Stroke in Neuroborreliosis

Eugene F. May, MD, and Bahman Jabbari, MD

A 20-year-old man suffered two thalamic infarctions during the course of neuroborreliosis and was successfully treated with intravenous ceftriaxone. Review of 11 additional cases of stroke and cerebral vasculitis in neuroborreliosis suggests that there is a meningovascular form of the infection with predilection for the posterior circulation and an association with the European strains of Borrelia burgdorferi. (Stroke 1990;21:1232-1235)

Lyme disease is a systemic disease caused by infection with the tick-transmitted spirochete Borrelia burgdorferi. The first stage of the disease is often manifested by a skin lesion, erythema chronicum migrans, at the site of the tick bite. This may be followed weeks to months later by a second stage, during which neurologic and cardiac symptoms and signs appear. Approximately 15% of patients with Lyme disease develop neurologic complications, the most common of which are meningoencephalitis, cranial neuritis, and radiculoplexitis. Strokes or vasculitis as complications of neuroborreliosis have been reported only rarely. In fact, some recent reviews of neurologic manifestations of Lyme disease fail to mention stroke as a complication. We report a patient with bilateral thalamic infarction associated with infection with B burgdorferi and review the subject of stroke in this disorder.

Case Report

The patient is a previously healthy 20-year-old man from California in the United States Army, stationed in southern Germany from late 1987 through the onset of his illness. In January 1989, he began to experience intermittent occipital headaches and was treated symptomatically with ibuprofen until March 15, when he suddenly developed light-headedness, vertical diplopia, and dysarthria. He was found to be afebrile and without meningismus. The neurologic examination disclosed dysarthric speech, a right central facial weakness, and mild clumsiness of the right upper extremity. Computed tomography (CT) and magnetic resonance imaging (MRI) (Figure 1, left) demonstrated an area of radiolucency and increased T2 signal consistent with infarction of the left posterior thalamus. Lumbar puncture revealed an inflammatory spinal fluid. Bacterial cultures were negative. The patient's diplopia resolved within 2 days and his light-headedness and incoordination resolved over the course of a week. However, he had persistent headaches. He was transferred to our facility on March 24 for further evaluation.

Multiple lumbar punctures showed persistent lymphocytic pleocytosis with elevated protein content and hypoglycorrhachia (Table 1). Serum and cerebrospinal fluid (CSF) bacterial, fungal, acid-fast bacillus, and viral cultures and titers were negative. Serum fluorescent treponeme antibody assay and serum and CSF VDRL were negative.

On April 19 the patient became acutely confused. On examination he was oriented to self and place only. His speech was accurate but slurred with occasional perseveration of answers to simple questions. There was a marked impairment of his short-term memory but good recall of remote events. He had a mild left central facial paralysis. Computed tomography and MRI of the head with contrast injection revealed a new area of infarction in the right anterior thalamus (Figure 1, right) and a resolving left posterior thalamic infarct.

The patient's problems with short-term memory and orientation improved over the next 24 hours but he remained hypersomnolent.

Immunofixation assays for antibody to B burgdorferi in serum and CSF were elevated (Table 1). Enzyme-linked immunosorbent assay performed on serum and CSF to detect antibodies to B burgdorferi was positive in both; optical density of the reaction in the serum sample was 1.016 (normal <0.106) and that in the CSF sample was 1.142 (normal <0.106). Western blot analyses of the immunoglobulin in the serum and CSF were also strongly positive for antibody to B burgdorferi. The patient was treated with a 2-week course of 1 g/day i.v. ceftriaxone. Over several weeks, he showed gradual improvement of his
short-term memory and hypersomnolence. He experienced no further cerebrovascular events, and repeat CSF and serum examination disclosed improvement in the CSF profile and progressive decrease of serum and CSF Lyme titers (Table 1). Computed tomography of the head with contrast performed on May 5 showed the small left thalamic hypodensity and a resolving right thalamic infarct.

