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One Reader at a Time...

FREE

PUBLIC HEALTH ALERT

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The Psychoimmunology of Lyme/Tick-Borne Diseases and its Association with Neuropsychiatric Symptoms

by Robert Bransfield, M.D.

INTRODUCTION

There are different degrees of evidence that infections and the immune reactions to them can cause degenerative neurological disease, mental illness, cognitive decline, developmental disabilities, personality changes and violence, and the pathophysiology needs better clarification [17]. Disease can result from an interaction of predisposing and precipitating factors [5]. When diseases are associated with infection, the infection is followed by immune and other reactions that can lead to a pathophysiological process resulting in dysfunction leading to symptoms and syndromes of dysfunction [5]. Ineffective treatment then can result in further disease progression [8]. Understanding the interaction between the immune system and nervous systems is critical, however, psychiatrists have little training and experience in immunology and immunologists have little training and experience dealing with psychiatry. However, the brain and immune systems have many similarities-both defend against threats by shifting allocation of resources as environments change; both have intracellular transmitters, receptors and feedback capability; there are similarities between the gut and immune barrier and the blood brain barrier (BBB); both have innate and learned capabilities and in both cases failures to shift from innate to learned responses result in pathology [9]. The brain and immune systems both switch back and forth, eliminating one threat then recovering before responding to the next threat.

MICROBES AND IMMUNE REACTIONS

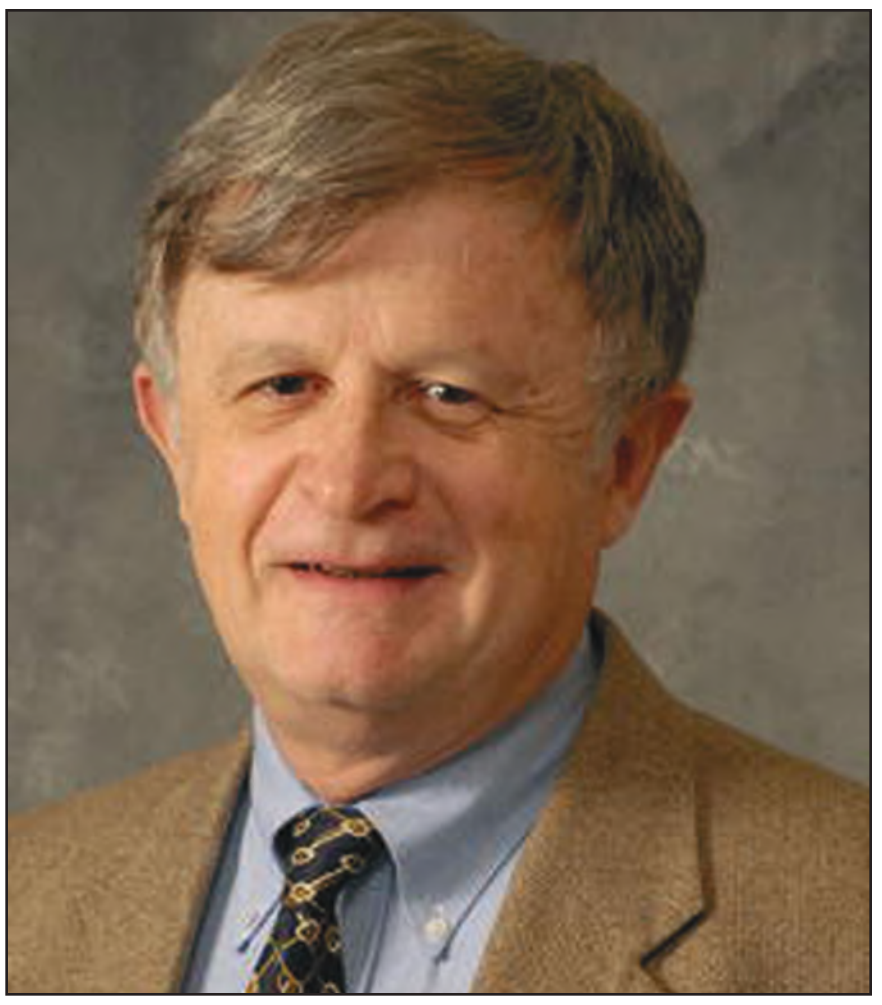
There are a number of environmental conditions that may provoke and/or weaken the immune system-infections, cancer, allergens, stress, sleep deprivation, vaccinations, trauma, toxins, degenerative changes, molecular mimicry, low glutathione levels, increased oxidative stress, metal toxicity, elevated leptin levels and some medical treatments [10-13]. Microbial effects are a major consideration for impacting neuronal functioning [14]. Thousands of peer-reviewed journal articles demonstrate the causal association between infections and mental illness and over 250 peer-reviewed scientific articles demonstrate the causal association between Lyme/tick-borne disease and mental illness [15].

