Bartonella sp. Bacteremia in Patients with Neurological and Neurocognitive Dysfunction[▽]

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We detected infection with a *Bartonella* species (*B. henselae* or *B. vinsonii* subsp. *berkhoffii*) in blood samples from six immunocompetent patients who presented with a chronic neurological or neurocognitive syndrome including seizures, ataxia, memory loss, and/or tremors. Each of these patients had substantial animal contact or recent arthropod exposure as a potential risk factor for *Bartonella* infection. Additional studies should be performed to clarify the potential role of *Bartonella* spp. as a cause of chronic neurological and neurocognitive dysfunction.

Bartonella henselae causes a prototypical illness characterized by fever and regional lymphadenopathy following a cat scratch or bite (8, 9). Cat scratch disease (CSD) is usually self-limited, and antibiotic therapy has minimal impact on the clinical course (11, 34). However, a spectrum of neurological manifestations, including ischemic stroke, cerebral arteritis, transverse myelitis, radiculitis, grand mal seizures, epilepsia partialis continua, status epilepticus, coma, and fatal encephalitis, in patients with CSD have been described previously (21, 34). Chronic neurological or neurocognitive syndromes associated with persistent *Bartonella* bacteremia are less well characterized. Neurological symptoms following a cat scratch have also been described in association with *B. quintana* infection, and recent evidence indicates that cats can harbor *B. quintana* (6, 13, 32, 37).

Although CSD is considered to be self-limiting, persistent intravascular infection of a child with *B. henselae* for 4 months after a cat scratch has been reported previously (2). Furthermore, we recently described chronic intravascular infection with both *B. henselae* and *B. vinsonii* subsp. *berkhoffii* in immunocompetent people with occupational animal contact and arthropod exposure (5). Cats are the primary reservoir hosts for *B. henselae*, whereas to date, *B. vinsonii* subsp. *berkhoffii* has been isolated only from dogs, coyotes, foxes, or people (9, 27). Domestic and wild canines serve as the primary environmental reservoir for *B. vinsonii* subsp. *berkhoffii*, and dogs can be involved in the transmission of *B. vinsonii* subsp. *berkhoffii* and *B. henselae* to people (7, 9, 10, 27, 36).

In this study, we report the isolation of *B. henselae* or *B. vinsonii* subsp. *berkhoffii* from, or the molecular detection of these pathogens in, blood samples from six people who exhibited a spectrum of neurological and neurocognitive abnormalities.

MATERIALS AND METHODS

Blood and serum samples from six individuals and cerebrospinal fluid from one patient were submitted by an attending physician to the Intracellular Pathogens Research Laboratory, Center for Comparative Medicine and Translational Research, College of Veterinary Medicine, North Carolina State University, Raleigh, for attempted isolation of a *Bartonella* species. We used a previously described approach incorporating preenrichment culture of blood in *Bartonella*-*Alphaproteobacteria* growth medium (BAPGM) and PCR (16). Bacterial isolation, PCR amplification, and cloning were performed using previously described methods (5, 6, 16, 27). Each blood sample was tested by PCR following direct DNA extraction from the blood sample, following preenrichment culture for at least 7 days, and following subculture onto a blood agar plate. An uninoculated BAPGM culture was processed simultaneously to assess for laboratory contamination. Methods used for DNA extraction, conventional and real-time PCR analyses targeting the *Bartonella* 16S-23S intergenic spacer region (ITS), cloning, and DNA sequencing were described previously (5, 16, 27). Sequences were aligned and compared with GenBank sequences by using AlignX software (Vector NTI suite 6.0; InforMax, Inc.) (16). *B. vinsonii* subsp. *berkhoffii*, *B. henselae*, and *B. quintana* antibodies were evaluated at the Centers for Disease Control and Prevention, Atlanta, GA, by using a modification of a previously described immunofluorescent-antibody assay (IFA) (12). Serially diluted serum samples that were IFA reactive at dilutions greater than 1:64 were considered positive for antibodies against *Bartonella* sp. antigens. Results are reported as the reciprocal of the end-point titer.

