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Short Communication

Clinical reasoning in feline epilepsy: what combination of clinical information is useful?

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Abstract

The study objective was to identify the association between clinical risk factors and the diagnosis of idiopathic (IE) or structural (SE) epilepsy in cats, using statistical models to identify combinations of discrete parameters from the patient signalment, history and neurological examination that could suggest the most likely diagnosis. Data for 138 cats with recurrent seizures were reviewed, of which 110 were valid for inclusion. Seizure aetiology was classified as IE in 57% and SE in 43% of cats. Binomial logistic regression analyses demonstrated that being a pedigree, older age at seizure onset (particularly over 7 years old), abnormal neurological examinations and ictal vocalisation were associated with a diagnosis of SE compared to IE, and that ictal salivation was associated with a diagnosis of IE compared to SE. These findings support the importance of considering interictal neurological deficits and seizure history in clinical reasoning.

Keywords: cat, seizure, idiopathic, structural, epilepsy

Epileptic seizures are a common presenting complaint in cats, affecting 1%–2% of the general feline population (Schriefl et al., 2008). Seizure manifestations may be different to those typically seen in dogs, but the underlying causes of seizure activity appear to be similar, with both idiopathic (IE) and structural epilepsies (SE). Despite many references and controversial data published about feline IE (Schriefl et al., 2008), there is only one large-scale study to date on the aetiology and classification of feline epilepsy (Pakozdy et al., 2010). The aim of this study was to evaluate aetiology in a different population of cats, and to provide clinicians with validated information with which to develop improved clinical reasoning when investigating seizures in cats.

The medical records of 138 cats with a history of recurrent epileptic seizures that had been presented for investigation between 2006 and 2016 at the Royal Veterinary College Small Animal Referral Hospital were reviewed retrospectively. The following data were extracted for each cat: signalment, history and neurological examination, seizure characteristics, magnetic resonance imaging (MRI) changes and cerebrospinal fluid results. All patients included in the study were required to have a complete epilepsy questionnaire and history, a neurological examination and a comprehensive investigation (complete serum biochemistry and haematology; and MRI of the brain -1.5 Tesla Gyroscan NT, Philips Medical Systems). Seizure aetiology was classified as IE or SE by an adapted version of the classification system published by the International Veterinary Epilepsy Task Force for dogs (IVETF tier II; De Risio et al., 2015). The IVETF classification system of IE is based upon seizure history, age at seizure onset, neurological examination, blood tests and urinalysis at the tier I confidence level, with the addition of MRI and CSF at tier II confidence level. As age at seizure onset and neurological examination status were to be investigated as predictors of IE vs. SE diagnosis in the present study, these factors were omitted from the classification stage. As such, cats were diagnosed with IE if they had a history of two or more unprovoked epileptic seizures occurring at least 24 h apart, no clinically significant abnormalities on minimum data base blood tests and urinalysis, unremarkable MRI of the brain and CSF analysis. The diagnosis of SE was based on the history of seizures and confirmed pathological findings in haematology, serum biochemistry, CSF analysis and/or morphological changes of the brain as identified by MRI. Hippocampal changes identified on MRI (in conjunction with clinical and ictal characteristics associated with hippocampal pathology) were considered as SE, as limbic encephalitis could not be ruled out (Pakozdy et al., 2013).

Data were first analysed at the univariable level using the Chi-squared (X^2) test for categorical variables and Mann-Whitney test for continuous variables, based on the non-normal distribution of the data (Table 1). The following variables were analysed: age at first seizure (continuous), gender, breed, type of seizure, ictal signs (salivation, vocalisation, rapid running, urination, defaecation, orofacial motor signs and mydriasis), presence/absence of the postictal signs and neurological examination status (normal/abnormal). Variables identified as being broadly associated with the outcome (IE vs. SE, $P \leq 0.2$) were taken forward for multivariable analysis using binary logistic regression models (SPSS, Version 22, IBM). A manual forward selection step-wise construction method was taken for model building. Two-way interactions were tested for between all variables in the final model. The final model was evaluated with the Hosmer-Lemeshow goodness-of-fit test. Results of univariate analyses were corrected for multiple comparisons using the False Discovery Rate (FDR), and $P<0.05$ was considered significant for all results.

