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BRIEF COMMUNICATION

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Retrospective evaluation of hyperproteinorrachia without pleocytosis (albuminocytologic dissociation) and survival in dogs

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Abstract

Background: Hyperproteinorrachia (raised cerebrospinal fluid total protein [CSF-TP]) without pleocytosis (HP) (also known as albuminocytologic dissociation) is identified in dogs with different neurologic diseases. However, the association between survival and increased CSF-TP is unknown.

Objectives: (a) Identify conditions commonly associated with HP in dogs and (b) investigate whether higher CSF-TP concentrations or other relevant factors are associated with 1-year survival.

Methods: This is a retrospective study that identified dogs with HP (Cisternal CSF-TP >0.30 g/L, Lumbar CSF-TP >0.45 g/L with total nucleated cell concentrations [TNCCs] and RBC counts within RIs) from 2008 to 2019: recording signalment, weight, vital parameters, inflammation, neuroanatomic localization, CSF-TP, sampling site, final diagnosis, etiologic classification, and 1-year survival. Corrected CSF-TP was calculated as CSF-TP minus 0.3 (cisternal) or 0.45 (lumbar or unknown). Descriptive statistics were produced, CSF-TP differences between groups (eg, neuroanatomic localizations) were evaluated using the Mann-Whitney *U* test or Kruskal-Wallis test (post-hoc testing). The Cox proportional hazards model was used for survival data. Statistical significance was set at a $P < 0.05$.

Results: In all, 39 dogs had HP, associated with 17 conditions, including neoplasia (n = 6), meningoencephalitis of unknown origin (n = 4) (MUO), and intervertebral disc disease (n = 4) (IVDD) as the most common conditions. There was no significant difference between the CSF-TP/corrected CSF-TP between 1-year survivors and non-survivors, nor was there a difference between different neuroanatomic localizations or etiologic classifications ($P > 0.05$). Neoplasia, after adjustment for age, was the only variable associated with a worse survival ($P = 0.01$ HR: 2.08 (95% CI: 1.65-39.2). CSF-TP was not associated with age ($P > 0.05$).

Conclusions: HP in dogs is associated with a wide range of conditions; the most common conditions are neoplasia, MUO, and IVDD. Higher CSF-TP levels do not correlate with a worse 1-year survival; however, they do correlate with neoplastic lesions.

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1 | INTRODUCTION

Hyperproteinorrachia without pleocytosis (HP) (also known as albuminocytologic dissociation) is defined by raised microprotein concentrations within cerebrospinal fluid (CSF)[1] and can be seen in dog CSF samples analyzed by veterinary clinical pathologists. The increase in protein is attributed to either (a) local intrathecal immunoglobulin production (eg, seen with inflammatory or neoplastic diseases) or neurologic tissue-derived proteins (eg, neurodegeneration leading to the release of cytoskeletal proteins), (b) increased blood-central nervous system (CNS) barrier permeability allowing blood-derived proteins to enter the CSF, or (c) interruption of CSF flow or absorption or, as is most likely, a combination of these scenarios.[2] The term albuminocytologic dissociation has not been used here as it does not accurately capture the associated pathophysiology leading to increased CSF total protein concentrations (CSF-TP); instead, it infers that hyperproteinorrachia is solely defined by albumin concentration increases. Many different disease processes can result in these circumstances; therefore, HP has a low specificity[1,2] and, recent consolidated literature regarding HP in veterinary species is lacking. As a consequence, receiving a diagnosis of HP is largely descriptive and frequently not informative for veterinarians.

The term albuminocytologic dissociation (HP without pleocytosis) was first coined in 1912, describing the phenomenon in human patients with spinal cord compression.[3] In human medicine, this finding is now associated with a wide variety of inflammatory (eg, Guillain-Barrè syndrome [GBS]), infectious (eg, viral meningitis), degenerative, and neoplastic conditions.[4] Recently, the importance of age-adjusted CSF-TP reference intervals has been described (with a small sex effect also reported), as human CSF-TP concentrations naturally elevate with increasing age, thus reducing the number of false-positive HP diagnoses.[4] The same age- (and sex-) association has not been widely reported within the veterinary literature. The magnitude of the protein elevation is not commonly reported as being an important criterion for clinical decision-making; however, Sahin et al (2017) identified a poorer 6-month prognosis (MRC Sum Score) in GBS patients with higher CSF-TP concentrations.[5] This raises the question of whether the magnitude of CSF-TP elevation could be predictive of prognosis or survival in veterinary patients with HP.

