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STANDARD ARTICLE

Testing for *Bartonella* ssp. DNA in cerebrospinal fluid of dogs with inflammatory central nervous system disease

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Background: Neurobartonellosis occurs in people. The role these organisms might play in inflammatory brain disease of dogs is unclear.

Hypothesis/Objectives: That *Bartonella* spp. DNA would be amplified more commonly from the CSF of dogs with inflammatory disease compared to those with noninflammatory disease. To report the prevalence of *Bartonella* spp. in dogs with and without inflammatory CNS disease with a commercially available PCR assay.

Animals: Cerebrospinal fluid (CSF) samples from 172 dogs from either Washington State University or Colorado State University.

Methods: Retrospective study. A search was performed of all medical records from dogs with CSF samples submitted to CSU's Center for Companion Animal Studies or Veterinary Diagnostic Laboratory from CSU or WSU for *Toxoplasma* or *Neospora* PCR assay. Increased CSF nucleated cell counts and an adequate volume of CSF must have been present to evaluate *Bartonella* spp. by PCR assay.

Results: Inflammatory CNS disease was confirmed in 65 dogs, none of which were positive for *Bartonella* spp. DNA. Of the other 107 dogs, one was positive for *B. henselae* DNA. The CSF from this dog contained red blood cells.

Conclusions and Clinical Importance: Failure to amplify *Bartonella* spp. DNA from the CSF of the dogs with inflammatory disease suggests the organism was not involved in the etiology of the disease, the organism was in the CNS tissues but not in the CSF, or the organism was present but in quantities undetectable by this PCR assay. The combination of PCR and culture is the most sensitive way to detect *Bartonella* spp. and the use of that technique should be considered in future studies.

KEYWORDS

bartonellosis, encephalomyelitis, meningitis, PCR, protozoal

1 | INTRODUCTION

Meningoencephalomyelitis of unknown origin (MUO), accounting for 25% of inflammatory central nervous system (CNS) disease in dogs, is suspected to be caused by an immune-mediated process.[1] Treatment with immunosuppressant drugs such as corticosteroids can alleviate clinical signs and delay disease progression. This suggests that dog inflammatory CNS disease is an immune-mediated disease, but whether the immune response is targeting an infection or is autoimmune is a critical open question.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CSU, Colorado State University; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; GME, granulomatous meningoencephalomyelitis; GRE, gradient-recalled echo; MUO, meningoencephalomyelitis of unknown origin; PCR, polymerase chain reaction; PD, proton density; RBC, red blood cells; STIR, short tau inversion recovery; T1W, T1-weighted; T2W, T2-weighted; WSU, Washington State University

A multitude of infectious agents are on the differential list for dogs with focal or multifocal neurological dysfunction, including bacterial, rickettsial, fungal, protozoal, and viral agents.[2,3] Preliminary research searching for an infectious etiology has failed to reveal a common infectious agent.[1,3–6] Within the past 15 years, various groups have utilized polymerase chain reaction (PCR), serology, culture, or immunohistochemistry to investigate viruses commonly implicated in CNS disease, but bacterial diseases, in particular bartonellosis, have not been studied extensively.[5–7]

A number of *Bartonella* spp. infected dogs.[8,9] In a recent multicentre study, prospectively collected CSF and brain tissue from 109 dogs with neurological signs was tested by PCR for *Ehrlichia*, *Anaplasma*, Spotted Fever Group *Rickettsia*, *Bartonella*, and *Borrelia* species. *Bartonella vinsonii* subsp. *berkhoffii* DNA was amplified in the brain tissue from 1 of 6 histopathologically confirmed cases of granulomatous meningoencephalomyelitis (GME), a type of MUO.[3] Based on the findings of that study, this paper focused its investigation on the role of *Bartonella* spp. in the pathogenesis of inflammatory CNS disease in a larger antemortem population of dogs.

