, oxidative stress, mitochondrial dysfunction and excitotoxicity that impair the development of the amygdala and other neural structures and neural networks resulting in a partial Klüver–Bucy Syndrome and other deficits resulting in autism spectrum disorders and/or exacerbating autism spectrum disorders from other causes throughout life.

Support for this hypothesis includes multiple cases of mothers with Lyme disease and children with autism spectrum disorders; fetal neurological abnormalities associated with tick-borne diseases; similarities between tick-borne diseases and autism spectrum disorder regarding symptoms, pathophysiology, immune reactivity, temporal lobe pathology, and brain imaging data; positive reactivity in several studies with autistic spectrum disorder patients for *Borrelia burgdorferi* (22%, 26% and 20–30%) and 58% for mycoplasma; similar geographic distribution and improvement in autistic symptoms from antibiotic treatment. It is imperative to research these and all possible causes of autism spectrum disorders in order to prevent every preventable case and treat every treatable case until this disease has been eliminated from humanity.

Background

An association between Lyme disease (LYD) and other tick-borne infections (TBI) during fetal

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doi:10.1016/j.mehy.2007.09.006

Please cite this article in press as: Bransfield RC et al., The association between tick-borne infections, ..., Med Hypotheses (2007), doi:10.1016/j.mehy.2007.09.006

development and in infancy with autism, autism spectrum disorders (ASD) and autistic symptoms has been noted by numerous clinicians and parents. Since environment changes faster than genes, the rapidly emerging epidemic and geographical spread of ASD suggests significant environmental contributors, that may include infections. A Lyme Induced Autism Foundation (LIAF) conference explored the association between *Borrelia burgdorferi sensu lato* (the bacterium that can cause Lyme disease and Borreliosis) as well as other tick-borne or infectious diseases and ASD. This article was written to collate information from conference presentations on this issue with other sources that further address this association.

Hypothesis

Chronic infectious diseases (CID), tick-borne infections (TBI); including *Borrelia burgdorferi sensu lato (Bbsl)* infections (Borreliosis or BI) often in the setting of other predisposing, provoking and perpetuating co-factors, may have direct effects, promote other infections, contribute to immunosuppression and immunomodulation in fetal development and infancy. This in turn contributes to innate and adaptive immune reactions to initiate and perpetuate effects in susceptible individuals that result in inflammation, molecular mimicry, changes in the kynurenine pathway causing increased quinolinic acid and decreased serotonin, oxidative stress, mitochondrial dysfunction and excitotoxicity that impair the development of the amygdala and other neural structures and neural networks resulting in a partial Klüver–Bucy Syndrome and other deficits resulting in ASD and/or exacerbating ASD from other causes throughout life.

Method of testing the hypothesis

Sources of information considered include MedLine, peer reviewed literature, LIAF Conference presentations and other medical related meetings, US Government statistics, unpublished data, Internet searches of relevant key words, databases and clinical observations. Comparisons were made between autism, ASD and CID and Borrelia infection/tick-borne infections (BI/TBI). The incidence of LYD, taken from CDC statistics, is ''per 100,000 [1]'' and the incidence of autism calculated by adding the Individuals with Disabilities Education Act (IDEA) autistic children ages 3–5 to the autistic students ages 6–21 served under IDEA, Part B, for each state in the Fall of 2005 [2]. This sum was then divided by each state population as of July, 2005.

Evaluation of the hypothesis

Clinical observations and case reports

A number of clinicians in addition to the authors have noted multiple cases of mothers with BI/TBI and children with ASD, infants infected with BI/TBI who had ASD or autistic symptoms, children infected with BI/TBI with autistic symptoms and children with ASD who acquired BI/TBI and displayed an exacerbation of ASD symptoms. In addition, teenagers and adults infected with BI/TBI often have some symptoms suggestive of ASD that include hyperacusis, emotional detachment, mood instability, a decline of speech and language and decreased muscle tone. Increased severity of symptoms is associated with infections at a younger age, genetic vulnerability, lengthy misdiagnosis, delayed treatment and coinfections (Bartonella, Mycoplasma, Babesia and other TBI). Burrascano reviewed 7000+ BI/TBI cases and concluded many chronically ill patients were polymerase chain reaction (PCR) + for Mycoplasma and Bartonella which may eclipse *Bbsl* as the ultimate cause of BI chronic morbidity [3].

