

Nervous System Lyme Disease: Is There a Controversy?

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ABSTRACT

Infection with the tick-borne spirochete, *Borrelia burgdorferi*, affects the nervous system in well-defined ways. Accurate diagnostic tools and effective therapeutic regimens are now well established. Persistent misconceptions about (1) the role and interpretation of laboratory tests, (2) what is and is not evidence of nervous system infection, and (3) what constitutes an expected response to treatment have fostered widespread perceptions that this disease is highly controversial. Infection causes the classically described triad of meningitis, radiculoneuritis, and cranial neuritis; however, virtually every known neurologic disorder has been blamed on this infection. For most (multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer disease, Parkinson disease), evidence is scant, nonexistent, or coincidental. For some (cerebral vasculitis with stroke, optic neuritis) a few case reports suggest a rare possible causal link.

KEYWORDS: Lyme disease, nervous system, neuroborreliosis, Garin-Bujadoux-Bannwarth syndrome, *Borrelia burgdorferi*

For reasons that are complex and have more to do with sociology and psychology than with medicine, the terms “Lyme disease” and “controversy” seem inextricably linked. Although the biology of this infection is now well understood, the ready acceptance of pseudoscience—reflecting a widespread mistrust and lack of understanding of science—has allowed some to argue that there are valid reasons to reject what is well-established medical fact and accept counter arguments based on superficially plausible rationalizations. These arguments have struck a resonant chord with many patients with a variety of neurologic and other disorders, who in turn have received a sympathetic ear from lawmakers and politicians, who are regrettably ill equipped to judge the scientific merits of the two sides of this erstwhile debate.

Arthropod-borne infections are a major public health problem worldwide, with malaria, dengue fever, and others affecting millions annually. As a result of extensive public health measures, such disorders have been remarkably uncommon in the United States and Western Europe—until now. As humans have chosen to live, work, and play in less developed areas, they now find themselves exposed to several previously irrelevant zoonoses—of which Lyme disease is the most common, with ~30,000 cases per year in the United States. This infection has several interesting biologic properties. It shares some features with its better-known fellow spirochete, syphilis (of which there are ~10–15,000 cases of primary and secondary disease reported annually in the United States¹), including having a tropism for the nervous system, and, when untreated, causing a chronic

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Emerging and Controversial Issues in Neurology: Infectious

Diseases; Guest Editor, Tracey A. Cho, M.D.

Semin Neurol 2011;31:317–324. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI: <http://dx.doi.org/10.1055/s-0031-1287652>.

ISSN 0271-8235.

infection—but one that remains exquisitely sensitive to widely available antibiotics.

BIOLOGY

The controversy rests on several foundational myths, each of which arises from small kernels of truth. First, it is commonplace to hear that Lyme disease is a new disorder about which little is known—an assertion that might have had merit 30 years ago when the debate began. However, the first description in the United States of the cutaneous lesion, erythema migrans, appeared over four decades ago;² the first report in the European literature appeared six decades before that.³ Neurologic involvement, the source of most of the misunderstanding and controversy, was first characterized in Europe in 1922,⁴ in the United States in 1979.⁵ A Medline search on “Lyme disease” now identifies over 9,000 publications. Clearly, assertions that this disorder is novel or unstudied are unwarranted.

The mythology then continues with concerns about the accuracy of diagnostic testing—and admittedly, it did take time to develop reliable diagnostic tools. As in syphilis, organism-based diagnostics are only sensitive in the earliest, localized phase of the illness. Microscopic examination of scrapings from syphilitic chancres or of erythema migrans biopsies generally demonstrates innumerable spirochetes. However, once *Borrelia burgdorferi* infection has disseminated, the number of organisms demonstrable is remarkably small. Even using the considerable power of the polymerase chain reaction is usually unhelpful, despite its ability to detect the genomic material from even very small numbers of organisms. So few spirochetes are present that on a single cerebrospinal fluid (CSF) sample some aliquots may contain bacteria while others may not.⁶ Microbiologic culture is even more challenging. Not only is the number of organisms small, the methodology is unwieldy. *B. burgdorferi* only grows in highly specialized media (BSK II), something that most laboratories do not routinely have available. Incubation must be at 33°C rather than 37°C, again a capability not routinely available. Finally, *B. burgdorferi* is so slow growing that cultures must typically be maintained for weeks. As a result, culture is not clinically practical.

