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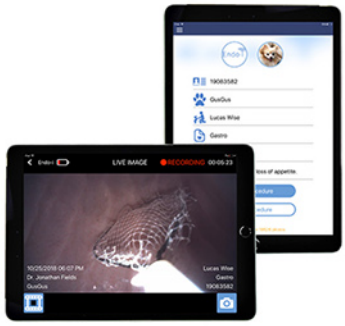

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Cerebrospinal fluid lactate in dogs with inflammatory central nervous system disorders

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Abstract

Background: Cerebrospinal fluid (CSF) lactate is frequently used as a biomarker in humans with inflammatory central nervous system (CNS) disorders including bacterial meningitis and autoimmune disorders such as multiple sclerosis.

Hypothesis: Cerebrospinal fluid lactate concentrations are increased in a subset of dogs with inflammatory CNS disorders.

Animals: One hundred two client-owned dogs diagnosed with inflammatory CNS disease.

Methods: Case series. Cases were identified both prospectively at the time of diagnosis and retrospectively by review of a CSF biorepository. Cerebrospinal fluid lactate was analyzed with a commercially available, handheld lactate monitor. Subcategories of inflammatory disease were created for comparison (eg, steroid-responsive meningitis arteritis, meningoencephalitis of unknown etiology).

Results: Cerebrospinal fluid lactate concentrations were above reference range in 47% of dogs (median, 2.5 mmol/L; range, 1.0-11.7 mmol/L). There was no significant difference in lactate concentrations between disease subcategories ($P = .48$). Significant but weak correlations were noted between CSF lactate concentration and nucleated cell count ($r = .33$, $P < .001$), absolute large mononuclear cell count ($r = .44$, $P < .001$), absolute small mononuclear cell count ($r = .39$, $P < .001$), absolute neutrophil cell count ($r = .24$, $P = .01$), and protein ($r = .44$, $P < .001$). No correlation was found between CSF lactate concentration and CSF red blood cell count ($P = .58$). There was no significant association of CSF lactate concentration with survival ($P = .27$).

Conclusions and Clinical Importance: Cerebrospinal fluid lactate concentrations could serve as a rapid biomarker of inflammatory CNS disease in dogs.

KEYWORDS

canine, encephalitis, meningitis, meningo, meningoencephalitis, myelitis

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; GME, granulomatous meningoencephalitis; MRI, magnetic resonance imaging; MS, multiple sclerosis; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid responsive meningitis-arteritis.

1 | INTRODUCTION

Cerebrospinal fluid (CSF) lactate is being increasingly evaluated as a potential biomarker of central nervous system (CNS) disease in dogs. Normative data and reference intervals for CSF lactate concentrations have been reported in dogs.[1-4] There are increases in CSF lactate concentrations in dogs with severe cognitive deficits,[5] and a trend to increasing values was noted in dogs with intracranial disease.[1] However, another study failed to detect a difference in CSF lactate values between dogs with or without structural intracranial disease.[6] Outside these few studies performed in small numbers of dogs, there is little information available related to CSF lactate in diseased dogs.

In humans, CSF lactate concentrations are increased in a variety of CNS disorders including mitochondrial disorders, inflammatory conditions, head trauma, and seizures.[7-11] Perhaps, the greatest utility in humans is to distinguish bacterial from aseptic meningitis.[12,13] However, lactate concentrations are also increased in some patients with presumed autoimmune inflammatory conditions such as neuromyelitis optica[14] and multiple-sclerosis.[15-18]

Recently, a handheld lactate monitor has been validated for quantification of L-lactate in canine blood and CSF and a CSF reference interval for this analyte has been established (1.02-2.49 mmol/L).[4,19] The purpose of this study was to evaluate CSF lactate concentrations in dogs with inflammatory CNS diseases. We hypothesized that many of these CSF samples would have lactate concentrations above the upper end of our established reference interval.