Historically, canine CSF protein electrophoresis was conducted to quantify albumin and immunoglobulin proportions helping to elucidate underlying disease mechanisms at play, thus increasing specificity.[6] This practice is now largely redundant with the advent of advanced diagnostics (eg, advanced imaging, infectious disease testing), allowing the diagnosis of specific neurologic conditions. However, not all cases can be extensively tested (eg, due to economic constraints), and advanced imaging has specificity limitations (specifically distinguishing inflammatory from neoplastic lesions); therefore, if more recently published, consolidated data regarding HP-associated conditions and factors associated with survival were available, clinical applications would be more easily identifiable. Consequently, we aimed to (a) identify the most common conditions associated with HP within a UK population of dogs, (b) investigate whether a higher CSF-TP concentration is associated with reduced survival times, and (c) identify if any other risk factors in patients with HP are associated with survival times.

2 | MATERIALS AND METHODS

2.1 | Data acquisition

Ethical approval for this study was obtained from the Department of Veterinary Medicine, University of Cambridge Ethics and Welfare Committee (CR359; 4/4/2019) in accordance with the University of Cambridge clinical research mandate. The patient record database from Central Diagnostic Services, University of Cambridge was searched for canine CSF samples with a microprotein result (2008-2019). HP cases were classified as having a CSF-TP concentration exceeding 0.30 g/L (cisternal) or 0.45 g/L (lumbar/no site recorded),[1] with a WBC count and RBC count not exceeding the upper reference intervals (WBC: 5 cells/μL and RBC: 8 cells/μL) (without a pleocytosis). Those without increased CSF-TP concentrations or with pleocytosis or hemodilution (ie, RBC count of >8 cells/μL) were excluded. No patients had repeated CSF analyses performed.

CSF-TP concentrations were analyzed on a Beckman Coulter AU480, using a pyrogallol red-molybdate complex, which is measured at 600 nm, according to the manufacturer's instructions. CSF-TP concentration was measured within 24 hours of sample collection, often within 1-2 hours.

Patient data (case number, species, breed, and sex) from the HP cases were collated, and presenting clinical examination, neuroanatomic localization (at admission), clinical pathology data, and definitive diagnosis (if reached) were recorded. A definitive diagnosis was made by the attending board-certified neurologist using all available patient data, including advanced imaging investigation (magnetic resonance imaging) and/or confirmation with histopathology. After collection, all data were anonymized.

Patient survival (defined as being alive 1 year after the analysis date for the CSF sample that showed HP) was recorded for each individual, and initially, information was obtained from patient records. Where this information was not present, the referring veterinary surgeon was contacted.

2.2 | Statistical analysis

Statistical analyses were performed using either GraphPad Prism (Version 8.4.2 [464], GraphPad software) or R Statistics (Version 3.6.3, The R project, https://www.r-project.org) software. Statistical significance was set at $P < 0.05$, and two-sided analyses were used exclusively. The data obtained from all individuals were grouped, and descriptive statistics were calculated. Each patient's definitive diagnosis (or the suspected diagnosis from the attending board-certified veterinary neurologist) was assigned to an etiologic

