Cerebrospinal fluid analysis in dogs: main patterns and prevalence of albuminocytological dissociation

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ORIGINAL RESEARCH

Cerebrospinal fluid analysis in dogs: Main patterns and prevalence of albuminocytological dissociation

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Abstract

Background: Albuminocytological dissociation (ACD) of the cerebrospinal fluid (CSF) is defined as an increased total protein concentration with normal total nucleated cell count. It is suspected to occur in diseases that alter the blood-brain barrier, increase the production of protein or obstruct the flow of CSF. The purposes of this study were to review the CSF analysis results of a large cohort of dogs with neurological conditions, to analyse the total prevalence of ACD and to describe which diseases have a higher prevalence of ACD.
Study design and methods: Medical records were retrospectively searched for dogs whom CSF was sampled from 2012–2019. Data collected included signalment, body weight, site of collection of the CSF, CSF analysis results, and final diagnosis.
Results: A total of 497 dogs met the inclusion criteria. ACD was identified in 16.5% (82/497) of dogs. The diseases with higher proportion of ACD were cranial nerve neuropathy (6/10; 60.0%), brain tumour (10/24; 41.7%), idiopathic vestibular disease (7/17; 41.2%) and brain vascular disease (4/13; 30.8%).
Clinical significance: This study describes the CSF patterns of the most common neurological conditions in dogs, also characterizing, for the first time in dogs, the prevalence and causes of ACD, which was identified in 16.5 % of the samples. The diseases with highest proportions of ACD were cranial nerve neuropathy, brain tumour, idiopathic vestibular disease and brain vascular disease.

KEYWORDS
canine, central nervous system, clinical pathology, neurology, total protein concentration

INTRODUCTION

Cerebrospinal fluid (CSF) is a clear, colourless ultrafiltrate of plasma, which surrounds and permeates the central nervous system (CNS). It is produced by the choroid plexuses within the ventricles and the leptomeningeal capillaries in the subarachnoid space and reabsorbed into the venous system mainly via the arachnoid villi, the cribriform lamina, veins and lymphatics around the spinal nerve roots and some cranial nerves.[1] CSF has important roles in the protection, nourishment and support of the CNS[1] and can offer an accurate reflection of any ongoing pathology.[2] CSF analysis alone rarely provides a definitive diagnosis, but combined with the history, clinical findings and advanced imaging, it remains an important diagnostic tool for patients with neurological signs.[2]

Standard CSF analysis includes total nucleated cells count (TNCC), red blood cells (RBC), total protein (TP) concentration and cytological evaluation.[2] Normal CSF does not contain RBC and has a TNCC of less than 5 cells/μL.[3] CSF TP concentration should not exceed between 25–30 mg/dL at the cerebellomedullary cistern (CMC) and 45 mg/dL at the lumbar subarachnoid space (LSS).[1–4]

Albuminocytological dissociation (ACD) is defined as an increased TP concentration with normal TNCC. The exact pathophysiology of ACD is unknown, but different mechanisms have been proposed, including the intrathecal production of specific proteins (IgG and myelin basic protein), dysfunction of the blood–brain barrier, dysfunction of the blood–nerve barrier, decreased CSF flow and sequestration of CSF in spinal cord compression.[5–7] In veterinary medicine, several diseases, such as idiopathic polyradiculoneuritis, extradural compressive lesions, intramedullary lesions (neoplasia and inflammatory or infectious diseases), idiopathic epilepsy, degenerative myelopathy, fibrocartilaginous embolism, trauma, vasculitis, trigeminal, facial and vestibular neuropathies have

been reported to cause ACD, yet the majority of them anecdotally.[3,8–12] In human medicine, several conditions have been traditionally associated with ACD including infectious and non-infectious meningoencephalitis, intra and extra-axial tumours, inflammatory polyneuropathy, hydrocephalus, angiitis of the CNS, cerebral venous sinus occlusion, optic nerve disease, facial neuritis, posterior reversible encephalopathy syndrome, structural spinal disorders, nervous system toxic exposure, dementia, epileptic seizures, strokes, intrathecal chemotherapy and subarachnoid hemorrhage.[6,13,14] In human medicine, the reported ACD prevalence is 31.4–31.8%, both analysed in large cohorts of patients with CSF collected in the LSS and using the traditional 45 mg/dL reference limit for TP concentration.[6,15]