Bacterial infections are recognized to be associated with many autoimmune diseases involving chronic inflammation and demyelination [16]. Possible modes of pathogenic action of bacteria include cytokines, toll-like receptor signaling, the interaction of heat shock proteins with the immune system, and nitric oxide. An autoregulatory loop might exist in the interaction of bacteria with the host and in pathogenic signal processing [17]. Two common questions are whether trauma is directly from the infection or from the host's immune or other reactions to the infection and another is whether symptoms in the central nervous system (CNS) are a result of infection within the CNS or whether the infection is outside the CNS but immune effects are causing CNS symptoms? Parasite effects include cell penetration, toxin release and incorporation of parasite genes into the host genome. Host immune effects include cytokine release, antibodies, inflammation and other cellular responses. Sickness syndrome is a useful model to differentiate the symptoms commonly associated with inflammation from the symptoms mediated by other processes. Sickness syndrome is mediated by the proinflammatory cytokines cascade with effects from interleukin 1 (IL), IL6, and tumor necrosis factor (TNF) [18]. Interferon treatment for Hepatitis C and other conditions is a good model for demonstrating inflammation mediated mental symptoms. Symptoms seen with interferon treatment include cognitive impairments, depression, anxiety, mania, irritability, impulsiveness, hostility, relapse of substance abuse and lassitude [19,20].

DISEASE PROGRESSION

It is recognized that chronic infections cause chronic stress, sleep disorders, cognitive impairments and chronic fatigue. Sleep disorders are commonly associated with chronic inflammatory diseases and chronic stress-related disorders. The best studied in this regard are rheumatoid arthritis, fibromyalgia, chronic fatigue syndromes and Lyme disease [21-23]. The bidirectional communication between the brain and the immune system contribute to inflammatory mediated disrupted sleep quality and conversely [24].

Cytokines produced by cells of the immune and nervous systems (particularly IL1beta and TNFalpha) regulate sleep, signal neuroendocrine, autonomic, limbic and cortical areas of the CNS to affect neural activity and modify behaviors, hormone release and autonomic function [23]. To demonstrate the association between inflammation, chronic fatigue and sleep disturbances, it has been demonstrated that sleep restriction increases IL6 and pain-related symptoms in healthy volunteers and impaired sleep correlates with impaired immune functioning [22, 24]. Growth hormone modulates adaptive immune response but growth hormone production is dependent upon the presence of delta sleep which is reduced in an inflammatory state [25]. Therefore,



increasing delta sleep is therapeutic while disease progression is fostered by nonrestorative sleep and is associated with fatigue, cognitive impairments, pain and emotional symptoms [26]. The consequences of both nonrestorative sleep and associated chronic stress reactions contribute to perpetuating the disease process and are associated with-decreased regenerative functioning, compromised immunity, oxidative stress and decreased resistance to infectious disease [22,25,26].

IMMUNE MEDIATED NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are a group of chronic, progressive disorders characterized by the gradual loss of neurons in discrete areas of the CNS. When neurodegenerative diseases are progressive, uncontrolled inflammation drives disease progression [27]. Substantial evidence has documented a common inflammatory mechanism in various neurodegenerative diseases. It has been hypothesized 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 [27]. There is evidence with depression, Alzheimer's disease (AD), schizophrenia and epilepsy to support this position. A meta-analysis of cytokines in major depression including 24 studies reports significantly higher concentrations of the proinflammatory cytokines TNFalpha and IL6 in depressed subjects compared with control subjects [28]. A meta-analysis of cytokines in AD which reviewed 86 studies strengthens the clinical evidence that AD is accompanied by an inflammatory response with particularly higher peripheral concentrations of IL6, TNF, IL1, transforming growth factor, IL12 and IL18 and higher CSF concentrations of transforming growth factor [29].

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, cere

"Lyme" ...cont'd pg 5

FEATURE

Three Easy, Fast, and Free Ways to Boost Your Immune System

by Amy B. Scher

Our bodies are so much more than what we see. We operate on an intricate energy system that affects all of our organs, muscles, glands and more. It is fueled by electrical impulses that run through the body. Accessing and balancing your body's subtle energies can make a huge difference in your health. While energy therapies are definitely not a new concept (Chinese Medicine is based on the body's energy system), they are finally gaining well-deserved attention. As Dr. Oz put it, they are "the next big frontier in medicine."

