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Postencephalitic epilepsy in dogs with meningoencephalitis of unknown origin: Clinical features, risk factors, and long-term outcome

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Abstract

Background: Although the presence of seizures in dogs with meningoencephalitis of unknown origin (MUO) has been associated with shorter survival times, data regarding the prevalence and risk factors for postencephalitic epilepsy (PEE) is lacking.

Objectives: To describe the clinical features, prevalence, risk factors, and long-term outcome of PEE in dogs with MUO.

Animals: Sixty-one dogs with presumptive diagnosis of MUO based on the clinicopathological and diagnostic imaging findings.

Methods: Retrospective study. Cases were identified by search of hospital medical records for dogs with suspected or confirmed MUO. Medical records of dogs meeting inclusion criteria were reviewed. Signalment, seizure history, clinicopathologic, and magnetic resonance imaging (MRI) findings were recorded.

Results: Among 61 dogs at risk of PEE, 14 (23%) dogs developed PEE. Three of 14 dogs with PEE (21%) developed drug-resistant epilepsy. Dogs with PEE were younger (P = .03; $OR_{adjusted}$ = 0.75; 95% confidence interval [CI], 0.58-0.98) and had significantly shorter survival times (log-rank test P = .04) when compared to dogs that did not develop epilepsy. The risk factors associated with the development of PEE were the presence of acute symptomatic seizures (ASS; P = .04; $OR_{adjusted}$ = 4.76; 95% CI, 1.11-20.4) and MRI lesions in the hippocampus (P = .04; $OR_{adjusted}$ = 4.75; 95% CI, 1.07-21.0).

Conclusions and Clinical Importance: Dogs with MUO and seizures at the early stage of the disease (ASS) seem to be at a higher risk of developing PEE.

Abbreviations: AED, antiepileptic drug; ASS, acute symptomatic seizures; CIs, confidence intervals; CNS, central nervous system; CSF, cerebrospinal fluid; GME, granulomatous meningoencephalomyelitis; HR, hazard ratio; IQR, interquartile range; MRI, magnetic resonance imaging; MUO, meningoencephalitis of unknown origin; NLE, necrotizing leucoencephalitis; NME, necrotizing meningoencephalitis; OR, odds ratio; OS, median overall survival time; PEE, postencephalitic epilepsy; SE, status epilepticus; T1W, T1-weighted; T2*, T2-weighted gradient recall echo; T2-FLAIR, T2-weighted fluid attenuation inversion recovery; T2W, T2-weighted; WBC, white blood cell.

KEYWORDS
dog, encephalitis, inflammatory central nervous system disease, meningitis, seizures

1 | INTRODUCTION

Meningoencephalitis of unknown origin (MUO) is a common immune-mediated, inflammatory central nervous system (CNS) disease in dogs. The term MUO encompasses all clinically diagnosed cases of granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME), and necrotizing leucoencephalitis (NLE).[1-3] In the absence of histopathologic confirmation, presumptive diagnosis can be established based on the combination of clinicopathological and advanced imaging findings.[1-4] Affected animals might display various neurological signs including seizures. Furthermore, meningoencephalitis can present with seizures not only in the early stage of the disease but can also lead to the later development of epilepsy.

Epilepsy is a complex disease characterized by recurrent unprovoked epileptic seizures.[5,6] Due to different underlying mechanisms as well as prognosis, it is important to distinguish acute symptomatic seizures (ASS) from late unprovoked seizures.[7,8] ASS are events occurring in close temporal association with an acute or an active CNS insult, whereas unprovoked seizures occur in the absence of a triggering condition or beyond the interval estimated for the occurrence of ASS.[9,10]

In human medicine, the prevalence of postencephalitic epilepsy (PEE) varies between studies, ranging from 6.1% to 46.5%[11-16] and, a substantial number of patients are refractory to antiepileptic drug (AED) treatment.[15-20]

Acute symptomatic seizures are 1 of the major risk factors for the development of PEE across different studies from human medicine.[11,15,16] Furthermore, certain MRI features such as T2-weighted fluid attenuation inversion recovery (T2-FLAIR) abnormality of mesial temporal structures, cortical and subcortical involvement, as well as gadolinium contrast enhancement are predictive of PEE in patients with infectious and autoimmune encephalitis.[15,16]

Although the presence of seizures in dogs with MUO has been associated with shorter survival times,[21-24] little is known regarding predictors of seizures and PEE. Therefore, the aims of this study were to report the clinical features, prevalence, risk factors, and long-term outcome of PEE in dogs with MUO. We hypothesized that dogs with ASS and MRI cortical involvement would be at a higher risk of developing PEE and that dogs with PEE would have shorter survival times.

2 | MATERIALS AND METHODS

2.1 | Case selection

The study was approved by the Research Ethics Committee of the School of Veterinary Medicine of the University of Glasgow (ref32a/17). The electronic database of the Small Animal Hospital of the University of Glasgow was retrospectively searched between 2006 and 2017 for dogs with a final or presumptive diagnosis of MUO.

The terms used for search were meningoencephalitis, meningoencephalitis of unknown origin, MUO, granulomatous meningoencephalomyelitis, GME, necrotizing meningoencephalitis, NME, leucoencephalitis, NLE, encephalitis, and meningitis.

A presumptive diagnosis of MUO was based on guidelines proposed by Granger et al.[3] Dogs met inclusion criteria if they had (1) complete medical history (2) suspected focal, multifocal, or diffuse intracranial lesion based on the neurologic examination findings, (3) evidence of single, multiple, or diffuse lesion on MRI performed at presentation, (4) inflammatory cerebrospinal fluid (CSF) analysis performed at presentation, and (5) dogs with GME, NME, NLE confirmed by histopathologic evaluation only had to have available medical records including history, ancillary tests results, and MRI. Dogs were excluded if they (1) were diagnosed with eosinophilic meningoencephalomyelitis, (2) were diagnosed with strictly spinal meningomyelitis, (3) had only the optic form of MUO (4) or had infectious meningoencephalitis, (5) had experienced a prior neurological insult, (6) had a history of seizures, (7) had an underlying disease which could result in reactive seizures, and (8) were lost to follow-up. The minimum duration of follow-up was 12 months since the documented diagnosis of MUO or until death.