A standardized questionnaire, approved by the North Carolina State University Institutional Review Board (IRB no. 4925-03), was completed by each individual and included questions on age, gender, animal and arthropod exposure, outdoor activity, travel, clinical symptoms, and comorbid conditions.

RESULTS

Patients included four females and two males, ranging in age from 14 to 54 years (Table 1). Substantial animal contact or recent arthropod exposure was a potential risk factor for *Bartonella* infection.

Patient 1 was a college student who received a severe cat scratch on her right hand that resulted in raised, red, nodular lesions which were diagnosed as CSD by a dermatologist. Approximately 1 year later, she developed fatigue, headaches, memory loss, disorientation, insomnia, poor coordination, tremors, and infrequent petit mal seizures. During the subsequent 2-year period, she experienced two grand mal seizures and was treated with gabapentin for epilepsy.

TABLE 1. Ages, genders, and neurological abnormalities of immunocompetent patients in this study and *Bartonella* species detected in the blood samples

Patient no.	Age (yr)	Gender[a]	*Bartonella* species[b] in blood sample(s)	Primary symptoms	Other abnormalities[d]	Reciprocal titer[c] of antibodies to:			Duration of illness	Potential risk factor(s)	Additional diagnosis(es)
						B. henselae	*B. vinsonii* subsp. *berkhoffii*	*B. quintana*			
1	23	F	*B. henselae* (H1)	Seizures, fatigue, memory loss/disorientation, headaches	D, I, IN, BV	256	128	256	3 yrs	Exposure to cats	CSD, epilepsy
2	41	F	*B. henselae* (SA2 and H1)	Fatigue, headaches	T, D, I, ML/D, BV	128	256	128	2 yrs	Exposure to cats, ticks, fleas, biting flies	Parvovirus infection
3	44	F	*B. vinsonii* subsp. *berkhoffii* (type II), *B. henselae* (H1)	Fatigue, headaches, blurred vision	T, I, ML/D	<32	<32	<32	5 yrs	Exposure to cats, biting flies	Lyme disease, babesiosis
4	54	F	*B. henselae* (H1)	Fatigue, headaches	D, I, IN, ML/D	32	<32	<32	5 yrs	Exposure to cats, fleas, ticks	Rosacea, arthritis, depression
5	49	M	*B. henselae* (SA2)	Paralysis, fatigue	T, D, I, IN	<32	<32	<32	6 mos	Exposure to cats, fleas, ticks, biting flies	Viral neuropathy, multiple sclerosis
6	14	M	*B. henselae* (H1)	Fatigue, migraines	D, I, IN, ML/D, BV	128	256	128	1 mo	Exposure to cats, ticks	Debilitating migraines

[a] F, female; M, male.
[b] *B. henselae* H1 and SA2 and *B. vinsonii* subsp. *berkhoffii* genotype II strains were identified by ITS sequencing.
[c] Titers are reported as the reciprocal of the end-point titer.
[d] D, depression; I, insomnia; IN, incoordination; BV, blurred vision; T, tremors; ML/D, memory loss/disorientation.

Patient 2, a golf coach, traveled extensively throughout the United States and other countries, had frequent arthropod exposure, and had lived on a farm as a teenager, during which time she had been bitten by a pig and pecked frequently by roosters, turkeys, and pheasants. Her illness was characterized by severe bouts of fatigue, accompanied by subtle neurological abnormalities (Table 1).

Patient 3 owned a horse farm, had frequent arthropod exposure, and reported at least yearly cat scratches. At the time of her initial blood sample, she had been ill approximately 4 years. She had been diagnosed previously with Lyme disease and babesiosis and had been treated with long courses of oral and intravenous antibiotics.

Patients 4 and 5 were veterinarians who reported weekly bites or scratches from cats, dogs, rodent pocket pets, and an assortment of wild and zoo animals. In association with a period of work-related stress, patient 4 developed debilitating depression, insomnia, fatigue, loss of coordination, memory loss, disorientation, and headaches of fluctuating severity that continued for over a year. Patient 4 maintained cats, chickens, cattle, dogs, and horses as pets.

