Canine Paroxysmal Movement Disorders

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KEYWORDS

• Episodic movement disorders • Hypertonicity • Episodic falling
• Hyperkinetic episode • Paroxysmal dyskinesia • Scottie cramp

KEY POINTS

- Paroxysmal dyskinesias form a heterogeneous group of disorders recognized with increasing frequency in dogs and characterized by episodic, involuntary, abnormal movements.
- Classification of these disorders in veterinary medicine has not been attempted, but most seem to be comparable to paroxysmal nonkinesigenic dyskinesia in humans.
- Hypertonicity of limbs characterized by sustained flexion (dystonia) and brief flexion (chorea) of muscles are common clinical signs.
- During an episode, affected animals do not exhibit autonomic signs, electroencephalographic abnormalities, or change in consciousness.
- Clinical signs do not usually respond to antiepileptic drugs.

INTRODUCTION

Movement disorders are a heterogeneous group of diseases in humans and animals characterized by involuntary movements without changes in consciousness. Episodic or paroxysmal movement disorders can be broadly classified into paroxysmal dyskinesias and episodic ataxias; episodic ataxias are usually grouped with hereditary ataxias and will not be considered further in this review. The paroxysmal dyskinesias are a fascinating group of central nervous system diseases that produce dramatic and often puzzling clinical signs, canine examples of which have been described in veterinary medicine from as early as the 1940s.[1] However, it is only recently that these diseases have been grouped together under the label of paroxysmal dyskinesia and their genetic causes investigated in detail. They are characterized by episodic hyperkinesis

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impairing posture and locomotion without loss of consciousness.[2] Chorea, dystonia, ballism, and athetosis are all signs of hyperkinesis that are common to the phenomenology of this group of diseases (**Box 1**). They are differentiated from seizures because, during episodes, consciousness and electroencephalography (EEG) are normal and there is a lack of autonomic signs. However, differentiation from seizures can be difficult, and now that the underlying genetic mutations are described in humans, it is becoming clear that specific mutations in dyskinesia patients may also be associated with seizures (eg, familial infantile convulsions with paroxysmal choreoathetosis) or a high frequency of seizure disorders in their families.[3]

Paroxysmal dyskinesias (PDs) can be primary, secondary, or part of more complex neurologic syndromes.[3] This review focuses on the primary PDs, in which patients are normal between episodes; however, it is important to note that an example of a secondary dyskinesia has been described in veterinary patients.[4] In humans, classification of PDs has evolved over time. Initially, they were described by their clinical signs, leading to terms such as paroxysmal choreoathetosis. More recently, a clinically useful classification system has been developed in which patients are categorized by the precipitants, age of onset and duration of attacks.[5] There are 3 main forms: (1) Paroxysmal kinesigenic dyskinesia (PKD), in which episodes are precipitated by sudden movements; (2) paroxysmal nonkinesigenic dyskinesia (PNKD), in which episodes are not triggered by movements, but may be associated with stress, alcohol, or caffeine; and (3) paroxysmal exertion-induced dyskinesia, in which heavy exercise produces signs.[5] A fourth form known as paroxysmal hypnogenic dyskinesia in which episodes occur during sleep has been reclassified as a frontal lobe epilepsy and removed from the classification system. Key features of each type of dyskinesia are listed in **Table 1**. Note also that the genetic causes described to date are listed and show that, although the clinical categorization is useful, genetic definition of the disorders shows crossover between types, and new classification systems in which the disease is first assigned to a category as described, and then assigned to a genetic category, are emerging.[3]

In veterinary medicine, paroxysmal dyskinesia has been used as a broad term to describe an abnormal, sudden, involuntary contraction of a group of skeletal muscles that recurs episodically.[6] This group of diseases is not well categorized and names

Box 1
Terms used to describe involuntary movements in human medicine

- Hyperkinesis: General term for increased muscle activity.
- Dyskinesia: Impairment of voluntary movements
- Chorea: Brief muscle contractions producing rapid movements similar to those seen during dancing. Frequently accompanied by athetosis giving rise to the term choreoathetosis.
- Dystonia: Sustained muscle contractions producing abnormal movements and postures
- Ballism: Flailing limb movements
- Athetosis: Writhing movements produced by sustained contraction of the trunk muscles. This is frequently accompanied by chorea.
- Movements affecting 1 side of the body are identified by the prefix "hemi"

Although the term dystonia is commonly used in canine reports, and ballism is occasionally reported, the terms chorea and athetosis are rarely used. This may reflect species differences or a failure to recognize these signs in dogs.

