Concurrent Infection of the Central Nervous System by Borrelia burgdorferi and Bartonella henselae

Evidence for a Novel Tick-borne Disease Complex

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Objectives: To investigate Bartonella henselae as a potential human tick-borne pathogen and to evaluate its role as a coinfecting agent of the central nervous system in the presence of neuroborreliosis.

Design: Case report study.

Setting: A primary health care center in Flemington, NJ, and the Department of Research and Development at Medical Diagnostic Laboratories LLC in Mt Laurel, NJ.

Subjects: Two male patients (aged 14 and 36 years) and 2 female patients (aged 15 and 30 years, respectively) with a history of tick bites and Lyme disease.

Main Outcome Measures: Laboratory and diagnostic findings before and after antimicrobial therapy.

Results: Patients residing in a Lyme-endemic area of New Jersey with ongoing symptoms attributed to chronic Lyme disease were evaluated for possible coinfection with Bartonella species. Elevated levels of B henselae–specific antibodies were found in these patients using the immunofluorescent assay. Bartonella henselae–specific DNA was detected in their blood. None of these patients exhibited the clinical characteristics of cat-scratch disease. Findings of cerebrospinal fluid analysis revealed the presence of both B henselae– and Borrelia burgdorferi–specific DNA. Bartonella henselae–specific DNA was also detected in live deer ticks obtained from the households of 2 of these patients.

Conclusions: Our data implicate B henselae as a potential human tick-borne pathogen. Patients with a history of neuroborreliosis who have incomplete resolution of symptoms should be evaluated for B henselae infection.

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Lyme disease is a tick-borne spirochetal disease caused by Borrelia burgdorferi and first recognized in this country in 1975 among children with acute arthritis in southeastern Connecticut. It is now the most commonly reported tick-borne illness in the United States. There are myriad potential neurologic manifestations, including aseptic meningitis, encephalitis, demyelinating encephalopathy, chorea, ataxia, seizures, cranial nerve palsies, myelitis, Guillain-Barré syndrome, mononeuritis multiplex, and benign intracranial hypertension. Mild chronic encephalopathy may be the most common neurologic symptom in patients with late-stage Lyme disease. The symptoms tend to be diffuse and nonspecific, and patients typically report memory loss, sleep disturbance, fatigue, and depression. The chronicity of these symptoms, despite parenteral antibiotic therapy, is well known to clinicians with experience in neuroborreliosis treatment. The cause of these persistent neurologic symptoms continues to be elusive.

Infections with Bartonella species have been reported in both immunocompromised and immunocompetent hosts. A wide spectrum of disease has been described in immunocompetent individuals, including bacillary angiomatosis, peliosis hepatitis, lymphadenitis, and aseptic meningitis with bacteremia and cat-scratch disease. Bartonella species are vector-transmitted, blood-borne, intracellular, gram-negative bacteria that can induce prolonged infection in the host. Persistent infections in domestic and wild animals result in a substantial reservoir of Bartonella organisms in nature that can serve as a source for inadvertent human infection. The prevalence of bacteremia...
METHODS

BLOOD SAMPLES AND ISOLATION OF PERIPHERAL BLOOD LYMPHOCYTES

Venous blood (10 mL) was obtained by venipuncture and collected in a yellow-top tube (ACD solution A; Becton Dickinson, Franklin Lakes, N.J.). Peripheral blood lymphocytes were isolated by the Ficoll-Hypaque gradient centrifugation of the blood (Sigma Chemical, St Louis, Mo) at 1600 rpm for 30 minutes, in a Centra CL2 labtop centrifuge (Fisher Scientific, Pittsburgh, Pa). The lymphocyte ring was isolated and rinsed twice with phosphate-buffered saline, and cells were stained with trypan blue to determine cellular viability.

