The Veterinary Journal 213 (2016) 33–37

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

# Natural history of canine paroxysmal movement disorders in Labrador retrievers and Jack Russell terriers

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ARTICLE INFO

*Article history:*
Accepted 3 March 2016

*Keywords:*
Seizure
Dog
Dyskinesia
Treatment
Progression

ABSTRACT

Delineation of the typical disease progression in canine paroxysmal dyskinesia (PD) may assist in evaluating therapeutic agents during clinical trials. Our objective was to establish the natural disease course in a group of dogs diagnosed with PD that received no medication. Fifty-nine dogs (36 Labradors, 23 JRTs) with clinically confirmed PD and a follow-up of ≥3 years were retrospectively reviewed.

Dogs with PD had a young onset, were triggered by startle or sudden movements, and had a male bias (75%) with the majority being entire sample population. Twenty-one dogs (36%) had at least one event comprising cluster episodes. Episode duration and frequency varied dramatically, even within an individual. Median follow-up was 7 years. No concurrent disease was identified in any dog that was investigated. The natural history was self-limiting with 32% entering remission and an improvement in 75%. Episodes reduced in terms of frequency and duration in Labradors and JRTs respectively. Remission was lower in dogs with cluster episodes than those without. These findings suggest that the diagnostic yield of advanced neuroimaging techniques in dogs with video footage and historical data supporting PD, without neurological deficits, is low. The presence of cluster episodes is of predictive value for the prognosis of canine PD. Future research should be cautious in reporting treatment response for PD without first considering the spontaneous remission rate and improvements in untreated dogs documented in this study.


## Introduction

Paroxysmal dyskinesias (PD) are increasingly described although they remain poorly characterised in veterinary literature. They are recognised as a group of hyperkinetic paroxysmal movement disorders whose main feature is involuntary sustained muscle contraction. In PD, recurrent episodes are assumed to be the result of a molecular or structural abnormality and treatment, when indicated, is targeted at controlling episode frequency and severity.

Known causes of PD in dogs are thus far limited to genetic (Forman et al., 2012; Gill et al., 2012; O'Brien et al., 2015), drug-induced (Kube et al., 2006; Mitek et al., 2013), and dietary factors (Lowrie et al., 2015). The first genetically mapped paroxysmal movement disorder was episodic falling syndrome in the Cavalier King Charles spaniel (Forman et al., 2012; Gill et al., 2012). Phenobarbital was found to elicit dyskinesia in an epileptic Chow (Kube et al., 2006). Border terriers suffer from canine epileptoid cramping syndrome (Black et al., 2013) which has been found to be a manifestation of gluten sensitivity (Lowrie et al., 2015). Although PD is most commonly of idiopathic or familial aetiology, other causes in people exist; for example, secondary or symptomatic dyskinesia is reported, resulting from structural central nervous system lesions such as multiple sclerosis, head trauma, cerebral palsy, cerebrovascular accidents or encephalitis (Bax et al., 2005; Lotze and Jankovic, 2003; Dale et al., 2009).

A current classification of human PD is one proposed by Demirkiran and Jankovic (1995), based solely on precipitating factors of the episodes and not phenomenology. This idea was born out of the observation that each type of PD can manifest with dystonia, chorea, athetosis, or a combination of abnormal movements. The classification distinguishes four categories:

1. paroxysmal kinesigenic dyskinesia (PKD) – incited by sudden movements.
2. paroxysmal nonkinesigenic dyskinesia (PNKD) – occurring spontaneously at rest
3. paroxysmal exertion-induced dyskinesia (PED) – precipitated by fatigue
4. paroxysmal hypnogenic dyskinesia (PHD) – attacks occur during sleep

Various therapies are reported in the management of these conditions in people. Phenobarbital (Harcourt-Brown, 2008), acetazolamide (Gill et al., 2012; O'Brien et al., 2015) and clonazepam (Garosi et al., 2002) have been prescribed with varying success in

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http://dx.doi.org/10.1016/j.tvjl.2016.03.007
1090-0233/

**Table 1**
Definitions of clinical signs that incorporate the term 'dyskinesia'.

| | |
|---|---|
| Chorea | An abrupt, unsustained contraction of different muscle groups |
| Athetosis | A prolonged, slow contraction of the trunk muscles resulting in bending and writhing of the body and precluding maintenance of a stable posture |
| Choreoathetosis | Involuntary movements that have characteristics of both chorea and athetosis |
| Ballism | An abrupt contraction of the limb muscles which results in flailing movement of the limb and is often unilateral |
| Dystonia | A sustained involuntary contraction of a group of muscles producing abnormal postures |

dogs. However, future therapies should be given with an understanding of the natural progression of this condition in order to establish their efficacy. The natural course of PD is unknown. Delineation of the typical disease progression may assist in the evaluations of therapeutic agents during clinical trials.

The following analysis was designed using the largest reported sample of dogs affected with PD to date. We performed this retrospective study to determine the prevalence of positive diagnostic findings in dogs with PD and to determine the natural course of this disease in two breeds of dog seen commonly with PD at our clinic; the Labrador and Jack Russell terrier (JRT).

## Materials and methods

The study was designed as a retrospective hospital based study with follow-up. Dogs included in this study were client-owned clinical cases diagnosed with PD evaluated between January 2005 and January 2015 that had received no medication for PD, and with a follow-up of at least 3 years. Criteria were used to limit the phenotype of cases included by restricting selection to Labradors and JRTs only. These breeds that were chosen with PD have not been previously characterised in these breeds, though they commonly present with PD in our clinic. Analysis of each breed was performed separately. Inclusion required video evidence of at least one typical episode of PD at the time of or following investigation and its assessment by a Board-certified neurologist. Dogs that had received treatment for PD were excluded from analysis. All dogs had to have at least a 6-month history of PD.

