BRAIN
REVIEW ARTICLE

Lyme neuroborreliosis: known knowns, known unknowns

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Lyme borreliosis affects the nervous system in three principal ways—mononuclear cell meningitis, cranial neuropathies and radiculoneuropathies—the last a broad term encompassing painful radiculopathy, unifocal and multifocal peripheral nerve involvement. Diagnostic tools have been significantly refined—including improved peripheral blood and CSF serodiagnostics—and much has been learned about the interactions between the causative pathogen and the nervous system. Despite these advances in our understanding of this disease, a broad range of other disorders continue to be misattributed to nervous system Lyme borreliosis, supported by, at best, limited evidence. These misattributions often reflect limited understanding not only of Lyme neuroborreliosis but also of what constitutes nervous system disease generally. Fortunately, a large body of evidence now exists to clarify many of these issues, establishing a clear basis for diagnosing nervous system involvement in this infection and, based on well performed studies, clarifying which clinical disorders are associated with Lyme neuroborreliosis, which with non-neurologic Lyme borreliosis, and which with neither.

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Abbreviations: BBB = blood–brain barrier; BCB = blood–CSF barrier; Bbsl = *Borrelia burgdorferi sensu lato*; *Bbss* = *Borrelia burgdorferi sensu stricto*; EM = erythema migrans; ITAb = intrathecal antibody production; LNB = Lyme neuroborreliosis; PNS = peripheral nervous system

Introduction

It has been 100 years since the first report describing what is now known as Lyme neuroborreliosis (LNB)—nervous system infection with *Borrelia burgdorferi sensu lato (Bbsl)*. That century-old report described a French sheep farmer who, 3 weeks after a tick bite, developed an enlarging erythematous rash, then months of severe, multifocal radicular pain with deltoid atrophy. With a CSF pleocytosis and weakly positive Wasserman it was concluded this was 'undoubtedly due to a spirochete'. Treatment with neoarsphenamine, the standard of care for neurosyphilis at the time, was followed by rapid symptom improvement.[1]

The clinical triad—various combinations of painful radiculoneuritis, meningitis and cranial neuropathy, occurring following *Ixodes species* tick bites and typically preceded by the unusual rash, erythema migrans (EM), became well known[2–5]. By the 1950s

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penicillin was shown effective.[6] In the 1970s the triad was recognized in the USA in association with newly described Lyme arthritis.[7] Following identification of the responsible tick-borne spirochetes, collectively *Bbsl*, in the 1980s, the term Lyme borreliosis came into use.

Despite advances in diagnostic tools and therapeutics, LNB remains the subject of considerable debate. Building on current understanding of LNB's pathophysiology, this review's goal will be to provide a rational approach to patients with neurological disorders in whom a diagnosis of LNB is being considered.

Epidemiology

Lyme borreliosis is transmitted among species exclusively by bites of hard-shelled *Ixodes species* ticks. Endemic regions have been slowly expanding, but infections remain most prevalent in specific geographic regions with temperate, moist climates. Most cases occur in the northeast and north central USA, Scandinavia and central Europe, particularly in exurban and suburban areas, where humans, reservoir hosts and larger animals (deer, bears, sheep—from which the local *Ixodes* sp. ticks derive their colloquial names) commingle. Four closely related *Bbsl* genospecies are responsible for most Lyme borreliosis. *B. burgdorferi sensu stricto (Bbss)* causes virtually all Lyme borreliosis in North America. In Europe *B. garinii* is the most likely to cause LNB, with additional cases attributable to *B. afzelii*, *Bbss and B. bavariensis*.

Infection occurs in a small percentage of individuals bitten by *Ixodes* ticks,[8] even where a high percentage of ticks carry *Bbsl*. Longer duration tick attachment increases risk of infection. Human data from the USA[9] indicate that at least 48 h attachment is required. Studies of the ticks and spirochetes prevalent in Europe suggest transmission may occur—both in experimental animals[10,11] and in humans[8,12]—somewhat more quickly, but infection risk similarly increases progressively the longer the attachment (>24 h).

It has long been believed that nervous system involvement is both qualitatively different and more frequent in European than US Lyme borreliosis. Expert reviews typically state that about 12% of European Lyme borreliosis patients develop LNB,[13] with individual studies ranging from 3%[14] in central Germany to 7% with 'moderate/severe neuro' involvement in Slovenia[15] to 16% in southern Sweden.[16–18] Among European patients with definite LNB, radiculoneuropathy occurs in more than half, cranial neuropathy in 40%.[19] In the USA, where Lyme borreliosis is reportable, 12.5% are diagnosed with LNB—with radiculoneuropathy in just under one-third, facial palsy in two-thirds, meningitis in ~10%.[20] In light of this qualitative and quantitative convergence of European and US LNB, an excellent European review concluded that 'the clinical picture of Lyme neuroborreliosis in North America and Europe seems to be more similar than is often assumed'.[13]

Pathophysiology of Lyme neuroborreliosis

Two factors underlie the importance of differentiating between LNB and non-neurological Lyme borreliosis. First, nervous system infections are generally more difficult to treat, and second, progressive, difficult-to-treat brain disorders are among the most feared of all illnesses.[21] Since extra-neurological infections may alter consciousness, cognition or other neurobehavioural functions, differentiating these from LNB is essential. Two mechanisms can mediate neurobehavioral effects of extra-neurological infections—nervous system entry either of bacterial exotoxins, which *Bbsl* appears to lack, or of peripherally produced cytokines. By definition, neither constitutes nervous system infection, so concerns about treatment-responsiveness are not relevant. This makes consideration of how pathogens invade the nervous system pivotal.

The nervous system is well protected by the blood–nerve (BNB), blood–CSF (BCB) and blood–brain barriers (BBB). The comparative simplicity of the peripheral nervous system (PNS) provides a useful paradigm—particularly as it is a frequent target in LNB—in both patients and experimentally infected rhesus macaques,[22] the only animal model of LNB. Peripheral nerve disease (non-LNB) generally falls into just one of three categories: demyelinating, length dependent axonal (typically reflecting neuronal failure), or multifocal with patchy axon damage. The last, mononeuropathy multiplex, generally attributable to vasculopathic processes, is virtually the only pattern seen in patients and experimental animals with PNS LNB.

