Overdiagnosis and overtreatment of Lyme neuroborreliosis are preventable

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Summary

The problems of diagnosis and treatment of Lyme neuroborreliosis can be minimised by strictly following the clinical diagnostic criteria, and understanding the pitfalls of laboratory tests. The diagnosis is based solely on objective clinical findings, with serologic test results used only to confirm the diagnosis. It must be underscored that serologic testing, when ordered without regard for clinical presentation (ie, used as a screen), may be misleading due to its extremely low positive predictive value. Enzyme-linked immunosorbent assay should always be confirmed by Western blot. The cerebrospinal fluid *Borrelia burgdorferi* antibody index is more meaningful than simple titres of specific antibody. Polymerase chain reaction is still a research tool and should not be utilised without clinical correlation. All serologic tests and polymerase chain reaction may remain positive long after successful treatment. Overdiagnosis and overtreatment can be minimised by following these guidelines.

Keywords: Lyme disease; neuroborreliosis; *Borrelia burgdorferi*

Lyme disease has become a leading vector-borne infectious disease all over the world, with 10–40% of patients eventually developing Lyme neuroborreliosis.¹ This clinical entity is another great mimicker, like tuberculosis and syphilis, as its clinical manifestations are protean. The high prevalence and mimicker status of Lyme neuroborreliosis increases the physician's responsibility for precise diagnosis and treatment.

In spite of advances in the diagnostic armamentarium, the diagnosis of Lyme disease and Lyme neuroborreliosis remains problematic. In one study only a third of patients referred to a Lyme disease clinic were found to have Lyme disease, either active or by history.² Diseases such as depression and cancer may be overlooked, if guidelines for diagnosis and treatment of Lyme neuroborreliosis are not followed carefully. In this paper, the importance of strictly following the criteria for clinical diagnosis is emphasised, and the pitfalls of the diagnostic methods are discussed.

Clinical features

A clinical consensus currently divides Lyme neuroborreliosis into early disseminated and late stages. Both the central nervous system (CNS) and peripheral nervous system (PNS), along with the blood vessels and meningeal coverings, may be involved in either stage. However, the pattern of nervous system involvement is different (table 1). This classification is helpful in understanding the correlation of the clinical spectrum of Lyme neuroborreliosis with serologic tests and treatment. Subtle differences in the clinical presentation of early and late Lyme neuroborreliosis patients in Europe and North America are related to the different *Borrelia burgdorferi* (Bb) genospecies on the two continents.

EARLY DISSEMINATED LYME NEUROBORRELIOSIS

The classic triad of this stage, also known as meningo-radicleoneuropathy, includes aseptic meningitis, cranial neuropathy, and painful radiculoneuritis which may occur alone or in combination. Acute encephalomyelitis is seen less frequently. Neurologic signs and symptoms develop from weeks to months after inoculation. The onset is acute or subacute. Accompanying erythema migrans and systemic signs and symptoms characteristic of early disseminated Lyme neuroborreliosis, may be present in up to two-thirds of cases. Neurologic involvement can occur without erythema migrans, however, and can be the first manifestation of the disease.³ Only 40% of patients recall tick bite. The absence of a history of travel to or residence in an endemic area tends to warn the clinician against the diagnosis of Lyme neuroborreliosis.

Table 1 Characteristic features of early and late Lyme neuroborreliosis

	Early disseminated LNB	Late LNB
Onset	Acute	Insidious
CNS	Lymphocytic meningitis Acute encephalomyelitis (focal hemispheric, basal ganglion, brainstem, cerebellum and spinal cord features)	Subtle chronic encephalopathy Chronic encephalomyelitis
PNS	Acute radiculoneuropathy (mononeuritis multiplex) Cranial neuropathy	Chronic radiculoneuropathy (mononeuritis multiplex)
CSF pleocytosis	75–85%	5% in CNS LNB, absent in PNS LNB
Anti-Bb Ab	80–90%	50% in CNS LNB
Treatment	Excellent	Rarely present in PNS LNB Slow and variable

CNS = central nervous system, PNS = peripheral nervous system, LNB = Lyme neuroborreliosis, Anti-Bb Ab = anti-*Borrelia burgdorferi* antibody

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Meningitis is the single most common presentation in early disseminated Lyme neuroborreliosis. Headache is the main complaint. Fever and meningismus are usually mild or absent. Therefore, a high index of suspicion is often required for the diagnosis. Somnolence, irritability, impaired memory, depressed mood, and behavioural changes are seen in half of the patients and may be interpreted as features of meningoencephalitis, but are difficult to separate from the effects of meningitis. The differential diagnosis includes other causes of aseptic meningitis. Examination of cerebrospinal fluid (CSF) shows a mononuclear pleocytosis, with elevated protein and normal glucose levels. CSF anti-Bb antibody (usually IgG or IgA) is present in 80–90% of patients, whereas CSF polymerase chain reaction (PCR) is positive in less than half of the patients.

