Investigating the potential for seizure prediction in dogs with idiopathic epilepsy:

Owner reported prodromal changes and seizure triggers

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Abstract

Background Canine idiopathic epilepsy (IE) is characterised by recurrent seizure activity, which can appear unpredictable and uncontrollable. The purpose of this study was to investigate the potential for seizure prediction in dogs, via exploring owner-perceived seizure prediction abilities, and identifying owner-reported prodromal changes (long-term changes in disposition that indicate forthcoming seizures) and seizure triggers (stimuli that precipitate seizures) in dogs with IE.

Methods An online international cross-sectional survey of 229 owners of dogs diagnosed with IE, meeting IVETF Tier I diagnostic criteria.

Results Over half of owners (59.6%) believed they were able to predict an upcoming seizure in their dog, of which nearly half (45.5%) were able to do so ≥30 minutes before the seizure commenced. The most common 'seizure predictors' were pre-seizure behavioural changes including increases in clinginess (25.4%), restlessness (23.1%) and fearful behaviour (19.4%). Nearly two-thirds of owners reported prodromal changes (64.9%), most commonly restlessness (29.2%), and nearly half (43.1%) reported seizure triggers, most commonly stress (39.1%).

Conclusions The relatively high prevalence of owner-reported prodromal changes and seizure triggers shows promise for utilising these methods to aid seizure prediction in dogs, which could open a window of time for pre-emptive, individualised drug interventions to abort impending seizure activity.

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26 **Keywords**: dog; epilepsy; idiopathic; prodrome; seizure; prediction; trigger

27

28 **Abbreviations**

29 AEDs – Anti-epileptic drugs

30 EEG – Electroencephalogram

31 IE – Idiopathic Epilepsy

32 IVETF – International veterinary epilepsy task force

33 QoL – Quality of Life

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Introduction

Epilepsy is the most common chronic neurological condition in dogs estimated to affect 0.6% of dogs in the UK (1). Seizures are considered to be spontaneous due to our current lack of understanding of the transition between the inter-ictal and the ictal stage. Anti-epileptic drugs (AEDs) are currently used to treat epilepsy in dogs, with most used chronically (every day) (2). Despite this, the majority of dogs do not respond adequately to AEDs (3) and often have side effects compromising quality of life (QoL) (4). This challenging situation demands novel ways of thinking and approaches to improve seizure control.

New studies suggest pulse dosing (giving AEDs when pre-ictal signs are noted or after a seizure) of add-on drugs is a strategy to overcome AED tolerance and increase efficacy (3, 5-7). As such, being able to predict impending seizures and use add-on AEDs in a pulsatile manner prior to abort the seizure event may improve patient QoL. Seizure prediction may also substantially improve owner as well as canine QoL. Seizures are recognised to be stressful for owner and dog alike (8), and thus giving owners the knowledge of when seizures may occur could improve their feelings of control, and reduce anticipatory anxiety (9). To enable such a paradigm shift in epilepsy treatment, the ability to accurately predict impending seizure activity is required. Electroencephalography (EEG) has been a key development in the prediction of seizure activity. Human and canine studies have successfully shown feasible seizure prediction using intracranial EEG, allowing for advanced warnings for patients for intervention (10-12). However, these prediction technologies require invasive procedures which are unlikely to be feasible clinically.

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59   Non-invasive seizure prediction methods in dogs may rely on identification of changes in a

60   dog's behaviour (e.g. activity levels or patterns of behaviour) prior to a seizure that can be

61   visually detected by their owner, or in the future, detected using technologies to automatically

62   measure behaviour change (e.g. inertia measurement units). Furthermore, the identification of

63   seizure precipitants ('triggers') that reliably precede seizures could allow time for owners to

64   take preventative action (e.g. pulsatile dosing of add-on AEDs), or trigger avoidance

65   programmes.

66

67   The international veterinary epilepsy task force (IVETF) consensus defines prodromes as "*a*

68   *long-term (hours to days) change in disposition and indicator of forthcoming seizures*" (13).

69   Prodromes are defined by being relatively long lasting in nature compared with focal

70   seizures, although both prodromes and focal seizures may present with similar signs e.g.