Bartonella henselae and *B. clarridgeaie* are transmitted by *Ctenocephalides felis*, and most cases of *Bartonella* spp. infection are identified in areas with high humidity and the presence of *C. felis*.[10] Colorado is semi-arid and so has few *C. felis* infestations or cats with evidence of *Bartonella* spp. exposure.[11] However, dogs do develop *Bartonella* spp. endocarditis in this area.[12]

Human cases of neurobartonellosis can occur in immunocompetent patients.[13–19] *Bartonella* spp. antibodies have likewise been detected in serum of some dogs with neurologic disease including meningoencephalitis, meningoradiculoneuritis, meningitis, and myelitis.[8,20–23]

The primary objective of this study was to report the prevalence of *Bartonella* spp. in client-owned dogs, with and without inflammatory CNS disease, with a commercially available PCR assay. A secondary objective was to stratify the results into groups of dogs with and without inflammatory CNS disease and by region where the exposure was likely to occur. It was hypothesized that *Bartonella* spp. DNA would be amplified more commonly from the CSF of dogs with inflammatory disease compared to those without in areas endemic for fleas.

2 | MATERIALS AND METHODS

2.1 | Selection criteria

Medical records and CSF samples submitted to the Center for Companion Animal Studies or the Colorado State University (CSU) Veterinary Diagnostic Laboratory from either the Washington State University (WSU) Neurology Department between January 2012 and September 2014 or the CSU Veterinary Teaching Hospital between January 2012 and September 2015 were reviewed. These samples had been submitted previously to be evaluated for the presence of *Toxoplasma gondii* and *Neospora caninum* DNA by PCR assays, all of which were negative; this readily available collection of CSF offered a large number of samples from dogs living in regions with either a high risk (Washington) or low risk (Colorado) for fleas, that were suspected of having neurological disease and subsequently had neurologic evaluations. Dogs were included in this study if there was an adequate volume of stored CSF and there was access to the medical record.

The medical records for each dog was reviewed and the dogs were classified as having inflammatory CNS disease if CSF pleocytosis [total nucleated cell count (TNCC) >5 nucleated cells/μL and red blood cell <4000 cells/μL] was present.[24] The type of inflammation was further characterized as lymphocytic (lymphocytes were > 60% of the TNCC), mononuclear (monocytes were > 70% or more of the TNCC), neutrophilic (neutrophils were > 60% of the TNCC), mixed (no single cell population predominated), undifferentiated (not indicated), eosinophilic (eosinophils were > 70% of the TNCC), or to have an eosinophilic component (absolute eosinophilic count ≥10 cells/μL).[25,26] The remainder of the cases were classified by two authors (AD and LB) as noninflammatory. The dogs were further classified based on neurologic examination, when this information was available, as being most consistent with focal neurologic dysfunction or most consistent with multifocal neurologic dysfunction.

All MRI studies (WSU MRI – Philips NT10 Gyroscan Intera 1.0 T MR imaging system; Philips Medical Systems, Andover, MA; CSU MRI – General Electric Signa LX 1.5 Tesla MR HiSpeed Plus System, GE Medical Systems, Milwaukee, WI) were performed on the region of interest based on neurolocalization determined by neurologic examination and were reviewed by a radiologist. Standard brain MRI studies included the sequences: transverse T1-weighted (T1W), sagittal and transverse T2-weight (T2W), transverse fluid-attenuated inversion recovery (FLAIR), transverse proton density (PD), transverse gradient-recalled echo (GRE), transverse diffusion weight images (DWI; CSU only), and transverse, sagittal and dorsal T1W postgadolinium (Magnevist [gadopentetate dimeglumine] 0.5 mmol/mL, Bayer, Whippany, NJ) images. Standard spine MRI protocol included sagittal and transverse T1W (CSU only), sagittal, transverse, and dorsal T2W, sagittal short tau inversion recovery (STIR; CSU only), transverse and sagittal T1W postgadolinium images; transverse FLAIR and GRE images as indicated (WSU only). MRI lesions suggestive of inflammatory CNS disease included areas of focal or multifocal hyperintensity on T2W images with or without T1W postgadolinium contrast enhancement of either the brain or spinal cord.

2.2 | Bartonella *spp. PCR assay*

The remnant CSF samples had been stored at −80°C in monitored freezers until processed for this study. The frozen CSF samples (total volumes ranging from 100 to 550 μL) were thawed at room temperature and were ultracentrifuged at 10 000*g* for 15 minutes. The supernatant was discarded, and the pellet (5 μL CSF mixed with 50 μL of PCR reaction mix) was assayed according to a previously published, single-tube, conventional PCR assay targeting the 16S-23S rRNA intergenic region.[27] In previous titration experiments, this assay was shown to amplify *B. henselae* DNA from 100% of samples were greater than 50 colony forming units per mL.[27] In unpublished experiments, the extraction method was used on CSF samples from dogs with varying nucleated cell counts to determine whether DNA was extracted by amplifying glyceraldehyde 3-phosphate dehydrogenase (GAPDH); all samples with >15 nucleated cells per μL were positive. In this study, all positive amplicons were sequenced to confirm the detected *Bartonella* spp.

