Lyme Disease: Neurology, Neurobiology, and Behavior

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The Lyme disease controversy can be largely linked to the misconception that neurobehavioral effects of illness constitute evidence of nervous system infection. Appropriate differentiation between neuroborreliosis (nervous system Borrelia burgdorferi infection) and Lyme encephalopathy (altered nervous system function in individuals with systemic but not nervous system infection)—or encephalopathies of other etiologies—would lessen the controversy considerably, as the attribution of nonspecific symptoms to supposed ongoing central nervous system infection is a major factor perpetuating the debate. Epidemiologic considerations suggest that the entities referred to as “posttreatment Lyme disease” and “chronic Lyme disease” may not actually exist but rather reflect anchoring bias, linking common, nonspecific symptoms to an antecedent medical event. On the other hand, there are data suggesting possible mechanisms by which posttreatment Lyme disease could occur.

Keywords. Lyme disease; nervous system; neuroborreliosis; Lyme encephalopathy; posttreatment Lyme disease syndrome.

“What we have here is a failure to communicate.”

Words matter. Profound disagreements may ensue when people use the same words differently, often reflecting significant differences in underlying but unstated assumptions. Although many factors contribute to the “Lyme disease controversy,” one of the most powerful, particularly from the patient’s perspective, may well be differing understandings of what constitutes neurologic disease. To the public, neurologic disease, particularly loss of cognitive function, is among the most feared of all illnesses [1, 2]. The suggestion that a patient might be suffering from a nervous system infection, such as with Borrelia burgdorferi, with the unstated implication that this will lead to progressive loss of brain function, is terrifying. Obviously every effort should be made to avoid inaccurately suggesting this is the cause of a patient’s difficulty.

It can be challenging to differentiate between neurologic disease and the broad range of other disorders affecting behavior. Whereas all behavior requires a properly functioning nervous system, nervous system function can be affected indirectly by systemic illnesses (eg, hypoglycemia, hepatic insufficiency, sepsis) in the absence of any direct nervous system damage. Similarly, psychiatric disease—although fundamentally neurobiological, and presumably attributable to problems with neurotransmission, neural network function, and learned behaviors—is biologically distinct from what is normally considered neurologic disease. Because neither systemic nor psychiatric disease inherently involves structural damage to the nervous system, these disorders have quite different implications for patients’ future neurologic functioning. For this reason, it is helpful to define what is meant by neurologic disease—which generally consists of medical conditions directly and primarily affecting the nervous system, with resulting abnormalities attributable to underlying structural changes in the central nervous system (CNS) or peripheral nervous system (PNS). It is the expectation of potentially progressive, irreversible nervous system...
destruction that makes these disorders so frightening. Psychiatric disorders, metabolic encephalopathies, and other neurobiological phenomena can have devastating effects on patients’ well-being—but are not presumed to result in inexorable nervous system degeneration.

How does this relate to “nervous system Lyme disease”? These words are actually used to describe at least 4 distinct disorders (see Tables 1 and 2) with different mechanisms and prognoses. The most straightforward is true nervous system infection, typically including lymphocytic meningitis, cranial neuritis, or various forms of radiculoneuritis (pain, weakness, and sensory changes suggesting damage to 1 or several nerves or nerve roots) [3]. Although these conditions are clearly caused by nervous system invasion by B. burgdorferi, microorganisms are remarkably difficult to demonstrate in samples from patients or experimentally infected animals—by culture, polymerase chain reaction, or histology. The presence of spirochetes appears to be necessary, as antimicrobial therapy is rapidly and dramatically effective. There appears to be a clear temporal sequence starting with early spirochete entry into the CNS [4], occurring as early as the first 2 weeks of disseminated infection, even in the absence of clinical evidence of CNS involvement.

