The Psychoimmunology of Tick Borne Diseases & its Association with Neuropsychiatric Symptoms

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Annual conference of the German Borreliosis Society, 9 April, 2011
Lyme-borreliosis and co-infections with a focus on neurologic and psychic manifestations

Wuppertal, Germany
Disclosure Statement
Robert Bransfield, MD, DLFAPA, PC

• Patients pay me money in return for trying to help them.
• Most of my income is paid directly from patients
• No psychoimmunology financial interests
• Speakers Bureau (currently): Astra Zeneca, Avanir, Cephalon, Merck, Novartis, Suvonion
Outline

• History and overview
• Basic psychoimmunology
• Immune Effects: Inflammation
• Immune Effects: Autoimmunity
• Autism
• Treatment implications
• Conclusion
Can Lyme Disease, Tick-Borne Infections and Immune Reactions from them Contribute to...

- Mental illness?
- Cognitive decline?
- Degenerative neurological disease?
- Developmental disabilities?
- Personality change?
- Violent & criminal behavior?
- Obesity?
- Improved functioning?
The History of Mental Illness

• You’re possessed by demons & need punishment...
• Your mother caused it & you need psychoanalysis...
• Your serotonin is low & you need Prozac...
• Your genes are bad, you can’t change them...
• Your immune system & chronic infections contribute & you need antibiotics & immune treatments...
• Regardless patients with “medically unexplained symptoms” & doctors who treat them are possessed by demons & need punishment...
Disease Progression Over Time

- Predisposing & precipitating factors
- Infections
- Immune & other reactions
- Pathophysiological processes
- Dysfunction
- Symptoms & Syndromes
- Ineffective Treatment
- Disease Progression
Basic Psychoimmunology
Brain & Immune Similarities

• Both defend against threats by shifting allocation of resources as environments change (internal-immune, external-brain)
• Both have intracellular transmitters, receptors & feedback capability
• Both have innate & learned capabilities
• Failures to shift from innate to learned responses result in pathology (persistent inflammation & autoimmune similar to persistent stress, anxiety, PTSD & depression)
10th Psychoimmunology Expert’s Meeting
Neuropsychimmunology of Severe Psychiatric Disorders-Interacting Compartments, cell systems and infectious agents in immune response

World Psychiatric Association, Psychoimmunology Section Symposium
Immune System

A healthy immune system switches back and forth, quickly eliminating one threat & resting before responding to the next.

- Innate Immune Response Cell Mediated, T Helper 1 (Th1)
  - Targets intracellular pathogens
  - Pre-formed elements - cytokines, complement, hypoxia recognition
  - Conserved over eons pattern molecules activated by pattern recognition that activate toll receptors that activate secondary messenger that activate NFkB which activates nuclear receptors.

- Adaptive or Humoral Immune Response, T Helper 2, (Th2)
  - Attacks extracellular pathogens
  - Antibody production
  - Cytokines released after antigen processing leads to B cell activity
  - Specific mechanisms beginning with dendrite cell recognition, engulfment, attachment of HLA DR, presentation to naïve T cell, presentation to B cell and ongoing presentation on monocyte
<table>
<thead>
<tr>
<th>Provokes &amp; Weakens the Immune System</th>
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<tr>
<td>Infections</td>
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<td>Cancer</td>
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<td>Allergens</td>
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<td>Stress</td>
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<td>Sleep deprivation</td>
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<td>Vaccinations</td>
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<td>Trauma</td>
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<td>Toxins</td>
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<td>Degenerative changes</td>
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<td>Foehn, barometric pressure drops</td>
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<td>Molecular mimicry</td>
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<td>Low glutathione levels</td>
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<td>Increased oxidative stress</td>
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<td>Metal toxicity</td>
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<td>Elevated leptin levels</td>
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<td>Some medical treatments</td>
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Bacterial Infections and the Pathogenesis of Autoimmune Conditions

- Bacterial infections are associated with many autoimmune diseases involving chronic inflammation and demyelination.