71   facial twitching, restlessness, anxiety (14, 15). Focal seizures can occur alone or before a

72   generalised seizure (focal with secondary generalisation) and are often very short in duration

73   (lasting seconds to minutes) (13). In comparison, prodromal changes may last for hours to

74   days before a seizure. Reported occurrence rates of prodromes in people with epilepsy are

75   between 6.9% - 47%, with most studies reporting changes at least 30 minutes before the

76   seizure itself occurs, to differentiate the seizure itself and the prodrome (16). Many people

77   report that their prodromes are characterised by behavioural changes including restlessness,

78   irritability, anger, mood changes, cognitive disturbances and physiological changes such as

79   increased urination, increased or decreased appetite (16, 17). Owners of epileptic dogs have

80   previously reported pre-seizure behaviour changes such as pacing, anxiety and attention

81   seeking, but these changes are yet to be explored in depth (18).

82

83 Seizure triggers (precipitating factors) can be defined as "*those circumstances that precede*

84 *the onset of an epileptic attack and are considered by both patient and neurologist to be a*

85 *possible explanation for why the seizure happened when it did, and not earlier or later*" (19).

86 Recognition of seizure-precipitating factors may support improved seizure control by either

87 their active avoidance, or taking mitigating action post-exposure. One study in human

88 epilepsy found that 62% of epilepsy patients can reliably identify at least one specific seizure

89 trigger (20). The study found that excitation and stress were the most common reported

90 seizure-precipitants. Furthermore, excitation, sleep deprivation, fever, watching television

91 and head trauma had a strong association with impending seizures in generalized epilepsy

92 (20). Another questionnaire-based study found that at least one seizure trigger was reported

93 by 89.8% of people with epilepsy and that 85.5% of their carers could also identify one

94 trigger (21). In this study, the most common triggers were tiredness, stress and sleep

95 deprivation (21). In addition, other studies have identified environmental changes as seizure

96 precipitants including changes in environmental temperature and barometric pressure (22).

97 To date, there are few published studies of potential seizure triggers in dogs with idiopathic

98 epilepsy. Most recently, a study of fifty dogs with idiopathic epilepsy found that almost three

99 quarters of dogs (n=37/50) had at least one 'seizure-precipitating' factor (23). Prior to this

100 study, only two studies had identified seizure triggers in dogs; estrus in entire female dogs

101 with idiopathic epilepsy (24) and potentially stressful events including visits to a veterinary

102 clinic, grooming or boarding facility in dogs with reflex epilepsy (25).

103

104 The aim of this study was to investigate owner recognition of potential prodromal changes

105 prior to seizure activity, potential factors that trigger their epileptic dog's seizures, and their

106 perceived ability to predict their own dog's seizures in a population of dogs diagnosed with

107 idiopathic epilepsy.

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Methods

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Study design and recruitment

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113 A cross sectional online survey was developed and conducted on an online survey platform

114 (©SurveyMonkey; www.surveymonkey.co.uk) between 9th January and 21st January 2018 to

115 explore seizure triggers and prodromal changes in dogs with idiopathic epilepsy (IE). The

116 questionnaire was composed of seven sections; about the owner, general information

117 regarding the owner's epileptic dog, veterinary diagnosis and classification of their dog's

118 epilepsy, clinical presentation of their dog's epilepsy, epilepsy management, seizure

119 prediction and seizure triggers. The questionnaire was promoted via the Royal Veterinary

120 College Canine Epilepsy Research social network page and sharing via online support groups

121 for owners of epileptic dogs. The study was approved by the local ethics committee (RVC

122 Animal Welfare and Ethics Committee; Ref: URN SR2017-1234).

123

Inclusion and Exclusion Criteria

124

125

126 The study aimed to recruit dogs affected by IE. Dogs were screened for IE by consecutive

127 diagnostic questions, beginning with whether they had ever had a seizure (yes/no). Those

128 owners answering no were categorised into the control group. For those answering yes, three

129 further screening questions were posed: (i) whether their dog had 2 or more seizures that

130 were at least 24 hours apart; (ii) whether their dog's first seizure occurred between the ages of

131 6 months and 6 years; and (iii) whether their vet had carried out blood and urine tests on their

132 dog and found no identifiable cause for their dog's seizures. If the owner answered yes to all

133 three questions, the dog was considered to meet the tier I diagnostic criteria for the

134 International Veterinary Epilepsy Task Force (IVETF) (13) and thus was classified as

135 affected. Dogs who had experienced seizure activity, but whose owners only responded 'yes'

136 to one or two of the above screening questions, were excluded from the study. All dogs

137 recruited were alive at the time of the questionnaire.

