Clinical features in Border terrier dogs with paroxysmal involuntary movements

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Abstract

Background -There have been anecdotal reports of episodic involuntary movements in the Border terrier dog breed for over a decade. Recently, it has been hypothesized that this condition may be a form of paroxysmal dystonic choreoathetosis. The aim of this study was to characterize the phenomenology and clinical course of this condition and compare it to known human movement disorders.

Methods - Data were collected retrospectively from clinical cases treated by veterinary neurologists and additional information was collected prospectively with an ad hoc online survey directed to owners of affected dogs.

Results - The episodes are characterized by generalized dystonia, tremors, titubation and in some cases, autonomic signs such as salivation and vomiting. The median age at onset of the episodes was 3 years and the interval between clusters of episodes could last several months. Most of the episodes occurred from rest and 67% of the owners reported that the episodes were associated with a trigger, most often excitement. Some owners reported an improvement after changing their dog's diet. We hypothesize that the Border terrier attacks represent a form of paroxysmal non-kinesigenic dyskinesia (PNKD).

Conclusions - The finding of a dystonia phenotype within an inbred population suggests a genetic predisposition and elucidating the genetic cause could facilitate improved understanding of dystonia. This genetic predisposition and the effect of treatment with anticonvulsant drugs and dietary changes on the severity of the paroxysms warrant further investigation on this condition.

Introduction

There have been anecdotal reports of episodic involuntary movements in the Border terrier dog breed for over a decade.[1, 2] A first attempt to characterise the clinical phenotype was only published recently.[3] The authors reported on the phenotypic characterization of 29 pure bred Border Terriers with Canine Epileptoid Cramping Syndrome and hypothesized that this condition may be a form of paroxysmal dystonic choreoathetosis. The study was based on a survey of owners of affected dogs and 50% of the owners reported an improvement in the frequency of the episodes after changing the dog's diet. The episodes in the Border terrier are characterized by whole body tremors with unimpaired consciousness. The aim of this study was to further characterize the phenomenology and clinical course of this condition collecting data from both

veterinary neurologists and owners of affected dogs and compare this condition to known human movement disorders.

Materials and methods

This study was approved by the ethical and animal care committee of the Royal Veterinary College, University of London, England (approval number URN 2011 1135). Owners of Border terriers with episodes of tremors or muscle spasms were invited to participate in an ad hoc online survey. The survey ran for four months, from April to July 2012. The questionnaire was designed by three board-certified veterinary neurologists and included 83 questions, including open and closed-ended questions. The inclusion criteria were breed (only dogs identified by the responder as Border terriers were included) and history of more than one episode of involuntary movements with apparent preservation of consciousness. Dogs described to have generalized tonic-clonic seizures were excluded from the study unless these were in addition to a different type of episodes characterized by paroxysmal involuntary movements with preservation of consciousness. The decision to include dogs with a history of generalized seizures was based on the fact that the co-occurrence of epilepsy and paroxysmal dyskinesias and ataxias is reported in humans and may be present also in veterinary patients.[4] Dogs older than 6 years at the onset of the clinical signs were excluded by the study if information on brain MRI and cerebrospinal fluid (CSF) analysis was not available, as they would be more likely to have a structural etiology for the episodes.[5] It was decided that each responder could enter only one affected dog and the information collected with the questionnaire was compared with information on clinical cases collected retrospectively. Description of the episodes provided in the survey and, when available video recordings, were reviewed to characterize the nature of the episodes. Some owners were contacted by e-mail for data verification. Questionnaires that included a detailed description of the episode and answers to a minimum of 50% of the 83 questions were included in the study.

Clinical cases were identified searching the medical records of the authors' practices from 2006 to July 2012 for Border terriers presenting with episodes of involuntary movements without loss of consciousness, and with a minimal work up including hematology and biochemical panel. Information on signalment, history and clinical presentation were derived retrospectively from the records of the clinical cases.