In veterinary medicine, there are no studies analysing the different causes and prevalence of ACD, and therefore it is unknown which diseases can disrupt the blood brain barrier enough to cause a leakage of proteins without affecting the cell count. Understanding the prevalence or the conditions associated with ACD in dogs could improve the diagnostic performance of the CSF analysis as well as our understanding of some canine neurological conditions.

The purposes of this study were to retrospectively review the CSF analysis results of a large cohort of dogs with neurological conditions, to analyse the total prevalence of ACD and to describe which diseases have a higher prevalence of ACD. Our hypothesis was that ACD is more common in traumatic and vascular diseases, and this could help with the presumptive diagnosis of these conditions.

MATERIALS AND METHODS

Study design

This is a retrospective, single-centre study performed at the Royal (Dick) School of Veterinary Studies, University of Edinburgh. All patients were client-owned dogs, and the samples were obtained during clinically indicated procedures. Ethical approval was obtained from the veterinary ethical review committee of the University of Edinburgh (VERC 84.19). Medical records of dogs with a CSF sampling performed in our hospital from January 2012 to February 2019 were retrospectively reviewed.

Medical records review

Information obtained from the medical records included signalment, body weight, site of collection of the CSF (CMC and LSS), total number of RBC, TNNC, TP concentration, colour of the CSF, cytology, advanced imaging (when available) and final or presumptive diagnosis. A surgery resident sofia garcia-pertierra (SGP) and a board-certified neurologist anna suñol (AS) examined all the medical records. Cases were excluded if the medical records or the CSF analysis results were incomplete.

For patients with CSF sampled on multiple occasions during the study period, only the samples collected on the first day were included in the study. If both CMC and LSS samples had been obtained on the same day, CMC samples were included for dogs with suspected encephalopathies, cranial nerves deficits and multifocal CNS diseases; and LSS samples were included for dogs with spinal cord and peripheral nervous system neurolocalisation.

CSF characterization

CSF samples were collected, under general anaesthesia, from the CMC or LSS in a routine manner[1] and stored into plain plastic and EDTA tubes. Analysis was performed within 1 hour of collection and included macroscopic analysis, RBC, TNCC, TP concentration and cytological examination. Cell counts were performed manually using a haemocytometer chamber (Neubauer Improved counting chamber, Marienfeld, Germany). A cytospin (Shandon Cytospin 3, Thermo Shandon, United Kingdom; programmed at 400 RPM for 7 minutes) was reviewed by a board-certified pathologist. For the protein concentration, the dye-binding pyrogallol red-molybdate method was used (Beckman Coulter AU480, Beckman Coulter, California, United States).

Pleocytosis was defined as TNCC > 5 cells/μL and was further split into mild (<50 cells/μL) moderate (≥50 and < 200 cells/μL) and severe (≥200 cells/μL).[16] The cytologic classification of CSF was considered neutrophilic when >25% neutrophils were present. Mononuclear or lymphocytic pleocytosis were described when >70% cells where mononuclear or lymphocytes, respectively. Mixed pleocytosis was considered when there was not a clear predominance of one type of cell, and eosinophilic pleocytosis when >1% of eosinophils were present.[16]

Protein content was classified as normal (CMC ≤ 30 mg/dL; LSS ≤ 45 mg/dL) or high (CMC > 30 mg/dL and LSS > 45 mg/dL). ACD was considered when the TNCC was ≤5 cells/μL, and the concentration of proteins was high (CMC > 30 mg/dL and LSS > 45 mg/dL).[2]

Cases with macroscopic appearance of blood contamination or more than 5000 RBC/μL were excluded from the analysis.[8] In cases where microscopic blood contamination was present, the TNCC was corrected by subtracting 1 cell/μL for every 500 RBC/μL and by subtracting 1 mg/dL to the measured protein concentration for every 1000 RBC/μL, as described elsewhere.[17]

