A Twist on Lyme: the Challenge of Diagnosing European Lyme Neuroborreliosis

Naila Makhani,1 Shaun K. Morris,2 Andrea V. Page,3 Jason Brophy,4 L. Robbin Lindsay,5 Brenda L. Banwell,1 and Susan E. Richardson6*

Division of Neurology,1 Division of Infectious Diseases,2 and Division of Microbiology,6 Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; Division of Infectious Diseases, Children’s Hospital of Eastern Ontario and University of Ottawa, Ottawa, Ontario, Canadaa; Division of Infectious Diseases, University Health Network and University of Toronto, Toronto, Ontario, Canada3; and Public Health Agency of Canada, Winnipeg, Manitoba, Canada6

Received 6 August 2010/Returned for modification 7 September 2010/Accepted 2 November 2010

Lyme neuroborreliosis is a tick-borne illness with central and peripheral nervous system manifestations. Clinical features and methods for accurate diagnosis differ across world regions owing to different causative Borrelia species. The importance of these distinctions is highlighted by a 12-year-old Canadian girl who acquired Lyme neuroborreliosis in Europe.

CASE REPORT

A 12-year-old girl was admitted to our hospital on 28 August 2007 with a 10-day history of mid-scapular back pain and 24 h of unilateral facial weakness 2 weeks after returning from a 1-month vacation in rural France. She had been horseback riding, but did not recall any insect or tick bites. Ambulation and bowel and bladder function were normal. There was no recent history of fatigue, myalgia, or arthralgia, and the family did not recall a preceding rash.

On examination, forward neck flexion elicited Lhermitte’s sign (electricity sensation down the spine indicative of cervical spinal cord pathology such as inflammation). A right-sided lower motor neuron facial nerve palsy and bilateral increased lower extremity tone were noted. Muscle power was normal in all muscle groups tested. Deep tendon reflexes were increased at the knees and ankles, and the left plantar response was extensor. There was reduced sensation to pinprick and temperature between the T4 and T6 sensory levels.

Magnetic resonance imaging (MRI) of the spine revealed increased T2-weighted signal in the spinal cord, mild spinal cord swelling, and diffuse gadolinium enhancement of the spinal meninges and proximal nerve roots (Fig. 1). Brain MRI was normal. The peripheral white blood cell (WBC) count and serum erythrocyte sedimentation rate were normal. The cerebrospinal fluid (CSF) protein level was elevated (1.25 g/liter; normal, 0.15 to 0.40 g/liter), and the concentration of CSF glucose was reduced (1.6 mmol/liter; normal, 2.1 to 3.6 mmol/liter). The CSF WBC count was 424 × 106 (87% lymphocytes), with zero red blood cells. Cytological analysis was negative for malignant cells. CSF bacterial cultures were negative. CSF PCR studies were negative for varicella-zoster virus, human herpesviruses 6 to 8, West Nile virus, herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, enterovirus, and Mycoplasma pneumoniae. Oligoclonal bands were present in the CSF, but not serum. CSF PCR using probes targeting Borrelia burgdorferi 23S rRNA genes was negative. Testing for intrathecal antibodies was not possible due to an insufficient amount of CSF.

Borrelia serology obtained 10 days after admission was positive by enzyme-linked immunosorbent assay (ELISA) using two different commercial kits, namely, the Immucor C6 ELISA (in which the antigen is the C6 peptide of the VlsE protein) and the Diagnostic Automation IgG and IgM ELISA (Borrelia burgdorferi B31 strain whole-cell sonicates) (Table 1). Confirmatory Western blot testing (MarDx) was negative for both anti-Borrelia IgG and IgM according to the manufacturer’s and CDC criteria for interpretation. The only band present on the MarDx IgG blots was p41. The results from IgM blots were less consistent, and blots had either p41 or no detectable bands present.