About two-thirds of patients with early disseminated Lyme neuroborreliosis have cranial neuropathies which can occur without other neurologic or systemic features and without preceding erythema migrans.⁴ The facial nerve is involved most commonly, although any of the cranial nerves may be involved. Remarkably, bilateral facial palsy is seen in approximately one-third of such cases. The differential diagnosis of bilateral facial palsy includes Guillain-Barre syndrome, acquired immunodeficiency syndrome (AIDS), various other causes of meningitis, and Tangier's disease.

Radiculoneuropathy develops in about one-third of patients with early Lyme neuroborreliosis. Severe radicular pain, paraesthesia and hyperaesthesia are the most common complaints. Motor and sensory deficits are typically asymmetric and multifocal: plexus, nerve roots and nerves may be involved, either singly or in combination. Uncommon presentations include paralysis of the diaphragm or abdominal muscles.² Rarely, patients may present with Guillain-Barre syndrome and CSF pleocytosis.⁵ The differential diagnosis includes diseases with neuropathy and/or CSF pleocytosis such as disc prolapse, diabetic proximal neuropathy, vasculitic neuropathy, cytomegalovirus radiculopathy, neurosarcoidosis and zoster sine herpete.

In meningoradiculoneuropathy, CSF shows features of meningitis. Headache, fever, facial palsy, truncal sensory/motor loss, and features of mononeuritis multiplex support the diagnosis of Lyme aetiology.

Acute encephalomyelitis, ie, brain and spinal cord parenchymal involvement, occurs in 10–20% cases of early disseminated Lyme neuroborreliosis in Europe, but rarely in North America. Diffuse involvement of the cerebral hemispheres may manifest as hallucinations, agitation, hypersomnolence, confusion, coma and seizures. Focal signs referable to cerebral hemispheres, basal ganglion, brainstem, cerebellum and spinal cord may be present. Virtually all patients have CSF lymphocytic pleocytosis.

LATE LYME NEUROBORRELIOSIS

Neurological manifestations usually develop months or years after the inoculation and may present as a syndrome with typical CNS and PNS abnormalities.

CNS abnormalities

The clinical presentation varies between North America and Europe. Encephalopathy is more common in North America, while encephalomyelitis is much more frequent in Europe. Encephalopathy is usually mild to moderate and may persist for years, if untreated. Complaints are usually vague: impaired memory and concentration, insomnia and hypersomnolence. Mild psychiatric disturbance in the form of depression, irritability and paranoia may be present. Chronic fatigue is a common accompaniment, but it never occurs alone.^{6,7} Objective neurologic findings are lacking. The differential diagnosis includes chronic fatigue syndrome, fibromyalgia, post-Lyme syndrome, depression, normal aging, early Alzheimer's disease and neurosyphilis. The clue to the diagnosis is a history of tick exposure or early cardinal clinical features of Lyme disease. Logigian, in a series of about 100 Lyme encephalopathy patients, found only one who did not have well recognised manifestations of early Lyme disease.⁸

Serum immunoreactivity by enzyme-linked immunosorbent assay (ELISA) and Western blot is nearly universal. However, seroreactivity only indicates exposure to the organism and does not establish that Bb is the cause of encephalopathy. CSF pleocytosis is present in 5% and protein content is increased in 20–45% of cases. Specific anti-Bb antibody is present in the CSF in half of cases. CSF PCR may be positive.

Overall, the patients with symptoms of encephalopathy fall into two groups. The first group of patients suffer from active Lyme neuroborreliosis. They usually show impaired performance on objective memory tests. CSF is abnormal in most cases, implying a neurologic basis.⁹ The symptoms of encephalopathy are usually reversible with antibiotic treatment. The second group comprises patients in whom the symptoms are possibly due to the psychological stress of

Lyme disease,¹⁰ depression,¹¹ toxic-metabolic effect of a systemic infection,¹² or an immune reaction.¹³ Examination of CSF in such cases does not usually reveal abnormalities. Formalised neuropsychological tests can be of great use in distinguishing between these two groups of patients. Although the pattern of abnormality seen in patients with Lyme encephalopathy is not unique, it is sufficiently different from patterns that occur with depression, anxiety, or Alzheimer's disease to differentiate Lyme encephalopathy from other causes of concentration and memory impairment.¹⁴ After antibiotic treatment, the neuropsychologic abnormalities have been reported to improve significantly.