To identify whether some diseases would tend to result in a specific TNCC/TP concentration pattern compared to other diseases, the TNCC/TP concentration values measured in the 12 most frequently diagnosed diseases were plotted. Idiopathic epilepsy, cluster seizures and status epilepticus

were diagnosed and classified based on current consensus.[18]

Finally, in a separate analysis, we compared the samples collected from CMC and LSS from the same dog at the same occasion. Due to the low number of dogs, which had double sampling, the comparison between TNCC and TP concentrations at these two sites was only performed for dogs ultimately diagnosed with steroid-responsive meningitis arteritis (SRMA).

Statistical analysis

Summary descriptive statistics were calculated to describe the population of patients and the characteristics of the CSF.

A Fisher's exact test was used to study the association between the presence of increased TNCC and a recent history (<5 days) of status epilepticus/cluster seizures.

For the dogs diagnosed with SRMA for which samples from both CMC and LSS were collected on the same day, a paired *t*-test was used to study the difference between the CMC and LSS samples.

Statistical analysis and figures were performed using R (R Foundation, Vienna, Austria) with RStudio (version 1.1.383, Boston, MA, USA). For all analyses, $p < 0.05$ was considered to be statistically significant.

RESULTS

Animals

During the study period, CSF sampling was performed in 510 dogs. Thirty-two dogs had been sampled twice, hence 542 CSFs were collected. Eleven out of the 510 CSFs were macroscopically blood contaminated (8 CMC and 3 LSS) and 2 had > 5000 RBC/ μL (1 CMC and 1 LSS), hence were excluded from the analysis. Therefore, 497 dogs were analysed. Forty-four per cent of the dogs (218/497) were female (149 neutered, 69 entire), and 56% were male (279/497; 168 neutered, 111 entire). Median age was 5.2 years (range: 1 month-15.6 years), and median body weight was 16.6 kg (range: 1.2–61.4 kg).

CSF characterization

The detailed characteristics of the CSF samples are summarised in Supplementary Information **1**. The most commonly diagnosed diseases were idiopathic epilepsy in 101 dogs (20.3%), meningoencephalitis of unknown origin (MUO) in 58 (11.7%), SRMA in 55 (11.1%), intervertebral disc disease in 32 (6.4%), brain tumour in 24 (4.8%), paroxysmal dyskinesia in 19 (3.8%), idiopathic peripheral vestibular disease in 17 (3.4%), fibrocartilaginous embolism in 16 (3.2%) and immune-mediated polyarthritis in 13 dogs (2.6%). All diagnoses are summarised in Supplementary Information **2**.

Four hundred and sixty-eight CSF (94.2%) were macroscopically clear. Twenty-two (4.4%) were classified as a mildly turbid and seven (1.4%) as turbid.

Pleocytosis was observed in 126 of 497 CSF (25.4%). Of these, forty-four (34.9%) showed a neutrophilic pleocytosis, 38 (30.2%) mononuclear, 24 (19.0%) lymphocytic, 18 (14.3%) mixed and 2 (1.6%) eosinophilic pleocytosis.

One hundred and ninety-five dogs (39.2%) had an increase in proteins of more than 30 mg/dL at the CMC or >45 mg/dL at the LSS, which was associated with pleocytosis in 113 of 195 (57.9%) of the cases. In the remaining 82 of 195 (42.1%), there was an ACD, representing 16.5% of the total number of cases. The two most common diseases associated with ACD in our population were idiopathic epilepsy in 12 of 82 and brain tumour in 10 of 82 CSF samples. However, when looking at the proportion of ACD for each specific disease, ACD was most frequently observed with cranial nerve neuropathy (6/10; 60.0%), brain tumour (10/24; 41.7%), idiopathic vestibular disease (7/17; 41.2%) and brain vascular disease (4/13; 30.8%), followed by others. All cases with ACD are summarised in Supplementary Information **3**.