LYME DISEASE SEROLOGIC EVALUATION

Serum samples were obtained from all 4 individuals and assayed by Western blot analysis for B burgdorferi IgG and IgM using the commercially available Marblot strip test system (MarDx Diagnostics, Carlsbad, Calif). The interpretation of B burgdorferi Western blot results satisfied the surveillance case definition of B burgdorferi infection of the Centers for Disease Control and Prevention.

DNA EXTRACTION

The lymphocytes were dissolved in 470 µL of tris-EDTA buffer (10 mM tris-hydrochloride [pH, 8.0] and 1 mM EDTA), 25 µL of 10% sodium dodecyl sulfate, and 12 µL of freshly prepared deoxyonuclease-free proteinase K (10 mg/mL). The mixture was incubated at 55°C for 2 hours; DNA was extracted by phenolchloroform extraction and ethanol precipitation. The purified DNA was dissolved in pyrogen-free, double-distilled water, and quantified using a Genesys-5 spectrophotometer (Spectronic Instruments, Rochester, NY). The purified, quantitated DNA was used as a template for PCR.

The PCR mixes (50 µL) contained extracted DNA (5 µL, 0.2 µg/µL), P24E and P12B primers (50 nM), 10 mM tris-hydrochloride (pH, 8.3), 50 mM potassium chloride, 3 mM magnesium chloride, 0.001% (wt/vol) gelatin, the nucleotides dATP, dCTP, dGTP, and dTTP (each at a concentration of 200 mmol/L), and 2.5 U of Taq DNA polymerase (Perkin-Elmer, Foster City, Calif). The PCR was carried out in 0.2-mL tubes. The thermocycler was a Perkin-Elmer GeneAmp PCR system 2400. The PCR program ran for 3 minutes at 94°C, followed by 40 one-minute cycles at 94°C, 1 minute at 56°C, and 1.5 minutes at 72°C. The program finished with an additional 10-minute extension step at 72°C. A 30-µL sample of the final reaction product was run on 1% agarose gel containing 0.5 µg of ethidium bromide per milliliter, and the gel was photographed under UV light. For optimization of the PCR conditions for clinical specimens, normal blood was artificially spiked with in vitro–cultivated B henselae. A controlled number of B henselae (American Type Culture Collection 49882, ATCC, Rockville, Md), ranging from 10 to 10³ pathogens was added to 5 mL of whole blood. These spiked samples were treated as described above. The PCR analysis of B burgdorferi, B microti, and Ehrlichia was carried out as described.10-13

HISTONE PCR

Aliquots (5 µL) of the newly extracted DNA were mixed in a 50-µL PCR reaction mixture containing 10× PCR buffer (Perkin Elmer), 3 mM magnesium chloride, 200 mM dNTP, 2.5 µL of Taq DNA polymerase (5 U/µL), and 1 µL (8 pmol) of 5'- and 3' histone amplifier primer set. The histone primer sets are complementary to the DNA of a constitutively expressed human histone gene H3.3 as described.13 The amplification process was subjected to 30 cycles of PCR (each cycle at 94°C for 45 seconds, 60°C for 45 seconds, and 72°C for 90 seconds) in a 2400 Perkin-Elmer DNA thermocycler. The histone primers served as internal controls for the sample’s DNA integrity, presence of inhibitors, and intersample equivalency of total amount of DNA analyzed.