When our energies are being disrupted, flow irregularly, or become sluggish and blocked, our bodies are not functioning at their optimal healing capacity. But, there are lots of things we can do to start to shift that-and they're free. Pretty cool, right?

Here are three energy medicine exercises that, when done regularly, can help strengthen your immune system.

1. Chill Out Your Triple Warmer Meridian

Meridians are energy pathways in the body responsible for bringing energy to certain parts of the body including muscles, organs and tissues. Your Triple Warmer meridian specifically governs your "fight or flight" response. If it's over-active, it is pulling energy away from other meridians and systems to sustain that over-active state. This can take a toll on your immune system.

To calm it when you are stressed:
Place your fingers at your temples. Hold for one deep breath, again breathing in through your nose and out through your mouth. On another deep in-breath, slowly slide your fingers up and around your ears, smoothing the skin while maintaining some pressure. On the out breath, slide your fingers down and behind your ears, press them down the sides of your neck, and hang them on your shoulders. Push your fingers into your shoulders and then, when you are ready, firmly drag forward, over the tops of your shoulders, and smooth them to the middle of your chest, with one hand resting on top of the other. Hold here for several deep breaths.

2. Thump Your Thymus Gland

"Thymus gland serves as the link between mind and body. It is the first organ to be affected by mental attitudes and stress. Hence activation and stimulation of the thymus is an essential, primary foundation of achieving and maintaining positive health." ~ Dr John Diamond

The thymus gland lies just beneath the upper part of the breastbone in the middle of the chest and is a specialized gland of the immune system. It's responsible for creating T-cells in the body, which are vitally important to the immune system.

To activate its energy: "Thump it" with a closed fist several times as you breathe. If you mimic Tarzan (you can use two fists if it feels better), you're doing it right! Tip: Thump the thymus in a waltz beat (one-two-three) with the emphasis on the first thump or beat, and you'll give it an extra boost.

3. Make Sure You're Moving Forward

Stress can reverse the energy flow through the meridians. Even walking will tire you if your energy is flowing backwards. Stimulating the K-27 points, the end points of the kidney meridian, gets the energy flowing in a forward direction through all your meridians and jump-starts your energy system.

The K-27 points are just under the clavicle, or collarbone. Place your index fingertips on the U-shaped notch, right about where a man knots his tie. Then move your fingers out to each side about an inch and drop them below the collarbone. Most people have small indentations in the skin there. Simple tap or rub them firmly as you take big deep breaths.
You know know three super-easy exercises to add to your daily practice. Do them before you get out of bed in the morning and before you go to bed at night, and you'll be starting and finishing your day with some serious immune system kick-ass!

pha

A Life-Changing Year

by Annalisa Walker

I am a 45-year-old wife, mother of three, and professional. I had always been the most optimistic, joyful, and healthy person as I journeyed through my very happy life. I had encountered some minor trials in my life, but nothing like what I encountered in October, 2011. October 27, 2011 is the day that I knew my life would never be the same.

However, October 27 wasn't the beginning of this very long journey. I need to go back three years prior to that. In the summer of 2008, I started feeling like I had bugs crawling across my forehead. I started experiencing a racing heart - even though I worked out every day by running four miles per day and doing kickboxing four days per week. I also started having abnormal hair loss. I had my PCP run blood work, and it always came back perfect. There was never one test that came back abnormal. These issues were annoying, but nothing that I couldn't get through on a day to day basis. The following year, I started experiencing white, squiggly lines through my vision. Again, there was nothing that was really affecting my day-to-day living. I chalked all of these annoying symptoms up to "getting older", and pushing myself harder than I knew I should. I am a Type-A personality, so I really never gave my body a chance to rest, relax, and rejuvenate.

On October 27, 2011 I was grocery shopping in Wal-Mart when I literally got electrocuted in my right eye. This happened two times for about 10 seconds each time. These shocks in my right eye literally dropped me to my knees. After the shocks I became very nauseous and disoriented. Somehow I made it out of Wal-Mart, drove home, told my husband what happened, and lay down on the couch the rest of the day. All day long as I lay on the couch feeling sick, I knew something bad had happened to me. However, I had no clue of what was to come the following weeks and months.