classification, based on the DAMNITV (degenerative, anomalous, metabolic, neoplastic, iatrogenic, idiopathic, inflammatory/immune-mediated, toxic, traumatic, or vascular) classification.[7] Corrected CSF-TP concentrations were calculated (CSF-TP concentrations [g/L] minus 0.30 [cisternal] or 0.45 [lumbar or unknown]) to account for the difference in protein reference interval limits at the two acquiescent sites. Normality was assessed using a Shapiro-Wilk test. The difference in the CSF-TP concentrations was assessed among all the neuroanatomical localizations, including grouping by the central nervous system (CNS), peripheral nervous system (PNS), brain (forebrain, cerebellum, and brainstem), and spinal cord (cervical and thoracolumbar regions). Then, the etiologic classifications were analyzed using a Kruskal-Wallis test with post-hoc testing (Tukey's multiple comparisons test) or a Mann-Whitney *U* test when only two groups were compared. The association between CSF-TP concentrations and age was evaluated using linear regression. For patients where the survival outcome was known at 1 year (all-cause mortality), the CSF-TP concentrations were compared using a Mann-Whitney *U* test. Overall survival data were calculated using the Kaplan-Meier analysis for all patients. All individuals that survived to 1 year or where incomplete (<1 year) survival data was identified were right-censored. Hazard ratios were calculated using a Cox proportional hazard model for the following continuous variables; age, CSF-TP and corrected CSF-TP, weight, temperature, heart and respiratory rate at presentation, and categorical variables, breed (stratified as breed types, such as mixed breed and terrier-type), sex, neurologic localization, the presence of inflammatory changes on hematology and/or biochemistry panels (defined as an inflammatory leukogram or increased positive acute-phase proteins, respectively), and disease classification. If the assumptions for the Cox proportional hazard model were violated, the n number was too low, or all individuals within that group were censored then the group was excluded from analysis. Schoenfeld residuals were calculated for each variable to ensure none violated the assumptions of proportional hazards.

3 | RESULTS

3.1 | Diseases associated with HP in dogs

From the records (748 CSF results with a microprotein value), 39 dogs with HP were identified. An additional 14 dogs with HP were excluded due to hemodilution of the sample. The presence of HP was associated with 17 different conditions (Table 1), and of those with neoplasia (n = 6), the exact neoplasm was undetermined in three patients. Intervertebral disc disease and meningoencephalitis of unknown origin (MUO) were the most commonly associated conditions. Definitive diagnosis of neoplasia was obtained in 4/6 patients through histologic examinations (either ante-mortem biopsies or post-mortem examination), including hemangiosarcoma (n = 1) and peripheral nerve sheath tumor (n = 3). Neoplasia was suspected in two others (lymphoma and one undetermined).

TABLE 1 Underlying conditions associated with hyperproteinorrhachia (HP) in 39 dogs

Disease category (DAMNITV) with diagnoses	Total cases N = 39
Degenerative	10
Intervertebral disc disease	4
Degenerative lesion; undetermined	3
Degenerative myelopathy	2
Lumbosacral stenosis	1
Anomalous	2
Supracollicular fluid accumulation	1
Congenital vertebral malformation	1
Neoplasia	6
Inflammatory	8
Meningoencephalitis of unknown origin	4
Trigeminal neuralgia or neuritis	2
Polyneuritis	1
Polymyositis	1
Idiopathic	4
Idiopathic epilepsy	3
Idiopathic peripheral vestibular disease	1
Toxic	2
Potassium bromide toxicity	1
Toxic insult; unknown agent	1
Vascular	5
Vascular lesion; undetermined	3
Fibrocartilaginous embolic myelopathy	2
Undetermined	2

DAMNITV: degenerative, anomalous, metabolic, neoplastic, iatrogenic, idiopathic, inflammatory/immune-mediated, toxic, traumatic, or vascular.

3.2 | CSF-TP in patients with HP

Descriptive data are summarized in Table 2A. The mean (±SD) CSF-TP concentration of all patients was 0.59 + 0.33 g/L with the predominant CSF sample site was cisternal (n = 26) (lumbar; n = 9, and not recorded; n = 4). The mean corrected CSF-TP concentration was 0.21 + 0.25 g/L. When separated by neuroanatomic localizations (Figure 1) or etiological classifications (Figure 2), there was no significant statistical difference between the CSF-TP concentrations ($P > 0.05$) across any of the subcategories. CSF-TP concentration was not associated with the age of the animal ($P > 0.05$) (Figure S1).

