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SHORT COMMUNICATION

Risk factors for cluster seizures in canine idiopathic epilepsy

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Abstract

Cluster seizures (CS), two or more seizures within a 24-hour period, are reported in 38-77% of dogs with idiopathic epilepsy (IE). Negative outcomes associated with CS include a reduced likelihood of achieving seizure freedom, decreased survival time and increased likelihood of euthanasia. Previous studies have found factors including breed, sex and neuter status are associated with CS in dogs with IE; however, only one UK study in a multi-breed study of CS in IE patients exists to the author's knowledge, and thus further data is required to confirm these results. Data from 384 dogs treated at a multi-breed canine specific epilepsy clinic were retrospectively collected from electronic patient records. 384 dogs were included in the study, of which nearly half had a history of CS (49.1%). Dogs with a history of CS had a younger age at onset than those without ($p=0.033$). In a multivariate model, three variables predicted risk of CS: a history of status epilepticus ($p=0.047$), age at seizure onset ($p=0.066$) and breed (German Shepherd Dog) ($p<0.001$). Dogs with a history of status epilepticus and dogs with an older age at seizure onset were less likely to be affected by cluster seizures. German Shepherd Dogs (71% experiencing CS) were significantly more likely to suffer from CS compared to Labrador Retrievers (25%) ($p<0.001$). There was no association between sex, neuter status, body size and CS. Further studies into the pathophysiology and genetics of CS are required to further understand this phenomenon.

Keywords: idiopathic epilepsy; seizure; cluster; canine; neuter; breed

Cluster seizures (CS), defined as two or more epileptic seizures within a 24-hour period in which the patient regains consciousness between epileptic seizures (Patterson, 2014; Thomas, 2010) are a common and distressing occurrence in many dogs with idiopathic epilepsy (IE), with reports of 38% to 77% of dogs with epilepsy experiencing CS (Fredso et al., 2014; Monteiro et al., 2012; Short et al., 2011). The temporal distribution of epileptic seizures is an important prognostic factor in IE, with dogs experiencing CS less likely to achieve remission (Packer et al., 2014), experiencing a decreased survival time (Arrol et al., 2012; Berendt et al., 2007; Monteiro et al., 2012; Saito et al., 2001) and an increased likelihood of euthanasia (Fredso et al., 2014) compared to dogs with single epileptic seizure episodes.

Sex and neuter status have been associated with the presence of CS in dogs with IE, with intact males twice as likely to suffer from CS than neutered dogs (Monteiro et al., 2012). Several breeds are reportedly predisposed to CS, with single-breed studies of the Border Collie and Australian Shepherd finding 94% and 68% of these breeds, respectively, had a history of CS (Hülsmeyer et al., 2010; Weissl et al., 2012). A recent multi-breed study found that German Shepherd Dogs (GSDs) and Boxers were more likely to suffer from CS than Labrador Retrievers (Monteiro et al., 2012). Boston Terriers, English Foxhounds, Lakeland Terriers, Pugs and Teacup Poodles have been reported to be predisposed to CS, although in over one third of cases in that study, epileptic seizures were not caused by IE (Bateman and Parent, 1998).

To the author's knowledge, only one study has examined CS in a population of dogs solely diagnosed with IE (Monteiro et al., 2012), and thus this study aimed to describe a further population of dogs with IE, to identify similarities and differences between risk factors for CS in these populations.

Data from dogs treated at a multi-breed canine specific epilepsy clinic at the Royal Veterinary College from 2005-2011 were retrospectively collected from electronic patient records. Dogs received a uniform diagnostic protocol, with only dogs reported to be diagnosed with IE, for which a cause was not identified (no remarkable findings on interictal neurological examination, haematology, biochemistry, brain MRI and CSF examination), included in the study. Clinical data were gained via standardised owner questionnaires for epilepsy patients, with CS defined as two or more seizures within a 24-hour period in which the patient regained consciousness between seizures (Patterson, 2014; Thomas, 2010), and status epilepticus (SE) as either (a) one continuous seizure lasting for more than 10 minutes without gaining consciousness (for generalized convulsive seizures) (Packer et al., 2014) or (b) two or more discrete epileptic seizures between which there is incomplete recovery of consciousness (Berendt et al., 2015). Seizure activity lasting less than 10 min without gaining consciousness was classed as a single seizure episode. Further variables recorded included signalment, age at onset of seizures, and size of dog as designated by the Kennel Club Breed Information Centre (classifying each breed as small, medium or large) (The Kennel Club, 2014).

Data were analysed in IBM SPSS Statistics v21. Cross tabulations and chi-squared tests were used to test for associations between categorical variables and CS, and Mann-Whitney U tests for continuous variables. Logistic regressions were carried out to examine the relationship between the occurrence of CS and potential explanatory variables (sex, neuter status, gender [female entire, female neutered, male entire, male neutered], breed, age, size and history of SE). Variables with liberal associations in univariable analyses ($P<0.3$) were taken forward for multiple logistic regression evaluation. Model development used backwards stepwise elimination. The presence of biologically-significant interactions was explored. Model fit was assessed using Hosmer-Lemeshow goodness-of-fit test statistics. Statistical significance was set at $P < 0.05$.

The study population comprised 384 dogs, of which 37.2% were male neutered, 25% male entire, 23.7% female neutered and 10.4% female entire. The median age at onset of seizures was 31.6 months (17.8-53.2 months). The most frequently reported breeds were Cross Breeds (n=55), Labrador Retrievers (n=52), Border Collies (n=34) and GSDs (n=31). The majority of dogs were classified as large (52%), with 34% medium and 14% small as per the UK Kennel Club's size classifications.