2.2 | Data collection

Data retrieved from the medical records was as follows: signalment, history, and physical and neurologic examination findings. The presence or absence of seizures before diagnosis and within the first week of diagnosis, seizure type (generalized or focal), frequency, and severity of seizures (isolated seizures, cluster seizures, status epilepticus [SE], and refractory SE) were recorded. Seizures were characterized mainly based on the medical history, owners' descriptions of the events, and where available based on the postencephalitic questionnaire. Results of CBC, biochemistry profile, serum antibody titers against *Neospora caninum* and *Toxoplasma gondii*, as well as CSF analysis results and MRI findings, were evaluated. Cerebrospinal fluid analysis was considered normal if white blood cell (WBC) count was ≤5 cells/μL. Pleocytosis was classified as mild, if WBC count was greater than reference ranges but less than 25 cells/μL, as moderate if WBC count was between 26 and 100 cells/μL, and as marked severe if WBC count was higher than 100 cells/μL. Protein concentration for cisternal and lumbar CSF collection was considered normal for less than 25 mg/dL and less than 35 mg/dL, respectively.[25] All MRI studies

were performed using a 1.5 Tesla system (Gyroscan ACS NT, Philips Medical System, Eindhoven, The Netherlands or Magnetom, Siemens, Camberley, United Kingdom) and included a minimum of sagittal, transverse, and dorsal T2-weighted (T2W) images and transverse T1-weighted (T1W) images of the entire brain. The T1W images were acquired before and after paramagnetic contrast administration (0.1 mmol/kg of gadopentetate dimeglumine, Magnevist; Bayer HealthCare Pharmaceuticals, United Kingdom). Most of these studies also included T2-FLAIR images and T2* gradient recall echo images. All sequences were reviewed on an open-source PACS Workstation DICOM viewer (Osirix Imaging Software, v 3.9.2, Pixmeo, Geneva, Switzerland) by a board-certified neurologist who was blinded to the PEE status. The anatomical regions for lesion location on MRI were as follows: cerebrum (frontal, piriform, parietal, temporal, and occipital lobes), olfactory bulb, hippocampus, thalamus, midbrain, cerebellum, pons, medulla oblongata, spinal cord, and meninges. Changes in hippocampus were subjectively divided into postictal or lesion-related. Bilateral, evenly and diffusely distributed symmetrical and non-contrast-enhancing changes were classified as postictal. The presence of concomitant postictal changes in piriform lobes and cingulate gyri, with the same MRI signal characteristics of hippocampus, was used to support the classification of hippocampal changes as postictal.[26,27] If the hippocampus was involved in the borders of an ipsilateral lesion, it was considered to be lesion-related. Lesions were described as focal, multifocal, or diffuse and unilateral or bilateral. Margins were classified as well- or ill-defined. Distribution within white and gray matter, cortical involvement, and the presence of T2-FLAIR perilesional edema were assessed. Gadolinium contrast enhancement was described as parenchymal, meningeal, or both. The degree of contrast enhancement was subjectively classified as mild, moderate, and severe. The presence or absence of mass effect, loss of cerebral sulci, and the presence and type of brain herniation (foramen magnum or caudal transtentorial) were recorded.

Dogs were divided into 2 groups, those with ASS and those without ASS. All cases were followed up until death or for at least 12 months since the diagnosis of MUO. At follow-up, information regarding the presence of seizures, seizure type, and the use of AED was gathered from hospital medical records alone, from medical records requested from referring veterinarian alone, or both hospital and referring veterinarian records, and if available from the owner. Both the veterinary surgeon and the owner were contacted by telephone, email, or by both. If available, additional data were obtained using a PEE questionnaire (enclosed in Appendix S1), which was posted to all owners. The type and duration of treatment, the presence of a relapse, survival times, and the cause of death were also recorded.

2.3 | Study definitions

Acute symptomatic seizures were defined as seizures preceding or occurring within 1 week of documented diagnosis of MUO. Seizures associated with relapse of MUO and occurring before or after 7 days of relapse of MUO were classified as reappearing symptomatic seizures. In the absence of diagnostic imaging studies, CSF analysis, or both diagnostic tests, the relapse of MUO was diagnosed based on the recurrence of previously described neurological deficits or development of new signs of neurological disease.

Late unprovoked seizures were defined as seizures occurring 1 week after documented diagnosis of MUO and not associated with a relapse of MUO.[9,10,28] Postencephalitic epilepsy (PEE) was defined as recurrent unprovoked seizures.[5,6,29] Drug-resistant epilepsy was defined as the persistence of uncontrolled seizures despite ≥2 appropriate AEDs at last follow-up.[30,31] Cluster seizures were defined as 2 or more seizures within 24-hour period. Status epilepticus was defined as greater than 5 minutes of continuous seizure activity or 2 or more seizures between which there is incomplete recovery of consciousness.[6] Status epilepticus was considered refractory if it failed to respond to the first- and second-line treatments.[32]

2.4 | Statistical methods

Numerical variables were presented as a median and interquartile range (IQR), and categorical variables were presented as a count and percentage in a group. Confidence intervals (CIs) for proportions were calculated using Wilsons's score method.

Risk factors for the occurrence of ASS and PEE were first identified using the Pearson's chi-square test or Fisher exact test if the expected count was in 2-by-2 contingency table and was below 5 (dichotomous variables). A Mann-Whitney *U* test was used for numerical variables or ordinal categorical variables with more than 2 categories. Factors for which *P*-value was below 0.1 were entered into the multivariable logistic regression model (as dummy variables if included more than 2 categories) according to the backward stepwise procedure. Crude odds ratios (OR) and adjusted odds ratios ($OR_{adjusted}$) with 95% CIs were presented to describe the result of the univariable and multivariable analysis, respectively. Goodness-of-fit of the logistic regression model was assessed using Nagelkerke's pseudo-R2 and Hosmer-Lemeshow test.

Prognostic factors of the median overall survival time (OS) in the course of MUO were first identified using the Mantel-Cox log rank test (dichotomous variables) or the univariable Cox proportional-hazard model (continuous variables). Factors for which *P*-value was below 0.1 were introduced in the multivariable Cox proportional hazard model according to the backward stepwise procedure. In the OS analysis, dogs were censored if they died from causes unrelated to MUO or were still alive at the end of the observation period. Crude hazard ratios (HR) and adjusted hazard ratios ($HR_{adjusted}$) with 95% CIs were presented to describe the result of the univariable and multivariable analysis, respectively. The OS of dogs in different groups were presented using the Kaplan-Meier plots.

