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Lyme Neuroborreliosis: Current Insights into Diagnosis and Management – A Narrative Review

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Abstract

Introduction and purpose: Lyme neuroborreliosis is a neurological manifestation caused by *Borrelia burgdorferi* infection, characterized by a wide range of clinical symptoms. The purpose of this narrative review is to provide an overview of this condition, focusing specifically on current challenges in diagnosis, neuroimaging and treatment. A comprehensive literature search was conducted across databases spanning the years 2015–2026. This review focuses on current international guidelines, meta-analyses of diagnostic parameters, as well as pivotal studies on advanced neuroimaging and the management of Lyme neuroborreliosis.

Description of the state of knowledge: Definitive diagnosis is often complicated by the limited early sensitivity of standard two-tiered serology. While the intrathecal antibody index (AI) remains the European diagnostic "gold standard," it may yield false-negative results in a proportion of early cases. The B-cell chemoattractant CXCL13 has emerged as a highly sensitive biomarker for early neuroinflammatory infection, often preceding the humoral response. Conversely, PCR exhibits restricted clinical utility due to its low sensitivity. Neuroimaging frequently reveals cranial nerve enhancement, while 3.0T proton magnetic resonance spectroscopy can detect subclinical metabolic dysfunction, such as reduced N-acetylaspartate levels, in radiographically normal brain tissue. Management necessitates antibiotics with high central nervous system penetration.

Summary: The long-term prognosis for LNB is generally favorable with prompt intervention. However, Post-Treatment Lyme Disease Syndrome (PTLDS) develops in a subset of patients, who suffer from persistent fatigue, "brain fog" and musculoskeletal pain despite the resolution of active infection. Managing these persistent symptoms remains a clinical challenge, as they significantly impact the quality of life despite successful spirochetal eradication.

Key words: Lyme neuroborreliosis, *Borrelia burgdorferi*, CXCL13, Bannwarth syndrome, facial nerve palsy, magnetic resonance spectroscopy.

Introduction and purpose

Lyme neuroborreliosis (LNB) is defined as a complex disseminated neurological manifestation of Lyme borreliosis (LB), a multisystem zoonotic infectious disease caused by spirochetes of the *Borrelia burgdorferi* sensu lato complex [1, 23]. Transmitted to humans via the bite of infected *Ixodes* ticks, LNB develops in approximately 10% to 15% of symptomatic *Borrelia* infections [4, 7, 12, 23].

In clinical practice, LNB is chronologically classified into early and late stages based on a six-month symptom duration threshold [5, 22, 24, 37]. Early LNB accounts for more than 95% of cases and typically manifests as meningitis, cranial neuritis (most frequently facial nerve palsy), or painful radiculoneuritis [7, 12, 16, 22, 34]. In contrast, late LNB is an exceedingly rare entity, occurring in approximately 2% to 5% of cases [1, 10]. The neurological deficits associated with late stages, such as spastic paraparesis, ataxia, and cognitive impairment, often develop insidiously over months or years [16, 31, 43].

Achieving a definitive diagnosis remains a significant clinical challenge due to the heterogeneity of presentations [1]. A critical dilemma arises from the fact that only 40% to 50% of patients recall a tick bite, and the pathognomonic erythema migrans (EM) rash is absent or unrecognized in 50% to 75% of LNB cases [1, 10, 16]. Furthermore, two-tiered serological testing exhibits limited sensitivity in the early phase of infection-often between 30% and 40%-as the IgM and IgG antibody response may take several weeks to reach detectable titers [13, 15, 41]. While the intrathecal antibody synthesis (antibody index) is considered the diagnostic "gold standard" in Europe, it may remain negative in approximately 20% of acute cases during the first six weeks of symptoms [24, 33].