2 | MATERIALS AND METHODS

2.1 | Animals, CSF sample collection, CSF analysis and outcome determination

Dogs that were referred to the NC State Veterinary Hospital for a variety of presenting complaints were included in the study. Inclusion criteria were CNS imaging (magnetic resonance imaging [MRI] or computed tomography [CT], with the exception of dogs diagnosed with steroid-responsive meningitis-arteritis [SRMA], see below), routine CSF analysis (nucleated and red blood cell counts, protein evaluation, and cytological evaluation), a clinical diagnosis of inflammatory CNS disease (see Diagnostic Groups below), and a complete medical record. Cerebrospinal fluid samples were collected as part of a routine diagnostic evaluation from the cerebellomedullary cistern or lumbar subarachnoid space. Informed, written client consent was obtained for the use of these samples for research purposes. Most samples were analyzed within 5 minutes of collection with a commercially available lactate monitor (Lactate Plus; Nova Biomedical, Waltham, Massachusetts) although some were evaluated after being frozen at −80°C.

The age at presentation, sex, breed, weight, clinical lesion localization, CSF collection site, CSF nucleated cell count, CSF red blood cell count, CSF protein, CSF cytological evaluation (percentage of small mononuclear cells, large mononuclear cells, neutrophils, and other cells), and CSF lactate concentration were recorded. In dogs with CSF collected from both the cerebellomedullary cistern and the lumbar subarachnoid space, CSF obtained from the site closest to the identified lesion was used for analysis. The CSF nucleated cell count was multiplied by the proportion of large mononuclear cells, small mononuclear cells, and neutrophils seen on cytological evaluation to generate absolute cell counts for each CSF sample.

Dogs could have normal CNS imaging or CSF analysis but had to have consistent abnormalities in 1 of these diagnostic tests in order to be included. Further inclusion criteria for imaging and CSF results are described below. Cases were excluded if CNS imaging revealed a well-defined, focal mass lesion or a parenchymal lesion in a distribution compatible with a cerebrovascular ischemic injury. Dogs were assigned to specific diagnostic groups based on clinical criteria including signalment, clinical signs, and diagnostic testing. The criteria for diagnosis of specific inflammatory CNS conditions are listed in more detail below.

The medical record was reviewed to determine if dogs survived to hospital discharge and in dogs that died spontaneously or underwent euthanasia, and the date of death was recorded. For dogs that were still alive at the last recorded visit, dog owners, referring veterinarians, or both were contacted to determine if the dog was still alive and if not, the date of death. The results of necropsy examinations were also recorded when available.

2.2 | Diagnostic groups

2.2.1 | Granulomatous meningoencephalitis, necrotizing meningoencephalitis, and necrotizing leukoencephalitis

These diagnoses were made after histological evaluation of the brain, cervical spinal cord, or both regions according to published reports.[20,21]

2.2.2 | Meningoencephalitis of unknown etiology

This diagnosis was made in dogs with suspected granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), or necrotizing leukoencephalitis (NLE) but in which histopathology of the nervous system was not performed. In these cases, the diagnosis was based on CNS imaging and CSF evaluation.[22] Imaging typically showed multifocal hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, with variable degrees of meningeal and parenchymal enhancement after IV administration of contrast (gadoversetamide, 0.1 mmol/kg [Optimark, Mallinckrodt Inc, St. Louis, Missouri] or iohexol, 2.2 mL/kg [Omnipaque 350 mgI/mL, GE Healthcare, Marlborough, Massachusetts]). Diffuse, ill-defined T2 and FLAIR hyperintense lesions were also noted. Cerebrospinal fluid evaluation typically showed a mononuclear pleocytosis. However, as a significant proportion of dogs with meningoencephalitis of unknown etiology (MUE) lack a pleocytosis and some dogs have a marked pleocytosis in the absence of imaging changes, an MUE diagnosis could be made with only imaging or CSF criteria.[23,24] Infectious disease testing varied somewhat in this cohort but was negative in all cases.

2.2.3 | Meningomyelitis

These cases were similar to MUE cases but with primary involvement of the spinal cord.

2.2.4 | Total MUE

As MUE is a clinical term used to indicate dogs suspected to have GME, NME, or NLE that do not have a histological diagnosis and many use the term MUE to encompass dogs with spinal cord involvement, dogs in the MUE, GME/NME/NLE, and meningomyelitis groups were combined to create this group.

