Title: Behavioural Changes in Dogs with Idiopathic Epilepsy

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Abstract

Breed-specific and broader cohort studies have shown behavioural changes in dogs following the onset of idiopathic epilepsy (IE). A cross-sectional, case-control questionnaire study was carried out to strengthen this body of evidence. Owners of eight breeds of dog completed an online questionnaire about their dogs' behaviour; once for control dogs and twice for dogs with IE, for both pre- and post-IE onset behaviour. Ninety-six (24.74%) dogs with IE and 292 (75.26%) age and breed matched control dogs met the inclusion criteria. Control dogs had significantly higher "Trainability" scores than dogs with IE (p=0.04). Post-IE, dogs had significantly higher "Dog-Directed Fear or Aggression" (p=0.02), "Non-Social Fear" (p=0.01), "Attachment/Attention-Seeking Behaviour" (p=0.04), "Attention-Deficit" (p=0.02) and significantly lower "Trainability" (p=0.02) than prior to the onset of IE. Medication status did not significantly affect any behavioural factor, but drug-resistant dogs had significantly less "Trainability" than drug-responsive (p=0.04) and partially drug-responsive dogs (p=0.03). Behavioural differences related to cognitive function are seen between dogs with IE and controls. Behavioural changes related to anxiety, attention and cognition are seen in dogs following the onset of IE. The ability to clinically define and diagnose behavioural comorbidities in dogs is much needed from both a clinical and research perspective.

Introduction

Psychological and neurodevelopmental comorbidities are reported to effect up to 50% of people with epilepsy[1–5], alongside neuropsychiatric and cognition impairments[6]. These comorbidities can have a drastic negative effect on health-related quality of life (QoL), sometimes more so than seizure frequency[7–12]. Carer-perceived QoL of a dog with idiopathic epilepsy (IE) is associated with the carers own QoL[13], and seizure activity can increase carer stress[14]. Breed-specific studies have reported behavioural changes in dogs with IE[15–17]. Larger studies have shown differences in behaviour of dogs pre- and post-onset of IE and between dogs with IE and controls[18–20]. Similar studies have used the Canine Behavioural Assessment and Research Questionnaire (CBARQ) but did not use the standard method for analysis[19]. Using the established tool and analysis method would allow more comparability between studies. A cross-sectional case-control questionnaire study was carried out with the aim to increase and strengthen the existing evidence base.

Method

Research was approved by the RVC animal and welfare ethical review board (URN M2015 0053). Owners of eight breeds of dog previously identified to be at increased risk of IE compared to cross breeds (Golden Retriever, Labrador, Cocker Spaniel, Border Terrier, German Shepherd Dog, Parson Jack Russell Terrier, Boxer, and Border Collie)[21] were recruited. Dogs aged between 6 months and 10 years old without neurological disease, aside IE were eligible for inclusion. Owners were recruited via social media to complete an online questionnaire containing two previously validated behavioural questionnaires (Appendix 1); the C-BARQ[22] and Dog-ADHD[23] rating scale in regards of their dogs' behaviour; current behaviour only for the controls, and behaviour both current and prior to onset of IE for the dogs with IE. Medication information, such as medications taken and change in seizure frequency on them, was collected to allow for allocation of drug-responsive, partially drug-responsive and drug-resistant categories[24].

Statistical analysis was carried out on IBM Statistical Package for the Social Sciences (SPSS) Version 23. Dogs were matched for age and breed. A mean score was calculated for each behavioural factor. Normality was assessed statistically, and the appropriate statistical test was utilised accordingly to compare groups such as control behaviour vs. current IE group behaviour, or behaviour of sub-categories of dogs with IE, e.g. medication status. All p-values were False Discovery Rate (FDR) corrected[a]. General Linear Mixed Models (GLMM) for binary outcomes using backwards selection were applied following univariate analyses to identify variables liberally associated (p<0.1) with the study group.

Results

Of 834 responses, 388 dogs were included; 96 (24.74%) with IE and 292 (75.26%) controls. Responses were excluded if they did not meet inclusion criteria, were incomplete, or to allow for matching. Average time since onset of IE was 32 months (range: 0-111 months). Controls had a significantly higher "Trainability" score, compared to the current IE group scores (p=0.04). Dogs with IE received significantly higher post-onset CBARQ scores for "Dog-Directed Fear or Aggression" (p=0.02), "Non-Social Fear" (p=0.01), "Attachment/Attention-Seeking Behaviour" (p=0.04), "Attention-Deficit" (p=0.02) and significantly lower "Trainability" (p=0.02) than prior to the onset of IE (Figure 1, Table 1). In a GLMM, these behavioural factors were not affected by other variables tested (e.g. age, seizure frequency, cluster seizures).

