

# Nervous system Lyme disease, chronic Lyme disease, and none of the above

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**Abstract** Lyme borreliosis, infection with the tick-borne spirochete *Borrelia burgdorferi* sensu lato, causes nervous system involvement in 10–15 % of identified infected individuals. Not unlike the other well-known spirochetosis, syphilis, infection can be protracted, but is microbiologically curable in virtually all patients, regardless of disease duration. Diagnosis relies on 2-tier serologic testing, which after the first 4–6 weeks of infection is both highly sensitive and specific. After this early, acute phase, serologic testing should rely only on IgG reactivity. Nervous system involvement most commonly presents with meningitis, cranial neuritis and radiculoneuritis, but can also present with a broader array of peripheral nervous system manifestations. Central nervous system infection typically elicits a cerebrospinal fluid pleocytosis and, often, intrathecal production of specific antibody, findings that should not be expected in disease not affecting the CNS. Treatment with recommended courses of oral or, when necessary, parenteral antibiotics is highly effective. The attribution of chronic, non-specific symptoms to “chronic Lyme disease”, in the absence of specific evidence of ongoing *B. burgdorferi* infection, is inappropriate and unfortunate, leading not only to unneeded treatment and its associated complications, but also to missed opportunities for more appropriate management of patients’ often disabling symptoms.

## Introduction

The terms Lyme disease and Lyme borreliosis are used to describe infection with the tick-borne spirochetes *Borrelia burgdorferi*, *B. garinii* and *B. afzelii* (as well as a few more recently identified but relatively uncommon related pathogens). Although the responsible microorganisms were only identified in the early 1980s [1–3], key clinical elements of these infections were described much earlier. In both Europe and the US, early descriptions were of the virtually unique erythroderm, erythema migrans (EM) [4, 5], the slowly expanding, sometimes target-like in appearance, often asymptomatic, erythroderm occurring with a delay of days to a few weeks at the site of the bite of an *Ixodes* tick.

Although the cutaneous changes were described first, it was involvement of other organ systems that brought this infectious disease to broader medical attention. In Europe, a brief 1922 case report [6] described a sheep farmer with a very large EM following a tick bite, who then developed intractable neuropathic pain with related muscle weakness and atrophy. He had a cerebrospinal fluid (CSF) pleocytosis and a slightly positive Wasserman test, based on which the authors concluded he had a non-syphilitic spirochetal infection, treated him with arsenic (state of the art anti-spirochete treatment at the time), and he rapidly recovered (after months of unremitting symptoms). For the next 6 decades, this disease was seen predominantly by European dermatologists and neurologists and was felt primarily to be a neurologic disorder, one that as early as the 1950s was treated with penicillin [7].

In the US, the first recognized extra-cutaneous manifestation was a form of childhood relapsing large joint oligoarthritis [8]—a disorder initially mistaken for juvenile

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rheumatoid arthritis, but ultimately identified as an infectious arthritis linked to preceding bites by hard shelled *Ixodes* ticks, often with an accompanying EM. It soon became clear that US patients who developed EM also developed lymphocytic meningitis, painful radiculoneuritis and cranial neuritis [9], just like patients infected in Europe. With the identification of the causative organisms, and subsequent sub-typing, it became clear that these disorders were all caused by closely related tick-borne spirochetes known collectively as *B. burgdorferi sensu lato*. Within this family, *B. burgdorferi sensu stricto* was found to be the sole agent in the US, but also the pathogen in a minority of European cases. In Europe *B. garinii* is the most common agent in patients with neurologic involvement, while *B. afzelii* more often causes cutaneous involvement [10]. Overall US patients are significantly more likely to have joint involvement or multifocal EM, while neurologic involvement occurs in about the same 10–15 % of patients infected in either Europe or the US.

Early US studies found that, just as with syphilis, Lyme disease could cause a protracted, chronic infection. Longitudinal studies [11] identified patients clearly infected for years. Importantly, when it became evident that this was an antimicrobial-responsive spirochetal infection, patients were found to be consistently cured by standard courses of antibiotics, regardless of disease duration. Also importantly, these studies identified significant numbers of individuals with compelling serologic evidence of prior infection—but no symptoms whatsoever.

From this, several conclusions should be evident: Lyme disease is an infectious disease that, untreated, may continue for years, causing rheumatologic, neurologic and other symptoms, but is largely curable with standard courses of antimicrobial therapy, regardless of disease duration [12]. Second, although diagnosis relies primarily on demonstration of an antibody response, the presence of antibodies may represent past (and now resolved) infection in which the patient's immune response cleared the infection, without ever requiring antibiotics—an observation independently supported by the observation that for decades before the introduction of penicillin treatment of Garin-Bujadoux-Bannwarth syndrome, many European patients developed EM or this neurologic syndrome and ultimately did well, without meaningful treatment or evident sequelae.