One year prior to testing in our laboratory, patient 5 developed an acute febrile illness and malaise, which abated over the next week. In the subsequent months, neurological symptoms consisted of stumbling during jogging, muscle weakness, and fatigue, which was thought to be associated with viral neuropathy. During the next year, symptoms worsened to the extent that running was no longer possible and he could not walk unaided any distance; leg myoclonus worsened, hand numbness became problematic, and resting three to four times a day was a necessity. Multiple sclerosis was diagnosed, and treatment with intravenous interferon, intravenous immunoglobulin G, and glucocorticoids was initiated.

Patient 6 was the 14-year-old son of a veterinarian, and although exposed to both cats and dogs, the boy did not report previous scratches or bites. Ten days after an attached tick was removed from his left ankle, the boy developed severe debilitating migraine headaches, which required him to be hospitalized. Because of the more rapid turnaround time of PCR than of serological testing, PCR testing was used initially to screen an extracted blood sample for *Anaplasma*, *Bartonella*, *Ehrlichia*, and *Rickettsia* DNA. Only *Bartonella* DNA was detected in the child's blood sample, and subsequently, sequential serological testing demonstrated seroreactivity to *B. henselae* and *B. quintana* and seroconversion to *B. vinsonii* subsp. *berkhoffii*. Despite multiple attempts, cloning and sequencing of the initial *Bartonella* amplicon were not successful; however, *B. henselae* DNA from an agar plate isolate obtained after BAPGM preenrichment culture was sequenced. Based upon seroconversion, infection with *B. vinsonii* subsp. *berkhoffii* was implicated; however, based upon culture results, the boy was infected with *B. henselae*.

Fatigue, insomnia, memory loss and/or disorientation, blurred vision and loss of coordination, headaches, and depression were the most commonly reported symptoms (Table 1). Seizures, severe paresis, and debilitating migraines were the predominant neurological abnormalities in patients 1, 5, and 6, respectively. Patients 2 to 4 each reported fatigue with accompanying neurological abnormalities that persisted for 3 to 5 years (Table 1).

TABLE 2. Serological, PCR, and culture results for a 23-year-old woman with progressive neurological dysfunction, seizures, and persistent *B. henselae* infection

Date (mo/day/yr) and sample type[a]	IFA reciprocal titer[b] of antibodies to:			PCR-BAPGM culture result[c] after:		
	B. henselae	*B. quintana*	*B. vinsonii* subsp. *berkhoffii*	Direct extraction	Enrichment culture	Blood agar plate isolation
5/26/2005, blood	256	128	256	*B. henselae* (H1)*	—	—
6/27/2005, blood	256	64	128	*B. henselae* (H1)*	*B. henselae* (H1)*	*B. henselae* (H1)*
9/20/2005, blood	256	128	128	—	—	—
2/10/2006, CSF	NT	NT	NT	—	*B. henselae* (H1)*	—
8/31/2006, blood	64	64	64	—	—	—

[a] CSF, cerebrospinal fluid.
[b] Titers are reported as the reciprocal of the end-point titer.
[c] Asterisks denote 16S-23S ITS DNA sequencing results.

Medical care, diagnostic evaluations, the timing of sample collection for *Bartonella* testing, and treatment interventions, including plasmapheresis, antibiotics, corticosteroids, intravenous immunoglobulin, anticonvulsants, and other drugs, were extensive and varied among patients. In all instances, there was an evaluation by one or more neurologists. In addition to receiving other symptomatic treatments, patients 1, 5, and 6 were treated specifically for their *Bartonella* infections and experienced progressive improvement (patients 1 and 5) or the resolution of disease manifestations (patient 6). Patient 1 was treated with doxycycline for 6 weeks, remains healthy, and has experienced no seizures during a 36-month follow-up period while receiving an anticonvulsant medication. Patient 5 was initially treated with doxycycline for 5 weeks, followed by azithromycin for 6 weeks and then by levofloxacin for 9 weeks. There was a progressive improvement in neurological status (improved muscle strength and coordination accompanied by a return to work as a veterinary surgeon). During the past year, this individual received doxycycline and rifampin, in conjunction with other treatments, which resulted in continued improvement in muscle strength, improved coordination when walking, less myoclonus, and no relapses, which typically occurred prior to the addition of antibiotics to the treatment regimen. Patient 6 was treated with azithromycin for 6 weeks, with a rapid and progressive decrease in the severity of migraines following the initiation of antibiotics. The boy gradually returned to all preillness activities with no residual neurological abnormalities. Patients 2 and 3 were treated with doxycycline without obvious long-term benefits. Patient 4 has received continuous doxycycline treatment for the past 2 years for rosacea and has experienced a decrease in headaches, back pain, and joint pain, although there are still occasional flare-ups of pain in the joints.

