CNS involvement is more varied. Conceptually, this can be divided into extra-axial disease such as meningitis, parenchymal disease such as encephalomyelitis, and CNS dysfunction without obvious structural CNS change. As with PNS involvement, when patients become symptomatic fairly early in infection, involvement tends to develop fairly rapidly with a prominent inflammatory response. Lymphocytic meningitis is the most common form of CNS involvement. Far more dramatic, but fortunately rare, is an encephalomyelitis. Patients develop focal inflammation of the brain or spinal cord parenchyma (34–36). This disorder occurs in perhaps 0.1% of patients with untreated *B. burgdorferi* infection, both in Europe and in North America. Involvement primarily involves the white matter; experimental evidence indicates that the spirochete preferentially adheres to oligodendroglia (37), perhaps accounting for this tropism. Typically, most patients present with a myelopathic picture with progressive gait spasticity and sphincter dysfunction. Others develop focal inflammation in the brain, with symptoms and findings appropriate to the site of inflammation. Seizures occur rarely if at all. Brain magnetic resonance imaging typically demonstrates areas of inflammation within white matter. Antibiotic therapy will generally arrest disease progression, and in many patients leads to some improvement. In some, in whom significant structural damage has occurred, residua will occur.

The mechanism underlying this disorder remains unclear. The few pathologic studies available demonstrate focal perivascular inflammation (38), similar to that seen in the peripheral nerve. There is some evidence to suggest that organisms are present in the region of inflammation (38), but this cannot yet be considered conclusive. The observation that patients can improve significantly after antibiotic treatment certainly supports the conclusion that viable bacteria play an essential role in this process. However, it has been extraordinarily difficult to culture spirochetes from such patients. To date, comparable lesions have not occurred in the monkey model. Although transient bacterial seeding of the neuraxis has been demonstrated in several animal models, in none has parenchymal brain or spinal cord damage been demonstrable (39).

Far more common is a mild confusional state, without focal neurologic signs. This phenomenon was originally reported in patients with systemic nonneurologic Lyme disease, typically patients with chronic arthritis (27,35). These individuals described difficulty with memory and cognitive functioning. Originally thought to be a peculiarly American phenomenon, similar observations have now been made in European patients (40). Mini-Mental Status testing and more formal neuropsychologic testing typically demonstrate significant, although not profound, cognitive deficits, all of which generally improve after antimicrobial therapy (41–43). Other evaluations in these patients are generally less informative. Magnetic resonance images in some demonstrate small regions of abnormality in the white matter. In most, scans are negative. CSF in some is negative; in others mild nonspecific abnormalities or occasionally even intrathecal antibody production is found. In some affected patients, this appears to be a mild version of the more dramatic encephalomyelitis. In others, there is little compelling evidence of CNS infection. In such individuals it has been postulated that this might be a toxic-metabolic encephalopathy secondary to infection outside the neuraxis. In one study, elevated concentrations of quinolinic acid were demonstrated in serum, with parallel elevations in the CSF (44). Quinolinic acid, a tryptophan metabolite, is produced in response to inflammation under the control of γ-interferon and tumor necrosis factor-α and is pharmacologically active at NMDA receptors where it can affect neuronal function. This model suggests a mechanism by which a soluble neuroimmunomodulator is produced in the periphery, diffuses into the CNS, and there has a pharmacologic action altering CNS function. Whether this or some other cytokine or other molecule actually plays such a role remains to be confirmed.

Finally, much has been said about how Lyme disease can masquerade as other neurologic diseases—an observation that stems in large part from the lack of specific, unique, gold standard diagnostic tests both for Lyme disease and for many other neurologic syndromes. The disorder that has most frequently been confused with neuroborreliosis has been MS. Because Lyme encephalomyelitis and MS both involve acute inflammation in the white matter, it is clear why some confusion could arise. Moreover, there is suggestive evidence that Lyme disease may be one of numerous nonspecific stimuli to inflammation within the CNS, which, perhaps by increasing local production of γ-interferon can trigger MS attacks. However, it is extremely unusual for Lyme encephalomyelitis to relapse after being definitively treated, and it is even more uncommon for patients with MS to have evidence of intrathecal production of antibodies against *B. burgdorferi*.

The confusional state has similarly led to concerns that Lyme disease could cause Alzheimer disease. Although, like many other infections, Lyme disease can lead to a transient worsening of cognitive functioning in affected patients, there is little to suggest that it causes a permanent progressive dementing illness resembling Alzheimer disease.