PRECAUTIONS AGAINST CONTAMINATION

The extraction of DNA and PCR were performed under sterile conditions and in separate rooms. In addition, all positive samples were confirmed by reextraction from the original sample, followed by amplification in triplicate. Bartonella henselae DNA–positive status was defined as samples that were positive initially, and in at least 1 of the replicates after reextraction. Pyrogen-free water was used in the isolation of DNA from the blood specimen. The Eppendorff microcentrifuge tubes and the PCR tubes were sterilized in an autoclave and UV irradiated. New Finn pipettes were used solely with the filter tips for PCR. Disposable plastic trays were used to prepare PCRs in a UV-irradiated PCR biohazard. Blood and CSF samples (n=10: 5 of CSF and 5 of blood) from individuals with no evidence of tick-borne disease were used in the PCR assays as negative controls. In addition, the patients in this study were the first in our laboratory to test positive for B henselae.
were also performed on *Bartonella* species. Polymerase chain reaction amplifications were obtained from patients with chronic Lyme disease residing in central New Jersey. These patients exhibited a variety of ongoing symptoms despite previous courses of antibiotic therapy. One of the coinvestigators, who was unaware of the clinical status of the study subjects, conducted polymerase chain reaction (PCR) analyses of cerebrospinal fluid (CSF) for both *Borrelia burgdorferi* and *Bartonella henselae*–specific DNA. Findings have generated interest in the role of *Bartonella* species as a possible human tick-borne pathogen.

Our study was based on clinical and laboratory data obtained from patients with chronic Lyme disease residing in central New Jersey. These patients exhibited a variety of ongoing symptoms despite previous courses of antibiotic therapy. One of the coinvestigators, who was unaware of the clinical status of the study subjects, conducted polymerase chain reaction (PCR) analyses of cerebrospinal fluid (CSF) for both *B. burgdorferi* and *B. henselae* species. Polymerase chain reaction amplifications were also performed on *Ixodes scapularis* ticks obtained from the households of 2 of these patients. The clinical course of these patients is described.

### RESULTS

#### CASE 1

Our first patient was a previously healthy 14-year-old male adolescent who developed gradually worsening frontal headaches, fatigue, and knee arthralgia. These symptoms were accompanied by low-grade fever, insomnia, and the inability to concentrate in school. He revealed that 3 months prior to the onset of illness, a small tick was removed from his scalp. However, he did not seek medical attention at that time.

Results of initial testing for Lyme disease and *Babesia* serology were negative. There was no improvement in his symptoms following a trial of therapy with doxycycline hyclate (200 mg/d for 6 weeks). The patient was unable to attend school owing to severe fatigue, headaches, and cognitive dysfunction. He was previously an excellent student with rare absences from school. Computed tomographic scans of the brain revealed no distinct abnormality.

Results of further testing revealed *B. henselae* in the blood (IgG titer, 1:64 using the immunofluorescence assay [IFA]). *Bartonella henselae*–specific DNA was successfully amplified from his blood and CSF (atraumatic spinal tap). Interestingly, results of PCR analysis of this same CSF specimen were positive for *B. burgdorferi* and *Babesia microti*. These findings have generated interest in the role of *Bartonella* species as a possible human tick-borne pathogen.

### Table 1. Sequences and Positions of Oligonucleotide Primers Used for *Bartonella henselae* Polymerase Chain Reaction Amplification

<table>
<thead>
<tr>
<th>Oligo Name</th>
<th>Oligo Sequence</th>
<th>Target Gene</th>
<th>Equivalent Nucleotide</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>P24E</td>
<td>GGA ATT CCC TTC TTC ATG TAG GCT GG</td>
<td>16S rRNA <em>Bartonella henselae</em></td>
<td>964-990</td>
<td>→</td>
</tr>
<tr>
<td>P12B</td>
<td>CGG GAT CCC GAG ATG TCT TTT GGA GAT TA</td>
<td>1243-1214</td>
<td>←</td>
<td></td>
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<tr>
<td>LY1</td>
<td>GAA ATG GCT AAA GTA AGC GGA ATT GTA C</td>
<td>Ly-1 chromosomal <em>Borrelia burgdorferi</em></td>
<td>16-42</td>
<td>→</td>
</tr>
<tr>
<td>LY2</td>
<td>CAG AAA TTC TGT AAA CTA ATC CCA CC</td>
<td>222-247</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>Bab1</td>
<td>CTT AGT ATA AGC TTT TAT ACA GC</td>
<td>ss-rDNA <em>Babesia microti</em></td>
<td>39-53</td>
<td>→</td>
</tr>
<tr>
<td>Bab4</td>
<td>ATA GGT CAG AAA CTT GAA TGA TAC A</td>
<td>251-275</td>
<td>←</td>
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<tr>
<td>HGE1F</td>
<td>GGA TTA TTC TTT ATA GCT TGC T</td>
<td>16S rDNA <em>Erhlichia</em></td>
<td>52-73</td>
<td>→</td>
</tr>
<tr>
<td>HGE3R</td>
<td>TTC CTT TAA GGA GGA TCT AAT CTC</td>
<td>948-971</td>
<td>←</td>
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<tr>
<td>HME1F</td>
<td>CAA TTG CTT ATA ACC TTT TGG T</td>
<td>52-73</td>
<td>→</td>
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</tr>
<tr>
<td>HME3R</td>
<td>CCC TAT TAG GAG GGA TAC GAC CTT</td>
<td>948-971</td>
<td>←</td>
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</tr>
</tbody>
</table>