CSF analysis in specific diseases

The detailed characteristics of the CSF for the most common diseases found in this study are summarised in Figure 1 and Table 1.

As expected, the highest TNCC and TP concentration levels were seen in diseases associated with marked CNS inflammation such as MUO and SRMA. However, 15 of 58 (25.9%) dogs diagnosed with MUO had a normal cell count and had been diagnosed based on the history, neurological examination and magnetic resonance imaging findings. Two of 55 dogs diagnosed with SRMA had normal cell count, and diagnosis was made based on differential cell count of more than 40% of neutrophils.[19] Out of the 101 dogs diagnosed with idiopathic epilepsy, five dogs (5.0%) had an increased cell count (median: 0 TNCC/μl, range: 0–28). Four of them were suffering from a cluster of epileptic seizures or status epilepticus at presentation. The last one had experienced one epileptic seizure 2 days before sampling. Conversely, twenty-nine dogs (28.7%) with idiopathic epilepsy presenting with clusters or status epilepticus had a normal TNCC. There was a statistically significant association between history of cluster seizures in idiopathic epilepsy and a high TNCC ($p = 0.04$, Fisher's exact test). Eight of the 32 cases (25%) diagnosed with intervertebral disc disease had an increased cell count (median 1.1 TNCC/μl, range: 0–97), and seven of 32 (21.9%) had ACD. Of the 17 dogs diagnosed with idiopathic vestibular syndrome (IVS), none had increased TNCC, and seven of 17 (41.2%) had ACD.

TABLE 1 Detailed characteristics of the CSF in the most common diseases found in 497 dogs

	Total number of cases and %	Location CSF tap	>500 RBC/μL	>5 TNCC /μL	Raised TP levels	ACD dissociation	Median TNCC/μL	Median TP	Cytology pattern for samples with high TNCC
Idiopathic Epilepsy	101/497 20.3%	98 CMC 3 LSS	4 (all CMC)	5	16	12/101 11.9%	0 (mean: 26.4; 0–28)	26.4 (mean; 26.4; 1–190)	4 monocytic, 1 neutrophilic
Meningoencephalitis of unknown origin	58/497 11.7%	53 CMC 5 LSS	7 (6 CMC, 1 LSS)	43	35	8/58 13.8%	11 (mean 152.2; 0–5049)	35.5 (mean 65.9; 9–696)	16 monocytic, 16 lymphocytic, 9 mixed, 2 neutrophilic
Steroid responsive meningitis arteritis	55/497 11.1%	50 CMC 5 LSS	12 (11 CMC, 1 LSS)	53	31	1/55 1.8%	50 (mean 600.6; 2–9247)	34 (mean 72.1; 8–780)	48 neutrophilic, 3 monocytic, 2 mixed
Intervertebral disc disease	32/497 6.4%	18 CMC 14 LSS	2 (2 LSS)	8	9	7/32 21.9%	1.1 (mean 9.1; 0–97)	28 (mean 39.8; 8–150)	2 monocytic, 2 neutrophilic, 2 lymphocytic, 2 mixed
Brain tumour	24/497 4.8%	18 CMC 6 LSS	4 (all LSS)	4	13	10/24 41.7%	1.1 (mean 3.4; 0–20)	33 (mean 39.2; 4–180)	2 monocytic, 1 lymphocytic, 1 mixed
Paroxysmal dyskinesia	19/497 3.8%	17 CMC 2 LSS	0	2	4	2/19 10.5%	1.1 (mean 4.8; 0–8)	26.0 (mean 28.0; 10–74)	1 monocytic, 1 mixed
Idiopathic vestibular	17/497 3.4%	16 CMC 1 LSS	0	0	7	7/17 41.2%	1.1 (mean 1.3; 0–4.4)	28.0 (mean 31.3; 7–93)	None
Fibrocartilaginous embolism	16/497 3.2%	6 CMC 10 LSS	0	4	4	3/16 18.8%	1.1 (mean 3.5; 0–26)	31 (mean 55.6; 14–280)	2 monocytic, 1 mixed, 1 lymphocytic
Brain vascular	13/497 2.6%	11 CMC 2 LSS	0	3	5	4/13 30.8%	1.1 (mean 3.4; 0–16.5)	27.0 (mean 36.8; 0–154)	1 monocytic, 1 lymphocytic, 1 neutrophilic
Spinal cord tumours	11/497 2.2%	8 CMC 3 LSS	1 (CMC)	6	6	1/11 9.0%	5.5 (mean 24.36; 0–140)	34 (mean 131.4; 11–613)	3 lymphocytic, 3 monocytic
Cranial nerve neuropathy	10/497 2%	9 CMC 1 LSS	0	0	6	6/10 60.0%	0.0 (mean 0.5: 0–2.2)	32.5 (mean 43.9; 13–96)	None
Polyradiculoneuritis	9/497 1.8%	6 CMC 3 LSS	1 (CMC)	0	2	2/9 22.2%	1.1 (mean 0.9; 0–2.2)	25 (mean 43.8; 10–154)	None