Clinical experience and historical review with adult patients subsequently diagnosed with chronic BI/TBI has shown dysfunctions and sensitivities comparable with clinical manifestations in ASD patients. For instance, adults with chronic BI/TBI often demonstrate development of new extreme sensitivities to environmental agents, including mercury/heavy metals, chemicals and fumes, food additives, (even simple allergens such as animal dander), etc. that rapidly lead to symptom exacerbation and clinical decline. Many also develop new gastrointestinal dysfunction, food intolerances/sensitivities, and food cravings for wheat and refined carbohydrates/sugar that actually *cause* symptom flares. As well, adults with underlying chronic BI/TBI have been observed to show a global decline after receiving routine immunization(s).

Symptom improvement in ASD patients has also been observed when administered antibiotics for childhood infections or when administered more extensive antimicrobial treatments specifically for ASD [4]. Short-term benefit from oral vancomycin treatment of regressive-onset autism has also been documented [5].

ASD and BI/TBI patients both have inflammatory bowel disorders associated with gastrointestinal symptoms [6,7]. Fried performed GI biopsies on

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15 children with documented prior LYD who had persistent gastrointestinal symptoms and 15/15 had chronic inflammation and were PCR positive for Borrelia DNA vs. 2/10 in Crohn's controls. 2/3 of these children had been treated with prior antibiotics for BI suggesting that BI and chronic inflammation can persist [8]. He also biopsied children with inflammatory bowel diseases and children with BI/TBI and demonstrated the presence of *Bbsl*, Bartonella, Mycoplasma, Babesia and *Helicobacter pylori*. The gastrointestinal symptoms improved in response to antibiotic treatment [9].

Gestational tick-borne/Borreliosis infections

It is recognized that gestational BI/TBI has been associated with adverse neurological consequences [10,11]. By logical similarity, BI/TBI can thus also contribute to ASD.

Jones et al. estimates he has seen approximately 300 cases of gestational BI/TBI. All of the mothers had untreated or inadequately treated BI/TBI either prior to or during pregnancy. He performed a comprehensive case history review on the charts of 102 gestational BI/TBI cases. In addition to Borreliosis, tick-borne and other coinfections identified included Babesiosis (14%), Strep (7%), Ehrlichiosis (6%), Leptospirosis (5%) and Mycosis (4%). 9% had been diagnosed with autism and 56% with attention deficit disorder. Psychiatric symptoms included irritability or mood swings (54%), anger or rage (23%), anxiety (21%), depression (13%), emotional (13%), OCD (11%) and suicidal thoughts (7%). Neurological symptoms included headache (50%), vertigo (30%), developmental delays (18%), tic disorders (14%), seizure disorders (11%), involuntary athetoid movements (9%) and hypotonia (7%). Sensory sensitivity symptoms included photophobia (43%), hyperacuity (36%), motion sickness (9%) and other (tactile, taste or smell) (23%). Cognitive symptoms included poor memory (39%), cognitive impairments (27%), speech delays (21%), reading/writing (19%), articulation (17%), auditory/visual processing (13%), word selectivity (12%), and dyslexia (18%). GI symptoms were common and included GERD (27%), abdominal pain (29%), diarrhea or constipation (32%), and nausea (23%). As a control, 66 mothers with Lyme disease who were treated with antibiotics prior to conception and during the entire pregnancy; all gave birth to normal healthy infants. However, 8 pregnancies resulted in *Bbsl* and/or *Bartonella henselae* positive placentas, umbilical cords, and or foreskin remnants. Those who were PCR positive were treated successfully with oral antibiotics [11].

Gestational transmission of *Bbsl* and other TBI may be more common than previously recognized and may be an important mode of infection in the ASD population. Also BI/TBI may be associated with sexual [12,13] and breast milk transmission [14,15].

Laboratory testing of ASD patients for tick-borne diseases

Pilot studies of ASD patients to test for BI/TBI have been conducted.

Vojdani tested Autism samples from different clinics in Northern CA, NY, NJ and CT. 22% of (12/54) tested IgG and IgM positive for *Bbsl* by Immunosciences Lab (Note: in this sample the Western Blot (WB) test used CDC surveillance criteria and did not include the full complement of *Bbsl* specific bands) [16].

A LIAF study tested the blood of 19 children with an ASD diagnoses plus an indication of immune dysfunction and five normal controls. Patients were not screened for BI before study entry. WB and IFA IgG and IgM were performed by IgeneX Laboratory. A result was considered *Bbsl* positive for exposure if there was reactivity of one or more *Bbsl* specific bands. 26% of the ASD children were positive compared to 0 controls [17].

Levine tested nine consecutive ASD patients in Connecticut in 2003 and all nine tested positive for *Bbsl* with WB by IGeneX Laboratory criteria.

