

# Neurological Complications of Lyme Disease

Syed Rizvi, MD, and Amanda Diamond, MD

**A tick-bite associated rash with later neurological manifestations, including paralysis and meningitis, had been documented in Europe for several years before Lyme arthritis was recognized in the 1970s.<sup>1-4</sup> The illness was later understood to be part of a multisystem disease caused by spirochetes and transmitted by *Ixodes* ticks.<sup>5,6</sup> *Borrelia burgdorferi*, although initially thought to be a single species, has been found to have several sub-species. These subgroups may be responsible for the variation in clinical symptoms observed in different parts of the world.<sup>7</sup>**

The pathophysiology of neuroborreliosis is difficult to demonstrate, but mimics other spirochetal infections. Infection is local with subsequent dissemination. During this time spirochete numbers are high. *B. burgdorferi* components that induce cytokine production by T and B cells produce immune activation and indirect cell damage. Central nervous system involvement is common and clinical syndromes tend to occur in stages.<sup>7</sup>

Lyme disease has been implicated in a variety of peripheral and central nervous system disorders. The neurological syndromes are often accompanied by more general complaints (arthralgias, fatigue, myalgias). Earlier neurological symptoms, or those occurring during dissemination within weeks to months, tend to be more clinically obvious and develop in an estimated 15% to 20% of patients.<sup>4</sup> Several late syndromes seem to follow a more insidious course.<sup>8</sup> For purposes of simplification, disorders of the peripheral and central nervous systems will be reviewed separately.

## NEUROBORRELIOSIS OF THE PERIPHERAL NERVOUS SYSTEM

The most common peripheral manifestations of Lyme disease are cranial neuropathies, peripheral neuropathies and radiculitis. However, many other syndromes, including a "Guillain Barré-like" syndrome, motor neuron disease, axonopathies, brachial and lumbar plexopathies, mononeuropathy multiplex and even myositis have been described.<sup>7</sup>

**Radiculoneuropathy.** Painful radiculitis is one of the most common early neurologic symptoms of Lyme disease in Europe. Incidentally, it was also part of the symptom-complex described in the first patient reported with the syndrome.<sup>1</sup> Usually occurring within the first weeks to months in the infection, the radiculoneuropathies of Lyme disease have included motor, sensory and mixed symptoms. They are usually self-limited and may be easily mistaken for nerve-impingement syndromes, with segmental symptoms of weakness, sensory or reflex changes.<sup>9</sup> The symptoms may not occur in the region of the tick bite. Electrodiagnostic testing usually shows multifocal mild sensorimotor involvement.<sup>10,11</sup>

**Cranial neuropathies.** Involvement of cranial nerves, particularly the seventh nerve, may be present in up to 50%-75% of all patients experiencing neurologic symptoms.<sup>4</sup> Multiple cranial nerves may be involved simultaneously.<sup>9</sup> Reports include symptoms of every cranial nerve except the olfactory nerve. The facial nerve involvement is reported to be bilateral in up to one third of cases.<sup>11</sup> Facial nerve symptoms may not affect taste or hearing, indicating that involvement may be outside the subarachnoid space. Additionally, CSF analysis in isolated Lyme disease facial palsy may be normal. Complete recovery occurs in 80-90% of patients within weeks to months.

**"Guillain Barré-like" syndrome.** Although rare, an acute and severe syndrome of diffuse polyneuropathy, including bifacial weakness, may mimic the symptoms of Guillain Barré. A CSF lymphocytic pleocytosis and/or neurophysiologic testing may help differentiate between the syndromes.<sup>7</sup>

**Peripheral neuropathy.** Symptoms of peripheral neuropathies in patients with Lyme disease tend to be primarily sensory, occurring in a stocking-glove fashion, although patchy paresthesias may also be noted. In some European patients, a dermatologic manifestation is often associated with the neuropathy. Labeled acrodermatitis atrophicans, the skin becomes tissue-thin and discolored.