2.2.5 | Steroid-responsive meningitis-arteritis

For inclusion, dogs with SRMA had to be less than 3 years of age at presentation and had to have cervical pain as their primary clinical sign, with minimal or no associated neurologic deficits. These dogs also had a CSF neutrophilic pleocytosis (unless chronically affected) and showed dramatic clinical improvement after the administration of glucocorticoids. When measured, these dogs had increased serum concentrations of C-reactive protein. Imaging of the CNS was not required for this group but if performed was limited to meningeal enhancement after IV administration of contrast with an absence of parenchymal lesions within the CNS.

2.2.6 | Infectious or presumed infectious meningoencephalitis or meningomyelitis

These dogs had evidence of CNS inflammation together with a positive test for an infectious disease, which might have included testing of blood or CSF for antigen, antibody titers, nucleic acids via polymerase chain reaction-based testing, or microscopic visualization of organisms in a clinical sample. Presumed infectious cases included dogs that had a clinical response to antibiotic administration without concurrent glucocorticoid or other anti-inflammatory or immunosuppressive medications.

2.2.7 | Miscellaneous

This group included dogs with idiopathic tremor syndrome, idiopathic hypertrophic pachymeningitis, eosinophilic meningoencephalitis, and 1 dog with a histologically confirmed infiltrative inflammatory condition involving the paraspinal musculature, meninges, and cervical spinal cord.

2.3 | Statistical analysis

Descriptive statistics were generated for age at presentation, weight, CSF nucleated cell counts, CSF red blood cell count, CSF protein, and CSF lactate concentration. A D'Agostino and Pearson normality test showed that the lactate values did not follow a normal distribution and therefore nonparametric evaluations were used to compare diagnostic groups. A Kruskal-Wallis test was used to compare lactate values between diagnostic groups. A Spearman correlation was used to examine the relationships between CSF parameters and lactate concentrations and between lactate concentrations and survival. Survival times were calculated from the date of CSF collection. Survival curves were constructed using the Kaplan-Meier method and compared using a log-rank test. Dogs that were still alive or lost to follow-up were censored at the last available contact date. Lactate concentrations of dogs that did or did not survive to be discharged from the hospital were compared using a Mann-Whitney test, and this test was also used to compare survival times in dogs with lactate concentrations within or above the reference interval. A P value < .5 was considered significant. All analyses were conducted using Prism (Version 7, GraphPad Software, Inc, La Jolla, California).

3 | RESULTS

A total of 102 dogs with a diagnosis of inflammatory CNS disease were included, with a variety of breeds represented. Descriptive statistics for individual diagnostic groups and the whole cohort are shown in Table 1. Lesions were localized to the following locations:

TABLE 1 Characteristics of dogs categorized in different inflammatory CNS groups

				Sex			
Diagnostic category	Number of dogs	Age (years)	Weight (kg)	M	MC	F	FS
GME/NME/NLE	8	7.6 (2.4-10.0)	19.3 (2.9-30.6)	1	3	0	4
MUE	44	6.1 (0.8-14.7)	6.7 (2.5-33.0)	2	15	0	27
Meningomyelitis	17	6.9 (1.8-11.9)	11.3 (2.0-32.4)	1	7	1	8
TMUE	69	6.6 (0.8-14.7)	7.6 (2.0-33.0)	4	25	1	39
SRMA	14	0.7 (0.4-1.5)	22.4 (10.0-29.1)	3	5	3	3
Suspect infectious	12	2.1 (0.1-10.8)	15.45 (2.0-34.6)	2	1	3	6
Miscellaneous	7	5.0 (1.5-11.0)	10.5 (6.2-30.6)	1	1	1	4
All cases	102	5.6 (0.1-14.7)	10.7 (2.0-34.6)	10	32	8	52

Age and weight values are expressed as median (range).
Abbreviations: CNS, central nervous system; FS, female spayed; GME, granulomatous meningoencephalitis; MC, male castrated; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid-responsive meningitis-arteritis; TMUE, total MUE.