For the next two weeks I felt somewhat weak, but again, nothing that I couldn't fight through. On Veteran's Day Weekend the same shocks happened again. I knew that I needed to call my doctor and schedule an appointment to discuss this. My doctor ran blood work again, which came back fine, and said I was experiencing abnormal migraines. During the next week I developed a very strange eye pressure, dizziness, numbness, neck pain, and a feeling that my legs and arms were not connected to my body. I scheduled appointments with an ENT, optometrist, rheumatologist, and my PCP again. These doctors found nothing wrong. They said to take some antibiotics for a possible sinus infection. Little did I know that these antibiotics would make me so sick that I thought I was going to die (which we know now was a herxheimer reaction from Lyme disease). These antibiotics are used for Lyme disease treatment, but my ENT had prescribed it for the sinus infection. The last day that I worked was November 16, 2011.

I became so sick I ended up being admitted to the hospital for three days. I had every blood test done that they knew of (including Lyme), CT scans, X-rays, and heart tests. The doctors could find nothing wrong, and discharged me with a diagnosis of fatigue. I went home and continued to get worse. My husband took me back to the hospital the following week and I was admitted again. This time they did a spinal tap, MRI, more CT scans, and more blood work. Again - nothing showed up showing anything was wrong. A counselor came in and saw me and let me know that "women my age often have nervous breakdowns and need to re-evaluate their lives. “Perhaps that is your situation," she stated. I let her know that a few weeks ago I was living a very happy, fulfilled life, and that MOST DEFINITELY was not my problem. I was discharged this time with a diagnosis of "stress."

By this time I was so weak that I needed help walking, could not drive, and had lost my short-term memory. My husband called his mom and she came down to stay to help with our children, as I could no longer take care of them. My family Googled my symptoms, and the only illnesses that kept popping up were HIV and Lyme disease. However, these tests had both shown up negative in the hospital. My sister said that someone she knew had a relative with Lyme disease. It really was the only disease that seemed to fit my case. We contacted this person, and she referred us to an LLMD in California. My PCP and this LLMD corresponded by telephone about my case, and determined that I just may in fact have Lyme disease. I started on antibiotics on December 14, 2011.

I became even sicker once I started on my antibiotic regimen and my homeopathic protocol. I could not get out of bed for days, I had panic attacks which lasted for three days, and became suicidal. I could not be left alone, as I could not take care of myself or my family.

After about three months I started to pull out of this nightmare. I could think again, was no longer suicidal (I had been on anti-psychotics during this time), and my pain had dissipated. I still had neurological symptoms eye issues, brain fog, dizziness, and fatigue/weakness. However, I could take care of myself and family again, although it was not nearly at the level I had prior to my Lyme diagnosis. I was functioning at about 50% of what I used to, but at least I was no longer bedridden.

During the spring and summer of 2012 I did not work. I did not have the strength or energy to go back to my job at the University. I was fortunate to have had enough sick leave built up over the years to be able to take a year off with pay. However, in August, 2012 I did not have an option and returned to work. It was a hard transition. There were days when I didn't think I would be able to make it through to the end of the day. As of May 2013 I have only missed one day of work since returning.

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Public Health Alert

The PHA is committed to researching and investigating Lyme Disease and other chronic illnesses in the United States. We have joined our forces with local and nationwide support group leaders. These groups include the chronic illnesses of Multiple Sclerosis, Lou Gehrig's Disease (ALS), Lupus, Chronic Fatigue, Fibromyalgia, Heart Disease, Cancer and various other illnesses of unknown origins.

PHA seeks to bring information and awareness about these illnesses to the public's attention. We seek to make sure that anyone struggling with these diseases has proper support emotionally, physically, spiritually and medically.

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The Hilarity of Temper Tantrums in the Lyme Community

Frequently Asked Questions of DR Wiseass

by DR. Wiseass

Recently, after a 6 ½ year hiatus from the Lyme community - DR. Wiseass courageously reappeared, unveiling her NEW site http://drwiseass.com in the process. Prior to her abrupt departure from the 'community' in 2007 - she had been quite a prolific blogger at www.twistofly-me.blogspot.com . While DR Wiseass feels the posts & personal information shared on both of these sites should be a sufficient explanation as to "WHO SHE IS" and "WHAT SHE'S ALL ABOUT" - she has be inundated on her own Facebook page with repetitive questioning, which people feel they have the RIGHT to know. So without further ado... the FAQ's:

1) Who IS DR Wiseass?

