Phenotypic characterisation of canine epileptoid cramping syndrome in the Border terrier

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OBJECTIVES: To characterise the phenotype of Border terriers suspected to be affected by canine epileptoid cramping syndrome and to identify possible contributing factors.

METHODS: Owners of Border terriers with suspected canine epileptoid cramping syndrome were invited to complete an online questionnaire. The results of these responses were collated and analysed.

RESULTS: Twenty-nine Border terriers were included. Most affected dogs had their first episode before 3 years of age (range: 0.2 to 7.0 years). The majority of episodes lasted between 2 and 30 minutes (range: 0.5 to 150 minutes). The most frequent observations during the episodes were difficulty in walking (27 of 29), mild tremor (21 of 29) and dystonia (22 of 29). Episodes most frequently affected all four limbs (25 of 29) and the head and neck (21 of 29). Borborygmi were reported during episodes in 11 of 29 dogs. Episodes of vomiting and diarrhoea occurred in 14 of 29, with 50% of these being immediately before or after episodes of canine epileptoid cramping syndrome (7 of 14). Most owners (26 of 29) had changed their dog’s diet, with approximately 50% (14 of 26) reporting a subsequent reduction in the frequency of episodes.

CLINICAL SIGNIFICANCE: This study demonstrates similarities in the phenotype of canine epileptoid cramping syndrome to paroxysmal dystonic choreoathetosis, a paroxysmal dyskinesia reported in humans. This disorder appears to be associated with gastrointestinal signs in some dogs and appears at least partially responsive to dietary adjustments.

INTRODUCTION

Paroxysmal dyskinesias are a group of movement disorders that are well described in human medicine. They are becoming increasingly recognised in animals (Meyers et al. 1969, Woods 1977, Nakahata et al. 1992, Ramsey et al. 1999, Penderis & Franklin 2001, Kube et al. 2006, Harcourt-Brown 2008, Packer et al. 2010) although they are often poorly characterised in the veterinary literature. A movement disorder strictly speaking encompasses any abnormal involuntary movement, but is often a term applied to those disorders that do not impair consciousness. Dyskinesia is a general term to describe hyperkinetic movement disorders. These involuntary movements can include ballismus (abrupt contraction of limb muscles causing a flailing movement of the limb, this is often unilateral, as in hemiballismus), dystonia (sustained involuntary contraction of a group of muscles producing abnormal postures), chorea (abrupt, non-sustained contraction of different groups of muscles in the same patient)
and athetosis (prolonged contraction of trunk muscles causing a bending or writhing motion, this often accompanies chorea, thus is described as choreathetosis). Paroxysmal dyskinesia is the term ascribed to movement disorders when involuntary movements or postures are not continuous, but occur suddenly with normal motor function and no neurological deficits in between episodes. Paroxysmal dyskinesias are distinguished from simple focal seizures by the character of the episodes including the movements observed, duration, triggers, absence of urination, defecation and hypersalivation (i.e. classic autonomic signs observed with seizures), lack of postictal behaviour, and (with very few exceptions) lack of seizure activity on ictal EEG recordings (Demirkiran & Jankovic 1995, Packer et al. 2010).

For human dyskinesia a modified classification system is applied based on precipitating factors, frequency, duration of attacks and response to treatment (Table 1) (Demirkiran & Jankovic 1995, Jankovic & Demirkiran 2002). Despite this, little is known about the underlying pathophysiology of the disease with the majority of cases appearing to be idiopathic or familial. However, recent advances include the identification of genetic mutations thought to be responsible for the disease (Lee et al. 2012, Groffen et al. 2013).

Canine epileptoid cramping syndrome (CECS) or Spike’s Disease is a disorder affecting Border terriers (BTs) that veterinarians have been aware of for over 10 years both in Europe and the USA, but which to date remains poorly characterised. It was hypothesised that this condition represents a breed-related paroxysmal dyskinesia. A survey was conducted of owners of BTs suspected to be suffering from CECS with the aim of characterising the phenotype and identifying possible contributing factors.

