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1 **Short Communication**

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

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25

26 **Abstract**

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

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39

40 *Keywords:* cat, seizure, idiopathic, structural, epilepsy

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

50
51 The medical records of 138 cats with a history of recurrent epileptic seizures that had
52 been presented for investigation between 2006 and 2016 at the Royal Veterinary College Small
53 Animal Referral Hospital were reviewed retrospectively. The following data were extracted for
54 each cat: signalment, history and neurological examination, seizure characteristics, magnetic
55 resonance imaging (MRI) changes and cerebrospinal fluid results. All patients included in the
56 study were required to have a complete epilepsy questionnaire and history, a neurological
57 examination and a comprehensive investigation (complete serum biochemistry and
58 haematology; and MRI of the brain -1.5 Tesla Gyroscan NT, Philips Medical Systems). Seizure
59 aetiology was classified as IE or SE by an adapted version of the classification system published
60 by the International Veterinary Epilepsy Task Force for dogs (IVETF tier II; De Risio et al.,
61 2015). The IVETF classification system of IE is based upon seizure history, age at seizure onset,
62 neurological examination, blood tests and urinalysis at the tier I confidence level, with the
63 addition of MRI and CSF at tier II confidence level. As age at seizure onset and neurological
64 examination status were to be investigated as predictors of IE vs. SE diagnosis in the present
65 study, these factors were omitted from the classification stage. As such, cats were diagnosed with
66 IE if they had a history of two or more unprovoked epileptic seizures occurring at least 24 h
67 apart, no clinically significant abnormalities on minimum data base blood tests and urinalysis,
68 unremarkable MRI of the brain and CSF analysis. The diagnosis of SE was based on the history
69 of seizures and confirmed pathological findings in haematology, serum biochemistry, CSF
70 analysis and/or morphological changes of the brain as identified by MRI. Hippocampal changes
71 identified on MRI (in conjunction with clinical and ictal characteristics associated with
72 hippocampal pathology) were considered as SE, as limbic encephalitis could not be ruled out
73 (Pakozdy et al., 2013).

74

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

88
89 Of the 138 health records assessed, a total of 110 cats met the inclusion criteria. The lack
90 of accurate examination/incomplete follow-up information ($n=20$) or a metabolic/toxic cause of
91 epileptic seizures ($n=8$) resulted in exclusion of 28 cases. Both pedigree and non-pedigree
92 (17.4% vs 82.6%) cats were included, both sexes (56% male vs 44% female), with a median age
93 (25th-75th percentile) of 68 months (23.0-144.0). The median age at first seizure was 65.0 (21.0-
94 142.5) and there was a significant difference between IE and SE cases (IE: 40.9 (17.8-40.0); SE:
95 111.0 (36.0-160.0); $MW=1993.0$, $p=0.001$; FDR-corrected: 0.004) (Figure 1). Several
96 categorical factors were liberally associated with type of epilepsy at the univariable level
97 ($P < 0.02$): age at seizure onset (under/over 7 years), ictal salivation and vocalisation, seizure type
98 (focal), pedigree status and neurological examination findings and thus taken forward to
99 multivariate modelling (Table 1).

100
101 Five factors remained significant in the final model (Table 2): one continuous, age at first
102 seizure, and four categorical, neurological examination findings, the presence of ictal salivation
103 ictal vocalisation, and pedigree status. No two-way interactions were found between the
104 significant variables. The model was able to accurately predict 75.2% of cases (82.3% of IE
105 cases and 66.0% of SE cases). with abnormal neurological examinations were at a 2.75 times
106 increased odds of being diagnosed with SE than IE, those that were pedigree were at a 5.55 times
107 increased odds of being diagnosed with SE than IE, those with ictal vocalisation at a 7.69 times
108 increased odds of being diagnosed with SE than IE, and those with ictal salivation were at an

109 0.25 times decreased odds of being diagnosed with SE than IE (Table 2). When included as a
110 continuous variable, age (in months) at seizure onset was significantly associated with epilepsy
111 type, with each month increase associated with a 1.01 increased odds of SE (Table 2). When
112 included as a binomial variable (over or under 7 years at seizure onset), cats over seven years at
113 seizure onset were at a 4.12 increased odds of SE (Table 3).