138

139 *Questionnaire data*

140

141 The questionnaire was divided into seven sections. In section A, (Owner Demographics),

142 Owners were asked to report their age, gender and country of residence. In section B

143 (Canine Demographics), owners were asked to report their dog's breed, age, sex, and neuter

144 status. In section C (epilepsy phenotype) owners were asked questions on the diagnosis of

145 their dog's epilepsy (e.g. whether a vet diagnosed their dog's epilepsy, what clinical tests

146 were performed, how old they were at their first seizure and their final diagnosis i.e.

147 structural or idiopathic epilepsy, and whether they primarily experienced focal or generalised

148 seizures). For clarity, generalised seizures were restricted to convulsive subtypes (tonic,

149 clonic, tonic-clonic) and absence or myoclonic seizures were not addressed. In addition,

150 owners were asked the average length their dog's seizure last for and how many seizures their

151 dog had experienced to date. In section D (anti-epileptic drug management) owners were

152 asked to report their dog's current anti-epileptic medications.

153

154 In the sections of particular interest to the study aims (seizure prediction, prodromal changes

155 and triggers) owners were initially asked an open ended question of whether they could

156 predict seizures, identify prodromal changes or seizure triggers, and if so, the reasoning

157 behind it in a free-text format, giving them the opportunity to report without bias.

158 Subsequently, this was followed by multiple choice lists of known prodromal changes or

159 triggers from the human epilepsy literature (26-29). To reduce bias introduced by exposure to

160 these lists, the respondent was unable to return to the previous question once completed to

161 avoid changing their answers.

162

163 In section E (Owner-perceived seizure prediction), owners were asked whether they could

164 predict their dog's seizure and if so, to explain why they believed they could and in what

165 timeframe. These free-text data were then categorized into four themes, which covered thirty-

166 three categories, with examples given below:

167   (1) Behavioural changes in their dog (e.g. increases in clinginess, increased sleep, fear,

168   attention-seeking, restlessness, eye movements, increased vocalisation, becoming

169   withdrawn, reduced attention, vomiting, decreased appetite, undefined behavioural

170   changes (i.e. owner noticed a change in behaviour but couldn't definitively define the

171   behaviour change), staring, facial and ear twitching, lip licking, reduced sleep,

172   reduced activity, increased activity, hyper salivation, pruritus, increased sniffing,

173   polyphagia, lethargy)

174   (2) Sensory changes in their dog (e.g. changes in smell of their dog)

175   (3) Changes in their other pet's behaviour (e.g. change in their companion cat's

176   behaviour, change in their companion dog's behaviour)

177   (4) The presence of seizure triggers (e.g. stress, overexertion, cold temperatures, changes

178   in routine and full moon).

179

180 A further category was created for owners who could predict seizure activity but were unsure

181 as to why they felt they could. Finally, owners were asked the longest timeframe they could

182 predict forthcoming seizure activity.

183

184 In section F (Seizure detection dogs), owners were asked whether they had any other dogs in

185 the same household as their epileptic dog and if so, whether they could predict upcoming

186 seizure activity based on the behaviour of their non-epileptic dog ('companion dog'). They

187 were then asked to explain why they felt their companion dog could help predict seizure

188 activity in an open text box, responses from which were read by the investigator (SLF) and

189 categorized into the following: increased vocalisation, running/pacing, licking their epileptic

190 dog, more clingy to their epileptic dog, aggressive behaviour towards their epileptic dog,

191 increased sniffing, withdrawn, pawing at their owner, stress, signs of fear/anxiety and a

192 change in behaviour but unable to identify.

193

194 In section G (Owner identification of prodromal signs), potential prodromal changes

195 identified by owners were reported using an open free-text box, which were then read by the

196 investigator (SLF) and categorized into the following: increase clinginess, excessive energy,

197 lack of energy, less responsive, more responsive, clumsy, ataxia, increased lameness,

198 reluctance to walk, excessive panting, withdrawn, quiet, increased sleep, unsettled sleep,

199 decreased sleep, increased lip licking, tense, increased vocalisation, decreased vocalisation,

200 whimpering, groaning, crying, screaming, change in quality/sound of vocalisation, hiding,

201 increased alertness, excessive self-grooming, shivering, vomiting, polyphagia, decreased

202 appetite, increased stiffness, hunched, diarrhoea, defecating in abnormal places, decreased

203 faecal output, increased faecal output, periuria and decreased frequency of urination.

204 Following this, owners were given a list of known prodromal changes derived from the

205 human literature and were asked to identify whether any of these changes had previously

206 been shown by their dog prior to seizure activity.