2.3 | Statistical evaluation

Descriptive statistics were used to present the proportions of dogs with different neurological findings and CSF findings in each of the two regions. For some findings, Fishers' exact test was used to compare groups of results (https://graphpad.com). Ages among groups were compared by Mann-Whitney *U* test (http://www.socscistatistics.com). Significance was defined a $P < .050$.

3 | RESULTS

Samples of CSF submitted from 172 cases from pure or mixed breed dogs from WSU (117 cases) or CSU (55 cases) were evaluated. Inflammatory CNS disease was confirmed in 65 dogs and the remaining 107 dogs were classified as noninflammatory CNS disease. *Bartonella henselae* DNA was amplified from one dog in the noninflammatory CNS group (107) and none of the dogs in the inflammatory CNS group (65). The sample from the one positive dog came from Washington and contained RBC (94 RBC/μL). The medical record was evaluated and no fleas were mentioned; however, it was not noted whether the dog was on a flea control product. The dog's neurologic examination was consistent with right-sided vestibular dysfunction.

Inflammatory CNS disease was detected in 42 dogs (35.9%) from WSU and 23 dogs (41.8%) from CSU (Table 1). This difference was not statistically different ($P = .50$).

The median age of the dogs with inflammatory CNS disease was 5 years (range, 2.4 months to 13 years) and the median age of the dogs with noninflammatory CNS disease was 7 years (2.0 months to 15 years); this difference was statistically significant, $P = .010$). Of the dogs with inflammatory CNS disease, there were 32 males and 33 females, and of the dogs without inflammation, there were 65 males and 42 females. There were no differences in sex distributions between the groups ($P = .16$).

In the group classified with inflammatory CNS disease, there were 9 mixed breed (13.8%), 5 pugs (7.7%), 5 Labrador Retrievers (7.7%), 4 Chihuahuas (6.2%); 3 each (4.6%) of the following: Yorkshire terrier, Boxer, Vizsla, German Shepherd dog, Golden Retriever (4.5% each); two each (3.1%) of the following: Bichon Frise, Shih Tzu, Dachshund, German Shorthaired Pointer, Miniature Schnauzer, and Cairn Terrier, and one each (1.5%) of other breeds.

In the noninflammatory group of 107 dogs, there were 17 Labrador Retrievers (15.9%), 11 mixed breeds (10.2%), 6 German Shepherd dogs (5.6%), 4 Boxers (3.7%); 3 each (2.8%) of the following: Australian sheepdog, Chihuahua, pug, and Yorkshire Terrier; and two each (1.9%) of the following: Schnauzer, Akita, Standard Poodle, Dachshund, Doberman Pinscher, English Setter, Husky, Mastiff, Pomeranian, Rottweiler, Border Collie, Boston Terrier, Flat Coat Retriever, German Short Haired Pointer, and Shih Tzu; and one each (0.93%) of other breeds.

The results of the neuroanatomic localizations, MRI characteristics, and administration of glucocorticoids before diagnostic imaging and CSF collection are summarized in Table 2.

The proportion of dogs with different types of CSF inflammation by group is shown in Table 1. The dogs with inflammatory CNS disease had a mean CSF protein concentration of 181.9 mg/dL (range < 0.05-1900 mg/dL), a mean total nucleated cell count of 391.5 cells/μL (range 6-6000 cells/μL), and mean RBC count was 285.5 cells/μL (range 0-3397 cells/μL). The characterization of pleocytosis was as follows: lymphocytic pleocytosis (31), mixed pleocytosis (21), monocytic pleocytosis (7), neutrophilic pleocytosis (4), and eosinophilic pleocytosis (1); one dog was classified as having an undifferentiated inflammatory pleocytosis. For dogs with a pleocytosis, the average percentage for each differential cell line was 49.6% lymphocytes (range 0-98), 27.8% monocytes (range 0-95), 18.4% neutrophils (range 0-97), 5.8% eosinophils (range 0-87), and 0.1% basophils (range 0-4). There were neither significant differences between lymphocytic and