Of the 138 health records assessed, a total of 110 cats met the inclusion criteria. The lack of accurate examination/incomplete follow-up information (n=20) or a metabolic/toxic cause of epileptic seizures (n=8) resulted in exclusion of 28 cases. Both pedigree and non-pedigree (17.4% vs 82.6%) cats were included, both sexes (56% male vs 44% female), with a median age (25^{th}-75^{th} percentile) of 68 months (23.0-144.0). The median age at first seizure was 65.0 (21.0-142.5) and there was a significant difference between IE and SE cases (IE: 40.9 (17.8-40.0); SE: 111.0 (36.0-160.0); MW=1993.0, p=0.001; FDR-corrected: 0.004) (Figure 1). Several categorical factors were liberally associated with type of epilepsy at the univariable level ($P<0.02$): age at seizure onset (under/over 7 years), ictal salivation and vocalisation, seizure type (focal), pedigree status and neurological examination findings and thus taken forward to multivariate modelling (Table 1).

Five factors remained significant in the final model (Table 2): one continuous, age at first seizure, and four categorical, neurological examination findings, the presence of ictal salivation ictal vocalisation, and pedigree status. No two-way interactions were found between the significant variables. The model was able to accurately predict 75.2% of cases (82.3% of IE cases and 66.0% of SE cases). with abnormal neurological examinations were at a 2,75 times increased odds of being diagnosed with SE than IE, those that were pedigree were at a 5.55 times increased odds of being diagnosed with SE than IE, those with ictal vocalisation at a 7.69 times increased odds of being diagnosed with SE than IE, and those with ictal salivation were at an

0.25 times decreased odds of being diagnosed with SE than IE (Table 2). When included as a continuous variable, age (in months) at seizure onset was significantly associated with epilepsy type, with each month increase associated with a 1.01 increased odds of SE (Table 2). When included as a binomial variable (over or under 7 years at seizure onset), cats over seven years at seizure onset were at a 4.12 increased odds of SE (Table 3).

Historically, the existence of IE in cats has been controversial among veterinary professionals, with some authors suggesting IE is rare or non-existent (Barnes et al., 2004). In our study, 57% of cats were diagnosed with IE, which is proportionally less frequent to what we have previously reported before in our canine referral population (64%) (Armasu et al., 2014). The prevalence of IE in this study is, however, higher than previously reported by others (54%, Rusbridge et al., 2005 and 38%, Pakozdy et al., 2010). Seizure aetiology was significantly associated with age at seizure onset and our study strengthens the finding of a former study (Pakozdy et al., 2010), which indicated that if the seizure onset occurred after 7 years of age, SE is more likely than IE. In our study, bilateral hippocampal T1 hypo/isointensity and T2 hyperintensity identified on MRI was recorded in 6% of cats associated with focal epileptic seizures and orofacial automatisms, which is lower than in a former study (11 %, Pakozdy et al., 2010).

These data have identified a feline profile that is associated with an increased likelihood of SE compared to IE; namely, pedigree cats presenting with focal epileptic seizures characterized by ictal vocalisation, whose seizures began at an older age, particularly over the age of 7 years old, and those with an altered interictal neurological status on examination. In contrast, if cats present with seizures that include ictal salivation, an increased likelihood of IE compared to SE was found. Age at seizure onset was one of the strongest predictors of SE in this study, and thus MRI may be particularly useful in cats presenting with their first seizure at an older age, especially those over 7 years of age (as also identified by Pakozdy et al., 2010), particularly if in combination with other risk factors identified here. The data described in Tables 2 and 3 can be used to help guide veterinarians as to whether a seizuring feline patient should be recommended for MRI based on a high likelihood of SE.

