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Clinical characterisation of a novel paroxysmal dyskinesia in Welsh terrier dogs

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ABSTRACT

Breed specific paroxysmal dyskinesias are increasingly recognised in veterinary medicine. We aimed to characterise the phenomenology, clinical course and prevalence of a previously unreported paroxysmal dyskinesia in the Welsh terrier breed. Clinical records of five Welsh terriers with paroxysmal episodes were reviewed. Additionally, owners of Welsh terriers were invited to complete a questionnaire with the aim of characterising paroxysmal episodes in the wider breed population.

Clinical examinations ($n = 5$) and diagnostic investigations ($n = 3$) of affected Welsh terriers were within normal limits, apart from mild-moderate ventriculomegaly on cranial magnetic resonance imaging ($n = 3$). The survey of Welsh terrier owners revealed episodes consistent with a paroxysmal dyskinesia in 41 (22.8%) of 177 respondents. Median age of onset was 59 months. Episodes were predominantly characterised by sustained hypertonicity with periods of limb flexion, abnormal head and body posture, with preserved consciousness. Episode duration ranged from 30 s to 30 min (median, 3 min 30 s), with frequency varying widely between dogs. Affected dogs demonstrated a stable to improving clinical course in most cases. This study investigated a previously unreported paroxysmal dyskinesia in Welsh terriers. Similar clinical signs within the breed were potentially consistent with an inherited cause, worthy of further investigation.

Introduction

Paroxysmal dyskinesias are a heterogeneous group of disorders characterised by recurrent episodes of involuntary and disordered movement or muscle tone with variable duration (Bhatia, 2011). Typical features include altered limb tone leading to abnormal movements or postures (dystonia), and other features of dyskinesia, including signs such as short episodes of muscle contractions resulting in rapid movement, writhing movements secondary to contraction of the muscles of the trunk and flailing limb movements (Urkasemsin and Olby, 2014; Cerda-Gonzalez et al., 2021). These disorders are becoming increasingly recognised in veterinary medicine and several, largely phenotypically distinct canine breed-specific forms have now been described (Lowrie and Garosi, 2017). Signs, age of onset and disease course are typically breed specific (Urkasemsin and Olby, 2014; Lowrie and Garosi, 2017). Currently, a presumptive diagnosis of paroxysmal dyskinesia is made on the basis of consistent clinical signs and the exclusion of other paroxysms such as seizures, where possible (Urkasemsin and Olby, 2014).

A hereditary basis is suspected in most dog breeds and a genetic mode of inheritance has been established in several dog breeds, including the Cavalier King Charles Spaniel, the Soft-Coated Wheaten terrier and the Chinook (Packer et al., 2010; Forman et al., 2012; Gill et al., 2012; Kolicheski et al., 2017). Accurate phenomenology and clinical characterisation of these breed-specific disorders is vital in order to better understand the underlying aetiology, as well as to facilitate successful genetic analyses. The primary aim of this study was to establish the clinical course and phenomenology of a previously unreported paroxysmal dyskinesia in the Welsh terrier dog breed, as well as to estimate the prevalence of this disorder in the breed.

Materials and methods

Institutional ethical approval was obtained from the Ethics and Welfare committee of the Royal Veterinary College (RVC), London (Approval number, URN SR2017-1103; Approval date, 7 July 2017).

Five Welsh terriers presented to the Queen Mother Hospital for Animals (QMHA), RVC, for further investigation of paroxysmal episodes of abnormal movement between September 2016 and September 2018.