The clinical importance of early LNB recognition is further emphasized by surveillance models, which suggest a potential increase in incidence that may be influenced by climate-driven changes in tick survival and geographic expansion [37, 38, 45]. Early identification is essential to initiate timely antibiotic therapy, which is generally associated with a favorable prognosis and the regression of neurological symptoms in a majority of cases [7]. Diagnostic delays or the misidentification of symptoms may lead to unnecessary medical interventions, such as the administration of intravenous immunoglobulins for LNB cases mimicking Guillain-Barré syndrome [1, 7, 38].

The purpose of this narrative review is to provide an overview of this condition, focusing specifically on current challenges in diagnosis, neuroimaging and treatment.

Etiology and Epidemiology of Lyme Borreliosis

Lyme borreliosis (LB) is caused by Gram-negative spirochetes belonging to the *Borrelia burgdorferi* sensu lato complex [25, 35, 37].
Microbiologically, these spirochetes are obligate parasites with limited metabolic capacity, lacking genes for the tricarboxylic acid cycle and relying exclusively on glycolysis for energy production [27, 28, 41]. Consequently, they are highly dependent on the host for essential nutrients, including lipids, amino acids, and nucleotides, which are acquired via broad-substrate membrane transporters [27, 41].

The *B. burgdorferi* sensu lato group encompasses more than 20 genospecies, of which at least six are pathogenic to humans [25, 27, 37]. Significant clinical heterogeneity is driven by these genospecies: *Borrelia burgdorferi* sensu stricto is the near-exclusive cause of LB in North America and is particularly arthritogenic, whereas European cases are predominantly driven by the neurotropic *Borrelia garinii* and the dermatotropic *Borrelia afzelii* [26, 27, 30, 41].
Lyme borreliosis is the most prevalent vector-borne infection in the northern hemisphere, with endemic regions spanning North America, Europe, and Asia [8, 13, 36]. In Poland, LB has been subject to mandatory surveillance since 1996, and the incidence of the disease is steadily increasing [35, 37]. In 2023, a total of 25,285 cases of LB were registered, representing a 45.6% increase compared to the previous year . The overall incidence in 2023 reached 67.1 per 100,000 inhabitants, with typical seasonality peaking in the third quarter (July–September). While the Podlaskie voivodeship (96.0 per 100,000) has traditionally been the most endemic region, the highest incidence in 2023 was recorded in the Małopolskie voivodeship at 122.9 per 100,000. Lyme neuroborreliosis (LNB) accounted for 1.83% of all Polish LB cases in 2023, yet it constituted 38.99% of all bacterial meningitis and encephalitis cases reported nationally. The most common species identified in Poland is *B. afzelii* [35].

The geographic range of LB is expanding northward and to higher altitudes due to climate change, which promotes tick survival during milder winters and accelerates the maturation of *Ixodes* vectors [13, 15, 37]. In Europe, *Ixodes ricinus* is increasingly found in urban green spaces, gardens, and parks, shifting the risk from purely rural to peri-urban environments [13,

15, 24]. Surveillance models project that the incidence of LB will increase by more than 20% in the coming decades as favorable conditions for tick proliferation continue to expand [7, 37, 38].

Pathophysiology and Pathology of Lyme Neuroborreliosis

Intrathecal Inflammatory Cascade and Cytokine Profiling

The clinical manifestations of LNB are primarily driven by the host's inflammatory response rather than direct spirochetal toxins [4, 30]. This response is orchestrated by lymphocytes, alongside CNS-resident cells such as microglia, astrocytes and oligodendrocytes. Among the inflammatory mediators, the B-cell chemoattractant CXCL13 is particularly notable; it is produced by mononuclear cells and reaches high concentrations in the CSF early in the infection, often before the development of intrathecal antibody synthesis [4, 16, 18]. Anti-inflammatory modulators like IL10 are subsequently induced to resolve this initial pro-inflammatory surge [4].