Serological testing at the Centers for Disease Control and Prevention identified antibodies to *Bartonella* spp. (IFA reciprocal titers of 64 or greater) in samples from three of six patients (patients 1, 2, and 6). Antibodies were not detected in samples from patients 3 (six serum samples spanning July 2005 to 14 September 2006), 4 (three serum samples spanning June to November 2006), and 5 (one serum sample). For patient 1, IFA titers of antibodies to *B. henselae*, *B. quintana*, and *B. vinsonii* subsp. *berkhoffii* in samples spanning a 4-month period remained stable and were decreased but still detectable 1 year later, following antibiotic treatment (Table 2). Patient 2 had reciprocal titers of antibodies to *B. henselae*, *B. quintana*, and *B. vinsonii* subsp. *berkhoffii* of 256, 128, and 128, respectively, when initially tested on 4 January 2005, after which a significant drop in antibodies occurred following antibiotic treatment, with reciprocal titers of less than 64 for all three test antigens in samples collected on 12 May 2005 and 11 September 2006. Patient 6 seroconverted to *B. vinsonii* subsp. *berkhoffii* antigens, developed the highest IFA titers of antibodies to this organism, and had a decremental decrease in titers following treatment with azithromycin (Table 3).

Based upon DNA sequencing of the ITS region, *B. henselae* was detected in blood samples from five individuals and coinfection with *B. vinsonii* subsp. *berkhoffii* and *B. henselae* was found in patient 3 (Table 1). Considering only the initial BAPGM blood culture results, *Bartonella* DNA was detected following direct extraction from the blood samples of four patients whereas *Bartonella* DNA was amplified only following BAPGM enrichment culture of samples from patients 2 and 5.

TABLE 3. Serological, PCR, and culture results for a 14-year-old boy with migraine headaches following recent tick exposure

Date (mo/day/yr) of blood sample	IFA reciprocal titer[a] of antibodies to:			PCR-BAPGM culture result after:		
	B. henselae	*B. henselae*	*B. henselae*	Direct extraction	Enrichment culture	Blood agar plate isolation
9/01/2005	256	128	512	+ (*Bartonella*)[b]	—	*B. henselae* (H1)
9/05/2005	512	256	2048	—	—	—
9/29/2005	512	256	1024	—	—	—
10/27/2005	128	128	256	—	—	—
10/12/2006	128	128	256	—	—	—

[a] Titers are reported as the reciprocal of the end-point titer.
[b] Unable to sequence the amplicon obtained using *Bartonella* genus ITS primers.

Following the subculture of aliquots from the liquid BAPGM enrichment cultures, isolates (*B. henselae*) were obtained from samples from patients 1, 2, 3, 4, and 6. Based upon sequential enrichment culture attempts, five individuals were found to be infected at more than one testing time point, as illustrated for patient 1 in Table 2. For this patient, the same *Bartonella* species and strain was detected in blood and cerebrospinal fluid samples obtained 9 months apart. Patient 6 had the shortest duration of symptoms and was assumed to have a recently acquired infection; seroconversion was documented, and after treatment with azithromycin, *Bartonella* bacteremia was not detected by blood culture or PCR (Table 3). For patient 2, an isolate of *B. henselae* (San Antonio 2 [SA2] like) was initially identified by sequencing, whereas *B. henselae* (Houston-1 [H1]-like) sequences were obtained only from blood extracted 6 months later, following the administration of clindamycin for gingivitis and a tooth root abscess. The *B. henselae* reciprocal IFA titer decreased from 128 to 32 during this same time interval. Patient 3 was coinfected with *B. vinsonii* subsp. *berkhoffii* and *B. henselae*, and patients 4, 5, and 6 were infected with *B. henselae* (H1 or SA2). At no time during this study was DNA amplified from an extraction control or from an uninoculated BAPGM culture control.