Two ictal signs were found to differentiate between the type of epilepsy, with cats that presented with ictal salivation less likely to have SE rather IE, and cats that presented with ictal vocalisation more likely to have SE than IE. Salivation has been repeatedly associated with several epilepsy syndromes, such as temporal lobe epilepsy and with diverse brain areas - fronto-

orbital cortex and cingulate gyrus, insula, operculum, and mesial temporal structures (Shorvon et al., 2000). The connection between seizure aetiology and ictal vocalisation remains unknown, because of potentially different origin pathophysiology, for example, vocalisation could be related to a convulsion of laryngeal or intercostal muscles, or a consequence of limbic system or frontal lobe involvement (Penfield et al., 1949). Frontal lobe epilepsy has been reported in dogs based on EEG analysis (Morita et al., 2002); however, vocalisation was not observed. The occurrence of other ictal signs such as orofacial motor signs, rapid running, urination, defaecation, mydriasis, tremor and postictal sign did not differentiate between the two epilepsy types, nor did the epileptic seizure type. The neurological examination remains the cornerstone for clinical reasoning in epilepsy to distinguish between IE and SE in dogs (Armasu el al., 2014). This study confirms the importance of the neurological examination, with cats with an abnormal neurological examination at a nearly three times increased odds of being diagnosed with SE than IE.

The goal of this study was to establish statistically significant parameters that were associated with epilepsy type, and could be used to improve clinical decision making in evaluating cats with presenting with recurrent seizures. These data confirm most findings of a former study (Pakozdy et al., 2010) and that feline epilepsy can be differentiated into IE and SE using statistically significant combinations of signalment and clinical parameters. In combination with other veterinarian and owner-related factors, the clinical information in this study can be used to decide whether further investigation with MRI and CSF are warranted to reach a diagnosis of IE or SE.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Figure 1: Boxplot of age of seizure onset (months) for cats with idiopathic epilepsy (n=62) and structural epilepsy (n=47). There was a significant difference between idiopathic epilepsy (40.9 months (17.8-40 months)) and structural epilepsy cases (111 months (36-160 months); MW=1993.0, p=0.001; FDR-corrected: 0.004).