114
115 Historically, the existence of IE in cats has been controversial among veterinary
116 professionals, with some authors suggesting IE is rare or non-existent (Barnes et al., 2004). In
117 our study, 57% of cats were diagnosed with IE, which is proportionally less frequent to what we
118 have previously reported before in our canine referral population (64%) (Armasu et al., 2014).
119 The prevalence of IE in this study is, however, higher than previously reported by others (54%,
120 Rusbridge et al., 2005 and 38%, Pakozdy et al., 2010). Seizure aetiology was significantly
121 associated with age at seizure onset and our study strengthens the finding of a former study
122 (Pakozdy et al., 2010), which indicated that if the seizure onset occurred after 7 years of age, SE
123 is more likely than IE. In our study, bilateral hippocampal T1 hypo/isointensity and T2
124 hyperintensity identified on MRI was recorded in 6% of cats associated with focal epileptic
125 seizures and orofacial automatisms, which is lower than in a former study (11 %, Pakozdy et al.,
126 2010).

127 These data have identified a feline profile that is associated with an increased likelihood
128 of SE compared to IE; namely, pedigree cats presenting with focal epileptic seizures
129 characterized by ictal vocalisation, whose seizures began at an older age, particularly over the
130 age of 7 years old, and those with an altered interictal neurological status on examination. In
131 contrast, if cats present with seizures that include ictal salivation, an increased likelihood of IE
132 compared to SE was found. Age at seizure onset was one of the strongest predictors of SE in this
133 study, and thus MRI may be particularly useful in cats presenting with their first seizure at an
134 older age, especially those over 7 years of age (as also identified by Pakozdy et al., 2010),
135 particularly if in combination with other risk factors identified here. The data described in Tables
136 2 and 3 can be used to help guide veterinarians as to whether a seizuring feline patient should be
137 recommended for MRI based on a high likelihood of SE.

138
139 Two ictal signs were found to differentiate between the type of epilepsy, with cats that
140 presented with ictal salivation less likely to have SE rather IE, and cats that presented with ictal
141 vocalisation more likely to have SE than IE. Salivation has been repeatedly associated with
142 several epilepsy syndromes, such as temporal lobe epilepsy and with diverse brain areas - fronto-

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

156
157 The goal of this study was to establish statistically significant parameters that were
158 associated with epilepsy type, and could be used to improve clinical decision making in
159 evaluating cats with presenting with recurrent seizures. These data confirm most findings of a
160 former study (Pakozdy et al., 2010) and that feline epilepsy can be differentiated into IE and SE
161 using statistically significant combinations of signalment and clinical parameters. In
162 combination with other veterinarian and owner-related factors, the clinical information in this
163 study can be used to decide whether further investigation with MRI and CSF are warranted to
164 reach a diagnosis of IE or SE.

165 **Conflict of interest statement**

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

168

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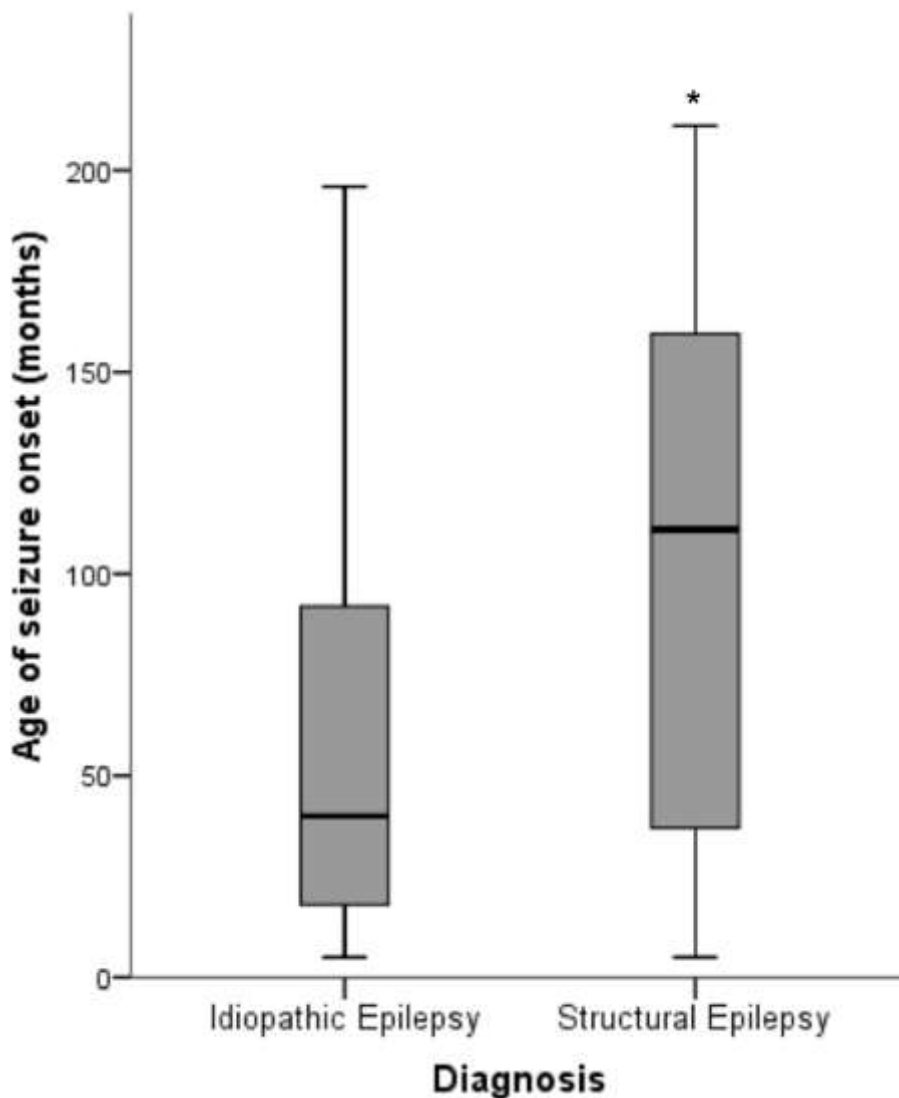
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208 **Figure 1: Boxplot of age of seizure onset (months) for cats with idiopathic epilepsy (n=62) and**
209 **structural epilepsy (n=47).** There was a significant difference between idiopathic epilepsy (40.9
210 months (17.8-40 months)) and structural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