TABLE 1 MRI and CSF distribution

		Sex		Age		MRI localization			
Category	(n)	Male	Female	Range	Median	Multifocal	Focal	Normal	No imaging
Lymphocytic pleocytosis – CO	10	6	4	0.8-10	6	5	3	1	1
Mixed pleocytosis – CO	10	3	7	0.2-12	7	5	2	3	0
Mononuclear pleocytosis – CO	1	1	0	10	NA	0	0	1	0
Neutrophilic pleocytosis – CO	1	0	1	6	NA	0	0	1	0
Undifferentiated pleocytosis – CO	1	1	0	3	NA	1	0	0	0
All inflammatory combined – CO	23	11	12	0.2-12	6	11	5	6	1
Lymphocytic pleocytosis – WA	21	10	11	0.67-12	4	8	7	4	2
Mixed pleocytosis – WA	11	5	6	1.0-8	6	5	1	4	1
Mononuclear pleocytosis – WA	6	3	3	0.33-11	7	1	3	0	2
Neutrophilic pleocytosis – WA	3	2	1	0.5-8	5	2	0	0	1
Eosinophilic pleocytosis – WA	1	1	0	2		1		0	0
All inflammatory combined – WA	42	21	21	0.5-12	5	17	11	8	4
All inflammatory combined – CO and WA	65	32	33	0.2-12	11	28	16	14	7
Noninflammatory – CO	33	23	10	0.25-13	8				
Noninflammatory – WA	74	42	32	0.17-15	8				
All noninflammatory – CO and WA	107	65	42	0.17-15	8	16	55	7	29

Distribution of CSF and MRI results from dogs suspected as having inflammatory CNS disease. MRI, magnetic resonance imaging.

TABLE 2 Demographics of dogs with and without inflammatory CNS disease

	Inflammatory group (n = 65)	Noninflammatory group (n = 107)
Neuroanatomic localization	30 (46.2%)	23 (21.5%)
Multifocal	13 (20.0%)	37 (34.6%)
Brain	15 (23.1%)	33 (30.8%)
Spine	7 (10.8%)	5 (4.7%)
Normal exam	0	4 (3.7%)
Neuromuscular	0	5 (4.7%)
Not available		
T2W hyperintensities on MRI	29 (49.2%)	16 (15.0%)
Multifocal	8 (13.6%)	23 (21.5%)
Brain	7 (11.9%)	26 (24.3%)
Spine	15 (25.4%)	29 (27.1%)
Normal exam	6 (9.2%)	7 (6.5%)
Not available	0	6 (5.6%)
Extraparenchymal		
GC administered before MRI/CSF	14 (21.5%)	21 (19.6%)
Yes	39 (60.0%)	81 (75.7%)
No	12 (18.5%)	5 (4.7%)
Unknown history		
Total dogs	65	107

Glucocorticoid administration before MRI and CSF, neuroanatomic localization, and T2W hyperintensities on MRI in dogs with and without inflammatory CNS disease. CSF, cerebrospinal fluid; GC, glucocorticoids; MRI, magnetic resonance imaging; T2W, T2 weighted.

mononuclear inflammation (P = .29), mixed and neutrophilic pleocytosis (P = .20), nor in age groups among types of inflammation between Colorado and Washington. Finally, when only those dogs with multifocal neurolocalization were evaluated separately, there was no difference between the type of pleocytosis and region (Colorado or Washington), sex, or age.