All statistical tests were 2-tailed, and a significance level (α) of 0.05 was assumed in all statistical tests except for univariable risk and survival analyses in which α was 0.1.

Statistical analysis was performed in TIBCO Statistica 13.3.0 (TIBCO Software Inc., Palo Alto, California).

3 | RESULTS

3.1 | Description of study population

One hundred eighty-eight cases with suspected meningoencephalitis were identified in the initial search. Of those 75 fulfilled inclusion criteria (Figure 1), 40 were females (53%) and 35 were males (47%), aged from 7 months to 13 years with a median of 4 years (IQR, 1.6-6.8 years). Twenty-three of 40 (57%) females and 19 of 35 (54%) males were neutered. Body weight ranged from 1.9 to 37.1 kg with a median of 9 kg (IQR, 6.6-19.2 kg). Sixty-one dogs survived 1 week after diagnosis of MUO and were included

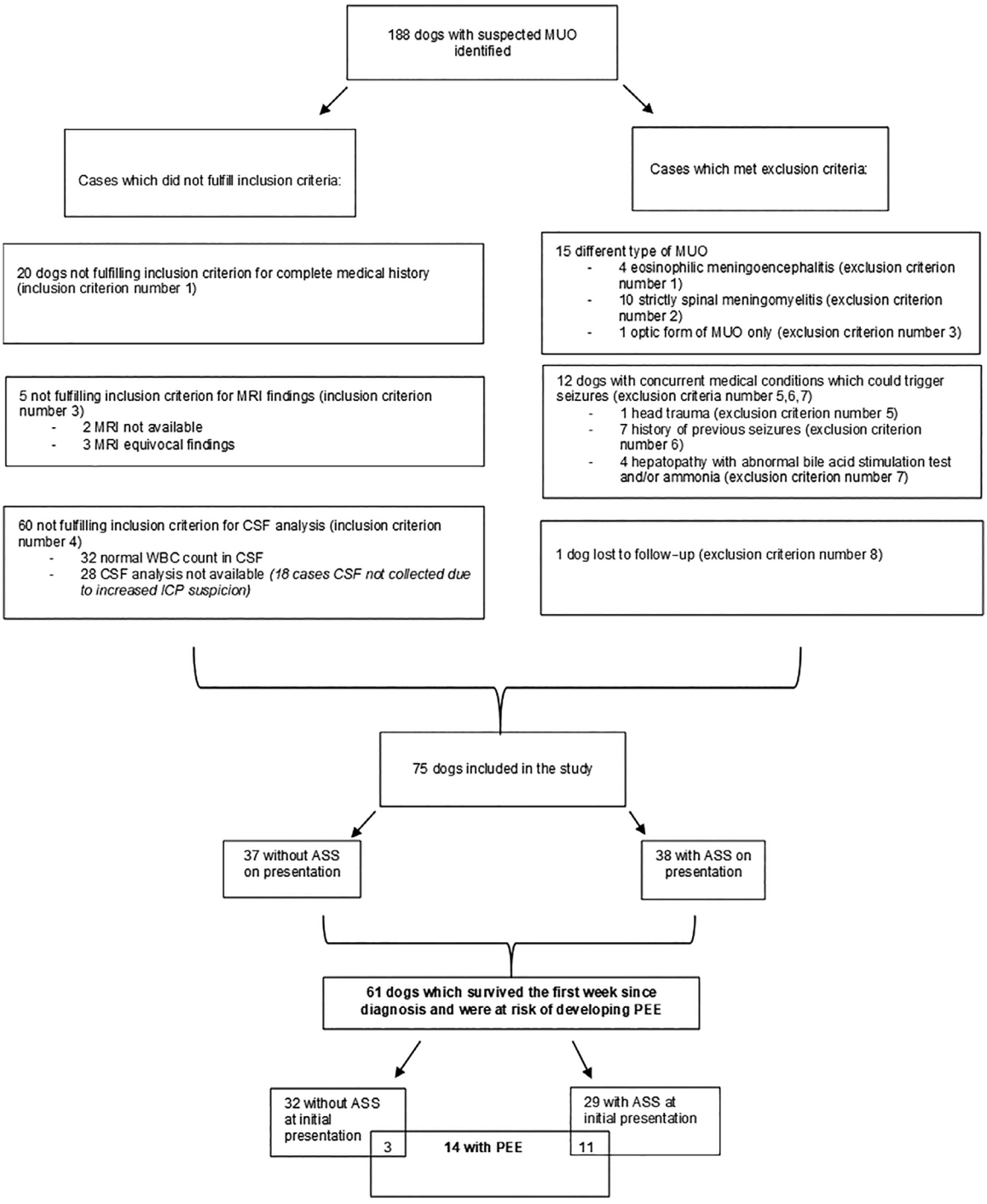

FIGURE 1 Flowchart of the case selection in the study. ASS, acute symptomatic seizures; CSF, cerebrospinal fluid; ICP, intracranial pressure; MRI, magnetic resonance imaging; MUO, meningoencephalitis of unknown origin; PEE, postencephalitic epilepsy; WBC, white blood cell

TABLE 1 Neurological examination findings in dogs with and without acute symptomatic seizures (ASS)

Neurological examination findings	Total number of cases n = 75, n (%)	Number of cases with ASS n = 38, n (%)	Number of cases without ASS n = 37, n (%)	*P*-value (chi-square or Fisher exact test)
Obtundation	40 (53)	26 (68)	14 (38)	.007[a]
Stupor	2 (3)	1 (3)	1 (3)	
Abnormal gait	42 (56)	9 (24)	33 (89)	.46
Circling	18 (24)	8 (21)	10 (27)	.46
Ataxia	33 (44)	16 (42)	17 (46)	.46
Paresis/plegia	13 (17)	6 (16)	7 (19)	.46
Abnormal posture	32 (43)	14 (37)	18 (49)	.42
Abnormal postural reactions	52 (69)	26 (68)	26 (70)	.80
Cranial nerve deficits	53 (71)	28 (74)	25 (67)	.43
Abnormal spinal reflexes	4 (5)	2 (5)	2 (5)	.99
Head, neck, or back pain	13 (17)	5 (13)	8 (22)	.49

[a]P values were calculated for dogs that presented either obtunded or stuporous.