207

208 Finally, in section H (seizure triggers), unprompted seizure triggers identified by owners were

209 reported using an open free-text box, which were then read by the investigator (SLF) and

210 categorized into the following: stress, food, excitement, exercise, flea/worm products, hot

211 temperatures, cleaning products, fireworks, storms, change in routine, loud noises, rosemary,

212 salt, hormones, air fresheners/scents, unwell, change in environment, raised voices, protein,

213 light, vaccinations, veterinary visits, television, rawhide, cold temperatures, tiredness, seizure

214 due to sleep, lack of sleep, full moon, anticipation of food and changes in atmospheric

215 pressure. Individual seizure triggers identified above were the further classified into the

216 following broad themes: catamenial changes, environmental changes, specific foods,

217 preventative healthcare, negative arousal, positive arousal, household products and

218 sleep/energy changes. Environmental changes included changes in light, television, storms,

219 pressure changes, storms, hot and cold climates. Negative arousal included stress, fireworks,

220 change in routine, loud noises, raised voices, illness and veterinary visits. Positive arousal

221 included excitement, exercise and anticipation of food.

222

223 **Statistical analysis**

224

225 Statistical analyses were performed in SPSS Statistics v 23 (SPSS, Inc., Chicago), with data

226 initially cleaned in Microsoft Excel. Chi squared tests were used to compare common

227 prodromal changes and seizure triggers with time scale owners felt they could predict seizure

228 activity within. Results were considered significant if $p < 0.05$. Data are presented as mean ±

229 standard deviation (SD), or median (25th-75th quartile) depending upon the distribution of

230 variables, which was assessed visually using histograms.

231

232 Questions in the survey were not mandatory and thus not all owners completed 100% of

233 questions asked. Owners with incomplete responses were not removed from the dataset to

234 maximise sample size; however, due to the potential for variation in baseline population

235 across the questions reported, the n is stated along with any quoted percentages throughout

236 the results.

237

238 **Results**

239

240 In total,363 owners participated in the online questionnaire; however, n=121 were excluded

241 for not completing the essential sections of the study, n=7 were excluded as they were

242 duplicates, and n=6 as the dogs had structural rather than idiopathic epilepsy. All dogs

243 included in the final analyses (n= 229) met Tier I idiopathic epilepsy diagnosis criteria (15).

244 Data on patient and disease characteristics will now be described (sections A-D).

245

246 **Section A: Owner Demographics**

247

248 The majority of owners who filled out the survey were female (n=200, 87.3%) and were in

249 the age category of 46-60 (N=90, 39.3%). The top three countries owners resided in were the

250 United States of America (n=94, 41%), United Kingdom (n=82, 35.8%) and Australia (n=13,

251 5.7%). The remaining responses (n=40, 17.5%) came from owners in 13 different counties.

252

253 **Section B: Canine Demographics**

254

255 A total of n=160 (69.9%) pure bred dogs and n=69 (30.1%) cross-bred dogs were included in

256 the sample. In total 57 dog breeds (n=229) were represented in the sample, the top three most

common being the Border Collie (n=28, 12.2%), Siberian Husky (n=12, 5.2%), German

Shepherd (n=8, 3.5%) and Golden Retriever (n=8, 3.5%). The mean age of dogs in the

sample was 67.0 months ± 31.9 and the mean weight was 25.3 kg ± 13.3. The majority of

patients were male neutered (n=124, 54.1%), followed by female neutered (n=64, 27.9%),

male entire (n=32, 14%) and female entire (n=9, 3.9%).

Section C: Epilepsy Phenotype

All dogs included in analyses met Tier I IVETF criteria (n=229), and of these cases, 34 dogs

met criteria for Tier II diagnosis of (14.8%). A total of 48 dogs were reported to have

experienced a period of status epilepticus (21%) and 189 dogs were reported to have

experienced a cluster seizure (82.5%). The median estimated number of seizures their dog

had experienced to date was 25 (12- 60), with the median number of seizures in the last three

months being 4 (2 - 8.25). The majority of seizures reported by owners tended to last up to 2

minutes (n=62, 27.1%) and were most commonly primary convulsive generalised seizures

(n=158, 69%).

Section D: Anti-Epileptic Drug Management

Of the dogs in the study, 206 of the 229 were reported to be treated with AEDs, with 134

(65%) dogs treated with more than one AED (polytherapy). The top three AEDs most

commonly used were phenobarbitone (n=163, 79.1%), levetiracetam (n=86, 41.7%) and

potassium bromide (n=84, 40.8%). Other medications reported by owners included imepitoin

(13.6%), zonisamide (20.9%), gabapentin (7.8%), chlorazepate (2.9%) and tiagabine (0.5%).