Twelve dogs (12.50%) were drug-naïve, 44 (45.83%) were receiving monotherapy and 40 (41.67%) were receiving polytherapy. Owner-reported medication status did not significantly affect any behavioural factor. Excluding drug-naïve dogs and dogs whose owners could not recall specific medication information; 21 (32.8%) were drug-responsive, 20 (31.3%) were partially drug-responsive and 23 (35.9%) were drug-resistant. Drug-resistant dogs had significantly less "Trainability" than drug-responsive (p=0.04) and partially drug-responsive dogs (p=0.03).

Discussion

Dogs with IE obtained significantly lower scores for "Trainability" than controls, similar to findings elsewhere[15,25]. Additionally, "Trainability" decreased following the onset of IE. This may reflect an impairment in learning and/or memory, which could be due to progressive damage from seizure activity, due to effect of the AED, due to ADHD-like behaviour or due to broader cognitive deficits without specific comorbidities like ADHD[4]. Cognition is a concern in people with epilepsy[26], and in dogs with IE[27,28]. Both Winter, et al. ,

[a] http://www.sdmproject.com/utilities/?show=FDR

(2018)[27]and Packer, et al., (2018)[28] showed increased canine cognitive dysfunction in dogs with IE compared to controls, but factors such as aetiology, progression and age of onset were different from classic canine cognitive dysfunction, suggesting a different aetiology in dogs with IE[28]. A decrease in “Trainability” may mirror reduced memory or learning abilities or early onset of canine cognitive dysfunction in the dogs in this study. Interestingly no effect from AEDs was found in this study or in Packer, et al., (2018)[28]. Though not the validated form of analysis, it may be pertinent to the reader to learn that changes in the pre- to post-onset “Trainability” C-BARQ scores were mostly impacted by reduced obeying of the sit command, reduced response to correction or punishment and increased distraction by sights, sounds and smells.

Behavioural changes were seen in the dogs with IE compared to the same dogs pre-IE onset, which can be categorised under anxious and attention-related behaviours, corroborating findings from other veterinary studies[17–19], despite using a different patient cohort, a different sampling method and different questionnaire tool, thereby strengthening the conclusions made by all studies.

In people, neurodevelopmental and psychiatric comorbidities have been found to have a bidirectional relationship with epilepsy[26,29–32], likely due to shared pathophysiological pathways via the hippocampus, amygdala and neuronal pathways[33–35]. Anxiety disorders are common amongst the general human population, but prevalence is higher in people with epilepsy[33]. Similarly, increased incidence of ADHD is seen in people with epilepsy compared to the healthy population[29]. In people, both anxiety and ADHD have been shown to have a bidirectional relationship with epilepsy[30,31,36].

No behavioural differences were found between drug-naïve dogs and those treated with monotherapy or polytherapy, contrary to findings elsewhere[17,25], potentially resulting from low numbers of drug-naïve dogs. Recent veterinary literature has discussed side effects of anti-epileptic drugs[37], their effect on anxiety in dogs with epilepsy[38,39] and use as anxiolytics[40]. Deciphering which behavioural changes are the result of a true comorbidity with epilepsy, and which are a consequence of medication is challenging[10,11,41]. Further prospective, longitudinal studies are required to untangle these effects in dogs with IE.

Drug-resistant and partially drug-resistant dogs received significantly lower scores for the C-BARQ subscale "Trainability" than partially drug-responsive dogs. Shihab, et al. (2011)[18] classified dogs as drug-responders or drug non-responders and reported significant

changes in “controlling aggression”, “demented behaviour” and “abnormal perception”, the latter two potentially contributing to decreased “Trainability” seen here. The relationship between drug-resistance and behaviour is a contentious issue in human epilepsy research, which poses the question of whether it is a result of the initial epilepsy phenotype or due to progressive degeneration of the brain with ongoing seizures, with supportive evidence for both sides[8,41–44]. It remains unknown whether treating a comorbidity might improve a dog’s response to AEDs[39], but it is important to consider that a drug-resistant dog may be more likely to exhibit clinical side-effects of medication thereby affecting a perceived behavioural difference[17]. A holistic approach, providing a considered and well-balanced treatment of the comorbidity alongside seizure frequency or intensity, should be adopted in such cases.
Limitations of this study include owner-reported IE and normalcy, and potential for recall and population bias.

Conclusion

Behavioural differences related to cognitive function are seen between dogs with IE and controls, and behavioural changes related to anxiety, attention and cognition are seen in dogs following the onset of IE, which could impact QoL. This suggests shared semiology and pathologic mechanisms of disease with epilepsy in people and support the dog as a naturally occurring model of IE. The ability to clinically define and diagnose behavioural comorbidities in dogs is much needed from both a clinical and research perspective. Further work should investigate the effects of specific AED protocols on behaviour.