TABLE 2 Correlation between acute symptomatic seizures (ASS) and magnetic resonance imaging (MRI) findings based on the univariable analysis of categorical risk factors of ASS

Hypothesized MRI risk factor	Category	n (%) of dogs with ASS among dogs of a particular category	*P*-value (chi-square of Fisher exact test)
Transtentorial brain herniation	Yes	9/10 (90.0)	.004
	No	29/65 (44.6)	
Parietal lobe lesion	Yes	21/30 (70.0)	.006
	No	17/45 (37.8)	
Cortical involvement	Yes	30/49 (61.2)	.01
	No	8/26 (30.8)	
Temporal lobe lesion	Yes	14/19 (73.7)	.02
	No	24/56 (42.9)	
Meningeal contrast enhancement	Marked	4/8 (50.0)	.02
	Moderate	9/15 (60.0)	
	Mild	24/37 (64.9)	
	No	1/15 (6.7)	
T2-FLAIR perilesional edema	Yes	35/62 (56.4)	.02
	No	3/13 (23.1)	

Note. Only variables with $P < .05$ are presented in the table.
Abbreviation: FLAIR, fluid attenuation inversion recovery.

in the analysis of the risk factors for the development of PEE (Figure 1).

Breeds presented included Lhasa Apso (6), Labrador (6), Pug (6), Maltese Terrier (6), crossbreeds (6), Bichon Frise (5), Cocker Spaniel (4), Chihuahua (3), West Highland White Terrier (3), Yorkshire Terrier (3), Jack Russell Terrier (3), Shih Tzu (3), French Bulldog (2), Boston Terrier (2), Border Collie (1), Border Terrier (1), Cairn Terrier (1), Doberman (1), English Spaniel (1), German Shepherd (1), Greyhound (1), Hungarian Vizsla (1), Lurcher (1), Miniature Pinscher (1), Papillon (1), Polish Lowland Sheepdog (1), Golden Retriever (1), Shar-Pei (1), Shetland Sheepdog (1), Staffordshire Terrier (1), and Weimaraner (1). Histopathological diagnosis was available for 6 dogs. Four dogs had GME and 2 NME.

3.2 | Clinical presentation and ASS

Thirty-eight (51%) dogs were presented with ASS and 37 (49%) without seizures (Figure 1). Dogs with ASS were significantly younger than dogs without seizures ($P = .02$). The median age of dogs with ASS was

3 years (IQR, 1.2-5.3) and 5 years for dogs without seizures (IQR 2.6-7.0). No significant difference was evident in sex (P = .42).

Neurological examination findings are presented in Table 1. Dogs with ASS were more frequently presented obtunded or stuporous (P = .007). Of those with ASS, 10 (26%) were presented with generalized seizures, 8 (21%) with focal seizures, 16 (42%) with both generalized and focal seizures, and the type of seizures was not specified for 4 (10%) cases. Eight (21.0%) dogs experienced isolated seizures, 27 (71%) had cluster seizures, and 7 (18%) cluster seizures which progressed to SE. Four (10%) dogs developed refractory SE. The seizure frequency and severity were insufficiently characterized for 3 (8%) cases. Twenty-seven owners responded to the PEE questionnaire. Among responders, 14 dogs were presented with ASS, 13 without seizures, and 6 developed PEE.

Five of the 37 (13%) dogs that presented without ASS developed seizures at a later stage. Three of these dogs presented seizures as a sign of MUO relapse (25, 31, and 71 weeks after initial diagnosis, respectively) and the remaining 2 did seizure while hospitalized for the initial event at days 8 and 10, respectively. Statistically significant differences in MRI findings between dogs with ASS and dogs without seizures included MRI cortical involvement (P = .01), caudal transtentorial brain herniation (P = .004), meningeal contrast enhancement (P = .02), and the presence of T2-FLAIR perilesional edema (P = .02) (Table 2). All variables are presented in Table 2A and B in Appendix S1.

3.3 | Clinical presentation and risk factors for PEE

Among 61 dogs, which survived the first week, 14 (23%) developed PEE (Figure 1). Similarly, to dogs with ASS, dogs with PEE were younger than dogs without PEE (P = .03). The median age of dogs with PEE was 2.5 years (IQR, 1.5-4.3 years) and 5 years (IQR, 1.6-7.0 years) for dogs without PEE.

Among dogs with PEE 11 (79%) presented with ASS, majority of dogs, 8 of 11 (73%), with PEE in the acute phase experienced cluster seizures, in which 2 dogs progressed to SE. Only 2 dogs (19%) were presented with a single seizure episode, and the seizure frequency was not specified for 1 case (9%).

Among them, 2 dogs experienced focal seizures (18%), 4 generalized (36%), and 3 (27%) both types of seizures. The information regarding seizure type was not available for 2 dogs (18%). The remaining 3 dogs with PEE which developed seizures at later stage of MUO experienced clusters seizures. One dog had only generalized and 2 dogs both generalized and focal seizures.

The variables significantly linked to the risk of PEE development are presented in Table 3. All variables included in the univariable analysis are presented in Appendix S1. In the multivariable analysis, the factors associated with PEE were ASS (P = .04; $OR_{adjusted}$ = 4.76; 95% CI, 1.11-20.4) and hippocampal lesion on MRI (P = .04); $OR_{adjusted}$ = 4.75; 95% CI, 1.07-21.0). Examples of MRI hippocampal lesions are presented in Figure 2 and cortical lesions in Figure 3.

3.4 | MUO treatment

The majority of dogs received treatment with cytosine arabinoside and prednisolone. In the group of dogs with ASS, 32 (84%) were treated with cytosine arabinoside and prednisolone and 6 (16%) with corticosteroids only. In the group of dogs without ASS, 29 (78.3%) received cytosine arabinoside and prednisolone, 7 (19%) had corticosteroids only, and 1 (3%) died before the treatment was initiated.