282   The following sections will describe owner perceived ability to predict forthcoming seizures

283   (section E), other dogs within the household's potential for seizure detection (section F),

284   prodromal signs owners reported from a list of those identified in the human literature that

285   relate to dogs (section G) and owner-reported seizure triggers reported in a free-text based,

286   unprompted manner (section H).

287

288   **Section E: Owner perceived seizure prediction**

289

290   Over half (n=136/228, 59.6%) of owners reported that they believed they were able to predict

291   an upcoming seizure. Of those owners who reported they could predict upcoming seizure

292   activity, the mean % of seizures they thought they had successfully predicted in their own

293   dog was 43.7% ± 28.5.

294

295   A variety of observable changes and seizure triggers were reported by owners who believed

296   they could predict upcoming seizures (n=134) that they used to predict seizure activity

297   (henceforth referred to as 'seizure-predictors'). The most frequently reported seizure-

298   predictors (generated by owners with no prompting) are shown in Figure 1. Of the 33

299   categories of seizure-predictors, observable behavioural changes were the most commonly

300   reported (28 out of 33 categories of seizure predictor, 84.8%), compared to seizure triggers,

301   with just 5 out of 33 categories of seizure predictor (15.2%). The top three reported

302   observable behavioural changes used to predict seizures were clinginess (n=34/134, 25.4%),

303   restlessness (n=31/134, 23.1%) and behavioural signs of fear (n=26/134, 19.4%).   The top

304   three unprompted seizure triggers owners used to predict seizures were changes in routine

305   (n=4/134, 3%), stress (n=2/134, 1.5%) and overexertion (n=2/134, 1.5%).

306   **(Figure One Here)**

307

Around one quarter of owners reported that they could only predict a seizure within 5

minutes before it started (n=38/134, 28.4%) (Figure 2); however, the majority of owners

(n=96/134, 71.6%) felt able to predict an impending seizure over five minutes before it

started, most commonly within 5-30 minutes (n=23/134, 17.2%). Overall, 45.5% of owners

(n=61/134)who believed they could predict seizures felt they could predict an impending

seizure over thirty minutes or more before the seizure commenced, which may represent

prodromal changes rather than focal seizure activity.

(Figure Two Here)

Table one compares the top three owner reported seizure-predictors (all of which may be

observable behavioural changes *or* seizures triggers) alongside timeframe of owner-reported

seizure prediction. Clinginess (26.5%) and fear (42.3%) were most commonly reported as

seizure predictors in owners who believed they could only detect a seizure occurring within

five minutes of it starting. In contrast, restlessness was the most commonly reported sign in

owners who believed they could detect a seizure occurring over 1 hour to 12 hours before it

started. There was no association between any of the three prodromal signs listed in table one

and the timeframe in which an owner felt could predict a seizure was going to occur (p>0.05).

332   Table 1: Timeframe of owner seizure prediction for the three most common owner-reported

333   seizure predictors

Seizure Predictor	Timeframe of owner seizure prediction							
	% cases	Less than five minutes	Five minutes to 30 minutes	30 minutes to one hour	One hour to 12 hours	12 hours to 24 hours	24 to 48 hours	48 hours to one week
Increased clinginess	25.4 (n=34)	26.5 (n=9)	11.8 (n=4)	8.8 (n=3)	23.5 (n=8)	23.5 (n=8)	5.9 (n=2)	0.0 (n=0)
Increased restlessness	19.4 (n=31)	29.0 (n=9)	6.5 (n=2)	6.5 (n=2)	32.3 (n=10)	16.1 (n=5)	6.5 (n=2)	3.1 (n=1)
Increased fearfulness	23.1 (n=26)	42.3 (n=11)	19.2 (n=5)	15.4 (n=4)	11.5 (n=3)	7.7 (n=2)	3.8 (n=1)	0.0 (n=0)

334

335   Table two compares the same data in a binomial manner: seizure prediction in thirty minutes

336   or less before the start of a seizure, or over thirty minutes before the start of a seizure.

337   Table 2: Comparison of under of over thirty minute timeframe of owner seizure prediction for

338   the three most common owner-reported seizure predictors

Seizure predictor	Timeframe of owner seizure prediction	
	30 minutes or less	Over 30 minutes
Increased clinginess	38.2% (n=13)	61.8% (n=21)
Increased restlessness	35.5% (n=11)	64.5% (n=20)
Increased fearfulness	61.5% (n=16)	38.0% (n=10)

339

340 Signs of restlessness (n=20, 64.5%) and clinginess (n= 21, 61.8%) were most commonly

341 reported in owners who could predict a seizure over 30 minutes before it started, whereas

342 increased fearfulness was more common in owners who could predict a seizure 30 minutes or

343 less before it started (n=16, 61.5%).