SEROLOGIC TESTING

Consequently, laboratory support for the diagnosis of Lyme disease, as in syphilis, relies almost entirely on demonstration of a serologic response to the organism. Other techniques have been tried, including among others, antigen detection in urine⁷ and measurement of T cell responses to *B. burgdorferi*, but none has proved accurate or useful.

As with any laboratory test, the first challenge is deciding when to obtain it—when does the test provide meaningful positive and negative predictive values? Obtained in a patient with a disorder not typically associated with Lyme disease, in a geographic area where there is no likelihood of exposure to the *Ixodes* ticks that are the only source of disease transmission, the probability of a false-positive substantially exceeds that of a true positive. On the other hand, in this setting, the negative predictive value is essentially absolute. Similarly, in an area where Lyme disease is highly prevalent, where 5 to 10% of the population may have positive serologies, a positive in a patient with an unrelated disorder (e.g., a fractured leg) is a biologic true-positive in the sense that it may well reflect actual exposure, but a false-positive in the sense that the exposure has no bearing on the patient's current medical problem.

As in all antibody-based diagnostic approaches, this method has three inherent shortcomings. Following exposure to any infectious organism, it takes time for the immune response to go through the necessary changes to produce a measurable amount of targeted antibody; as such, patients are initially seronegative.⁸ In the case of Lyme disease, this period lasts several weeks to a month or so (notably shorter than the corresponding window for HIV infection). Second, following infection, the antibody response typically persists following eradication of the infection, to protect the host should reexposure occur. This means that a positive serology is, at best, evidence of exposure to the organism at some point in time—and not necessarily evidence that it is the cause of the current symptoms. Finally, antibodies respond to molecular conformations, not to specific organisms, (i.e., there is cross reactivity with epitopes of other organisms) resulting in false-positives.

Although the first two considerations simply require interpreting test results rationally, the last posed significant technical challenges as different laboratories tried different approaches to optimize both sensitivity and specificity. The currently recommended two-tier testing approach⁹ works very well. An enzyme-linked immunosorbent assay (ELISA) is used as a screening test, measuring total antibody that binds to the responsible organism. If the results of this are positive or borderline (both defined statistically), the sample is then tested by Western blot, to determine the specific proteins to which the antibodies bind. Consensus criteria define a positive IgM Western blot as having two of three specific bands, a positive IgG blot as 5 of 10 specific bands.⁹ These criteria are not based on anything unique about the specified bands but rather derive from a statistical analysis of a large number of patients' samples, determining which combinations of bands provide the best positive and negative predictive value for the diagnosis. Importantly, these criteria should not be used in individuals in whom the ELISA is negative, as this is

largely outside the conditions used to define them originally. Very importantly, the normal immune response begins with production of less-specific IgM antibodies that, within weeks, switch to more specific IgG antibodies. Consequently, IgM criteria are only applicable in the first month or so of disease. After that, an isolated positive IgM Western blot is almost certainly a false-positive and is certainly irrelevant. Finally, some laboratories have adopted their own unique criteria for interpreting Western blots; these have not been scientifically validated and should not be used clinically.

Because of the normal lag in development of the antibody response, and because erythema migrans occurs rapidly (within 30 days) after spirochete inoculation, many patients with erythema migrans have negative serologies.¹⁰ This has been repeatedly and incorrectly cited as evidence that serologies are unreliable. In fact, all it means is that in very acute disease if an individual at risk of exposure to Lyme disease develops a typical erythema migrans, the still-developing antibody response is diagnostically irrelevant and treatment should begin. Some early work suggested that early treatment could abrogate the immune response while not completely eradicating infection.¹¹ This observation has not been replicated, and the conclusion is almost certainly incorrect. The situation is presumably analogous to that in animal studies of experimental syphilis infection in which incomplete early treatment led to a slight delay in development of a measurable antibody response, without altering either the subsequent immune response or the course of the infection.¹² However, the notion of “seronegative” Lyme disease persists, enabling all subsequent myths.