**MATERIALS AND METHODS**

**Case recruitment**

Cases were recruited by an appeal in the veterinary media (The Veterinary Times and Veterinary Record) for primary veterinary surgeons to respond with BTs in their care that were likely to be suffering from CECS. This specified cases that had been reported to exhibit episodes of gait abnormalities ranging from ataxia to an inability to stand; with contractions of the abdominal, neck and back muscles resulting in abnormal posturing, and contractions/cramping of the appendicular muscles causing extensor rigidity or flexion of the limbs. Additional cases were recruited via solicitation through a contact (JG) involved in online support for owners of suspected CECS-affected BTs. All owners, subsequently involved in the online questionnaire agreed to their animal’s clinical details being interrogated.

**Inclusion criteria**

Inclusion criteria were in place to exclude other disease processes that may be misinterpreted as CECS. In the cases recruited via primary veterinarians full medical records were also requested and reviewed. The study was directed towards purebred BTs only. BTs were required to have at least a one-year history of episodes of abnormal involuntary hyperkinetic movement or muscle tone, without urination, defecation, hypersalivation or loss of consciousness. Metabolic, cardiovascular, respiratory, orthopaedic and other neurological conditions were excluded as far as possible by full medical records, clinical examination findings and blood test results where available (only available in cases recruited from primary veterinarians). Episodes were reviewed by video footage where available or detailed telephone questioning of the owners. Once confirmed as likely sufferers, owners were invited to complete an invitation-only online survey (this survey can be viewed at: http://www.surveymonkey.com/s/DVSCECS2012).

**Study design**

Questions were embedded within the survey to further screen animals and respondents for answers not consistent with the definition of CECS for the purpose of exclusion from the study. The majority of questions were closed questions with multiple choice answers. Questions directed towards the characteristics of the episodes also included an opportunity to provide a description of the episodes with the following open question: “In your own words please describe in detail what happens during a typical episode, including 1. How the episodes look when they start, 2. How the episodes progress, 3. Whether your dog appears to be rigid or limp, or both, 4. Whether your dog tends to stand up/sit down/lie down during an episode. If they vary then please describe how they tend to differ”. A total of 50 questions were divided into those that screened dogs for CECS as discussed above, and those that provided detailed phenotypic information in terms of the signalment of animals, possible precipitating factors, therapeutic trials where relevant and the characteristics of the episodes. For the former, the owners were asked to describe the event in their own words but also to answer a number of questions about the events themselves including: duration and frequency of the events themselves including: duration and frequency of the

| Type of movement disorder | Age of onset | Duration | Frequency | Trigger | Response to AEDs |
|---------------------------|-------------|----------|-----------|---------|-----------------|
| Paroxysmal kinesigenic choreathetosis (PKC)/Paroxysmal kinesigenic dyskinesia (PKD) | Childhood/early adolescence | Typically <2 minutes | High (up to 100 per day) | Precipitated by sudden movements | Yes |
| Paroxysmal dystonic choreathetosis (PDC)/Paroxysmal non-kinesigenic dyskinesia (PN KD) | Childhood/early adolescence | 5 minutes to 4 hours | Few per day-none for months | Alcohol, fatigue, caffeine, excitement | Not typically effective |
| Paroxysmal exertion induced dyskinesia (PED) | Childhood/early adolescence | 5 to 30 minutes | Daily one per month | Precipitated by prolonged muscle exertion | Not typically effective |
| Paroxysmal hypogenic dyskinesia (PHD) | Childhood in familial, aduuthol in sporadic | 30 to 45 seconds | 5 times a night 5 times a year | During non-REM sleep | May be effective |

AEDs antiepileptic drugs
episodes; body parts affected and the order of their involvement; types of movement; presence of autonomic signs such as salivation, urination or defecation; presence of borborygmi; awareness of the dog to its surroundings, ability to ambulate and presence of air licking.

**RESULTS**

There were 33 respondents to the request for cases in total, 20 of 33 were from primary veterinary surgeons and 13 of 33 were from the contact. Four cases were excluded (2 of 20 from primary veterinary surgeons and 2 of 13 from the contact) as they did not meet the inclusion criteria. One respondent’s BT had been suffering from suspected episodes for a shorter time period than the designated 1 year required to fulfill inclusion criteria (1 month), one BT was reported to urinate during the episodes, one BT was reported to urinate and defecate during episodes and one BT reportedly salivated during the episodes. The remaining 29 BTs were considered to be exhibiting CECS and the owners of these BTs were invited to complete the questionnaire. Episodes were reviewed by video footage (15 of 29) or detailed telephone questioning of the owners (14 of 29). Responses to the survey for all 29 BTs were analysed. Screening questions were investigated. No significant underlying metabolic, cardiovascular, respiratory, orthopaedic or other neurological conditions were identified in any respondent. For this reason, none of the 29 BTs were excluded at this stage.