Two potential mechanisms have been proposed for *Bbsl* PNS involvement—haematogenous spread[23] versus tracking along nerves from the site of inoculation.[24] In European Garin-Bujadoux-Bannwarth syndrome (GBBS) radicular symptoms often occur in the same dermatome as EM, suggesting spirochete migration along nerves.[25] Evidence against this model includes that pain often is not limited to a single dermatome[24] and the frequent involvement of anatomically dispersed nerves—e.g. patients with radiculopathy and cranial neuropathy, bilateral facial nerve palsies, or neurophysiological demonstration of multiple unrelated sites.[26] In one study no patients with EM and facial nerve palsy had EM on the face[27]; in about 30% radicular symptoms did not match the EM site. Notably, most experimentally tick-bite-infected rhesus macaques develop inflammatory changes in multiple anatomically unrelated nerves.[22]

If infection spreads haematogenously, pathogens must access nerves either as they cross the already haematogenously infected subarachnoid space, or within peripheral nerves themselves. Notably, although meningitis often co-occurs with PNS involvement, CSF has been normal in a third of patients with early LNB radiculopathy[15] (personal communication, F. Strle). CSF was similarly acellular in half[28] with early LNB facial nerve palsy (FNP). Moreover, in LNB FNP differing involvement of dysgeusia, hyperacusis or muscle function implicates varying sites peripheral to the subarachnoid space, even when CSF is abnormal.[28] Similarly, neuroimaging can demonstrate prominent peripheral involvement[29–31] (Fig. 1). Finally, neurophysiological testing, and more recently ultrasound imaging of involved peripheral nerve,[32] often indicates more disseminated peripheral nerve damage than is apparent clinically—typically indicative of damage peripheral to the nerve roots,[26,33,34] in aggregate, suggesting a mononeuropathy multiplex. If LNB meningitis, radiculopathy and cranial neuropathy can all occur independently, it appears meningeal involvement, while often co-occurring with PNS LNB, is not pathophysiologically essential.

Direct nerve infection can be best understood in terms of peripheral nerve anatomy, particularly its neurovascular unit. Nerves consist of fascicles, each with myriad axons enveloped by endoneurium, surrounded by perineurium, with fascicles bound together by a tough connective tissue sheath, the epineurium. Nerve blood supply, the vasa nervorum, originates in the epineurium, where it has fenestrated endothelium, then penetrates the perineurium, where endothelial cells become joined by tight junctions, with surrounding pericytes. Perineurial cells similarly are joined by tight junctions, together with the endothelium forming

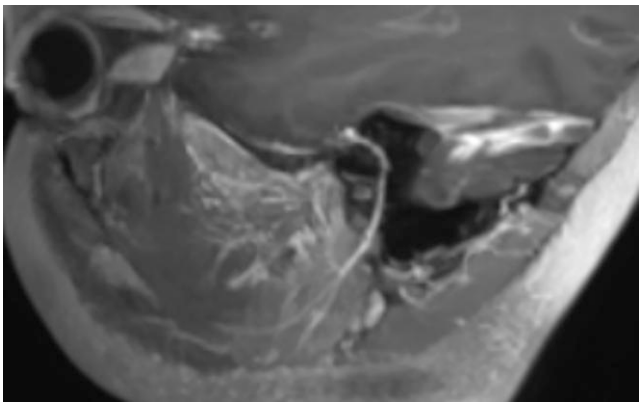

Figure 1 MRI of involved facial nerve in LNB. 3D T_1-weighted and fat saturated post-contrast image (reformatted in oblique sagittal plane parallel to the course of the nerve with 10 mm maximum intensity projection) demonstrating pathological enhancement of the right facial nerve in a patient with LNB-associated right facial palsy. Superiorly is the typical tuft of enhancement at the distal intracanalicular segment, typically evident in standard axial views in customary diagnostic imaging in early disease. The abnormal, intense enhancement of the nerve is evident as it continues first horizontally, then vertically, in the geniculate ganglion, tympanic and mastoid segments. In this case, but not in all LNB-associated facial palsies, enhancement extends extracranially into the parotid segment. Image courtesy of Dr Elisabeth S. Lindland, BorrSci study group. Sorlandet Hospital, Norway.

the difficult to penetrate BNB—a barrier with relative weaknesses at nerve terminals and dorsal root ganglia (DRG). BNB notwithstanding, most experimentally infected rhesus macaques develop a mild mononeuropathy multiplex, with nerve biopsies demonstrating the expected patchy axon loss and perivascular inflammatory infiltrates—at a minimum involving epineurial vessels. Nerve biopsies in PNS LNB,[31,35–37] while infrequently obtained, show similar changes—with epineurial perivascular inflammation; less frequently plasma cells and lymphocytic infiltrates surround endoneurial vessels.[22,33,37] Importantly, pathologic changes in sural (sensory) nerves would not be expected if damage were limited to the subarachnoid space, proximal to DRG, so, like neurophysiological findings, biopsies indicate LNB causes a mononeuropathy multiplex. Notably in neither patients nor experimental animals is there evidence of blood vessel wall necrosis—required to diagnose vasculitis. Paradoxically, although the antibiotic responsiveness of this nerve damage implicates active infection in its pathogenesis, in only one instance[31] has it been possible to demonstrate intact spirochetes in nerve. No study has demonstrated spirochete antigens or immune complexes in nerve that might directly link infection to nerve damage. A reasonable argument could be made that the absence of demonstrable spirochetes may result from sampling limitations, with very patchy nerve involvement making it unlikely that a biopsy would capture the key site. However, the demonstrated extent of nerve involvement—as seen in the facial nerve in Fig. 1, and in published ultrasound images of involved nerves[32]—suggest peripheral nerve pathology is sufficiently extensive that biopsies should be informative. A plausible inference is that infection, perhaps starting with haematogenous spread to the epineurium, triggers a local inflammatory response, occasionally extending into the endoneurium damaging the nerve itself. In sum, considerable evidence suggests LNB peripheral nerve involvement begins with haematogenous dissemination of a small number of spirochetes to the vasa nervorum, where immune amplification results in vasocentric damage to fascicles with multifocal—potentially reversible—axonal damage.