Data obtained from web-based survey was compared to data derived from the records of clinical cases and differences were considered significant at $P \leq 0.05$ [analyses conducted with R version 3.0.1, The R Foundation for Statistical Computing (2013)]. The effect of the independent variable (group: prospective online questionnaire or retrospective clinical cases) on continuous dependent variables was analyzed by a generalized linear model (GLM) if the dependent variable was normally distributed and variances homogeneous, and by Kruskal-Wallis one-way analysis of variance if data violated assumptions of normality and homogeneity. Binomial dependent variables (i.e., response either "yes" or "no") were modeled according to the independent variable by GLM with a binomial link function.

Results

Study population

There were 99 responders to the survey; 62 questionnaires did not meet the inclusion criteria including a detailed description of the episodes and answers to a minimum of 50% of the questions and were therefore excluded from analysis. Eighteen clinical cases were identified in the medical records of four UK veterinary referral hospitals. However, two dogs (one in the survey and one in the clinical group) were subsequently excluded from the study due to a late onset of clinical signs and a lack of information on brain MRI and CSF analysis. In total, information on 53 affected Border terriers (36 questionnaires and 17 clinical cases) was analyzed in this study. Forty-four dogs were in United Kingdom, 3 in United States of America and one each in Canada, Australia, Germany and Sweden. Seven owners reported knowledge of similar

episodes in dogs related to theirs. There were 28 male and 23 female dogs, of these 10 were sexually intact dogs and 40 were neutered, information on the gender of 2 dogs and on the reproductive state of a female dog was not available. The dogs were aged between 10 months and 14 years (median, 6 years) at the time of the survey.

Results of statistical analysis

There was no significant difference between the survey group and the clinical cases group for any of the continuous variables, such as age of onset of clinical signs, frequency of the episodes, highest number of episodes per day, median duration of the episodes and recovery time, and duration-dose of treatment. Also, no significant difference was detected for any of the binomial dependent variables such as bilateral clinical signs, presence of increased muscle tone, ability to stand and presence of autonomic signs. Since no significant differences were detected between the survey group and the clinical cases group for any of the continuous or binomial dependent variables, we report the data below as one group.

Age of onset

The age of onset of the attacks was 3.1 +/- 0.3 years (mean +/- SE, median 3 years, N=51 dogs, range 0.3 to 6.5 years).

Occurrence of events

Most of the episodes occurred from rest (87% or 34/39 dogs), with less from sleep (50% or 19/38 dogs) or during exercise (42% or 18/43 dogs). In 75% (30/40) of the dogs the episodes occurred at any time during the day, the remaining dogs tended to have episodes in the evenings (nine dogs) or during the night (five dogs). Most of the owners (67% or 29/43 dogs) reported that the episodes were associated with a trigger (excitement, n=10; stress, n=9; food, n=7; extreme temperatures, n=6; loud sudden noise, n=5; visual stimuli and startle, n=3 dogs each).

Characterization of the episodes

The videos illustrate the typical presentation of the episodes based on the authors' experience. The episode in video 1 appeared to be triggered by excitement, developing seconds after the dog

was separated from the owner and admitted to the hospital. Generalized body tremors were evident throughout the episode and were associated with an involuntary lateral body sway similar to titubation. The dog's gait became progressively stiff and hypometric until the dog comes to a stop with a wide based stance and showed generalized tremors. The dog was examined by one of the authors (KMH) during this paroxysm of generalized dystonia, he appeared to be conscious and was found to have normal menace response in both eyes and conscious postural reactions in all four limbs, no autonomic signs were detected. Diazepam 1 mg/kg per rectum, followed by 0.5 mg/kg intravenously did not appear to have an effect; the clinical signs subsided gradually over the course of approximately 5 minutes.