DR Wiseass is the pseudonym of an older gal suffering with chronic invisible illness for the greater part of her life. She was diagnosed with Lyme disease in November 2004, and decided in 2005 to start a blog as a vehicle to work through her own struggles as well as triumphs with this most insidious disease. She chose to keep her true identity anonymous because:

A) She likes to write about her in-laws. No one in their right mind would openly make jokes about their in-laws using their real damn name! DUH!

B) At one brief (stressful) point in time, using her real name, she was quite a vocal advocate in the Lyme community, and found it most necessary to keep the distinction between her real identity and her 'say-ANYTHING' pseudonym. She's smart enough to know some people either don't understand or "can't handle" her satirical, sometimes raunchy sense of humor, so she quite wisely has kept both identities separate.

C) It's her username on Lyme disease message board. While there are so many good people helping out on most message boards, she also knows there are also some very strange folks on there too. In this techno day & age where one's name & home address are linked for anyone to see - DR. Wiseass KNOWS better than to reveal her true identity ...at least NOT with her loud mouthed propensity toward speaking the truth....often with MUCH profanity!

D) It's her pseudonym; her "gimmick"; her "brand" in which she delivers her own unique brand of humor.

2) OK, but WHO is DR Wiseass? What's her REAL NAME?

DR. Wiseass is the pseudonym of a humorous blogger that often enjoys using satire & sarcasm to get her points across. She employs a pseudonym for her comical writing style because she would never want to hurt the feelings of her family & friends, even though they sometimes do the most comical (stupid) things.

DR. Wiseass uses an anonymous pseudonym because it also allows her to be more honest & often truly 'vulnerable' with regards to her experience as a patient with chronic invisible illness - knowing much too well the day-to-day struggle and cruel injustices heaped upon chronic Lyme disease patients.

3) But I NEED to know WHO she really is! So WHO is she?

DR Wiseass understands first-hand the over-whelming frustration of brain-fog, as it is a common feature - an overlapping symptom - of many chronic invisible illnesses. Because of this, she invites you to return on a different day when, perhaps, the 'fog has lifted' and you can better understand that which has already been presented repeatedly.

4) But it's my RIGHT to know who she is!

DR. Wiseass wonders if, during your childhood, you were not told "NO" very often. Going on that premise, she gently & with compassion welcomes you to the world of adults when she says:

NO. NO, it isn't your RIGHT to know.

You DO have a RIGHT to pursue happiness, and if you can't be happy with DR Wiseass's brand of humor while respecting her RIGHT to privacy - then you are ENCOURAGED to seek happiness & LAUGHTER elsewhere. Anger, even a sense of "righteous anger" that many with chronic illness experience is really NOT conducive to healing. DR. Wiseass wants you to find a place where you may comfortably laugh your ass off! And YES, even YOU - even though you've been rather mean & uninviting to her.

5) I'm a blogger too. I've been writing for YEARS, and I've never felt the need to HIDE behind a pseudonym! I don't think there's any accountability when writing under a pseudonym!

Hmmm... DR. Wiseass does find this to be an interesting, and possibly a valid point - to some degree. However, she doesn't feel that utilizing a pseudonym and refusing to give in to the demands of others to be equivalent to "hiding":

A) Thanks to YEARS upon YEARS in therapy, DR. Wiseass knows that when people are angry, especially

if they are part of a gang mentality or are engaged in that popular past-time called "cyber-bullying" - they are actually incapable of understanding logical presentations, for they are operating out of their 'animal brain' - their limbic system. DR Wiseass knows those that are angry are better dealt with at a later time. Therefore - if DR. Wiseass refuses to answer you - it is often because she is sleeping, at the pharmacy, in the bathroom, writing blog posts, spending time with her family, OR because she doesn't think any answer she provides you with will be satisfactory to you, and therefore deems her time too important to waste in attempting such.

B) As far as writing is concerned, DR. Wiseass wonders if your inability to understand her choice to maintain anonymity via a pseudonym is because you assume your writing styles are the same. They are not.

C) IF DR. Wiseass is indeed, 'hiding' at all, it is actually for the benefit of her offspring, who just might want to be President of the United States one day - or NOT. Either way, the anonymity chosen by DR. Wiseass is meant to assure nothing she says or writes ever reflects badly upon her child(ren).

6) I still think she's just HIDING. I don't trust people who hide. Why should I TRUST her?

YOU SHOULDN'T!