NERVOUS SYSTEM LYME DISEASE

One of the biggest challenges relates to misconceptions about what is meant by nervous system disease in general, and nervous system Lyme disease, or neuroborreliosis, in particular. Neurologic disease results from demonstrable changes in the peripheral nervous system, the central nervous system (CNS) or both. Though admittedly a broad range of disorders can cause nervous system disease, breaking this down into readily identifiable groups based on shared features is helpful.

Peripheral nervous system disease can be divided into disorders affecting myelin (demyelinating neuropathies such as Guillain-Barré syndrome), axons, or the two together—the last typically due to an extrinsic process, such as a vasculitis or vasculopathy (often a multifocal process known as a mononeuropathy multiplex, such as in diabetes mellitus).

Central nervous system disease can affect the brain or spinal cord parenchyma (e.g., stroke, multiple sclerosis, Alzheimer disease, epilepsy) or the CSF space (e.g., meningitis, idiopathic intracranial hypertension).

Importantly, many other disorders alter neurobehavioral function, but are not neurologic diseases; for example, psychiatric disorders, syncope, and metabolic encephalopathies. The tendency to attribute all manner of behavioral changes to neurologic disease is not only misguided, but very unfortunate. First, for most patients the possibility of a potentially progressive neurologic disorder is among the most frightening of all possible medical diagnoses. Second, inappropriately postulating a neurologic cause often leads to substantial wasted resources—the inevitable brain imaging studies in patients with syncope or metabolic encephalopathies never demonstrate clinically relevant information.

Early Lyme disease is typically separated into acute localized disease (the single erythema migrans) and acute disseminated disease, which is the consequence of systemic spread of spirochetes, often with symptoms typical of a bacteremia, such as fever and diffuse aches and pains. Erythema migrans is virtually unique. As spirochetes migrate centrifugally through the skin away from the site of inoculation, they elicit an expanding erythroderm that expands day by day, typically becoming many (>5) centimeters in diameter and persisting for days to weeks. As the outer margin expands, more central areas may revert to their normal pallor, resulting in a target-like appearance. Much like a syphilitic chancre, the rash is often remarkably asymptomatic—neither painful nor even pruritic. In disseminated disease, symptoms reflect the bacterium's organotropisms for the heart (typically causing heart block), joints (arthritis or arthralgias), or the nervous system. Even in untreated individuals, symptoms of acute disseminated disease generally subside, with a subset of these patients subsequently developing signs of late disseminated infection—in the United States most commonly a relapsing large joint oligoarthritis. In rare patients, the nervous system can be affected late in infection, although this is now seen rarely, if ever, presumably reflecting widespread aggressive treatment of early disease.

CLINICAL PHENOMENA OF NEUROBORRELIOSIS

Nervous system involvement in Lyme disease occurs predominantly as part of acute disseminated disease, affecting 10–15% of infected individuals.¹³ Patients most often develop all or part of the classic triad defined years ago by Garin and Bujadoux;⁴ lymphocytic meningitis (in isolation in ~2%), cranial neuritis (~8%), and radiculoneuritis (~3%). In ~80% of individuals with cranial neuritis, the facial nerve—either unilaterally or bilaterally—is involved.

The frequency of radiculoneuritis is difficult to estimate, given how often it is misdiagnosed. These patients present with severe dermatomal pain with

sensory, motor, and reflex changes corresponding to the involved dermatome. The site of involvement, which can be a limb or the trunk, may relate to the site of the tick bite. Pain is severe, neuropathic in character, and often intractable. Truncal involvement can be misdiagnosed as visceral disease, limb involvement as a mechanical radiculopathy.