Most cases of chronic encephalomyelitis have been reported from Europe, although well-documented North American cases have also been described.¹⁵ Neurologic signs may be multilevel, reflecting involvement of brain, spinal cord, and cranial and peripheral nerves. Insidious onset and progressive worsening over months to years distinguishes this from similar features seen in early Lyme neuroborreliosis. In most cases, the clinical features of late Lyme neuroborreliosis do not resolve spontaneously. Variable improvement may be noted after antibiotic treatment.

PNS abnormalities

About one-third of patients with late Lyme neuroborreliosis suffer from mild chronic radiculoneuropathy. This is different from the meningeradiculoneuropathy seen in the early disease. It causes less striking signs and symptoms and does not improve spontaneously. Motor involvement is rare. Sensory symptoms are usually asymmetric and patchy. Radicular pain in the limbs or trunk is less common. Neurologic examination is usually normal. The CSF of patients with neuropathy alone is rarely abnormal. However, with concomitant encephalopathy, increased CSF protein content and intrathecal production of anti-Bb antibody may be seen. A more severe peripheral neuropathy with unique skin changes, known as acrodermatitis chronica atrophicans, is common in Europe. This is manifested as bluish-red oedematous cutaneous lesions on the feet at onset. Atrophy and wrinkling of the involved skin occurs later.

Laboratory diagnosis

Laboratory support is necessary only to confirm the diagnosis (table 2). The diagnosis should never be made solely on the basis of serologic tests. It is prudent not to order serologic tests for patients with vague symptoms such as chronic fatigue in isolation without any cognitive symptoms or other Lyme-related finding.

CSF EXAMINATION

Changes in CSF include: lymphocytic pleocytosis of up to 3750 cells/mm³ (usually 100–170), protein 100–300 mg/dl (or even up to 1300 mg/dl in cases of longer duration), slightly low glucose (only in cases of longer duration), and the presence of oligoclonal bands of IgG in about 90% of cases. While abnormal CSF in a seropositive person helps confirm that a neurologic syndrome is due to Bb, normal CSF should not be used to exclude Lyme neuroborreliosis. Documentation of the extent of CSF abnormalities provide a baseline from which the subjective improvement may be confirmed by objective improvement in the CSF. The abnormalities should show improvement on repeat examination, although immune markers as well as increased protein may remain present in the CSF for many years.

Isolation of the organism is the gold standard test for the diagnosis for the majority of the bacterial diseases. Bb is difficult to culture from biological specimens due to its fastidious growth habits and low number. Since a positive CSF culture is seen in less than 10% of Lyme neuroborreliosis cases, isolation of Bb is less useful diagnostically.¹⁶

Table 2 Current status of laboratory procedures for diagnosis for Lyme neuroborreliosis

Laboratory tests	Advantages	Limitations
CSF culture	Gold standard	Low yield procedure
Serum ELISA		False +ve/ false-ve common
2 step Serum ELISA & Western blot	Highly sensitive and specific for systemic LD	Interlaboratory variability + Occasional false +ve
Intrathecal anti-Bb Ab index	Highly specific for LNB	Western blot less objective
PCR	Sensitivity moderate to high	False -ve in late CNS; absent in late PNS LNB; occasional false +ve
		Research tool at present; false +ve if contamination

CSF = cerebrospinal fluid, anti-Bb Ab = anti-*Borrelia burgdorferi* antibody, PCR = polymerase chain reaction, CNS = central nervous system, PNS = peripheral nervous system, LD = Lyme disease, LNB = Lyme neuroborreliosis

SERUM ANTIBODY TESTS

Serum antibody tests are useful for the diagnosis of Lyme disease. In Lyme neuroborreliosis, they play an important role in detecting not only previous exposure to Bb, but also the systemic activity of the organism. ELISA has replaced indirect immunofluorescent assay as the serum antibody test of choice because it is more objective. Its important drawback is false positive results, which occur in diseases such as other spirochetal diseases, tuberculous meningitis, bacterial endocarditis, rheumatoid arthritis, systemic sclerosis, infectious mononucleosis, Rocky Mountain spotted fever and AIDS.

An early negative serologic result does not rule out the disease, as a second specimen taken 3–4 weeks later may be positive. Failure of the seroconversion of the second specimen may be expected if antibiotic treatment were started promptly, based on the clinical diagnosis. In those cases when the clinical diagnosis is less certain and the decision is made not to treat the patient, a negative second specimen argues against the diagnosis of Lyme disease/Lyme neuroborreliosis.