TABLE 2 Cerebrospinal fluid variables in dogs with inflammatory CNS disease

	Collection site				
Diagnostic category	CCSF	LCSF	Nucleated cell count (cells/μL)	Red blood cell count (cells/μL)	Protein (mg/dL)
GME/NME/NLE	7	1	237.5 (7-1702)	201 (3-533)	203.1 (36.0-981.5)
MUE	35	9	67 (0-5320)	41 (0-12 100)	60.5 (1.4-915.0)
Meningomyelitis	12	5	176 (1-1160)	45 (0-12 800)	138.8 (26.2-537.5)
TMUE	54	15	130 (0-5320)	43 (0-12 800)	83.6 (1.4-981.5)
SRMA	13	1	897.5 (4-5267)	1069 (25-40 000)	102.1 (25.9-318.9)
Suspect infectious	9	3	119 (3-1773)	23 (0-1440)*	57.7 (15.6-958.0)
Miscellaneous	7	0	7 (3-1002)	20 (3-1833)	34.0 (12.6-225.3)
All cases	83	19	133.5 (0-5320)	45 (0-40 000)	83.1 (1.4-981.5)

Nucleated cell count, red blood cell count, and protein values are expressed as median (range).
Abbreviations: CNS, central nervous system; CCSF, cerebellomedullary cistern cerebrospinal fluid; GME, granulomatous meningoencephalitis; LCSF, lumbar subarachnoid space cerebrospinal fluid; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid-responsive meningitis-arteritis; TMUE, total MUE.
*In 1 sample, the red cell count was not available.

TABLE 3 Cerebrospinal fluid lactate concentrations in dogs with inflammatory CNS disease

Diagnostic category	Number	Median lactate (range) (mmol/L)	Mean lactate (mmol/L)	Samples above reference interval (%)[a]
GME/NME/NLE	8	2.5 (2.1-7.0)	3.7	4 (50)
MUE	44	2.45 (1.0-8.4)	2.9	20 (45)
Meningomyelitis	17	2.7 (1.3-6.6)	2.9	10 (59)
TMUE	69	2.5 (1.0-8.4)	3.0	34 (49)
SRMA	14	2.1 (1.1-4.9)	2.4	6 (43)
Suspect infectious	12	2.6 (1.0-11.7)	3.1	6 (50)
Miscellaneous	7	1.9 (1.5-4.1)	2.2	2 (29)
All cases	102	2.5 (1.0-11.7)	2.9	48 (47.1)

Abbreviations: CNS, central nervous system; GME, granulomatous meningoencephalitis; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid responsive meningitis-arteritis; TMUE, total MUE.
[a]Reference interval is 1.02-2.49 mmol/L.

TABLE 4 Survival in dogs with inflammatory CNS disease

			Median survival (range) (days)	
Diagnostic category	Number	Whole cohort	Lactate within reference interval	Lactate above reference interval
GME/NME/NLE	8	1 (1-843)	1 (1-1)	1 (1-843)
MUE	44	Not reached[a] (1-2433)	Not reached (1-1674)	839 (1-2433)
Meningomyelitis	17	439 (5-2225)	520 (5-601)	302 (6-2225)
TMUE	69	839 (1-2433)	Not reached (1-1674)	839 (1-2433)
SRMA	14	Not reached (7-1720)	Not reached (7-1720)	549 (165-744)
Suspect infectious	12	170 (1-500)	170 (1-500)	Not reached (1-463)
Miscellaneous	7	Not reached (1-651)	Not reached (1-651)	72 (1-143)
All cases	102	843 (1-2433)	Not reached (1-1720)	839 (1-2433)

Abbreviations: CNS, central nervous system; GME, granulomatous meningoencephalitis; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid-responsive meningitis-arteritis; TMUE, total MUE.
[a]The median survival time was not reached in some groups where >50% of animals were still alive.

forebrain in 15 dogs (14.7%), brainstem in 16 dogs (15.7%), cerebellum in 4 dogs (3.9%), cervical myelopathy or cervical pain in 28 dogs (27.5%), thoracolumbar myelopathy in 5 dogs (4.9%), diffuse spinal pain in 3 dogs (2.9%), and multifocal CNS in 31 dogs (30.1%). Magnetic resonance imaging was performed in 92 dogs (90.2%), CT in 5 dogs (4.9%), 1 dog (1.0%) was imaged with both modalities, and