The same patients have been discovered to develop an **axonal neuropathy\*** in the affected limb.<sup>9</sup> In the case of chronic infection, it has been estimated that one in four patients may have peripheral nerve involvement. These patients may present with mainly sensory symptoms.<sup>10,11</sup>

## NEUROBORRELIOSIS OF THE CENTRAL NERVOUS SYSTEM

**Meningitis.** Although many syndromes involving the central nervous system remain controversial, several have been well-defined. Certainly, the early appearance of lymphocytic meningitis is well recognized. Mildly increased CSF pressure with headache and papilledema may occur. The lymphocytic pleocytosis usually includes tens to hundreds of lymphocytic cells per mL. A mild elevation of protein may also be seen, with CSF glucose usually remaining within a normal range to minimally decreased.<sup>12</sup> The 'typical' symptoms that usually occur with 'aseptic' meningitis, such as photophobia, headache and neck stiffness, are extremely variable with Lyme meningitis.<sup>11,12</sup>

**Intracranial hypertension syndrome.** A rare complication of Lyme disease resulting in headache and potential papilledema, this syndrome seems to be associated more often with children and adolescents. CSF abnormalities may occur. There does not appear to be a correlation with female sex or obesity, as with pseudotumor cerebri.<sup>11,13</sup>

**Encephalomyelitis.** A chronic manifestation of Lyme disease, encephalitis is rare in North American (nearly all cases have been reported in Europe). On MRI there is evidence of parenchymal involvement. This can include hemispheric or brainstem abnormalities and is usually nonspecific, although may mimic ischemic patterns.<sup>11</sup>

**Myelopathy.** Patients may present with symptoms of transverse myelitis so that Lyme disease should be considered in the diagnosis of these patients.<sup>11,14</sup> Rarely, a transverse myelopathy may accompany Lyme radiculoneuritis. This

typically occurs at the same level as radicular involvement and may be preceded by a leptomeningitis.<sup>12</sup>

**Lyme encephalopathy.** This may be the most common late neurologic manifestation of Lyme disease. Patients express difficulties with concentration, sleep disturbance, emotional lability, memory and attention.<sup>11, 15, 16</sup> Despite studies including requirements for CSF abnormalities and SPECT imaging, the definitive diagnosis of Lyme encephalopathy remains elusive.<sup>16</sup> In the consideration of acute encephalopathy, one should note that persons with Lyme-induced cognitive changes likely have a mild encephalitis; these patients should not be confused with mental status changes associated with systemic symptoms.<sup>17</sup> Such patients are likely to have objective findings on neuropsychiatric testing and such a diagnosis should only be made in the presence of appropriate findings after testing has been performed by a qualified professional. This is distinct from the more subjective symptoms patients often experience for weeks to months following an episode of acute infection with *B. burgdorferi* (discussed below).

**Post-Lyme disease.** Several patients who have had Lyme disease have been noted to have other psychiatric and cognitive symptoms, such as fatigue, cognitive slowing and depression. These patients are sometimes diagnosed with post-Lyme disease. It is unlikely that these symptoms indicate persistent neurologic infection, and studies have not shown that antimicrobial therapy is helpful in these patients.<sup>18</sup>

## DIAGNOSIS OF NEUROLOGIC LYME DISEASE

The crucial element for the consideration of neurologic Lyme disease is the presence of an indicative neurologic symptom. Laboratory data should be complimentary and supportive of clinical findings. In evaluating response to therapy, the clinician must remember that many neurologic illnesses improve with time, regardless of treatment.<sup>17</sup> Unfortunately, sensitivity of culture in nervous system infections is low (only about 10% in CSF in Lyme meningitis). The sensitivity of PCR testing appears to be low as well. Confirmation of the diagnosis, therefore, relies largely on serologic

testing. Spinal fluid can, however, be tested for the presence of anti-*B. burgdorferi* antibodies.<sup>19</sup>

The American Academy of Neurology (AAN) guidelines for the diagnosis of neurologic Lyme disease include the consideration of exposure to ticks in an endemic region, clinical abnormalities other than those affecting the nervous system (including cardiac, rheumatologic and dermatologic symptoms), and adequate laboratory support (proof of the presence of *B. burgdorferi* or immunologic evidence of exposure) in addition to the causally-related neurologic disease or syndrome.<sup>20</sup>