Over the years, at least 2 factors contributed to misunderstandings about the manifestations of this potentially chronic infection—limitations in diagnostic technologies and a misinterpretation of what does—and does not—constitute nervous system involvement, or neuroborreliosis.

## Diagnosis

Because the causative microorganisms are challenging to culture from patients, clinical diagnosis has relied primarily on serologic testing. As with any evolving technology, early serologic tests were imprecise; false positives and false negatives were significant issues. Perhaps by analogy to syphilis, in which any reactivity in a reaginic assay is considered diagnostic, diagnosis has usually rested on the results of a single serologic test, rather than acute and convalescent titers, as is done with most other serodiagnosis. This approach may also have been spurred by the pragmatic need to be able to diagnose and treat a bacterial infection without waiting 4 to 6 weeks for a convalescent titer. Several early studies tried to improve on diagnosis by looking at T cell recognition [13] of *B. burgdorferi*—an approach that was ultimately found to have low specificity [14] and therefore is no longer used—but this approach led to an early focus on 'seronegative Lyme disease'. The observation that during the first 4 weeks of infection (when patients are likely to present with EM) as many as 50% of patients may be seronegative [15]—the natural consequence of the normal process by which B cells select, multiply and ultimately produce measurable quantities of specific antibodies—further fostered the notion that serologic testing overall has very low sensitivity, whereas in fact by 4–6 weeks of infection sensitivity of currently available techniques is excellent.

Problems with test specificity have been addressed by using Western blots as a second tier of testing, used primarily in patients with positive or borderline enzyme linked immunosorbent assays (ELISAs), to verify the specificity of the antibody response [16]. In the US, 10 epitopes have been identified such that patients with IgG reactivity to any 5 are highly likely to have had Lyme borreliosis. This diagnostic approach is more complex in Europe where the presence of multiple strains has made the selection of all-encompassing criteria more challenging.

Problems with interpretation remain, but primarily with specificity, not sensitivity [12]. IgM Western blots are particularly problematic. Requiring recognition of just 2 of 3 specified antigens, these are frequently misinterpreted. False positives are frequent, both because of the broad cross reactivity of all IgM antibodies, and the fact that it is statistically more likely to have chance cross reactivity to 2 of 3 antigens than to 5 of 10. Importantly since virtually all patients will develop IgG reactivity by week 4 to 6 of infection, at that point IgM results should not be relied on at all and diagnosis should be based **solely** on IgG immunoreactivity and criteria. In recent years assays for antibodies to the C6 peptide—a domain shared among the different borrelia species responsible for both European

and US Lyme borreliosis—have been found to be quite useful, and may ultimately play a role in simplifying serodiagnosis [17–19].

Serologic techniques have also proven useful in the diagnosis of central nervous system (CNS) infection. As in a number of other infections, migration of micro-organisms into the CNS leads to local production of CXCL13 [20], a B cell attracting chemokine, as a result of which B cells enter the CNS, select for those more specific for the causative organism, and then multiply, producing a relative excess of *B. burgdorferi*-specific antibody in the CSF [21–24]. Demonstration of the presence of this intrathecally produced antibody requires consideration of how much specific antibody is present in serum, and how much specific and non-specific antibody passively crosses the blood brain barrier, potentially confounding CSF assays. Since normal CSF IgG concentration is about 1–2 mg/100 mL, and since none of this is normally produced in the CNS, this antibody must be filtering into CSF from serum. Diagnostic laboratories account for this in a number of ways. Conceptually the easiest to understand involves measuring IgG in serum and CSF, diluting both to the same final IgG concentration, then measuring the amount of specific antibody in each, looking at the ratio of the results. If the amount of antibody in CSF is more than would be expected from passive transfer from serum, the ratio will be greater than 1.0.

This corrects for 2 potentially problematic situations. In patients whose serum is ‘positive’ for anti-*B. burgdorferi* antibody, a similar elevated proportion of specific antibody will enter the CSF; performing a conventional antibody assay on the CSF would correctly conclude that there is more specific antibody in CSF than in healthy controls, despite the absence of CNS infection. However, by comparing CSF to the patient’s own serum, this technique makes clear this is just a reflection of peripherally produced antibody, filtering into the CSF. The more problematic situation occurs when there is blood brain barrier breakdown for other reasons. In this situation the total amount of antibody crossing the leaking blood brain barrier is increased. Without correcting for this leakage, any CSF antibodies that bind to *B. burgdorferi*—whether that binding is specific or non-specific—will be under-diluted and therefore present in greater than expected concentration in the diluted CSF sample, resulting in higher than appropriate results and misinterpretation as evidence of intrathecally produced antibody.