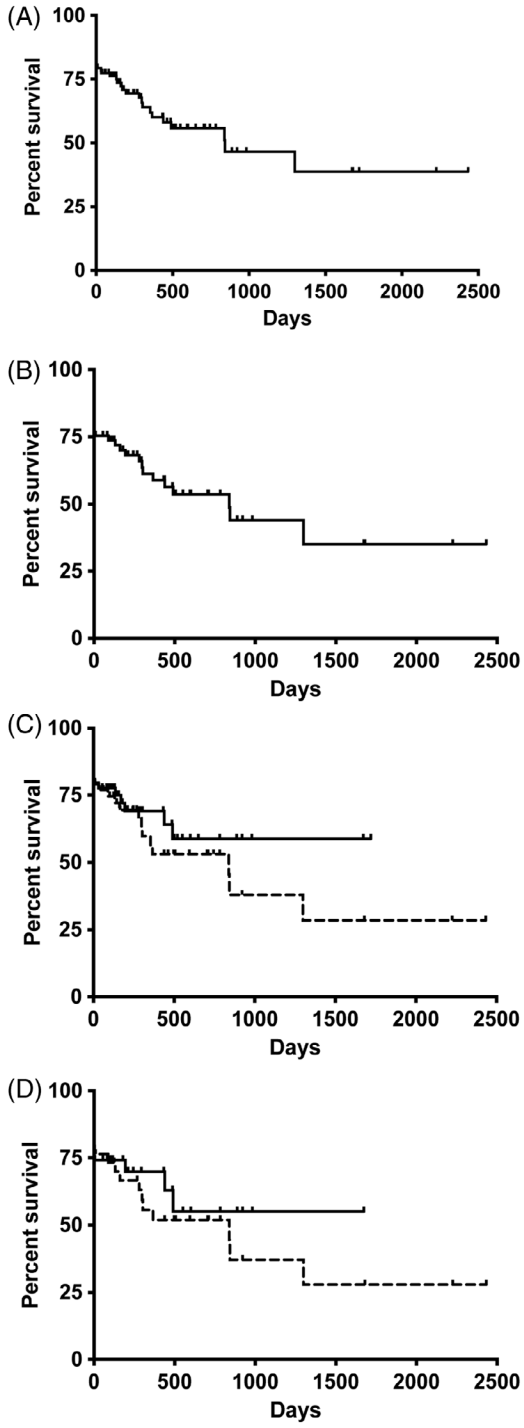

FIGURE 1 Survival curves for (A) the whole cohort of dogs with inflammatory CNS disease and (B) dogs with MUE, meningomyelitis, or histologically diagnosed GME, NME, or NLE (TMUE). There was no difference in survival of dogs with (C) inflammatory CNS disease and either normal CSF lactate (solid line) or increased CSF lactate (dashed line) (P = .74) or (D) TMUE dogs with either normal CSF lactate (solid line) or increased CSF lactate (dashed line) (P = .52). Ticks represent dogs that were censored during analysis. CNS, central nervous system; CSF, cerebrospinal fluid; GME, granulomatous meningoencephalitis; MUE, meningoencephalitis of unknown etiology; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid responsive meningitis-arteritis; TMUE, total MUE

4 dogs (3.9%) with SRMA did not have advanced CNS imaging. Eighty-three CSF samples (81.4%) were collected from the cerebellomedullary cistern, and 19 (18.6%) from the lumbar subarachnoid space. Characteristics of the CSF analysis for each diagnostic group are shown in Table 2. Due to limited sample volume, total protein concentration was not available for 5 cases. A total of 90/102 (88.2%) dogs had pleocytosis and 78/97 (80.4%) dogs had increased CSF protein concentrations.

The CSF lactate results are shown in Table 3. There was only 1 dog with a confirmed diagnosis of bacterial meningitis, and the lactate concentration was 11.7 mmol/L. There was no significant difference in lactate concentrations between the diagnostic groups (P = .48) and no obvious relationship between lactate and breed (data not shown). Significant but weak correlations were noted between CSF lactate concentration and nucleated cell count (r = .33, P < .001), absolute large mononuclear cell count (r = .44, P < .001), absolute small mononuclear cell count (r = .39, P < .001), absolute neutrophil cell count (r = .24, P = .01), and protein (r = .44, P < .001). No correlation was found between CSF lactate concentration and red blood cell count (P = .58).