This rapidly triggers local production of CXCL13 [5], a B-cell–attracting chemokine produced by monocytes in response to B. burgdorferi outer surface proteins. The resultant B-cell proliferation within the CNS leads to a cerebrospinal fluid (CSF) pleocytosis and local production of specific antibody. No aspect of this process is considered controversial, although the mechanism by which such a small number of spirochetes can cause such pathogenically substantial nervous system inflammation remains unclear. One suggested mechanism relates to a B. burgdorferi surface protein that may both facilitate invasion across the blood–brain and blood–nerve barriers, and lead to the release of proinflammatory fibronectin fragments. Inflammatory cytokines released in response to these fragments might underlie this immune amplification [6]. Similarly uncontroversial is the fact that patients who suffer neurologic damage, such as facial nerve palsy, may have neurologic residua following successful antimicrobial treatment; just as with synovial damage from Lyme arthritis, Lyme disease–induced nervous system damage may persist despite microbiologic cure.

Rarely, this infection will involve the parenchyma of the spinal cord (myelitis) or brain (encephalitis). Spinal cord involvement has been described primarily in European patients with

Table 1. Categorization and Characteristic Findings of Illnesses That Can Impact Behavior

<table>
<thead>
<tr>
<th>Category</th>
<th>Neurologic</th>
<th>Systemic (Extraneurologic)</th>
<th>Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural change in nervous system</td>
<td>Yes</td>
<td>Not required and usually only in extreme cases</td>
<td>None</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Cell loss, damage</td>
<td>Altered physiologic milieu</td>
<td>Altered neurotransmission, neural net function, learned behaviors</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Limited</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>CNS effects of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic label for nervous system</td>
<td>Meningitis: infection in subarachnoid space</td>
<td>Encephalopathy</td>
<td>Broad range of psychiatric diagnoses; generally sparing cognition</td>
</tr>
<tr>
<td>Effect on CNS function</td>
<td>Meningitis: meningeal irritation (headache); increased intracranial pressure (altered alertness) or spread to underlying parenchyma</td>
<td>Altered cognition and behavior due to peripherally produced cytokines and other soluble molecules crossing BBB</td>
<td>Unmasking or accentuation of underlying psychiatric disorder by physiologic stress</td>
</tr>
<tr>
<td>CNS imaging (CT, MRI)</td>
<td>Meningitis: inflamed thickened meninges</td>
<td>Generally normal but, if severe, diffuse brain edema</td>
<td>Normal</td>
</tr>
<tr>
<td>CSF cells, protein, glucose</td>
<td>Increased inflammatory cells, protein, variable glucose</td>
<td>Generally normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td>Must cross BBB</td>
<td>BBB irrelevant</td>
<td>BBB irrelevant</td>
</tr>
<tr>
<td>PNS effects of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on PNS function</td>
<td>Focal or multifocal</td>
<td>Altered biochemical milieu</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Diagnostic aid</td>
<td>Neuropathology</td>
<td>Neuropathology</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PNS, peripheral nervous system.
radiculoneuritis, in whom there may be segmental inflammation at the same level as the symptomatic nerve roots. Encephalitis is extremely uncommon, but is manifest by focal clinical (spasticity, ataxia, sensory loss, or other objective findings) and magnetic resonance imaging (MRI) abnormalities reflecting the site(s) of involvement. Encephalomyelitis is presumed to be due to infection and inflammation within the CNS parenchyma and is similarly responsive to antimicrobial therapy.

**NEUROBEHAVIORAL CHANGES WITHOUT CNS INFECTION**

The controversy about “nervous system Lyme disease” actually relates to 3 other disorders often included under the same rubric—disorders that are actually neurobiological but not neurologic (ie, they do not involve active nervous system infection, inflammation, or damage). Unfortunately, the inappropriate attribution of these symptoms to nervous system infection immediately terrifies patients, who often become convinced they are suffering from an irreversible and devastating brain disorder.

**Lyme Encephalopathy**
The first of these 3, and the one that probably has led to all subsequent confusion, is the disorder originally described as “Lyme encephalopathy” [7–9]. This impairment of memory and cognitive function was described in patients with active, ongoing systemic but not parenchymal CNS Lyme disease. The term was introduced to distinguish this disorder from actual brain *B. burgdorferi* infection, the latter more correctly termed “encephalitis” [10]. Lyme encephalopathy, analogous to toxic-metabolic encephalopathies in myriad other inflammatory states, reflects altered CNS function but not CNS infection. It is probably mediated by peripherally produced soluble neuroimmunomodulators that cross the blood–brain barrier, causing neurobehavioral changes [10, 11]. Like true nervous system Lyme disease, this disorder usually clears rapidly with antimicrobial therapy, demonstrating the necessary role of active infection.