3.3 | CSF-TP and survival in patients with HP

Complete patient survival at 1 year post-HP identification was available for 21 patients, and within this group there was no difference in the CSF-TP or corrected CSF-TP concentrations between

TABLE 2 Summary of the descriptive statistics from dogs with HP for the entire dataset (n = 39; All) (A) and for the survival data (n = 29) (B), including covariates analyzed using a Cox Proportional Hazard analysis. Dogs labeled as Other Dog breeds included Weimaraner, French Bulldog, Bernese Mountain Dog, Border Collie, Shih Tzu, Chihuahua, and Husky

(A)	Number or mean (±SD)
n	39
CSF protein (g/L)	0.59 (±0.32)
Corrected CSF protein (g/L)	0.21 (±0.25)
Weight (kg)	20.6 (±11.7)
Age (y)	8.5 (±3.2)
Sex	
Male	26
Female	13
Breed	
Other dog breeds	10
Terrier	10
Spaniel	7
Retrievers	7
Racing	2
Schnauzer	2
CSF collection site	
Cisternal	26
Lumbar	9
Not reported	4
Vital parameters at presentation	
Temperature (°C)	38.2 (±0.60)
Pulse (per min)	94 (±23)
Respiration (per min)	26 (±9)
Neurological localization	
CNS: Forebrain/brainstem/cerebellum	15
CNS: Cervical (C1-C5)	4
CNS: Brachial SC (C6-T2)	1
CNS: Thoracolumbar (T3-L3)	7
CNS: Lumbosacral SC (L4-S2)	4
PNS	6
Multifocal	2
Clinicopathological markers of inflammation?	
Yes	4
No	21

	Cox proportional hazard analysis				
(B)	Survival data	Exponentiated coefficient	Hazard ratio	95% Confidence interval	*P*-value
n	29				
CSF protein (g/L)	0.51 (±0.21)	−0.76	0.47	0.008-26.7	0.71
Corrected CSF protein (g/L)	0.16 (±0.20)	0.08	1.09	0.02-52.7	0.97
Weight (kg)	19.4 (±10.1)	−0.05	0.94	0.87-1.027	0.19
Age (y)	7.7 (±3.0)	0.27	1.30	1.0-1.71	0.05

(Continues)

TABLE 2 (Continued)

	Cox proportional hazard analysis				
(B)	Survival data	Exponentiated coefficient	Hazard ratio	95% Confidence interval	*P*-value
Sex					
Male	16	−0.27	0.77	0.20-2.90	0.70
Female	13	Referent			
Breed					
"Other" dog breeds	11	Referent			
Terrier	9	2.49	12.01	0.98-72.00	0.06
Spaniel	5	1.79	5.99	0.54-66.72	0.15
Retrievers	4	0.97	2.65	0.17-42.30	0.49
CSF collection site					
Cisternal	21	Referent			
Lumbar/not reported	8	−1.14	0.32	0.04-2.57	0.28
Vital parameters at presentation					
Temperature (°C)	38.1 (±0.50)	0.23	1.26	0.31-5.2	0.74
Pulse (per min)	90 (±20)	−0.01	0.99	0.95-1.028	0.55
Respiration (per min)	27 (±9)	0.015	0.98	0.89-1.15	0.82
Neurologic localization					
CNS	13	Referent			
PNS	5	1.10	3.00	0.71-12.65	0.13
Multifocal	3	0.27	1.31	0.15-11.23	0.81
Hematologic markers of inflammation present					
Yes	4	Referent			
No	12	0.48	1.61	0.18-13.8	0.66
Disease categorization (DAMNITV)					
Neoplasia	6	2.40	11.07	2.6-47.4	0.001
Other	23	Referent			
Degenerative	6				
Idiopathic	3				
Anomalous	1				
Toxic	1				
Inflammatory	7				
Vascular	4				
Undetermined	1				

animals that survived to 1 year (CSF-TP 0.44 ± 0.12 g/L and corrected CSF-TP 0.11 ± 0.11 g/L; n = 12) and non-survivors (CSF-TP 0.46 ± 0.20 g/L and corrected CSF-TP 0.14 ± 0.15 g/L; n = 9) ($P > 0.05$) (Figure 3).

Survival data were available for 29 patients (eight patients had incomplete survival data; known to be alive on a set day less than 365 days after the HP diagnosis). Nine patients did not survive to 1 year, and all were euthanized as a direct result of their neurologic status or condition (neoplasia n = 5, vascular n = 3, and idiopathic n = 1). When stratified by etiologic classification, a diagnosis of neoplasia was associated with a significantly shorter survival time (median survival time (MST) = 22 days, survival range = 1-180 days) compared with all other categories ($P < 0.001$) (Vascular MST = 341 days, survival range = 4-365 days) (Figure 4). The univariable analysis identified neoplasia as being negatively correlated with survival ($P < 0.05$, Hazard Ratio (HR): 11.07) (Table 2B) when the non-neoplastic diseases were combined and compared with neoplastic diseases.