Abbreviations: ACD, albuminocytological dissociation; CMC, cerebellomedullary cistern; LSS, lumbar subarachnoid space; TNCC, total nucleated cell count; TP, total proteins concentration.

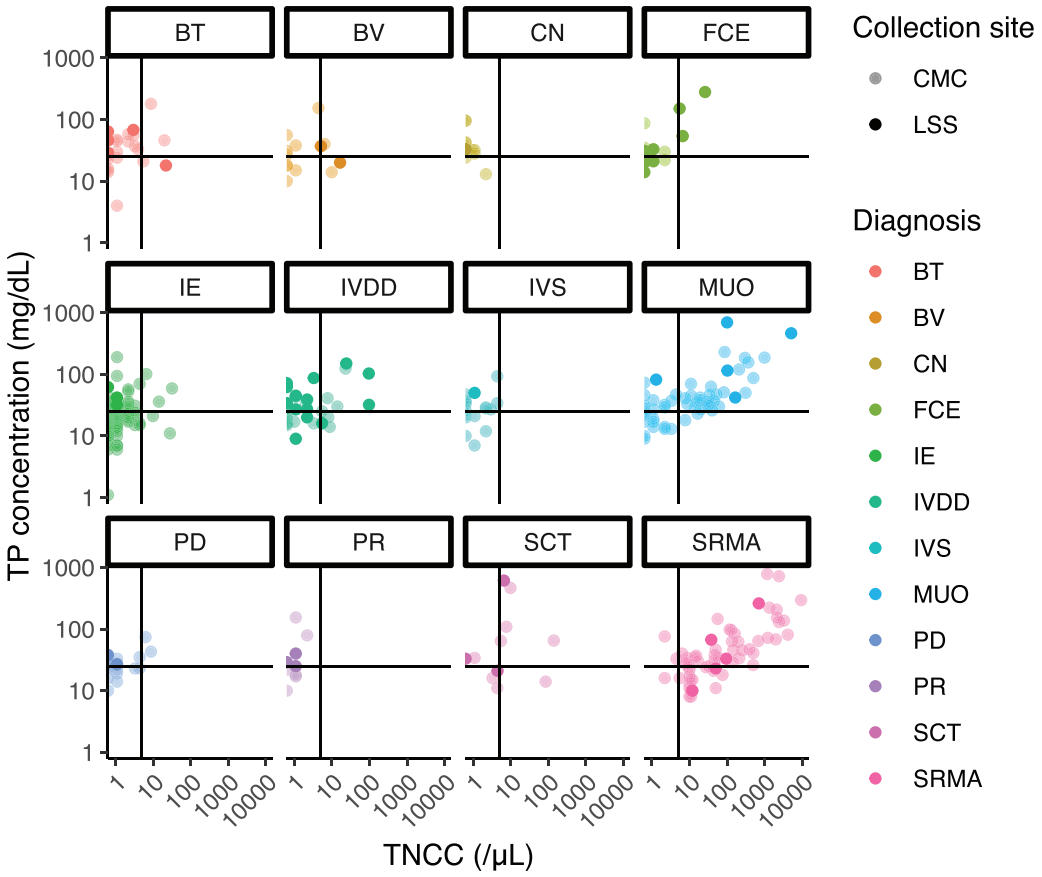

FIGURE 1 Detailed characteristics of the CSF in the most common diseases found in this study. The CSF findings of each condition are represented in a plot. The total nucleated cell count (TNCC) can be found on the x-axis and the total protein concentration (TP concentration) on the y-axis