Thirteen (93%) of 14 dogs which developed PEE received treatment with cytosine arabinoside and prednisolone and 1 (7%) had

TABLE 3 Variables significantly related to the risk of development of postencephalitic epilepsy (PEE) in the univariable analysis

Hypothesized risk factor	Category	n (%) of dogs with PEE among dog of a particular category	Chi-square test or Mann-Whitney *U* *P*-value	OR (95% CI)
Age			.03	0.75 (0.58-0.98)
Seizure activity				
Acute symptomatic seizures	Yes	11/29 (37.9)	.007	5.91 (1.45-24.1)
	No	3/32 (9.4)		
MRI				
MRI frontal lobe lesion	Yes	11/33 (33.3)	.03	4.17 (1.03-16.9)
	No	3/28 (10.7)		
MRI temporal lobe lesion	Yes	7/14 (50.0)	.01	5.71 (1.53-21.4)
	No	7/47 (14.9)		
MRI hippocampal lesion	Yes	6/11 (54.5)	.01	6.30 (1.54-25.7)
	No	8/50 (16.0)		

Note. Only variables with P < .05 are presented in the table.
Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio.

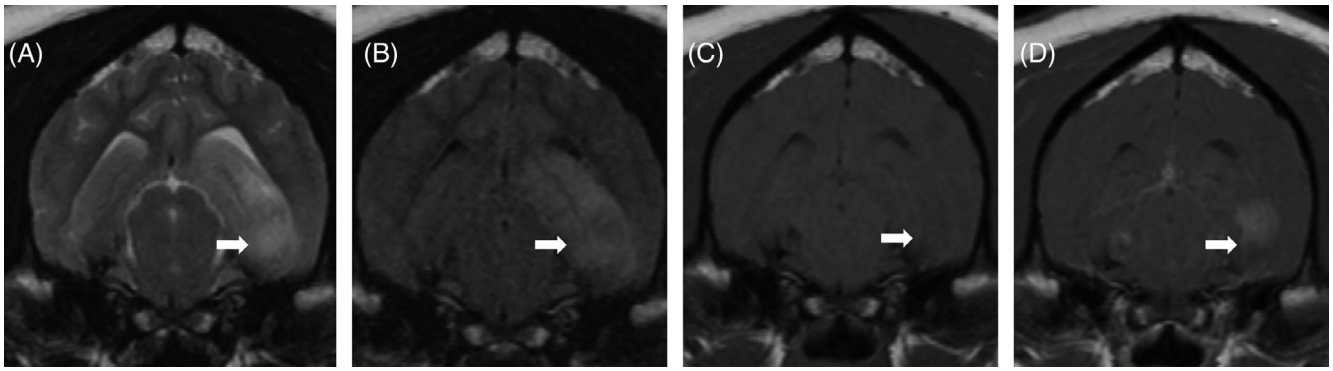

FIGURE 2 Transverse magnetic resonance T2WI (A), fluid attenuation inversion recovery (B), T1WI (C), T1WI-gad (D) of the brain of a dog with postencephalitic epilepsy with a lesion affecting the left hippocampus (white arrow). The images were obtained at the times of diagnosis of meningoencephalitis of unknown origin. T1WI, T1-weighted images; T2WI, T2-weighted images

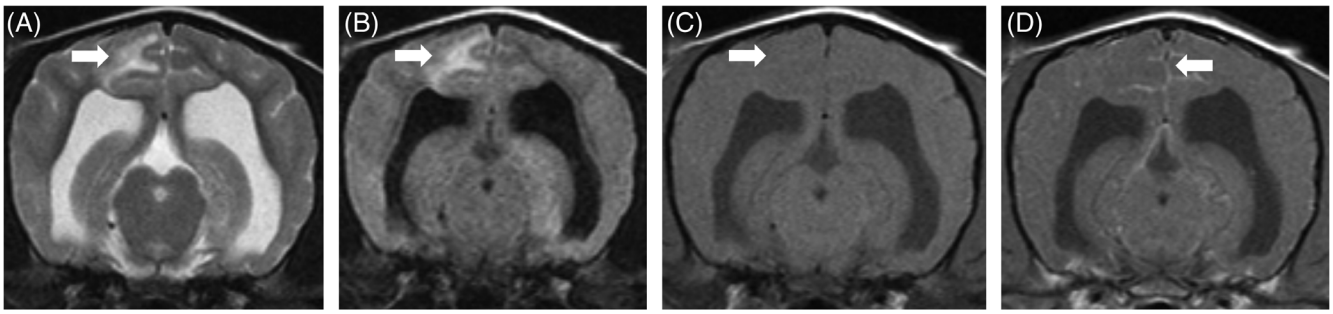

FIGURE 3 Transverse magnetic resonance images T2WI (A), fluid attenuation inversion recovery (B), T1WI (C), T1WI-gad (D) of the brain of a dog with postencephalitic epilepsy with a lesion affecting the cerebral cortex (white arrow). The images were obtained at the time of diagnosis of meningoencephalitis of unknown origin. T1WI, T1-weighted images; T2WI, T2-weighted images

corticosteroids only. Treatment with corticosteroids only was not predictive of PEE (P = .66).

In each group of dogs regardless of the presence or absence of ASS, 12 dogs had a relapse of MUO. In the ASS group, 8 dogs had seizures as a sign of a relapse of MUO and 3 of them had PEE.

In the non-ASS group, 3 cases experienced seizures as a sign of a relapse of MUO and 2 of them had PEE. The first dog with PEE and relapse with seizures experienced first seizure 11 days after diagnosis and a relapse of MUO with seizures 500 days after the diagnosis. The second dog experienced the first relapse 175 days after the diagnosis and the first single seizure 17 days after the first relapse of MUO. This dog had a second relapse of MUO manifested with seizures 656 days after the diagnosis of MUO. One dog with PEE had a relapse of MUO without seizures. Overall, 5 cases with PEE experienced a relapse.

3.5 | Antiepileptic treatment

Patterns of AED use in dogs with ASS and PEE at discharge after hospitalization for the initial event and at 12-month follow-up are presented in Table 4. The choice of AED was at the discretion of the clinician in charge of the case or referring veterinarian.

At the time of writing this report, 6 dogs with ASS were still alive and did not experience any further seizures. Three of these dogs continued treatment with AED. Two dogs stopped phenobarbital after 6 and 12 months. One dog discontinued levetiracetam 12 months after diagnosis of MUO.

One dog with PEE did not receive any AED at the time of discharge as it did not initially present with seizures. Despite the development of PEE, this dog never received AED treatment. At the last follow-up, 3 of 14 (21%) cases with PEE developed drug-resistant epilepsy. Two dogs were treated with phenobarbital, levetiracetam, and potassium bromide and 1 dog with phenobarbital, gabapentin, and potassium bromide. The later became resistant to AED 3 years after the diagnosis.