The other 2 entities, referred to as “posttreatment Lyme disease syndrome” (PTLDS) and “chronic Lyme disease,” are unresponsive to antimicrobial therapy and are the principal source of debate.

**Posttreatment Lyme Disease Syndrome**

Posttreatment Lyme disease syndrome has been defined as “the presence of any of: widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesias, or dysesthesias . . . interfering with . . . function . . . within 6 months after . . . initial diagnosis and treatment . . . and . . . persist[ing] for at least 6 months” [12, 13]. The symptoms overlap extensively with those of Lyme encephalopathy, differing primarily by the requirement that encephalopathy occur in patients with active extraneurologic infection, whereas PTLDS patients have already been appropriately diagnosed with and treated for Lyme disease. Such symptoms are often present immediately after treatment—as they may be following treatment of other infections—and usually resolve over time. PTLDS is diagnosed when symptoms persist for 6 or more months.

**Chronic Lyme Disease**

Chronic Lyme disease has not been formally defined, but is operationally described as including “persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features . . .” [14]. Notwithstanding that the listed symptoms are not necessarily neurologic, many of them overlap with those of PTLDS. However, diagnosing chronic Lyme disease requires neither objective manifestations of Lyme disease, nor laboratory evidence of *B. burgdorferi* infection. Despite compelling evidence that antimicrobial therapy is ineffective in this disorder [13, 15, 16] many individuals given this diagnosis receive long, complex, and sometimes harmful courses of antimicrobial, anti-inflammatory, and other therapy.

**RELATIONSHIP OF PTLDS AND CHRONIC LYME DISEASE TO B. BURGDORFERI INFECTION**

The key questions concerning these 2 entities are (1) whether they truly exist, and (2) if they do, what might the underlying

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**Table 2. Neurobehavioral Syndromes in Lyme Borreliosis**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Objective Evidence of Lyme Disease (Clinical/Laboratory)</th>
<th>Objective Evidence of Active <em>B. burgdorferi</em> Infection</th>
<th>Neurobehavioral Abnormalities</th>
<th>Response to Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>Required/required</td>
<td>Required</td>
<td>Focal</td>
<td>Yes</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Required/required</td>
<td>Required</td>
<td>Cognitive</td>
<td>Yes</td>
</tr>
<tr>
<td>Posttreatment Lyme disease</td>
<td>Required/required</td>
<td>No</td>
<td>Cognitive</td>
<td>No</td>
</tr>
<tr>
<td>Posttreatment Lyme disease</td>
<td>Required/required</td>
<td>No</td>
<td>Cognitive</td>
<td>No</td>
</tr>
<tr>
<td>Chronic Lyme disease</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>No</td>
</tr>
</tbody>
</table>
mechanism be? With regard to the existence of PTLDS, 30% or more of patients treated for Lyme disease may report persisting, subjective posttreatment symptoms. However, several controlled trials have shown that identical symptoms are equally common in patients without Lyme disease [17–20]. The few studies suggesting relatively more frequent subjective symptoms following treated Lyme disease show no increase in corroborating objective abnormalities [21, 22]. Studies of the general population (without Lyme disease) indicate that up to a third of the normal, healthy population experiences the same symptoms to a varying degree [23, 24], the same frequency as that found in the control populations of Lyme disease posttreatment studies. In the absence of any objective evidence of disease in these treated patients, and given that the identical symptoms are equally prevalent in control individuals, it seems plausible that the entity PTLDS is simply an example of anchoring bias. Patients who have been treated successfully for Lyme disease and subsequently experience common symptoms that they have heard are attributable to PTLDS incorrectly conclude that these nontypical symptoms are indeed the sequela of *B. burgdorferi* infection, perpetuating the notion of this construct.

