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Review

Inflammation and central nervous system Lyme disease

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ABSTRACT

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.

Contents

Lyme disease, the most common vector-borne disease in the United States, is prevalent in countries throughout the northern hemisphere. The infectious agent of Lyme disease, *Borrelia burgdorferi* (*B.b.*), is transmitted to the host during the blood meal of an attached, infected Ixodes tick. The initial inflammatory response to the *B.b.* infection results in a localized skin rash (erythema migrans) and may be followed by systemic inflammation, such as in the joints, heart, muscle, and central and peripheral nervous systems. The purpose of this article is to review what is known about inflammation in neurologic Lyme disease, with an emphasis on the central nervous system.

The agent of Lyme disease, the spirochete *B. burgdorferi*, was first identified in 1982 (Burgdorfer et al., 1982). Two years later it was isolated from the CSF of a patient with meningoradiculitis (Pfister et al., 1984). Invasion of the central nervous system occurs early, as demonstrated by *B.b.*'s isolation from the CSF 18 days after tick bite (Allal et al., 1986). Early invasion into the CNS has also been demonstrated by PCR within the first 2 weeks of developing multiple erythema migrans rashes, but only half of the patients had CNS symptoms at that time (Luft et al., 1992). A later much larger study of 200 adults with multiple erythema migrans confirmed early CNS involvement, with abnormal CSF results in 31% of the patients (Maraspin et al., 2002). The primary *B.b.* genospecies that cause Lyme disease include *B.b. sensu stricto, Borrelia afzelii, and Borrelia garinii* (Wilske et al., 2007). Only *B.b. sensu stricto* has been reported in the United States. The specific clinical manifestations in Europe differ partly by genospecies with *B. garinii* being the agent most commonly isolated from patients with Lyme neuroborreliosis whereas *B. afzelii* is the primary isolate from skin lesions. A retrospective analysis of culture confirmed cases of neuroborreliosis demonstrated different

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clinical features by genospecies (Strle et al., 2006). The clinical diagnosis of neuroborreliosis was readily made in 19/23 *B. garinii* cases but missed in 9/10 *B. afzelii* cases because the symptomatic presentation was less specific. Neuroborreliosis in the *B. afzelii* cases less often demonstrated radicular pains and meningeal signs, more often reported dizziness, and rarely was associated with a CSF lymphocytic pleocytosis. Robust inflammatory responses are more typical of neuroborreliosis in Europe than in the United States, most likely due to the differences in antigenic expression of *B. garinii* vs. *B. burgdorferi*, sensu stricto.

Neurologic Lyme disease (also known as Lyme neuroborreliosis) may manifest clinically when *B.b.* infects the central and/or peripheral nervous system. Neurologic involvement occurs 1–4 weeks after the initial infection (Pachner et al., 2001b), often causing inflammation, primarily in the subarachnoid space and perineural tissue. Clinically, the former may manifest as meningitis that is typically characterized by lymphocytic pleocytosis in the CSF (Ackermann et al., 1984; Pachner and Steere, 1985). Other widely accepted manifestations of neuroborreliosis include meningoradiculitis (a.k.a. Bannwarth's syndrome), cranial neuritis, encephalopathy, peripheral neuropathy, and less commonly, encephalitis and encephalomyelitis. Neuropsychiatric disorders have also been reported secondary to Lyme disease in Europe and in the United States, ranging from depressive states to mania, psychosis, and dementia (Fallon and Nields, 1994).

Insight into the pathogenesis of neurologic Lyme disease has emerged from clinical reports from human cases, *in vitro* experiments using neural cells, and *in vitro* and *in vivo* studies of the impact of *B.b.* infection on the rhesus macaque.. The rhesus macaque has provided the best animal model for studies of neuropathogenesis, as it is the one species that has been found to show consistent central nervous system (CNS) manifestation of Lyme disease (Pachner et al., 2001b).

This paper will review evidence for neuroinflammation in Lyme disease in both the human and animal model.

Clinical reports in humans

Approximately 10–15% of patients with untreated Lyme disease develop neurologic manifestations, typically due to inflammation in either the peripheral nerves, the meningeal lining or parenchyma of the brain itself. Pathology reports from human cases have reported lymphocyte and plasma cell infiltration in the meninges and perivascularly in the nerve roots, dorsal root ganglia, and gray matter of the brain and spinal cord (Duray and Steere, 1988; Meier and Grehl, 1988; Meurers et al., 1990). Neurologic symptoms may occur early in the disease, while the EM rash is still present (Luft et al., 1992), or many months after the initial infection.

