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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.

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

Abbreviations

AEDs – Anti-epileptic drugs

EEG – Electroencephalogram

IE – Idiopathic Epilepsy

IVETF – International veterinary epilepsy task force

QoL – Quality of Life

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.

Non-invasive seizure prediction methods in dogs may rely on identification of changes in a dog's behaviour (e.g. activity levels or patterns of behaviour) prior to a seizure that can be visually detected by their owner, or in the future, detected using technologies to automatically measure behaviour change (e.g. inertia measurement units). Furthermore, the identification of seizure precipitants ('triggers') that reliably precede seizures could allow time for owners to take preventative action (e.g. pulsatile dosing of add-on AEDs), or trigger avoidance programmes.

The international veterinary epilepsy task force (IVETF) consensus defines prodromes as "*a long-term (hours to days) change in disposition and indicator of forthcoming seizure*s" (13). Prodromes are defined by being relatively long lasting in nature compared with focal seizures, although both prodromes and focal seizures may present with similar signs e.g. facial twitching, restlessness, anxiety (14, 15). Focal seizures can occur alone or before a generalised seizure (focal with secondary generalisation) and are often very short in duration (lasting seconds to minutes) (13). In comparison, prodromal changes may last for hours to days before a seizure. Reported occurrence rates of prodromes in people with epilepsy are between 6.9% - 47%, with most studies reporting changes at least 30 minutes before the seizure itself occurs, to differentiate the seizure itself and the prodrome (16). Many people report that their prodromes are characterised by behavioural changes including restlessness, irritability, anger, mood changes, cognitive disturbances and physiological changes such as increased urination, increased or decreased appetite (16, 17). Owners of epileptic dogs have previously reported pre-seizure behaviour changes such as pacing, anxiety and attention seeking, but these changes are yet to be explored in depth (18).

Seizure triggers (precipitating factors) can be defined as "*those circumstances that precede the onset of an epileptic attack and are considered by both patient and neurologist to be a possible explanation for why the seizure happened when it did, and not earlier or later*" (19). Recognition of seizure-precipitating factors may support improved seizure control by either their active avoidance, or taking mitigating action post-exposure. One study in human epilepsy found that 62% of epilepsy patients can reliably identify at least one specific seizure trigger (20). The study found that excitation and stress were the most common reported seizure-precipitants. Furthermore, excitation, sleep deprivation, fever, watching television and head trauma had a strong association with impending seizures in generalized epilepsy (20). Another questionnaire-based study found that at least one seizure trigger was reported by 89.8% of people with epilepsy and that 85.5% of their carers could also identify one trigger (21). In this study, the most common triggers were tiredness, stress and sleep deprivation (21). In addition, other studies have identified environmental changes as seizure precipitants including changes in environmental temperature and barometric pressure (22). To date, there are few published studies of potential seizure triggers in dogs with idiopathic epilepsy. Most recently, a study of fifty dogs with idiopathic epilepsy found that almost three quarters of dogs (n=37/50) had at least one 'seizure-precipitating' factor (23). Prior to this study, only two studies had identified seizure triggers in dogs; estrus in entire female dogs with idiopathic epilepsy (24) and potentially stressful events including visits to a veterinary clinic, grooming or boarding facility in dogs with reflex epilepsy (25).

The aim of this study was to investigate owner recognition of potential prodromal changes prior to seizure activity, potential factors that trigger their epileptic dog's seizures, and their perceived ability to predict their own dog's seizures in a population of dogs diagnosed with idiopathic epilepsy.

Methods

Study design and recruitment

A cross sectional online survey was developed and conducted on an online survey platform (©SurveyMonkey; www.surveymonkey.co.uk) between 9th January and 21st January 2018 to explore seizure triggers and prodromal changes in dogs with idiopathic epilepsy (IE). The questionnaire was composed of seven sections; about the owner, general information regarding the owner's epileptic dog, veterinary diagnosis and classification of their dog's epilepsy, clinical presentation of their dog's epilepsy, epilepsy management, seizure prediction and seizure triggers. The questionnaire was promoted via the Royal Veterinary College Canine Epilepsy Research social network page and sharing via online support groups for owners of epileptic dogs. The study was approved by the local ethics committee (RVC Animal Welfare and Ethics Committee; Ref: URN SR2017-1234).

