

# Lyme Neuroborreliosis in Adults: Clinical Aspects

Lyme neuroborreliosis is caused by the tick-borne spirochete *Borrelia burgdorferi* (Bb) sensu lato. The Bb sensu lato complex consists of at least three human pathogenic species; Bb sensu stricto, *B. garinii* and *B. afzelii*. All are endemic in Europe, whereas Bb sensu stricto is the only species detected in North America. This may account for clinical differences in American and European neuroborreliosis. In this short review we convey basic facts, our own experience and some new knowledge of clinical manifestations, diagnostics, treatment and prognosis of Lyme neuroborreliosis in European adult patients.

## Clinical manifestations

At least 80% of European patients with neuroborreliosis present with facial weakness due to facial neuritis, or lancinating pain, numbness and sometimes weakness in an extremity, the chest or abdomen due to spinal radiculitis, or a combination of these (Bannwarth's syndrome).<sup>1,2</sup> More unusual symptoms are diplopia due to oculomotor, trochlear- or abducens neuritis,<sup>3</sup> visual loss due to retrobulbar optic neuritis,<sup>4</sup> hearing loss due to acoustic neuritis,<sup>5</sup> dizziness due to vestibular neuritis,<sup>6</sup> shortness of breath due to diaphragmatic paralysis,<sup>7</sup> and isolated muscle weakness and fasciculations due to selective involvement of motor neurons and motor roots.<sup>8</sup> A recent report describes a patient with an autoimmune-mediated motor neuropathy with conduction blocks and GM1 antibodies concomitant to, and probably triggered by infection with Bb.<sup>9</sup> Symptoms from the central nervous system are rare, but some patients may present with weakness and clumsiness of both legs due to myelitis,<sup>10</sup> or memory loss, confusion, unsteadiness, parkinsonism,<sup>11</sup> or opsoclonus myoclonus due to focal encephalitis.<sup>12</sup> Vasculitis may account for acute stroke like or relapsing symptoms with hemiparesis and aphasia.<sup>13,14</sup> Most patients with Lyme neuroborreliosis suffer from

constitutional symptoms in addition to their neurological complaints, but it should be emphasized that headache, fatigue, paresthesias or malaise alone are not typical symptoms of Lyme neuroborreliosis.

The onset of Lyme neuroborreliosis is usually subacute with progression over weeks, so-called early or stage II Lyme neuroborreliosis. Some cases are self-limiting, even without treatment. Less than 10% of untreated cases progress slowly over months and years, so-called late, or stage III, Lyme neuroborreliosis.<sup>1</sup>

## Laboratory confirmation

Due to the low yield from culture and polymerase chain reaction (PCR) in Lyme neuroborreliosis, we are left with indirect laboratory diagnostic methods. Both an elevated cell count in the cerebrospinal fluid (CSF) and elevated CSF-to-serum Bb antibody index, indicating intrathecal Bb antibody production, have to be present to confirm definite Lyme neuroborreliosis.

In day to day practice, however, diagnostics may be a challenge because the CSF Bb antibody index has a low sensitivity (about 75%) in patients with a symptom duration of less than six weeks,<sup>15</sup> and the CSF cell count may be normal in rare patients infected with certain genotypes of Bb.<sup>16</sup> It therefore seems reasonable to introduce the term possible Lyme neuroborreliosis. Suggested case definitions with two levels of diagnostic accuracy are presented in Table 1.

Different other laboratory tests such as CSF CXCL<sup>13,17,18</sup> LTT MELISA,<sup>19</sup> and Bb specific immune complexes,<sup>20</sup> may in the future be helpful diagnostic markers, but they need further validation.

## Antibiotic treatment

All patients with Lyme neuroborreliosis should be treated with antibiotics to achieve rapid resolution of symptoms, and, theoretically, to prevent further dissemination



**Dr Unn Ljøstad** is a consultant clinical neurologist based at Sørlandet Hospital, Kristiansand, Norway. She will present her doctoral thesis on 'Lyme neuroborreliosis, diagnostics and treatment in European adult patients' later this year.



**Dr Åse Mygland** is Consultant Neurologist at Sørlandet Hospital Kristiansand and Assistant Professor at the Institute of Clinical Medicine, University of Bergen, Norway. She has a special interest in managing patients with neuromuscular and inflammatory neurological disorders.

