Introduction

Lyme disease is a tick borne spirochetal infection that causes a multi-systemic disease. When identified, diagnosed and treated in a timely manner, most of the acute cases will recover and be cured; however, about ten percent of the infected individual will develop a chronic, antibiotic resistant condition, which is believed to be autoimmune (the immune system is confused and cannot differentiate between our healthy body and foreign antigens and starts attacking our own body). The autoimmune process attacks the brain, the peripheral nerves, the joints and the muscles and is better documented in the rheumatologic literature (Steere et al. Autoimmune mechanisms in antibiotic treatment-resistant Lyme arthritis. JAI. 2001; 16:263-266). This chronic condition will vary in severity, from a very debilitating affliction to one with occasional aches and pains. The very sick individuals cannot be gainfully employed, are usually bedridden and in addition to their physical ailments, may suffer from a severe cognitive deficit, with difficulties of memory and concentration along with psychiatric manifestations (depression, anxiety, OCD and even psychosis) which are part of the neurologic complication of this condition (brain disease rather than a psychiatric condition). The percentage of chronic conversion in the undiagnosed (and untreated) cases is probably much higher (see below). The chronic condition can be managed (but not cured) in varying degrees of success.

Lyme disease is a continued and escalating public health issue. In 2009 around 40,000 new cases of Lyme disease were reported in the US, which is more than a 4 fold increase since reporting started in 1991. One fourth of the reported cases are from New England. (http://www.cdc.gov/about/grand-rounds/archives/2011/pdfs/PHG). There is a steady annual increase in the incidence of Lyme disease, except in years where no funding for reporting was available.

The ratio between reported and diagnosed cases is a source of major debate and ranges between 1:2 to 1:10. Accepting a ratio of 1:5 brings the number of diagnosed cases in 2009 to 200,000.

A major problem in assessing the magnitude of this serious public health issue is the undiagnosed cases. The reasons for failure to diagnose Lyme disease varies from lack of the typical telltale sign, the ECM rash; unreliable diagnostic tests; an atypical clinical presentation; a co-infection (another infectious disease transmitted by the same tick); etc. Many of the undiagnosed cases will go on to develop a chronic illness, which is usually no longer responding to short or long courses of antibiotics, since it becomes an ill defined autoimmune disease (as discussed below). For future calculations, we will use the very conservative assumption that the annual undiagnosed cases for 2009 was 200,000, the same as the estimated diagnosed figure.

Similar estimates of autoimmunity were given in a more recent review of “chronic” Lyme disease (Feder HM et al. A critical appraisal of “chronic Lyme disease.” *N Engl J Med* 2007;357:1422-30).

Based on the numbers listed above a fair (and probably underestimated) statement is that since 2009, each year at least 40,000 patients are added to the chronically ill pool, which adds up to about 350,000 patients since reporting started in 1991. Today, in 2012, it will be fair to expect that about 0.5 million patients in the US are chronically ill due to Lyme disease (one in 600 people), of them 125,000 live in New England (1% of the population), which is around 30,000 patients in Connecticut. These numbers are based on the 2010 Census ([http://2010.census.gov/2010census/data/](http://2010.census.gov/2010census/data/)) and the CDC Lyme Disease incidence report: [http://www.cdc.gov/lyme/stats/chartstables/incidencebystate.html](http://www.cdc.gov/lyme/stats/chartstables/incidencebystate.html).

Schism and polarization within the medical community, heated by patient activism, resulted in ignoring the problem, preventing our strong and capable medical and scientific communities from finding the long overdue answers.

Rather than continuing the true search for answers, Lyme disease research was derailed by unrelated agendas.

Not unlike the political arena the magnitude of the problem requires a bipartisan effort. Our brilliant and capable physicians and scientists should refocus only on one target – finding a solution to the problem.
The Diagnosis and Treatment of Chronic Lyme disease (AKA: post treatment Lyme disease)

Patients with chronic illness and symptoms which can be seen in post treatment (“chronic”) Lyme disease are usually seen by numerous physicians who are perplexed by the complexity of their symptoms. There are no conclusive studies assessing the prevalence (see above) of this condition, or its mechanisms, even though recent literature stemming from unprecedented collaboration between main stream authorities on Lyme disease (IDSA) and leading neuroscientists might have found a partial explanation to the neurologic aspect of the chronicity (Chandra et al. Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. Brain Behav Imm. 2010; 24:1018-1024).