Inclusion and Exclusion Criteria

The study aimed to recruit dogs affected by IE. Dogs were screened for IE by consecutive diagnostic questions, beginning with whether they had ever had a seizure (yes/no). Those owners answering no were categorised into the control group. For those answering yes, three further screening questions were posed: (i) whether their dog had 2 or more seizures that were at least 24 hours apart; (ii) whether their dog's first seizure occurred between the ages of 6 months and 6 years; and (iii) whether their vet had carried out blood and urine tests on their dog and found no identifiable cause for their dog's seizures. If the owner answered yes to all

three questions, the dog was considered to meet the tier I diagnostic criteria for the International Veterinary Epilepsy Task Force (IVETF) (13) and thus was classified as affected. Dogs who had experienced seizure activity, but whose owners only responded 'yes' to one or two of the above screening questions, were excluded from the study. All dogs recruited were alive at the time of the questionnaire.

Questionnaire data

The questionnaire was divided into seven sections. In section A, (Owner Demographics), Owners were asked to report their age, gender and country of residence. In section B (Canine Demographics), owners were asked to report their dog's breed, age, sex, and neuter status. In section C (epilepsy phenotype) owners were asked questions on the diagnosis of their dog's epilepsy (e.g. whether a vet diagnosed their dog's epilepsy, what clinical tests were performed, how old they were at their first seizure and their final diagnosis i.e. structural or idiopathic epilepsy, and whether they primarily experienced focal or generalised seizures). For clarity, generalised seizures were restricted to convulsive subtypes (tonic, clonic, tonic-clonic) and absence or myoclonic seizures were not addressed. In addition, owners were asked the average length their dog's seizure last for and how many seizures their dog had experienced to date. In section D (anti-epileptic drug management) owners were asked to report their dog's current anti-epileptic medications.

In the sections of particular interest to the study aims (seizure prediction, prodromal changes and triggers) owners were initially asked an open ended question of whether they could predict seizures, identify prodromal changes or seizure triggers, and if so, the reasoning behind it in a free-text format, giving them the opportunity to report without bias.

Subsequently, this was followed by multiple choice lists of known prodromal changes or triggers from the human epilepsy literature (26-29). To reduce bias introduced by exposure to these lists, the respondent was unable to return to the previous question once completed to avoid changing their answers.

In section E (Owner-perceived seizure prediction), owners were asked whether they could predict their dog's seizure and if so, to explain why they believed they could and in what timeframe. These free-text data were then categorized into four themes, which covered thirty-three categories, with examples given below:

(1) Behavioural changes in their dog (e.g. increases in clinginess, increased sleep, fear, attention-seeking, restlessness, eye movements, increased vocalisation, becoming withdrawn, reduced attention, vomiting, decreased appetite, undefined behavioural changes (i.e. owner noticed a change in behaviour but couldn't definitively define the behaviour change), staring, facial and ear twitching, lip licking, reduced sleep, reduced activity, increased activity, hyper salivation, pruritus, increased sniffing, polyphagia, lethargy)

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

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

(4) The presence of seizure triggers (e.g. stress, overexertion, cold temperatures, changes in routine and full moon).

A further category was created for owners who could predict seizure activity but were unsure as to why they felt they could. Finally, owners were asked the longest timeframe they could predict forthcoming seizure activity.

In section F (Seizure detection dogs), owners were asked whether they had any other dogs in the same household as their epileptic dog and if so, whether they could predict upcoming seizure activity based on the behaviour of their non-epileptic dog ('companion dog'). They were then asked to explain why they felt their companion dog could help predict seizure activity in an open text box, responses from which were read by the investigator (SLF) and categorized into the following: increased vocalisation, running/pacing, licking their epileptic dog, more clingy to their epileptic dog, aggressive behaviour towards their epileptic dog, increased sniffing, withdrawn, pawing at their owner, stress, signs of fear/anxiety and a change in behaviour but unable to identify.

In section G (Owner identification of prodromal signs), potential prodromal changes identified by owners were reported using an open free-text box, which were then read by the investigator (SLF) and categorized into the following: increase clinginess, excessive energy, lack of energy, less responsive, more responsive, clumsy, ataxia, increased lameness, reluctance to walk, excessive panting, withdrawn, quiet, increased sleep, unsettled sleep, decreased sleep, increased lip licking, tense, increased vocalisation, decreased vocalisation, whimpering, groaning, crying, screaming, change in quality/sound of vocalisation, hiding, increased alertness, excessive self-grooming, shivering, vomiting, polyphagia, decreased appetite, increased stiffness, hunched, diarrhoea, defecating in abnormal places, decreased faecal output, increased faecal output, periuria and decreased frequency of urination. Following this, owners were given a list of known prodromal changes derived from the human literature and were asked to identify whether any of these changes had previously been shown by their dog prior to seizure activity.