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Conflict of Interest:

Holger Volk: Served as paid consultant for Boehringer Ingelheim and CEVA animal health. Served as contract researcher for: Nestle 2012–2014 and 2017–2019, dietary modification of epilepsy in dogs; Desitin Pharma, 2012, the role of levetiracetam in a referral hospital; industrial Funding, 2014–2015, investigating the effects of imepitoin behavioural, physiologic and owner reported indicators of anxiety in dogs treated for idiopathic epilepsy. Received competitive research grants for: RCVS pump primer grant, 2010–2013,

pharmacometabonomic profiling of epileptic dogs; Waltham Foundation, 2011–2014, determination of plasma omega-3 fatty acid status in dogs with primary epilepsy and relationship to antiepileptic drug metabolism; CASE BBSRC PhD studentship, 2012–2016 metabolic profiling of epilepsy in dogs; American Kennel Club, American Health Foundation, 2016– 2018, Investigating the Effect of a Ketogenic Medium Chain Triglycerides Supplement on the treatment of Canine Idiopathic Epilepsy and its behavioural comorbidities; BBSRC, 2017-2020, Investigating the relationship between epilepsy, drug-resistance and affective disorders in the domestic dog.

Clare Rusbridge: Employed by the University of Surrey and Fitzpatrick Referrals Ltd, Surrey, GU7 2QQ. She has served as a paid consultant for Boehringer Ingelheim. The University of Surrey and Fitzpatrick Referrals did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of authors' salaries.

Rowena Packer: Received industrial funding as a co-applicant from Boehringer Ingelheim (2014–15; Investigating the effects of imepitoin on behavioural, physiologic and owner-reported indicators of anxiety in dogs treated for idiopathic epilepsy) and Nestle (2017–19; Dietary modification of epilepsy in dogs). Received competitive research grants from the American Kennel Club (2016–18; Investigating the effect of a ketogenic medium chain triglycerides supplement on the treatment of canine idiopathic epilepsy and its behavioural comorbidities); BBSRC (2017–20; Investigating the relationship between epilepsy, drug-resistance and affective disorders in the domestic dog; BB/P001874/1) and (2017–2020; Comorbidity and characteristics of canine neurodevelopmental disorders and their impact on animal welfare; BB/P 010881/1).

Figure 1: Mean score for each behavioural factor for dogs with IE and controls (A) and mean score for each behavioural factor for dogs pre- and post-onset of IE (B). * = p<0.05

Table 1: Mean scores for each behavioural factor across each group, value and FDR-corrected p-value.

Behavior Factor	Control Mean (SD)	Current IE Mean (SD)	Z	p (FDR corrected)	Pre IE Mean (SD)	Current IE Mean (SD)	Z	p (FDR corrected)
Stranger Aggression	0.807 (0.871)	0.759 (0.898)	-1.175	0.240 (0.360)	0.654 (0.819)	0.783 (0.950)	-0.364	0.716 (0.859)
Dog Aggression	1.196 (1.143)	1.053 (1.220)	-1.568	0.117 (0.248)	0.700 (1.050)	1.112 (1.277)	-2.284	0.005 (0.020)*
Owner Aggression	0.095 (0.257)	0.158 (0.359)	-1.977	0.048 (0.180)	0.143 (0.351)	0.1308 (0.299)	-0.169	0.866 (0.945)
Stranger Fear	0.751 (0.956)	0.660 (0.945)	-0.840	0.401 (0.535)	0.479 (0.765)	0.664 (0.948)	-1.387	0.166 (0.285)
Non-Social Fear	0.963 (0.798)	1.029 (0.940)	-0.284	0.776 (0.847)	0.740 (0.792)	1.038 (0.887)	-3.380	0.001 (0.012)*
Pain Sensitivity	0.806 (0.886)	0.842 (0.949)	-0.423	0.672 (0.806)	0.652 (0.930)	0.805 (0.896)	-2.110	0.035 (0.070)
Separation	0.220 (0.453)	0.357 (0.660)	-1.539	0.124 (0.248)	0.351 (0.747)	0.357 (0.689)	-0.031	0.975 (0.975)
Attachment	1.875 (0.855)	2.078 (0.754)	-2.431	0.015 (0.090)	1.960 (0.852)	2.077 (0.788)	2.402	0.017 (0.048)*
Chasing	2.000 (1.012)	1.789 (1.106)	-1.881	0.060 (0.180)	0.784 (1.095)	1.856 (1.114)	0.749	0.455 (0.683)
Excitable	2.568 (1.001)	2.545 (1.011)	-0.174	0.862 (0.862)	2.588 (1.053)	2.595 (0.962)	0.379	0.705 (0.859)
Trainability	2.961 (0.537)	2.762 (0.636)	-2.932	0.003 (0.036)*	2.914 (0.731)	2.741 (0.657)	-2.821	0.005 (0.020)*
Attention	0.696 (0.414)	0.789 (0.513)	-1.350	0.177 (0.303)	0.675 (0.521)	0.806 (0.534)	-2.685	0.007 (0.021)*

Current IE = behavioural score for dogs with idiopathic epilepsy at present
Pre IE = behavioural score for dogs with idiopathic epilepsy prior to the onset of seizure activity
* denotes a statistically significant result following false discovery rate (FDR) processing

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