Increasing age is associated with the development of some types of neoplasia within the nervous system.[8] After adjustment for age, a diagnosis of neoplasia remained significantly associated with reduced survival to 1 year in the HP patients (survival ~ disease classification + age; disease classification – $P = 0.01$ HR: 2.08 [95% CI: 1.65-39.2], Age – $P = 0.36$ HR: 1.14 [95% CI: 0.86-1.54]).

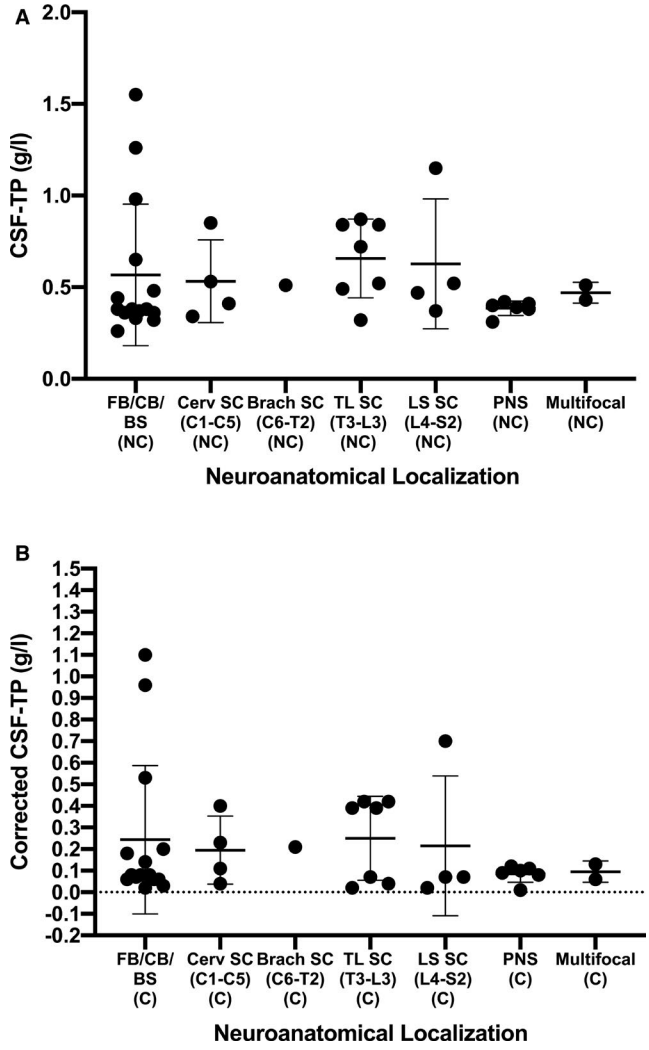

FIGURE 1 Graphical depiction of cerebrospinal fluid total protein (CSF-TP) concentrations in dogs with hyperproteinorrachia without pleocytosis (HP) grouped by different neuroanatomic localizations A, reported CSF-TP concentrations (non-corrected CSF-TP [NC]) B, Corrected CSF-TP (corrected [C]). No statistically significant differences were noted between any of the group comparisons. Dots reflect individual patient values, with the mean and standard deviation