Discussion

Lyme disease is a well-recognized clinical entity and is associated with a variety of central and peripheral nervous system complications. In series of patients who contracted Lyme disease in the United States, the most common neurologic manifestations are meningoencephalitis, cranial neuropathies, and radiculopathies, with a wide variety of rarer neurologic manifestations.1,9,10

European strains of B burgdorferi are antigenically heterogeneous, and only a few strains are closely related to pathogenic American strains.9 In Europe, systemic infection with B burgdorferi is not associated with cardiopathy or arthritis,9 and although common central nervous system manifestations are similar to those reported in the United States, in some European cases cerebrovascular complications develop.2–8

Table 2 is a summary of the reported cases of vasculopathy and stroke in neuroborreliosis. Cerebral angiopathy was demonstrated angiographically3,4,8 in several of these patients. The vertebrobasilar system (References 2, 4, 6, and 8; present case) was commonly involved, often resulting in thalamic infarcts (References 4 and 6, present case) (Table 2). The majority of the reported patients had an insidious course, demonstrating vascular deficits months after initial infectious symptoms. Most patients reported persistent headaches but had minimal or no meningeal signs. All cases demonstrated lymphocytic pleocytosis in the CSF with an elevated protein content, often with a depressed glucose level. Hypoglycorrachia is unusual in neuroborreliosis and may relate to severity and duration of the illness.11 Treatment with appropriate antibiotics invariably resulted in no recurrence of cerebral infarcts, a halt in disease progression, or recuperation from deficits. In one reported case, even perivascular white matter changes visualized on MRI resolved shortly

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Lyme titer (IgG)</th>
<th>CSF Leukocytes (no./mm³)</th>
<th>Protein (mg/dl)</th>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/28</td>
<td>1:512</td>
<td>770</td>
<td>210</td>
<td>26</td>
</tr>
<tr>
<td>4/4</td>
<td>1:512</td>
<td>498</td>
<td>195</td>
<td>32</td>
</tr>
<tr>
<td>4/21</td>
<td>1:512</td>
<td>410</td>
<td>169</td>
<td>40</td>
</tr>
<tr>
<td>4/27</td>
<td>1:1,024</td>
<td>143</td>
<td>135</td>
<td>40</td>
</tr>
<tr>
<td>5/4</td>
<td>1:256</td>
<td>25</td>
<td>81</td>
<td>48</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid. Significant Lyme titer is at least 1:256.
Table 2. Reported Cases of Vasculopathy in Neuroborreliosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical history</th>
<th>Latency</th>
<th>ECM</th>
<th>Headache</th>
<th>Serum</th>
<th>CSF</th>
<th>CSF findings</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanny and Häuselmann²</td>
<td>74</td>
<td>F</td>
<td>Hemiparesis, hemianopsia, dysphagia, R occipital and B cerebellar infarcts</td>
<td>Weeks</td>
<td>...</td>
<td>...</td>
<td>1:1,024</td>
<td>...</td>
<td>114 WBC/μl</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>F</td>
<td>Hemiparesis, multiple perivascular white matter lesions</td>
<td>3 weeks</td>
<td>...</td>
<td>...</td>
<td>1:1,024</td>
<td>...</td>
<td>Mononuclear pleocytosis (140 WBC/μl) normal protein</td>
<td>+</td>
</tr>
<tr>
<td>Midgard and Hofstad³</td>
<td>49</td>
<td>M</td>
<td>Spastic paraparesis, capillary infant; diffuse cerebral vasculitis by angiography</td>
<td>&gt;1 year</td>
<td>?</td>
<td>+</td>
<td>Strongly increased</td>
<td>54 WBC/μl, elevated protein</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>Uldry et al⁴</td>
<td>40</td>
<td>F</td>
<td>Ataxic hemiparesis, confusion, skew, limited upgaze, B thalamic infarcts; diffuse cerebral vasculitis by angiography</td>
<td>1 year</td>
<td>+</td>
<td>+</td>
<td>1:256</td>
<td>1:128</td>
<td>Lymphocytic pleocytosis (27.5 WBC/μl) elevated protein, normal glucose</td>
<td>+</td>
</tr>
<tr>
<td>Weder et al⁵</td>
<td>24</td>
<td>M</td>
<td>Temporoparietal infarct</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1:2,560</td>
<td>...</td>
<td>1,125 WBC/μl, elevated protein, hypoglycorrhachia</td>
<td>+</td>
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<tr>
<td></td>
<td>61</td>
<td>F</td>
<td>&quot;Multi-infarct syndrome&quot;</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1:1,280</td>
<td>...</td>
<td>136 WBC/μl, elevated protein, hypoglycorrhachia</td>
<td>+</td>
</tr>
<tr>
<td>Kohler et al⁶</td>
<td>20</td>
<td>M</td>
<td>Adynamia, B hemiparesis, B thalamic infarcts</td>
<td>Present-</td>
<td>...</td>
<td>+</td>
<td>1:16</td>
<td>1:128</td>
<td>30 WBC/μl, elevated protein</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>M</td>
<td>Delirium, aphasia, R hemiparesis, multiple periventricular and white matter lesions</td>
<td>Present-</td>
<td>...</td>
<td>+</td>
<td>1:64</td>
<td>1:256</td>
<td>550 WBC/μl, elevated protein</td>
<td>+</td>
</tr>
<tr>
<td>Schmutzhard et al⁷</td>
<td>44</td>
<td>F</td>
<td>Sudden left hemiparesis</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>High</td>
<td>High</td>
<td>130 WBC/μl, intrathecal antibody production</td>
<td>+</td>
</tr>
<tr>
<td>Veenendal-Hilbers et al⁸</td>
<td>27</td>
<td>F</td>
<td>Papilledema, L face and arm weakness, vertebrobasilar arteritis</td>
<td>3 months</td>
<td>...</td>
<td>+</td>
<td>1:480</td>
<td>...</td>
<td>250 WBC/μl, elevated protein, hypoglycorrhachia</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>M</td>
<td>Cocaine use, dysarthria, quadriplegia, vertebrobasilar arteritis</td>
<td>6 months</td>
<td>...</td>
<td>+</td>
<td>1:120</td>
<td>1:32</td>
<td>33 WBC/μl, elevated protein, hypoglycorrhachia</td>
<td>±</td>
</tr>
<tr>
<td>May and Jabbari (present case)</td>
<td>20</td>
<td>M</td>
<td>Adynamia, central VIIth, B thalamic infarcts</td>
<td>3 months</td>
<td>...</td>
<td>+</td>
<td>1:512</td>
<td>1:1,024</td>
<td>770 WBC/μl, elevated protein, hypoglycorrhachia</td>
<td>+</td>
</tr>
</tbody>
</table>