Blood tests were performed in 24 of 29 BTs including haematology, biochemistry, electrolytes (immediately after an episode in 1 BT), thyroid blood tests (not specified), toxoplasma serology, neospora serology, adrenocorticotropic hormone (ACTH) stimulation and pre and postprandial serum bile acids. One BT had biochemistry results consistent with pancreatitis and another was diagnosed with hypothyroidism. Four BTs had subclinical increases in liver parameters (alkaline phosphatase activity, alanine transaminase activity and serum bile acids) that were attributed to ongoing phenobarbital therapy at the time of sampling. All the other blood test results were reported within their respective reference intervals. Three of the twenty-nine BTs underwent magnetic resonance imaging and cerebrospinal fluid collection and analysis (cell count, cytology and protein concentration) and these results were reported as normal. All BTs had full clinical examinations performed by a veterinary surgeon and no abnormalities were detected. Three BTs had neurological examinations performed by board-certified neurologists: these findings were also normal.

**Clinical cases**

No sex predisposition was identified (15 of 29 males and 14 of 29 females). The majority of BTs were neutered (25 of 29). Age at onset ranged from 0-2 to 7-0 years of age, with a mean and median age of 3-0 years. The mean duration for exhibiting signs was 4-5 years (range: 1-0 to 11-0 years). The majority of episodes were reported to last between 2 and 30 minutes (25 of 29) (range: 0-5 to 150 minutes). Most owners reported no change in duration with time (19 of 29). Episode frequency overall was variable both between and within individual BTs, with the majority of owners (15 of 29) reporting clusters over a few days interspaced by weeks or months of normality. Most BTs (16 of 29) had at some point experienced multiple episodes (up to 3) in a 24-hour period.

The majority of owners (18 of 29) felt they could predict an episode with their BTs becoming quieter (11 of 29), seeking to be near owners (6 of 29), vomiting bile or eating grass (4 of 29). Most owners (18 of 29) described similar behaviour after the episode, with dogs being quieter (11 of 29), seeking to be near owners (4 of 29) or hungry (3 of 29). Once an episode had commenced none of the respondents felt they were able to change the course of the episode. However, 23 of 29 owners elected to comfort their dogs by stroking or holding them during the episode. The most frequent observations during the episodes were difficulty walking (27 of 29), mild tremor (21 of 29) and dystonia (22 of 29). There was no observed trend between the propensity for BTs to stand up (14 of 29) or lie down (15 of 29) during an episode, although the majority of dogs (22 of 29) were reported to have periods when they were unable to stand. Less frequently, air licking (14 of 29), excessive stretching (14 of 29) and extensor rigidity of all four limbs (14 of 29) were reported. Episodes most commonly affected all four limbs (25 of 29) and head and neck (21 of 29), with the back and abdomen (16 of 29) and tail (11 of 29) less frequently involved. Borborygmi were reported in 11 of 29 BTs during the episode. Twenty of the twenty-nine owners felt their dogs appeared to be uncomfortable during an episode. Some owners (10 of 29) felt that CECS had a negative impact on their dog’s quality of life.

Although the majority of episodes appeared to be totally random (16 of 29), owners identified excitement (10 of 29), waking from sleep (13 of 29) and stress (9 of 29) as consistent circumstances of occurrence. Episodes did not appear to be induced by sudden movement. Fourteen of the twenty-nine BTs were reported to be prone to episodes of vomiting and diarrhoea with 50% of these occurring immediately before or after episodes of CECS (7 of 14). Food intolerance was suspected in a number of BTs in this study (11 of 29). Another common complaint in affected BTs was skin disease (15 of 29), with no other significant concurrent conditions being identified. Most owners (26 of 29) had changed their BT’s diet after a suspicion of CECS was made, with the majority (19 of 29) selecting a diet that claimed to be hypoallergenic or a single protein and carbohydrate source. Over 50% of the dogs that participated in a diet change (14 of 26) were felt by the owners to respond to this with a subsequent reduction in the frequency of episodes. Therapeutic trials with phenobarbital (5 of 29), potassium bromide (2 of 29), diazepam (3 of 29) and buscopan (3 of 29) appeared to fail in reducing the frequency or duration of episodes in the BTs in which they were trialled. The dosage of these medications was available in 5 cases (4 of 5 of the phenobarbital cases, 1 of 2 of the potassium bromide cases, 2 of 3 buscopan cases) and was considered adequate in all cases (the doses were all greater than 3 mg/kg phenobarbital every 12 hours, serum phenobarbitalone levels were available in 3 of 5 phenobarbital cases and were within the therapeutic range).
A dose of 2 mg and 5 mg diazepam was reportedly administered rectally in 2 of 3 cases and failed to abort the episode.