Positive serologic tests in early Lyme disease are usually low-level positives. High titer in the early stage of the disease indicates past or recurrent infection. A positive serologic test, regardless of titer, indicates past exposure to Bb and does not reflect disease activity. Therefore, the presence of serum reactivity alone is not sufficient to diagnose Lyme neuroborreliosis.

A high level positive serology is seen in the majority of chronic Lyme disease/Lyme neuroborreliosis cases. However, negative, low level or decreasing Bb titers can occur in untreated chronic Lyme disease cases due to impaired immune response.¹⁷ Patients presenting with possible late Lyme neuroborreliosis and a low reactive or borderline Bb titer should be thoroughly examined for other diseases.

Western blot or immunoblot is considered more specific than ELISA for diagnosing Lyme disease/Lyme neuroborreliosis. It is less often falsely positive than ELISA, as long as the criteria of a sufficient number of antibody bands required for the diagnosis, is satisfied. However, there are a few inherent problems with this test. Unlike HIV Western blot, Lyme Western blot is not a confirmatory test because of the presence of common and cross-reacting bacterial antigens expressed by different Bb genospecies. Reading of the band intensity is subjective and needs a lot of experience. If the treatment of Lyme neuroborreliosis has been initiated early on the basis of clinical criteria, the test result may be negative.

To improve the diagnostic efficacy in Lyme neuroborreliosis, the US Center for Disease Control recommends a two-step serologic evaluation. Bb Flagella-based ELISA (FLA-ELISA), the first step, is a screening test because of the presence of flagellin epitopes in numerous other bacteria. IgM and IgG Western blot, the second step, is performed only for samples scored positive or equivocal by the ELISA. The Western IgG blot is considered positive if five of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 60, 66 and 93 kDa. Western IgM blot is considered positive if two of the following bands are present: 23, 39, 41 kDa.¹⁸ The sensitivity of the combined two-step ELISA and Western blot was 100% (17/17) in a recent study in early and late Lyme neuroborreliosis. The specificity was 100% (0/113) for healthy blood donors and 90% (11/111) for persons with autoimmune disorders.¹⁹ More studies are needed to confirm these results.

CSF ANTIBODY TEST

CSF anti-Bb antibody index is currently the best indicator of Lyme neuroborreliosis. It measures brain compartment synthesis of spirochete-specific antibodies and is much more meaningful than total specific antibody in CSF, which reflects passive diffusion of blood antibody. The technique normalises CSF and serum to the same IgG concentration, then runs the paired samples for anti-Bb antibodies by routine ELISA. Local CSF antibody production is implied when the CSF anti-Bb antibody index (CSF optical density / serum optical density) is greater than one.

Intrathecal anti-Bb antibody production is helpful when positive, because it strongly suggests CNS involvement by the spirochete. In spite of high specificity, false positive intrathecal anti-Bb antibody production was noted in three out of 77 patients in one series.²⁰ Also, a negative result does not rule out Lyme neuroborreliosis. Intrathecal anti-Bb antibody was positive in 92% of patients with meningitis, and 42% of patients with late CNS Lyme neuroborreliosis, but was absent in patients with late PNS Lyme neuroborreliosis in one series.²¹

CSF-PCR

The combination of a variable serologic response and difficult isolation has made detection of spirochetal genomic material an area of interest. PCR-based methods can detect less than 10 Bb organisms in the biologic samples and such

Major pitfalls in the diagnosis of Lyme neuroborreliosis

Patient interpreted to have active or persistent Lyme neuroborreliosis because of:

- positive Lyme serology at the onset of disease
- persistently positive Lyme serology even after adequate therapy
- persistently positive PCR even after adequate therapy
- persistent vague symptoms after adequate treatment (post-Lyme disease syndrome)

Patient interpreted not to have Lyme neuroborreliosis because of:

- no history of tick-bite
- negative Lyme serology
- negative CSF
- negative PCR

detection is highly specific. However, PCR has two important drawbacks. First, the extreme sensitivity of PCR can result in false positive result due to contamination. This problem can be controlled in a research laboratory by careful attention to controls and to laboratory technique. Second, the presence of PCR-detectable organisms does not prove the presence of clinically active disease because the organisms may be dead or alive.²²

In one study,²² nested pairs of oligonucleotide primers were designed to recognise the C-terminal region of Bb outer surface protein A (OspA). PCR detected Bb OspA DNA in 10 of 11 patients with Lyme encephalopathy, 28 of 37 patients with inflammatory Lyme neuroborreliosis, seven of seven seronegative patients with Lyme-compatible disorders, and none of 23 patient controls. In addition, PCR results predicted clinical results accurately in eight patients in whom CSF was tested before and after parenteral antibiotics.²² In other studies, however, PCR was found to have methodological problems and was positive in only 25–50% of cases.^{23–24} More studies are needed to evaluate its sensitivity and specificity before it becomes a routine test. Nevertheless, PCR may be used to corroborate the diagnosis in equivocal cases.