Cluster seizures had been experienced by nearly half of all dogs (49.1%), and SE by 15.9%. Although a higher percentage of dogs with CS were male (64.0%) and neutered (60.8%), nearly half of all female (48.9%) and male dogs (49.2%) experienced CS, with the same pattern seen in neutered (48.7%) and entire (48.9%) dogs. When gender (sex and neuter status combined) was considered, 47.5% of female entire dogs were affected by CS, 48.4% female neutered, 49.5% male entire and 48.9% male neutered. There was no significant association between sex, neuter status, gender and CS ($p>0.05$) (Table 1). Dogs with CS were significantly younger at seizure onset (28 months; 14.7-28 months) than those without CS (35 months; 18.8-56.5 months) ($p=0.033$). The breeds most frequently reported with CS were Cross breeds (n=23), GSDs (n=22), Border Collies (n=21) and Labrador Retrievers (n=13). There was a trend towards breed being associated with CS ($p=0.061$). The occurrence of CS in each individual breed was compared with the Labrador Retriever (as in Monteiro et al., 2012). GSDs (71% CS, $p<0.001$), Boxers (67%, $p=0.001$), Cavalier King Charles Spaniels (67%, $p=0.002$), Staffordshire Bull Terriers (62%, $p=0.007$) and Border Collies (62%, p=0.001) were significantly more likely to suffer from CS compared to Labrador Retrievers (25% CS) at the univariate level. No significant association was found between CS and size (48% large, 38% medium, 14% small; p>0.05). There was a trend between a history of CS and SE, with 52.4% of dogs with no history of SE having a history of CS, compared to 38.9% of dogs with a history of SE (p=0.068).

[Table 1]

In the final logistic regression, three factors remained: breed (GSD) (p=<0.001), age at onset (p=0.066) and SE (p=0.047) (Table 2). Model fit was improved by the inclusion of the non-significant factor age at onset of seizures. GSDs were at higher risk of CS (OR: 8.08), with 71% of GSDs with a history of CS compared to 25% of Labrador Retrievers. Dogs with a history of SE were at lower risk of CS (OR: 0.535). There was a trend towards dogs with a higher age at seizure onset (per year) being at lower risk of CS (OR: 0.992).

[Table 2]

This study described CS in a UK referral population of dogs diagnosed with IE. Nearly half of dogs had a history of CS (49.1%) which is similarly high to the findings of Monteiro and others (2012) (41%). Both of these studies were derived from referral populations, which may be biased towards difficult to treat patients, and thus studies of CS in first opinion practice populations may provide more representative figures. Despite a similar prevalence of CS, differences were found between these studies. Although GSDs and Boxers were found to be more affected by CS than Labrador Retrievers in both studies, three further breeds, the Cavalier King Charles Spaniel, Staffordshire Bull Terriers and Border Collie were identified in this study at the univariate level. This study confirmed the severe phenotype of IE in the

Border Collie, as previously reported (Hülsmeyer et al., 2010). Studies into the genetics of CS are required to further understand these breed differences.

The effect of neuter status and gender of dogs found by Monteiro and others (2012) could not be replicated here, with nearly equal proportions of male and female and neutered and entire dogs experiencing CS. This effect has not been demonstrated elsewhere in the veterinary or human literature (Tauboll et al., 1991), and at present no reliable conclusions can be drawn on their effects due to the lack of focused research and robust scientific evidence (Van Meervenne et al., 2014). The median age at onset of IE for dogs with CS was lower than previous other reports at 28 months, versus previous reports of 3-5 years (Bateman and Parent, 1998; Monteiro et al., 2012).The association with CS is novel and may represent a higher degree of pathology associated with a more severe seizure phenotype that is quicker to manifest clinically. There was a significant association between CS and SE; with dogs with a history of SE at a reduced risk of CS; however, this has not been found in previous studies (Monteiro et al., 2012; Saito et al., 2001) and requires further investigation.

This study has confirmed a high prevalence of CS amongst dogs with IE, a predisposition to CS in several breeds, and novel associations between CS and earlier onset of seizures and a history of SE. Further studies into the pathophysiology and genetics of CS are required to further understand this phenomenon.

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Table 1. Bivariate associations between cluster seizures and explanatory variables

Variable	Statistical test	
	X^2	P value
Sex	0.003	0.960
Neuter status	0.001	0.967
Gender (Sex x Neuter status)	0.052	0.997
Breed	82.329	0.061
Body size	2.142	0.343
Status epilepticus	3.340	0.068
	Mann-Whitney U	P value
Age at seizure onset	15670.0	0.033

Table 2. Variables significantly associated with cluster seizures in multivariate binomial logistic regression (reference category = cluster unaffected)

Variable	Category	Odds Ratio	95% CI	P value
Status epilepticus	Affected	0.535	0.289-0.991	0.047
Breed	GSD	8.080	2.761-23.643	<0.001
	Other	3.631	1.751-7.530	0.001
	Labrador Retriever	Reference		
Age at seizure onset	-	0.992	0.984-1.001	0.066

Highlights

- luster seizures (CS) in dogs with epilepsy are associated with negative outcomes
- We conducted a retrospective study of CS risk factors in a canine epilepsy clinic
- Half of dogs in the epilepsy clinic population had experienced CS
- Dogs with status epilepticus and dogs with an older age at seizure onset were less likely to be affected by CS
- No association between sex or neuter status and CS as previously found