344

345 **Section F: Seizure detection dogs**

346

347 Nearly two thirds of owners (n=141/222, 63.5%) stated that they had more than one dog in

348 their household. Of these 141 owners, 36 (25.5%) stated that they believed their non-

349 epileptic 'companion dog' can detect seizure-predicting activity in their epileptic dog, or

350 change behaviour themselves prior to their epileptic dog's seizure. The top three reported

351 signs they had identified in their non-epileptic dog prior to a seizure included increased

352 clinginess (n=11/36, 30.5%), change in normal frequency of vocalisation (n=9/36, 25.0%)

353 and increased sniffing around their epileptic dog (n=6/36, 16.6%).

354

355 **Section G: Owner identification of prodromal signs**

356

357 When owners were asked to report if they thought their dog exhibited changes in behaviour

358 before seizure activity occurred, 64.9% reported that their dog did. The top three behaviour

359 changes reported spontaneously (without prompts) included restlessness (29.2%), clinginess

360 (25.0%) and fear (12.0%) respectively. When given a list of prodromal behaviours reported

361 in the human literature (Figure 3), 72.3% of owners (n=154/213) reported at least one

362 behavioural change before a seizure occurs. The top three most commonly reported

363 prodromal changes from this list were clinginess (n=70/154, 45.5%), excessive energy

364 (n=40/154, 26.0%) and unsettled sleep (n=39/154, 25.3%).

17

365   **(Figure Three Here)**

366

367   **Section H: Seizure Triggers**

368

369   Of 216 owners, nearly half (n=93/216, 43.1%) of owners reported that they believed certain

370   stimuli can trigger their epileptic dog to seizure, compared to 35.2% (n=76/216) of owners

371   who were unsure if certain stimuli can trigger their epileptic dog to seizure and 21.8%

372   (n=47/216) who believed no stimuli triggered their epileptic dog to seizure. Of the 93 owners

373   that reported seizure triggers, the most reported trigger was stress (n=36/93, 38.7%) (Figure

374   4). Other reported triggers include foods, flea/worm products, exercise, environmental

375   changes, specific stress triggers e.g. storms, fireworks, change in routine etc.

376   **(Figure Four Here)**

377

378   After categorization into broad themes (Figure 5), negative arousal e.g. stress (39.1%) was

379   reported as the most common trigger of seizure activity, followed by environmental changes

380   (16.1%), food (15.5%), positive arousal e.g. excitement (13.0%), household products (6.8%),

381   preventative healthcare (6.8%), sleep/energy changes (1.9%) and catamenial changes (0.6%)

382   respectively.

383

384   **(Figure Five Here)**

385

386   **Discussion**

387

388   This study has for the first time quantitatively investigated owner-perceived seizure

389   prediction abilities and identified potential prodromal changes in dogs with idiopathic

390   epilepsy. In addition, it has added to the growing literature on seizures triggers in this

391   population. The results indicate that just under two thirds of owners believe that they are able

392   to predict forthcoming seizure activity in their own dog. For those owners whose perceived

393   prediction abilities are based on observation of pre-seizure behaviour changes, it is possible

394   that these owners are detecting focal seizure activity rather than true prodromal behaviour;

395   however, this is impossible to differentiate without ambulatory EEG. Detection and

396   classification of focal seizure activity is challenging when observing seizures, and there is

397   low clinical agreement between veterinary specialists and first opinion vets when observing

398   paroxysmal events that may be focal seizures (30).   Despite this potential source of

399   confusion, many owners felt they were able to predict forthcoming seizure activity half an

400   hour or longer before seizure activity began, and thus the behavioural signs they are

401   observing and using to predict seizure activity are less likely to be focal seizure activity due

402   to the relatively enduring nature of prodromal signs identified e.g. restlessness (15). The

403   majority of human studies investigating prodromes use thirty minutes or more as a defining

404   feature of this phenomenon (17, 31-33). Compared with human epilepsy studies investigating

405   pre-seizure changes, the number of people who are able to predict their own forthcoming

406   seizures using prodromal signs ranges from 2% (31) to 87.1% (21). Although both of these

407   studies had a high number of participants, their differences in predictive ability may stem

408   from variations in their methodology; varying from a structured interview versus a

409   questionnaire with predefined symptoms respectively. In the current study, the percentage of

410   owners that could predict their dog's forthcoming seizures when unprompted (59.6%) was

411   similar to when prompted with specific signs (64.9%) increasing the accuracy and reliability

412   of these results.