- Possible modes of pathogenic action of bacteria are discussed, viz. the role of cytokines, Toll-like receptor signaling, the interaction of heat shock proteins with the immune system, and the role of nitric oxide. An auto-regulatory loop might exist in the interaction of bacteria with the host and in pathogenic signal processing. These studies reveal potential therapeutic targets.
Is Trauma from Infection or from the Host’s Immune Reaction?

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Host</th>
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<tr>
<td>• Cell penetration</td>
<td>• Cytokine release</td>
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<td>• Toxin release</td>
<td>• Antibodies</td>
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<td>• Incorporation of parasite genes into host genome</td>
<td>• Inflammation</td>
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</table>
Direct or Immune Effects Causing Pathophysiology?

Infection or Complex Interactive Infections

Pathophysiology Causing Symptoms

Immune Effects Th1 & Th2
Immune Effects: Inflammation

- Inflammation
- Inflammation associated with Lyme disease
Sickness Syndrome Resembles Depression
(Mediated by Proinflammatory Cytokines IL-1, IL-6, and TNF)

- Anhedonia
- Malaise
- Hypersomnia
- Anorexia
- Social Withdrawal
- Poor Concentration
- Weakness

Cytokines Induce Sickness Behavior

Chronic Infections and Stress

• Chronic infections cause chronic stress
• Chronic stress reactions and non-restorative sleep contribute to perpetuating the disease process & are associated with:
  – Decreased regenerative functioning
  – Compromised immunity
  – Oxidative stress
  – Decreased resistance to infectious disease
Bidirectional Communication between the Brain and the Immune System: Implications for Physiological Sleep and Disorders with Disrupted Sleep

• Cytokines produced by cells of the immune and nervous systems regulate sleep.
• Particularly interleukin-1beta and tumor necrosis factor-alpha, signal neuroendocrine, autonomic, limbic and cortical areas of the CNS to affect neural activity and modify behaviors (including sleep), hormone release and autonomic function.
• Sleep disorders are commonly associated with chronic inflammatory diseases and chronic age- or stress-related disorders. The best studied are rheumatoid arthritis, fibromyalgia and chronic fatigue syndromes.

Variability in Sleep Patterns in a Normal Adult vs a Patient With Major Depression

Adapted with permission from Winokur A, Reynolds CF III. *Primary Psychiatry*. Nov/Dec 1994:22-27.

Please see important safety information on accompanying slides and full prescribing information.
Delta Sleep and Lyme Disease

• Chronic fatigue & sleep disturbances are prevalent in Lyme disease. (1)
• Sleep restriction increases IL-6 and pain-related symptoms in healthy volunteers (2)
• Impaired Sleep Correlates with Impaired Immune Functioning (3)
• Growth hormone is dependent upon delta sleep & modulates immune response (4)
• Increasing delta sleep is therapeutic

(1) Greenberg HE; Ney G; Scharf SM; Ravdin L; Hilton E. Sleep, 18(10):912-6 1995
(2) M. Haack, E. Sanchez, J. Broussard, M. Regan, J. Mullington
J Pain; April 2004, Supplement 1 • Volume 5 • Number 3
Disease Progression

Non-Restorative Sleep

Fatigue | Cognitive Impairments | Emotional Impairments | Pain Sensitivity | Immune Dysfunction
Hepatitis C & Interferon Treatment

• A good model for inflammation mediated mental symptoms
• Symptoms include depression, anxiety, mania, irritability, impulsiveness, hostility, relapse of substance abuse & lassitude.[1]
• Cognitive impairments

[1] Henry, Castera, Demotes-Mainard
Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression

- Neurodegenerative diseases are a group of chronic, progressive disorders characterized by the gradual loss of neurons in discrete areas of the central nervous system (CNS).
- Substantial evidence has documented a common inflammatory mechanism in various neurodegenerative diseases. We hypothesize that in the diseased CNS, interactions between damaged neurons and dysregulated, overactivated microglia create a vicious self-propagating cycle causing uncontrolled, prolonged inflammation that drives the chronic progression of neurodegenerative diseases.