Abbreviations: BT, brain tumour; BV, brain vascular; CMC, cerebellomedullary cistern; CN, cranial nerves neuropathies; FCE, fibrocartilaginous embolism; IE, idiopathic epilepsy; IVDD, intervertebral disc disease; IVS, idiopathic vestibular syndrome; LSS, lumbar subarachnoid space; MUO, meningoencephalitis of unknown origin; PD, paroxysmal dyskinesia; PR, polyradiculoneuritis; SCT, spinal cord tumour; SRMA, steroid responsive meningitis-arteritis.

Nine dogs were diagnosed with polyradiculoneuritis, none had an increased TNCC, and 2/9 (22.2%) had ACD.

Comparison of CMC and LSS samples

Twenty dogs had two CSF samplings performed on the same day (for each dog, one sample was collected from the CMC, and one from the LSS). Nine out of 20 were female (four neutered, five entire), and eleven were male (four neutered, seven entire). Median age was 1.8 years (range: 5 month-8.3 years), and median body weight was 11.2 kg (range: 4–30.7 kg).

The most common final diagnosis was SRMA in 10 of 20 (50%), and only those cases were compared. The CSF findings from the CMC and LSS puncture in these SRMA cases were consistent with each other and did not yield to a different clinico-pathological conclusion, with the exception of one dog ultimately diagnosed with SRMA for which only the CMC sample was diagnostic of the disease. There was no statistically significant difference between the CMC and LSS findings for the amount of RBC ($p = 0.30$, paired *t*-test), TNCC ($p = 0.65$, paired *t*-test) and protein levels ($p = 0.05$, paired *t*-test).

DISCUSSION

In this population, ACD was identified in 16.5% of the samples (82/497) using >30 mg/dL for CMC samples and >45 mg/dL for LSS samples as cut-off value for increased TP concentration. The diseases with higher proportions of ACD were cranial nerve neuropathy (6/10; 60.0%), brain tumour (10/24; 41.7%), idiopathic vestibular disease (7/17; 41.2%) and brain vascular disease (4/13; 30.8%).

In addition, this study confirmed previous CSF findings on specific neurological diseases. Fifteen of 58 (25.9%) dogs diagnosed with MUO had a normal cell count. Our results were similar to those published in a systematic review by Granger et al,[20] with 457 cases diagnosed with histopathology or a combination of signalment, localisation, advanced imaging, CSF analysis and negative infectious titres. Results of that study showed that 16% of dogs with granulomatous

meningoencephalitis, 22% of dogs with MUO and 12.5% of dogs with necrotising meningoencephalitis had a normal TNCC.[20] Five dogs of 101 diagnosed with idiopathic epilepsy (4.9%) had an increased cell count, and 12 of 101 (11.9%) had ACD. A recent study looking at the diagnostic value of CSF in dogs with idiopathic epilepsy reported similar frequency of pleocytosis (7.0%; 14/199 dogs) and ACD (8.0 %; 16/199) compared to our results.[8] In that study, no association was found between an abnormal CSF finding and a history of clusters seizures or status epilepticus.[8] This is in contrast to our results, where increased TNCC was more frequently observed in idiopathic epileptic dogs with a history of status epilepticus or cluster seizures. We also found that ACD was frequently seen with IVS (7/17; 41.2%) and cranial nerve neuropathy (6/10; 60.0%); this is in line with a previous study, which identified ACD in 69 % of dogs diagnosed with idiopathic vestibular and facial neuropathy of unknown origin.[12] In addition, trigeminal neuropathy has been reported to cause ACD in three of six dogs with trigeminal disorders,[10] in two of nine dogs with presumptive trigeminal nerve sheath tumour, and one of 12 dogs with idiopathic unilateral masticatory muscle atrophy.[11] Similarly, in people, both vestibular and facial neuropathy have been associated with ACD.[13,14] As expected, ACD was also identified in cases of acute polyradiculoneuritis (2/9; 22.2%), which is in agreement with a previous canine study, where the CSF of three out of seven dogs (43 %) showed ACD.[21] Furthermore, acute polyradiculoneuritis in dogs has been proposed as a canine model of Guillain-Barré syndrome in humans,[22] and in people, ACD is considered one of the key factors to diagnose this condition and has been reported in 80% of the patients.[23]