The second video (Video 2) is an excerpt of a slightly different type of episode. The complete video showed the dog in sternal recumbency turning his head side-to-side, manifesting progressive stiffening of the muscles of limbs, trunk, and neck. Then, the dog developed titubation and tremors and dystonia affecting limbs, tail and trunk. An episode of vomiting was followed by panting and salivation. When the dog attempted to walk the limb movements were initiated but not controlled appropriately and there was poor coordination between joint flexor and extensor muscles,

Owners reported muscle tremors in 85% (40/47) of the dogs, 57% (27/47) of the owners indicated that the tremors affected the trunk and 49% (23/47) limbs, see Table 1 for more details on the clinical presentation, information derived from survey and clinical cases groups was pooled. During the episodes both sides of the body were similarly affected in 85% (39/46) of the dogs. The owners described increased muscle tone during the episodes in 82% (37/45) of the dogs. Sixty-four per cent (27/42) of the dogs could not stand during an episode, 43/45 (95%) owners reported their pet was able to look at them in the eyes during an episode and had no apparent impairment in consciousness, the owners of the remaining 10 dogs (2 negative and 8 blank answers) were contacted and provided a statement or video suggesting no impairment in their dogs' consciousness during an episode (e.g. attempting to eat during an episode). Fifty-six

179 percent (26/46) of the owners described autonomic signs such as salivation, urination, defecation
180 or vomiting associated with the episodes, more frequently salivation (22/46) and vomiting (11/46)
181 in 48% and 24% of dogs respectively. Twenty-nine owners reported that their dogs experienced
182 always the same type of episode and 18/47 dogs (38%) had different types of episodes. In 13 dogs,
183 the episodes differed from each other in severity or duration; the owners of five dogs also
184 described sporadic generalized tonic-clonic seizures with loss of consciousness. In two dogs, one
185 single generalized seizure was observed one and two years prior of the onset of the attacks
186 described here. Information on frequency and duration of the episodes and recovery time is
187 reported in Table 2.

188 **Diagnostic work up and co morbidity**

189 Blood work (haematology, biochemistry and bile acid stimulation test) performed in 55% (15/27)
190 of the dogs did not reveal any significant clinical abnormality. One dog had an inter-ictal
191 electroencephalogram (EEG) performed and another dog had electromyography performed while
192 under general anaesthesia, both diagnostic procedures had normal results. Head MRI was
193 performed in 15 dogs (13 dogs in the clinical cases group and 2 dogs from the survey group for
194 whom normal brain MRI results were reported by owners) and did not revealed any significant
195 abnormality.

196 The cerebrospinal fluid analysis was slightly abnormal in 2/11 dogs, one sample of cerebrospinal
197 fluid was defined as mildly reactive based on the presence of reactive lymphocytes and activated
198 macrophages on cytology; cell count and protein content were normal. Another cerebrospinal
199 fluid analysis showed a total nucleated cell count of 11 cells/µL (normal < 5 cells/µL), mixed
200 pleocytosis and normal protein content. The neurological examination in both dogs was normal;
201 long-term follow up was not available.

202 Twenty-eight percent (7/25) of the dogs had concurrent dermatological conditions, 7 dogs had
203 otitis externa and 5 of these dogs had also suspected allergic dermatitis; gastrointestinal problems
204 affected 16% (4/25) of the dogs.

Clinical course and treatment

The frequency of the episodes was variable, from one per day to one per year; 6 owners reported a progressive increase in frequency and 2 owners reported clusters of episodes within a week with intervening normal periods of several months. Thirty-five per cent (18/51) of the dogs received medication for this condition, and 17 of these dogs were receiving anticonvulsant medications, one dog received clomipramine. One dog treated with potassium bromide and 8/10 (80%) dogs treated with phenobarbital showed an improvement in the frequency of the episodes. Three dogs receiving phenobarbital had not experienced an episode in one (n=1) or two years (n=2), 3 other dogs had a significant (>50%) decrease in the frequency of the episodes, none of these dogs had a concurrent history of seizures.

Five owners (5/41 or 12%) reported an improvement after switching to a different commercial diet (n=4) or elimination of a specific type of treats (i.e. rawhide chews, n=1), two dogs were reported to be free of episodes for one and eight years, and two owners reported a significant (>50%) decrease in the frequency of the episodes.