3.6 | Outcome

Median overall survival time for all dogs in our study regardless of the presence or absence of seizures was 103 weeks (IQR, 3-429 weeks) (Figure 4). One-week survival rate was 81.3% (95% CI, 71.1%-88.5%) and the 1-year survival rate was 59% (95% CI. 47.4%-69.1%). Forty of 75 (53%) dogs died due to reasons related to MUO. Seven dogs (9%) died of other reasons and 28 (37%) were alive at the time of the last

TABLE 4 Number of dogs receiving individual treatment with antiepileptic drug (AED), in dogs with acute symptomatic seizures (ASS) and postencephalitic epilepsy (PEE) at discharge and at 12-month follow-up

	ASS n = 38, n (%)		PEE n = 14, n (%)	
	Discharge	12-month	Discharge	12-month
No AED	3 (10)	5 (26)	1 (7)	1 (7)
Phenobarbital	16 (61)	8 (57)	9 (64)	3 (33)
Levetiracetam	6 (23)	4 (28)	2 (14)	1 (11)
Phenobarbital and levetiracetam	4 (15)	1 (7)	1 (7)	2 (22)
Phenobarbital and potassium bromide	0 (0)	1 (7)	0 (0)	1 (11)
Phenobarbital, levetiracetam, and potassium bromide	0 (0)	0 (0)	0 (0)	1 (11)

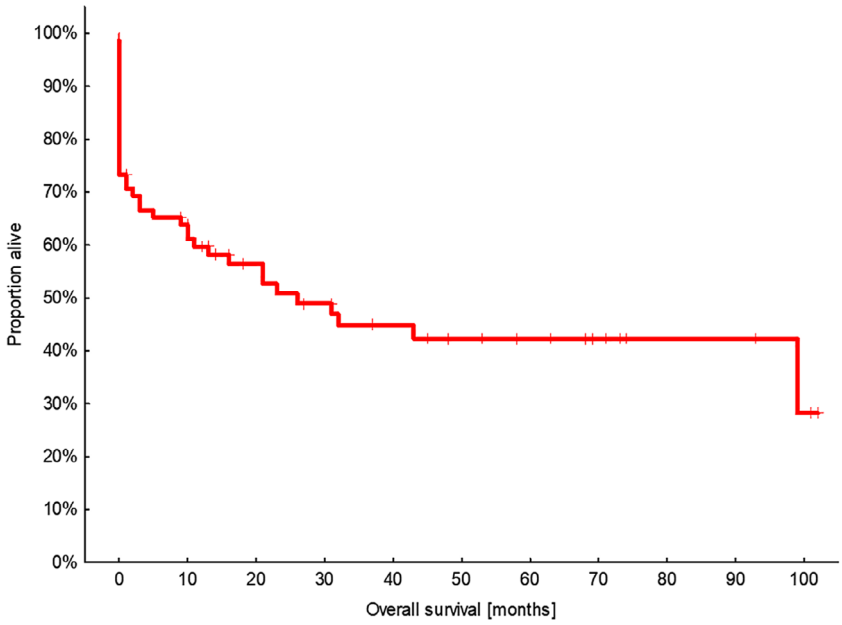

FIGURE 4 Kaplan-Meier curve used to determine the median overall survival time in all dogs with meningoencephalitis of unknown origin

TABLE 5 The variables significantly linked with death in the course of the disease in the univariable analysis

Hypothesized risk factor	Univariable Cox proportional hazard model *P*-value	HR (95% CI)
MRI loss of cerebral sulci	.03	2.11 (1.07-4.16)
MRI brain herniation	.04	1.94 (1.03-3.67)
MRI transtentorial brain herniation	.002	3.11 (1.49-6.47)
Marked/moderate meningeal contrast enhancement	.03	2.01 (1.06-3.80)

Note. Only variables with $P < .05$ are presented in the table.
Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

follow-up. The duration of the long-term follow-up ranged from 52 to 439 weeks. In the multivariable analysis of the risk factors of death in the course of MUO, only caudal transtentorial brain herniation (P = .004; $HR_{adjusted}$ = 2.95; 95% CI, 1.41-6.15) remained significant. Neither the presence of acute nor late seizures was related to the higher risk of death. The treatment with corticosteroids only was not linked to death in the course of MUO. The variables significantly linked to death in the course of MUO are presented in the Table 5. All variables included in the univariable analysis are presented in Appendix S1. There was no statistically significant difference in the OS between dogs with ASS and without seizures (Figure 5).

The analysis of OS in dogs at the risk of developing PEE included 61 dogs, which survived the first week following diagnosis. There were 14 dogs with PEE (23%) and 47 (77%) without PEE. Dogs with PEE had significantly shorter OS than dogs without PEE (P = .04). Median overall survival time of dogs with PEE was 16 months (95% CI, 4-28 months); the OS of dogs without PEE could not be established as >50% of dogs survived till the end of the observation period (Figure 6).

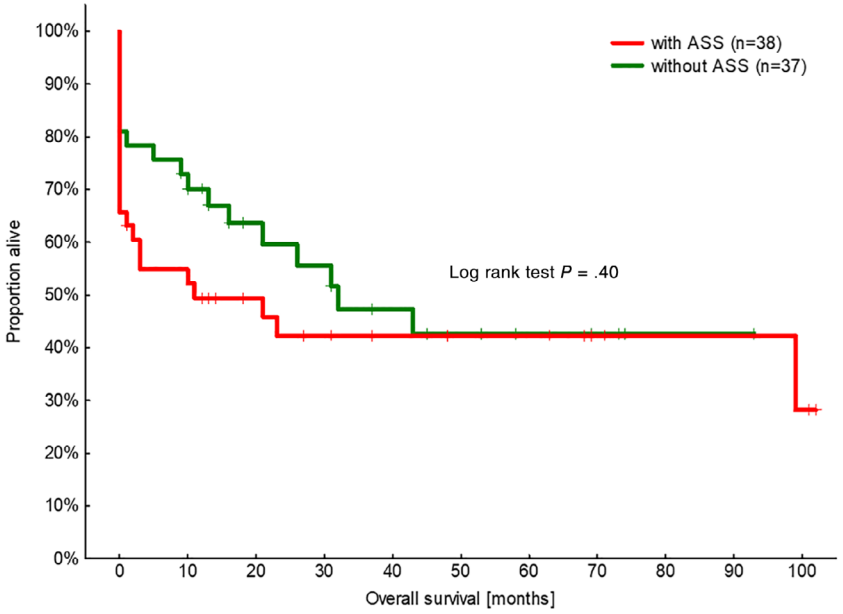

FIGURE 5 Kaplan-Meier estimates of the survival time for dogs with meningoencephalitis of unknown origin. Dogs were assigned into 2 groups based on the presence (red line) or absence (green line) of acute symptomatic seizures. There was no significant difference between groups (P = .40). PEE, postencephalitic epilepsy