Analogously, to infect the CNS, pathogens must cross the BBB or BCB. The three-layered BBB is more formidable, with endothelial cells joined by tight junctions, surrounded by pericytes, (which can serve as microglia, 'backstopping' the endothelium), in turn surrounded by astrocytic foot processes, the glia limitans. CSF is formed primarily in the choroid plexus, principal site of the simpler BCB. Here, fenestrated vessel endothelium is immediately apposed to epithelium (CSF-facing ependyma) with these epithelial cells joined by tight junctions—a monolayer barrier. The remainder of the CSF space is lined by ependymal cells (ventricles) or pia (brain's surface), both presenting mechanical barriers but neither with tight junctions—the BBB-BCB difference perhaps accounting for *Bbsl* (like West Nile virus and other pathogens) more commonly causing meningitis than encephalitis. However, analogous to PNS epineurial perivascular inflammation, this suggests a mechanism by which pathogens, once in the subarachnoid and contiguous perivascular CSF spaces, could occasionally reach the brain from the BBB's abluminal side. In extreme instances this might explain what has been attributed to a CNS vasculitis in LNB.[38,39] Extremely rare LNB patients develop strokes, beaded changes on cerebral angiography and inflammatory CSF. No histopathological evidence has ever confirmed a true vasculitis. However, inflammation in the subarachnoid space could either directly, or through involvement of the vasa vasorum, cause large artery strokes, while a vasocentric process in the Virchow Robin spaces, analogous to that around epineurial vessels in peripheral nerve, could provide a plausible pathophysiological mechanism for small vessel strokes.

A paradox in CNS LNB is how, as in peripheral nerve, so few organisms elicit such a marked inflammatory response. *Bbsl* seeds the CNS early in acute dissemination.[40,41] In response, brain resident monocytes and microglia, likely in the CSF-contiguous perivascular spaces, produce cytokines, particularly CXCL13.[42–44] CXCL13, present in CSF in particularly high concentration in spirochetal nervous system infections,[45] then attracts B cells into the CNS. Once in the CNS, these B cells proliferate to produce *Bbsl*-specific antibodies intrathecally—providing a quite specific tool to diagnose CNS LNB. Notably, the underlying mechanism of CNS LNB is always inflammatory; considering a CNS disorder to be linked to LNB without CNS inflammation is not consistent with the known pathophysiology. Importantly, an analogous immune amplification mechanism in peripheral nerve could underlie a process by which a very small number of spirochetes could trigger significant multifocal peripheral nerve injury, similarly explaining this multifocal infectious neuropathy without demonstrable spirochetes.

Diagnostic testing

Since serum anti-*Bbsl* antibodies are usually detectable at initial LNB presentation, serology is the diagnostic test of choice.[9] To improve specificity, standard two-tiered testing (STTT)—screening samples using an ELISA or similar test, with reflex to IgM and IgG immunoblots—is recommended in the USA and many European countries.[9,46] First-tier ELISAs[47,48] use key immunodominant epitopes or antigens from relevant strains—in the USA primarily *Bbss*,[49] in Europe, multiple genospecies and regional strains.[50] When first-tier tests are positive or equivocal, IgM and IgG immunoblots are performed and interpreted according to specified criteria.[9,50] With less strain heterogeneity, US immunoblot criteria

are more stringent (Table 1). Substantially greater strain heterogeneity makes it impossible to use uniform, pan-European assays and interpretive criteria (Table 1), with assays in each region incorporating different antigens from different strains to maximize reactivity to the most relevant species. Even within one region (Table 1) different criteria may be used to accommodate the range of locally prevalent strains.[51,52] Notably, while US and European assays and interpretive criteria perform comparably with US-acquired infections, not surprisingly US assays have lower sensitivity in European-acquired infections.[53,54]

Recently the US Center for Disease Control and Prevention endorsed alternative, modified two-tiered testing (MTTT), which still retains the first-tier ELISA but replaces immunoblots with a second (sometimes third) orthogonal ELISA (or similar) (Table 1).[55,56] MTTT is at least as sensitive as STTT in early LNB, without sacrificing specificity.[57,58] Comparable efforts to develop modified criteria with European assays appear promising.[59]

As with most serologic tests, those for Lyme borreliosis have two inherent limitations when used to support the diagnosis of an active infection. Since it takes time for the host immune response to produce measurable serum antibody, infected patients may initially be seronegative—a window which in Lyme borreliosis may extend to 4–6 weeks, occasionally overlapping with the onset of LNB. While obtaining acute and convalescent-phase serological tests, as in other infections, would help address this, this cannot inform initial treatment decisions. Because of this delayed antibody detectability, both European Guidelines[60] and older US studies[28] described a small proportion of patients with early LNB having negative serum ELISAs and/or two-tier testing. Newer serological techniques, such as the first tier ELISAs described above, using key immunodominant antigens, make such initially negative serum ELISAs quite rare[61]—although occasional positive ELISAs with negative second tier tests might still occur. In such uncommon instances with non-diagnostic ELISAs or two-tier tests, diagnosis requires a high clinical index of suspicion, including careful search for an EM rash, and potentially CSF examination.

The other limitation of serological testing is that serum antibodies typically remain elevated long after resolution of infection. Consequently, a positive serological test result can only be considered evidence of past or present infection, not proof of current infection. A corollary is that serological tests following treatment provide little information about treatment efficacy—positive results do not indicate continued infection.

More unconventional methods—urine antigen capture assays, the 'LM' blood microscopy method,[62] the 'improved' serum culture method[63] or non-serological indirect detection methods (e.g. lymphocyte transformation tests, quantitative CD57 lymphocyte assays)—should be avoided as either invalidated or lacking adequate clinical validation.[64–66]

Diagnosis of Lyme neuroborreliosis

Assessment of CSF plays an important role in diagnosing CNS LNB and is required to meet European Federation of Neurologic Societies (EFNS) criteria for definite LNB[60]—with one exception. Many patients with acrodermatitis chronica atrophicans (ACA), a rare, late cutaneous manifestation seen almost exclusively in European Lyme borreliosis, have an associated polyneuropathy,[34,67] typically with normal CSF. Such individuals are considered to have definite LNB if other aetiologies of the neuropathy have been excluded and if the patient has positive two-tier testing—becoming positive at or within 6 weeks of presentation,[60] regardless of CSF findings (Table 2).