Diagnosis

The diagnosis of definite Lyme neuroborreliosis can be made when there is a history of exposure to appropriate ticks in an area endemic for Lyme disease, a compatible neurologic abnormality without other cause, and at least one of the following:

- history of well-documented erythema migrans
- history or presence of lymphocytoma or ACA
- seroconversion or four-fold rise in titer of anti-Bb antibodies in paired serum specimens
- intrathecal CSF anti-Bb antibody production
- other organ system involvement typical of Lyme disease with raised titers of specific serum antibody²⁵
- culture, histologic or PCR proof of presence of Bb²⁶

Until a 'gold standard' diagnostic test is established, it is reasonable to accept a less restrictive criteria for the diagnosis of Lyme neuroborreliosis, for example, a compatible neurologic abnormality without other cause, and either serum immunoreactivity to Bb with no demonstrable rise in the antibodies, or tick bite or travel or residence in an endemic area.²⁵ Failure to treat these probable or possible cases in time, may have far reaching consequences.²⁶ Other diagnoses should always be considered in these cases before antibiotic treatment is prescribed. Major pitfalls in the diagnosis of Lyme neuroborreliosis are summarised in the box.

Treatment

An algorithm for the diagnosis and treatment is provided in the figure. Lyme neuroborreliosis is not a medical emergency in the majority of cases. Therefore, a thorough evaluation of the patient must be done before making major management decisions.

Controversy exists regarding management of patients with mild confusion/memory changes, absent Lyme-related objective clinical findings, absent CSF pleocytosis and absent serum or CSF Bb antibodies and in whom late Lyme neuroborreliosis is suspected. Unequivocal clinical guidelines are lacking. Most experts believe that this clinical situation is distinctly unusual,⁶ and suggest that repeating the tests in a different laboratory or Bb DNA CSF PCR⁶ may be helpful in some instances. Halperin *et al* suggest that empirical oral antibiotic therapy may be effective in such cases.²⁶ On the other hand, treating such cases with antimicrobial agents is considered questionable by some.⁶

Invasion of the brain parenchyma by spirochete-like organisms has been demonstrated by immunochemistry, and with great difficulty by silver impregnation technique in humans.²⁷ On this premise, it is hypothesized that Lyme meningitis is a meningoencephalitis. Therefore, when designing a treatment regimen, one must pay attention not only to sensitivity of the organism but also to the ability of the regimen to provide adequate CSF and, if possible, brain levels.

Once neurologic abnormalities develop, parenteral treatment is usually required. Patients with early Lyme neuroborreliosis improve with parenteral antibiotic therapy, although they have also been known to recover without any therapy. Antibiotics certainly lead to a faster resolution of symptoms. The usual duration of therapy is about 2–4 weeks. Meningitis resolves within days to weeks; other features may take months to improve. An exception to the use of parenteral

Table 3 Antimicrobial therapy of Lyme neuroborreliosis

Condition	Recommended therapy	Alternative therapy
Meningitis, radiculoneuritis, Encephalitis, polyneuropathy, encephalomyelitis. Cranial neuritis (normal CSF)	ceftriaxone × 2–4 weeks ceftriaxone × 2–4 weeks doxycycline × 2–4 weeks	penicillin, cefotaxime penicillin, cefotaxime amoxicillin, ceftriaxone

Complaints of headaches, arthralgias, fatigue, malaise, mild cognitive abnormalities, and sleep disturbances even after adequate antibiotic therapy is known as 'post-Lyme disease syndrome'.³⁵ This phenomenon is not unique to Lyme disease. Similar symptoms have been noted after influenza, hepatitis and infectious mononucleosis. Controversy exists regarding its pathogenesis. A protracted immune activation by the bacterium is implicated. Symptomatic treatment with ibuprofen or amitriptyline, and exercise may be helpful.

Patients with new onset fatigue, depression and a positive Lyme serology should be treated on the merits of history (tick bite, joint swelling, skin manifestations). If cognitive symptoms are present, spinal tap is advisable. Treatment is necessary if CSF is abnormal. Extraordinary emphasis placed on vague symptoms like depression and fatigue may lead to errors in diagnosis.

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