Latency, period from onset of symptoms of neuroborreliosis to first stroke; ECM, erythema chronicum migrans; CSF, cerebrospinal fluid; F, female; M, male; R, right; B, Bilateral; L, left; WBC, leukocytes.

*After treatment, Wokke et al¹² reported two additional patients who may have experienced stroke during infection with *B burgdorferi*, but the nature of their lesions is less clear than that of the other reported cases, so they have been excluded from review.

The mechanism of cerebral infarction resulting from borrelial infection is unclear. There is a pathologically proven vasculitis that has been shown to affect peripheral nerve and skin in Lyme disease.⁶¹⁰ Many of the patients discussed above with vascular complications had erythema migrans and cranial nerve or radicular signs, which may have been due to such local peripheral lesions. However, the majority of them (including ours) lacked the clinical evidence of widespread systemic vasculitis. We believe that the presence of CSF pleocytosis and hypoglycorrhachia in the reported cases of stroke suggests that there is secondary spread of infection from inflamed meninges to the penetrating blood vessels. The other important spirochetal disease, syphilis, is widely known to cause such a meningovasculitis in the brain and spinal cord (Heubner's arteritis). Tuberculosis, mucormycosis, and infections with rarer organisms may also produce this complication.¹³ *B burgdorferi* has been demonstrated to have access to the central nervous system,¹⁴ but whether vascular inflammation is due to direct infection of the vessel wall with *B burgdorferi* or to an immunologic mechanism, such as circulating immune complexes or cross-reactive antibodies, remains unclear.⁴

In summary, these observations indicate that strokes can occur in persons with neuroborreliosis in association with meningitis and CSF pleocytosis. It is
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important to recognize that concurrent systemic or meningeal symptoms may be absent. All reported cases have occurred in patients infected in Europe, but the condition may be underreported in the United States. The pathologic process shows a predilection for the posterior circulation, often resulting in thalamic infarcts, and may be the result of direct extension of infection or inflammation from the meninges to the blood vessels rather than from a systemic vasculitis. The serious and possibly permanent deficits that may result from strokes make it imperative that infection with \textit{B} burgdorferi be suspected in any atypical stroke so that prompt, appropriate treatment can be initiated.

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References


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