The clinical features of a lower motor neuron facial nerve palsy, meningoaradiculitis, CSF pleocytosis, positive serology by ELISA, and recent travel to an area of endemicity led to the presumptive diagnosis of transverse myelitis due to Lyme neuroborreliosis. Intravenous ceftriaxone was administered for 28 days starting on the day of presentation to the hospital. The back pain and Lhermitte’s sign resolved within 48 h. Facial weakness remained marked after 2 weeks of antibiotic therapy, leading to treatment with 7 days of oral prednisone. Nearly complete recovery of facial expression occurred within 12 weeks of presentation.

In order to reconcile the indeterminate initial laboratory investigations for Lyme borreliosis with the patient’s clinical symptoms and response to antimicrobial therapy, further serologic analysis was performed (Table 1). The original serum sample taken on the day of admission showed a positive screening ELISA result and negative North American IgM and IgG Western blots (i.e., MarDx). Serum samples taken 17 days, 6 weeks, and 3 months after disease onset showed the same results. Given our child’s history of European travel, IgM and
IgG Western blots using the European assay were performed with the Trinity Biotech EU-Lyme IgM and EU Lyme VlsE IgG Western blot systems, respectively. These test systems incorporate low-passage antigens of *Borrelia afzelii* “PKO” and *Borrelia garinii*, which appear to be exclusive to Europe and Japan. Banding patterns are interpreted on a modified MiQ 12000 interpretive criteria, which requires the presence of two or more bands (i.e., p17, p39, p41 and *B. afzelii* [PKO] or *B. garinii* 22-kDa protein OspC) to be considered positive. The European IgM Western blot was found to be positive beginning 1 week after admission (17 days after onset of symptoms and 7 days after onset of treatment) and persisted for 3 months after presentation. These samples produced bands corresponding to the p41 and *B. garinii* 22-kDa OspC regions. IgG antibodies remained undetectable on the European Western blot when serum was tested 3 months postpresentation.

We highlight the challenge of diagnosing European Lyme neuroborreliosis in a Canadian child. Lyme neuroborreliosis is a systemic *Borrelia* infection with neurological involvement. With rare exceptions, the causative species in North America is *Borrelia burgdorferi* sensu stricto. In Europe, at least three species may be responsible, including *Borrelia burgdorferi* and, more commonly, *Borrelia garinii* or *Borrelia afzelii*. Transmission to humans typically occurs through the bite of an infected *Ixodes* species of tick (e.g., *Ixodes scapularis* in North America and *Ixodes ricinus* in Europe). Although human infection can occur throughout the year, most cases occur during early summer months when the nymphal stage is most active (3).

Recognition of the symptoms of Lyme borreliosis is essential for prompt diagnosis and treatment. North American Lyme borreliosis generally manifests itself in three distinct clinical stages (reviewed in reference 20). Well-characterized neurological symptoms attributable to Lyme borreliosis include a primarily lymphocytic meningitis with or without painful cranial neuritis or polyradiculitis, encephalomyelitis, and peripheral neuropathy (11). Importantly, the clinical features of European Lyme borreliosis are different from those of North American disease (13, 17, 20). Erythema migrans is often slower spreading and appears less intensely inflamed in European cases and so may be less readily recalled by patients. The most common presentation of European Lyme neuroborreliosis is the triad of Banworth’s syndrome (lymphocytic meningitis, cranial neuropathy, and painful radiculitis) rather than aseptic meningitis, which is seen more commonly in North American disease. Additionally, if left untreated, infections caused by European *Borrelia* genospecies are more likely to progress to chronic low-grade encephalitis. The most common clinical presentation of Lyme neuroborreliosis in children is peripheral facial nerve palsy, occurring in up to 71% of patients, followed by aseptic meningitis (7, 18). Transverse myelitis, other cranial neuropathies, and ataxia have been rarely reported in children (4, 14–16, 19). Nonspecific symptoms such as fatigue, headache, and myalgias are common, and neurological examination was normal in 21% of children in one Dutch study (7).