*Oligo indicates oligonucleotide primer; rRNA, ribosomal RNA; and rDNA, ribosomal DNA. Arrows indicate the direction of the primer.*
However, his arthralgia persisted throughout his therapy. A second lumbar puncture was done after 28 days of cefotaxime treatment. The 16S ribosomal RNA of *B henselae* was successfully amplified from DNA isolated from peripheral blood lymphocytes and CSF (Figure 1, lanes 1 and 2, respectively). Twenty-eight days after antimicrobial therapy, *B henselae* DNA was not detected in the blood and CSF of this patient (Figure 1, lanes 3 and 4 to 5, respectively). To increase the sensitivity of our PCR, the amount of input DNA isolated from the CSF was doubled. *Bartonella henselae* DNA was not detected after therapy (Figure 1, lane 5). In addition, *B burgdorferi* DNA was no longer detected (data not shown).

**CASE 3**

The third patient was a 15-year-old female adolescent with a history of Lyme disease treated with an 8-week course of doxycycline hyclate (200 mg/d). Following this therapy, the patient developed a gradual recurrence of symptoms over a 3-month period. She described arthralgia primarily affecting the hips, knees, and ankle joints. These symptoms were accompanied by fatigue, night sweats, headache, photophobia, menstrual irregularity, depressed mood, dizziness, insomnia, and the inability to concentrate in school. She was previously an excellent student, but she was unable to attend school for a 2-month period owing to this symptom complex.

There was no history of cat exposure and no known history of tick bite. *Bartonella henselae* serologic testing was done, and the results revealed the presence of *B henselae*–specific antibodies (IgG titer, 1:64 using IFA). Neuroborreliosis was suspected, and a lumbar puncture was performed. Results of CSF analysis revealed the presence of both *B burgdorferi*–specific DNA (Figure 2, lane 1, before antimicrobial therapy) and *B henselae*–specific DNA (PCR method). Treatment was initiated with a 28-day course of intravenous ceftriaxone sodium (2 g/d). The patient experienced symptomatic improvement by the end of the ceftriaxone regimen, and a second lumbar puncture was done. *Borrelia burgdorferi*–specific DNA was no longer detectable (Figure 2, lane 4, after antimicrobial therapy); however, *B henselae*–specific DNA persisted. It should be mentioned that this lumbar puncture was atraumatic (0 red blood cells per high-power field).

At this point, treatment was changed to intravenous azithromycin (500 mg every 12 hours). Most of her previously mentioned symptoms returned within 3 days of starting doxycycline therapy, including confusion and the inability to concentrate. Antibiotic therapy was changed to intravenous azithromycin (500 mg/d for 14 days). Her symptoms resolved promptly under azithromycin treatment. Specifically, her ability to read and perform mathematical tasks improved greatly. She reported improvement in memory, more restful sleep, and no further headache.