Discussion

The objective of this study was to describe the phenomenology of paroxysmal involuntary movements in Border terriers to advance our knowledge of this condition and generate hypotheses for future pathophysiology and genetic studies.

The limitations of this study were its retrospective nature and the use of information derived from a questionnaire for 36/53 dogs (68%). Information from clinical cases was compared by means of statistical analysis with information derived by the questionnaire and pooled together after finding no significant differences for binomial or continuous variables. The objective was to achieve a better characterization of this rare condition of Border terrier dogs that presents with recurrent episodes of involuntary movements of brief and variable duration similar to paroxysmal dyskinesias described in humans.[6]

231 Border terriers of either gender in Europe, North America and Australia develop attacks of
232 involuntary movements at the median age of 3 years. Their frequency is variable from multiple
233 attacks per day to 1 per year; the median duration of the attacks is 5 minutes, but in 30% of the
234 dogs the attacks lasted between 15 minutes to 2 hours. During the episodes the dogs appear to be
235 disoriented, but responsive to stimuli, with dystonia, tremors affecting neck, trunk and limbs, and
236 titubation (Video 1). Affected dogs are normal in between episodes based on the results of the
237 neurological examination in 17/53 dogs (32%) and owners' evaluation in 36/53 dogs (68%). The
238 clinical presentation of the described Border terrier attacks is similar to primary or familial forms
239 of paroxysmal dyskinesias in humans.[6]
240 The phenotypic classification of paroxysmal dyskinesias in humans is based on precipitating
241 factors and, at this time, includes three types of paroxysmal dyskinesias: paroxysmal kinesigenic
242 (PKD), non-kinesigenic (PNKD), and exercise induced (PED).[7] Paroxysmal kinesigenic
243 dyskinesias (PKDs) are triggered by sudden movements and the attacks are typically brief, lasting
244 only seconds. Attacks of paroxysmal non-kinesigenic dyskinesia (PNKD) have a longer duration
245 compared with PKD and are not induced by sudden movement but can be triggered by alcohol,
246 coffee, or strong emotions. Finally, attacks of paroxysmal exercise-induced dyskinesia (PED) are
247 triggered by physical exhaustion after continuous exertion.[7] Most of the attacks in Border terriers
248 occurred from rest (87% or 34/39 dogs), but some owners (67% or 29/43 dogs) reported that the
249 attacks could be associated with a trigger, in particular excitement, stress and food. We
250 hypothesize that, since a kinesigenic trigger was not identifiable, the Border terrier attacks
251 represent a form of paroxysmal non-kinesigenic dyskinesia (PNKD). Similar to the Border terrier
252 attacks, PNKD attacks in humans tend to occur only few times per year (up to several times per
253 week) and last longer than in PKD (from 10 minutes up to 12 hours, although usually not longer
254 than 1 hour).[6] Eighty percent of genetically proven cases of human PNKD were found to have a
255 combination of dystonia and chorea; however 12% had only dystonia as seen in Video 1 and 2 of
256 Border terriers attacks. [6] Primary PNKD usually has no other associated interictal signs similar to

the Border terriers in this study that had episodes of involuntary movements for a median time of 27 months without developing neurological signs between episodes. PNKD attacks in humans begin with premonitory symptoms, such as a sensation of tightness in 1 limb, involuntary movements of the mouth, or anxiety; when the involuntary movements ensue, they often affect only one side of the body and tend to spread or even generalize, similar observations of anxiety and stiffening of one limb preceding the attacks and generalization of the attacks were also made by owners of affected Border terriers as reported in Table 1.[6]