Chronic Lyme disease presents even greater challenges, as it is a diagnosis that is often made in the absence of any objective evidence the patient ever had Lyme disease. From an epidemiologic perspective, population studies indicate that incapacitating fatigue—a hallmark of chronic Lyme disease—occurs in about 2% [24] of otherwise healthy individuals. Prevalence of chronic Lyme disease symptoms is difficult to estimate, although study recruitment data may be informative [15, 16]. In a study of persisting posttreatment fatigue [15], the 10% of screened patients who were enrolled represented about 3% of incident cases in the authors’ catchment area during the study period [25], comparable to the 2% incidence of severe fatigue in the general population. In a study of patients with posttreatment cognitive impairment [16], performed by investigators associated with supporters of the chronic Lyme disease construct, 3368 subjects were screened between January 2000 and April 2004 but only 37 met criteria and were enrolled. Assuming the study drew patients from the surrounding states of Connecticut, New Jersey, New York, and Rhode Island, this represented <0.1% of incident cases reported to the Centers for Disease Control and Prevention (CDC) during that time [26]. If patients came from a broader geography, or if the recent CDC estimate that only about 10% of diagnosed, treated Lyme disease cases are reported [27], that 0.1% would decrease substantially (as would the 3% in the fatigue study). Combining the cross-sectional observation that 2% of the general population has such symptoms at any given time, and assuming that the 4 1/3 years of study recruitment represents about 5% of average US adult life expectancy, results in an estimated 0.1% risk of any randomly selected healthy individual developing these symptoms by chance during the study’s enrollment period—comparable to the estimated incidence based on study recruitment.

**POSSIBLE ETIOLOGIES**

These epidemiological observations notwithstanding, it is conceivable that there is a small subset of patients treated for Lyme disease who do indeed have a posttreatment syndrome. If so, what mechanisms might underlie this disorder, or, if chronic Lyme disease is a valid concept, its overlapping symptoms? Because additional antimicrobial therapy is not helpful [13, 15, 16], a noninfectious explanation would seem necessary. Several studies suggest that patients who have been treated for Lyme disease may produce antineural antibodies [28, 29]. However, the presence and concentration of these antibodies do not appear to correlate with the presence or absence of post-Lyme disease symptoms [29]. Alternatively, just as there is indirect evidence that cytokines may contribute to the symptoms of Lyme encephalopathy, there is limited evidence suggesting interferon α may be elevated in patients with posttreatment Lyme disease. However, levels do not change following treatment with either ceftriaxone or placebo, and do not appear to vary with changes in symptomatology [29].

Studies in experimentally infected animals have raised the possibility of persisting posttreatment persocial symptoms. From the demonstration of bacterial detritus, consisting of both morphologically intact bacterial cells and cell fragments, following antimicrobial treatment [30, 31]. Although there is some evidence of transmission of these organisms to feeding ticks, to date there is no evidence that they can transmit symptomatic infection—that is, fulfill Koch’s postulates. In the absence of evidence of true ongoing infection, might the bacterial debris play a role? One recent in vitro study suggests that this debris could trigger both an immune response and glial apoptosis [32]. Alternatively, a mechanism proposed for posttreatment Lyme arthritis might play a role. It has been suggested that persisting spirochete detritus [31] might periodically leak into joints [33], eliciting an inflammatory response [32]—that is, an acute arthritis. Although biologically plausible, this must be reconciled with the observations that, unlike Lyme arthritis, PTLDS symptoms are not particularly episodic, and are not associated with any objective evidence of end-organ inflammation, particularly in the nervous system, where CSF is invariably bland and MRI fails to demonstrate any parenchymal CNS inflammation.

It is also important to consider the real relevance of animal and in vitro observations to human disease. Lyme disease is a zoonosis. It naturally occurs in many different species, some of which serve as reservoir hosts, tolerating prolonged, asymptomatic infection and even spirochemia; that is, despite having an intact immune system, these hosts do not eliminate
infection. Obviously such immune host–spirochete interactions vary among species, making cross-species inferences problematic. In humans, the immune system clearly recognizes and attacks *B. burgdorferi*, as evidenced by the inflammatory component of carditis, arthritis, meningitis, or other clinical manifestations essential to the diagnosis of Lyme disease—without which, by definition, PTLDS cannot develop.