Two other technical approaches are used for the same analysis. Probably the most robust is to perform capture assays, which intrinsically detect the proportion of specific antibody, eliminating several intermediate measurements and dilutions. Other laboratories use a variety of mathematical approaches—a method that is helpful but since

several of the quantities involved are non-linear functions of antibody concentration, may be less accurate.

Specificity of this approach is excellent. There is some cross reactivity in other spirochetal infections. Of these only syphilis is likely to cause actual ongoing CNS infection. Since this can usually be diagnosed with a non-specific reaginic test [rapid plasma regain (RPR), venereal disease research laboratory (VDRL), historically, the Wasserman] this is rarely an issue. The bigger challenge is that apparent excess CSF antibody may persist for a decade or more after curative treatment [25] meaning that, analogous to peripheral blood serologies, a positive test implies there has been CNS infection, but not necessarily that it is currently active or relevant. However just as in neurosyphilis, since active infection is almost always accompanied by a CSF pleocytosis, elevated CSF protein or both, these non-specific markers can be used to judge whether infection is currently active. Some studies further suggest that measurement of CSF CXCL13, though not necessarily specific for Lyme disease [26], may provide an additional useful marker of disease activity [27–29].

This diagnostic approach is useful only in patients with possible CNS infection. As with any CSF-based diagnostic technique, if infection is limited to the peripheral nervous system (PNS) and not the CNS, there is no a priori expectation of B cell proliferation within the CNS compartment, so this approach may be uninformative.

The remaining major limitation is that diagnostic sensitivity is difficult to assess, given the absence of other unambiguous diagnostic tools. The European Federation of Neurologic Societies (EFNS) has developed diagnostic criteria for neuroborreliosis that require neurologic symptoms, a CSF pleocytosis and intrathecal antibody production to diagnose definite neuroborreliosis [27]. Two of the 3 criteria are required for the diagnosis of possible neuroborreliosis. This has 2 inherent consequences: the sensitivity of intrathecal antibody production measurement is, by definition 100 %. Second, if PNS neuroborreliosis can occur in the absence of a CSF immune response, this will be excluded by definition from consideration as even possible neuroborreliosis. One US study of primarily early Lyme meningitis patients found that 13 of 15 such patients had intrathecal antibody production [30]. A second US study that included a broader range of patients found this to be present in 11 of 24 of patients [24]. Obviously this is an area in need of further study.

## Neuroborreliosis

As originally characterized, neuroborreliosis includes all or part of a clinical triad—a CSF pleocytosis, usually but not invariably lymphocyte predominant, typically with 20 to

several hundred cells/mm<sup>3</sup>; cranial neuropathy, most commonly facial nerve paresis, which can be unilateral or bilateral; and a painful radiculoneuritis, just as was described by Garin and Bujadoux [6, 9]. Of these, the meningitis may have symptoms typical of ‘aseptic meningitis’, or may be asymptomatic. Cranial neuropathy may less commonly affect the nerves to the extraocular muscles, occasionally the trigeminal or acoustovestibular, or rarely others. The radiculoneuritis may preferentially affect the dermatome that was the site of the tick bite, typically includes severe neuropathic pain and can result in muscle weakness and atrophy in the affected dermatomes.

Over the years, the spectrum of PNS involvement has expanded. Hopf [31] described patients with acrodermatitis atrophicans (an uncommon late dermatologic manifestation, described exclusively in patients infected with European strains) who had a more disseminated patchy polyneuropathy. Other series have described plexopathies and a broader range of mononeuropathy multiplex, including a confluent mononeuropathy, resembling a diffuse polyneuropathy [32, 33]. Importantly, all respond well to appropriate antibiotic therapy [33].

Although meningitis is fairly common, other forms of CNS involvement are quite rare. Children can develop increased intracranial pressure with their meningitis, causing a picture clinically identical to pseudotumor cerebri [34, 35]. Adults rarely develop parenchymal CNS involvement. Best described is spinal cord involvement at the segmental level of the radiculopathy in Garin-Bujadoux-Bannwarth syndrome. Rare patients with parenchymal brain involvement have been described as well [23, 36]. Even these forms of disease respond well to antimicrobial therapy, although if there has been irreversible structural damage in the CNS, there may be neurologic sequelae.

## Lyme encephalopathy

In the 1980s, when it was not uncommon to see patients who had had recurring episodes of Lyme arthritis for a number of years, it became apparent that many such individuals were aware of low grade cognitive and memory deficits—deficits that resolved following antibiotic treatment [23, 24]. Since these patients did not have focal CNS deficits on exam, significant abnormalities on brain imaging, or CSF findings consistent with ‘definite neuroborreliosis’ [37], it was concluded that this was likely a ‘toxic metabolic encephalopathy’—the term ‘encephalopathy’ chosen to differentiate this from brain infection or encephalitis. Unfortunately, this construct became more broadly adopted to describe patients with chronic fatigue-

like states, in the absence of anything more specific for Lyme disease.