Such patients with distinct peripheral nerve disease notwithstanding, CSF exam is often of critical importance in patients with inflammatory CNS disorders, where it usually provides the only way to differentiate between LNB and other infectious or demyelinating processes. In patients in whom the differential diagnosis includes potentially more threatening meningeal or parenchymal CNS disorders, CSF examination is essential to exclude these other disorders. In individuals treated for LNB, knowledge of pretreatment CSF abnormalities can be helpful if a follow-up CSF examination is needed because treatment response appears incomplete. Crucially, when CSF is obtained the correct tests must be performed.

Direct organism detection in CSF, using nucleic acid detection or culture, has quite low diagnostic sensitivity (<20%),[9] likely due to very low spirochete numbers in CSF. With such poor negative predictive value, this is not recommended for routine use.[9] However, other CSF findings are typically informative, particularly in CNS LNB. As in all CNS bacterial infections, CNS LNB almost invariably elicits inflammatory CSF changes. Even if some aspects of LNB were to have an autoimmune aetiology (although no compelling evidence supports this), autoimmune encephalitis is also usually associated with inflammatory CSF. Consequently, individual outliers notwithstanding, if a patient's CNS disorder is to be attributed to LNB, CSF should provide evidence of an inflammatory response.

CNS LNB typically elicits a mononuclear cell CSF pleocytosis, with a modest elevation of protein and normal glucose. Particularly in European patients, overall CSF immunoglobulin synthesis is often elevated, including CSF-specific oligoclonal bands. Intrathecal synthesis of *Bbsl*-specific antibody (ITAb) is often present. Assessment of intrathecal synthesis of pathogen-specific antibodies (Fig. 2 and Tables 3 and 4)—a technique also used in other CNS infections[68]—is predicated on the assumption that the presence of a pathogen in the CNS will lead to selective intrathecal production of antibodies targeting it (Fig. 2C). If only an unpaired CSF sample is available (without matched serum), the biggest challenge in interpreting the result lies in identifying a valid 'normal' comparator. Collection of a large number of 'normal' CSF samples is impractical—and, as discussed below, problematic for other reasons. When laboratories are asked to assess isolated CSF samples, they typically can only compare results to normal serum values. Such determinations rely on the observation that, as demonstrated in Fig. 2A, a small amount of serum immunoglobulin normally enters CSF (up to 4–5 mg% IgG in CSF, 500–1500 mg% in serum) with CSF, on average, containing about 1/250th of serum IgG. Laboratories therefore typically adopt a standard CSF dilution to match this 'normal' expectation and compare the resulting CSF antibody measurement to serum normal values.

This approach has two important limitations—as would comparison to accumulated 'normal' CSF. Since antibodies of a given class and subclass should enter CSF equally, regardless of their antigenic target, seropositive patients, in whom elevated peripheral antibodies are reflected in CSF, will presumably all have 'positive' CSF results—reflecting passive antibody entry, not local synthesis (Fig. 2A). On the other hand, in seronegative patients with increased BBB/BCB permeability (Fig. 2B), there will be disproportionate entry of all peripheral IgG. In this setting, measurement of pathogen-specific CSF antibody, without correction for the overall increase in immunoglobulin, will reflect the excess of all antibodies, with the increase in non-specific background reactivity causing apparent specific antibody excess—even when no

Table 1 European and US serological two-tiered testing algorithms

	First tier test	Second tier test	Immunoblot interpretive criteria for a positive result	
			IgM	IgG
European STTT *One example of immunoblot criteria*[51]	ELISA (total antibody or separate IgM + IgG)	IgM, IgG immunoblots	*B. afzelii*: ≥1 of p39, OspC, p17 or a strong p41 *B garinii*: ≥ 1 of 39, OspC or a strong p41	*B afzelii*: ≥2 of p83/100, p58, p43, p39, p30, OspC, p21, p17, p14 *B garinii*: ≥1 of p83/100, p39, p30, OspC, p21, p17b
US STTT	ELISA (total antibody or separate IgM + IgG)	IgM, IgG immunoblots	≥2 of the following three bands must be present: 24 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla). Positive results are disregarded if signs or symptoms present for >30 days.	≥5 of the following 10 bands must be present: 18 kDa, 21 kDa (OspC), 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa
US MTTT[56]	ELISA (total antibody)	Orthogonal ELISA (total antibody or separate IgM + IgG)	NA	NA

IgM = immunoglobulin M; IgG = immunoglobulin G; STTT = standard two-tiered testing; MTTT = modified two-tiered testing, using two or more separate ELISAs that are sufficiently different from one another in their antigenic constituents or assay principles that using them together improves specificity compared with the individual tests ('orthogonal'); NA = not applicable .

Table 2 European Federation of Neurological Societies criteria for LNB[67]

Compatible neurological symptoms (Table 3)
CSF pleocytosis
Intrathecal production of *Bb* specific antibody
Definite LNB: 3/3[a]
Possible LNB 2/3[b]

Bb = *Borrelia burgdorferi sensu lato*, using antigens appropriate to that region in standard immunoassays.
[a]In European late LNB with peripheral neuropathy, considered definite if acrodermatitis chronica atrophicans (a unique cutaneous change, not described in North American patients) and positive peripheral blood serology.
[b]If no ITAb, positive serum IgG two-tier testing by 6 weeks after onset.

Bbsl-specific antibody at all is present. To avoid such errors, comparing the 'proportion' of CSF and serum antibodies specific for *Bbsl* is essential—with demonstration that the proportion of specific antibodies is greater in CSF providing compelling evidence that that pathogen has been present in the CNS.