## Correspondence to:

Unn Ljøstad,  
Department of Neurology,  
Sørlandet Hospital,  
Servicebox 416,  
4604 Kristiansand, Norway.  
Email. unn.ljostad@sshf.no

**Table 1: Suggested case definitions**

Definite neuroborreliosis	Possible neuroborreliosis
All three criteria fulfilled	Criterion 1 and one of a-d
1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons 2. CSF pleocytosis (>5 leucocytes/mm <sup>3</sup> ) 3. Intrathecal Bb antibody production	1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons a. CSF pleocytosis (> 5 leucocytes/mm <sup>3</sup> ) b. Intrathecal Bb antibody production c. Bb antibodies in serum d. Erythema migrans during the last four months

**Table 2: Suggested treatment guidelines for European adult patients with Lyme neuroborreliosis**

<b>Drug</b>	<ul style="list-style-type: none"> <li>• First choice:               <ul style="list-style-type: none"> <li>o Oral doxycycline 200 mg daily</li> </ul> </li> <li>• Alternative choices:               <ul style="list-style-type: none"> <li>o IV ceftriaxone 2 g daily</li> <li>o IV penicillin G 3 g X 3-4</li> <li>o IV cefotaxime 2 g X 3</li> </ul> </li> </ul>
<b>Treatment duration</b>	2-4 weeks
<b>Repeated course with a different drug</b>	Should be restricted to patients with definite Lyme neuroborreliosis who do not improve after first course (exceptionally rare)
<b>Post Lyme disease syndrome</b>	Symptomatic treatment

and persistence of the infection. European Concerted Action on Lyme Borreliosis (EUCALB) suggests 14-30 days courses of IV ceftriaxone, IV penicillin, oral amoxicillin or oral doxycycline for early subacute Lyme neuroborreliosis, and 30 days courses of IV ceftriaxone or IV penicillin for late Lyme neuroborreliosis.<sup>21</sup> IV regimens with penicillin and ceftriaxone have similar efficacy, and it has recently been shown that oral doxycycline for 14 days is as efficient as IV ceftriaxone for 14 days in adult European patients.<sup>2</sup> We therefore suggest oral doxycycline as a first treatment choice for Lyme neuroborreliosis in adults, due to lower cost and easier administration. Suggested treatment guidelines are presented in Table 2. Enhanced therapeutic efficacy of extended treatment beyond two to three weeks is not well documented. The issue of longer treatment duration in all, or subgroups of, patients with Lyme neuroborreliosis, thus remains to be answered.

### How to handle 'possible' Lyme neuroborreliosis

In our opinion patients who fulfill the criteria for possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. If one course does not lead to lasting improvement, a search for other causes of the symptoms should be sought.

### Outcome after treatment

Outcome after treatment for Lyme neuroborreliosis is debated. A Swedish questionnaire follow-up study found persistent complaints 2.5 years post-treatment in 50% of patients who had experienced neu-

roborreliosis, as compared to 16% in control patients who had experienced erythema migrans.<sup>22</sup> Most of the complaints were subjective such as headache, attention problems, memory difficulties, depression and paresthesia. The real burden of remaining symptoms and neurological abnormalities after treatment for Lyme neuroborreliosis, as well as the pathophysiological mechanisms of post-Lyme disease syndrome, should be better charted in well designed studies. It seems clear that additional prolonged antibiotic treatment does not give any benefit in post-Lyme disease syndrome, and it should be remembered that treatments continued for months carry substantial risk for the patients.<sup>23</sup> Anecdotal reports of better response to long-term or repeated antibiotic treatment exist, but this could be due to placebo effect, which is known to occur in at least 30% of cases. A positive Bb antibody index may last for years and is not a suitable marker for treatment response.

### Conclusion

We suggest two levels of diagnostic accuracy for clinical practice; definite and possible Lyme neuroborreliosis. Treatment with 2-4 weeks courses of IV ceftriaxone, penicilline or oral doxycycline are effective. We recommend oral doxycycline for two weeks as the first treatment choice. Patients with possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. Extensive antibiotic treatment is not recommended under any circumstances. The prognosis of neuroborreliosis and pathophysiology of post-treatment conditions need further studies.

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