Eighty-one of 102 dogs (79.4%) survived to hospital discharge. Thirty-nine dogs (38.2%) died or were euthanized, and 63 (61.8%) were censored in the survival analysis. Survival times for the diagnostic groups are shown in Table 4 and Figure 1. When considering all diagnostic groups, there was a significant difference in survival, but this was primarily driven by the short survival in the group that had a histological diagnosis, an obvious confounding factor. When this group was removed or when the total MUE group was compared with the non-MUE groups, there was no significant difference in survival (P = .31). There was no correlation between lactate concentration and overall survival (P = .27) or difference in concentrations between those dogs that did or did not survive to hospital discharge (P = .58). In addition, although there was some divergence of the survival curves (Figure 1), survival was not different between dogs with lactate concentrations within or above the reference interval (P = .38).

4 | DISCUSSION

We found that 47% of dogs with inflammatory CNS disease had CSF lactate concentrations above our established reference interval and that this proportion did not vary substantially between diagnostic groups. The CSF lactate concentration correlated weakly with CSF nucleated cell counts and protein but not with red blood cell counts. Cerebrospinal fluid lactate concentrations were not associated with overall survival or survival to hospital discharge.

Two prior studies of CSF lactate have been performed in dogs with intracranial disease with conflicting results.[1,6] However, both studies evaluated small numbers of dogs with a variety of disorders (11 and 13 dogs with documented structural disease), and it is not surprising that the results varied. Meningoencephalitis was diagnosed in only 2 and 4 of the dogs in these studies, precluding reasonable comparison to our results.

Lactate has been extensively studied in human CSF and is increased in a number of conditions, including mitochondrial disorders, head

trauma, and inflammatory conditions.[8-11] Indeed, one of the greatest utilities of this analyte is distinguishing bacterial from aseptic meningitis, a common clinical conundrum in humans.[12,13] The only dog in our study with a confirmed diagnosis of bacterial meningitis had a CSF lactate concentration of 11.7 mmol/L. It is also possible that bacterial infections went undetected in some of the dogs in this study. However, this seems unlikely as bacteria were not observed on cytological examination; most samples displayed a mononuclear pleocytosis and a majority of animals responded favorably to prolonged immunosuppressive treatment.

Cerebrospinal fluid lactate is increased in subsets of human patients with multiple sclerosis (MS), a well-known, immune-mediated inflammatory CNS disorder.[15,17,18] This can occur in patients with both primary progressive and remitting-relapsing forms of the disease, particularly during exacerbations, relapses, or with secondary progression.[17,18] Despite this, a number of MS patients have CSF lactate concentrations within established reference intervals.[15,16,25] However, even when CSF lactate concentrations remain within normal reference intervals, these concentrations can be higher than those seen in control groups.[16,18] In addition, CSF lactate concentrations have been correlated with injury severity as measured by progression/disability scores,[16] markers of neuronal damage,[16] and the presence of inflammatory plaques on MRI.[17,25]

An increased CSF lactate concentration in MS patients has been attributed to CNS inflammation. In addition to its correlation with inflammatory plaques on imaging, Simone et al found that CSF lactate concentration correlated with CSF mononuclear cell counts.[17] Most of the dogs in this study had a mononuclear pleocytosis, often with a predominance of small mononuclear cells or lymphocytes. Although we could demonstrate only a weak correlation between absolute lymphocyte count and lactate concentrations and some dogs (primarily in the SRMA group) with a neutrophilic pleocytosis also had increased lactate concentrations, it is possible that CSF lactate concentrations might relate to the activation status of lymphocytes within the CSF in some dogs. During the rapid proliferation associated with antigenic stimulation, lymphocytes are known to utilize aerobic glycolysis, which results in the generation of large amounts of extracellular lactate, a phenomenon known as the Warburg effect.[26,27] This phenomenon was originally described in neoplastic cells and occurs in a variety of cancers, including lymphoma.[28-30] Thus, it is possible that some dogs had an abundance of actively proliferating lymphocytes within the CSF and lactate concentrations in these individuals served as a proliferative marker. This would be supported by our observation that some of the highest CSF lactate concentrations noted in this study were from dogs with a marked lymphocytic pleocytosis and those noted to have extensive lymphocyte proliferation within perivascular spaces of the CNS at necropsy.