In fact, you probably shouldn't TRUST most of the people you've "friended" on your Facebook page. DR. Wiseass feels trust should be earned. That's why DR. Wiseass isn't trying to seek donations from you, date you, stalk you, or sell you anything. Instead, DR. Wiseass was simply seeking your cyber-friendship out of a sense of community.

IF, in spite of her "opening up" to everyone via her NEW and OLD blog sites mentioned above - if you continue to feel unsettled by DR. Wiseass's anonymity - by all means "unfriend" her OR don't accept her friendship to begin with. Ultimately, it is your choice, which DR. Wiseass certainly respects, and she wishes you well as you go on your way.

7) Well, why is she so SARCASTIC? I think SARCASM can be RUDE!

You don't get the comedy channel, do you?

Most individuals who aspire to comedy at any level (regardless of whether YOU find them funny) utilize sarcasm to some degree. Most of the time when DR. Wiseass is using sarcasm, she is attempting to be funny. HOWEVER, there are indeed times DR. Wiseass uses sarcasm INSTEAD of saying or writing what she may truly WANT to say because she doesn't want to be as rude and inappropriate as she's certainly capable of being. In other words, her sarcasm is a gift which she shares with you - regardless of the reason. You may choose to take offense, if you'd like. Again, that's YOUR choice.

8) I don't think SARCASM is funny. I think it's hurtful.

DR. Wiseass understands many people will not understand her special brand of humor. In such circumstances, she ENCOURAGES you to GO AWAY, for it is not her desire to be hurtful to anyone.

9) Well I've heard BAD things about her from some of my friends; is she BAD?

In response to the 1st part - your friends must not really know DR. Wiseass very well, as DR. Wiseass is certainly not familiar with your friends. Furthermore, DR. Wiseass feels it is probably best we keep it that way.

Regarding part 2 of your question: Define "bad".

10) I still think she needs to PROVE to me she's a Lyme disease patient. How do I KNOW?

DR. Wiseass feels it would be an unnecessary inconvenience, as well as an invasion of privacy, to have to hunt down her Western Blot results from Igenex labs to prove her Lyme disease diagnosis, or any other diagnosis to anyone on a website. Besides, Lyme disease is a clinical diagnosis and the various LLMD's she has seen over the years are currently unavailable for comment.

11) I still think I DESERVE to know who she is. Why can't she tell me in a private message?

Due to DR. Wiseass's ongoing physical illness, she tires quite easily. At this point, she would like to convey how very fatigued she has become by these incomprehensible questions, and finds your obsession with her identity a bit disturbing. Furthermore, she would like to suggest you find a new hobby, watch a little television, or perhaps give yourself a much-needed enema.

12) Why does she talk or write about herself in 3rd person? I think that's creepy.

DR. Wiseass is disheartened to think anyone would judge her writing style as 'creepy'. ...but that whole 3rd person thing is weird, isn't it?

13) OK, well, one other thing....

NO!

I do so hope these FAQs help answer the incessant questions which have recently been posted by several individuals on my Facebook site: https://www.facebook.com/dr.wiseass.1, as I am quite finished with this conversation. It is now both my hope & intention to spend my valuable "operational" time writing about the hardships & triumphs faced by those with chronic invisible illness. But then, maybe I just did.

Until next time...

Hugs & Kisses,

DR. Wiseass

~NOT a real doc; just a real wise ASS!

pha

"Lyme" ... cont'd from pg 1

-bral vasculature, and the BBB may be involved which support the inflammatory theory of schizophrenia that was formulated over a 100 years ago [30]. There is a rapidly growing body of evidence that supports the involvement of inflammatory mediators in epilepsy-released by brain cells and peripheral immune cells-in both the origin of individual seizures and the epileptogenic process. Aspects of brain inflammation and immunity were first described and subsequently, it was demonstrated how seizures cause inflammation, and whether such inflammation, in turn, influences the occurrence and severity of seizures and seizure-related neuronal death [31].

Immune mediated mechanisms include inflammatory and autoimmune mechanisms. The inflammatory mediated effects associated with neurodegenerative disease and include oxidative stress, excitotoxicity, proinflammatory cytokine effects and altered tryptophan metabolism.

INFLAMMATORY MEDIATED MECHANISMS

Oxidative stress and oxygen free radicals or activated oxygen has been implicated in diverse environmental stresses and appears to be a common contributor in neurodegenerative diseases [32].