Nicolson tested 48 ASD patients with forensic PCR and Southern Blot confirmation. 20–30% (depending upon the lab) were positive for *Bbsl*. 58% were positive for Mycoplasma species while 5% of 45 age matched controls were positive for Mycoplasma (Odds ratio = 13.8) with 35% *M. fermentans* vs. 0% control, 33% *M. pneumoniae vs.* 5% control, 10% *M. homonis* vs. 0% control, 2% *M. penetrans* vs. 0% control and 25% were *M. fermentans* and other species. Also 8% were positive for *C. pneumoniae* vs. 2% of controls (Odds ratio = 5.6) and 29% were positive for Human Herpes Virus-6 (*HHV*-6) vs. 8% of controls. 6.5% of healthy family members were positive for Mycoplasma and 8% were positive for *HHV*-6 ($P < 0.001$) [18]. He also reported WB positive BI patients had a 68% coinfection rate with Mycoplasma (M. *Fermentans* was 70%), Bartonella, Ehrlichia, and Babesia [18,19].

Other laboratory findings

Testing patients with autism and BI/TBI also reveals biochemical similarities. Disorders of an

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oxidoreductive system in CSF and serum, increases of superoxide dismutase, increased glutathione peroxidase activity, increased concentration of serum malondialdehyde and decreased glutathione have been detected in neuroborreliosis and BI [20]. In autism, several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, altered glutathione levels and homocysteine/methionine metabolism, increased malondialdehyde levels [21] and reduced glutathione [22].

Brain imaging tick-borne diseases/Borreliosis and autism

Both BI/TBI and ASD patients demonstrate significant temporal lobe dysfunction. In autism the cerebral cortex, hippocampus, and amygdala showed trends toward being disproportionately smaller in the developing autistic brain [23]. In addition smaller amygdala volume correlates with impairments in nonverbal social impairment in autistic patients [24]. Infectious encephalopathies associated with autistic symptoms have demonstrated lesions of the temporal lobes [25]. PET scanning of neuroborreliosis patients demonstrates the most striking finding was hypometabolism, which correlates with decreased activity, in the temporal lobes in 74% patients. Temporal lobe involvement is likely associated with memory disturbances seen in many BI patients [26].

Both BI/TBI and ASD demonstrate predominately white matter encephalopathy. Regional cerebral blood flow suggests that Lyme encephalopathy may primarily affect cerebral white matter [27]. Disruption of white matter tracts between regions implicated in social functioning may contribute to impaired social cognition in autism [28].

Both ASD and BI/TBI patients demonstrate sensory hyperacusis and this clinical observation is supported by brain imaging of patients with BI that demonstrates increased thalamus activity and increased activity in auditory and visual areas of cortex [29].

Epidemiological findings: Lyme disease/tick-borne disease and autism

A causal association is suggested if the geographical patterns of ASD and BI/TBI overlap and are comorbid more than would be expected by random association. In a geostatistical review of CDC and IDEA statistics 10 out of the top 15 states overlap for the incidence of autism and LYD (MN, ME, MA, MD, CT, WI, RI, NJ, PA, VA).

Theoretical issues: genes, infections and autism

Most commonly human diseases are caused by the interaction of environmental insults and susceptibility genes. Many of the susceptibility genes result in human response to environmental factors and infection. Environmental insults contributing to ASD may include a complex interaction with infections, heavy metals, biotoxins, allergens, nutritional excesses/deficits and possibly vaccines. In addition physiological and psychological changes associated with chronic unremitting stress contribute to chronic psychiatric symptoms and a chronic immunocompromised and inflammatory state [30]. Neurological disease precipitated by an interaction of these environmental insults and susceptibility factors often results in a pathogenic interaction that includes inflammation, oxidative stress, mitochondrial dysfunction and excitotoxicity resulting in neuronal dysfunction [31].

Klüver–Bucy Syndrome, infections and autism

The amygdala theory of autism describes a neural network that comprises the ''social brain'', which includes the amygdalae. Since autism involves deficits in social functioning, it is plausible that autism may be caused by an amygdala abnormality and the Klüver–Bucy Syndrome is an experimental model that partially replicates autism [32].

Klüver and Bucy removed the temporal lobes bilaterally in rhesus monkeys which caused them to be unable to recognize objects or faces (visual agnosia), emotional changes, a desire to explore everything (hypermetamorphosis), oral tendencies and hypersexualism. The monkeys became emotionally dulled with less facial and vocal expressiveness. They were also less fearful of things that would have instinctively panicked them, even after aversive exposure (placidity). Patients with temporal lobe trauma demonstrate some of these features, including other temporal lobe symptoms, such as memory disorders, bulimia, communication impairments and visual agnosia.