Diagnosis

Before making a diagnosis of “Chronic” Lyme disease, a relentless effort should be made to rule out other conditions which can have a similar clinical picture. Over-diagnosis of Lyme disease, may lead to a dangerous under-diagnosis of other conditions and over treatment with antibiotics. Chronic Lyme disease cannot be diagnosed based on clinical symptoms solely. It cannot be diagnosed by using tests which are not FDA approved. Desperate patients and the lack of reliable diagnostic tests for Lyme disease (see below) led to the appearance of expensive, non FDA approved laboratories and tests.

Testing for Lyme disease.

Direct Methods (none are FDA approved) – the direct identification of the pathogen can be done by

1. Culture (growing the spirochete from a fluid or tissue sample obtained from a patient in a culture medium, which is very difficult and hard to reproduce. It is used mainly in research laboratories and recently by one commercial laboratory, which appears to have too many positive results (50% - 70%).

2. PCR (polymerase chain reaction), enzymatic amplification the nucleic acid of the spirochete from the specimen until it reaches a detectable quantity that can be identified. This methodology is prone to contamination and false positives (the test is positive but there is no infection), but is the most commonly used direct method.

3. Dark field microscopy with immune fluorescence staining. Accurate, but available only in research labs and requires the presence of spirochetes in the specimen.

Serologic tests (FDA approved) – Indirect identification of the infection by measuring the immune response of the host. Will fail when the patient is immune deficient (is not making enough antibodies), or the number of pathogens is overwhelming (bad infection – where all the antibodies are tied to the spirochete and not enough are available for serologic detection).
1. ELISA (enzyme linked immune sorbent assay) is a colorimetric quantitative technique that measures the intensity of the immune response against the pathogen - the serum of the patient (which may contain antibodies against the spirochete) is mixed with a standardized amount of diced Lyme pathogens (antigens). After incubation, during which the antibodies bind to the antigens, a reagent that connects only to the antibody-antigen complexes is added. After the attachment, the reagent changes its color. The color intensity of the solution is than measured and converted to antibody concentration. The assay is accurate but it will be also positive with other spirochetal infections and in a variety of autoimmune conditions (false positive).

2. IFA (Immunoflourescent Assay) – similar to the ELISA, but uses a different color binding reagent (fluorescent).

3. C6 Peptide. Similar to the ELISA in process, but instead of having a diced spirochete solution as antigenic source, it uses only one protein (antigen) from the spirochetal coat – the C6 peptide – which is more specific and results in many less false positives. It also supposed to correlate with a more recent infection.

4. Western blot (immunoblot). A qualitative technique that measures the presence of antibodies against the various proteins of the spirochete. The serum interacts with a strip of gel onto which a mixture of spirochetal proteins are applied. They are separated according to their size (the smaller migrates the farthest on the gel). This results in the smallest protein (with a molecular weight of 18kd) ending at one end of the strip and the largest protein (with a molecular weight of 93kd) – at the opposite. After the antibody – antigen complex is stained – there is a visible “band” at the location of each spirochetal protein against which antibodies were formed.


“A two-test approach for active disease and for previous infection using a sensitive enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by a Western immunoblot was the algorithm of choice. All specimens positive or equivocal by a sensitive EIA or IFA should be tested by a standardized Western immunoblot. Specimens negative by a sensitive EIA or IFA need not be tested further. When Western immunoblot is used during the first 4 weeks of disease onset (early LD), both immunoglobulin M (IgM) and immunoglobulin G (IgG) procedures should be performed. A positive IgM test result alone is not recommended for use in determining active disease in persons with illness >1 month’s duration because the likelihood of a false positive test result for a current infection is high for these persons. If a patient with suspected early LD has a negative serology, serologic evidence of infection is best obtained by testing of paired acute- and convalescent-phase serum samples. Serum samples from persons with disseminated or late-stage LD almost always have a strong IgG response to Borrelia burgdorferi antigens.