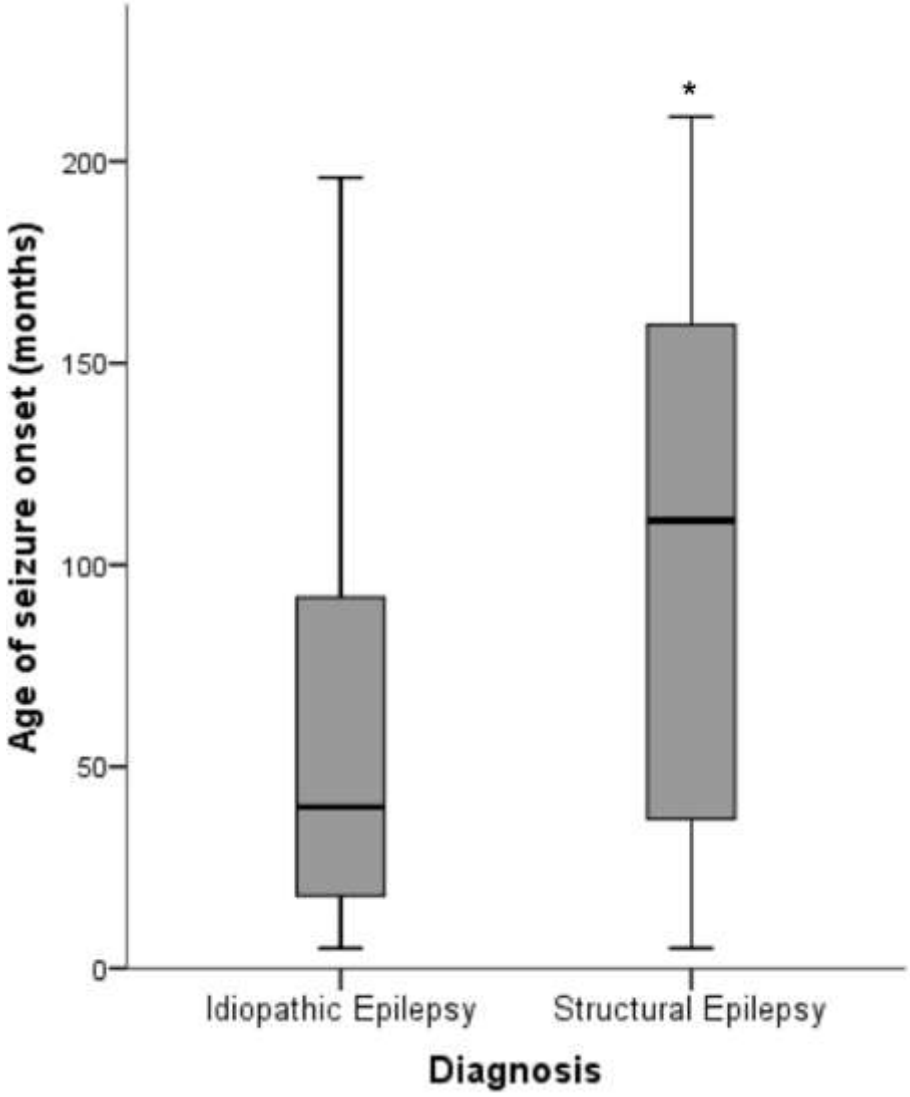

Table 1

Comparison of sex, breed, type of seizure, ictal or postictal signs and neurological examination findings between IE and SE cats (n=110)

Main variable	Parameter	IE		SE		X^2	P	FDR corrected
		N	%	N	%			
Age at onset	Under 7 years old	45	72.6	19	40.4	11.4	0.001	0.004
	Over 7 years old	17	27.4	28	59.6			
Sex	Female	27	43.5	22	46.8	0.12	0.735	0.840
	Male	35	56.5	25	53.2			
Breed	Pedigree	6	9.7	13	27.7	6.01	**0.014**	**0.037**
	Non Pedigree	56	90.3	34	72.3			
Type of seizure	Focal seizure	14	22.6	19	40.4	4.03	**0.045**	0.103
	Generalized seizure	41	66.1	23	48.9	3.26	0.071	0.128
	Focal seizure with secondary generalisation	7	11.3	4	8.5	0.23	0.633	0.780
Ictal signs	Salivation	25	40.3	8	17.0	6.88	**0.009**	**0.029**
	Vocalisation	4	6.5	14	29.8	10.56	**0.001**	**0.004**
	Rapid running	3	4.8	7	14.9	3.24	0.072	0.128
	Urination	37	57.8	27	42.2	0.15	0.873	0.873
	Defaecation	7	53.8	6	46.2	0.10	0.799	0.852
	Orofacial motor signs	13	48.1	14	51.9	0.52	0.283	0.411
	Mydriasis	8	50	8	50	0.28	0.535	0.713
Neuro exam findings	Normal	49	79.0	23	48.9	10.80	**<0.001**	**0.005**
	Abnormal	13	21.0	24	51.1			
Postictal signs	Present	37	59.7	33	70.2	1.29	0.204	0.326
	Absent	25	40.3	14	29.8			

228 **Table 2:** Binomial logistic regression model examining the risk factors associated with types of epilepsy

229 in 130 cats

Variable	Sub-category	Odds Ratio (OR)	95% CI	Wald	P
Breed	Pedigree	5.55	1.57-19.60	7.08	0.008
	Non Pedigree	1 (base)	-	-	-
Age at seizure onset (months)	Continuous	1.01	1.01-1.02	8.94	0.003
Neurological examination findings	Abnormal	2.75	1.02-7.38	4.03	0.045
	Normal	1 (base)	-	-	-
Ictal salivation	Yes	0.25	(0.79-0.80)	5.49	0.019
	No	1 (base)	-	-	-
Ictal vocalisation	Yes	7.69	(1.92-30.89)	8.27	0.004
	No	1 (base)	-	-	-