Hui-Ming Gao and Jau-Shyong Hong. *Cell*. Trends in Immunology Vol.29 No.8
Different immune reactions directly influence neuronal proliferation, differentiation, migration, and apoptosis. Microglia become activated after stress, trauma, or infection. They react with tissue repair or induction of immune responses: phagocytosis, secretion of cytokines, neuronal growth factors, and antigen presentation. Microglial activation may sustain chronic brain inflammation. NK, natural killer.
Oxidative Stress

“Oxygen free radicals or activated oxygen has been implicated in diverse environmental stresses in plants and animals and appears to be a common participation in most, if not all, degenerative conditions in eukaryotic cells. The peroxidation of lipids, the cross-linking and inactivation of proteins and mutations in DNA are typical consequences of free radicals”
Excitotoxicity

Homocysteine Metabolism in the Brain

Inadequate remethylation leads to increased Hcy levels which are excitotoxic.
Elevated CRP Level Linked to Decline in Executive Function and Frontal Lobe Damage

• This study shows a link between elevated levels of high-sensitivity C-reactive protein (hs-CRP), an indicator of low-grade inflammation, and decline in executive function.

Proinflammatory Cytokines

- **Interferon alpha**: (early) fever, anorexia, hypoglycemia, low BP & cardiac contractility
- **Tumor Necrosis Factor alpha**: fever, anorexia
- **Interleukin 1 beta**: fever, anorexia, social withdrawal, fatigue, self-destructive behavior
- **Interleukin 6**: fever, hippocampus mediated memory deficits, suicide, aggressiveness
Cytokine Activation Causes Psychiatric Symptoms

• Interleukin-6 Is Elevated in the Cerebrospinal Fluid of Suicide Attempters and Related to Symptom Severity (1)
• Interluken-1Beta & Self-Inflicted Aggressive Behavior (2)
• Interluken-1Beta Causes Fatigue (3)

Interleukin-1 Receptor Activation by Systemic Lipopolysaccharide Induces Behavioral Despair Linked to MAPK Regulation of CNS Serotonin Transporters

- Our studies identify interleukin-1 receptor and p38 MAPK-dependent regulation of neuronal 5-HT transporter as one of the mechanisms by which environmentally driven immune system activation can trigger despair-like behavior in an animal model, encouraging future analysis of the pathway for risk factors in neuropsychiatric disorders.

Tryptophan, Serotonin & Inflammation

• Kynurenine pathway a major route of L-tryptophan catabolism with a number of metabolites that include:
  – Kynurenic acid NMDA antagonist (neuroprotective, unless excessive)
  – Quinolinic acid NMDA agonist (neurotoxic)

• In an inflammatory state there is decreased serotonin & a shift to quinolinic acid rather than kynurenic acid.
IDO and interferon--induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity

The enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan (TRP) into kynurenine (KYN) and which is stimulated by proinflammatory cytokines, may be implicated in the development of IFN--induced depressive symptoms, first by decreasing the TRP availability to the brain and second by the induction of the KYN pathway resulting in the production of neurotoxic metabolites.

This study does support a role for IDO activity in the pathophysiology of IFN--induced depressive symptoms, through its induction of neurotoxic KYN metabolites.
IDO shifts tryptophan metabolism from serotonin to quinolinic acid
Neuroactive Kynurenines in Lyme Borreliosis

• We conclude that CSF quinolinic acid is significantly elevated in B burgdorferi infection---dramatically in patients with CNS inflammation, less in encephalopathy.

• The presence of this known agonist of NMDA synaptic function---a receptor involved in learning, memory, and synaptic plasticity---may contribute to the neurologic and cognitive deficits seen in many Lyme disease patients.

A Meta-Analysis of Cytokines in Major Depression

• This meta-analysis (24 studies) reports significantly higher concentrations of the proinflammatory cytokines TNF-α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the inflammatory response system.

Dowlat Y et al. Biological Psychiatry.
A Meta-Analysis of Cytokines in Alzheimer’s Disease

- A review of 86 studies strengthen the clinical evidence that AD is accompanied by an inflammatory response, particularly higher peripheral concentrations of IL-6, TNF-, IL-1, TGF-, IL-12 and IL-18 and higher CSF concentrations of transforming growth factor.

Swardfager W, Krista Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. BIOL PSYCHIATRY 2010
Inflammation, Psychosis, and the Brain

• Hundreds of studies of schizophrenic illness in adults have documented immunological abnormalities in these patients.