Mechanisms of Neuronal Loss and Mitochondrial Dysfunction

Neuronal injury in LNB occurs through both direct and indirect pathways. Direct mechanisms involve the adherence of *B. burgdorferi* to neural and glial cells, which can trigger glial and neuronal apoptosis. Indirect injury is mediated by the release of neurotoxic cytokines, such as TNF-α and IL-6, from activated microglia [40]. Pathological studies in nonhuman primate models and human case reports have demonstrated diffuse demyelination, astrocytosis, and microgliosis [31, 40]. Advanced diagnostic tools like proton magnetic resonance spectroscopy (1H-MRS) at 3.0T have revealed a statistically significant decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the frontal lobes of LNB patients, even in areas appearing normal on conventional MRI [40].

Peripheral Nervous System Pathology

In the peripheral nervous system (PNS), pathogenesis involves interstitial lymphoplasmacytic infiltration forming clusters around epineurial and perineurial capillaries. Spirochetes may be harbored by macrophages, leading to the degeneration of perineurial cells and increasing the permeability of the blood-nerve barrier. This local production of inflammatory and cytotoxic mediators results in multifocal axonal loss of the nerve roots and distal segments [5].

Classification of Neuroborreliosis

Early Lyme Neuroborreliosis

Early Lyme neuroborreliosis (LNB) develops within the early disseminated stage of infection, typically manifesting between 1 to 12 weeks following the initial tick bite [5, 24, 30]. This stage encompasses more than 95% to 98% of all diagnosed LNB cases [16, 22, 36]. The clinical spectrum is primarily defined by meningitis, cranial neuritis, and painful radiculoneuritis, which can occur separately or simultaneously [4, 23, 30, 39]. Symptoms at this stage often include fatigue, headache, and neck stiffness, though some patients-particularly children-may also exhibit nonspecific features such as loss of appetite or mood changes [24, 30]. While the prognosis for early LNB is generally favorable with prompt antibiotic intervention, approximately 10% to 50% of patients may report persistent subjective symptoms such as memory impairment or asthenia [19, 32, 44].

Late Neuroborreliosis

Late LNB is defined by the presence of neurological symptoms for a duration exceeding 6 months [5, 24]. This manifestation is exceedingly rare, representing less than 2% to 5% of the total LNB population [1, 10, 43]. Pathologically, it is characterized by an active and ongoing inflammatory process within the brain, spinal cord, meninges, and leptomeningeal vessels [43, 45]. The clinical spectrum of late LNB includes chronic progressive encephalomyelitis, characterized by spastic paraparesis or quadriparesis, ataxia, and bladder dysfunction [1, 10, 16, 45]. Other features include cerebral vasculitis, which may lead to ischemic stroke, and cognitive impairment that can occasionally mimic rapidly progressing primary dementia [10, 23, 27, 43, 45].

Key Clinical Syndromes

Facial Nerve Palsy

Facial nerve palsy (FNP) is the most common specific neurological manifestation of LNB, accounting for approximately 80% of all cranial nerve involvement [16, 17, 29, 36]. Although unilateral presentation is more frequent, bilateral involvement occurs in 25% to 33% of cases and should immediately prompt clinical suspicion of neuroborreliosis [16, 22, 23, 29, 36]. In pediatric populations within endemic regions, LNB is the etiology of acute FNP in 58% to

65% of cases [46]. Furthermore, LNB is responsible for up to 50% of all pediatric cases of bilateral facial nerve palsy [11]. While the majority of patients achieve complete recovery within 1 to 2 months, persistent facial dysfunction is reported in 18% to 22% of cases, with facial synkinesis specifically occurring in 5% to 10% of patients [16, 24, 36, 46].

Bannwarth Syndrome

Bannwarth syndrome, or lymphocytic meningoradiculitis, represents the most frequent manifestation of early disseminated LNB in European adults [2, 16, 17, 36]. It is characterized by a classic triad of symptoms: painful radiculopathy, cranial neuritis, and CSF lymphocytic pleocytosis [3, 9, 11, 34, 37]. The associated radicular pain is described as severe, segmental, and "zoster-like," with a burning, stabbing, or tearing character [10, 16, 17, 22, 36]. A distinguishing feature of this pain is its nocturnal exacerbation and its relative resistance to conventional analgesics [10, 16, 17, 22, 36]. Approximately 75% of patients develop neurological deficits, such as paresis or segmental sensory disturbances, within 1 to 4 weeks following the onset of pain [10, 16, 36].