In addition to the classic neurologic triad of meningitis, cranial neuritis, and radiculitis, Lyme disease can cause encephalopathy and much less commonly encephalomyelitis (Reik et al., 1979; Ackermann et al., 1985; Halperin, 1991), pseudotumor cerebri in children (Kan et al., 1998), and cerebellitis (Neophytides et al., 1997). Encephalomyelitis (Hansen and Lebech, 1992; Liegner et al., 1998) is reported more often in Europe than in the United States.

Encephalopathy refers to the mild to moderate cognitive deficits that patients with neurologic Lyme disease may experience. Typically, patients experience problems with verbal fluency, short-term memory, and slower processing speed, often referring to their experience as one of brain fog (Kaplan and Jones-Woodward, 1997; Keilp et al., 2006); these cognitive deficits may be accompanied by peripheral sensory findings on neurologic examination in up to 70% of patients and systemic symptoms such as fatigue, sleep disturbance, emotional lability, and depressed mood (Fallon et al., 2008).

Myelitis, a less common manifestation of neuroborreliosis, refers to the inflammation of the parenchyma of the spinal cord that usually results in weakness, dysautonomia, and sensory loss(Hansen and Lebech, 1992). Rarely, the parenchyma of the brain may be affected by vasculitic changes, resulting in seizures or stroke, or white matter inflammation, resulting in subacute MS-like manifestations. When the brain is involved, patients may experience a wide array of neurologic and neuropsychiatric symptoms.

In peripheral nervous system Lyme disease, patchy multifocal axon loss has been associated with epineural perivascular inflammatory infiltrates (Camponovo and Meier, 1986; Kindstrand et al., 2000). Perivascular and vascular inflammatory processes may also be involved in CNS Lyme disease, with several case reports of stroke attributed to neurologic Lyme disease (Oksi et al., 1996; Keil et al., 1997; Topakian et al., 2007). CNS involvement from vascular or perivascular inflammation is understandable given that adherence of the spirochete to the endothelium lining of blood vessel walls leads to the release of inflammatory mediators which in turn recruit leukocytes to the perivascular tissue; damage to the blood–brain barrier may then ensue with penetration of *B.b.* into the CNS (Garcia-Monco et al., 1990; Sellati et al., 1995). The perivascular mononuclear cell infiltrates observed in cerebral cortex infected with *B.b.* consist predominantly of T-helper cells (Meurers et al., 1990) . The infiltrates are associated with mild, spongiform changes, a focal increase in microglial cells, as well as an infiltration of lymphocytes and plasma cells in the leptomeninges (Duray, 1989). *B.b.* spirochetes are usually present in very low numbers in the CNS, and thus infection by itself does not likely cause much direct dysfunction or damage. However, *B.b.* may cause disease indirectly via the induction of inflammatory mediators, such as cytokines and chemokines.

One of the earliest case reports of CNS vasculitis was in a child with positive Lyme serology and several months of severe arthritis who died during a protracted seizure (Millner et al., 1991). Post-mortem histological studies of brain tissue showed general vasculitis, and spirochetes that were thought to be *B.b.* were demonstrated by silver staining. Several case reports since then have further demonstrated an association between infection with *B. b.* and CNS vasculitis. In a brain biopsy study of the inflammatory brain lesions of 3 patients with neurologic Lyme disease and brain MRI abnormalities, Oksi reported that all 3 patients had histopathologic evidence of perivascular or vasculitic lymphocytic inflammation (Oksi et al., 1996). Two of the 3 patients demonstrated *B.b.* DNA by PCR analysis of the inflammatory brain tissue; these patients had no prior antibiotic treatment at the time of the first PCR assay, and thus the positive findings likely indicated active infection. The inflammatory brain lesions constricted or disappeared after antimicrobial therapy, further supporting a *B.b.*-induced disease process. Similar vasculitis findings have also been seen in autopsy studies (Bertrand et al., 1999).