Finally, in section H (seizure triggers), unprompted seizure triggers identified by owners were reported using an open free-text box, which were then read by the investigator (SLF) and categorized into the following: stress, food, excitement, exercise, flea/worm products, hot temperatures, cleaning products, fireworks, storms, change in routine, loud noises, rosemary, salt, hormones, air fresheners/scents, unwell, change in environment, raised voices, protein, light, vaccinations, veterinary visits, television, rawhide, cold temperatures, tiredness, seizure due to sleep, lack of sleep, full moon, anticipation of food and changes in atmospheric pressure. Individual seizure triggers identified above were the further classified into the following broad themes: catamenial changes, environmental changes, specific foods, preventative healthcare, negative arousal, positive arousal, household products and sleep/energy changes. Environmental changes included changes in light, television, storms, pressure changes, storms, hot and cold climates. Negative arousal included stress, fireworks, change in routine, loud noises, raised voices, illness and veterinary visits. Positive arousal included excitement, exercise and anticipation of food.

Statistical analysis

Statistical analyses were performed in SPSS Statistics v 23 (SPSS, Inc., Chicago), with data initially cleaned in Microsoft Excel. Chi squared tests were used to compare common prodromal changes and seizure triggers with time scale owners felt they could predict seizure activity within. Results were considered significant if $p < 0.05$. Data are presented as mean ± standard deviation (SD), or median (25th-75th quartile) depending upon the distribution of variables, which was assessed visually using histograms.

Questions in the survey were not mandatory and thus not all owners completed 100% of questions asked. Owners with incomplete responses were not removed from the dataset to maximise sample size; however, due to the potential for variation in baseline population across the questions reported, the n is stated along with any quoted percentages throughout the results.

Results

In total,363 owners participated in the online questionnaire; however, n=121 were excluded for not completing the essential sections of the study, n=7 were excluded as they were duplicates, and n=6 as the dogs had structural rather than idiopathic epilepsy. All dogs included in the final analyses (n= 229) met Tier I idiopathic epilepsy diagnosis criteria (15). Data on patient and disease characteristics will now be described (sections A-D).

Section A: Owner Demographics

The majority of owners who filled out the survey were female (n=200, 87.3%) and were in the age category of 46-60 (N=90, 39.3%). The top three countries owners resided in were the United States of America (n=94, 41%), United Kingdom (n=82, 35.8%) and Australia (n=13, 5.7%). The remaining responses (n=40, 17.5%) came from owners in 13 different counties.

Section B: Canine Demographics

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

The following sections will describe owner perceived ability to predict forthcoming seizures (section E), other dogs within the household's potential for seizure detection (section F), prodromal signs owners reported from a list of those identified in the human literature that relate to dogs (section G) and owner-reported seizure triggers reported in a free-text based, unprompted manner (section H).

Section E: Owner perceived seizure prediction

Over half (n=136/228, 59.6%) of owners reported that they believed they were able to predict an upcoming seizure. Of those owners who reported they could predict upcoming seizure activity, the mean % of seizures they thought they had successfully predicted in their own dog was 43.7% ± 28.5.

A variety of observable changes and seizure triggers were reported by owners who believed they could predict upcoming seizures (n=134) that they used to predict seizure activity (henceforth referred to as 'seizure-predictors'). The most frequently reported seizure-predictors (generated by owners with no prompting) are shown in Figure 1. Of the 33 categories of seizure-predictors, observable behavioural changes were the most commonly reported (28 out of 33 categories of seizure predictor, 84.8%), compared to seizure triggers, with just 5 out of 33 categories of seizure predictor (15.2%). The top three reported observable behavioural changes used to predict seizures were clinginess (n=34/134, 25.4%), restlessness (n=31/134, 23.1%) and behavioural signs of fear (n=26/134, 19.4%). The top three unprompted seizure triggers owners used to predict seizures were changes in routine (n=4/134, 3%), stress (n=2/134, 1.5%) and overexertion (n=2/134, 1.5%).

(Figure One Here)

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 ($p>0.05$).

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

Table two compares the same data in a binomial manner: seizure prediction in thirty minutes or less before the start of a seizure, or over thirty minutes before the start of a seizure.

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

Signs of restlessness (n=20, 64.5%) and clinginess (n= 21, 61.8%) were most commonly reported in owners who could predict a seizure over 30 minutes before it started, whereas increased fearfulness was more common in owners who could predict a seizure 30 minutes or less before it started (n=16, 61.5%).