Using phenomenological classification and in conjunction with the history, a diagnosis of PD was suspected in accordance with previous diagnostic guidelines (Packer et al., 2010; Black et al., 2013; Lowrie et al., 2015). Briefly, a diagnosis of PD was suspected when dogs had episodes in the absence of mentation alterations, autonomic signs, abnormal inter-ictal signs and post-ictal behaviour. Furthermore, the core movement had to be dyskinesia; that is, involving movement of the limb(s) (i.e. chorea, athetosis, dystonia or ballism; see Table 1 for definitions). Video examples are available of Labradors and JRTs having typical episodes (see Appendix: Supplementary Video S1 and S2). Clinical data were extracted, including signalment, duration and frequency of clinical signs (including the length of observation period over which these data were based), triggers (i.e. owners were asked if anything they had identified could trigger an episode) and survival data. Clinicopathologic data and diagnostic imaging results were also recorded where performed to identify concurrent disease processes.

Follow-up was assessed via telephone interview with the owners of the dogs and/or referring veterinarians. The information obtained included current episode frequency and duration, presence or absence of cluster episodes, potential episode triggers, whether the dog was currently alive or dead, and, if applicable, the date and presumed cause of death.

Two observational periods were chosen to assess episode frequency and duration; presentation and follow-up. The first observational period was calculated as the number of episodes per month in the 6 months prior to presentation at our clinic. Episode frequency at follow-up was calculated as the number of episodes per month in the 2 years preceding follow-up or in the 2 years prior to death and provided the second observational period. Episode duration in these observational periods was assigned to one of the following categories; <2 min, 2–5 min, 5–10 min, 10–30 min, 30–60 min, 60–120 min, and >120 min.

Cluster episodes were defined as more than one episode in a week. Remission of PD was defined as no episodes for ≥2 years. Remission was defined as either 'early' (i.e. within 24 months of onset), or 'late' (i.e. ≥24 months following onset).

## Results

Fifty-nine dogs met the inclusion criteria and were included in the analysis incorporating 36 Labradors and 23 JRTs. The majority (53/59) of owners kept a diary of each observed episode.

### *Signalment*

The median age of the 36 Labradors at episode onset was 2 years 3 months (range, 9 months to 10 years 8 months). Seven Labradors were female (19%; 2/7 neutered) and 29 were male (81%; 9/29 neutered). In contrast, the median age of onset in JRTs was 4 years 8 months (range, 1 year to 8 years) with 8/23 being female (35%; 5/8 neutered) and 15/23 being male (65%; 4/15 neutered).

### *Triggers*

Episodes began most commonly following extremes of temperature in JRTs (83%; 19/23 dogs) and after sudden movements or being startled (58%; 21/36 dogs) or with excitement (25%; 9/36 dogs) in Labradors. The episodes always occurred at home and never happened when sleeping or during exercise. No diurnal rhythm was observed in any dog and many owners described stress or variation in daily routine as an inciting factor in both breeds.

### *Frequency and duration of episodes*

The median duration of clinical signs in all dogs at presentation was 9 months (range 6 to 23 months); 10 months in Labradors (range 7 to 23 months) and 8 months in JRTs (range 6 to 21 months). The reported median frequency at presentation was one episode every 3 weeks in Labradors (range, one every 6 months to 12/month) and one per month in JRTs (range, one every 6 months to two per month). Nineteen Labradors (19/44; 43%) and seven JRTs (2/23; 9%) had at least one event comprising cluster episodes. On average, duration of episodes in both Labradors and JRTs was similar (Figs. 1,2) although episodes varied dramatically in this respect, even within an individual.

### *Results of investigations*

All dogs had unremarkable haematology and biochemistry profiles. Creatine kinase was increased in three dogs (all Labradors). Further testing in some dogs, which did not reveal any abnormalities, included dynamic bile acid testing (n = 25); urinalysis (n = 19); serum ammonia (n = 14); thyroid status (n = 8); ACTH stimulation test (n = 3); pre- and post-exercise plasma lactate and pyruvate concentrations (n = 2); acetylcholine receptor antibody serology (n = 2); ionised calcium (n = 1); echocardiogram (n = 12); halter monitoring during an episode (n = 1); cardiac (n = 2) and abdominal ultrasound (n = 14); radiographs of the chest (n = 17), abdomen (n = 2), stifles (n = 4), hips (n = 6) and spine (n = 1); urinary organic acids (n = 3); *Neospora* (n = 6) and *Toxoplasma* (n = 5) serology; electrophysiology (motor nerve conduction and electromyography: n = 5); CSF examination (n = 48); and MRI of the brain (n = 48), lumbosacral spine (n = 3), thoracic spine (n = 3), cervical spine (n = 3), and lumbar spine (n = 3).

### *Follow-up*

Median follow-up time (from first observed episode to date of death or follow-up) in all dogs was 7 years. The median follow-up time was 6 years 8 months (range, 3 years to 12 years 2 months) in Labradors and 9 years (range, 3 years 4 months to 14 years 10 months) in JRTs.

The frequency and duration of episodes was reported to have decreased in 25/36 (86%) Labradors, progressed in five Labradors and remained static in six Labradors at follow-up (Fig. 1). Owners of JRTs reported an improvement in duration and frequency in 19/23 (57%) dogs, a deterioration in 2/23 and a static course in 2/23 dogs (Fig. 2). Median frequency at follow-up was one episode every