**DISCUSSION**

This survey provides some important and useful clinical data concerning CECS in BTs. There appears to be no sex predilection and the majority of BTs suffer their first episode before the age of three years. Similar findings in terms of the signalment of cases were reported in a recent study on paroxysmal dyskinesia in the Chihuahua (Pack et al. 2010). The described duration of episodes was typically less than 30 minutes but could be significantly longer with apparent clustering over a few days (up to 3 in a 24 hour period) interspaced with many weeks or months of normality. This pattern of variations in frequency has been reported in other breed-related movement disorders (Meyers et al. 1969, Penderis & Franklin 2001) and suggests that CECS is a waxing and waning disorder. Once an episode started owners felt they were unable to alter its course. Most episodes were characterised by difficulty in walking, mild tremor and dystonia, with air licking, excessive stretching and extensor rigidity of all four limbs. Episodes often affected all four limbs and the head and neck, with the back and abdomen and tail commonly but less frequently involved. Movement did not induce episodes and most were reported to be totally random in terms of circumstance of occurrence. However, owners identified excitement, waking from sleep and stress as possible triggers. Therapeutic trials with phenobarbital, potassium bromide, diazepam and buscopan apparently failed in all BTs in which they were attempted.

The majority of owners felt they could predict an episode with BTs becoming quieter, seeking to be near owners or vomiting or eating grass and similar behaviour was often noted after an episode. Such observed behavioural changes before and after episodes closely parallel pre and postictal behaviour associated with epileptic seizures; consequently movement disorders are at risk of being misidentified as seizure disorders, particularly when a clinician is unfamiliar with relevant breed-related disorders. Abnormalities in behaviour before and after episodes are by no means considered pathognomonic for a seizure disorder; prodromal symptoms including headache, muscle tension, tingling and dizziness are reported in humans affected by paroxysmal dyskinesias before onset of an episode (Demirkiran & Jankovic 1995). Similar signs before onset of an episode appear to be possible in BTs affected by CECS.

The phenotype for CECS revealed by this study suggests that it is consistent with a paroxysmal dystonic choreoathetosis/paroxysmal non-kinesigenic dyskinesia (PDC/PNKD) when using the modified classification scheme applied to paroxysmal dyskinesias in humans (Table 1) (Demirkiran & Jankovic 1995, Jankovic & Demirkiran 2002). CECS is not precipitated by movement, and does not occur exclusively during sleep making paroxysmal kinesigenic choreoathetosis/paroxysmal kinesigenic dyskinesia (PKC/PKD), paroxysmal exertion induced dyskinesia (PED) and paroxysmal hypnogenic dyskinesia (PHD) less likely. The duration of episodes was typically 2 to 30 minutes (range: 30 seconds to 2.5 hours); this longer duration is also typical of PDC type paroxysmal dyskinesias, as is the variable but relatively low frequency (discussed above). The lack of response to antiepileptic medications is also a finding consistent with PDC (Jankovic & Demirkiran 2002). Fatigue, excitement and stress have been reported to be triggers in humans with PDC/PNKD. This study identified a possible link with excitement, stress and waking from sleep in affected BTs, but this was not a consistent finding and the majority of episodes appeared to be random.