Several methods are used for this (Table 4), each with strengths and weaknesses. Widely used in Europe[69] and in some major US labs[70] is the Reiber formula. For this, CSF and serum albumin and immunoglobulin concentrations are quantitated, pathogen-specific antibody is measured in both at standard dilutions, then the albumin and immunoglobulin concentrations are used to mathematically correct for multiple variables that affect their CSF concentrations, producing a calculated specific antibody index (AI). Perhaps the most technically elegant approach, and requiring the least CSF, is a capture assay[71] which directly measures the proportion of total antibody in CSF and serum that is specific for the target antigens. A third approach, like the Reiber method, starts by measuring CSF and serum immunoglobulin concentrations, but then dilutes both fluids so post-dilution immunoglobulin concentrations are identical, and then performs pathogen-specific ELISAs on both[72]—an approach developed to circumvent the non-linear relationship between antibody concentration and the measured pathogen-specific ELISA result. Although one very small study suggests the capture method may be more sensitive,[73] no large systematic study has compared methods—and the capture assay is no longer widely commercially available. Moreover, procedures have not been standardized; none is US FDA cleared.[70]

Regardless of technique, ITAb measurement provides a useful diagnostic tool—although precise estimates of its sensitivity and specificity are limited by the absence of alternative reference tests for comparison. However, in any patient with elevated overall intra-CNS immunoglobulin synthesis (oligoclonal bands, increased IgG synthesis rate) if this increase is due to LNB there should be evidence that much of that overall immunoglobulin directly targets *Bbsl*.

Notably, presumably because of lower background CSF IgG concentration, ITAb can sometimes be detectable before a patient is seropositive, providing a potential diagnostic tool in very early LNB. However, like peripheral blood serologies, ITAb can remain elevated years after successful treatment, similarly limiting its utility in differentiating active from past infection.[74] However, if CNS LNB is active other CNS inflammatory changes should be evident (Table 3).

Finally, immunoblots can be performed on CSF—but are not recommended.[9,70] As with measurements of ITAb, these would need to be performed on CSF and serum concurrently, with appropriate adjustment for overall antibody concentration in both. Since interpretation of individual bands is typically not quantitative, arithmetically correcting for differences in total antibody concentration is not possible. If a standard compensatory CSF dilution is used, this will be susceptible to the same limitations as in ITAb assessment. If total antibody concentrations are measured and dilutions adjusted accordingly (rarely done in clinical laboratories) the required multiple non-standardized steps will potentially introduce technical errors in a procedure that is quantitatively imprecise to begin with.

Measurement of CSF CXCL13—although not yet widely available—may also prove informative. Assay techniques and normal value ranges have not yet been standardized, limiting clinical utility at this point. However, this cytokine is often elevated in CNS inflammatory disorders,[75,76] particularly so in CNS spirochaetal infections.[77,78] While it lacks specificity, it is almost always quite elevated early in CNS-involving LNB, providing excellent negative predictive value. Moreover, it decreases quickly with successful antimicrobial therapy, making it one of the few objective markers of treatment efficacy (although its concentration parallels CSF leucocyte count and IgG synthesis[76]).

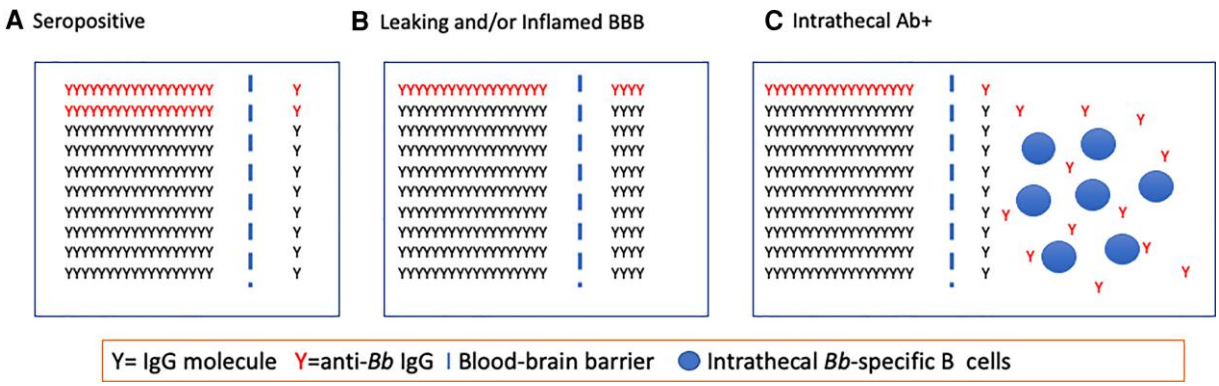

Figure 2 Intrathecal antibody concentration. Cartoon comparing CSF to serum immunoglobulin concentrations. (Serum to the *left* of the BBB, CSF to the *right*). In the normal state (**A**), a small amount of serum immunoglobulin enters CSF. CSF antibody is increased (**B**) with increased BBB/BCB permeability, such as in stroke, demyelinating disease or (**C**) with increased synthesis of targeted antibody in response to a specific pathogen within the CNS. When testing CSF in isolation, without comparison to that patient's serum, laboratories typically use a standard CSF dilution (e.g. 1:1) establishing an IgG concentration approximating that in diluted serum (typically diluted 1:500). Values are then compared to serum normal controls. (**A**) In seropositive patients with normal BBB/BCB permeability, this will result in falsely 'positive' results, reflecting passive entry of excess serum anti-*Bbsl* antibodies. (**B**) If, for any reason, BBB/BCB permeability increases, the total amount of CSF IgG will be increased. Unless a correction is made for this, measurements of any specific antibody will similarly be increased, again giving false positive results. (**C**) CNS infection with *Bbsl* leads to in-migration of B cells that synthesize *Bb*-specific antibody. After appropriately accounting for non-specific entry of all IgG into the CNS, measurement allows demonstration of the ITAb.

Clinical

General

The earliest sign of *Bbsl* infection is typically EM, usually developing days to weeks after infection, in contrast to the virtually immediate local allergic reaction to tick saliva. EM represents an inflammatory reaction to local spirochete proliferation and centrifugal migration. Typically 5+ cm in diameter EM expands day by day, often to an impressive size, despite which it is often asymptomatic. Consequently, it may go unnoticed if in difficult to visualize anatomic locations. Infection may remain localized or may disseminate—the latter often accompanied by typical systemic symptoms of infection—arthralgias, myalgias, headache. Dissemination may lead to multiple secondary EMs—each recapitulating the evolution of the initial one. Cardiac involvement is infrequent[20] (~1%) but can result in symptomatic heart block. Untreated patients may subsequently develop Lyme arthritis—particularly with *Bbss*.