Excitotoxicity and inadequate remethylation leads to increased homocysteine levels which are excitotoxic [33]. Elevated C-reactive protein levels are linked to a decline in executive function and frontal lobe damage. There is an association between elevated levels of high-sensitivity C-reactive protein, an indicator of low-grade inflammation, and decline in executive function [34].

Proinflammatory cytokines include Interferon alpha, IL1beta and IL6. Cytokine activation has been associated with psychiatric symptoms. For example, IL6 is elevated in the cerebrospinal fluid of suicide attempters and is related to symptom severity, memory deficits and aggressiveness and IL1beta is associated with self-inflicted aggressive behavior and fatigue [35-37]. Besides cytokine effects, IL1 receptor activation by systemic lipopolysaccharides has been demonstrated as one of the mechanisms by which environmentally driven immune system activation can trigger despair-like behavior in an animal model [38].

It has been proposed that parasites improve their survival by evolving mechanisms to change host behavior and some of these mechanisms are mediated by changes in serotonin and other monoamines [39]. Inflammation provoked by parasites impacts the conversion of tryptophan into serotonin. The kynurenine pathway is a major route of Ltryptophan catabolism into serotonin with a number of metabolites that include-kynurenic acid which is an NMethylDaspartic acid (NMDA) antagonist (neuroprotective, unless excessive), quinolinic acid which is a NMDA agonist (neurotoxic). In an inflammatory state there is decreased serotonin & a shift to quinolinic acid rather than kynurenic acid. The enzyme indoleamine 2,3dioxygenase (IDO), which converts tryptophan into kynurenine and which is stimulated by proinflammatory cytokines, is implicated in the development of interferoninduced depressive symptoms, first by decreasing the serotonin availability to the brain and second by the induction of the kynurenine pathway resulting in the production of neurotoxic metabolites. In persistent infections associated with persistent inflammation, chronic activation of TNFalpha stimulates interferongamma, which overactivates IDO, the ratelimiting enzyme for catabolism of tryptophan in the brain. Overactivated IDO causes neurotoxicity, and immune suppression of cytotoxic T cells. Underactivation of IDO is known to cause autoimmune reactions, but it has recently been discovered that overactivated IDO causes autoimmune B cell antibody production [40]. CSF quinolinic acid is significantly elevated in a number of CNS infections including Borrelia burgdorferi (Bb) 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 [41].

INFLAMMATION AND LYME/TICKBORNE DISEASES

Lyme disease, caused by the bacterium Bb, has been recognized to cause multisystemic signs and symptoms, including peripheral and central nervous system disease. Some immune mediated pathophysiology seen in Lyme/Tick-Borne Diseases (LYD/TBD) 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 [42].

Increased levels of the proinflammatory cytokines IL6, IL8, IL12, IL18 and interferon and of the chemokines CXCL12 and CXCL13 have been reported in the CSF of patients with neurologic Lyme disease [43]. The magnitude of IL6 in human serum and CSF has been shown to correlate with disease activity in neurologic Lyme disease [44]. Elevated levels of IL6 can cause symptoms of fatigue and malaise, common to many infectious conditions as well as Lyme disease [45]. Borrelia species induce activation of IL17 production. The chemokine CXCL13 is a key regulator of B cell recruitment to the cerebrospinal fluid in acute Lyme neuroborreliosis CSF CXCL13 and can be used as a diagnostic marker for infection [46-48].

Bb spirochetes express lipoproteins on the outer membrane of the Borrelia cell wall that is known to be proinflammatory. These lipoproteins attract neutrophils and have 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. Bacterial & Borrelia lipoproteins can disseminate from the periphery to inflame the brain [43]. There are some other immune pathological processes associated with Lyme disease. The neuropsychiatric Herxheimer reaction appears to be an adverse immune reaction to treatment although the exact mechanism is not well-clarified [49]. In the phase II AN1792 trial of active anti-amyloid beta immunization against AD, there were two patients fulfilling clinical AD criteria who were diagnosed with Lyme neuroborreliosis during screening who developed meningoencephalitis associated with destructive neuroinflammation apparently provoked by an interaction of the vaccine and the presence of Lyme neuroborreliosis [50]. The immune reactions seen in LYD/TBD are different from the immune reactions seen in chronic fatigue syndrome and this may partially be explained by the distinguishing cerebrospinal fluid protein complements that are seen in these patients when compared to healthy controls [51].