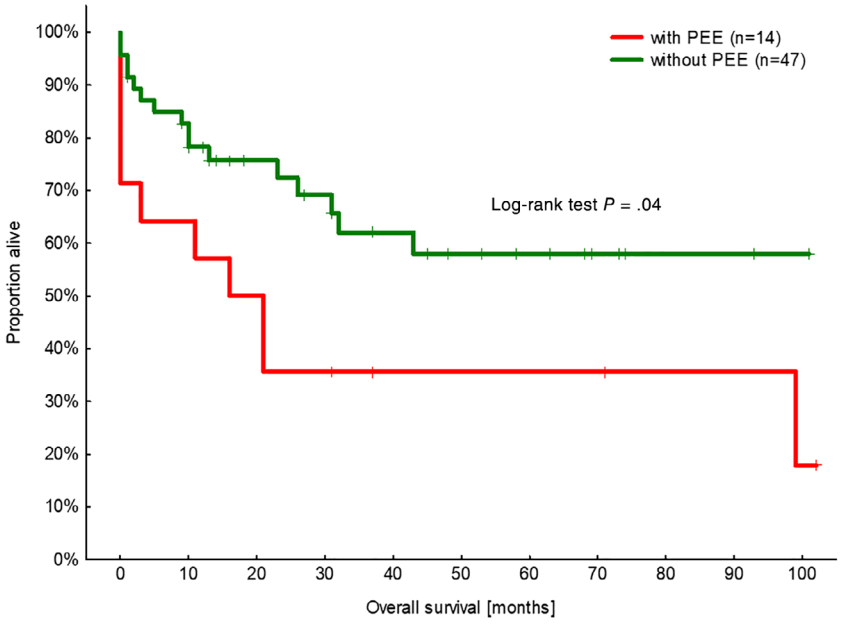

FIGURE 6 Kaplan-Meier estimates of the survival time for dogs with meningoencephalitis of unknown origin. Dogs were assigned into 2 groups based on the presence (red line) or absence (green line) of postencephalitic epilepsy. Survival time was significantly different between groups (P = .04). ASS, acute symptomatic seizures

4 | DISCUSSION

The present study assessed the prevalence, risk factors, and long-term outcome of PEE in dogs with MUO. Acute symptomatic seizures were present in 51% of dogs with MUO and 23% developed recurrent unprovoked seizures consistent with PEE. Of these, 21% developed drug-resistant epilepsy. The presence of ASS and hippocampal lesions on MRI was identified as predictors of PEE. Dogs with PEE were younger and had significantly shorter survival times when compared to dogs without PEE.

The prevalence of ASS in dogs with MUO in this report was 50%, which is higher than in previously published studies, in which it ranged from 23% to 37.5%.[21,22] Similar variations between studies have been reported in human medicine and could be due to differences in inclusion criteria.[11-16] Interestingly, the presence of ASS was a major risk factor for PEE in this study. This finding is in agreement with previous studies in humans in which patients with seizures in the acute phase of encephalitis were much more likely to develop seizures in long-term follow-up compared to patients without seizures.[11,15,16]

In human medicine, focal seizures are associated with seizure recurrence not only in PEE but also in other types of epilepsies.[15,16,33] In this study, 42% of dogs experienced both generalized and focal seizures and 21% had only focal seizures. The type of seizures was not associated with the development of PEE. However, seizure

classification was often based on the owner's description of the events; therefore, some focal seizures could have remained undetected.

The present study showed that the proportion of dogs with ASS and PEE was higher among young individuals. Young age was also reported as 1 of the predictors of seizures in viral or nonspecific encephalitis in human studies.[34] These results are in contrast to data obtained from studies on animal models, where older rats were found more susceptible to seizure induction than their younger counterparts.[35,36]

In a previous study of Pugs with NME, all dogs presented with seizures.[37] Unfortunately, due to the low number of cases with a confirmed histopathological diagnosis in the present study, it was not possible to evaluate the effect of type of inflammatory CNS disease (NME versus GME) on PEE. The cause of encephalitis remains unexplained in 20%-60% of human cases.[38-40] However, the etiology of encephalitis plays an important role in determining the prevalence of seizures and subsequent epilepsy. In a recent study on drug-resistant PEE in children, herpes virus encephalitis and encephalitis of unknown etiology were the most common causes, with a prevalence of drug-resistant epilepsy of 33% and 20%, respectively.[15] In a study focused on the adult population, the prevalence of PEE among patients with autoimmune encephalitis reached 46.5% and with infectious encephalitis 34.9%.[16]

The only imaging predictive factor of PEE in dogs in this study, which remained significant on multivariate analysis, was the presence of lesions affecting the hippocampus. This finding is similar to those of a recent study on childhood drug-resistant PEE.[15] Although the presence of brain abnormalities on MRI following a single seizure or SE is considered as the origin of epilepsy,[41] certain MRI changes might be related to seizures and difficult to distinguish from the primary inflammatory process. Due to the retrospective nature of our study, subsequent MRI could not be obtained to compare with the baseline images and some of the changes described as lesion related could have represented postictal changes.

In this study, we classified bilateral, evenly distributed, and symmetrical changes in the hippocampi as postictal hence more likely to be related to seizure and not the inflammatory process itself. It has been reported that postictal changes in dogs can be appreciated in piriform lobes, temporal lobes, hippocampus, and cingulate gyrus and usually resolve within 16 weeks.[26] Therefore, the presence of concomitant postictal changes in piriform lobes and cingulate gyri, with the same MRI signal characteristics of hippocampus, was used as well to support the classification of hippocampal changes as postictal.

We also recognize that unilateral hippocampal changes could have been postictal and not necessarily lesion-related. In the present study, the presence of contrast enhancement and involvement of the affected hippocampus in the borders of the neighboring lesion were used to attribute hippocampal MRI abnormality to the lesion itself.