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These dogs were identified by retrospective review of clinical records for Welsh terriers presenting for further investigation of paroxysmal episodes or seizure-like episodes for a five-year period between September 2013 and September 2018. Video footage of the dogs during an episode was used in order to make a presumptive diagnosis of a paroxysmal dyskinesia. Abnormal episodes were classified as a suspected paroxysmal dyskinesia if dogs exhibited defined episodes of abnormal, involuntary movement (dyskinesia) leading to writhing or abrupt involuntary repetitive movements of the limb, trunk or neck, which were hypo or hyperkinetic, and/or sustained muscle contraction resulting in abnormal posture (dystonia) with the absence of signs suggestive of epileptic seizure activity such as tonic-clonic movements, impaired consciousness, hypersalivation, urination and/or defecation during the episodes, according to recently proposed veterinary classification (Cerda-Gonzalez et al., 2021). Dogs that did not return to normal immediately post episode were excluded given that a postictal period could not be ruled out. The duration of episodes was recorded in all cases. All dogs had complete physical and neurological examinations. Three of the dogs had magnetic resonance imaging (MRI) of the brain and cisternal cerebrospinal fluid (CSF) analysis. All MRI sequences were obtained with a 1.5 T unit (Intera Pulsar System, Philips Medical Systems). In all cases, two board-certified veterinary neurologists (JF and DW) independently reviewed the MRI sequences available. Full CSF analysis included a total nucleated cell count (TNCC, cells/mL), protein concentration (g/L) and cytological examination. A TNCC $\leq$ 5/mL and a protein concentration $\leq$ 0.25 g/lL were considered normal. Ambulatory electroencephalography (EEG) was performed in one dog (Lifelines Limited).

To investigate the presence of these findings in the wider population, owners of Welsh terriers were invited to participate in an online questionnaire, regardless of whether the owners had seen any abnormal episodes or not (see Appendix A: Supplementary material). The request was made between October 2017 and April 2018 through the Welsh terrier Club, UK and via a dedicated Welsh terrier group on social media. A description of typical signs associated with paroxysmal dyskinesias was provided along with a video recording of a Welsh terrier demonstrating a suspected episode of paroxysmal dyskinesia (see Appendix A: Supplementary material).

In the first section of the questionnaire, owners were asked to provide the date that the questionnaire was completed, along with details including gender, neuter status and age, as well as any medical history. Owners were then asked if their dog had exhibited episodes consistent with those described. Only those that answered 'yes' to this question were required to answer the questions in the remainder of the questionnaire. In the second section of the questionnaire a combination of open and closed questions were used to establish the phenomenology of episodes and clinical course. Episode descriptions, along with review of any available video recordings were used to divide dogs into affected and non-affected groups. Affected dogs were those that had episodes consistent with a paroxysmal dyskinesia according to the above definition.

Results

Clinical cases

Five Welsh terriers presented to the QMHA with a history of paroxysmal episodes of abnormal movements between September 2013 and September 2018. Video recordings were reviewed in all cases and were consistent with paroxysmal dyskinesia based on the criteria above. All dogs demonstrated episodes of dystonia with dyskinesia (writhing or abrupt involuntary limb movements) with normal mentation and an absence of autonomic signs. A precipitating event or clinical factor could not be identified in any dog (n = 0). Three dogs were male neutered while one was female neutered, and one female with a median age at presentation of 67 months (40–85 months). The median age of onset of paroxysmal episodes was 31 months (15–73 months) and all dogs were considered normal by their owners in between episodes. The frequency of episodes varied between dogs ranging from 1/week to 1–2/year. The median duration of episodes was 4 min (3–12 min). General physical and neurological examinations were normal in all dogs. Haematology and serum biochemical profiles were also within normal limits in all dogs.

Cranial MRI revealed a mild (n = 1) or moderate (n = 2) generalised dilation of the lateral ventricles as well as an absent septum pellucidum in the three dogs for which it was performed (Fig. 1). Cisternal CSF analysis was performed in two dogs and was within normal limits in each case with a median TNCC of 0.50/mL (0–1/mL) and median protein concentration of 0.22 g/L (0.18–0.26 g/L). Electroencephalogram (EEG) was unremarkable with no evidence of interictal epileptiform activity in one dog for which it was performed, with no paroxysmal events witnessed during the recording period.