Stroke as a manifestation of Lyme disease is rare, especially in the United States. Most reports have described patients with ischemic stroke and underlying cerebral vasculitis, but there are also reports of subarachnoid hemorrhage and intracerebral hemorrhage (May and Jabbari, 1990; Topakian et al., 2007, 2008). Early case reports of stroke in neuroborreliosis mostly involved the vertebrobasilar system, often resulting in thalamic infarcts (Uldry et al., 1987; Veenendaal-Hilbers et al., 1988; May and Jabbari, 1990). One report (Keil et al., 1997) describes a 20-year-old man who was diagnosed as having *B.b.* induced vasculitis with secondary thalamic infarction based on CSF evidence of intrathecal antibody synthesis, MRI evidence of a right thalamic infarct, and angiographic evidence of stenosis of the right thalamic vessels. However, more recent reports have also found a predilection for involvement of the anterior circulation and circle of Willis (Wilke et al., 2000; Heinrich et al., 2003; Schmiedel et al., 2004; Topakian et al., 2008). The course of illness in many of these cases has been insidious, demonstrating vascular deficits months after initial infectious symptoms. The European cases demonstrated lymphocytic pleocytosis in the CSF with elevated protein content. Treatment with appropriate antibiotics invariably halted the disease progression with no recurrence of cerebral infarcts and most often led to a recuperation from deficits. In some cases, perivascular white matter changes

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visualized on MRI have resolved shortly after treatment (May and Jabbari, 1990).

When Lyme disease affects the brain and spinal cord, it can look like multiple sclerosis (MS) (Ackermann et al., 1985). In 1988, Pachner described two patients with Lyme disease whose MS-like neurologic symptoms responded well to antibiotic therapy for Lyme disease (Pachner, 1988). The brain MRI among patients with Lyme disease may at times be suggestive of a demyelinating disease. A recent review (Hildenbrand et al., 2009) described two patients with Lyme disease who had neuroimaging findings partially suggestive of MS. The first patient, whose illness started with an EM rash and developed into meningitis, had a MRI which revealed callososeptal interface involvement remarkably similar to that in MS. Arcuate and confluent subcortical white matter involvement was also present, but without periventricular white matter disease. The patient's symptoms improved after IV ceftriaxone. The second patient was an elderly man with 2 years of cognitive decline, positive serologic and CSF titers with evidence of intrathecally produced *B.b.*-specific antibodies, and MRI-findings suggestive of a demyelinating disease—a dot–dash appearance of the callososeptal interface as well as a periventricular distribution of involvement; this patient improved with iv ceftriaxone therapy. Resolving MS signs and symptoms however in the context of Lyme disease may simply reflect the waxing and waning course of relapsing remitting MS and be unrelated to Lyme disease or it may reflect the improvement that would be expected after antibiotic therapy for Lyme disease. That *B.b.* may exacerbate MS or be a trigger for a MS-like inflammatory demyelinating disease of the CNS is not a surprising hypothesis, as infections with foreign agents are thought to either activate myelin-specific T cells by molecular mimicry, via cross-recognition of a bacterial and a myelin peptide, or by bystander activation, via inflammatory cytokines (Martinet al., 2001). As a result of *B.b.* infection, autoreactive antibodies may develop to myelin and myelin components (Suchanek et al., 1986; Garcia-Monco et al., 1988; Martin et al., 1988). Sequence homology has been noted between myelin basic protein and *B.b.* spirochetal flagellin (Weigelt et al., 1992) and there are studies demonstrating cross-reactive polyclonal and monoclonal antibodies which recognize flagellar antigenic determinants as well as epitopes on neural cells (Sigal and Tatum, 1988; Aberer et al., 1989; Fikrig et al., 1993). Such cross-reactivity could contribute to a chronic, relapsing-remitting, *B. burgdorferi*-triggered, immune-mediated neurological disorder similar to MS.

Case series from neurologic centers have revealed conflicting results. In one non-controlled investigation, 19 of 283 consecutive patients from a MS center in a Lyme endemic area had borderline or positive Lyme ELISAs although none initially gave a history suggestive of clinical Lyme disease (Coyle et al., 1993b). Of the 10 ELISA seropositive patients who underwent lumbar puncture, 5 had detectable CSF anti-*B.b.* antibodies; none showed intrathecal production of these antibodies. Four of these 5 patients with positive CSF serology received a course of antibiotics (3 with IV ceftriaxone, 1 with oral doxycycline), but this did not prevent subsequent neurological relapses, which were characteristic of MS. The authors concluded that the finding of reactive Lyme serology in an MS patient with no suggestive features of the infection was unlikely to indicate neurological Lyme disease. A more recent controlled study of seroreactivity however once again suggests a possible relationship between *B.b.* and MS. This clinical study (Chmielewska-Badora et al., 2000) reported ELISA testing for the presence of anti-*B.b.* antibodies in a total of 769 patients hospitalized for various neurological diseases. Twice as many patients with MS tested positive on the *B.b.* ELISA compared to the non-MS neurologic patients ($p = 0.04$), suggesting that MS may be associated with *B.b.* infection. This latter study unfortunately did not report follow-up Western blot testing or results from spinal fluid studies. A much smaller controlled study (Brorson et al., 2001) examined CSF from 10 patients with the diagnosis of relapsing-remitting MS and from 4 controls without MS or a history of Lyme disease. Examined blind to diagnosis using transmission electron microscopy, cystic structures were observed in the CSF of 10/10 MS patients but not in the CSF of any of the 4 controls. In each of the 10 MS patients these structures were positively immunolabeled with a non-specific polyclonal anti-spirochetal antiserum, however none of the CSF samples demonstrated *B.b.* DNA by PCR using the OspA primer. This study, therefore, while supportive of spirochetal-related cystic structures in the CSF, did not support a specific connection between these cystic structures and *B.b.* infection.