A number of infections associated with causing symptoms of Klüver–Bucy Syndrome and/or ASD include Rubella, *Herpes simplex*, Herpes virus family, *Borna*, *Varicella*, *Cytomegalovirus*, *Mycoplasma pneumoniae*, *Shigella*, *Syphilis*, Neurocysticercosis,

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malaria, Toxoplasmosis, *Blastocystis*, Rubeola, [25,33–35].

Neural networks, neurodevelopment, autism and borreliosis

Infection associated immunological events in early fetal life have a stronger neurodevelopmental impact than later infections. They can have adverse effects on cell proliferation and differentiation; predispose the developing nervous system to undergo additional failures in subsequent cell migration, target selection, and synapse maturation, eventually leading to multiple brain and behavioral abnormalities apparent later in life [36]. Brain developmental processes (i.e. cell proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis) occur at vulnerable periods during the development of the nervous system and are sensitive to environmental insults that can contribute to autism [37]. Younger has demonstrated on biopsies that small nerve fiber disruption can occur in Lyme vaccine recipients and BI/TBI patients who subsequently may heal in response to anti-infective treatment [38].

Borreliosis and borrelia related complex

Ticks suck the blood of rodents and may transmit unknown pathogens in a bite. *Bbsl*, the principal organism associated with BI/TBI, is one of the most complex bacteria known to man. Some other known pathogens include two other Borrelia species and 300 different strains of Borrelia. Interactive coinfections may include *M. fermentans*, *M. pneumoniae*, other Mycoplasma species, *Babesia microti*, *Babesia duncani*, other piroplasms, *Chlamydia pneumoniae*, *Rickettsia rickettsia*, *Coxiella burnetti*, *Anaplasma phagocytophilum*, *Ehrlichia*, *Bartonella henselae*, *Bartonella quintana* and over 38 species of viruses [39]. When multiple microbes grow together, they can stabilize interactions between species, resulting in marked changes in their symbiotic nature and altered functioning [40].

In addition, BI/TBI and tick saliva cause immunosuppression [41–43] which may result in activation of herpes or other infections that can be contributors in causing ASD. There is a broad spectrum of clinical manifestations of those with BI/TBI and other CID. BI/TBI can range from an asymptomatic chronic carrier state to only occasional symptoms at times of immunologic stress (e.g. physical/emotional trauma, exhaustion, other acute infection, etc.) to chronic fluctuating low level symptoms to severe multi-system dysfunction to possible death. The conditions determining the specific clinical manifestations may include characteristics of the organism(s) (virulence, inoculation, etc.) and the susceptibility of the host (genetics, immune system functioning, heavy metals, environmental toxins, gastrointestinal health, physical/psychological stressors, nutrient deficiencies/excesses, other infection(s) and other immunologic insults).

Tick-borne/borreliosis infections and psychiatric illness

BI/TBI cause a spectrum of psychiatric illnesses, cognitive impairments, neurological symptoms and seizures [44]. Pathophysiological mechanisms include invading, penetrating, injuring or killing host cells; indirect injury at a distance (coagulation cascade of proteins, activation of coagulation system, blebs, microthrombi, septic emboli); biological amplification-cascade of injury; reservoir inside of host, leeching- ''nutrient sapping;'' toxins; gene sequence incorporation into host genome; immune effects—inflammation, molecular mimicry, immunosuppression and Herxheimer pathophysiology and invasion of human neuronal and glial cells [45,46]. Infections in the body that do not pass through the blood brain barrier may still impact the brain indirectly by immune activation that affects the brain. All the clinical manifestations, acute or chronic, are characterized by strong inflammation. *Bbsl* can induce the production of several proinflammatory and anti-inflammatory cytokines and chronic forms can evolve due to an aberrant innate proinflammatory response [47] with brain inflammation [48].

CSF quinolinic acid is significantly elevated in BI and quinolinic acid is a known agonist of *N*-methyl-D-aspartate (NMDA), a receptor involved in learning, memory, and synaptic plasticity which may contribute to the neurological and cognitive deficits seen in many LYD patients [49]. Tryptophan is metabolized primarily along the kynurenine pathway and two components are now known to have marked effects on neurons in the central nervous system—quinolinic acid which is neurotoxic and kynurenic acid is an antagonist at several glutamate receptors and is neuroprotective. A third kynurenine, 3-hydroxykynurenine, can produce oxidative stress by increasing the production of reactive oxygen species (ROS) and contribute to neuronal damage. Proinflammatory cytokines associated with infection increase indoleamine 2,3-dioxygenase (IDO) which converts tryptophan into kynurenine, thereby reducing central tryptophan, the precursor of serotonin, and increasing quinolinic acid. This