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218 **Table 1**
 219 Comparison of sex, breed, type of seizure, ictal or postictal signs and neurological examination findings
 220 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			

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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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 231

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)

234

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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236

237 **Supplementary material**

238
239 The medical records of the Royal Veterinary College Small Animal Referral Hospital
240 were searched for cats with a history of recurrent epileptic seizures that had been presented for
241 investigation between 2006 and 2016. The following inclusion criteria in cats were extracted:
242 breed, age, gender, neuter status, age at seizure onset, time from first seizure until diagnosis,
243 seizure pattern (generalized, motor activity involved the whole body; focal, motor activity in
244 some muscles or muscle groups with or without generalization; or mixed seizures where some
245 seizures were focal and some were generalised), seizure episodes (single seizures; cluster
246 seizures, more than one seizure within 24 hours and status epilepticus), seizure symmetry
247 (symmetrical motor activity with both body sides involved simultaneously; or asymmetrical
248 motor activity where seizures exclusively affected one side of the body, or those that commenced
249 on only one side); neurological examination results (normal or abnormal), magnetic resonance
250 imaging (MRI) results, CSF results (cell count and protein) and infectious disease testing.

251 593 cats underwent brain MRI of which 138 cats with recurrent epileptic seizures. 110
252 cats had been diagnosed with idiopathic or structural epilepsy and 8 cats with reactive epilepsy
253 (renal or hepatic encephalopathy, hyperthyroidism). The lack of accurate
254 examination/incomplete follow-up information (n=20) or a metabolic/toxic cause of epileptic
255 seizures (n=8) resulted in exclusion of 28 cases. All cases we included (110) had to have
256 complete records of an epilepsy questionnaire and history, a comprehensive investigation
257 (including complete blood cell count; serum biochemical profile and dynamic bile acid testing;
258 MRI of the brain and a neurological examination. If the haematological and biochemical data
259 did not provide a cause for the seizures, and MRI and CSF examinations did not identify any
260 abnormalities, cats were considered to have 'idiopathic epilepsy'. The diagnosis of SE was based
261 on the history of seizures and confirmed pathological findings in haematology, serum
262 biochemistry, CSF analysis and/or morphological changes of the brain as identified by MRI. The
263 most common aetiology of SE was intracranial neoplasia (n = 24), Meningoencephalitis (n=11),
264 degenerative diseases (n=6), vascular disorders (n=4), anomalous (n=4) and brain trauma (n=2).

265 MRI of the brain: 1.5-Tesla Gyroscan NT, Philips Medical Systems; T1, T2 and FLAIR
266 weighted pre and post gadolinium contrast in the sagittal, transverse or dorsal sequences. The
267 MRI diagnosis rendered by a combination of both radiologist and neurologist. Serology testing
268 for feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), feline infectious
269 peritonitis (FIP), and toxoplasmosis were requested. In an European study, infectious disease
270 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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