Of these five Welsh terriers, two underwent treatment trials with anti-seizure medication. One dog received oral levetiracetam (Keppra, UCB Pharma SA) at 20 mg/kg q8h for 2 weeks and the other received both oral phenobarbital (Epiphen, Vetoquinol) at 3 mg/kg q12 h for 2 years and imepitoin (Pexion, Boehringer Ingelheim Animal Health) at 10 mg/kg q12 h for 3 years prior to presentation with no reported change in episode frequency during treatment. Three dogs were started on a gluten-free diet, with no prior testing for anti-gluten antibodies and no subsequent change in episode frequency reported. Long-term follow-up was available for two dogs after 895 days and 584 days, respectively, with both dogs alive and demonstrating a stable frequency of episodes and normal neurological examination at that time. The other three dogs were lost to long-term follow-up.

Questionnaire data

Study population

The questionnaire was completed for 177 Welsh terriers; 76 had abnormal episodes reported. A combination of open and closed questions were used to establish the nature of events, which included a request for a description of episodes (Q.5) and more directed questions regarding the mental status of the dog (Q.12) and any associated autonomic signs (Q.13; Appendix A: Supplementary material). Of the 76 Welsh terriers with abnormal episodes, 35 were excluded either due to a description that was not consistent with paroxysmal dyskinesia (n = 8), an inadequate description of episodes (n = 25; Cerda-Gonzalez et al., 2021), or clinical signs that were suggestive of vestibular events (n = 2) based on the criteria stated above. Of those eight dogs that had a description that was not consistent with paroxysmal dyskinesia, six had features suggestive of epileptic seizures (jaw chattering, n = 4; tonic-clonic movement and altered mentation, n = 2) one had a persistent tremor, and another dog was reported to have persistent restless behaviour. The description of episodes of the remaining 41 dogs were consistent with a suspected paroxysmal dyskinesia, with video footage available for review in three. Specifically, they demonstrated periods of abnormal movement with no periods of tonic-clonic movement, altered mentation or autonomic signs. All further analyses were performed on the data obtained from the questionnaire. The sex, neuter status and age of the dogs at the time the questionnaire was completed were recorded (Table 1). The median age of onset of signs in the affected group was 59 months (range, 8–156 months).

Episode characterisation

Phenomenology was similar among the 41 affected dogs, and was typically consistent with the example shown in Appendix A: Supplementary material. All but four dogs demonstrated episodes of dystonia (sustained muscle contraction) resulting in abnormal postures. These were characterised by sustained limb dystonia with periods of limb flexion (n = 35; 85.4%), which predominantly affected the thoracic limbs (n = 27/35; 77.1%). Abnormal body posture with lateral neck and

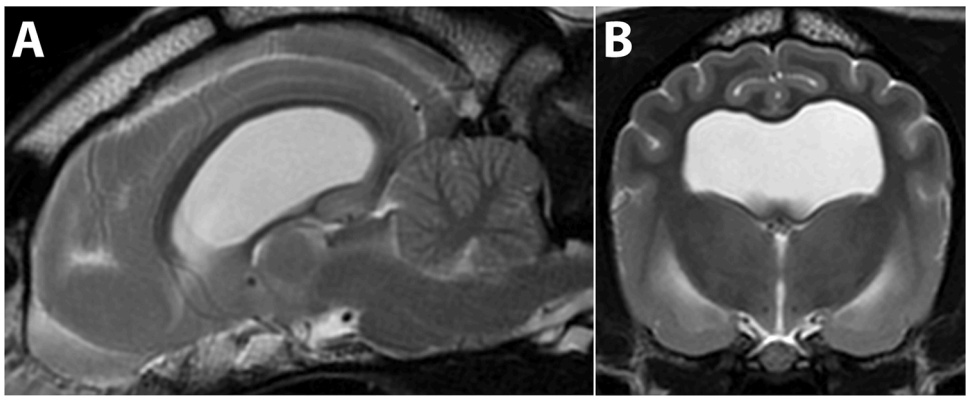

Fig. 1. MRI findings in Welsh Terrier dogs with suspected paroxysmal dyskinesia. Mid-sagittal (A) and transverse (at the level of the thalamus) (B) images of a dog with suspected paroxysmal dyskinesia. Note ventriculomegaly with generalised dilatation of the lateral ventricles and absent septum pellucidum (A, B).