Experimental evidence for the role of inflammation in CNS Lyme disease

B.b. spirochetes express lipoproteins on the outer membrane of the borrelial cell wall that are known to be pro-inflammatory. More than 8% of the coding sequence of strain B31 is devoted to presumed lipoprotein sequences (Fraser et al., 1997; Casjens et al., 2000) . 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). Little is known about the surface protein expression of spirochetes that persist in the human host, but the non-human primate model suggests a downregulation of OspA, OspB, and OspC with a persistence only of antibody to flagellin (Cadavid et al., 2000). Once in the tissue, the spirochetal presence may invoke a severe inflammatory response or no obvious inflammation at all, clearly indicating that the inflammatory response is multi-determined. Of particular interest from the rhesus macaque studies was the observation that while there is a robust inflammatory response to the spirochete in other organs, inflammation in the parenchyma of the CNS is often mild or absent (Pachner et al., 2001b).

In order to get to the CNS, the spirochete must first spread through the skin and enter the blood stream and evade immune-mediated killing. Transmission is assisted through several immune evasion strategies of the *B.b.* spirochete. Through the process of phase variation, lipoproteins are up- or down-regulated with a consequent impact on the host inflammatory response, partly influenced by environmental pressures such as temperature and pH variations. For example, the lipoprotein OspA, a potent stimulator of neutrophils (Morrison et al., 1997) and proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α (Haupl et al., 1997), is downregulated in the tick shortly after a blood meal enabling the spirochete's migration to the salivary gland (Schwan and Piesman, 2000; Strother et al., 2007) and then may be upregulated in expression in the CSF of the human host (Coyle et al., 1993a; Schutzer et al., 1997). OspC is a strong immunogen whose expression is downregulated shortly after initial infection—an act which helps in evasion as Osp C is an effective target for protective immunity (Xu et al., 2008). Antigenic variation of the outer membrane protein VlsE is another immune evasion mechanism that is thought to enable *B.b.* to persist (Norris, 2006). Immune evasion may also be facilitated by the surface binding of immunoinhibitory proteins that diminish complement-mediated killing, as for example with the binding of host complement regulatory factor H or factor H-like proteins which is mediated through the expression of complement regulator-acquiring surface proteins (CRASPS) (Kraiczy et al., 2002) and OspE-related proteins (Alitalo et al., 2005).

Factors external to *B.b.* also impact upon spirochetal survival. In the non-human primate model, for example, dexamethasone treatment results in a decrease in anti-*B.b.* antibodies and enables a 3–4 higher spirochetal load in tissue (Pachner et al., 2001a). In other animal models and in humans with Lyme disease, a blunted immune response may also occur due to concomitant steroid treatment or to coinfection with another tick-borne pathogen, such as *Babesia microti*, which some reports suggest leads to a more protracted course of Lyme disease with increased severity of disease and persistent symptoms

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(Dattwyler et al., 1988; Krause et al., 1996; Cadavid et al., 2000; Straubinger et al., 2000).

In the United States, *B.b.* is presumed to spread systemically primarily through the blood stream, as borrelia have been cultured in 35–45% of plasma samples from patients with early Lyme disease (Wormser et al., 2001; Coulter et al., 2005). Entrance into the CSF of humans has been demonstrated by both PCR and culture (Cerar et al., 2008). Passage across the vascular endothelium is the most likely mechanism for *B.b.*'s entry into the CNS, at least in the U.S. species of *B.b.* While *B.b.* freely crosses non-brain vascular endothelium to enter non-CNS tissues (Comstock and Thomas 1989), the mechanism by which it passes across the more protective endothelial cells of the blood–brain barrier remains unresolved (Grab et al., 2005). It has been postulated that the spirochete in European species most responsible for neuroborreliosis (*B. garinii*) may pass along the peripheral nerves to the nerve roots, thus accounting for the greater frequency of meningopolyradiculitis in Europe than in the U.S. (Rupprecht et al., 2008b).