MOLECULAR MIMICRY/AUTOIMMUNE MEDIATED MECHANISMS

Paraneoplastic limbic encephalopathies and pediatric autoimmune diseases associated with strep (PANDAS) are good models to understand the effects of autoantibodies directed against intracellular neuronal antigens and the associated psychiatric symptoms. In paraneoplastic and non-paraneoplastic limbic encephalitis, voltagegated potassium channel limbic encephalitis, Hashimoto's encephalopathy, antiNMDA and other glutamate receptor encephalitis, encephalitis associated with gammaaminobutyric acid signaling and systemic lupus erythematosus neurons are excited to death by autoantibodies resulting in neurotoxicity [52,53]. PANDAS is an interaction of a Streptococcal infection in a genetically susceptible individual at a young age which can result in obsessive compulsive disorder, tics and sometimes attention span difficulties. PANDAS is often comorbid with LYD/TBD and the broader categorization has been referred to as pediatric infection-triggered autoimmune neuropsychiatric disorders. Symptom flares follow a strep infection and correlate with increased antibody production [54-56]. Lyme surface antigens can cause molecular mimicry and associated autoimmune symptoms. Bb spirochetes surface glycolipids may elicit crossreactive antibodies and IgM Bb flagella antibodies crossreacted with neuronal antigens [43]. Antineural antibody reactivity has been demonstrated in patients with a history of Lyme borreliosis and persistent symptoms. Antineural antibody reactivity was found to be significantly higher in the Lyme patients with prior treatment and persistent symptoms (PLS) group than in the postLyme healthy and normal healthy groups [57]. Immunohistochemical analysis of PLS serum antibody activity demonstrated binding to cells in the central and peripheral nervous systems. The presence of antineural antibody reactivity in patients with PLS demonstrates 'objective immunologic abnormalities' and

"Lyme" ...cont'd pg 6

"Lyme" ...cont'd from pg 5

underscores the pathophysiologic nature of PLS and discredits the psychosomatic theory advanced by some as the cause of persisting symptoms [58]. Since immunologic abnormalities can be caused by an ongoing infectious process, a growing list of animal and human studies supports persistent infection in post-treatment Lyme patients, and 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; it is likely that persistent infection with the Lyme spirochete Bb may be driving production of these antibodies [59].

CHRONIC INFECTIONS, LYME/TICK-BORNE DISEASE, IMMUNE EFFECTS AND AUTISM SPECTRUM DISORDER

There has been recent attention to the association between chronic infections, LYD/TBD and autism spectrum disorders (ASD). Immune reactivity associated with these infections in the mother, fetus and child appear to adversely affect developing neural tissue and contribute to the pathophysiology associated with autism spectrum disorders. Possible pathophysiological mechanisms include both inflammatory processes as well as autoantibodies to developing neural tissue [5,6,60,61].

During postnatal life, an intact BBB 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 proinflammatory cytokines in the brain, as well as activation of 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 ASD [62].
One mouse model for cytokine-mediated effects associated with ASD is demonstrated by maternal injection of IL6 at different gestational stages is associated with different deficits associated with ASD [63].
Autoantibodies targeting brain proteins have been discovered in both children with autism and their mothers and 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. One model of autoimmune mediated effects associated with ASD is demonstrated by exposing rhesus monkeys to IgG from mothers of children with autism which results in the appearance of ASD symptoms [64]. In addition, 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 [5].

CONCLUSION

When looking at the clinical and basic science research on the subject articles it is apparent that persistent infection and associated inflammation and molecular mimicry mechanisms are associated with gradually increasing encephalopathy and gradually increasing mental symptoms. Cognitive symptoms begin as executive dysfunction and mild cognitive impairments and may gradually progress to dementia while emotional symptoms begin with insomnia, reduced frustration tolerance, irritability and dysthymia and may progress to anxiety disorders, depression, impulsivity and personality disorders and subsequently psychosis and/or suicidal and homicidal tendencies. Many of the neurological, cognitive and psychiatric symptoms associated with LYD/TBD appear to be mediated by immune mechanisms. Therefore greater interaction is needed between infectious disease specialists, immunologists and mental health practitioners.

LIST OF ABBREVIATIONS

CNS = Central nervous system
IL = Interleukin
TNF = Tumor necrosis factor
AD = Alzheimer's disease
BBB = Blood brain barrier
NMDA = NMethylDaspartic acid
IDO = Indoleamine dioxygenase
PANDAS = Pediatric autoimmune diseases associated with strep
PLS = LYME patients with prior treatment and persistent symptoms
ASD = Autism spectrum disorders

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**** remainder of references will be on the online article due to space restrictions.****