• First-episode psychosis in children is associated with evidence of increased inflammation.

• Increasing evidence now suggests that the glia, cerebral vasculature, and the BBB may be involved.

• Our results support the inflammatory theory of schizophrenia that was formulated over a 100 years ago and perhaps offer hope that prevention of chronicity can occur if the first episode of psychosis is rapidly and effectively controlled.

The role of inflammation in epilepsy

Here, we focus on the rapidly growing body of evidence that supports the involvement of inflammatory mediators—released by brain cells and peripheral immune cells—in both the origin of individual seizures and the epileptogenic process. We first describe aspects of brain inflammation and immunity, before exploring the evidence from clinical and experimental studies for a relationship between inflammation and epilepsy. Subsequently, we discuss how seizures cause inflammation, and whether such inflammation, in turn, influences the occurrence and severity of seizures, and seizure-related neuronal death. Further insight into the complex role of inflammation in the generation and exacerbation of epilepsy should yield new molecular targets for the design of antiepileptic drugs, which might not only inhibit the symptoms of this disorder, but also prevent or abrogate disease pathogenesis.

Progressive Infection & Inflammation is Associated with Increasing Encephalopathy & Increasing Mental Symptoms

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<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td>Executive dysfunction</td>
<td>Increasing cognitive deficits</td>
<td>Dementia</td>
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<tr>
<td>Reduced frustration tolerance, irritability, dysthymia</td>
<td>Anxiety disorders, depression, impulsivity, personality disorders</td>
<td>Major psychiatric disorders, psychosis, suicide, homicide</td>
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Increasing Neurological, Multisystemic Symptoms & Fatigue
Balanced Inflammation

- Inflammation could have a protective role and promote regeneration of damaged neurons. We do not yet know how to achieve a "balanced" inflammation. Because some novel anti-inflammatory treatment might have detrimental consequences, carefully monitoring disease progress in patients treated with this category of drugs is indispensable.

- A variety of neurological diseases the initial triggers differ significantly, while the subsequent pathways involving inflammatory processes and causing brain damage share certain pathological mechanisms.

Neuropsychiatric Herxheimer Reaction

- Treating syphilis or Lyme/tick-borne disease patients with antibiotics may cause a Jarisch-Herxheimer reaction.
- This reaction may exacerbate any symptom caused by the infection.
- A sudden appearance of depression, suicide attempts, agitation & violence may be a part of this reaction. “You can’t bear to live. It is beyond the imagination.”
- Slowly starting the antibiotic, close observation & psychotropics are helpful.
Inflammation and Central Nervous System Lyme Disease

• Lyme disease, caused by the bacterium Borrelia burgdorferi, can cause multi-systemic signs and symptoms, including peripheral and central nervous system disease. This review examines the evidence for and mechanisms of inflammation in neurologic Lyme disease, with a specific focus on the central nervous system, drawing upon human studies and controlled research with experimentally infected rhesus monkeys. Directions for future human research are suggested that may help to clarify the role of inflammation as a mediator of the chronic persistent symptoms experienced by some patients despite antibiotic treatment for neurologic Lyme disease.

Some Lyme Pathophysiology is a Failure to Shift from Th1 to Th2

- Persisting immune activation causes the cytokine storm in chronic Lyme.
- In these patients, the innate immune system is not turned off by a series of specific immune peptides.
- Specific genetic types are more prone to this phenomenon.
- (Compare this to posttraumatic stress disorder.)
Increased levels of the proinflammatory cytokines IL-6, IL-8, IL-12, IL-18 and interferon γ and of the chemokines CXCL12 and CXCL13 have been reported in the CSF of patients with neurologic Lyme disease (Weller et al., 1991; Grusell et al., 2002; Widhe et al., 2002, 2005). The magnitude of IL-6 in human serum and CSF has been shown to correlate with disease activity in neurologic Lyme disease (Weller et al., 1991).