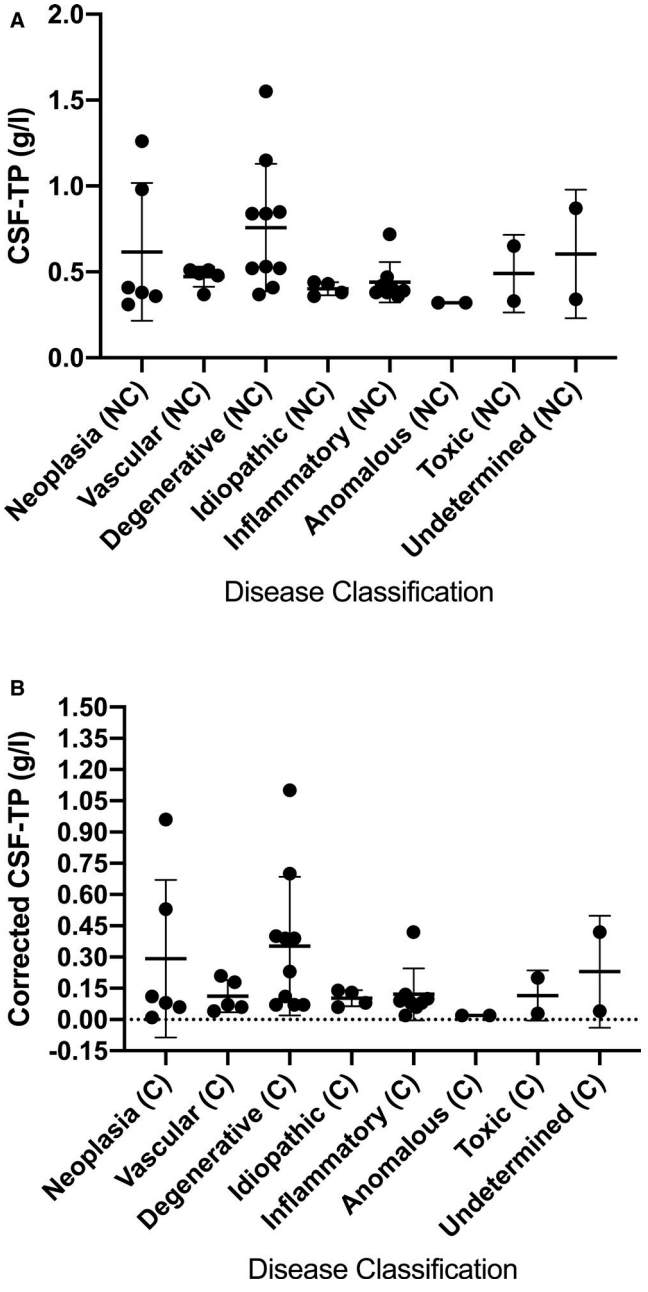

FIGURE 2 Graphical depiction of cerebrospinal fluid total protein (CSF-TP) concentrations in dogs with hyperproteinorrachia without pleocytosis (HP) grouped by different disease classifications (DAMNITV). A, reported CSF-TP concentrations (non-corrected CSF-TP [NC]). B, Corrected CSF-TP (corrected [C]). No statistically significant differences were noted between any of the group comparisons. Dots reflect individual patient values, with the mean and standard deviation. DAMNITV, degenerative, anomalous, metabolic, neoplastic, iatrogenic, idiopathic, inflammatory/immune-mediated, toxic, traumatic, or vascular

4 | DISCUSSION

This retrospective study highlighted that canine HP is associated with many different conditions, confirming its lack of specificity to a particular canine neurologic condition. In addition, the authors suggest that clinical pathology terminology should substitute albuminocytologic dissociation with HP to reflect all possible pathophysiologic abnormalities accurately.

The most common conditions associated with HP were neoplasia, MUO, and IVDD, which collectively, to the best of the authors' knowledge, have not been previously reported in the veterinary literature. However, this is in line with other research articles investigating the clinicopathologic features of individual neurological diseases.[8-11] Interestingly here, three dogs with HP associated with neoplasms were diagnosed with peripheral nerve sheath tumors, whereas HP has been more commonly associated with intracranial neoplasias.[8] HP is known to occur with extradural synovial cysts and type 1 intervertebral disc herniation causing chronic compressive myelopathy in dogs,[10,12] resulting from impaired CSF flow and localized inflammation.