DISCUSSION

All six patients in this study were infected with *B. henselae*, and as has been reported previously for people and for dogs, patient 3 was coinfected with *B. henselae* and *B. vinsonii* subsp. *berkhoffii* (5, 15, 16). Patient 6 was either coinfected or was chronically infected with *B. henselae*, the organism that was isolated, and subsequently infected with *B. vinsonii* subsp. *berkhoffii*, as reflected by the documentation of seroconversion. Historically, *B. henselae* infection when associated with CSD has been considered a self-limiting illness (8, 9, 34). Our results from a previous study and from this study and our unpublished data indicate that some immunocompetent individuals develop persistent intravascular *B. henselae* infections (5). Based upon the findings reported in published studies, the culture of patient blood samples by using an insect-based liquid culture enrichment medium can enhance the success of obtaining a subculture isolate or, alternatively, can increase *Bartonella* bacterial numbers to a level such that organism-specific DNA sequences can be detected by PCR (5, 6, 16, 25). Similar to the subjects in a previous study in which the preenrichment approach was used, each person in this study was immunocompetent and each had a history of animal or arthropod contact (5). Also, consistent with the data in the previous report, patients 2, 3, and 4 were middle-aged women who reported neurocognitive abnormalities including fatigue, insomnia, memory loss, disorientation, and frequent headaches. The intermittent detection of bacteremia in some untreated immunocompetent individuals suggests that *B. henselae* can induce a relapsing pattern of bacteremia or that the organism load in blood is at times below the level of detection afforded by the combined preenrichment culture-PCR approach (5). It is important to emphasize that the isolation of *B. henselae* and *B. vinsonii* subsp. *berkhoffii* from, or the molecular detection of these pathogens in, samples from the patients in the study does not confirm causation. Three of six individuals appeared to respond to antibiotic treatments, whereas the responses in three patients were minimal or transient.

The neuropathogenesis of *B. henselae* infection remains incompletely understood. *B. henselae* can invade and colonize human dendritic cells, CD34 progenitor cells, erythrocytes, and vascular endothelial cells (14, 28). In vitro intracellular infection of feline microglial cells has also been demonstrated previously (31). In a previous study involving a patient with classical CSD accompanied by encephalopathy, *B. henselae* DNA was amplified from an epitrochlear mass and from the cerebrospinal fluid (18). The involvement of the central nervous system in patients with CSD is infrequent, and the spontaneous resolution of neurological abnormalities, without residual neurological dysfunction, is the most frequently reported outcome (18). However, there may be exceptions, as illustrated by the case of a 17-year-old girl who developed epilepsia partialis continua 6 weeks after being scratched by a cat, followed by residual partial epilepsy (34). We hypothesize that patient 1 in this study developed persistent intravascular *B. henselae* infection and progressive neurological involvement following a cat scratch. Despite reporting other neurological problems, this patient denied having a history of muscle pain, loss of sensation, numbness, and joint pain, which were frequently reported abnormalities in two previous studies (5, 22). Identical *B. henselae* 16S-23S ITS sequences were amplified from samples obtained from patient 1 on three independent occasions. These DNA sequences were obtained by five different approaches, including direct extraction from blood (two samples), BAPGM enrichment blood culture, BAPGM enrichment cerebrospinal fluid culture, and isolation from an agar plate subculture. These results were also obtained at three different sample collection and processing times spanning 9 months, during which time the patient maintained stable *B. henselae* antibody titers. Based upon ITS sequences, all isolates obtained from this individual were most similar to the H1 type strain of *B. henselae* (ATCC 49882), which was originally isolated from the blood of a human immunodeficiency virus-infected person.