413

Owners were more able to recognise and use observational changes in their dog to predict seizures than recognising seizure triggers as predictors of seizure activity. The top three reported behavioural changes (that may represent the prodrome) when owners were unprompted were restlessness, clinginess and fear, and the top three reported when prompted with a list were clinginess, excessive energy and unsettled sleep. All of these clinical signs could be related to anxiety and stress induced prior to a seizure occurring, which may change the dog's emotional state. In a review examining prodromal activity in human epilepsy patients, anxiety and irritability were found to be in the top four of commonly reported pre-seizure behaviours (14). Recent evidence has shown that the presence of epilepsy in canine patients increases the likelihood of behavioural co-morbidities (34). These include disorders of affective (emotional) state including fear and anxiety (35). Fear and anxiety may be heightened during the prodromal phase, associated with an increase in brain neuronal activity and pre-ictal spikes noted which have been evident with placement of intracranial electroencephalography in humans (36). This increase in pre-seizure spikes prior to a seizure has been demonstrated in canine patients with intracranial EEG, in research using the dog as a model of human epilepsy (12), but whether concurrent behavioural changes occur with these spikes has not been explored to date.

More owners identified clinginess and restlessness in a timeframe of 30 minutes or more before a seizure to enable seizure prediction whereas, more owners identified signs of fear in a timeframe of less than 30 minutes before a seizure to enable seizure prediction. An explanation to the early identified sign of fear may be that owners are observing a focal epileptic seizure that then evolves into a generalised seizure rather than a true prodromal change. It is well documented in the literature that a large proportion of human epileptic patients fail to identify focal seizures (37-39). In addition, in a study of veterinary neurology

439 specialists and non-specialists that reviewed videos of paroxysmal activity and reported if a

440 seizure occurred or not, focal seizures were the least agreed upon seizure type, highlighting

441 the complexity of discriminating seizure activity from non-seizure activity (30). In a previous

442 study. 80% of dogs with focal epilepsy were described as exhibiting behavioural signs

443 include signs of anxiety (e.g. trying to escape, shaking, whining) which without EEG

444 confirmation could be epileptic or non-epileptic in origin (40).

445

446 Sleep deprivation and reduced sleep quality in human patients is one of the most frequently

447 reported seizure precipitants and has been found to be a behaviour change observed

448 preceding seizure activity (41). As such, changes in sleep may be both a seizure trigger and

449 also a prodromal change; however, the relationship between sleep and epilepsy has yet to be

450 explored in dogs. Total sleep deprivation i.e. sleep deprivation for 24hrs or longer can lead to

451 seizures in people with epilepsy (42). Partial sleep deprivation as a trigger for seizure activity

452 still remains unclear with a significant amount of human epileptic patients reporting this as a

453 trigger (43) however, EEG-based studies have found no relationship between partial sleep

454 deprivation and seizure occurrence (44). A recent human epileptic study that investigated

455 partial sleep deprivation over a 24 and 72 hour period using self-reported diaries showed no

456 association with small amounts of sleep loss and seizure activity (45). Measurements of sleep

457 quality of dogs using non-invasive polysomnography has been investigated and compared to

458 human EEG recordings (46). In that study, dogs had electrodes attached for around three

459 hours, and results demonstrated comparable results to both human and other mammalian

460 sleep studies, where an increase in sleep disturbance is associated with increased daily

461 activity (46).

462

463 It is likely that some seizure triggers in dogs and humans interact with one another. Reduced

464 sleep quality may be a result of daytime stress, which was found to be the most common

465 seizure trigger reported by owners of their dogs with epilepsy in the current study. Human

466 epilepsy patients have reported stress as a seizure trigger for many years (21, 26, 27, 41, 43,

467 47-54) with many mouse models showing an increase in seizure frequency when exposed to

468 environmental stressors (55). However most experimental rodent models of epilepsy are not

469 naturally occurring, therefore having their own limitations (56). A limitation of this

470 questionnaire based study is owner's definition of the term 'stress', which is likely to vary

471 between owners. Neuroscientists currently define stress as "*conditions where an*

472 *environmental demand exceeds the natural regulatory capacity of an organism, in particular*

473 *situations that include unpredictability and uncontrollability*" (57). Stress may have a key

474 role in the precipitation of seizure activity that owners seem to be able to identify