**CASE 4**

Our fourth study subject was a 30-year-old woman who became ill within a week after the removal of 2 ticks from her skin. She complained of fever, frontal headache, dizziness, fatigue, and upper extremity arthralgia. She noticed several small ticks on her pet cat, and these were subsequently identified as *I scapularis*. These ticks were positive for *B henselae*–specific DNA and negative for *B burgdorferi*–specific DNA. Her headaches and dizziness intensified, and computed tomographic images of the brain were taken, which revealed no distinct brain abnormality. Nonetheless, her neurologic symptoms persisted. *Bartonella henselae* was found on serologic testing (IgG titer, 1:256 using IFA). *Bartonella henselae*–specific DNA was amplified from her blood.

This patient exhibited no laboratory evidence of babesiosis, ehrlichiosis, or Lyme disease by PCR or West-
Nearly half of these patients with generalized headache and restlessness and may present with aches, and a marked improvement in energy levels. After antimicrobial therapy, our study subjects exhibited improved cognitive function, resolution of headaches, and a marked improvement in energy levels (Table 3).

**Table 2. Summary of Pretreatment Laboratory Data and Symptoms**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Bartonella henselae Antibody IgG</th>
<th>B henselae PCR Blood</th>
<th>B henselae PCR CSF</th>
<th>Lyme PCR CSF</th>
<th>Lyme Western Blot</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Borderline</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*PCR indicates polymerase chain reaction; CSF, cerebrospinal fluid; plus sign, positive findings; and minus sign, negative findings.

**Table 3. Summary of Posttreatment Laboratory Data and Symptoms**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Bartonella henselae PCR Blood</th>
<th>B henselae PCR CSF</th>
<th>Lyme PCR CSF</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>2</td>
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<tr>
<td>3</td>
<td>–</td>
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</tr>
</tbody>
</table>

*PCR indicates polymerase chain reaction; CSF, cerebrospinal fluid; plus sign, positive findings; and minus sign, negative findings; and ellipses, not applicable.

COMMENT

Both *B henselae* and *B burgdorferi* have a well-established ability to infect the central nervous system, with a variety of resultant neurologic consequences. Cases of encephalopathy due to *B henselae* infection have been well described. Patients typically complain of persistent generalized headache and restlessness and may present with combative behavior. Nearly half of these patients with encephalopathy can develop seizures that may range from focal to generalized, and from brief and self-limited to status epilepticus. *Bartonella henselae*-induced encephalopathy may be a relatively frequent cause of status epilepticus in school-aged children. The ability of this pathogen to cause persistent dementia following encephalitis has been demonstrated. Neuroophthalmic effects, including loss of vision, have been well documented. Cat-scratch disease is the most commonly recognized manifestation of human infection with *B henselae*. Interestingly, none of our study subjects displayed the clinical characteristics of cat-scratch disease. There have been no previously reported cases of tick-borne *B henselae* infection in humans. Vector competency has not been clearly established for tick species, and knowledge related to vector transmission of *Bartonella* organisms is very incomplete. Vector-mediated transmission of *B henselae* to cats via fleas has been demonstrated. Three of our study subjects had no prior exposure to cats. Our fourth patient removed several small ticks from her cat, and these tested positive for *B henselae* using PCR. This case was included in our study to illustrate that *B henselae* infection could be acquired as a tick-borne disease independent of *B burgdorferi* infection. One of our patients found a live deer tick in his household that tested positive on PCR analysis for both *B henselae* and *B burgdorferi*. These findings implicate the deer tick as a potential carrier of *B henselae*.

Three of our patients had a history of chronic Lyme disease with persistent symptoms despite previous attempts at antibiotic therapy. The concurrent finding of *B henselae*– and *B burgdorferi*–specific DNA in their CSF probably explains their prior lack of response to antibiotic therapy directed exclusively at Lyme disease. There were 8 CSF samples obtained from other patients during the same period that were negative for *B burgdorferi* infection. One of our patients included in our study to illustrate that *B henselae* infection could be acquired as a tick-borne disease independent of *B burgdorferi* infection. One of our patients found a live deer tick in his household that tested positive on PCR analysis for both *B henselae* and *B burgdorferi*. These findings implicate the deer tick as a potential carrier of *B henselae*.