Table 1
Age, sex and neuter status of Welsh terriers affected and not affected by dyskinesia.

	Affected	Not affected
n (% of all dogs)	41 (23.2)	101 (57.0)
Sex (%)		
Female	23 (56.1)	46 (45.5)
Male	18 (43.9)	55 (54.5)
Neuter status (%)		
Female entire	5 (12.1)	11 (10.9)
Female neutered	18 (44.0)	35 (34.7)
Male entire	5 (12.2)	13 (12.9)
Male neutered	13 (31.7)	42 (41.5)
Age (months)[a]		
Median	96	67
Range	23–197	2–192

[a] At the time the questionnaire was submitted.

spine flexion ($n = 15$; 36.6%), kyphosis ($n = 7$; 17.1%) and abnormal head posture ($n = 4$; 9.8%) were also reported. During episodes ten dogs exhibited features characterised by short bursts of muscle contraction affecting one or more limbs ($n = 6$; 14.6%). Writhing movements involving the neck or trunk were seen in four dogs (9.8%). Consciousness was perceived preserved in all dogs ($n = 41$; 100.0%). Autonomic signs, with the exclusion of gastrointestinal signs after the event, were not a feature of episodes in any of the included cases. Dogs were most commonly standing during episodes ($n = 27$; 65.9%); however, some were lying down at times during the episode ($n = 14$; 34.1%). The duration of episodes ranged from 30 s to 30 min (median, 3 min and 30 s). Episodes occurred multiple times daily in some dogs, while in others they were rarely witnessed (<1/year) with a median of two episodes/month. Although most dogs did not have any other clinical signs associated with the episodes ($n = 27$; 65.9%), some dogs ($n = 14$; 34.1%) exhibited gastrointestinal signs, such as vomiting, diarrhoea, flatulence and borborygmi following episodes.

Occurrence of events

A precipitating factor could not be identified in most dogs ($n = 32$; 78.0%), however when identified ($n = 9$; 22.0%) most appeared to be associated with stress, excitement or exercise ($n = 6/9$; 66.7%). Some dogs experienced episodes that appeared to be precipitated by factors that include feeding ($n = 3/9$; 33.3%), hot weather ($n = 1/9$; 11.1%) or a change in position (standing from lying down; $n = 1/9$; 11.1%).

Clinical progression

All but two dogs ($n = 39$; 95.1%) were reported to be normal in between the episodes. Of the two other dogs, one was reported to be lethargic but otherwise clinically well. Another developed right pelvic limb paresis and vestibular signs six years after the onset of signs of a paroxysmal dyskinesia. Given the lack of clinical progression in the first case and time period between the onset of paroxysmal episodes and other neurological signs in the latter these signs were deemed unlikely to be related to the reported events.

Of those responders that could comment on the progression of episodes ($n = 26$; 63.4%) most were reported to demonstrate a stable ($n = 10/26$; 38.5%) or improving ($n = 8/26$; 30.8%) clinical course regarding the frequency, duration and severity of episodes. A proportion of affected dogs ($n = 8/26$; 30.8%), however, demonstrated a worsening clinical course. These observations were made over a median period of 36 months (range, 0–146 months). Episodes were not perceived by the owners to affect the quality of life in the majority of dogs ($n = 26/41$; 63.4%).

Treatment

Sixteen dogs in the affected population (n = 16, 39.0%) received medication or a diet trial aimed at management of paroxysmal episodes. The treatment that was administered varied and included: medical management with non-steroidal anti-inflammatory medication (n = 1), steroid medication ($n = 1$), muscle relaxants ($n = 1$), or anti-epileptic medication (phenobarbital, levetiracetam, zonisamide, potassium bromide, gabapentin and diazepam; $n = 9$); diet trials with gluten-free ($n = 3$), grain-free ($n = 1$) or raw diets ($n = 1$); and nutritional supplements ($n = 1$). In common with a recent report of a Welsh terrier dog with paroxysmal dyskinesia (Green and Olby, 2021), a possible positive treatment response was reported in two dogs receiving levetiracetam. However, due to the wide variety of non-standardised interventions provided it was not possible to meaningfully evaluate response to treatment.