On the other hand, even if a few viable spirochetes were to persist in some subjects in a manner that protects the organisms from ongoing interactions with the host’s immune system, their significance is questionable. In general (ie, in other infections) it is improbable that antimicrobial therapy eradicates every microorganism in every patient. More likely, antimicrobials generally kill the vast majority of microorganisms, with the host immune system either eradicating the remainder or establishing an ongoing, asymptomatic “balance of power.” Clinical observations in many situations suggest that persistence of viable organisms can be harmless (eg, Ghon complexes in tuberculosis, herpes viruses in neurons, *Treponema pallidum* in treated human immunodeficiency virus patients with syphilis [34])—so long as the immune system remains effective. Because Lyme disease has not been found to be an issue in immunocompromised hosts (and as there is no evidence that patients with chronic Lyme disease are immunocompromised), it can be surmised that treatment in humans results in either complete eradication of organisms or such thorough suppression that even compromised immune systems can keep rare persisting organisms under control. As in the listed examples of persisting infections, the absence of systemic immune activation makes it unlikely that such a persisting—but contained—infestation would play any role causing systemic or other remote symptoms.

The biologic plausibility of chronic Lyme disease is more problematic. The lack of response to antimicrobial therapy and the inability to demonstrate viable organisms in patients, coupled with the fact that many diagnosed patients lack laboratory support for the diagnosis or a history of characteristic objective abnormalities, renders this entity highly suspect. Proponents have argued that the disorder is caused by small numbers of persisting organisms hidden from the host immune system either by their location or by concealment of spirochete surface antigens. However, such a mechanism creates a logical paradox. If ongoing neurobehavioral symptoms are mediated by soluble neuroimmunomodulators released in response to *B. burgdorferi*, how would such a process be triggered by a few organisms that are immunologically invisible? The more recent argument that symptoms are due to multiple coinfections with other organisms such as *Balosia*, *Bartonella*, *Anaplasma*, and others that might be similarly concealed, is no more compelling, for the same reasons. The only alternative mechanism for “action at a distance” would be if *B. burgdorferi*—or coinfecting organisms—released exotoxins. As *B. burgdorferi*’s genome has been sequenced in its entirety, and does not encode recognizable exotoxins, this seems improbable [35].

Regardless of whether the symptom complexes referred to as PTLDS and chronic Lyme disease are causally related to *B. burgdorferi* infection, their frequency and impact require consideration of other possible etiologies. Although a substantial number of patients have depressive symptoms [36,37], the majority do not; hence, the syndrome cannot be attributed to depression. However, there does appear to be a consistent psychologic substrate. Resilience, an individual’s ability to respond to both physiologic and psychological stressors, returning to a prior level of normal functioning after a significant adverse experience, is an important, measurable psychological attribute [38]. Presumably related to both underlying neurobiologic mechanisms and learned behaviors, it is reflected in 2 attributes, positive and negative affect. A prospective study of patients treated for Lyme disease found, like others, that 1 year after treatment, one-third of patients reported chronic symptoms that they attributed to Lyme disease. In a multivariate analysis, low positive affect at baseline, independent of the severity of acute symptoms, was the single best predictor of which individuals would develop these persisting symptoms.

This premorbid characteristic of how an individual responds to the stress of illness may well play a crucial role in the development of this neurobehavioral syndrome [38–40].

**CONCLUSIONS**

Of the 4 neurobehavioral syndromes attributed to *B. burgdorferi* infection, encephalitis, with clinical, imaging, and CSF findings clearly indicative of focal, structural involvement of the CNS parenchyma, is both rare and clearly related to CNS infection. The diagnosis of Lyme encephalopathy should be used to describe patients with altered cognitive function and active infection that does not involve brain parenchyma. Post–Lyme disease treatment syndrome may or may not exist; if it does, it is probably quite infrequent, and probably represents a neurobehavioral response to illness rather than an immunologic or infectious process. There is no evidence to suggest that chronic Lyme disease, as the term is commonly used, exists as a distinct pathophysiologic entity or is related to *B. burgdorferi* infection.

Much can be learned from additional studies of this infection. In particular, generalizable insights may be gleaned about neurobiologic effects and mechanisms in other systemic illness. Critical in advancing this understanding, though, will be clearly differentiating among the effects of actual nervous system infection, the neurobehavioral consequences of extraneurologic infection, and the neurobiologic consequences of recovery from a significant medical stressor.
Notes

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