Cranial neuropathies are not uncommon in other basilar meningitides, leading to the logical but probably largely incorrect assumption that Lyme disease-associated cranial neuropathies are similarly attributable to nerve root damage in the inflamed subarachnoid space. Clinical and neurophysiologic observations suggest that in Lyme disease, although meningitis often co-occurs, it is not a requirement.¹⁴ In fact, at least in the case of the facial nerve, involvement is probably usually part of a more widespread mononeuritis multiplex.¹⁵ Similarly, although it would be logical to assume that Lyme radiculoneuritis is caused by nerve root inflammation by the meningitic process, in fact it too is not invariably associated with meningitis. Because patients can also present with the picture of a brachial or lumbosacral plexopathy, or of other mononeuropathies, and all share the same neurophysiologic patterns, it is quite likely that all reflect a multifocal, patchy inflammatory process affecting the peripheral nerve—a mononeuropathy multiplex.¹⁵ Even those uncommon patients with the clinical picture of a more diffuse polyneuropathy almost certainly have a confluent mononeuropathy multiplex. This conclusion is further supported by the limited histopathologic evidence available from patients, and by the fact that a mononeuropathy multiplex occurs in the vast majority of experimentally infected rhesus macaque monkeys,¹⁶ the only valid animal model of human neuroborreliosis.

Although there is good evidence that facial nerve palsies and radiculoneuropathies can all be attributed to a mononeuropathy multiplex, there are few data to provide insights into the mechanisms underlying other, less-frequent cranial neuropathies. Case reports and series describe patients with involvement of the extraocular muscles (diplopia), trigeminal (pain and numbness), and vestibuloacoustic (dizziness, hearing changes) nerves.¹⁷ However, too little information is available to provide pathophysiologic insights. Descriptions of lower cranial nerve involvement are so rare as to be uninterpretable.

Most challenging are descriptions of cases of optic neuritis. Because the optic nerve is actually a CNS pathway and not a peripheral nerve, one might expect very rare involvement analogous to parenchymal brain involvement. In fact, most case reports are highly questionable (see¹⁸ for a detailed review), although rare instances have occurred where it is possible Lyme disease actually did cause optic neuritis.¹⁹

Parenchymal brain and spinal cord involvement occurs,²⁰ but is now very rare. When CNS infection does

occur, as in other infections, this is almost invariably evidenced by abnormalities in the CSF. At a minimum, there should be a lymphocytic pleocytosis and/or elevated protein concentration.^{21,22} In patients who have had CNS inflammation of significant duration, there is often evidence of local production of specific antibody within the CNS—referred to as intrathecal antibody production, and evidenced by the presence of proportionately more specific antibody in the CSF than in serum.^{23–25} The sensitivity of this approach is unclear, and probably depends on the clinical context. However, in individuals with active and persistent CNS inflammation—many of whom develop CSF oligoclonal bands and increased total immunoglobulin production and constitute the basis for the assertion that Lyme disease can mimic multiple sclerosis, one would expect that the excess antibody present in the CSF would be specific for the inciting organism.²⁶

The European literature suggests that a significant number of patients with radicular symptoms exhibit myelopathic findings related to the symptomatic root level.²⁷ Corresponding observations in the United States are too rare to draw any conclusions regarding this. Although years ago it was suggested that brain involvement occurs in ~0.1% of untreated individuals,²⁶ most investigators who formerly described these patients now see them rarely or never. Magnetic resonance imaging studies in these rare patients suggested brain involvement was analogous to the patchy multifocal inflammatory process occurring in the peripheral nerve.²¹ Unfortunately, these rare observations have now resulted in routine reporting of many brain MRIs with non-specific white matter abnormalities as being consistent with Lyme disease—a statement that may be true in the strictest sense, but is not helpful as the probability of this being the explanation of the observed abnormality is vanishingly small.

One recurrent debate is whether Lyme disease can cause a CNS vasculitis and stroke-like events. The evidence here is complex.²⁸ From a serologic perspective in many of the published case reports, laboratory results consist of ELISAs without supporting Western blots. Because vasculitides are commonly associated with a nonspecific polyclonal gammopathy, patients with vasculitis can easily have false-positive serologic tests. As a result, many of the published cases have convincing evidence of a vasculitis, but very unconvincing evidence of Lyme disease. On the other hand, some of the cases have good evidence for Lyme disease, but the diagnosis of a stroke was based on the subacute onset of a focal deficit with an MRI demonstrating a focal area of increased T2 signal—hardly convincing evidence of a vasculitis. Drawing on insights from peripheral nerve involvement, although there are commonly perivascular inflammatory infiltrates, there has never been evidence of vessel wall necrosis or damage—the usual *sine qua non* for the

diagnosis of a true vasculitis. Having said all this, there are a very few case reports of individuals who have had stroke-like events, with good laboratory support for the diagnosis of Lyme disease and angiographic findings suggestive of vasculitis.²⁹ In these rare individuals, a causal link may exist; however, these observations are remarkably rare in contrast to the frequent description of Huebner arteritis in neurosyphilis.