Patient 5 had the most severely debilitating neurological abnormalities. This previously healthy 49-year-old veterinarian developed progressive muscle weakness, myoclonus, paresis, and severe fatigue, which followed an acute febrile illness. Initially, a viral infection was diagnosed, and subsequently, multiple sclerosis was diagnosed. Neurological dysfunction resulted in a curtailment of prior athletic activities, such as jogging, and ultimately this individual required assistance during extended walks. Previously, a chronic inflammatory demyelinating polyradiculoneuropathy was reported as a complication of CSD in a 3-year-old boy (29). Six weeks after the onset of classical CSD, the boy developed difficulty in walking, an inability to run or climb stairs, and susceptibility to frequent falling, which became progressively worse during the subsequent 8 weeks (29). Potentially, *B. henselae* infection in patient 5 in this study induced an immune-mediated demyelinating central nervous system disease that mimicked multiple sclerosis.

Blood from the 14-year-old boy described in this study was provided by the attending neurologist when the boy's mother, a companion animal veterinarian, contacted our laboratory, to which she routinely submitted diagnostic samples for testing for tick-borne organisms in the blood of cats and dogs. Al-

though vector competence has not been established for tick transmission of *Bartonella* species, there is both case-based and seroepidemiological evidence supporting transmission by *Rhipicephalus sanguineus* and *Ixodes scapularis* (4, 8, 9). Several recent studies have found *Bartonella* DNA in questing ticks, ticks attached to animals, or ticks attached to human beings (1, 23, 35). In addition, there are previously described case studies in which tick attachment preceded the onset of illness and the documentation of *B. henselae* infection in children or adults (24, 26). Unfortunately, concurrent or prior exposure to cats or kittens and the potential for persistent *B. henselae* infection in children or adults with a history of tick attachment limit the utility of case-based evidence of *B. henselae* transmission by ticks. More recently, investigators from the United States and Poland have documented concurrent infection of the central nervous system with *Borrelia burgdorferi* and *B. henselae*, supporting the possibility of the cotransmission of these pathogens by *Ixodes* spp. (20, 33). Similar to patients 2, 3, 4, and 6 in this study, four individuals residing in a region where *B. burgdorferi* was endemic reported frontal headaches, cognitive dysfunction, and fatigue in a study by Eskow and colleagues, and *B. henselae* DNA was amplified from the blood and/or cerebrospinal fluid samples (20). Also, similar to the 14-year-old boy in this study, one individual in the study by Eskow et al. became ill within a week after the removal of two attached ticks, whereas a second individual became ill 3 months after the removal of a tick from the scalp and, for the other two chronically ill patients, the timing of tick attachment was unknown. Evolving evidence appears to support the potential for the transmission of *B. henselae* to people following tick attachment.

Most recently, our research group has amplified and sequenced DNA of four *Bartonella* species from saliva samples obtained from healthy or sick dogs (17). Although the finding of *Bartonella* DNA does not confirm the presence of viable *Bartonella* organisms in an animal's mouth, it does indicate that bites or contact with saliva from cats or dogs may be an incompletely defined risk factor for the transmission of these organisms to people (17). Prospective studies are needed to determine the variability in the duration of infection and the prevalence of *Bartonella* bacteremia among healthy humans and various patient populations and to evaluate bite wounds as a mode of *Bartonella* transmission to people and the clinical relevance of long-term intravascular infection with these bacteria. Other authors have proposed that *Bartonella* spp. represent an exceptional example of a "stealth pathogen," suggesting that chronic vascular infection can ultimately predispose to complex disease expression, including but perhaps not limited to angiogenesis (30). Comparative medical data obtained from *Bartonella*-infected dogs and people would strongly support this contention (8, 9). As cats and dogs serve as reservoir hosts for *B. henselae* and *B. vinsonii* subsp. *berkhoffii*, respectively, pet contact may represent an incompletely defined risk for disease transmission to people, particularly individuals such as veterinarians, animal handlers, and farmers with extensive animal contact (3, 7, 10, 17, 36). The additional use of a combined approach of enrichment culture and PCR should assist in the microbiological detection of *B. henselae* and *B. vinsonii* subsp. *berkhoffii*. Clearly, joint efforts by physicians and veterinarians are required to further address the role of *Bartonella* species as con-

temporary pathogens in sick animals and in human patients (8, 9, 19).

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