Another theory for the increased CSF lactate concentrations noted in humans with MS is related to impaired energy metabolism secondary to mitochondrial dysfunction.[16,18] Children with CNS dysfunction secondary to inherited mitochondrial disorders are well documented to have increased CSF lactate.[9,10,31] It is possible that mitochondrial dysfunction is playing a role in dogs with inflammatory CNS disorders, but this will require further study.

The monitor used in this study requires a small volume of CSF (.7 μL) to generate an accurate measurement and takes 13 seconds to complete once testing is initiated. This method has particular utility for dogs with MUE as these are frequently small or toy breed dogs in which a limited quantity of CSF can be collected. This paucity of sample can limit the use of other lactate analyzers, particularly benchtop units. The short analysis time allows for a rapid, "cage-side" analysis of CSF lactate, and we have found this to be a useful method of supporting a presumptive diagnosis of meningoencephalitis before the results of conventional CSF evaluation are available. This information might also facilitate the early initiation of anti-inflammatory or immunosuppressive therapy in some dogs with severe clinical signs in which increased intracranial pressure and brain herniation are concerns.

This study did not find a consistent relationship between CSF lactate and prognosis, looking at either overall survival or survival to hospital discharge. Survival analyses in clinical veterinary patients must be interpreted cautiously as most dogs experienced euthanasia as opposed to natural death, which is driven by a number of factors including owner preferences and financial constraints. This study is no exception, and it is possible that we were unable to detect a true relationship between CSF lactate, disease severity, and prognosis due to these confounding factors.

As previous canine studies showed that blood contamination was unlikely to alter standard CSF variables with red blood cell counts less than 13 230 cells/μL[32] and human studies have suggested that even marked blood contamination has no effect on lactate concentrations,[33,34] we chose not to exclude cases with red blood cell contamination in this study. In addition, a preliminary analysis comparing red blood cell counts and lactate concentrations showed a complete lack of correlation (n = 102, P = .86, Spearman r = .018), and we further observed that many substantially blood-contaminated samples had lactate concentrations within the reference interval.

There are several limitations of this study. First, there is some ambiguity in terms of the diagnoses being made by using clinical parameters for most cases instead of histopathology. However, we used well-established clinical guidelines for establishing these diagnoses.[23,35-37] Additionally, the histopathology group closely resembled the others in terms of the distribution and range of CSF lactate concentrations. Finally, inclusion of a few incorrect diagnoses would be unlikely to substantially alter the main results or conclusions of the study. Secondly, we did not account for the potential effect of seizure activity on CSF lactate concentrations, which has been shown to alter this analyte in some human studies.[38,39] The effect of seizures on CSF lactate in dogs requires further study. A third limitation relates to the potential effect of blood lactate on CSF lactate. Prior studies in experimental animals and humans have demonstrated that lactate does not freely cross the blood-brain or blood-CSF barriers,[40-43] and instead relies on monocarboxylic acid transport systems.[44] As a result, blood and CSF lactate concentrations are relatively independent. Although there are few studies available in dogs, the prior study that validated

the Lactate Plus meter for canine CSF showed that although CSF and blood lactate were correlated, this correlation was very weak.[4] Therefore, although blood lactate concentrations might have influenced CSF concentrations, we suspect that this influence was minimal. However, this relationship also warrants further study.

In conclusion, approximately half of all the dogs with inflammatory CNS disorders as well as those with MUE had increased CSF lactate concentrations. The Lactate Plus monitor provides a useful method of obtaining a rapid analysis of this analyte with very small sample volumes, potentially facilitating the diagnosis of MUE in the hospital. Cerebrospinal fluid lactate was weakly correlated with CSF nucleated cell counts and protein but not with red blood cell counts and did not show a consistent relationship with survival. The mechanisms by which CSF lactate is increased in dogs with inflammatory CNS disorders might include microbial infection, lymphocyte proliferation, and mitochondrial dysfunction but require additional study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflicts 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

This study was conducted on samples obtained during the course of a routine diagnostic evaluation; IACUC approval is not required for such studies at our institution. However, written, informed consent was obtained from all owners for the use of these samples for research purposes.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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