Finally, links have been suggested between Lyme disease and motor neuron disease,^{30–32} Parkinson disease,³³ Alzheimer disease,^{34,35} and other neurologic disorders. At this point, there is no convincing evidence that any of these are more than chance co-occurrences.

LYME ENCEPHALOPATHY

This entity is, without doubt, the preeminent example of how misattribution of neurobehavioral symptoms to neurologic disease has contributed to the Lyme disease controversy. In the 1980s, as the phenomenology of Lyme disease was first being elucidated, several investigators noted that many patients, virtually all of whom had other clinical evidence of active inflammatory disease attributable to Lyme disease—primarily arthritis—described symptoms of cognitive slowing, memory difficulty, and a variety of related neurocognitive problems.^{21,36,37} Identical symptoms are prominent in virtually every other known inflammatory disease—pneumonia, urinary tract infections, severe viral illnesses of many sorts, rheumatoid arthritis, to name just a few—and in those contexts are not considered to be indicative of CNS infection, inflammation, or anything else that might be considered a nervous system disease. Rather, this is well recognized as a “toxic metabolic encephalopathy,” almost certainly mediated by circulating cytokines or other soluble neuro-immunomodulators, which cross the blood—brain barrier and physiologically alter brain function.³⁸

Early work focused on determining if these symptoms were due to a mild form of the very rare encephalitis described above, or were in fact an encephalopathy due to systemic and not nervous system changes. As reflected in the choice of the word “encephalopathy” to describe the syndrome, it was determined that in the vast majority of instances, this was a toxic metabolic encephalopathy. Initially, a very few individuals were identified in whom this was attributable to a mild encephalitis—individuals identifiable by virtue of inflammatory changes in their spinal fluid, and often by findings on MRI.³⁶ However, in the overwhelming majority of individuals with these symptoms, there was nothing to suggest the presence of nervous system involvement. Some have tried to sustain the argument for brain involvement by using brain imaging with qualitative single photon emission computed tomography (SPECT) scans—a test that is as nonspecific as it is unreliable.

Unfortunately, this construct has proven highly problematic. First, telling a patient they have a brain infection, and supporting it with a pseudoscientific laboratory test, such as a SPECT scan, terrifies patients and intimidates nonneurologist physicians, who are often very uncomfortable with neurologic diagnoses. Second, some have argued that this symptom complex is specific to Lyme disease; therefore, the presence of these symptoms in isolation warrants a diagnosis of Lyme disease, regardless of the presence or absence of anything else indicative of the presence of this infection. Coupling this myth with the fundamental misconceptions about diagnostic testing and treatment response has resulted in the current “controversy” about “chronic Lyme disease.”

In fact, population studies have shown these encephalopathy-like symptoms to be highly prevalent in the normal population—and of severity sufficient to disrupt daily activities in up to 2% of the population at any given time.³⁹ Given the prevalence of these symptoms in medically healthy individuals as well as in patients with all types of other inflammatory processes, diagnosing *B. burgdorferi* infection based solely on these symptoms is clearly inappropriate. This notwithstanding, there are those who routinely make the diagnosis of “chronic Lyme disease” based solely on such symptoms, even in individuals who have never had exposure to *Ixodes* ticks, erythema migrans, or a positive serology, and treat them with a variety of prolonged and complex antimicrobial regimens. Multiple studies have now clearly shown^{40–43} that this approach carries significant risk, but no substantive benefit.

TREATMENT

It bears emphasizing that appropriate treatment requires appropriate diagnosis, and the diagnosis of neuroborreliosis requires laboratory confirmation—typically with serologic testing. In rare patients with very early disease (e.g., cranial neuropathies), clinical disease may precede the development of a measurable antibody response. Because the neurologic phenomena are far less pathognomonic than erythema migrans, diagnosis of such patients may require a convalescent serology performed several weeks later. Conversely, in patients with no potential exposure to Lyme disease, or with clinical presentations outside the range of disorders known to occur in this disease, serologic tests should only be performed with great caution—as false-positives will substantially outnumber true-positives.