Elevated levels of IL-6 can cause symptoms of fatigue and malaise, common to many infectious conditions as well as Lyme disease (Pachner et al., 1997).
Borrelia species induce inflammasome activation and IL-17 production through a caspase-1-dependent mechanism

- We describe for the first time the role of the inflammasome-dependent caspase-1 activation of cytokines in the regulation of IL-17 production induced by Borrelia spp. As IL-17 has been implicated in the pathogenesis of chronic Lyme disease, these data suggest that caspase-1 targeting may represent a new immunomodulatory strategy for the treatment of complications of late stage Lyme disease.

The chemokine CXCL13 and Lyme disease

- The chemokine CXCL13 is a key regulator of B cell recruitment to the cerebrospinal fluid in acute Lyme neuroborreliosis [1]
- CSF CXCL13 can be used as a diagnostic marker for NB in children [2, 3]

Lyme Proinflammatory Lipoproteins

- B.b. spirochetes express lipoproteins on the outer membrane of the borreliial cell wall that are known to be pro-inflammatory. (Fraser et al., 1997; Casjens et al., 2000; Garcia-Monco and Benach 1997)

- These lipoproteins attract neutrophils (Szczepanski and Benach, 1991) and have been shown to be 50- to 500-fold more active inducers of cytokines and mitogens of B cells than lipoproteins of other organisms, such as Escherichia coli (Weis et al., 1994).

- B.b.'s surface lipoproteins are proinflammatory (Benach 1997).

Bacterial & Borrelia Lipoproteins can Disseminate from the Periphery to Inflame the Brain

• We conclude that some bacterial lipoproteins can disseminate from the periphery to inflame the brain. (1)

• Borrelia Lipoproteins Can Disseminate from the Periphery to Inflame the Brain. (2)

(1) Londono D, Cadavid D. Bacterial Lipoproteins Can Disseminate from the Periphery to Inflame the Brain. *Am J Pathol*. 2010 Apr 29; [Epub ahead of print]

(2) Cadavid D. Borrelia Lipoproteins Can Disseminate from the Periphery to Inflame the Brain. 11th Lyme & Tick Borne Diseases Conference. Oct 2, 2010.
Neuroinflammation Screening in Immunotherapy Trials against Alzheimer's Disease

• Due to side effects in the form of meningoencephalitis in the interrupted phase II AN1792 trial of active antiamyloid beta (Abeta) immunization against Alzheimer's disease (AD), there has been concern that anti-Abeta immunization may cause destructive neuroinflammation.

• Here, we report on two patients fulfilling clinical AD criteria who were diagnosed with Lyme neuroborreliosis during screening before inclusion in anti-Abeta immunotherapy trials.

• The two cases illustrate the necessity of careful biochemical screening for neuroinflammatory/neuroinfectious conditions before an AD diagnosis is made and before clinical AD patients are included in trials of therapy that could impact the immune system. Should the two cases have been included and deteriorated, additional investigations might have led to the erroneous conclusion that therapy-induced meningoencephalitis had occurred.

Immune Effects: Autoimmunity

- Autoimmunity
- Autoimmunity associated with Lyme disease
Autoimmune Encephalopathies

• Paraneoplastic limbic encephalopathy
  – autoantibodies directed against intracellular neuronal antigens

• Nonparaneoplastic limbic encephalitis
  – voltage-gated potassium channel limbic encephalitis
  – Hashimoto’s encephalopathy
  – Anti-NMDA & other glutamate receptor encephalitis

• Encephalitis associated with GABAergic signaling

Neurons excited to death by SLE autoantibodies

- By holding a gated ion channel in an open position, autoantibodies found in 40–50% of patients with systemic lupus erythematosus (SLE) alter synaptic transmission and cause neurotoxicity. This mechanism, according to new data obtained using mouse hippocampal slices.

Emma Leah E. *Nature Reviews Rheumatology* 7, 1 (January 2011)
Pediatric Autoimmune Diseases Associated with Strep (PANDAS)

- Strep infections in a genetically susceptible individual at a young age can result in OCD, tics and sometimes attention span difficulties

- Often comorbid with Lyme/tick-borne disease PITAND (Pediatric Infection-triggered Autoimmune Neuropsychiatric Disorders)

- Symptom flares follow a strep infection and correlate with increased antibody production

- ASO & anti-DNA titers may be elevated

- Antibiotics are effective in treating and preventing these symptoms

- IVIG & plasmapheresis can also be effective.
Lyme Surface Antigens Cause Molecular Mimicry

• B.b. spirochetes surface glycolipids may elicit cross-reactive antibodies. (Garcia-Monco and Benach 1997)

• IgM B.b. flagella antibodies cross-reacted with neuronal antigens (Sigal and Tatum, 1988; Sigal, 1993; Sigal and Williams, 1997).

Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms

- Anti-neural antibody reactivity was found to be significantly higher in the PLS (post treatment) group than in the post-Lyme healthy (p<0.01) and normal healthy (p<0.01) groups.

- Immunohistochemical analysis of PLS serum antibody activity demonstrated binding to cells in the central and peripheral nervous systems.

Anti-neural antibody reactivity in patients with post-treatment Lyme disease I

- This study demonstrating ‘objective immunologic abnormalities’ underscores the pathophysiologic nature of post-treatment Lyme disease and discredits the psychosomatic theory advanced by some as the cause of persisting symptoms (Hassett et al., 2009). However, immunologic abnormalities can be caused by an ongoing infectious process.
Anti-neural antibody reactivity in patients with post-treatment Lyme disease II

• A growing list of animal and human studies supports persistent infection in posttreatment Lyme patients (Phillips et al., 2005; Stricker and Johnson, 2008; Barthold et al., 2010). Furthermore, current models of autoimmunity in other diseases suggest that persistent infection is required for the production of autoantibodies such as the antineural antibodies described by Chandra and colleagues (Tam, 2006; Stricker and Johnson, 2008). Thus it is likely that persistent infection with the Lyme spirochete Borrelia burgdorferi may be driving production of these antibodies.

Stricker R, Johnson L. Brain, Behavior, and Immunity
Autism
Chronic Infections, Lyme/Tick-Borne Disease & Autism Spectrum Disorder


The Immune System’s Role in the Biology of Autism

• The discovery of autoantibodies targeting brain proteins in both children with autism and their mothers. In particular, circulating maternal autoantibodies directed toward fetal brain proteins are highly specific for autism.

• Additionally, data suggest there may be a defect in signaling pathways that are shared by the immune and central nervous systems.
Brain Inflammation & anti-Neural Antibodies

- During postnatal life, an intact blood–brain barrier limits the entry of immune species into the brain. Lymphocytes, macrophages, various cytokines, and antibodies are generally maintained in the periphery. However, the blood–brain barrier is permeable during fetal development and can be compromised by infections and environmental exposures throughout life. The absence of a complete barrier allows immune components access to the brain. Individuals with autism show increased pro-inflammatory cytokines in the brain, as well as activation of resident immune cells known as microglia. Additionally, antibodies that target brain tissues have been described in both children with autism and their mothers. These immunological phenomena may interfere with normal brain development and function, potentially contributing to the development and/or symptoms of autism spectrum disorders.
Blood–brain barrier (BBB)

Circulation

Brain

Cytokines

Activated lymphocytes and macrophages

Anti-CNS antibodies

Environmental exposure and breach of the BBB

Neuronal damage or repair

Activation of microglia: local immune response

Antibodies: blocking or stimulatory
• Immune reactivity in the mother, fetus and child appear to adversely effect developing neural tissue and contribute to the pathophysiology associated with autism spectrum disorders. This reactivity can be evoked by a number of causes including both acute and persistent infections such as *Anaplasma*, *Babesia*, *Bartonella*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Ehrlichia*, *Human heprevirus-6*, *Mycoplasma* (in particular *Mycoplasma fermentans*) and *XMRV*. Possible pathophysiological mechanisms include both inflammatory processes as well as autoantibodies to developing neural tissue.
Maternal Immune Activation Alters Fetal Brain Development through Interleukin-6

Here we show that the cytokine interleukin-6 (IL-6) is critical for mediating the behavioral and transcriptional changes in the offspring. A single maternal injection of IL-6 on day 12.5 of mouse pregnancy causes prepulse inhibition (PPI) and latent inhibition (LI) deficits in the adult offspring. Moreover, coadministration of an anti-IL-6 antibody in the poly(I:C) model of MIA prevents the PPI, LI, and exploratory and social deficits caused by poly(I:C) and normalizes the associated changes in gene expression in the brains of adult offspring. Finally, MIA in IL-6 knock-out mice does not result in several of the behavioral changes seen in the offspring of wild-type mice after MIA. The identification of IL-6 as a key intermediary should aid in the molecular dissection of the pathways whereby MIA alters fetal brain development, which can shed new light on the pathophysiological mechanisms that predispose to schizophrenia and autism.

Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism

- Rhesus monkeys gestationally exposed to IgG class antibodies from mothers of children with ASD consistently demonstrated increased whole-body stereotypies across multiple testing paradigms. These monkeys were also hyperactive compared to controls.
Is autism spectrum disorder partially autoimmune?

Based upon three different studies, antibodies that react to the 36, 37, 39, 61 and/or 73 kDa bands on Western Blot testing are associated with provoking an immune reaction and contribute to causing autism. Reactivity to these bands is also associated with *Borrelia burgdorferi* and to a lesser degree to *Bartonella henselae, Bartonella quintana, Mycoplasma, Chlamydia pneumonia and Streptococcus pneumoniae*.

Treatment Implications
Psychotropics are also Antimicrobial & Immune Modulating

- Antidepressants modulate cytokine functioning (1)
- The immunostimulating and antimicrobial properties of lithium and antidepressants (2)
- Immunomodulatory effect of SSRIs on human T lymphocyte function and gene expression (3)
- Antiviral & immunomodulatory effect of lithium (4)

2 Lieb J. J Infect. 2004 Aug;49(2):88-93
3 Taler, et al. European Neuropsychopharmacology
4 Rybakowski JK. Pharmacopsychiatry. 2000 Sep;33(5):159-64.
Drugs that Increase Delta Sleep Decrease Inflammation

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<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Reference</th>
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<tr>
<td>Tiagabine</td>
<td>GAT-1 inhibitor</td>
<td>(Mathias et al., 2001)</td>
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<tr>
<td>Gaboxadol</td>
<td>Selective extrasynaptic GABA A agonist</td>
<td>(Deacon et al., 2007)</td>
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<tr>
<td>Gabapentin</td>
<td>α2-δ site on voltage-gated calcium ion channels</td>
<td>(Bazil et al., 2005)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>α2-δ site on voltage-gated calcium ion channels</td>
<td>(Hindmarch et al., 2005)</td>
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<tr>
<td>GHB</td>
<td>GABA$_B$/GHB agonant</td>
<td>(Pardi et al., 2006)</td>
</tr>
<tr>
<td>Ritanserin</td>
<td>Partially selective 5HT$_{2A}$ receptor antagonist</td>
<td>(Dahlitz et al., 1990)</td>
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<tr>
<td>Eplivanserin</td>
<td>Antagonist of Serotonin 2A Receptors</td>
<td>(Hindmarch et al, 2008)</td>
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<tr>
<td>Mirtazapine</td>
<td>Multiple receptors, including 5HT$_2$ antagonist</td>
<td>(Shen et al., 2006)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Multiple receptors, including 5HT$_2$ antagonist</td>
<td>(Sharpley et al., 2005)</td>
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<tr>
<td>Trazodone</td>
<td>Multiple receptors, including 5HT$_2$ antagonist</td>
<td>(Mendelson, 2005)</td>
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<tr>
<td>Quintiapine</td>
<td>Unpublished data</td>
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(GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyrate; 5HT, serotonin)

Treatment Options to Reduce Glutamate Mediated Excitotoxicity

- Ceftriaxone [1]
- Memantine [2]
- Acetylcarnitine [3]
- Dextromethorphan hydrobromide & quinidine sulfate [4, 5]

Conclusion

• Many of the psychiatric symptoms of Lyme and associated tick-borne diseases are mediated by immune mechanisms.
• Therefore greater interaction is needed between infectious disease specialists, immunologists and mental health practitioners.
I Invite you to join us for the ILADS Meetings in:

- **Augsburg**: 27-28 May, 2011, in Augsburg, Deutschland im Augustana Saal, Annahof Augsburg
- **Toronto**: 25-30 October ILADS 2011, 12th Annual Scientific Conference, Fairmont Royal York
Thank You
Dankeschön