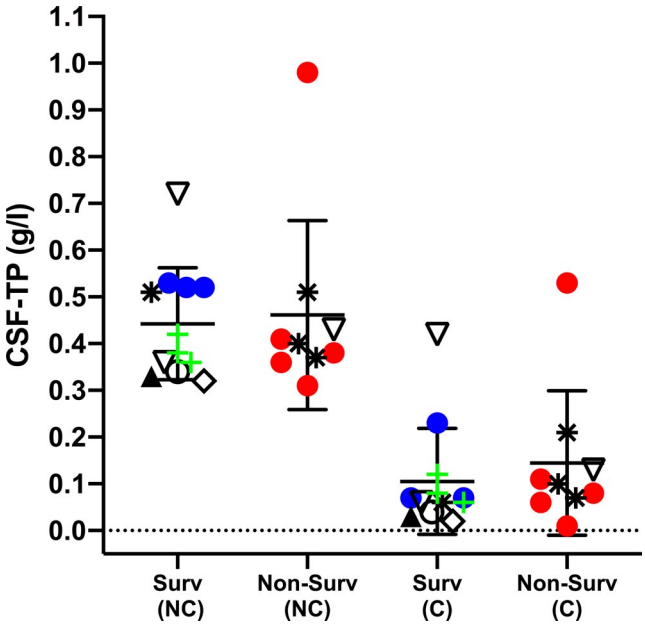

FIGURE 3 Graphical depiction of cerebrospinal fluid total protein (CSF-TP) concentrations in dogs with hyperproteinorrachia without pleocytosis (HP) showing there was no statistically significant difference between CSF protein levels (with non-corrected CSF-TP values [NC] or with corrected CSF-TP values [C]) of 1-year survivors (Surv) and non-survivors (Non-Surv). Each individual patient value is represented, with the mean and standard deviation; red dot—patients with neoplasia, blue dot—patients with a degenerative condition, black star—patients with a vascular condition, green cross—patients with an inflammatory condition, black inverted triangle—patients with an idiopathic condition, black diamond—patient with an anomalous condition, black triangle—patient with a toxic condition and a black circle—patient with an undetermined condition classification

This is also the first paper evaluating the survival to 1 year of dogs with HP irrespective of the underlying etiopathogenesis or condition; survival in MUO patients was not reported to be associated with CSF-TP concentrations.[9] No correlation between CSF-TP concentrations (including when correct for the sampling site) and survival was identified, and while this might be a true reflection of HP, the heterogeneity of the conditions included could also have influenced this lack of a correlation. Notwithstanding, grouping the conditions into general categories of disease etiology (eg, degenerative conditions) did not highlight any significant differences in CSF-TP that could have been influenced by the inclusion of other conditions. Indeed, neoplastic conditions were associated with the poorest 1-year survival, and these HP cases typically had only modest CSF-TP elevations (Figures 2 and 3). However, expanding this study to include more individuals from the most common diseases present would have allowed more disease-specific statements to be made.

Unsurprisingly, adverse 1-year survival in dogs with HP was only associated with neoplasia (even after adjustment for age). Neoplasia of the nervous system has been reported to have poor survival in dogs, given the challenges resulting from a lack of efficacious therapies, space-occupying lesions within the CNS, and severe compromise to an animal's quality of life.[8] However, the elevation of CSF-TP in dogs with neoplasia appears to depend on the location and type of the neoplasia, such as choroidal plexus carcinomas, which have been shown to have very high CSF-TP often attributed to altered endothelial cell permeability and basement membrane integrity.[13] No choroidal plexus tumors were included in this population of dogs.

We also found no difference in CSF-TP and neuroanatomic localizations, which could reflect sampling remote from the site of pathology; a recent study has also highlighted that CSF should be sampled at the site closest to the neuroanatomic localization to gain a true