Discussion

This study provides the first clinical characterisation of a novel paroxysmal dyskinesia in the Welsh terrier dog breed. Episodes were most commonly characterised by defined periods of dystonia (leading to altered posture) and or other signs of dyskinesia (leading to abnormal, involuntary and repetitive movement of the limb, trunk or neck) with retained consciousness and no autonomic signs during episodes. The age of onset and duration of episodes were variable with no consistent trigger factors identified. Dogs were typically normal in between episodes and diagnostic investigations performed in three clinical cases did not identify a specific underlying cause. Given the prevalence of consistent clinical signs in the surveyed population of Welsh terriers, a paroxysmal dyskinesia of suspected hereditary underlying aetiology is worthy of further investigation in this breed.

Dyskinesias in humans represent a heterogeneous group of disorders with significant overlap in phenomenology of episodes (Erro et al.,

2014). The most common clinical signs exhibited by affected Welsh terrier dogs were sustained limb flexion, consistent with previous definitions of dystonia, while a proportion displayed abrupt, irregular limb movement or writhing consistent with previous descriptions of dyskinesia (Cerda-Gonzalez et al., 2021). Dyskinesia was most commonly seen in association with dystonia but was occasionally occurred in isolation. A classification system has been devised for use in human patients, which groups individuals into the following three categories according to the precipitating event: paroxysmal kinesigenic dyskinesia (sudden movement); paroxysmal non-kinesigenic dyskinesia (typically occur spontaneously without any recognised triggers, however, alcohol, caffeine, fatigue, emotional excitement, hunger, fever and concentration have been reported as precipitating factors); and paroxysmal exertion-induced dyskinesia (Demirkiran and Jankovic, 1995; Bruno et al., 2007). Categorisation schemes such as this provide an important platform for genetic analyses and sub classification according to causative mutation. Dogs closely parallel human patients in the development of disease (Pennisi, 2004; Sutter and Ostrander, 2004; Shearin and Ostrander, 2010; Richter et al., 2015), and to date, paroxysmal dyskinesias have been reported in several canine breeds, including the Cavalier King Charles Spaniel (CKCS), Scottish terrier, Chinook, Border terrier, Springer spaniel, Boxer, Bichon Frise, Soft-coated wheaten terrier, Labrador retriever, Jack Russell terrier, Maltese terrier (Polidoro et al., 2020) and the German short haired pointer (Lowrie and Garosi, 2017). Of paroxysmal dyskinesia affected breeds episodic falling syndrome identified in CKCS and Scottie cramps in Scottish terriers are typically triggered by exercise, stress or excitement and could therefore be classified as paroxysmal exertion-induced dyskinesia. However, in common with findings presented here in the Welsh terrier breed, according to the human classification scheme the vast majority of these breed-specific primary paroxysmal dyskinesias in dogs can be classified as paroxysmal non-kinesigenic dyskinesia (Lowrie and Garosi, 2017).

Twenty three percent of the questionnaire population had signs indicative of a paroxysmal dyskinesia. While this suggests a high prevalence in the Welsh terrier population it is important to note that this was a survey aimed at characterising paroxysmal dyskinesia and so will be susceptible to bias, in that owners with affected dogs may be more likely to complete the survey. A more systematic review of the Welsh terrier population to include data gained from breeding club mailings to owners of Welsh terriers or gathering information as part of a wider health survey for the breed, may help to support these provisional findings. Nonetheless, the high number of affected dogs, phenotypic overlap and clustering of episodes in the Welsh terrier breed are consistent with an underlying inherited cause. Detailed clinical characterisation of this paroxysmal dyskinesia in the Welsh terrier, coupled with future pedigree and genetic analyses may advance our understanding of the pathophysiology of this rare condition in canine patients, leading to a greater understanding and more targeted therapies.