Section F: Seizure detection dogs

Nearly two thirds of owners (n=141/222, 63.5%) stated that they had more than one dog in their household. Of these 141 owners, 36 (25.5%) stated that they believed their non-epileptic 'companion dog' can detect seizure-predicting activity in their epileptic dog, or change behaviour themselves prior to their epileptic dog's seizure. The top three reported signs they had identified in their non-epileptic dog prior to a seizure included increased clinginess (n=11/36, 30.5%), change in normal frequency of vocalisation (n=9/36, 25.0%) and increased sniffing around their epileptic dog (n=6/36, 16.6%).

Section G: Owner identification of prodromal signs

When owners were asked to report if they thought their dog exhibited changes in behaviour before seizure activity occurred, 64.9% reported that their dog did. The top three behaviour changes reported spontaneously (without prompts) included restlessness (29.2%), clinginess (25.0%) and fear (12.0%) respectively. When given a list of prodromal behaviours reported in the human literature (Figure 3), 72.3%of owners (n=154/213) reported at least one behavioural change before a seizure occurs. The top three most commonly reported prodromal changes from this list were clinginess (n=70/154, 45.5%), excessive energy (n=40/154, 26.0%) and unsettled sleep (n=39/154, 25.3%).

(Figure Three Here)

Section H: Seizure Triggers

Of 216 owners, nearly half (n=93/216, 43.1%) of owners reported that they believed certain stimuli can trigger their epileptic dog to seizure, compared to 35.2% (n=76/216) of owners who were unsure if certain stimuli can trigger their epileptic dog to seizure and 21.8% (n=47/216) who believed no stimuli triggered their epileptic dog to seizure. Of the 93 owners that reported seizure triggers, the most reported trigger was stress (n=36/93, 38.7%) (Figure 4). Other reported triggers include foods, flea/worm products, exercise, environmental changes, specific stress triggers e.g. storms, fireworks, change in routine etc.

(Figure Four Here)

After categorization into broad themes (Figure 5), negative arousal e.g. stress (39.1%) was reported as the most common trigger of seizure activity, followed by environmental changes (16.1%), food (15.5%), positive arousal e.g. excitement (13.0%), household products (6.8%), preventative healthcare (6.8%), sleep/energy changes (1.9%) and catamenial changes (0.6%) respectively.

(Figure Five Here)

Discussion

This study has for the first time quantitatively investigated owner-perceived seizure prediction abilities and identified potential prodromal changes in dogs with idiopathic

epilepsy. In addition, it has added to the growing literature on seizures triggers in this population. The results indicate that just under two thirds of owners believe that they are able to predict forthcoming seizure activity in their own dog. For those owners whose perceived prediction abilities are based on observation of pre-seizure behaviour changes, it is possible that these owners are detecting focal seizure activity rather than true prodromal behaviour; however, this is impossible to differentiate without ambulatory EEG. Detection and classification of focal seizure activity is challenging when observing seizures, and there is low clinical agreement between veterinary specialists and first opinion vets when observing paroxysmal events that may be focal seizures (30). Despite this potential source of confusion, many owners felt they were able to predict forthcoming seizure activity half an hour or longer before seizure activity began, and thus the behavioural signs they are observing and using to predict seizure activity are less likely to be focal seizure activity due to the relatively enduring nature of prodromal signs identified e.g. restlessness (15). The majority of human studies investigating prodromes use thirty minutes or more as a defining feature of this phenomenon (17, 31-33). Compared with human epilepsy studies investigating pre-seizure changes, the number of people who are able to predict their own forthcoming seizures using prodromal signs ranges from 2% (31) to 87.1% (21). Although both of these studies had a high number of participants, their differences in predictive ability may stem from variations in their methodology; varying from a structured interview versus a questionnaire with predefined symptoms respectively. In the current study, the percentage of owners that could predict their dog's forthcoming seizures when unprompted (59.6%) was similar to when prompted with specific signs (64.9%) increasing the accuracy and reliability of these results.

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

specialists and non-specialists that reviewed videos of paroxysmal activity and reported if a seizure occurred or not, focal seizures were the least agreed upon seizure type, highlighting the complexity of discriminating seizure activity from non-seizure activity (30). In a previous study. 80% of dogs with focal epilepsy were described as exhibiting behavioural signs include signs of anxiety (e.g. trying to escape, shaking, whining) which without EEG confirmation could be epileptic or non-epileptic in origin (40).