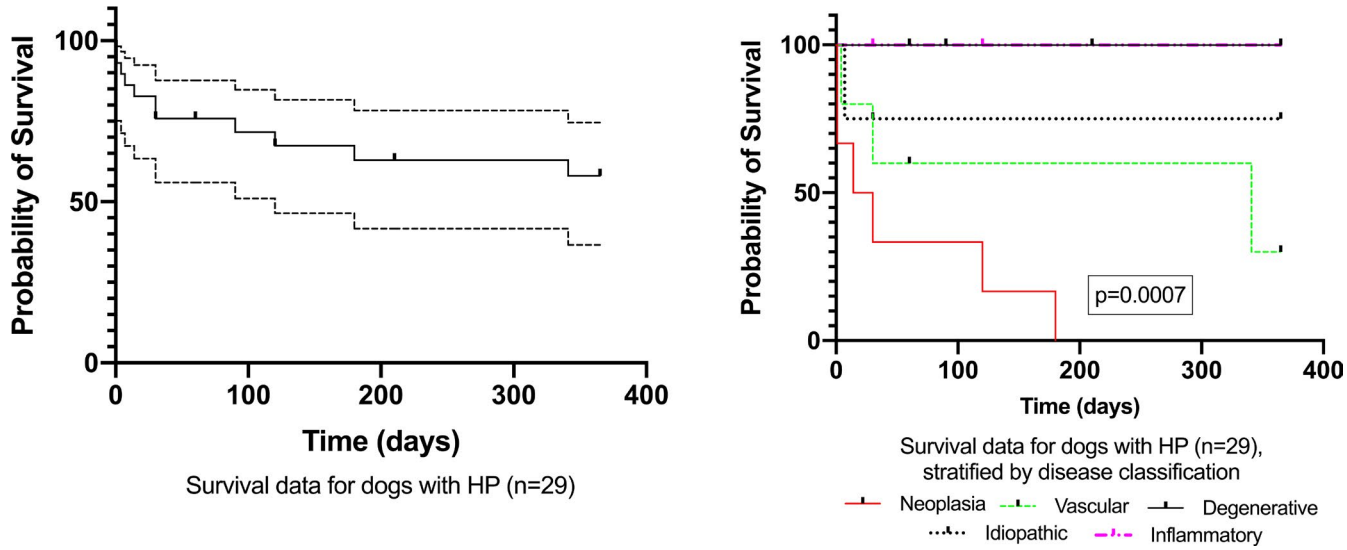

FIGURE 4 Kaplan-Meier survival plots for all dogs with hyperproteinorrachia without pleocytosis (HP) (left) (dotted lines: 95% confidence intervals), and those dogs with HP stratified by disease classification whereby dogs with HP and neoplasia had a statistically significant shorter survival time (median survival time of 22 days) ($P = 0.0007$) compared with the "Other" disease classifications. Censored individuals are plotted with a vertical line. Patients with toxic, undetermined, and anomalous conditions are not shown (n = 1 survival to 1 year per condition)

reflection of the focal neurologic environment.[14] The neurology service at the University of Cambridge typically chooses the sampling site closest to the neuroanatomic localization, which was reflected by most sampling sites being from lumbar sites in dogs with neuroanatomic localizations caudal to the thoracolumbar spine (7/9).

Age-specific reference intervals for CSF-TP have recently been recommended in people.[4] No data have been published to support this need in canine patients. Age-corrected canine CSF-TP reference intervals would be difficult to achieve due to the different life expectancies associated with different breeds. Therefore, it is important to report that this study did not find any association between age and CSF-TP levels, indirectly suggesting that this association might not be a phenomenon in aged dogs. Further studies investigating an association between CSF-TP concentrations and age in non-diseased dogs would need to be performed to corroborate these findings.

The inclusion criteria for this study were stringent, whereby any hemodiluted samples were excluded. It has been reported that moderate hemodilution (RBC <13 200 cells/mm^3) does not cause a significant increase in the CSF-TP[15]; however, even a small elevation in CSF-TP could cause the inclusion of false-positive HP cases, potentially leading to incorrect conclusions being drawn.

The three main limitations of this research include the retrospective nature of the study, the relatively low number of dogs included, and, potentially, differences in sample acquisition times between individuals and the stage of disease. The archives were searched over an 11-year period, and only approximately 5% of the CSF samples with a CSF-TP result were identified as having HP. This low number also precluded disease-specific survival analysis. Therefore, multicenter studies would be needed to expand case numbers, which could allow further analyses to be performed.

The timing of sample acquisition was not standardized across the HP cases included, as this is individually recommended based on disease presentation. Consequently, it means that some dogs may have been sampled during the acute phase of the underlying disease, whereas others could have been sampled during the chronic or resolving phases. As the aim of this study was to investigate different conditions that result in HP and the relationship of HP to survival, the lack of a standardized CSF sampling time point is likely less important than if a sole condition associated with HP was being investigated.

In conclusion, HP in dogs is associated with a wide range of conditions, most commonly neoplasia, MUO, and IVDD. The higher CSF-TP concentrations did not correlate with a worse 1-year survival; however, neoplastic lesions do. Increasing age in dogs does not appear to be associated with increasing CSF-TP concentrations.

DISCLOSURE

The authors have indicated that they have no affiliations or financial involvement with any organization or entity with a financial interest in, or in financial competition with, the subject matter or materials discussed in this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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