There has also been interest in the potential overlap of Lyme neuroborreliosis with motor neuron disease (45). The radiculoneuropathy of Lyme disease commonly has a more prominent motor than sensory component, leading to some potential for confusion. If, in addition, the patient has myelopathic involvement, the combination of upper and lower motor neuron signs may resemble amyotrophic lateral sclerosis. However, assessment of CSF and careful clinical analysis will usually differentiate between these disorders.
Finally, anecdotal reports have suggested associations with Parkinson's disease and a variety of psychiatric disorders. No systematic studies have substantiated these associations to date, so for now these associations must be considered conjectural.

TREATMENT

There continues to be considerable controversy concerning the optimal treatment of Lyme neuroborreliosis (Tables 2 and 3). Several randomized blinded studies demonstrated that oral treatment with either doxycycline or amoxicillin for 3 weeks is highly effective in early disease (46). In patients with Lyme arthritis, oral regimens can also be effective (47). In patients with more longstanding or more severe disease or involvement of the CNS, parenteral treatment is generally chosen, typically a third-generation cephalosporin such as ceftriaxone or cefotaxime. Most studies have shown the two agents to be equally effective. Studies comparing 2- and 4-week regimens also failed to prove that a longer course was more beneficial (48,49). However, anecdotally, many centers that treat large numbers of patients have observed CNS relapses in patients who have received just 2 weeks of therapy; it has consequently become commonplace to treat for 4 weeks when using parenteral therapy. Although some recommend substantially longer courses, there is no scientific evidence that this confers any additional benefit; however, because of the widespread feeling that such prolonged courses are needed, the National Institutes of Health has recently initiated a study to address this issue.

Two other regimens may be useful in the treatment of CNS disease. One European study demonstrated that oral doxycycline was highly effective in most patients with Lyme meningitis (50); however, long-term follow-up in this group was limited. Similarly, in patients with PNS disease, including some with facial nerve paralysis, oral regimens may be effective. However, this has not been studied extensively, and at this point treatment of these patients must be individualized. Finally, parenteral penicillin has been used for years, with considerable efficacy. The organism does tend to be more sensitive to ceftriaxone and cefotaxime, particularly at concentrations achieved by these drugs in the CNS. Ceftriaxone has generally become the preferred agent for parenteral therapy both because of some studies suggesting greater efficacy and also because of ease of dosing.

CONCLUSION

Lyme disease, a recently described spirochosis, frequently affects the CNS and PNS. It does so in one of several distinct manners. PNS involvement is due to a mononeuropathy multiplex but may be manifest as a monoradiculopathy, mononeuritis, or more diffuse process. CNS involvement is most frequently manifest as a benign lymphocytic meningitis. Rare patients develop a focal or multifocal leuкоencephalomyelitis. Some patients develop encephalopathy that may be due to either a mild encephalitis or the remote effects of a non-CNS infection. Accurate diagnosis of CNS infection requires assessment of CSF, with measurement not just of CSF anti-Borrelia antibody but of actual intrathecal antibody production. When the diagnosis is secure, antimicrobial therapy is usually successful.

REFERENCES


### TABLE 3. Treatment suggestions

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>IV ceftriaxone or cefotaxime or penicillin or? po doxycycline</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>IV ceftriaxone or cefotaxime or penicillin</td>
</tr>
<tr>
<td>PNS (peripheral neuropathy, radiculoneuropathy, cranial neuropathy)</td>
<td>CSF; oral regimens may be effective CSF; as encephalomyelitis</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>CSF; oral regimens may be effective CSF; as encephalomyelitis</td>
</tr>
</tbody>
</table>

PNS, peripheral nervous system; CSF, cerebrospinal fluid.

### TABLE 2. Treatment regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>2 g IV q24h</td>
<td>14–28</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g IV q8h</td>
<td>14–28</td>
</tr>
<tr>
<td>Penicillin</td>
<td>3–4 MU IV q4h</td>
<td>14–28</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100–200 mg po b.i.d.</td>
<td>21–30</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500–1,000 mg po q.i.d.</td>
<td>10–30</td>
</tr>
</tbody>
</table>

*a*Ceftriaxone should probably not be used in the third trimester of pregnancy.

*b*Doxycycline should not be used in pregnant women or in children age 8 or under.

From Ref. 51.


Wormser GP. Treatment and prevention of Lyme disease, with emphasis on antimicrobial therapy for neuroborreliosis and vaccination. *Semin Neurol* 1997;17:45–52.