The mechanisms by which *B.b.* infection leads to glial and neural cell impairment may be due to: (a) the direct action of spirochetes or spirochetal products on neural cells; (b) the induction by spirochetes of local, neurally produced cytotoxic or inflammatory mediators; or (c) the induction of an amplified inflammatory response, mediated by cross-reactive antibodies or cellular immune mediators.

While much has been learned about the pathogenesis of Lyme arthritis from the mouse model of Lyme disease, the rhesus macaque is the preferred animal model for neurologic Lyme disease, as it exhibits signs of Lyme disease in many of the same organ systems as the human, such as the skin and the peripheral and CNS, with production of EM rashes, antibodies to *B.b.* antigens, CSF pleocytosis and meningeal inflammation (Pachner et al., 1995).

B.b. can invade the brain parenchyma, as evidenced in mice, rabbits and adult rhesus macaques following inoculation of the spirochete (Pachner et al., 1994, 1995). Adherence of *B.b.* to brain capillaries would lead to focal inflammation at the interface of the basement membrane of the capillary endothelium and the adjacent astroglial membrane, resulting in capillary permeability changes. The spirochete may then cause direct damage to oligodendroglial cells, possibly resulting in demyelination (Baig et al., 1991). Abundant evidence exists confirming that *B.b.* spirochetes adhere to murine neural and glial cell lines, primary neural cells, and primary rat brain cultures. Indeed, a recent *in vitro* study (Livengood and Gilmore, 2006) confirmed that *B.b.* not only adheres to but also invades human neuroglial and cortical cells; these internalized spirochetes were viable although there were no direct cytopathic effects. If the invasion of neural cells by *B.b.* also occurs *in vivo* in the human host, this would be an important mechanism by which *B.b.* avoids the host's immune response while potentially also causing functional damage to neural cells during infection of the CNS. While *B.b.* itself does not produce any known endotoxin (Norgard et al., 1996), damage to neural cells may occur secondary to *B.b.* adherence, possibly due to surface lipoproteins such as OspA which can activate neural cells to release proinflammatory cytokines and chemokines and induce apoptosis and astrogliosis (Ramesh et al., 2003).

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). The chemokines attract B cells, which are elevated in patients with CNS Lyme disease compared to other CNS infections (Cepok et al., 2003, 2005). Most interestingly, several studies (Rupprecht et al., 2005; Ljostad and Mygland, 2008) now have documented elevated levels of CXCL13 in the CSF of patients with active neurologic Lyme disease, a chemokine that is produced by monocytes and dendritic cells in response to Borrelial infection, with one study documenting a concentration in the CSF that was 114 times higher than in the serum (Rupprecht et al., 2008b). The CXCL13 expression in the CSF precedes the intrathecal production of *B.b.* specific antibodies (Rupprecht et al., 2006) and may account for the high ratio of B lymphocytes and plasma cells in the CSF. This data provides further support for the humoral immune response in Lyme neuroborreliosis (Cadavid 2006) and for the role of the CNS as an ectopic germinal center (Narayan et al., 2005). Increased production of the neuromodulator quinolinic acid has been demonstrated in the CSF of patients with neurologic Lyme disease (Halperin and Heyes, 1992). The level of quinolinic acid, an excitotoxin and N-methyl-D-aspartate (NMDA) agonist, correlated strongly with CSF leukocytosis and was noted to be greater in patients with CNS inflammation and less in Lyme 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.

