Toward a Better Understanding of European Lyme Neuroborreliosis

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Lyme borreliosis occurs in parts of both North America and Eurasia. The most common clinical manifestation is the characteristic skin lesion erythema migrans (EM) [1]. Other manifestations include arthritis, meningitis, mononeuritis multiplex, and myocarditis. In North America, the only well-established cause of Lyme borreliosis is *Borrelia burgdorferi*, whereas in Europe most cases are caused by *Borrelia afzelii* or *Borrelia garinii* and only a minority by *B. burgdorferi* [1].

Different species of Lyme borrelia have propensities to cause different clinical manifestations [1, 2]. Evidence based on culture, polymerase chain reaction (PCR) testing, serologic patterns, or other methodologies indicates that *B. garinii* is the species of Lyme *Borrelia* most often associated with European Lyme neuroborreliosis [2–4]. Although *B. burgdorferi* is well known to cause Lyme neuroborreliosis in the United States, available evidence indicates that infection with particular subtypes is disproportionately associated with neurologic involvement [5, 6]. Thus, neurotropism is a virulence characteristic not equally shared by all Lyme *Borrelia* species or by all subtypes of a given species. The same is true for species and strains of relapsing fever *Borrelia* [7, 8].

In this issue of *Clinical Infectious Disease*, Ogrinc et al [9] report the results of lumbar punctures performed on a subgroup of patients with EM with symptoms or signs that raised the possibility of Lyme meningitis. A primary finding was that patients with radicular pain, peripheral facial nerve palsy, and/or meningeal signs were likely to have meningeal inflammation. Symptoms of headache, memory or concentration problems, paresthesias, dizziness, fatigue, neck pain, and nausea or vomiting were not indicative of meningitis.

In our experience, even just 1 or 2 doses of antibiotic will negatively affect the yield of borrelial cultures.

In the Ogrinc et al study [9], only 5 of the 31 (16.1%) patients with meningitis had a positive CSF culture, but 4 of the 5 (80%) positive cultures grew *B. garinii*. Indirect evidence, however, suggested that *B. garinii* was responsible for many of the other cases. Of the 12 patients with a positive skin culture for *B. garinii*, 9 (75%) had CSF pleocytosis, compared with only 3 of 41 (7.3%) patients with a positive skin culture for *B. afzelii* (P < .001). In addition, among the 12 patients with both a positive skin culture and CSF pleocytosis, 9 (75%) were infected with *B. garinii*.

Another remarkable observation was that CSF pleocytosis was more common in patients whose EM skin lesions grew at a substantially faster rate. The largest
EM diameter increased at a rate of 2 cm per day in patients with CSF pleocytosis compared with just over 1 cm per day in those without CSF pleocytosis [9]. In a prior study of culture-confirmed Slovenian patients with EM, of whom 53 had B. garinii and 200 B. afzelii infection, the rate of increase of the largest EM diameter in B. garinii–infected patients was also approximately twice that of B. afzelii–infected patients [11]. In the latter study, the daily increase in the EM surface area was 12.5 cm² in B. garinii–infected patients compared with just 3 cm² per day in those with B. afzelii infection (P < .001). These findings also suggest that most of the cases of Lyme meningitis in the Ogrinc et al study [9] were caused by B. garinii.

What accounts for the neurotropism of B. garinii or for its ability to cause more rapid expansion of EM skin lesions has not been defined [12–14]. It has been suggested that B. garinii may cause radiculoneuritis by neural spread [15, 16] rather than by hematogenous dissemination, which would be consistent with the infrequency of positive blood cultures for B. garinii in patients with proven B. garinii skin or CSF infection in the Ogrinc et al study [9]. However, it also could be argued that an insufficient quantity of plasma was cultured to exclude spirochetaemia. Studies in the United States have suggested that yields are much greater if at least 9 mL of plasma is cultured [17], whereas 4 mL to 5 mL was cultured by Ogrinc et al [9]. However, multiple EM skin lesions, which are thought to arise by hematogenous dissemination from the original site of the tick inoculation of the spirochete to other skin sites, were not found disproportionately in patients with meningitis. This argues against the hypothesis that spirochetaemia went undetected. In a prior Slovenian study [3], evidence for radiculoneuritis was present in 65% of 23 patients whose CSF cultures grew B. garinii, suggesting that dorsal root, dorsal root ganglia, or other peripheral nerve locations may be common sites of infection in neuroborreliosis due to B. garinii infection. Based on the consistently low yields of culture and the generally low rates of positive PCR assays on CSF samples of Lyme neuroborreliosis cases in both Europe and the United States [3, 9, 18, 19], it seems clear that spirochetes are present in low numbers or not at all in the subarachnoid space of such patients.

In the Ogrinc et al study [9], B. afzelii grew from the CSF of 1 of the 130 (0.76%) patients without CSF pleocytosis and represented the sole positive CSF isolate from these patients. To interpret this observation properly, it would have been desirable to have confirmed this finding by an independent method such as a PCR assay. Without confirmation, it is impossible to exclude laboratory contamination as the cause of this phenomenon, which has been described for CSF cultures by other investigators [20]. However, other possible explanations include very early infection preceding the development of pleocytosis, contamination of CSF with blood-borne spirochetes introduced by the lumbar puncture needle, or central nervous system invasion without pathology, as has been postulated to occur with Treponema pallidum in certain patients with early syphilis [21].

The presence of EM reliably establishes the diagnosis of Lyme disease. Thus, patients with EM who in addition have seventh nerve palsy, meningeval signs, or radiculopathy can quite reasonably be considered as having Lyme neuroborreliosis, provided that coinfection with a tick-borne encephalitis virus is excluded. Thus, the findings in the Ogrinc et al study [9] are helpful in clarifying the pathogenesis of various symptom complexes in Lyme borreliosis. However, the implications for therapy are less clear. Because studies in Europe have demonstrated that treatment of Lyme neuroborreliosis with oral doxycycline is as effective as parenteral therapy with ceftriaxone [22, 23], documentation of CSF abnormalities would not necessarily alter the choice of treatment. Although CSF analysis might provide a baseline for judging treatment response, currently recommended antimicrobial regimens appear to be sufficiently effective that serial CSF examinations are generally unnecessary. Thus, outside of a research study, lumbar puncture is probably not necessary in the majority of European patients with EM, whether or not there is a suspicion of neurologic involvement.

Note

Potential conflicts of interest. G. P. W. has received research grants from the Centers for Disease Control and Prevention, the National Institutes of Health, ImmuneXics Inc, Bio-Rad, DiaSorin Inc, and bioMérieux; holds equity in Abbott; has served as an expert witness in malpractice cases involving Lyme disease and in a disciplinary action for the Missouri Board of Registration for the Healing Arts; and has served as an unpaid board member for the American Lyme Disease Foundation and as a consultant to Baxter for Lyme vaccine development. J. J. H. has served as an expert witness in several medico-legal cases concerning Lyme disease and has equity in Abbott, Bristol-Myers Squibb, Johnson & Johnson, and Merck.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