It was recommended that an IgM immunoblot be considered positive if two of the following three bands are present: 24 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla) (Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. J Clin Microbiol 1995;33:419–22).

It was further recommended that an IgG immunoblot be considered positive if five of the following 10 bands are present: 18 kDa, 21 kDa (OspC), 28 kDa, 30 kDa,
Unfortunately the inconsistencies of the test results between different laboratories and even in the same laboratory are so frequent – that it is difficult to trust their reports.

For example, a Western blot test can be run 3 times on the same specimen: the first, when ordered as such (Western blot); the second, if an ELISA with reflex Western blot is also ordered (meaning that the Western blot test will be automatically performed if the ELISA is positive); and for the third time, if a C6 peptide with reflex Western blot is ordered. It is not unusual to receive both a positive and a negative IgM and/or IgG Western blot reports, in the same patient, from the same sample. A difference in one band turns the test from negative to positive and vice versa.

The Western blot is usually interpreted visually, which results in a significant interobserver variability. One laboratory attempted to solve this problem by implementing a mechanized reading of the blot. This resulted in changing the test from a qualitative to a quantitative one, with significant underinterpretation.

It is clear that more accurate tests are needed and more so, a test that will tell us if the infection is active. Such a test, if accurate will cut down the number of cases treated with unnecessary prolonged antibiotic courses and prevent many patients from acquiring a chronic illness. When this test develops, it should be used widely in areas where Lyme is endemic, when patients present with an atypical illness.

What are the possible explanations of developing “chronic” Lyme disease?

1. **Persistent Lyme infection.** In spite of the IDSA’s treatment recommendations stating that two weeks (range 10 – 21 days) of oral antibiotics (doxycycline, amoxicillin, or cefuroxime), are sufficient to treat Lyme disease diagnosed by ECM (Bull’s eye) rash, there is culture supported data, suggesting otherwise (Wormser. et al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America Clin Inf Dis 2006;43:1089-134; Hunfeld et al. Risk of culture-confirmed borrelial persistence in patients treated for erythema migrans and possible mechanisms of resistance. Int J Med Microb 2006; S1,233-241).

There should be more flexibility in the number of days of antibiotic treatment. *Initial treatment should be extended if the diagnosis is firm and the patient’s condition did not improve.* This is supported by recent studies conducted in mice and monkeys that show that even after prolonged antibiotic courses, the treated animals can contain infective spirochetes (Hodzic et al. Persistence of B. burgdorferi following antibiotic treatment in mice. Antimac Ag & Chemoth. 2008; 52:1728-36. Embers ME, Barthold SW, Borda JT, et al. Persistence of Borrelia burgdorferi in Rhesus Macaques following antibiotic treatment of disseminated infection. PLos One. 2012; 7:e29914)

2. **Persistent presence** of non infective Lyme spirochetes after adequate antibiotic treatment leading to an ongoing disease. The immune system can attack a dead micro-organism or its fragments and in the process of the
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attack damage healthy surrounding tissues. Recently (July 2012), the Yale group led by Linda Bockenstedt, showed the presence of fragments of the spirochete long after the infection. It means that one doesn’t need the entire spirochete to cause an on-going damage. Persisting spirochetal antigens can do it (Bockenstedt et al. Spirochete antigens persist near cartilage after murine Lyme borreliosis therapy. J Clin Invest. 2012;122:2652-2660). If a dead spirochete or its fragments contains a protein which has some resemblance to one of our own body proteins – then it can start or perpetuate an autoimmune process (see below).

In this context, it was shown that inflammation can be triggered by some of the spirochetes lipoproteins (OspA, OspB). Inflammation is caused by irritating our immune cells that in turn secrete cytokines that damage our own tissues. So damage to the tissues can result from inactive spirochetes, just by the irritating nature of the proteins they carry (Fallon et al. Inflammation and central nervous system Lyme disease. Neurobiology of Disease 2010;37:534-41).