Using the monkey model, investigators have been able to examine the effect of *B.b.* infection on neural tissue and its relationship to both the adaptive and acquired immune response. The production of cytokines or other inflammatory mediators as a result of *B.b.* stimulation of neural cells may cause secondary damage. On stimulation with recombinant OspA, rhesus monkey primary cultures make IL-6 and TNF and show astrocyte proliferation and apoptosis (Ramesh et al., 2003). In the presence of *B.b.*, primary cultures of astrocytes or microglia produce IL-6, TNF-α, IL-8, and the macrophage inflammatory proteins CCL3 and CCL4 (Bernardino et al., 2008). Further work (Ramesh and Philipp, 2005) has demonstrated that specific inhibition of the mitogen-activated protein kinase p38 and Erk1/2 MAPK (lipoprotein active enzymes) led to an inhibition of TNF-α production by astrocytes in response to *B.b.* lipoprotein stimulation, and totally abrogated production of this cytokine when both MAPK pathways were inhibited simultaneously; this finding suggests a potential strategy to control inflammation and apoptosis in Lyme neuroborreliosis. On *ex vivo* stimulation of monkey brain frontal lobe glial cells with the spirochete *B.b.*, the inflammatory immune mediators IL-6, IL8, IL1-β, COX-2, and CXCL13, were visualized in glial cells *in situ* with concomitant oligodendrocyte and neuronal apoptosis (Ramesh et al., 2008); in addition, using microarray analyses, altered transcripts were found of multiple genes that regulate the immune response, including corticotrophin releasing hormone, G-protein coupled 6 which is involved in microglial activation, the CC chemokine FAM19A1, a natural killer cell receptor, and STAT 3 which regulates the activation and function of Il-6, Il-8, and COX-2. Although TNF was not visualized in brain sections, TNF-α transcript in spirochete stimulated tissues was noted to be significantly increased by microarray analysis (21.7 fold) as well as by real-time PCR (7.43 fold) (Ramesh et al., 2008). Many of these immune mediators are involved in the inflammatory response in humans with neurologic Lyme disease as well as in other neurodegenerative diseases, such as multiple sclerosis, and in collagen vascular diseases, such as systemic lupus erythematosus and scleroderma.

To explore in the monkey model whether a similar inflammatory response occurs *in vivo* as was demonstrated *ex vivo* with a potentiation of glial and neuronal apoptosis, a recent experiment (Ramesh et al., 2009) inoculated *B.b.* into the cisterna magna of rhesus macaques. Within 1 week post-inoculation there was an increased expression in the CSF of IL-6, IL-8, CCL2, and CXCL13 and a monocytic and lymphocytic pleocytosis; not until 3 weeks post-inoculation was there the development of an acquired immune response with anti-*B.b.* C6 serum antibodies. This inflammatory response to *B.b.* infection resulted in histopathological changes consistent with acute neurologic Lyme disease, such as leptomeningitis and radiculitis, as well as Schwann/satellite cell and neuronal apoptosis in the dorsal root ganglia. Inflammatory infiltrates were seen in the dura mater and

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frontal cortex in 3 of 5 infected monkeys, close to parenchymal areas in which immunofluorescence staining detected *B.b.* antigen. IL-6 was produced by both astrocytes and neurons of spinal cord tissue. The chemokines CXCL13 and CCL2 were detected in the microglia of the spinal cord and in endothelial cells, primarily in periventricular areas of the brain. Other investigators have also confirmed the production of IL-6 and CXCL13 in Borrelial-infected rhesus monkey and human tissues (Pachner et al., 1997; Narayan et al., 2005; Pachner and Steiner, 2007). The monocyte chemotactic protein CCL2 may assist in the recruitment of T cells to the CNS and alter blood-brain barrier permeability while CXCL13 likely led to the abundance of B cells in spirochete-inoculated animals. This study confirmed that in the monkey model the innate immune response of CNS glial and endothelial cells to *B.b.* mediates the inflammation and damage seen in acute LNB and that this can occur prior to the onset of specific acquired immunity as measured by the appearance of anti-C6 antibodies. The absence of significant apoptosis in the brain and spinal cord tissue in this *in vivo* model differs from what was seen in the *ex vivo* study, perhaps due to lower interaction of *B.b.* with brain parenchyma compared to the dorsal root ganglia.

Patients with neurologic Lyme disease who have persistent symptoms after treatment are plagued primarily by fatigue, pain, and cognitive dysfunction. Of note, 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). IL-6 is pyrogenic, promotes B cell differentiation, stimulates the synthesis of acute phase reactants, and can also contribute to pain by increasing the sensitivity of nerve endings (Dickson et al., 1993; Rasley et al., 2002). TNF-α is pyrogenic, stimulates prostaglandin synthesis, and with other cytokines plays a key role in complex cognitive processes at the molecular level, such as synaptic plasticity, neurogenesis, and neuromodulation (McAfoose and Baune, 2009). IL1-β, a key player in the mediation of the CNS inflammation (Friedman, 2005), has been shown to cause synaptic inhibition in rats (Zeise et al., 1992) and to suppress long-term potentiation *in vitro* in mice (Katsuki et al., 1990), suggesting a pathogenic mechanism that may be involved in the learning and memory problems often seen in patients with neurologic Lyme disease. Cyclooxygenase 2, a pro-inflammatory enzyme involved in the formation of prostanoids and which has been detected in both astrocytes and microglia exposed to *B.b.*, is expressed in chronic active demyelinating lesions of patients with multiple sclerosis (Carlson et al., 2006) and has been shown to contribute to motor and cognitive dysfunction (Cernak et al., 2001) and to the modulation of neuropathic pain (Ma and Quirion, 2005). Inflammatory mediators in vascular endothelial cells exposed *ex vivo* to *B.b.* spirochetes have also been reported (e.g., IL1B, IL8, and COX-2) (Ramesh et al., 2008), perhaps playing a key role in the development of vasculitis in Lyme disease.