In common with people, primary (idiopathic, presumed genetic or genetic) paroxysmal dyskinesias are the most common form recognised in the canine population (Urkasemsin and Olby, 2014; Lowrie and Garosi, 2017). However, sporadic reports of secondary paroxysmal dyskinesias exist in the veterinary literature, such as those secondary to drug administration, such as phenobarbital and propofol (Kube et al., 2006; Mitek et al., 2013). Interestingly, the three Welsh terriers that underwent further investigation into suspected paroxysmal dyskinesia had ventriculomegaly suggestive of reduced brain volume identified on cranial MRI. One of these dogs also underwent interictal awake ambulatory EEG with no evidence of abnormal epileptiform activity. Reports of paroxysmal dyskinesias secondary to structural brain disease are very scarce in the veterinary literature, with only sporadic descriptions reported (Lowrie and Garosi, 2017). Ventriculomegaly is a common incidental finding in many dogs and the relationship between imaging findings and clinical signs is currently unclear (Laubner et al., 2015). The lack of reports of normal brain MRI findings in the Welsh terrier breed makes it difficult to draw conclusions regarding any clinical significance related to the ventriculomegaly and absence of the septum pellucidum. Although worthy of further investigation in larger numbers, the relevance of these findings is therefore currently unclear and to the authors' knowledge, have not previously been associated with paroxysmal dyskinesia in human or veterinary patients.

Episode phenomenology was similar among the affected Welsh terrier population ($n = 41$), with strong similarities to previous reports of dogs and humans with paroxysmal dyskinesias (Urkasemsin and Olby, 2014; Lowrie and Garosi, 2017). While epileptic seizures cannot be completely excluded in the absence of an EEG recording obtained during an episode, epileptic seizures appear an unlikely cause of the episodes, given that dogs exhibited generalised features, including the involvement of limbs on both sides of the body, and consciousness was preserved. Thirty four percent of dogs exhibited gastrointestinal signs following episodes, including vomiting, diarrhoea, flatulence and borborygmi. Interestingly, gastrointestinal signs, including borborygmi and vomiting have been reported in approximately 50% of Border terrier dogs that have a paroxysmal gluten sensitive dyskinesia in a single study and in 22% and 24% of Border terrier dogs of subsequent studies (Black et al., 2014; Marioni-Henry et al., 2016; Stassen et al., 2017; Lowrie et al., 2018). Further investigations of any etiological and clinical overlaps between Welsh terrier and Border terrier breeds are warranted, particularly given the phenotypic similarities and shared terrier breed ancestry. The majority of owners reported a stable or improving clinical course over time, consistent with other canine and human paroxysmal dyskinesias (Forman et al., 2012; Urkasemsin and Olby, 2015; Waln and Jankovic, 2015; Lowrie and Garosi, 2016).

The results of this study need to be viewed in relation to the inherent limitations of retrospective investigations, such as a lack of complete follow-up information in the clinical cases. Results from the wider population were also derived from an owner questionnaire and are therefore dependent on the accuracy of owner descriptions, with paroxysmal dyskinesias often a challenging diagnosis to make. While video footage was not a requirement for inclusion in the current study, stringent criteria and carefully selected questions were applied before cases were included in the affected group in order to maximise the validity of results. However, as a result, it is possible that this study overestimates the prevalence of paroxysmal dyskinesia in the breed. Although the lack of video footage should be considered when interpreting these findings, this study design likely allowed the evaluation of a larger population of Welsh terrier dogs than would be possible if the ability to capture video footage was a requirement. Despite these limitations and those discussed above regarding questionnaire-based surveys, the results of this study provide an important database and initial step for future investigations aimed at confirming the suspected hereditary basis within the Welsh terrier dog breed, as well as to ultimately establish the underlying aetiology which may inform potential therapy.

Conclusions

This study appears to be suggestive of a breed-related paroxysmal dyskinesia in the Welsh terrier, with characteristic clinical features. Further studies are required to determine the heritability of the disorder as well as the presence of a potential underlying genetic cause.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2022.105801.

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