4 | DISCUSSION

Inflammatory and infectious diseases of the CNS are an important group of disorders, as they often cause severe neurologic dysfunction and can result in death of the dog. Meningoencephalitis of unknown origin is a relatively common condition in dogs whose etiopathogenesis remains elusive. Antemortem diagnosis relies on neurologic signs, CSF, MRI, and infectious disease testing, with histopathology necessary for definitive diagnosis.[28] Infectious agents thought to cause neurologic disease in dogs include rickettsial, viral, fungal, bacterial, and protozoans, in particular *T. gondii* and *N. caninum*.[2,3] In a recent study, *Bartonella* was isolated in the brain tissue of one dog.[3]

Failure to amplify *Bartonella* spp. DNA from the CSF of the 65 dogs with inflammatory disease in this study suggests either the organism was not a causal agent, the organism was in the CNS tissues but not in the CSF, or the organism was present but in quantities undetectable by this PCR assay. There might be selection bias in the population of dogs presented to tertiary hospitals and, therefore, included in this study. Because the application of flea and tick prevention reduces the infection rate, at least in experimentally infected cats, it could be speculated that pets belonging to families who have financial resources permitting them to proceed with MRI and CSF analyses, are also more likely to be treated with monthly flea and tick prevention and are consequently at less risk for bartonellosis.[29] This remains speculation, however, since the use of such preventives were not noted in the medical records to which we had access.

Of the 172 CSF samples, only one was positive for *B. henselae* DNA. This dog had vestibular dysfunction and did not have inflammatory CNS disease, but the CSF contained red blood cells (94 RBC/μL), which could have altered the PCR results. Because *Bartonella* spp. have an intraerythrocytic phase, we speculate that minimal peripheral RBC contamination in the CSF of dogs with systemic *Bartonella* spp. infection may lead to positive *Bartonella* PCR assay results in the absence of CNS disease association. Thus, positive PCR for *Bartonella* spp. DNA in the CSF of dogs must be interpreted in light of RBC present within the sample.

Diagnosis of bartonellosis is complex, clinically, microbiologically, and pathologically. This is attributable to many factors related to the numerous species within the genus *Bartonella*, antigenic and virulence differences among strains and subspecies, and the diverse cell tropism. In addition, the ability to induce persistent occult infections in both reservoir and nonreservoir hosts, and the extraordinarily low levels of bacteremia found in nonreservoir hosts, make diagnosing bartonellosis challenging.[16] A limitation of this study was the application of PCR alone in the detection of *Bartonella* spp. The combination of PCR and culture has been found to be the most sensitive way to detect *Bartonella* spp. in samples from dogs and humans and the use of that technique should be considered in future studies.[16] Negative results in single PCR assays may not fully exclude *Bartonella* spp. from the differential list.

Another limitation of this study was the unavailability of historical information regarding prior or concurrent use of antibiotics in these dogs. However, *Bartonella* DNA is frequently detected, and a microbiological diagnosis achieved, despite antibiotic treatment.[30] This might reflect a high proportion of treatment failure, as previously suspected. Similarly, there was no statistical association with enhanced PCR detection and glucocorticoids in that study; however, few dogs were treated with glucocorticoids. Whether glucocorticoids treatment might facilitate molecular diagnosis of bartonellosis remained uncertain.

Inflammatory CNS disease is commonly identified with infectious causes being rarely detected. Management with judicious use of immunosuppressive therapies in many of these cases affords a positive outcome.[31–35] Immunosuppression in the face of infection by *N. caninum* can lead to exacerbation of the disease, which can have a fatal outcome.[36,37] The results presented here further demonstrate that *T. gondii*, *N. caninum*, and *Bartonella* spp. infections are rarely identified in dogs with the neurological manifestations reported here. Despite this, screening for these and other infectious agents before immune suppression is prudent because the consequences could be catastrophic.

In this study, toy breed dogs predominated in the inflammatory CSF group, with samples from pugs and Chihuahuas representing 7.7

and 6.2% of the population, respectively. This is not surprising, as MUO tends to affect toy breeds more frequently.[2,26,31,38] However, 28 dogs (43.0%) were large breeds (>15 kg). This proportion is larger than what was reported by a recent study, in which 25% of dogs presumptively diagnosed with inflammatory CNS disease were considered large breeds (>15 kg).[39] This likely represents a regional difference in the population of preferred breeds but it demonstrates that inflammatory CNS disease should be considered in large breed dogs.

5 | CONCLUSIONS

Similar to other reports, an apparent role of *Bartonella* spp., *T. gondii*, and *N. caninum* in dog inflammatory CNS disease was not identified. Many complexities exist in the diagnosis of bartonellosis and its contribution might be underestimated. Furthermore, positive PCR for *Bartonella* spp. DNA in the CSF of dogs must be interpreted in light of the number of RBC within the sample as well as the presence of inflammation or systemic infection.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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