Finally, PNKD attacks in humans occur spontaneously at rest but more often after provocation by alcohol or coffee.[7] Interestingly, some of the findings in our study seem to suggest an association between severity of the Border terrier attacks and diet: five owners reported an improvement in the frequency of the episodes after switching to a different commercial diet and, for one dog, after discontinuing rawhide chews. Similar findings were reported by Black and colleagues, in a recent study describing this condition in 29 Border terriers; the study was based on an owner survey and the authors reported that excitement, stress and waking from sleep could trigger the episodes in some dogs, however, in the majority of the dogs the episodes appeared to occur at random.[3] In Black's study, 26/29 (90%) owners changed their dog's diet suspecting an association between the attacks and diet.[3] The majority of the owners selected hypoallergenic diets and over 50% of the owners that participated in the survey reported a reduction in the frequency of the episodes.[3] The limited number of dogs in our study and the fact that the new diets were all different does not allow conclusions to be drawn. It is possible that the response to a change in diet might be a placebo effect, as previously described in canine epilepsy trials, and induced by similar anecdotal claims reported on the World Wide Web.[8] It is also possible that the new diets improved the Border terriers' general health status and reduced their stress, in fact 28% of the dogs in this study presented recurrent skin and ear problems and 16% of the dogs had recurrent gastrointestinal problems, which may be associated with an underlying food hypersensitivity. However, there is mounting evidence of an influence of the brain-gut-microbiome axis on central nervous system

283 neurotransmission and enteric glial cells have been involved in the pathophysiology of
284 gastrointestinal disease such inflammatory bowel disease, gluten ataxia, but also Parkinson
285 disease.[9-11] An association between diet and severity of Border terriers attacks as suggested by our
286 findings and Black's study needs to be verified with a prospective study, however, if this
287 hypothesis was to be confirmed, the Border terrier dogs could represent an ideal spontaneous
288 model to investigate the effects of diet on paroxysmal dyskinesias.
289 The Border terriers included in Black's study presented with episodes of abnormal involuntary
290 hyperkinetic movements or muscle tone; dogs with concurrent urination, defecation,
291 hypersalivation were excluded from the study.[3] In our study, we found that 56% of the dogs with
292 similar episodes of involuntary movements showed autonomic signs during the episodes, most
293 commonly hypersalivation and vomiting reported in 48% and 24% of the dogs respectively. The
294 presence of autonomic signs could indicate that the episodes are part of a syndrome affecting
295 multiple areas of the nervous systems as in the case of some channelopathies described in
296 humans.[12]
297 The owners of five Border terriers in this study reported that their dogs also had generalized
298 tonic-clonic seizures with loss of consciousness, clonic movements and autonomic signs; four of
299 the dogs were clinical cases examined by veterinary neurologists, the owner of the last dog
300 (shown in Video 2) was contacted by e-mail and reported a progression toward more severe
301 episodes and suspected generalized seizures, however, video recordings of the suspected seizures
302 were not available for review. Further studies on this subset of Border terriers affected by
303 paroxysmal dyskinesia and possibly generalized seizures are necessary to elucidate the relation
304 between them and their significance in terms of treatment and prognosis. This association may be
305 coincidental since epilepsy is commonly diagnosed in UK Border terriers, in fact a recent study
306 found that in United Kingdom Border terriers are 2.7 times more likely to present epilepsy than
307 crossbred dogs.[13] However, an association between paroxysmal dyskinesia and other neurological
308 disorders, like epilepsy and ataxia, has also been observed in individual human patients or

families.[4] Recently, a mutation in the KCNMA1 gene, encoding the pore-forming a subunit of the large conductance calcium-sensitive potassium (BK) channel, has been discovered in a large human family with coexistent generalized epilepsy and paroxysmal dyskinesia.[14] Sixteen affected individuals presented epileptic seizures (n = 4), paroxysmal nonkinesigenic dyskinesia (n = 7) or both (n = 5).[14]

In this study we described the phenomenology of paroxysms of involuntary movements with preservation of consciousness reported in Border terriers and found clinical similarities between this condition and paroxysmal non-kinesigenic dyskinesia described in humans. The finding of a dystonia phenotype within an inbred population suggests a genetic predisposition. Purebred dogs represent an invaluable tool for mapping and cloning genes affecting human health.[15, 16] The unique history of the dog population characterized by founder effect and periodic population bottlenecks along with stringent breeding programs led to a closed genetic pool within each breed. [17, 18] This reduced genetic variation compared with humans simplifies the mapping of simple and complex diseases' genes. Investigation of the genetic cause of the Border terrier phenotype could improve understanding and treatment of the human condition.