Meningitis

Lyme meningitis is a subacute inflammatory process and is the primary manifestation of early LNB in North America [26, 31]. Clinically, it often presents with an insidious onset of headache and fatigue, while traditional meningeal signs like high fever and neck stiffness may be mild or entirely absent [8, 11, 15, 30, 39]. In the pediatric population, isolated meningitis (without radicular pain) is significantly more common than in adults [16, 24, 36]. CSF analysis characteristically demonstrates lymphocytic pleocytosis, with average cell counts ranging between 170 and 220 cells/µl [16, 33, 39]. Biochemical analysis typically shows mildly elevated protein (hyperproteinorachia), normal glucose concentrations, and normal or slightly elevated lactate levels [3, 7, 16, 26, 39]. Intrathecal antibody synthesis is the diagnostic gold standard, with IgM production occurring in 80% to 100% of acute cases [16, 24, 25, 31].

Atypical and Rare Neurological Manifestations

Ophthalmoplegia and Spastic Quadriparesis

Complex neurological manifestations such as ophthalmoplegia and spastic quadriparesis are rare, representing approximately 2% to 4% of LNB cases. Documented cases include patients

presenting with bilateral ophthalmoparesis, dysarthria, and an ascending pyramidal pattern of weakness. This clinical phenotype may indicate an evolving myelopathic process, potentially accompanied by urinary incontinence and autonomic dysfunction. While initial neuroimaging of the brain and entire spine may appear normal in these instances, cerebrospinal fluid (CSF) analysis typically demonstrates persistent lymphocytic pleocytosis. These manifestations are often initially mismanaged as Guillain-Barré syndrome (GBS), though the presence of hyperreflexia and inflammatory CSF findings should prompt consideration of neuroborreliosis. [1]

Childhood Stroke Associated with LNB

Childhood arterial ischemic stroke (AIS) is an exceptionally rare complication of LNB, accounting for less than 1% of cases. The underlying pathophysiology involves focal cerebral arteriopathy (FCA) or infectious vasculitis, where spirochetal invasion triggers perivascular lymphocytic infiltration and subsequent thrombosis or vasoconstriction of small penetrating arteries [14, 20]. A systematic review identified 12 reported cases of LNB-associated childhood AIS, with 75% involving the posterior circulation. Long-term management necessitates antibiotic therapy alongside secondary stroke prophylaxis with acetylsalicylic acid (ASA) to mitigate the high risk of early recurrence associated with inflammatory FCA [20].

Secondary Dementia or Encephalitis

Secondary dementia due to LNB is a rare manifestation of chronic progressive meningoencephalomyelitis, occurring in approximately 2% to 6% of cases. These patients typically exhibit signs of subcortical dementia, including deficits in memory, attention, and executive function, which develop more rapidly than in primary degenerative conditions like Alzheimer's disease. In approximately 50% of reported cases, the clinical triad of dementia, gait disturbance, and voiding dysfunction led to an initial misdiagnosis of normal pressure hydrocephalus (NPH) [43]. Encephalitis represents a severe CNS manifestation, affecting roughly 3.3% of LNB patients, and may present with acute confusion, seizures, or personality changes [1, 16, 34].

Diagnostic Framework and Challenges

Standard Two-Tiered Serologic Testing

The current diagnostic standard for disseminated Lyme borreliosis (LB) remains two-tiered serologic testing, which utilizes a sensitive enzyme immunoassay (EIA) or indirect fluorescent antibody (IFA) followed by supplemental IgM and IgG immunoblots for samples with positive or equivocal results [7, 13]. A primary limitation of this algorithm is its low sensitivity during the initial weeks of infection-consistently observed between 30% and 40%-as the host's humoral response requires time to develop, with Borrelia-specific IgM antibodies becoming detectable from the third week after exposure and IgG antibodies from the sixth week [10, 13]. Furthermore, the interpretation of immunoblots is frequently complicated by the subjective nature of band analysis and potential cross-reactivity with other pathogens, such as Epstein-Barr virus or other spirochetal infections, which can result in false-positive IgM results [13, 25]. A significant longitudinal challenge arises from the fact that IgG and IgM antibodies can persist for years following successful antibiotic treatment, rendering serology incapable of differentiating between an active infection and a previous infection [10, 16, 25]. Consequently, serological testing is primarily indicated when there is sufficient clinical suspicion [10, 16].