---

### ...prolonged courses of antibiotics do not improve outcomes and are not recommended.

---

Additionally, the US Centers for Disease Control and Prevention (CDC) has recommended a two-tier system to test for anti-*B. burgdorferi* antibodies. Serologic testing starts with **enzyme-linked immunosorbent assay (ELISA)**, with usually high sensitivity depending on acuity of infection and organ systems involved, and low specificity due to cross-reacting antigens.<sup>21</sup> Seropositivity may remain for years and can occur in up to 10% of the asymptomatic population in endemic areas. The antibody may not be detected within the first 2 to 6 weeks after exposure, so retesting (or treatment without testing in cases with Erythema migrans) may be important in cases of high clinical suspicion. Borderline or positive results are then confirmed by Western blot. IgM testing is recommended only acutely in disease, when clinical history is limited to 1 to 2 months, and requires 2 of 3 possible bands (sensitivity 32%). Confirmatory testing of IgG presence requires 5 of 10 possible bands (sensitivity 83%). Given lower sensitivities, clinical judgment should be used in patients with positive ELISA whom do not meet Western blot criteria. Also, positive Western blot performed without ELISA may be deceptive and should not be used.<sup>19, 20, 21</sup>

Given the high incidence of *B. burgdorferi* antibody in the CSF of patients who are seropositive but without neuroborreliosis, other tests for the diagnosis of central nervous system disease have been evaluated. A recent study by Blanc, et.al.<sup>22</sup> suggested the use of an **anti-*Borrelia* antibody index (AI)**. The AI is the ratio of anti-*Borrelia* IgG in CSF to anti-*Borrelia* IgG in the serum and is considered positive if greater than or equal to two. The study noted 74 patients with diagnoses of other neurologic diseases all had positive CSF Lyme antibodies; only two of those patients had a positive AI (specificity of 97%). The sensitivity of positive AI was determined to be 75%. The authors suggested the following criteria for diagnosis of neuroborreliosis: presence of four of the following five items. 1) no past history of neuroborreliosis, 2) positive CSF anti-*Borrelia* antibodies, 3) positive anti-*Borrelia* antibody index, 4) favorable outcome after specific antibiotic treatment, 5) no other etiologic diagnosis.<sup>22</sup>

Researchers have also described a B-cell-tropic chemokine, CXCL13, which appears abnormally elevated in CSF of patients with Lyme neuroborreliosis. If confirmed, this cytokine might serve as a marker to assist in the confirmation of the diagnosis of neuroborreliosis.<sup>23</sup>

## TREATMENT OF NEUROBORRELIOSIS

Although the general recommendation in the US is to use parenteral antibiotics whenever the nervous system is involved, there is considerable evidence in the European literature suggesting oral doxycycline (200-400mg/day) may be equally effective in most patients. At the recommended doses it appears that the CSF concentrations of doxycycline exceed minimum inhibitory concentration for most strains. Although there are strain differences between United States and Europe, there probably is not a significant difference in antimicrobial susceptibility.<sup>24</sup> Also, prolonged courses of antibiotics do not improve outcomes and are not recommended. The duration of parenteral treatment suggested is 2 to 4 weeks, with no data showing any definite advantage of prolonged treatment.<sup>25, 26</sup> Oral regimens are generally given for 30 days.

**Table 1. Antimicrobial regimens for the treatment of nervous system Lyme disease**

Medication	Adult dose	Pediatric dose
<b>Oral regimens</b>		
Doxycycline	100 (-200) mg BID	Aged = 8 years: 4 mg/kg/day in 2 divided doses; max 200mg/dose
Amoxicillin (when doxycycline contraindicated)	500 mg TID	50 mg/kg/day in 3 divided doses; max 500 mg/dose
Cefuroxime (when doxycycline contraindicated)	500 mg BID	30 mg/kg/day in 2 divided doses; max 500 mg/dose
<b>Parenteral regimens</b>		
Ceftriaxone	2 g IV daily	50-75 mg/kg/d in single dose, max 2 g
Cefotaxime	2 g IV Q8H	150-200 mg/kg/day in 3-4 divided doses; max 6 g/day
Penicillin G	18-24 MU/day, divided doses Q4H	200-400,000 U/kg/day divided Q4H, max 18-24 MU/day

The AAN published practice parameters for the treatment of nervous system Lyme disease in March, 2007. It recommended:

- 1) Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement (Level B recommendation).
- 2) Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives but supporting data are lacking.
- 3) Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

Treatment regimens are listed in Table 1.