Neurological manifestations

In both Europe and the USA, the most common presentations involve various combinations of lymphocytic/monocytic meningitis, cranial neuropathy and radiculoneuritis (Tables 2 and 3), typically occurring early in infection. Meningitis symptoms vary widely, from minimal, to severe headaches with photosensitivity and neck stiffness. Facial nerve involvement represents 80% of cranial neuropathies and can be bilateral—concurrently or in rapid succession. Radiculoneuropathy classically causes severe, dermatomal neuropathic pain, comparable to that seen in mechanical, diabetic or zoster radiculopathies. Sensory symptoms often extend beyond a single dermatome; muscle weakness and atrophy may develop in the affected nerve distribution. PNS involvement can include brachial or lumbosacral plexopathies, more localized mononeuropathies or a mononeuropathy multiplex.

Reported frequencies of neurologic manifestations vary among different populations. In the USA, ~60% of diagnosed LNB patients develop facial palsy, 30% radiculoneuropathy, 10% isolated meningitis.[20] In Europe, among adults, frequencies of facial palsy and radiculoneuropathy are the reverse[61]; in children[79–82] headache is the most frequent symptom, FNP the most common finding (46%), radiculoneuropathy very infrequent. Long term prognosis appears to be comparably favorable in adults and children.[81] A particular concern, primarily in children, is that LNB can cause a pseudotumour cerebri-like picture. Most such patients have a CSF pleocytosis,[83] suggesting a pathophysiology different from idiopathic intracranial hypertension; however severe visual impairment can ensue, so recognition and specific treatment are essential. Overall incidence of LNB[84] appears to have declined in recent years, at least in Denmark, perhaps reflecting earlier Lyme borreliosis recognition and treatment, more accurate LNB diagnosis, or both.

European patients may develop a late cutaneous manifestation, ACA, diagnosed rarely if ever in North America, while US patients more frequently develop frank arthritis—differences attributed to differing *Bbsl* strains. Patients with these late extraneurological manifestations may develop a more indolent and disseminated mononeuropathy multiplex, often with normal CSF[36,60] exemplifying a common diagnostic challenge. While PNS involvement accompanied by inflammatory CSF can readily meet criteria for possible or definite LNB (Table 2), given the high prevalence of seropositivity in endemic areas[36,85,86] seropositive patients with PNS disease and normal CSF must be diagnosed based on other, more characteristic features such as ACA, facial palsy, or otherwise unexplained radiculoneuropathy following an identified tick bite or EM. In such circumstances treatment for LNB may be reasonable, but as always, appropriate alternative diagnoses must be carefully considered, to avoid misattributing a neuropathy to incidental, irrelevant seropositivity.

Finally, parenchymal CNS involvement occurs infrequently—primarily a myelopathy at the involved root level in GBBS. Described as occurring in about 4%[61,87] of European LNB, a recent study found it in just 1/134 patients with definite LNB.[19] Regardless of frequency, since parenchymal CNS involvement represents an infectious myelitis or encephalomyelitis, CSF should be consistently diagnostic. Diagnosing parenchymal CNS LNB absent CSF inflammation and ITAb is problematic.

Table 3 Suggested testing algorithms in Europe and the USA

	Europe	USA
	Plausible exposure	
Clinical signs/symptoms	Meningitis, cranial neuritis, painful radiculoneuritis, mononeuropathy, plexopathy, mononeuropathy multiplex; rarely myelitis or other parenchymal CNS inflammation	
Recommended testing		
Serum	STTT[a]	STTT or MTTT[a]
CSF		
If strong clinical suspicion		
First tier (ELISA) negative	Yes	Yes
First tier (ELISA) positive or borderline	Yes	Yes – if parenchymal CNS inflammation else optional – particularly to exclude other diagnoses
CSF testing		
CSF/serum *Bb* antibody index[b]	Yes	Yes
CSF *Bb* antibody alone	No	No
CSF PCR or culture for *Bb*	No	No
CSF western blot	No	No
CSF cells, protein	Yes	Yes
CSF IgG synthesis	Reiber calculation	IgG index or synthesis rate
Oligoclonal bands	Yes	May be informative

[a]STTT/MTTT = standard and modified two-tiered testing (Table 1).
[b]Antibody index, see Table 2.

CNS disorders without CNS inflammation

Lyme encephalopathy

There is likely nothing related to Lyme borreliosis that has provoked more controversy than 'Lyme encephalopathy'. First described in patients with active infection, this was originally conceptualized as the same cognitive and memory difficulty seen in patients with other systemic, non-neurological infectious and inflammatory disorders.[88] This is rarely associated with CNS *Bbsl* infection or inflammation—by MRI or CSF—including the absence of identifiable CSF cytokine abnormalities.[45] Recent observations suggest an association with peripheral activation of Th17-related cytokines,[45] a pattern also seen in antibiotic-resistant, presumably immune-mediated Lyme arthritis[89] and suggested in neuromyelitis optica[90] and multiple sclerosis.[91] Whether this association is in any way specific, related to any other post-treatment symptoms, or more broadly informative remains to be seen.

Unfortunately, this symptom complex has become the major construct underlying 'post-treatment Lyme disease symptoms' (PTLDS), which similarly has been broadly misconstrued as evidence of a chronic brain infection—despite overwhelming evidence to the contrary. This has created a level of fear about 'nervous system Lyme disease' that underlies much of the public concern about Lyme borreliosis.

When can atypical manifestations be attributed to Lyme neuroborreliosis?

Establishing causal relationships between other neurological disorders and LNB requires both compelling systematic data and biological plausibility. An important (Bayesian) limitation of serodiagnostic testing is that positive predictive value depends on its only being used in appropriate settings[9] (Table 3)—i.e. in individuals without plausible exposure false positives may well exceed true positives. Moreover, high background seropositivity (13+%) in some populations[85,86] makes coincidental seropositivity an important confounder. Importantly, given LNB's pathophysiology, association of CNS disorders without CNS inflammation is inherently unlikely.