Data from Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26(6):1157–65.

Table 1
Comparison of key features in the 3 main categories of human paroxysmal dyskinesia

	PKD	PNKD	PED
Trigger	Sudden movements	Caffeine, alcohol, strong emotion	Prolonged exercise
Duration of signs	<2 min	10 min to 12 h, usually <4 h	Mean 2–5 min, ≤2 h
Age of onset	1–20 y	Early childhood, mean 8 y	2–30 y; mean, 5 y
Frequency of signs	Multiple attacks a day, improves and may resolve with age	Clusters several times a year	Dependent on exercise
Known genetic causes	*PRRT2*	*PRRT2, MR-1, KCNMA1*	*GLUT1, MR-1*
Treatment	Respond to anti-epileptic drugs and carbamazepine	Avoid triggers; clonazepam effective in majority of patients; haloperidol, gabapentin, and L-dopa may be of benefit	Ketogenic diet, gabapentin.

Abbreviations: GLUT1, glucose transporter type 1 gene (also known as *SLC2A1*); *KCNMA1*, calcium-activated potassium channel, subfamily M, alpha member 1; *MR-1*, myofibrillogenesis regulator 1 (the function of this gene is poorly understood); PED, paroxysmal exertion-induced dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; *PRRT2*, proline-rich transmembrane protein 2 gene (defects in this transmembrane protein are thought to destabilize synapses and alter neuronal excitability but the pathophysiologic basis requires more investigation).

given to different disorders include hypertonicity syndrome, episodic falling, hyperkinetic episodes, and dyskinesia. Similar to their human counterparts, they are distinguished from seizures by an absence of autonomic signs, EEG abnormalities, or changes in consciousness during episodes. Affected animals are normal between episodes. Nevertheless, when faced with a patient exhibiting episodic neurologic signs, a careful workup is needed to rule out other disorders. Transient, self-limiting, involuntary movements can be a result of disorders of the central nervous system (PDs, epileptic seizures, episodic ataxia), vestibular dysfunction, disease of muscle (eg, muscle cramps from a variety of causes), or peripheral nerve hyperexcitability (eg, hypocalcemia, myokymia, neuromyotonia). A logical approach to these cases is provided in **Fig. 1**.

Hereditary paroxysmal dyskinesias have been described in Scottish Terriers,[7] Cavalier King Charles Spaniels,[8] Chinooks[9] and Border terriers.[10] Episodic head tremors are recognized as hereditary or breed-associated disorders in the Doberman pinscher[11] and the English bulldog[12] and may represent a form of paroxysmal dyskinesia. Sporadic cases have been reported in a variety of breeds, the details of which are summarized in **Table 2**.[6,13]

INHERITED DISEASES

Episodic Falling in Cavalier King Charles Spaniels

Cavalier King Charles spaniels suffer from familial paroxysmal exercise-induced dyskinesia, also known as episodic falling, which has been recognized within the breed since the 1960s, but was first reported in the 1980s,[8] at which time it was suspected to be a myopathy.[14,15] It is also known as sudden collapse, muscle hypertonicity, and hyperekplexia, although the latter term is misleading because "hyperekplexia"