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increase may produce over stimulation of hippocampal (NMDA) receptors, which leads to apoptosis and hippocampal atrophy. Both ROS overproduction and hippocampal atrophy in the temporal lobes caused by NMDA over stimulation have been associated with CNS pathology [50]. Abnormal development of the hippocampus and associated structures are also associated with autism [51]. In addition, quinolinic acid significant reduces glutamic acid decarboxylase (GAD) activity which is reduced in autism [52,53] and, in addition to oxidative stress, [54] is associated with decreased Purkinke cells in the cerebellum in autism [55].

Immune responses in ASD, Borreliosis and *Mycoplasma* infections

ASD patients have reduced natural killer cells and elevated tumor necrosis factor (TNF) alpha in CSF [56]. Maternal proinflammatory cytokine reactions to infection, including interleukin (IL) 6, are the damaging factors associated with autism [57,58]. Brain tissue and CSF demonstrate innate neuroimmune reactions play a pathogenic role in a proportion of autistic patients with microglia activation [59]. A Th1/Th2 imbalance towards Th2 and elevated brain specific antibodies supports autoimmunity [58].

BI has similarities to ASD since both have been associated with a combination of inflammatory and autoimmune pathophysiology. BI is associated with causing damaging inflammation within the central nervous system with the stimulation of increased production of IL-6 and TNF-alpha by microglia and CNS symptoms are also associated with *Bbsl* antibodies against neural tissue [60–62]. Both ASD and chronic BI/TBI patients are more likely to have HLA-DR4 genotypes [63,64].

Pathogenic Mycoplasma, a cofactor in 70% of BI/TBI patients, carried by ticks and congenitally transmitted, has also been associated with lymbic system dysfunction, microglia activation, reduced natural killer cells, both inflammatory and autoimmune reactions with increased production of IL-1, IL-6, and TNF-alpha and immune reactions to neural tissue and greater susceptibility to herpes and other viral infections [65,66].

BI/TBI patients may experience activation of latent infections and symptom flares from vaccines which may explain the symptom exacerbation reported in some ASD patients following vaccines [61,67,68].

Infections, inflammation, innate immune responses, oxidative stress and neuronal insults can contribute to the pathophysiology of autism [69,70].

Further evaluation of the hypothesis

Further research is needed to explore infectious causes and contributors in addition to all predisposing, precipitating and perpetuating contributors of ASD along with the associated pathophysiology. To achieve this, there is a need for pathophysiological studies, epidemiological studies to explain regional differences in the incidence of ASD, testing both parents and ASD patients for BI/TBI, clarifying the interaction of copathogens and other cofactors in the pathophysiological process and anti-infective treatment studies. If it is proven these or other pathogens are contributory, it would be necessary to explore whether we are seeing more systemically weakened and immunologically compromised children and adults because there is a growing epidemic of chronic infections, more chronic infections because our physiologic systems and immunity are becoming progressively challenged and compromised or both. On his deathbed Louis Pasteur changed his views and stated—''Bernard was right, I was wrong. The germ is nothing, the milieu is everything''.

Consequences of the hypothesis and discussion

It may cost $3.2 million to care for one autistic person in their lifetime [71] and the preliminary data suggests Borreliosis may be a contributor in 20–30% of ASD, and pathogenic Mycoplasma may be a contributor in 58%. If 20% or 58% of the 560,000 recognized cases of ASD in the US can be prevented or more effectively treated, this could result in a savings of $358 billion to $1 trillion in addition to incalculable human impact of this disease. If this hypothesis is further proven and accepted, screening pregnant woman and ASD patients for BI/TBI (eventually with microarrays) and providing more effective earlier treatment with antibiotics when appropriate may be indicated to assist towards reducing the current ASD epidemic. It is important to address the other environmental contributors that increase the impact of these infections diseases. It is imperative to research all possible causes, prevent every preventable case and treat every treatable case of ASD.

Acknowledgements

Costs associated with publication were funded by an unrestricted grant from the LIAF. The authors

would like to thank and recognize the contributions of Tami Duncan (LIAF President) and Kathy Blanco (LIAF Vice President); all the participants of the 2007 LIAF conference; Anthony R. Torres, MD and Raphael Stricker, MD for manuscript review; Sharon De Nunzio for geostatistical assistance; Charles Ray Jones, MD for decades of expertise and dedication in helping hundreds of children with BI/TBI and ASD and the efforts by patients and the commitment of family members and helping professionals.

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