Ten dogs ultimately diagnosed with SRMA underwent CSF sampling from CMC and LSS on the same day. A discrepancy on the clinicopathological conclusion between the two samples was observed in one case, where only the CMC sample was diagnostic of SRMA. Recent studies have highlighted the potential clinical benefit of collecting both CMC and LSS CSF samples.[24–26] More specifically, Carletti et al[24] studied a population of 111 dogs diagnosed with SRMA with paired CSF samples (CMC and LSS). In eight of 111 patients, only one of the two samples had an increased TNCC.[24] The differential cell count of the samples with low TNCC would still have been diagnostic of SRMA in six of eight cases, based on the presence of more than 40% of neutrophils.[19,24]

Traditionally, when CMC and LSS puncture sites have been compared, a higher number of TNCC in samples from the CMC and higher level of TP concentration in samples from the LSS have been found.[25] The CSF sampling is usually performed caudally to the suspected site of the lesion in the CNS. Therefore, CMCs are usually collected for intracranial and cervical pathologies and LSS for spinal cord pathologies or in cases which CMC cannot be performed.[2] Results from a recent study comparing paired CMC and LSS in dogs with spinal cord disease suggested that results from the LSS were more sensitive for identifying pleocytosis and elevated protein concentrations compared to the CMC collection.[25] Another study, with 51 paired samples showed significant difference between collection sites and recommended LSS collection for thoracolumbar disease, while suggesting a potential benefit of both (CMC-LSS) collections for intracranial and cervical diseases.[26] In the current study, no significant differences were found in the number of TNCC, RBC and TPs when comparing both locations. However, the difference between our results and the results previously published could be due to the low number of cases with paired CSF samples, especially when analysing TP concentration levels ($p = 0.05$). Our results regarding concurrent CMC and LSS CSF sampling apply to SRMA only and should not be extrapolated to other CNS conditions.

This study has some limitations, mainly related to its retrospective nature. There is a possible selection bias as this sample is not necessarily representative of the overall population of dogs with neurological conditions, given CSF sampling was only performed when clinically indicated. In addition, the clinical reasoning behind the decision on the CSF collecting site (CMC or LSS) for each case was not specified in the medical records. Therefore, not all the samples included in the study were consistently taken caudally to the lesion, which could have influenced our results. Given the overall lack of knowledge of the causes and clinical impact of TP concentration changes and ACD in CSF in dogs, these results highlight the importance of further research in this area and still leave clinicians with the need to decide what level of protein elevation or ACD may be a relevant clinical finding for each specific patient. Hence, CSF analysis results should always be evaluated in combination with the neurological examination and other diagnostic tests.

CONCLUSION

In conclusion, this study evaluated for the first time the prevalence of ACD in a population of dogs referred for suspected neurological conditions. ACD was identified in 16.5 % of the samples, and cranial neuropathy, brain neoplasia, idiopathic vestibular peripheral disease and brain vascular were the most frequently associated diseases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

OFF-LABEL ANTIMICROBIAL USE

Authors declare no off-label use of antimicrobials.

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

This study is approved by the Veterinary Ethic Review Committee of Edinburgh University. Informed written consent was obtained from all owners.

HUMAN ETHIC APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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