Cerebrospinal Fluid Analysis: AI, CXCL13, and IgM Index

Cerebrospinal fluid (CSF) analysis is essential for confirming Lyme neuroborreliosis (LNB), with the detection of intrathecal antibody synthesis (antibody index, AI) considered the diagnostic "gold standard" in Europe [10, 25]. The AI is calculated by comparing specific anti-*Borrelia* antibody concentrations in the CSF and serum, adjusted for blood-brain barrier (BBB) permeability using total IgG and albumin ratios [18, 26]. While the AI achieves a sensitivity exceeding 99% in late LNB, it may remain negative in 10% to 30% of early cases where symptoms have persisted for less than six weeks [7, 16].

To address these early diagnostic gaps, the B cell-attracting chemokine CXCL13 has emerged as a highly sensitive biomarker, often reaching significant concentrations in the CSF before the development of a measurable antibody response [4, 16]. A comprehensive meta-analysis of pooled data from 18 studies demonstrated that CSF CXCL13 possesses a diagnostic sensitivity of 89% and a specificity of 96% for acute LNB [1, 16]. However, CXCL13 is not pathognomonic for LNB and can be elevated in other neuroinflammatory conditions, including neurosyphilis, multiple sclerosis, and CNS lymphoma [4, 16, 31]. Furthermore, the total IgM index has been suggested as an accessible complementary marker that, when combined with the specific AI and CXCL13, may help optimize diagnostic sensitivity in early and pediatric LNB [21].

Direct Diagnostic Methods in LNB

Direct detection of *Borrelia burgdorferi* through polymerase chain reaction (PCR) or culture from CSF is characterized by exceptionally high specificity (nearly 100%) but restricted clinical utility due to low sensitivity [6, 10]. Meta-analyses indicate that the median sensitivity of CSF PCR in acute neuroborreliosis is only 21% to 23%, largely because spirochetes are rarely free-sequestered in the CSF and typically adhere to host tissues [18, 24, 26]. While PCR sensitivity remains limited, it may provide supplementary diagnostic value in highly specific early-stage, seronegative cases [16, 18]. Because *Borrelia* DNA can persist even after spirochetal killing, a positive PCR result does not always equate to an active, replicating infection [27]. Consequently, direct diagnostic methods are not routinely recommended for first-line testing, though they remain a viable consideration for immunocompromised individuals who may exhibit an impaired humoral response [10, 16, 18].

Neuroimaging: MRI Findings and Proton Spectroscopy

The primary role of neuroimaging in LNB is to exclude alternative etiologies, yet contrast-enhanced MRI reveals pathological findings in a significant proportion of acute cases [12, 14, 45]. The most frequent abnormality is cranial nerve enhancement on contrast-enhanced brain scans, with the facial (CN VII) and oculomotor (CN III) nerves preferentially affected [12, 14]. Interestingly, imaging findings often lack a direct clinical correlation; for instance, significant oculomotor nerve enhancement is frequently seen in patients without evident ophthalmoparesis [1, 12, 14]. Other suggestive findings include leptomeningeal enhancement (identified in 13% of brain and 62% of spinal scans) and smooth enhancement of the cauda equina nerve roots [7, 14].

Advanced neuroimaging using 3.0T proton magnetic resonance spectroscopy (1H-MRS) provides insights into subclinical metabolic alterations. Research has demonstrated a statistically significant decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the frontal lobes of LNB patients, even in brain regions that appear normal on conventional MRI [2, 40]. Furthermore, elevations in the choline peak have been documented in inflammatory foci, reflecting increased cell membrane turnover and active inflammation [23].