Although the clinical features of our patient were highly

---

**TABLE 1. Summary of laboratory diagnostic testing results**

<table>
<thead>
<tr>
<th>Date (mo/day/yr)</th>
<th>Sample</th>
<th>ELISA</th>
<th>Western blot (MarDx)</th>
<th>European Western blot (Trinity Biotech EU)</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C6 (Immunetics)</td>
<td>IgM and IgG (Diagnostic Automation)</td>
<td>IgM</td>
<td>IgG</td>
</tr>
<tr>
<td>8/28/07</td>
<td>CSF</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>8/29/07</td>
<td>Serum</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>9/4/07</td>
<td>Serum</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>9/26/07</td>
<td>Serum</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>11/28/07</td>
<td>Serum</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*NSQ, not sufficient quantity; NP, not performed.*
suggestive of Lyme neuroborreliosis, investigations using diagnostic methods optimized for North American *B. burgdorferi sensu stricto* were largely negative. Specific testing for an immune response to European strains of the organism was suggestive but not conclusive for an acute infection. While our patient did have serum anti-*Borrelia* IgM antibodies detectable by Western blotting, she did not subsequently develop IgG seropositivity by this procedure. The ViSE C6 peptide used in the ImmuneNet ELISA is a conserved sequence found in *Borrelia burgdorferi* and the European genospecies *B. afzelii* and *B. garinii*, which provides an extremely *Borrelia*-specific assay. Positive results in a C6 ELISA often precede the development of a positive IgG Western blot (presence of five or more significant bands), which appears to be the case for this patient. While the absence of detectable Western blot IgG antibodies is quite surprising given the extent of neurological involvement at the time of presentation, the lack of a Western blot IgG antibody response after treatment is not. Studies have clearly demonstrated the negative impact of antimicrobial treatment on the production and subsequent detection of Western blot IgG antibodies (1). Alternatively, isolated elevations in anti-*Borrelia* IgM serum antibodies are present in up to 20% of children with other neurological diagnoses, including viral meningitis and headache (5).

There is no “gold standard” diagnostic test for Lyme neuroborreliosis. Direct culture of *Borrelia* species and PCR are of low sensitivity; therefore, laboratory diagnosis instead relies on the detection of anti-*Borrelia* antibodies. In North America, testing follows a two-step algorithm (8, 9). Serum samples are screened for antibodies with an ELISA, a relatively sensitive, but not specific test. Confirmatory testing is then performed using Western blotting, which is specific, but not sensitive. The sensitivity of the two-step approach is well described in intrathecal antibody testing, which may be less than 40% in cases of acute stage 1 Lyme borreliosis. Direct culture of *Borrelia burgdorferi* strains induce variable host antibody responses leading to reduced reliability of serum Western blot analysis (10, 12). For the diagnosis of European Lyme neuroborreliosis, examination of the ratio of intrathecal to serum antibodies may be a more sensitive test (5, 6). In this case, diagnostic testing was initiated in accordance with Canadian Public Health Laboratory Network guidelines, which recommend consideration of CSF PCR, and not intrathecal antibody testing, in patients with neurological symptoms (8). Although determination of a CSF-to-serum antibody index is a more sensitive test for Lyme neuroborreliosis acquired in Europe, no residual CSF remained for this analysis.

Lyme neuroborreliosis should be considered in the differential diagnosis of new neurological symptoms in children and adults with histories of travel to areas of Lyme endemicity both within and outside of North America. The geographic site of potential exposure must be disclosed to the diagnostic laboratory so that the appropriate assays may be employed. Timely recognition and treatment are imperative in order to facilitate recovery and to prevent long-term sequelae.

We are indebted to Antonia Dibernardo and Katarina Bernat of the Public Health Agency of Canada for their invaluable technical expertise on the laboratory diagnostics components of this investigation.

**REFERENCES**