Paroxysmal dyskinesias reported in the veterinary literature most commonly would be categorised as PDC/PNKC (Ramsey et al. 1999, Penderis & Franklin 2001, Packer et al. 2010). One report described a paroxysmal dyskinesia typical of PKC/PKD in a German shorthaired pointer (Harcourt-Brown 2008). Although not characterised in the literature as such, episodic falling syndrome in the Cavalier King Charles spaniel (Heritage & Palmer 1983) and “scottie cramp” in Scottish terriers (Meyers et al. 1969) are likely to represent fundamentally similar conditions (Penderis & Franklin 2001). At this stage the classification of the type of paroxysmal dyskinesia provides no information in terms of the likely aetiology or mechanism of the dyskinesia present. The neuroanatomical localisation of paroxysmal movement disorders is unknown although they are postulated to be due to abnormal neurotransmission either because of an abnormality in the transmitter itself, ion channels or a cognate receptor (Comu et al. 1996, Ophoff et al. 1996, Bressman et al. 1998, Ptacek & Fu 2002, Hamann et al. 2003, Du et al. 2005).

The main differential diagnosis for paroxysmal dyskinesia is focal seizures. It can be challenging in humans and animals to distinguish between the two (Beaumanoir et al. 1996). Ideally, differentiation might be achieved using intra-ictal electroencephalogram (EEG) monitoring (Demirkiran & Jankovic 1995, Beaumanoir et al. 1996). Unfortunately, intra-ictal EEG recording is rarely feasible in veterinary medicine because of the low likelihood of witnessing an event. Inter-ictal EEG recording is unlikely to be sufficiently sensitive to be relied upon for differentiation. Inter-ictal EEG recordings in humans are reported to be sensitive in 29 to 55% of cases of epilepsy (Marsan & Zivin 1970, Salinsky et al. 1987, Goodin et al. 1990), with a reported sensitivity of 65% in dogs (Berendt & Gram 1999). Intra-ictal or inter-ictal EEG recording was not performed on any BTs in this study, and the diagnosis of a paroxysmal dyskinesia was based on the overall phenomenology of the episodes in CECS. There are several reasons that this is considered more likely to represent a paroxysmal dyskinesia rather than epileptic seizures. During episodes BTs remained fully conscious throughout despite movement affecting all four limbs, whereas if this was due to epileptic seizure activity it would imply bilateral cerebral hemisphere involvement which would be expected to impair consciousness (Beaumanoir et al. 1996). Simple focal seizures in which consciousness is normally intact have clinical signs that are suggestive of unilateral cerebral hemisphere involvement and therefore unilateral clinical signs (Licht et al. 2002), this is not consistent with the generalised signs observed in BTs in this study. Furthermore, simple focal seizures often progress to become generalised or involve altered consciousness (Berendt et al. 2004), this
was not observed in any cases submitted to this study. Second, focal seizures are normally brief in duration (less than 10 minutes) (Licht et al. 2002, Berendt et al. 2004), whereas episodes of CECS have been reported in this study to last longer than 2 hours in some instances. The reported inability to control these episodes by conventional antiepileptic medications provides further supportive evidence that they are not likely to be seizures of cortical origin. Finally, autonomic signs were consistently absent, a feature unusual to seizures. Despite this it is not possible to completely rule out the presence of an epileptic disorder. The finding that BTs exhibited signs that may represent pre and post-ictal behaviour is not conclusive for seizures as they may not be cerebral in origin and could be displayed due to the hypothesized abdominal discomfort immediately associated with the episode.

This study revealed an apparent association between borborygmi and other gastrointestinal signs and CECS. Indeed the only consistent concurrent diseases identified by the study were skin disease and suspected food intolerance. Most owners who changed their dog’s diet reported a subsequent improvement with a reduction in frequency of episodes. These factors suggest that there may be a role for gastrointestinal function and possibly underlying food allergy or intolerance. An equivalent example from the human medicine field may be the association between movement disorders and gluten hypersensitivity in coeliac disease (Hall et al. 2007). However, the possibility of a coincidental disease process cannot be ruled out. The prevalence of skin disease has been reported as 1.79% and gastrointestinal disorders as 1.19% in all BTs registered with the Kennel Club completing spikes-disease/home.html; www.borderterrier-cecs.com).

In conclusion, this study provides valuable information on the phenotype of CECS in the BT, a disorder hypothesised to be a paroxysmal dyskinesia, which should be classified as PDC/PNKD when applying the human modified classification system. This represents an important first step in the approach to investigating CECS. The ultimate aim is to achieve the same outcome as that of episodic falling syndrome in the Cavalier King Charles spaniel, where the gene responsible for this disorder has been identified and a genetic test made available (Forman et al. 2012, Gill et al. 2012). This work also highlights the need for further investigation into the role of the gastrointestinal system and dietary influences on this disorder.

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

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