Persistent presence of the spirochete without causing any illness should be also considered. A recent discovery of Borrelia burgdorferi by PCR in the brain of the “Iceman” who lived in the Neolithic period in the Italian Alps 5,300 years ago raises the question of coexistence. The “Iceman” died from an arrow wound and was healthy otherwise. He was frozen for all those years until recently thawed for his autopsy (was found frozen in a glacier in 1991 - Hall SH. Iceman Unfrozen. National Geographic. 2011; 220:118-133). It is possible that like some other pathogens, B. burgdorferi sits in our body inactive and then one day, due to one stimulus or the other becomes active again.

If the spirochete has been residing in our bodies since the Neolithic age, why is it reaching only now epidemic proportions? The answer is complex. Ecologic changes (reforestation, population shift to the suburbs, a change in the viral population that makes bacteria pathogenic, etc.). Decreased immunity due to a more “sterile” upbringing and increase in autoimmune diseases, in general ( Jackson Nakazawa D. The Autoimmune Epidemic. Touchstone, NY 2008).

3. **Persistent/ untreated infection of other tick borne agents**, transmitted by the same ticks (“co-infections”).

4. **Re infection.** Living in a Lyme endemic area, where about 50% of the tick bites go undetected, unnoticed re-infection can result in a “chronic” picture. This includes the “co-infections”.

**If after the infections are identified and treated adequately the patient continues to be symptomatic, there are two main processes that can explain the patient’s condition:**

1. Residual damage from either of the above (e.g. brain damage resulting in white matter lesions leading to permanent neurologic deficits).

2. The post Lyme autoimmune syndrome is probably the most common cause for the chronic illness, the rheumatologic aspects of which were described in the literature over 20 years ago (Steere et al. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. NEJM. 1990 ; 323:219 – 223.
It was also shown by Aledini and Latov that “Antibodies against OSPA epitops of Borrelia burgdorferi cross react with neuronal tissue” (Journal of Neuroimmunology. 2005; 159:192-195) explaining why the post Lyme autoimmune syndrome is not only a rheumatological condition, but also a neurological.

Under the autoimmune category, the post Lyme vaccination syndrome should be included (Latov et al. - Neuropathy and cognitive impairment following vaccination with the OSPA protein of Borrelia burgdorferi. J Periph Ner Sys 2004;9:165-167).

A different group of researchers showed that Osp-A shares similar amino acid sequence with the streptococcal protein M, that is similar to a human muscle protein, myosin, that triggers human autoimmune conditions such as carditis (disease of the heart), arthritis and possibly other post streptococcal conditions (Raveche et al. Evidence of Borrelia autoimmunity-induced component of Lyme carditis and arthritis. J Clin Microb. 2005;43:850-856).

The recent collaboration between Latov, Aledini, Wormser and Klempner (who was the PI of the extramural NIH “chronic” Lyme study in the late 90’s - Klempner et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. NEJM 2001;345:85-92), showed that the sera of patients with “chronic” Lyme disease contain anti-neuronal antibodies (Chandra et al. Anti-neuronal antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. Brain Behav Imm. 2010;24:1018-1024).

Recent studies of proteomic patterns (a test for the patterns of protein components) generated by the cerebrospinal fluids of patients with “chronic” Lyme further supports that this disease entity is unique and cannot be “lumped” with other syndromes (Schutzer, S. E etal. Distinct cerebrospinal fluid proteomes differentiate post-treatment Lyme disease from chronic fatigue syndrome. Plos One 2011;6:e17287).

In the past three years, we have found that many patients with “chronic” Lyme disease exhibit anti-neuronal antibodies and increased Cam II kinase activity (antibody mediated neuronal damage via calcium channel activation), as found in Dr. Cunningham’s laboratory at the University of Oklahoma (Kirvan et al. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nature Med. 2003;9:914-920), supporting, again, the autoimmune nature of “chronic” Lyme.  
We found that both the peripheral and central nervous system are targeted in post Lyme and post Lyme vaccine illnesses. Unlike the known autoimmune nature of demyelinating neuropathy of large fibers, many of those patients experience immune neuropathies of sensory and autonomic ganglia.
Treatment

When facing “chronic” Lyme, with an autoimmune flavor, one should consider treatment with a combination of hydroxy chloroquine and a macrolide.