#### REFERENCES

1. Garin B. *J Med Lyon* 1922;71:765-7.
2. Bannwarth A. *Arch Psychiatr Nervenkr* 1944;117:161-85.
3. Steere, AC, Malawista SE, et. al. *Arthritis Rheum* 1977;20:7-17.
4. Said, G. *Neurol Clinics* 2007;25:115-37.
5. Burgdorfer W, Barbour AG, et. al. *Science* 1982;216:1317-9.
6. Steere, AC, Grodzidki, RL, et. al. *NEJM* 1983;308:733-40.
7. Halperin, JJ. *J Neurol Sci* 1998;153:182-91.
8. Halperin, JJ, Luft, BJ, et. al. *Neurol* 1989;39:753-9.
9. Halperin, JJ. *Muscle Nerve* 2003;28:133-43.
10. Halperin, JJ, Luft, B, et. al. *Brain* 1990;113:1207-21.
11. Coyle, PK. Lyme disease. *Curr Neurol Neurosci Rep* 2002;2:479-87.
12. Pachner, AR, Steere, AC. *Neurol* 1985;35:47-53.
13. Kan, L, Sood, SK, Maytal, J. *Pediatr Neurol* 1998;18:439-41.
14. Mantiene, C, Albuher, JF, et. al. *Neuroradiol* 2001;43:485-8.
15. Logigian EL, Kaplan RF, Steere, AC. *J Infect Dis* 1999;180:377-83.
16. Logigian EL, Johnson KA, et. al. *Neurol* 1997;49:1661-70.
17. Halperin, JJ. *Vector Borne Zoonotic Dis* 2002;2:241-7.
18. Halperin JJ, Shapiro ED, Logigian E, et. al. *Neurol* 2007;69: 91-102.
19. Halperin, JJ. *Curr Treat Options Neurol* 2007;9:93-100.
20. Halperin JJ, Logigian EL, et al. *Neurol* 1996;46:619-27.
21. Aguero-Rosenfeld ME, Wang G, et. al. *Clin Microbiol Rev* 2005;18:484-509.

22. Blanc F, Jaulhac B, et. al. *Neurol* 2007;69: 953-8.
23. Rupprecht TA, Pfister HW, et. al. *Neurol* 2005;65:448-50.
24. Karlsson M, Hammers S, et. al. *Antimicrobial agents Chemother* 1996; 40:1104-7.
25. Klemperer M, Hu L. et. al. *NEJM* 2001;345:85-92.
26. Krupp LB, Hymann LG, et. al. *Neurol* 2003; 60:1923-60.

Syed Rizvi, MD, is Director, Rhode Island Hospital Multiple Sclerosis Center, and Assistant Professor of Clinical Neurosciences, Warren Alpert Medical School of Brown University.

Amanda Diamond, MD, is a Neurology Fellow, Warren Alpert Medical School of Brown University.

#### Disclosure of Financial Interests

Syed Rizvi, MD, has no financial interests to disclose.

Amanda Diamond, MD. Consultant: Guidant, Teva, Berlex (Bayer), Genentech, Cordis.

#### Discussion of drug used off-label or under investigation:

Doxycycline, amoxicillin, ceftriaxone, ceftriaxime and penicillin are not FDA-approved for the treatment of Lyme disease, but all have been shown either effective or have evidence indicating efficacy.

#### CORRESPONDENCE:

Syed Rizvi, MD  
2 Dudley Street, suite 555  
Providence RI 02903  
Phone: (401) 444-3799  
e-mail: SRizvi@lifespan.org