There is limited evidence that secondary damage may arise due to an ongoing molecular mimicry process. *B.b.*'s surface lipoproteins are proinflammatory and its surface glycolipids may elicit cross-reactive antibodies (Garcia-Monco and Benach 1997). *B.b.*-specific IgM antibodies against flagellin of *B.b.* have been found that cross-reacted with neuronal antigens (Sigal and Tatum, 1988; Sigal, 1993; Sigal and Williams, 1997). Other researchers (Alaedini and Latov, 2005) found cross-reactive human neural epitopes that share amino acid sequences with *B.b.* OspA protein; antibodies against two of the homologous OspA peptides were found by immunohistochemistry to react *in vitro* with neurons in human brain, spinal cord and dorsal root ganglia. A recent case report describes the development of an autoimmune-mediated polyneuropathy in a patient after well-documented and antibiotically treated borrelial CNS infection that responded well to subsequent intravenous immunoglobulin therapy (Rupprecht et al., 2008a). Further suggesting the possibility of an autoimmune process comes from the report (Katz 2009) of a series of 26 patients with painful neuropathy attributed to either the OspA vaccine (Latov et al., 2004) or borrelial infection who had persistent symptoms post-antibiotic treatment. Patients had serologic evidence of OspA and either nerve-conduction study confirmed neuropathy or diminished epidermal nerve fiber density. After open label non-randomized treatment with intravenous immunoglobulin, there was a significant mean increase in epidermal nerve fiber density on repeat testing and all patients reported an improvement in their neuropathic symptoms.

Future directions

Evidence from research with non-human primates infected with *B.b.* indicates that regulation and modulation of the acute inflammatory response and the resultant neural dysfunction and damage is substantially initially driven by the innate immune response of the cells of both the central and peripheral nervous systems. While only the *ex vivo* monkey study demonstrated CNS oligodendrocyte and neuronal apoptosis (Ramesh et al., 2008), the *in vivo* and *ex vivo* studies together confirm that *B.b.* infection can initiate the production of inflammatory mediators and cause neural dysfunction or injury.

Cytokines are known to induce prominent systemic and CNS behavioral effects, collectively shaping the subjective, behavioral and physiological components of the sickness response (Dantzer, 2001), and influencing a range of monaminergic and peptidergic neurotransmitter changes (Anisman et al., 2008). The sickness response, which includes fever, neuroendocrine activation, and sickness symptoms such as anorexia, somnolence, reduced motor activity, and malaise, is adaptive when it is limited to the peri-infection period. This sickness response becomes problematic when it is prolonged, as may occur with ongoing cytokine activation due to the persistence of a triggering organism or antigen or as a result of a sensitized brain cytokine system that is less likely to turn off after the infection is gone (Teeling and Perry, 2009). This sensitization of the brain cytokine system is thought to occur under conditions of repeated activation (Anisman et al., 2003), stimulation in early phases of development (Nawa et al., 2000), or prior exposure to environmental stressors (Tilders and Schmidt, 1999). Neuropsychiatric symptoms may emerge from ongoing cytokine stimulation, as has been demonstrated by the emergence of depression in approximately 20–30% of patients when given prolonged treatments with IL-2 or IFN-α to fight cancer or viral infection (Capuron and Dantzer, 2003). Ongoing cytokine activation may represent one important contributor to the chronic persistent symptoms of fatigue, pain, and cognitive dysfunction that patients may continue to experience despite having been treated for Lyme disease. Ongoing cytokine activation may also help to explain why patients with previously treated well-documented Lyme disease have been shown to have a four-fold greater rate of concurrent depression than patients with medically unexplained symptoms who do not have a clear history for Lyme disease (Hassett et al., 2008). While the central release of cytokines and prostaglandins by microglial cells may be triggered by *B.b.* in the CNS as has been demonstrated in the non-human primate model, the presence of persistent organism directly in the CNS however may not necessarily be required for the induction of cytokines and sickness symptoms as research in other animal models has demonstrated that peripheral inflammation alone can trigger the brain cytokine system via afferent neural pathways from the periphery to the CNS (Dantzer et al., 2008). Evidence to support a role for the cytokine system in the persistence of Lyme symptoms comes from a study that demonstrated persistently elevated levels of IFN-γ in the CSF cells from patients with chronic neuroborreliosis but not from patients with recovered neuroborreliosis (Widhe et al., 2004). To unravel why some patients may go on to develop chronic symptoms, future prospective research among patients with acute