Management and Therapeutic Strategies

Antibiotic Regimens for Lyme Neuroborreliosis

The management of Lyme neuroborreliosis (LNB) necessitates the administration of antibiotics with proven penetration into the central nervous system (CNS), including doxycycline, ceftriaxone, cefotaxime, and penicillin G [24]. Meta-analyses of randomized controlled trials indicate that orally administered doxycycline demonstrates non-inferiority to intravenous beta-lactams regarding the regression of neurological manifestations at 12 months (RR: 0.98, 95% CI: 0.68; 1.42) [10, 16, 19]. In clinical practice, current guidelines generally recommend an adult doxycycline dosage of 200 mg daily for a duration of 14 days, with the possibility of extending the regimen up to 21 to 28 days in cases of severe CNS involvement. Alternatively, intravenous ceftriaxone is standardly administered at a dose of 2 g once daily for adults and 50 to 75 mg/kg daily for children [19, 31, 36, 39]. Cefuroxime axetil and amoxicillin serve as alternative oral options for peripheral manifestations, though their efficacy in confirmed meningitis is less documented than that of doxycycline [27, 29, 36].

Post-Treatment Lyme Disease Syndrome (PTLDS) and Outcomes

Definition and Patient-Reported Outcomes

Post-treatment Lyme disease syndrome (PTLDS) is defined as the presence of subjective symptoms-primarily fatigue, cognitive dysfunction, and widespread musculoskeletal pain-that persist for at least 6 months following the completion of guideline-compliant antibiotic therapy [4, 13, 16, 32]. The estimated prevalence of PTLDS ranges between 10% and 20% of treated patients, although some cohorts report rates as high as 54% depending on the stringency of the case definition [4, 13, 16, 30]. Patient-reported outcome measures (PROMs) often highlight a significant burden on daily functioning, with symptoms such as "brain fog" memory impairment, and chronic sleep disturbance being the dominant drivers of morbidity [13, 42]. While long-term prognosis for definite neuroborreliosis is generally favorable, some patients exhibit persistent deficits on neuropsychological testing and a poorer mental health-related quality of life compared to normative data [31, 42].

Summary

Lyme neuroborreliosis (LNB) is a complex, disseminated neurological manifestation resulting from infection by spirochetes of the *Borrelia burgdorferi* sensu lato complex, affecting approximately 10% to 15% of symptomatic individuals. According to the sources, the condition is chronologically classified into early LNB, which accounts for over 95% of cases, and late LNB, an exceedingly rare form occurring in fewer than 5% of patients. Global incidence is rising due to climate-driven expansion of tick habitats; for instance, in Poland, LNB constituted nearly 39% of all bacterial meningitis and encephalitis cases reported in 2023.

The pathophysiology is primarily driven by the host's intrathecal inflammatory response, characterized by the early elevation of the B-cell chemoattractant CXCL13 in the cerebrospinal fluid (CSF). Early clinical presentations typically include meningitis, painful radiculoneuritis known as Bannwarth syndrome, and cranial neuritis, with facial nerve palsy representing 80% of cranial involvement. Conversely, late LNB manifests as chronic progressive encephalomyelitis, often resulting in spastic paraparesis, ataxia, or cognitive deficits.

Diagnostic precision is hampered by the low sensitivity of two-tiered serology in early infection, making the detection of intrathecal antibody synthesis the diagnostic "gold standard" in Europe. Advanced neuroimaging, such as 3.0T proton magnetic resonance spectroscopy, can identify subclinical metabolic dysfunction, even when conventional MRI appears normal. Management necessitates antibiotics with central nervous system penetration, such as oral doxycycline or intravenous ceftriaxone, which demonstrate high efficacy in mitigating clinical symptoms. Despite successful treatment, 10% to 20% of patients develop Post-Treatment Lyme Disease Syndrome (PTLDS), suffering from persistent fatigue and cognitive impairment.

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