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232 Table 3. Binomial logistic regression model examining the risk factors associated with types of

233 epilepsy in 130 cats (with age included as a binomial variable as in Pakozdy et al, 2010)

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Variable	Sub-category	Odds Ratio (OR)	95% CI	Wald	P
Breed	Pedigree	5.68	1.62-19.90	7.37	0.007
	Non Pedigree	1 (base)	-	-	-
Age at seizure onset	Under 7 years old	4.12	1.57-10.78	8.29	0.004
	Over 7 years old	1 (base)	-	-	-
Neurological examination findings	Abnormal	2.70	1.01-7.19	3.93	0.047
	Normal	1 (base)	-	-	-
Ictal salivation	Yes	0.24	0.08-0.77	5.75	0.016
	No	1 (base)	-	-	-
Ictal vocalisation	Yes	7.50	1.87-30.00	8.11	0.004
	No	1 (base)	-	-	-

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Supplementary material

The medical records of the Royal Veterinary College Small Animal Referral Hospital were searched for cats with a history of recurrent epileptic seizures that had been presented for investigation between 2006 and 2016. The following inclusion criteria in cats were extracted: breed, age, gender, neuter status, age at seizure onset, time from first seizure until diagnosis, seizure pattern (generalized, motor activity involved the whole body; focal, motor activity in some muscles or muscle groups with or without generalization; or mixed seizures where some seizures were focal and some were generalised), seizure episodes (single seizures; cluster seizures, more than one seizure within 24 hours and status epilepticus), seizure symmetry (symmetrical motor activity with both body sides involved simultaneously; or asymmetrical motor activity where seizures exclusively affected one side of the body, or those that commenced on only one side); neurological examination results (normal or abnormal), magnetic resonance imaging (MRI) results, CSF results (cell count and protein) and infectious disease testing.

593 cats underwent brain MRI of which 138 cats with recurrent epileptic seizures. 110 cats had been diagnosed with idiopathic or structural epilepsy and 8 cats with reactive epilepsy (renal or hepatic encephalopathy, hyperthyroidism). The lack of accurate examination/incomplete follow-up information (n=20) or a metabolic/toxic cause of epileptic seizures (n=8) resulted in exclusion of 28 cases. All cases we included (110) had to have complete records of an epilepsy questionnaire and history, a comprehensive investigation (including complete blood cell count; serum biochemical profile and dynamic bile acid testing; MRI of the brain and a neurological examination. If the haematological and biochemical data did not provide a cause for the seizures, and MRI and CSF examinations did not identify any abnormalities, cats were considered to have 'idiopathic epilepsy'. The diagnosis of SE was based on the history of seizures and confirmed pathological findings in haematology, serum biochemistry, CSF analysis and/or morphological changes of the brain as identified by MRI. The most common aetiology of SE was intracranial neoplasia (n = 24), Meningoencephalitis (n=11), degenerative diseases (n=6), vascular disorders (n=4), anomalous (n=4) and brain trauma (n=2).

MRI of the brain: 1.5-Tesla Gyroscan NT, Philips Medical Systems; T1, T2 and FLAIR weighted pre and post gadolinium contrast in the sagital, transverse or dorsal sequences. The MRI diagnosis rendered by a combination of both radiologist and neurologist. Serology testing for feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), feline infectious peritonitis (FIP), and toxoplasmosis were requested. In an European study, infectious disease was rarely diagnosed in seizing cats (2 of 125 cases) in an urban environment, although the study

271 suggested that there can be geographic differences (Pakozdy et al., 2010). For older cats, thyroid
272 hormone concentration was tested to rule out hyperthyroidism.
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274 Pakozdy, A., Sarchachi Ali, A., Leschnik, M., et al. 2010. Clinical comparison of primary
275 versus secondary epilepsy in 125 cats. J Feline Med Surg; 12:910–916.
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