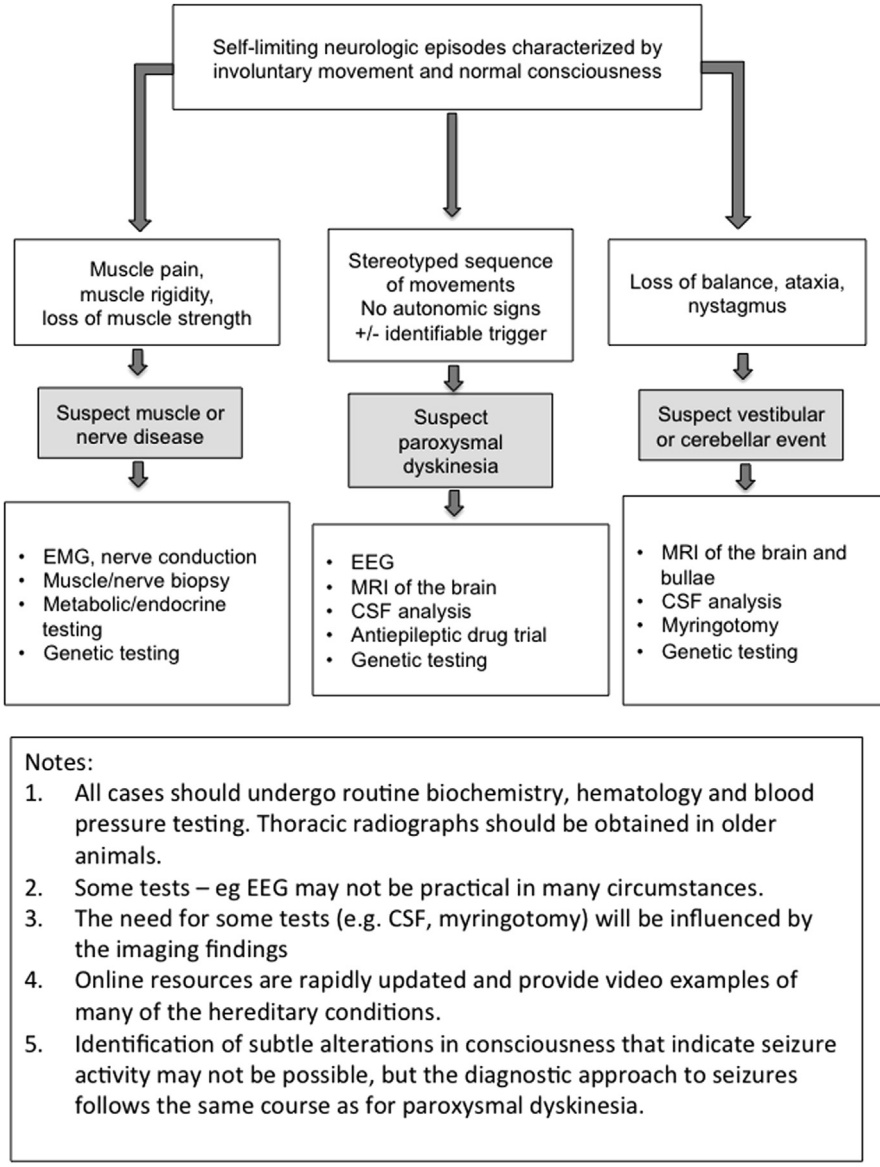

Fig. 1. Logical approach to a dog with an involuntary movement disorder.

describes startle disorders that are triggered by unexpected stimuli such as noise and touch and classically caused by mutations in the genes involved in glycinergic synaptic transmission.[16] The age of onset of episodic falling episodes ranges from 3 to 48 months.[8] Episodes are triggered by exercise, excitement, and stress, and as such it may be more accurately classified as a PNKD. Affected dogs exhibit progressive muscular hypertonicity during an episode during which there is marked dystonia of the pelvis or all 4 limbs. Typically, an episode is characterized by lowering of the head, arching of the lumbar spine, stiffness of the limbs that creates a 'deer-stalking' posture, and falling over.[8,15] The duration of episodes varies among cases ranging

from a few seconds to several minutes[8,15] and they are self-limiting or can be limited by interaction with the owner.[8] There is no loss of consciousness during the period of collapse. There are no significant clinical or neurologic abnormalities and no spontaneous discharges on electromyography in between episodes.[15] The benzodiazepine, clonazepam (0.5 mg/kg every 8 hours), has been used to treat episodic falling effectively[17] and acetazolamide is also reported to be beneficial. An autosomal-recessive mode of inheritance has been demonstrated.[18] On postmortem examination, a variety of changes have been described in skeletal muscle, such as enlargement and proliferation of the sarcoplasmic reticulum, but these are likely to be secondary to excessive muscle contractions.[14,15,19] Recently, this dramatic condition has been linked to a deletion in the gene *BCAN*[18,19] that encodes a protein called brevican. This protein is a component of the extracellular matrix proteoglycan complex and is found at high levels in the central nervous system as part of the perineuronal network. In particular, it is found at the nodes of Ranvier in large-diameter axons and is thought to play a role in homoeostasis of the microenvironment in the face of fluctuating ion concentrations. It is proposed that disruption of these extracellular complexes results in alterations in nerve conduction and in synaptic stability.[19] As is typical for all genetic disease, there is phenotypic variability and both research groups that described the mutation identified dogs homozygous for the mutation, but with no reported clinical signs. They theorized that these dogs may simply not have exerted themselves to the point of producing signs, but it is important to note that mouse *BCAN* knockouts are clinically normal. Moreover, compensatory pathways involving upregulation of other proteoglycans may occur and account for the observation that some dogs can become clinically normal after a period of years.[18] This genetic test is offered at http://www.aht.org.uk/cms-display/genetics_canine.html.