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413 Table 1. Description of the attacks and clinical signs preceding and following them.

	Question type and response rate	Clinical presentation	Number of dogs
Clinical signs preceding the episodes	Clinical signs (CEQ, RR = 58% or 31/53 dogs)	Normal	13
		Disorientated	11
		Ataxic	11
		Fearful	8
		Anxious	7
		Staring	6
		Pacing	5
		Crying	3
		Lethargic	2
	Additional clinical signs reported by the owners (OEQ, RR = 96% or 51/53 dogs)	Stiffening of one limb	2
		Loud intestinal sounds, hypermetric gait	1 dog each
	Autonomic signs (CEQ, RR = 87% or 46/53 dogs)	Salivation	4
		Vomiting	1
Signs during the episode	Clinical signs (OEQ, RR = 96% or 51/53 dogs)	Tremors	30
		Loss of limb control	19
		Ataxia	18
		Muscle contractions	17
		Panting	15
		Hypermetric gait, arched back	4 each
		Head nodding, licking lips, head held down, swaying of the body side to side (titubation)	3 dog each
		Loud intestinal noise, yawing, scooting backwards, distressed, watering eyes	2 dog each
		Pawing at head, head turn	1 dog each
	Muscle tone (CEQ, RR = 85% or 45/53)	Increased muscle tone	37
		Normal	4
		Decreased muscle tone	4
	Side of the body affected (CEQ, RR = 87% or 46/53)	Both sides affected	39
		Left side	4
		Right side	3
	Tremor localization (CEQ, RR = 89% or 47/53)	Trunk	27
		Limbs	23
		Face	3
		All of the above	8
		None of the above	7
	Autonomic signs (CEQ, RR = 87% or 46/53 dogs)	Salivation	17
		Vomiting	5
		Urination	3
		Defecation	1
Clinical signs following the episodes	Clinical signs (CEQ, RR = 64% or 34/53 dogs)	Normal	12
		Lethargic	14
		Ataxic	12
		Fearful	8
		Disorientated	7
		Staring	3
		Pacing, anxious, crying	1 dog each
	Autonomic signs (CEQ, RR = 87% or 46/53 dogs)	Salivation	1
		Vomiting	5
		Urination	3
		Defecation	1

414 CEQ – close-ended question, OEQ – open-ended question, RR – response rate.

415

Table 2. Frequency and duration of the episodes and recovery time in Border Terriers with paroxysms of involuntary movements.

Parameters	Results
Frequency of the episodes (RR = 53% or 28/53)	1 per day to 1 per year (median 1.5 episodes per month)
Highest number of episodes per day (RR = 92% or 49/53)	1 to 6 episodes per day (median 1 episode per day)∗
Duration of episodes (RR = 74% or 39/53)	10 seconds to 2 hours (median 5 and ½ minutes)°
Duration of the recovery time (RR = 68% or 36/53)	Immediate recovery to 2 days (median 7 and ½ hours)

RR = response rate, ∗35% or 17/49 dogs had more than one episode per day, °31% or 12/39 dogs had episodes lasting between 15 minutes and 2 hours

Legends to videos

Video 1. The dog in this video has a 1 year and 5 month history of recurrent episodes with a recent increase in frequency to daily episodes. The dog was examined by a veterinary neurologist during a paroxysm of generalized dystonia and was found to have normal menace response in both eyes and conscious postural reactions in all four limbs, muscle tone was increased in all four limbs.

Video 2. Paroxysmal involuntary movements in a Border terrier dog with a 3-year history of episodes progressing in duration. The video displays the dog with generalized tremors, and dystonia, more evident in the back legs. Panting and excessive salivation are also visible. When the dog walks toward the box the leg is intentionally flexed but the movement exaggerated.