However, not all changes triggered by seizures are reversible. The most commonly described sequel of acute MRI changes is the development of cortical atrophy and gliosis. These permanent changes can lead to further development of an epileptogenic lesion.[41,42] Therefore, the definitive distinction between postictal and lesion-related changes could only be established based on the histopathological examination findings.

The role of hippocampus in epileptogenesis is well-known.[43] In humans, mesial temporal lobe epilepsy is the most common form of refractory epilepsy.[44] The pathophysiological hallmark of this specific epilepsy is sclerosis of the hippocampus. However, the exact mechanisms responsible for the development of epilepsy might differ depending on the degree of hippocampal sclerosis and underlying etiology.[45] An early initial CNS insult can lead to further development of late-onset of epilepsy,[46] or antibody-mediated limbic encephalitis can be the cause of mesial temporal lobe epilepsy.[47]

In veterinary medicine, limbic encephalitis with voltage-gated potassium channel antibodies has been described only in cats.[48,49] Considering the lack of subsequent imaging studies, CSF analysis, and histopathological examination of the brain tissue, it is impossible to state whether the pathophysiological mechanism of subsequent PEE in our study was the result of irreversible changes in the brain, particularly in the hippocampus, temporal and frontal lobes, or caused by chronic ongoing inflammation.

Median overall survival time of all dogs in this study was 103 weeks. Dogs with features of increased intracranial pressure, particularly caudal transtentorial brain herniation and loss of cerebral sulci on MRI, were at a higher risk of death. Acute symptomatic seizures were not associated with death in the course of MUO. These results are consistent with 1 report on prognostic factors and outcome using a standard treatment protocol, which was used for the majority of the cases also in our study.[4] However, in the majority of previously published studies, the presence of seizures was linked to death or poor outcome in dogs with MUO.[21-23] The lack of association between ASS and mortality in our study could arise from differences in inclusion criteria between studies. In order to include only cases with the inflammatory process, results of CSF analysis were required for inclusion in the present study. Therefore, we might have excluded cases with a more severe clinical picture and being at risk of deterioration following CSF collection.

In previously published studies,[4,50-53] the combination of prednisolone with cytosine arabinoside improved survival times in dogs with MUO. In this study, the majority of dogs were also treated with cytosine arabinoside and prednisolone. Treatment with corticosteroids only was associated neither with mortality in the course of MUO (P = .16) nor with the development of PEE (P = .66). However, the duration of the treatment and intervals between cycles varied between individuals. Therefore, the direct comparison of survival times and risk factors of PEE between dogs treated with cytosine arabinoside combined with prednisolone or corticosteroids only was not performed as it could lead to inaccurate results and limit the study population.

An important aspect of treatment in dogs with MUO and seizures is treatment with AED. The long-term use of AED is recommended in case of an identifiable structural brain lesion or history of brain insult.[54] The optimum type and duration of AED treatment for patients with ASS or PEE have not been established in either veterinary or human medicine.[17,28] However, it has been reported in humans that aggressive control of ASS, particularly SE, plays a crucial role in the prevention of the development of drug-resistant epilepsy.[55] In this study, of 7 dogs that experienced SE, 3 dogs died within the first 24 hours and 2 developed PEE. Currently, there are no evidence-based guidelines on the

choice of AED in veterinary medicine regardless of the cause of epilepsy.[54,56] In this study, following initial stabilization, a greater number of dogs with seizures received phenobarbital followed by levetiracetam. Approximately 21% of dogs with PEE developed drug-resistant epilepsy; however, the same percentage of dogs required only 1 AED and 28% required 2 AED to control the seizures satisfactorily.

Limitations of the present study include its retrospective nature and small sample size. Currently, there is no consensus on the definition of the time period preceding PEE. Definitions vary between studies and depend mainly on the duration of the follow-up period and AED treatment used.[11-16] Therefore, seizures that occur just outside the subjectively defined time period could still be related to an active phase of the inflammatory process. We decided to follow the most commonly acknowledged definition from the human literature, and we chose a 7-day cutoff period.[5,9,10,29] However, we recognize that this could be controversial, particularly for 2 cases with PEE which experienced the first seizure episode 8 and 10 days after diagnosis. Therefore, one could argue that these 2 cases should be included in the ASS group.

Seizures related to relapse of MUO were classified as provoked seizures and called reappearing symptomatic seizures. Human medicine guidelines for epidemiologic studies on epileptic unprovoked seizures related to the antecedent conditions are categorized into 2 subgroups: remote symptomatic unprovoked seizures and symptomatic unprovoked seizures. The first category encompasses seizures related to conditions resulting in a static lesion. The second category compromises cases with progressive CNS disorders.[57] In our study, the latter category could cover seizures occurring just outside the window for ASS and reappearing symptomatic seizures.

Furthermore, the lack of standardized long-term treatment protocols with AED could have masked seizure activity potentially leading to the underestimation of the PEE prevalence. In this study, 5 cases continued AED treatment until the end of the observation period despite not showing any seizure activity. How many of these cases could have experienced seizures remains a matter of speculation. Moreover, for the majority of cases with seizures, the seizure semiology was classified on the basis of the owner's or referring veterinarian's description of the event. Lastly, the histopathological confirmation was available only for 6 cases which is 1 of the most common limitations of MUO studies. However, the requirement of histopathological confirmation of diagnosis would have constituted survival bias and further limit the study population.

Prospective, multicenter studies are recommended with a larger number of cases and standardized treatment and investigation protocols to fully determine the risk factors and prevalence of PEE in dogs with MUO. Moreover, the guidelines for the use of AED need to be established further.

5 | CONCLUSION

In the present study, half of the dogs with MUO experienced ASS and almost ¼th developed PEE. The presence of ASS and hippocampal lesions on MRI was the strongest predictors of PEE. Dogs with PEE were younger and had a significantly shorter survival time when compared to dogs without PEE.

This high prevalence of both seizures and epilepsy has significant implications on the management and prognosis of dogs with MUO, as it carries the potential to provide an additional burden to an already unpredictable disease. Although some cases developed drug-resistant epilepsy, the vast majority (79%) of cases with PEE achieved satisfactory seizure control with AED treatment.

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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.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed.

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SUPPORTING INFORMATION

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

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