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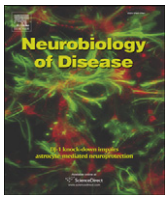

Review

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