**Hydroxychloroquine + Macrolides**

The rationale of the treatment is:

2. Hydroxychloroquine has also immune modulating properties and is classified as a weak DMARD (disease modifying anti rheumatic drug). It interferes with the functioning of T- and B- Lymphocytes, monocytes and macrophages by entering their lysosomes and increasing the lysosomal pH, which inhibits the ability of these cells to produce and release inflammatory cytokines and hydrolytic enzymes. Clarithromycin possesses anti-inflammatory properties and potentiates the effects of hydroxychloroquine. I have seen many patients with intractable arthritis improve when macrolides are added (“Anti-inflammatory activity of macrolide antibiotics”. The Journal of Pharmacology and Experimental Therapeutics. January 2000, 156-163; Ianaro et. al). Immune modulation and anti inflammatory properties are especially advantageous in the setting of post Lyme autoimmune syndrome.

**Benzanthine Penicillin**

When hydroxychloroquine /macrolide combination is not effective, cannot be tolerated (allergic reactions, GI side effects, tinnitus, contact dermatitis, psoriasis flair up, ophthalmologic contraindications, etc.), or when hydroxychloroquine has reached its maximal safe cumulative dosage (1,000G) - intramuscular benzanthine G penicillin (Bicillin LA) is an option (Marco AC and Accrdo S. Long term treatment of chronic Lyme disease with benzanthine penicillin. *Ann Rheumat Dis* 1992;51:1007-1008). The mechanism of action of benzanthine penicillin (other than the obvious antimicrobial) is unknown. Why 3% of the daily intravenous dose of penicillin can achieve much better results when injected intramuscularly once a week? One explanation is that the bacteriocidal signal it sends is not strong enough to activate defense mechanisms of the spirochete, but enough to suppress the expression of the outer surface proteins (mainly OspA and OspB) which are known to trigger inflammation (Rupprecht et al. The pathogenesis of Lyme neuroborreliosis: from infection to inflammation. *Molecular Medicine*. 2008;14:205-12).
Another explanation is that Bicillin is an effective anti streptococcal treatment and that the autoimmune morbidity is perpetuated by streptococcal presence. I have had a significant number of patients with Chronic Lyme disease who did not get better on long courses of oral and/or intravenous antibiotics, but responded to weekly Bicillin shots within a month or two. This treatment is so benign, that I offer it now prior to hydroxychloroquine and clarithromycin, in spite of its poorly explained mechanism of action.

**Intravenous Immunoglobulins (IVIG)**

**Are not indicated for the treatment of Lyme disease per se.** They are indicated when there is immune deficiency or neurologic conditions of autoimmune nature complicating Lyme disease.

Autoimmune diseases affect about 5% of individuals in developed countries. Autoimmunity is the patho-physiologic mechanism in neurologic conditions affecting the myelin of the peripheral and central nervous system, the basal ganglia, the post synaptic membrane, the hippocampal pyramidal cells and Purkinje cells, among other targets, in a variety of autoimmune conditions of the nervous system. Autoimmunity is believed to be a result of complex interactions between genetic traits and environmental factors. Infections and vaccinations are some of the more known environmental factors. Among other known mechanisms are myeloproliferative conditions and other neplasms (through a paraneoplastic mechanism).

The outer surface protein A of *Borrelia burgdorferi* (OspA) is a lipoprotein with a molecular weight of 31kd that possesses immuno-stimulatory properties that can activate pro-inflammatory toll-like receptors of the immune system. Receptors of this kind are also expressed in a variety of neuronal elements including Schwan cells, microglia, astocytes and oligodendroglia, which probably contribute to the development of inflammatory responses affecting the entire nervous system. The OspA has a partial amino acid sequence (165-173) homologous to that of hLFA-1 (human lymphocytic function associated antigen-1) that results in activation of T cells to this auto antigen ending in an autoimmune disease (autoimmune disease caused by “molecular mimicry” mechanism).