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neurologic Lyme disease should include comprehensive neuropsychiatric, developmental, and risk histories as well as markers of inflammation (CRP, sialic acid, cytokines, prostaglandin E2, C3a) both at the early stages and in long-term follow-up; such a strategy is needed to elucidate the complex interplay between infection, host vulnerabilities, the immune response, and long-term outcome.

Structural brain imaging among patients with neurologic Lyme disease may demonstrate punctate white matter lesions on T2 weighted images, most commonly seen in acute disease, as in meningitis or encephalitis, but also reported in up to 41% of patients with later disease, such as Lyme encephalopathy; resolution of the signal hyperintensity may occur in up to 50% of the encephalopathy patients after treatment (Halperin et al., 1989). Among patients with persistent neurologic symptoms after treatment for neurologic Lyme disease, controlled MRI studies have not demonstrated an increased burden of white matter hyperintensities (Aalto et al., 2007), indicating that structural damage is not the explanation for persistent symptoms. Functional imaging studies, however, of patients with later stage neurologic Lyme disease using either Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) scans have consistently demonstrated abnormalities suggestive of impaired blood flow and/or metabolism, which may improve after antibiotic treatment (Fallon et al., 1997; Logigian et al., 1997). Our recent functional imaging study using brain scans of patients with persistent Lyme encephalopathy used $H_2^{15}O$ to assess blood flow, with and without a hypercapnic challenge, and 2-deoxy-2-(^{18}F)-D-glucose to assess metabolism (Fallon et al., 2009). This study demonstrated that the deficits primarily reflect abnormalities in cerebral metabolism, although there was evidence for a component of vascular compromise as well. The patients with Lyme encephalopathy had a diminished ability to increase cerebral blood flow in response to a hypercapnic challenge compared to age-, sex-, and education-matched controls, a finding that would suggest vascular compromise (as perhaps from inflammation) as part of the disease process. The precise cause of these objective vascular and metabolic deficits however is unclear. While some of these patients do respond to repeated antibiotic therapy, the antibiotic responsiveness itself need not indicate persistent infection as antibiotics are also known to have roles in modulating glutamate (Rumbaugh et al., 2007) and in reducing inflammation (Bernardino et al., 2009).

The animal models of neurologic Lyme disease raise the question of whether activated glial cells and their soluble products are responsible for persistent brain dysfunction, such as deficits in short term memory, verbal fluency, and processing speed (Keilp et al., 2006). To explore the possibility that microglia are activated in CNS disease, it is now possible to conduct brain PET imaging studies using radioactive ligands that target microglia. The translocator protein (TSPO) (18 kDa) is expressed primarily on microglia when activated in CNS injury (Banati 2002). *In vivo* imaging can document the expression of TSPO using radiolabeled ligands such as [^{11}C]-PK11195 which is the best studied of the tracers. PET studies using PK11195 have been conducted for a vast range of CNS diseases, including Rasmussen's encephalitis, multiple sclerosis, neurodegenerative diseases, and infectious diseases (HIV, Herpes encephalitis), with many studies showing increased retention of PK11195, suggesting microglial activation (Cagnin et al., 2007). PK11195 however has limitations, chief of which is a low binding signal and poor permeability of the non-compromised blood–brain barrier (Banati et al., 2000; Vaalburg et al., 2005) resulting in poor sensitivity. Other TSPO radioligands are now being studied, with early reports for some suggesting higher binding affinity to TSPO (Okuyama et al., 1999; Maeda et al., 2004). The application of these PET radioligands in future controlled studies to patients with both acute and chronic CNS Lyme disease holds the promise of determining whether activated microglia are present at different stages of neurologic Lyme disease and whether TSPO binding can serve as a biomarker of ongoing disease activity and treatment response.

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