This concept evolved into what is now termed ‘chronic Lyme disease’. In the process, four key elements were forgotten. First, the described patients had clear evidence of ongoing infection and immune activation—in most cases arthritis but occasionally other forms of end organ involvement. Second, their encephalopathic symptoms were indistinguishable from those experienced by patients with other forms of protracted infection/inflammation—be it another chronic infection or even a poorly controlled autoimmune disease. Third, by definition these individuals did not have nervous system disease. They had neurobehavioral changes, presumably mediated by circulating neuro-immune modulators, but nervous system infection was not a necessary element of this disorder. Since the possibility of brain infection and neurologic deterioration is probably the most feared of all forms of medical illness, misattributing these symptoms to a non-existent brain infection has added tremendously to these patients’ fear of what is happening to them. Finally, these symptoms, just like the symptoms associated with actual brain infection, resolved following appropriate recommended courses of antibiotic treatment. Response often was delayed for several months, but it was the expected outcome.

While some have argued that ‘chronic Lyme disease’ causes protracted difficulty requiring prolonged, aggressive antimicrobial treatment, this argument lacks both a clear basis in compelling evidence [38–41], and biologic plausibility. We know that patients with significant *B. burgdorferi* infection of the brain or other end organs almost always respond to standard courses of antimicrobial therapy [42]. Why should these patients not respond? Two arguments have been offered to explain this observation (other than the obvious one that the disorder is not caused by infection with *B. burgdorferi* or other identified microorganisms). First has been the suggestion that the disease is caused by small numbers of organisms that have concealed themselves from the host immune response—perhaps by adopting a bleb or cyst form [43], by concealing themselves in a biofilm or by otherwise limiting their interaction with the immune system. The fundamental problem with this argument is that it inherently eliminates any possible pathophysiologic mechanism. Interactions between an infecting microorganism and the host have just 2 potential mechanisms—secretion of an exotoxin by the microbe, or as a byproduct of the host immune response to the organism. Since there is no evidence *B. burgdorferi sensu lato* secretes any exotoxins, the mechanism would require the organisms’ interacting with the host immune system. If the disease model requires that a very small number of organisms are present but are concealed from

the immune system, there is no remaining pathophysiologic mechanism available.

The other argument that is offered is that symptoms relate to co-infections with other tick-borne infections, such as ehrlichia, anaplasma or babesia. The principal shortcoming of this model is that (unlike Lyme borreliosis) there is no evidence that these organisms ever cause chronic infection or symptomatology.

This unfortunately creates a great divide for patients diagnosed with Lyme disease. Those who have Lyme disease may be quite symptomatic, but if correctly diagnosed and treated with recommended regimens, can almost always expect a full recovery. Unfortunately there is a large second group of individuals who have been led to believe that their chronic and truly disabling symptoms are due to a chronic brain infection with *B. burgdorferi* and that the lack of response to treatment that should be curative is evidence of just how intractable this infection is. This misattribution of their symptoms to an infection which most of them have never had only further feeds their fear, frustration and anger at mainstream medicine, which sadly does not always have good answers for them.

## Conclusion

In both Europe and the US, Lyme disease presents a fascinating microcosm of the tension between modern evidence-based medicine and a more traditional phenomenologic approach to clinical medicine. Unfortunately the latter has led to widespread misattribution to ‘chronic Lyme disease’ of symptoms that are prevalent, potentially disabling, but not specific to any particular identified disease. Even worse from patients’ perspectives, these symptoms have been attributed to a supposed chronic, difficult to eradicate nervous system infection, a possibility that is, for most people, quite terrifying. By maintaining a rigorous, evidence-based approach both to neurologic disease in general, and to *B. burgdorferi* infection in particular, hopefully public anxiety can be mitigated, and patients offered treatment that is appropriate to their symptoms, and not potentially as deleterious as prolonged courses of unnecessary antibiotics.

**Conflict of interest** The author receives royalties from “Lyme disease – An evidence-based approach. CAB International. Oxfordshire UK. 2011”, MedLink and Up to Date, serves on the editorial boards of Neurology, The Neurologist, and Current Neurology & Neuroscience Reports, has served as an expert witness in medical malpractice suits related to nervous system Lyme disease and lectures on Lyme disease for the American Academy of Neurology and multiple academic institutions.

**Ethical approval** This article does not contain any studies with humans and animals performed by the author, but does reference

previous work published by the author, all of which was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** This paper does not report any new studies and therefore IRB approval was not needed.

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