Neurodegenerative diseases

A population-based study[92] using the administrative database incorporating all Danish medical records from 1995 to 2015 compared the 2067 patients with *Bbsl*-specific ITAb to 20 687 age and sex-matched controls, finding no increased incidence of dementia, Alzheimer's disease, Parkinson's disease, motor neuron disease, epilepsy or Guillain-Barre syndrome among those with ITAb. A prospective 6-year study of 689 French farmers, aged 65 and over,[93] found no higher incidence of cognitive or functional decline among seropositive individuals. A study comparing 491 Dutch patients with amyotrophic lateral sclerosis (ALS) to 982 matched controls found no association between ALS and anti-*Bbsl* antibodies.[94] Of 414 ALS patients seen at Massachusetts General Hospital, four had positive two-tier testing. Ceftriaxone treatment in two had no effect.[95] Importantly, there is no geographic correlation between ALS and Lyme disease in the USA.[96]

This notwithstanding, rare patients with neurodegenerative disorders have been hypothesized to have the disorder as a result of Lyme borreliosis, been treated with antibiotics, and appeared to improve clinically. Of 1594 patients with dementia screened serologically for Lyme borreliosis, 38 were found to be seropositive. CSF was examined in 34/38. CSF ITAb was elevated in 20—notably in none was there a CSF pleocytosis, suggesting the ITAb reflected past, not currently active infection. Following treatment,[97] seven (0.4%) 'stabilized or improved slightly' and were felt to have Lyme dementia; the possibilities of this being an infection temporarily worsening an underlying dementia, or more likely, that this reflected prior, unrelated infection, were not discussed. Balancing these anecdotal observations against the strong epidemiological data, a relationship appears highly unlikely.

Table 4 Available methods of determining antibody index

	Reiber[a]	Capture ELISA	Standard ELISA
Samples			
CSF, serum, within a day	Yes	Yes	Yes
Measure			
Total CSF and serum [IgG] (other classes if needed)	Yes	No	Yes
Total CSF and serum [albumin]	Yes	No	No
Bb specific IgG (other classes if needed)	Yes	Yes	Yes
Technical:			
Measure (each measure requires additional CSF)	CSF and serum [IgG], [albumin], [IgG(*Bb*)] *Bb* ELISAs at standard dilutions	Proportion CSF IgG specific to *Bb* Proportion serum IgG specific to *Bb*	CSF and serum [IgG], [IgG(*Bb*)]. Dilute serum, CSF to same final [IgG] and *Bb* ELISAs on both
	Optional: same for IgA, IgM	Optional: same for IgA, IgM	Optional: same for IgA, IgM
Calculations	AI = $Q(Bb)_{IgG}/Q_{IgG}$	AI = $([IgG(Bb)_{CSF}]/[[IgG_{CSF}])/([IgG(Bb)_{ser}]/[[IgG_{ser}])$	AI = ratio of *Bb* ELISAs
Advantages			
Volume of CSF needed	More	Least	More
Adjust for age, site CSF obtained	Yes	No	No
Adjust for very elevated total Q_{IgG} relative to $Q_{albumin}$	Yes, including replacing Q_{IgG} with a maximum Q_{Lim} when overall intrathecal IgG synthesis ($Q_{IgG} > Q_{Lim}$)	No	No
Technical concerns	Non-linear relation of ELISA value to concentration may distort at extremes; normative data with logarithmic relationships, potentially distorting at extremes	Assay more difficult to create	Measurements of IgG, albumin and subsequent dilution susceptible to error

AI = antibody index; [IgG] = concentration of IgG; [IgG] = total IgG; [IgG(*Bb*)] = IgG specific to *Bbsl*, using antigens relevant to geographic region; Q = ratios of [IgG] etc. in CSF to serum, both total and *Bb* specific; $Q_{IgG} = [IgG_{CSF}]/[IgG_{serum}]$; $Q(Bb)_{IgG} = [IgG(Bb)_{CSF}]/[IgG(Bb)_{serum}]$; $Q_{Albumin} = [Albumin_{CSF}]/[Albumin_{serum}]$
In capture assays, the single immunoassay readout is the proportion of immunoglobulin specific to the test antigen e.g. $IgG(Bb)_{CSF}]/[[IgG_{CSF}]$ without a need to determine the two individual values.
[a]Widely used in Europe[69] and some laboratories in the USA.[70]

Psychiatric disease

A study using the above-described records of all 2067 Danes with ITAb, combined with the national health database[98] found psychiatric diagnoses and hospitalizations to be no more frequent in patients with definite LNB. A second study of the same population dataset[99] (not incorporating ITAb data) concluded psychiatric disorders were more frequent in Lyme borreliosis (not LNB) generally [incidence rate ratio (IRR) 1.28, 95% confidence interval (CI) 1.20, 1.37]—but failed to point out that earlier work with the same database[100,101] found an even greater increase in psychiatric diagnoses with 'any' infection (IRR 1.62; 95% CI, 1.60–1.64) or autoimmune disorder (IRR 1.45; 95%CI, 1.39–1.52). Notably, when the Lyme borreliosis analysis was limited to the 12 616 patients administratively coded as LNB[99]—explicitly not based on ITAb—there was no increase in psychiatric diagnoses. Consistent with this, among 517 patients undergoing acute psychiatric hospitalization in an endemic area just one had a positive Lyme ELISA—but negative western blot.[102]

An often-cited study used multiple assays to compare 926 newly hospitalized psychiatric patients to 884 healthy control subjects.[103] Psychiatric patients were more likely to be positive in at least one of four assays, but two-tier testing was more frequently positive in healthy controls. Abnormal results in psychiatric patients were due entirely to unconventional tests. A second study of the same population[104] found no specific psychiatric diagnosis disproportionately represented among either seropositive or seronegative patients.