All of our patients were tested for other tick-borne diseases (*Babesia* and *Ehrlichia*). The results were nega-
tive on PCR analysis (data not shown). All of our patients exhibited varying levels of \( B\) henselae-specific antibodies on IFA. However, in a significant number of cases, the diagnosis cannot be made on the basis of IFA antibody testing alone.\(^{20}\) Serologic testing was performed, including for IgM, and the IgM results were negative in these 4 cases. The limitations of serologic testing for \( B\) henselae have been described.\(^{30}\) The sensitivity of culture for this organism is low when compared with PCR-based detection methods.\(^{31}\) Polymerase chain reaction detection of \( B\) henselae is especially useful in cases with a broad differential diagnosis\(^{32,33}\) and PCR played a pivotal diagnostic role in our study.

Despite antibiotic treatment, some patients with Lyme disease persistently exhibit symptoms associated with chronic Lyme disease syndrome or post-Lyme syndrome. These symptoms include neurocognitive impairment, persistent arthralgia, fatigue, and subjective memory loss.\(^{34}\) The persistent symptomatology might be attributed to several factors. First, coinfections: in addition to transmitting \( B\) burgdorferi, a tick may harbor other pathogens, including \( B\) bartonellosis, \( Ehrlichia\), and \( Bartonella\) species.\(^{35}\) These multiple pathogens may survive Lyme antimicrobial therapy and be responsible for the persistent symptoms in individuals with post-Lyme syndrome. The importance of considering these coinfesting agents in the differential diagnosis cannot be overstated. Second, genetic predisposition might play a role in chronicity, pathogenesis, antimicrobial resistance, and prognosis for patients with Lyme disease.

There have been no previously reported cases of concurrent Lyme disease and \( B\) henselae infection. The zoonotic potential for human infection with \( Bartonella\) species has recently been well described.\(^{36}\) High levels of bacteremia are currently being documented in numerous domestic and wild animal species.\(^{37}\) Our data implicate \( B\) henselae as yet another tick-borne pathogen. Further vector competency studies are needed. The fact that our cases of concomitant central nervous system infection with \( B\) henselae and \( B\) burgdorferi were diagnosed in a 1-month period suggests that these coinfections may occur relatively frequently.

Acquisition of simultaneous coinfection of \( B\) burgdorferi and \( Ehrlichia\) or \( Bartonella\) by \( I\) scapularis ticks is well documented.\(^{35-38}\) It was shown that the presence of either \( B\) burgdorferi or human granulocytic ehrlichiosis (HGE) in \( I\) scapularis ticks did not affect acquisition of the other agents from an infected host. In addition, transmission of the agents of Lyme disease and HGE by individual ticks was equally efficient and independent. Immunoserologic evidence of coinfection with \( B\) burgdorferi, \( Bartonella\), and HGE among individuals in tick-endemic areas is well documented. In one study it was reported that of 96 patients with Lyme borreliosis, 9 (9.4%) demonstrated immunoserologic evidence of coinfection.\(^{39}\)

The results presented herein provide evidence for coinfection, perhaps explaining the variable manifestations and clinical responses noted in some patients with tick-borne diseases. In certain clinical settings, laboratory testing for coinfection is of great value to ensure that appropriate antimicrobial treatment is given. Clinicians continue to be challenged to explain the pathophysiology behind chronic Lyme disease. Persistent symptoms following even aggressive therapy for Lyme disease continue to frustrate both patients and their physicians. We put forth concurrent \( B\) henselae infection as one reason for ongoing symptoms in chronic Lyme disease. We consider this an introductory study and look forward to a more comprehensive evaluation of the role \( B\) henselae plays as a coinfesting agent in chronic Lyme disease. However, we are convinced that concomitant \( B\) henselae infection should be considered in neuroborreliosis cases refractory to standard therapy.

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REFERENCES


