



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

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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.

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Background

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

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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

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. hominis* 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

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,

malaria, Toxoplasmosis, *Blastocystis*, Rubella, [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 burnetii*, *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

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 significantly reduces glutamic acid decarboxylase (GAD) activity which is reduced in autism [52,53] and, in addition to oxidative stress, [54] is associated with decreased Purkinje 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 limbic 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 infectious diseases. It is imperative to research all possible causes, prevent every preventable case and treat every treatable case of ASD.

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