Preemptive antibiotic treatment in seronegative patients is rarely indicated, the one possible exception being two specific subsets of patients with facial nerve palsies, and then if and only if there has been significant risk of exposure in the preceding 30 days. Bell palsy is highly unusual in young children; consequently, in

Table 1 Nervous System Lyme Disease: Treatment

Disorder	Adults	Children (Dose not to exceed adult total)
Acute neuroborreliosis (meningitis, radiculitis, cranial neuritis)	Ceftriaxone* 2 g/d IV; 2–4 wk	50–75 mg/kg/d
	or	
	Cefotaxime 2 g q8/ IV; 2–4 wk	150–200 mg/kg/d in 3 divided doses
	or	
	Penicillin, 20–24 million units IV/d; 2–4 wk	300,000 units/kg/d
	or	
Encephalomyelitis	Probably doxycycline [†] 100 mg PO b.i.d. to q.i.d. for 3–4 wk	≥8 years; 1–2 mg/kg b.i.d.
	Possible alternatives: Amoxicillin 500 mg PO t.i.d.; 21 d	50 mg/kg/d in 3 divided doses
	or	
	Cefuroxime axetil 500 mg PO b.i.d.; 21 d	30 mg/kg/d in 3–4 divided doses
Chronic or recurrent neuroborreliosis (e.g., treatment failure after 2 wk of treatment)	Ceftriaxone* or cefotaxime IV as above, for 3–4 wk	

IV, intravenously; PO, orally; q8, every 8 hours; b.i.d., twice a day; t.i.d., three times a day; q.i.d., four times daily.

Modified from Ref.⁴⁹ by permission of JRCPE.

*Ceftriaxone should not be used late in pregnancy.

[†]Doxycycline should not be used in pregnant women or children under the age of 8 years.

endemic areas in warm weather months, oral antibiotic treatment might be considered prior to obtaining a convalescent serology in such a child. Similarly, this may be reasonable in a seronegative adult with bilateral facial nerve palsies, something that otherwise is quite unusual. However, even in highly endemic areas, three fourths of patients with summertime unilateral facial nerve palsies do not have Lyme disease;¹⁴ obviously, treating all of these individuals with antibiotics would be inappropriate. On the other hand, Lyme disease-related facial nerve palsies generally recover completely, even without antibiotic treatment, making immediate antibiotic treatment less urgent.

As summarized in multiple published guidelines (Table 1),^{44–46} Lyme disease is highly responsive to antimicrobial therapy, even when the nervous system is involved. Current European guidelines⁴⁷ (where there is over a half-century of experience treating neuroborreliosis with antibiotics⁴⁸) indicate that for Lyme meningitis, radiculitis, and cranial neuritis, oral treatment with doxycycline is usually sufficient. There have been no corresponding studies completed in the United States where the responsible strain of spirochete is slightly different, so oral treatment is considered a reasonable option, although the evidence remains incomplete. Similarly, there are no studies comparing oral to parenteral treatment in parenchymal CNS disease, so parenteral regimens are recommended for these uncommon patients.

It is generally assumed that oral antibiotics are sufficient for situations where disease is limited to the peripheral nervous system. CSF examination is often

recommended to detect co-occurring meningitis; however, because the European studies indicate that meningitis is also responsive to oral antibiotics, this also requires clarification. Multiple studies of extended treatment show no substantive and lasting benefit beyond that provided by standard 2- to 4-week courses, but a substantial increase in complications.^{40–42}

CONCLUSIONS

Lyme disease is a multisystem infection caused by the tick-borne spirochete *B. burgdorferi*. The nervous system is involved in 10 to 15% of infected individuals. Parenchymal CNS infection is very rare. In contrast, a toxic metabolic encephalopathy often accompanies active systemic (i.e., not nervous system) inflammatory disease (as it does in myriad other settings) and is completely nonspecific. CNS involvement is almost always marked by inflammatory changes in the CSF. Diagnostic testing (ELISAs and Western blots) is now highly accurate once the immune response develops (typically within 30 days of infection). Treatment with simple, several week-long courses of antibiotics is highly effective.

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