475 spontaneously. Stressful events appear to be common precipitants of seizures in dogs with

476 'reflex epilepsy', where seizure activity is triggered by exposure to specific locations or

477 situations. These were found to include visits to a veterinary clinic (35/43 dogs), grooming

478 facility (24/43 dogs), or boarding facility (13/43 dogs) (25). Stress was found to be the most

479 common seizure precipitant in a recent study using a pre-defined list to explore seizure

480 precipitants by owners of dogs with idiopathic epilepsy (stress=6/29 owners, 21%). In

481 addition, that study demonstrated that some potentially stressful scenarios, for example;

482 having visitors at home (11/37, 30%), a change in the life situation (10/37, 27%), and a

483 change in the daily routine (9/37, 24%) were considered by owners to be seizure precipitants

484 (23). Stress has been a target for epilepsy management in several human studies (21, 58, 59);

485 however, this avenue of epilepsy management is yet to be explored in our canine patients but

486 may be a tool for improving seizure control.

487

488 A novel finding in this study was the frequency with which owners believe 'companion dogs'

489 to their epileptic dogs can aid seizure prediction. Seizure-alert dogs are used for some human

490 epilepsy patients and are reported to detect impending seizures in people, by being alerted to

491 subtle human behavioural changes prior to a seizure occurring (60-62). Seizure-alert dogs

492 have been reported to detect a range of seizure types including atonic, focal and generalised

493 seizures (60, 63, 64). To date there has not been any investigations of with the use or efficacy

494 of seizure-alert dogs for dogs with epilepsy. In people with epilepsy, a study reported a

495 sensitivity estimate of 80% and specificity of 100% (61). If dogs are also able to be trained to

496 detect seizures in other dogs, this could be a potential avenue for seizure prediction in the

497 multi-dog household. A key disadvantage of using an assistance dog as a monitoring tool in

498 general is that they are unable to monitor during their own sleep, and thus large sections of

499 the day may be missed, and the carer of the affected person or animal may also need to be

500 present to detect changes. However, this novel avenue may allow for owners to exploit

501 existing dog-dog relationships within their household and improve their abilities to predict

502 seizures.

503

504 This study has highlighted a variety of novel findings that may hold promise for non-invasive

505 seizure detection in the future; however, further prospective research is needed in this area to

506 validate the phenomenon of prodromal changes in dogs without reliance on owner reports

507 e.g. non-invasive technologies to detect behaviour and/or physiological changes. In addition,

508 owner seizure prediction abilities could be tested in a prospective manner using electronic

509 diaries to verify the accuracy of their prediction abilities over a length of time.

510

511 **Conclusion**

512

513 This study has for the first time documented that a high proportion of owners perceive that

514 they can predict seizure activity in their dog, using a variety of potential prodromal changes

515 and seizure triggers to detect upcoming activity. As these data are owner reported, further

516 objective studies are needed to confirm these results in a prospective manner; however, if

517 detection of prodromal changes or robust identification of triggers is successful, this may

518 open a window of opportunity for drug intervention in this period. This could allow for new

519 avenues of 'smart' anti-epileptic drug management i.e. individualised drug management,

520 exploiting this timeframe for administration of drugs in a pulsatile manner to attempt to

521 thwart impending seizure activity.

522

523 **Acknowledgements**

524

530

531 **References**

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Figure and Tables Legends

Figure one: Owner reported seizure predictors of forthcoming seizure activity (with no prompting) including both observable behavioural changes (28 categories) and seizure triggers (5 categories) (from n=136 owners, 59.6% of the total population sampled for this question = 228)

Figure 2: Owner perception of the timeframe they believe they can successfully detect forthcoming seizure activity within. N.B. The emboldened lines delineate changes under or over 30 minutes prior to a seizure, which may separate potential focal seizure activity from longer-term prodromal changes

Figure 3: Prodromal behaviours reported by owners when given a list of those previously reported in the human literature (from n=154 owners reporting prodromal changes, 72.3% of the total population sampled for this question; n = 213).

Figure 4: Unprompted owner reported seizure triggers in dogs with idiopathic epilepsy (n=93 owners)

Figure 5: Using data from Figure 4, owner reported seizure triggers in dogs with idiopathic epilepsy categorized into broad themes (from n=93 owners reporting triggers in their dog)

Table 1: Timeframe of owner seizure prediction for the three most common owner-reported seizure predictors

707   Table 2: Comparison of under of over thirty minute timeframe of owner seizure prediction for

708   the three most common owner-reported seizure predictors