As discussed earlier, it was shown that certain sequence of amino acids on the OspA can trigger the formation of anti-neuronal autoantibodies (Aledini and Latov. Antibodies against OSPA epitops of *Borrelia burgdorferi* cross react with neuronal tissue. *Journal of Neuroimmunology.* 2005; 159:192-195). Osp-A shares similar amino acid sequence to the streptococcal protein M, that is similar to myosin and triggers immune carditis, arthritis and even Sydenham’s chorea (Raveche et al. Evidence of Borrelia autoimmunity-induced component of Lyme carditis and arthritis. *J Clin Microb.* 2005;43:850-856).

Both Lyme disease and the Lyme vaccine (LYMЕrix - Latov et al. - Neuropathy and cognitive impairment following vaccination with the OSPA protein of *Borrelia burgdorferi*. *J Peripheм Ner Sys* 2004;9:165-167)) can trigger neurologic autoimmune disease. Since the Lyme vaccine is a pure preparation of OspA (coated onto aluminum hydroxide), it is reasonable to assume that this protein is also responsible for the autoimmune disease triggered by Lyme infection. This autoimmune disease is especially common in individuals with class II, MHC HLA DR4 (DRB1*0401), whose macrophages identify the amino acid sequence shared by the OspA and our body proteins as “non-self” attach to it and present it to the T & B lymphocytes.
Persisting presence of IgM antibodies reacting to the OspA, which is not reported by common laboratories (Western Blot band 31), might be an indicator of an autoimmune condition triggered by this protein. The fact that patients with this condition have a disease of both peripheral and central myelin, also supports the etiology (post Lyme/LYMErix autoimmune), since it is uncommon for patients with “pure” MS, who have a disease of the central myelin, to have peripheral neuropathy. And vice versa, it is uncommon to have MS when having demyelinating neuropathy.

The most common Lyme associated autoimmune conditions affecting the central and peripheral nervous system myelin result in "white matter lesions" on brain MRI's which are associated with a wide range of neuropsychiatric manifestations; damage to the basal ganglia/ sub thalamic nucleus resulting in bizarre and disabling movement disorders and; peripheral nerve conditions such as Guillain Bare, CIDP and even multifocal motor neuropathy with block, but more frequently ganglioneuropathy of the sensory and autonomic nerves.

Intravenous immunoglobulins (IVIG) are widely used for treatment of a variety of diseases, but mainly in autoimmune neurologic conditions (Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. JAMA. 291:2367-75, 2004).

Their exact mechanism of their action is unknown, but there are several possibilities:

a. They probably bind to the idiotypes via their anti idiotypic variable portion, blocking the interactions between the idiotypes and idiotypic antigens that usually lead to autoimmune disease.

b. IVIG bind to the Fc receptors of the macrophages preventing phagocytosis and to the Fc receptors of the autoantibodies in the antigen-antibody complex, preventing activation of the complement.

c. They bind to the C3 complement fraction and impeding the complement cascade.

The major advantage of IVIG therapy is achieving significant immuno modulation with arrest of the autoimmune process, which is comparable to high dose steroids or cytotoxic agents, without immunosuppression and its associated risks.

In multiple sclerosis, the effects of beta-interferons on susceptibility to infections are not clear. By modifying the host inflammatory response they can impair the body’s ability to fight infection. The recent natalizumab (Tysarbi) experience (Warnke et al. Natalizumab and Progressive Multifocal Leukoencephalopathy. Arch Neurol.2010; 67:923-930) showed that the only two patients receiving natalizumab that developed PML (progressive multifocal leukoencephalopathy), where those also receiving Avonex (beta-interferon 1-alpha). This means that the beta interferons are not so safe when patients have an ongoing infection.

Our view is that in conditions where autoimmune processes are linked to infections and it is not clear whether the infection is active or not, IVIG treatment should be tried first. High dose steroids and/or immunosuppressive agents should be considered as a treatment option only when IVIG fail, or contraindicated.
Selected Publications on the topic:

Grzegorz S. Nowakowski, MD; and Amiram Katz, M Epilepsia partialis continua as an atypical presentation of cat scratch disease in a young adult. *NEUROLOGY* 2002;59:1815-1816


Katz, A and Berkley JM. Diminished Epidermal Nerve Fiber Density in Patients with Antibodies to Outer Surface Protein A (OspA) of B. burgdorferi Improves with Intravenous Immunoglobulin Therapy. *Neurology* 2009;72(S3):A55.