Sleep deprivation and reduced sleep quality in human patients is one of the most frequently reported seizure precipitants and has been found to be a behaviour change observed preceding seizure activity (41). As such, changes in sleep may be both a seizure trigger and also a prodromal change; however, the relationship between sleep and epilepsy has yet to be explored in dogs. Total sleep deprivation i.e. sleep deprivation for 24hrs or longer can lead to seizures in people with epilepsy (42). Partial sleep deprivation as a trigger for seizure activity still remains unclear with a significant amount of human epileptic patients reporting this as a trigger (43) however, EEG-based studies have found no relationship between partial sleep deprivation and seizure occurrence (44). A recent human epileptic study that investigated partial sleep deprivation over a 24 and 72 hour period using self-reported diaries showed no association with small amounts of sleep loss and seizure activity (45). Measurements of sleep quality of dogs using non-invasive polysomnography has been investigated and compared to human EEG recordings (46). In that study, dogs had electrodes attached for around three hours, and results demonstrated comparable results to both human and other mammalian sleep studies, where an increase in sleep disturbance is associated with increased daily activity (46).

It is likely that some seizure triggers in dogs and humans interact with one another. Reduced sleep quality may be a result of daytime stress, which was found to be the most common seizure trigger reported by owners of their dogs with epilepsy in the current study. Human epilepsy patients have reported stress as a seizure trigger for many years (21, 26, 27, 41, 43, 47-54) with many mouse models showing an increase in seizure frequency when exposed to environmental stressors (55). However most experimental rodent models of epilepsy are not naturally occurring, therefore having their own limitations (56). A limitation of this questionnaire based study is owner's definition of the term 'stress', which is likely to vary between owners. Neuroscientists currently define stress as "*conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability*" (57). Stress may have a key role in the precipitation of seizure activity that owners seem to be able to identify spontaneously. Stressful events appear to be common precipitants of seizures in dogs with 'reflex epilepsy', where seizure activity is triggered by exposure to specific locations or situations. These were found to include visits to a veterinary clinic (35/43 dogs), grooming facility (24/43 dogs), or boarding facility (13/43 dogs) (25). Stress was found to be the most common seizure precipitant in a recent study using a pre-defined list to explore seizure precipitants by owners of dogs with idiopathic epilepsy (stress=6/29 owners, 21%). In addition, that study demonstrated that some potentially stressful scenarios, for example; having visitors at home (11/37, 30%), a change in the life situation (10/37, 27%), and a change in the daily routine (9/37, 24%) were considered by owners to be seizure precipitants (23). Stress has been a target for epilepsy management in several human studies (21, 58, 59); however, this avenue of epilepsy management is yet to be explored in our canine patients but may be a tool for improving seizure control.

A novel finding in this study was the frequency with which owners believe 'companion dogs' to their epileptic dogs can aid seizure prediction. Seizure-alert dogs are used for some human epilepsy patients and are reported to detect impending seizures in people, by being alerted to subtle human behavioural changes prior to a seizure occurring (60-62). Seizure-alert dogs have been reported to detect a range of seizure types including atonic, focal and generalised seizures (60, 63, 64). To date there has not been any investigations of with the use or efficacy of seizure-alert dogs for dogs with epilepsy. In people with epilepsy, a study reported a sensitivity estimate of 80% and specificity of 100% (61). If dogs are also able to be trained to detect seizures in other dogs, this could be a potential avenue for seizure prediction in the multi-dog household. A key disadvantage of using an assistance dog as a monitoring tool in general is that they are unable to monitor during their own sleep, and thus large sections of the day may be missed, and the carer of the affected person or animal may also need to be present to detect changes. However, this novel avenue may allow for owners to exploit existing dog-dog relationships within their household and improve their abilities to predict seizures.

This study has highlighted a variety of novel findings that may hold promise for non-invasive seizure detection in the future; however, further prospective research is needed in this area to validate the phenomenon of prodromal changes in dogs without reliance on owner reports e.g. non-invasive technologies to detect behaviour and/or physiological changes. In addition, owner seizure prediction abilities could be tested in a prospective manner using electronic diaries to verify the accuracy of their prediction abilities over a length of time.

Conclusion

This study has for the first time documented that a high proportion of owners perceive that they can predict seizure activity in their dog, using a variety of potential prodromal changes and seizure triggers to detect upcoming activity. As these data are owner reported, further objective studies are needed to confirm these results in a prospective manner; however, if detection of prodromal changes or robust identification of triggers is successful, this may open a window of opportunity for drug intervention in this period. This could allow for new avenues of 'smart' anti-epileptic drug management i.e. individualised drug management, exploiting this timeframe for administration of drugs in a pulsatile manner to attempt to thwart impending seizure activity.

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683 **Figure and Tables Legends**

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

688

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

693

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

697

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

700

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

703

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

706

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