MRI abnormalities

LNB may occasionally cause focal areas of brain inflammation, visualizable on MRI.[105,106] However, it has become commonplace to suggest an association between non-specific white matter (NSWM) MRI abnormalities and this infection. Two controlled studies, with <100 LNB patients,[107,108] found no difference in NSWM abnormalities compared to control subjects. A third, population-based study found MRI useful primarily to exclude other diagnoses.[109] No larger studies have been published but this association with a non-specific finding lacks biological plausibility. Recent US guidance recommends against including Lyme borreliosis in the differential diagnosis of such MRI findings.[9]

Treatment

As in any nervous system infection, treatment requires organism-appropriate antimicrobials. Recommendations differentiate parenchymal (brain, spinal cord) CNS infection from all others. Parenteral treatment is recommended for the very rare parenchymal infections, not based on evidence but because other parenchymal CNS infections generally require such treatment to achieve

therapeutic CNS concentrations. For all other LNB, choices include intravenous ceftriaxone, cefotaxime or penicillin G or oral doxycycline[9,60] for 14–21 days, with oral and parenteral regimens considered equally effective.

Although extensive evidence supports such treatment in clear-cut LNB, questions often arise when patients with other neurological or psychiatric disorders are found to have positive two-tier test results. Such patients raise two distinct questions: (i) do the benefits outweigh the risks of treating this particular patient for possible Lyme disease and, if so, how much treatment would be appropriate; and (ii) is a pathophysiological link between Lyme borreliosis and this neurological disorder plausible?

As detailed above, in CNS disorders without CNS inflammation, CNS LNB is extremely unlikely and aggressive antimicrobial treatment is usually not warranted. PNS involvement without CSF inflammation can be more challenging. If there is other evidence of Lyme borreliosis (EM, ACA, Lyme arthritis) recommended treatment regimens are reasonable. In less clear-cut instances this decision must consider the risk of misdiagnosis, of side effects and concerns about promoting antimicrobial resistance.

Symptoms occurring following treatment for Lyme borreliosis

The symptom complex, in other situations summarized under the rubric 'medically unexplained symptoms' (MUS), typically including combinations of fatigue, sleep disturbance, perceived memory and cognitive difficulty, multifocal pain, and other highly disruptive symptoms, causes significant impairment in up to 2% of the general population at any given time, with lesser impairments in substantially more.[110,111] These symptoms have been described with some frequency in patients who have been treated for Lyme borreliosis,[112] leading to the construct PTLDS.

Studies of symptoms following actual LNB are reassuring. The above-cited study of the 2067 Danish patients with definite LNB[113] (Table 2, EFNS criteria), found no evidence of long-term adverse effects on functioning. A systematic review of prior controlled LNB treatment trials,[114] stratifying patients as having definite, probable or possible LNB,[60] found residual symptoms were significantly more frequent in patients without CSF findings of definite LNB[114] and found no patients treated for definite LNB experienced persistent fatigue. A study of 58 Norwegian patients with LNB found none developed cognitive symptoms in the 12 months following treatment.[115] These studies, taken together, support the conclusion that such post-treatment symptoms are not related to CNS infection, a conclusion further supported by treatment trials of additional antimicrobials, which have consistently failed to demonstrate any persisting benefit, while incurring significant treatment related morbidity,[116–120] particularly with unconventional, prolonged regimens. Notably, one retrospective uncontrolled study of 139 definite LNB patients found residua in about one-quarter[19]; this included both residua of initial neurological deficits and of subjective symptoms. Prior work from this group suggests objective residua (pareses etc.) figured prominently.[27]

To address the possibility that these symptoms, in isolation, reflect extra-CNS *Bbsl* infection, it is helpful to estimate their positive predictive value for Lyme borreliosis. Using often cited extreme estimates that up to 23% of Lyme borreliosis patients develop these symptoms after treatment[121] and that the USA has up to 440 000 Lyme borreliosis cases annually,[122] the symptoms' positive predictive value would be just 1.5%—i.e. a Lyme borreliosis diagnosis based on these symptoms alone would be wrong at least 98.5% of the time.

Multiple studies suggest persistent post-treatment symptoms occur at similar rates in Lyme borreliosis and controls.[123–128] Two—totalling almost 4500 patients[129,130]—found no association between such symptoms and IgG Lyme borreliosis seropositivity.[131] Another, comparing 1786 predominantly EM patients to separately collected controls found persistent symptoms to be somewhat more common in patients[132]—a finding potentially explained by patient expectations,[133] as a large, randomized treatment trial found the best predictors of recovery without late symptoms were initial expectation of recovery and belief that treatment was with antimicrobials, not placebo.[133] As emphasized in the updated US guidelines[134] the comparable rates of this symptom complex in Lyme borreliosis patients and controls raises 'the possibility that this phenomenon, in whole or in part, may represent anchoring to a recent diagnosis of Lyme disease.' In sum, the data regarding the likelihood of persistent symptoms in extra-CNS disease suggest a frequency comparable to controls, although a slight increase might be possible. However, the absence of an association with LNB appears clear.

Recently updated US,[9] German[61] and French[46] clinical guidelines all recommend against additional antimicrobials in such patients, highlighting risks of prolonged treatment—risks including not only the complications and costs of prolonged administration of unnecessary antimicrobials but also the risk of delay in correct diagnosis[135] in patients who are seeking help with disabling symptoms[136]—symptoms which may have been incorrectly attributed to ongoing or, worse, 'chronic' Lyme disease.

Conclusions

The goal of this paper has been to facilitate a common foundational understanding of LNB. Key to this is appreciating what does, and does not, constitute nervous system disease. As should be clear, it is highly unlikely that *Bbsl* infection causes neurodegenerative disorders—particularly in the absence of any evidence of CNS inflammation. A causal relationship with MUS or psychiatric disorders[114,125,137,138] seems highly unlikely—although becoming ill with inflammatory or infectious disorders in general might precipitate or aggravate symptoms of such disorders in individuals otherwise predisposed to them—i.e. this might reflect a class effect, true of any infection. Many questions remain. By what mechanism do spirochetes reach the nervous system? If a very small bacterial load triggers LNB, by what amplifying mechanism does this occur? Does this suggest other, non-antimicrobial interventions? Might this inform treatment of other infections? And if post-infectious symptoms occur, what is the pathophysiological mechanism and might this explain other post-infectious states? Hopefully the framework provided here will allow more focus on these fundamental questions.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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