PNKD in Chinooks

Familial PNKD has been reported in the Chinook with the age of onset ranging from 2 to 60 months, but the majority of dogs first developing signs by 3 years of age.[9] Initially, these episodes were known as Chinook seizures, but closer examination revealed that the episodes were not epileptic. Episodes are not triggered by sudden movements or exercise, and can last between 1 and 60 minutes. The frequency of occurrence also varies widely from several episodes per day to a handful of episodes in the dog's entire lifetime. The phenomenology as described by owners in questionnaires was remarkably consistent between cases and includes flailing or kicking (ballism), sustained limb flexion combined with repetitive small limb movements and, occasionally, head tremor. The dogs remain fully conscious and responsive throughout the episode, although owners report they may be lethargic afterward. A video of an episode is available at: http://www.canine-epilepsy.net/Chinook/chinook.html. Dogs are neurologically normal between episodes and interictal analysis including pre and post exercise lactate and pyruvate levels, EEG, magnetic resonance imaging, and cerebrospinal fluid examination from 2 affected dogs, was unremarkable.[9] An autosomal-recessive mode of inheritance has been identified by segregation analysis and it is interesting to note that epilepsy also occurs in the same family lines, and even coincidentally with PNKD in 2 dogs. The causative genetic disorder has not yet been determined.

Scottie Cramp in Scottish Terriers

PNKD in Scottish Terriers, also known as Scottie cramp, hyperkinetic episodes, and hypertonicity syndrome has been recognized since the 1940s[1] and was investigated extensively in the 1970s.[7,20–23] Age of onset of ranges from 1 to 84 months, but in most cases clinical signs start early in life (approximately 6 months). Episodes are

Table 2
Summary of clinical manifestations of paroxysmal dyskinesias in dogs

Canine Breed	Disease	Triggers	Age of Onset (mo)	Duration (min)	Frequency	Progression	Clinical Signs	Treatment
Inherited disorders (autosomal recessive)								
Cavalier King Charles spaniel[8,18,19]	Episodic falling	Exercise, stress, excitement	3–48 (most cases at 3–4 mo)	Seconds to minutes	Depends on triggers	Frequency and duration of episodes decreased with age and treatment	Dystonia of hind limbs or all 4 limbs, lowering of the head close to the ground, arching of the lumbar spine, stiffening of limbs, increasing of muscle tone, developing the deer-stalking posture, falling over	Clonazepam
Scottish terrier[7,20–26]	Scottie cramp	Stress, excitement, exercise	1–84 (most cases <12 mo)	5–20	Depends on triggers	Severity and frequency decreased with time	Dystonia of hind limbs or all 4 limbs, lowering of the head close to the ground, arching of the lumbar spine, stiffening of limbs, increasing of muscle tone, developing the deer-stalking posture, falling over	Fluoxetine, diazepam
Chinook[9]	Paroxysmal nonkinesigenic dyskinesia	Unidentified	2–60 (most cases <36 mo)	1–60	Several per day to few per year	NR	Flexion of limb(s), repetitive, small range movements of limb(s) and ballism, head tremors	NR
Border terrier[10]	Canine epileptoid cramping syndrome	Vary: waking up, excitement, stress, hot/cold temperature	2.5–84 (most cases <36 mo)	0.5–150	Several per day to per months or years	NR	Inability to stand or walk, involuntary flexion or extension of 1 or multiple limbs, mild tremor, dystonia, borborygmi	Diet change

Sporadic reports								
Wheaton terrier[13]	Paroxysmal dyskinesia	N/A	12–24	NR	Several per day to few per year; tend to cluster	NR	Prolonged pelvic limb flexion, rigidity, and back spasms with variable involvement of thoracic limbs	Diazepam
Bichon Frise[27]	Paroxysmal dyskinesia	Random	46.5	NR	10 times per day to 1 time per week	Unchanged within 1 year	Hyperflexion of 1 limb with progression to other limbs, dystonia, rapid flexion and extension of limb, hyperflexion of thoracic spine	NR
Boxer[28]	Paroxysmal dyskinesia	Unidentified, possibly excitement	2	1–5	10 episodes per day to 2 episodes per 6 mo	Frequency and duration of episodes decreased with age	Briefly sustained hyperflexion of a single thoracic or pelvic limb, unilateral dystonia of the neck, face, and trunk	NR
German shorthaired pointer[29]	Paroxysmal dyskinesia	Excitement, prolonged activity or exercise	12	10–30, 180	Trigger dependent	NR	Arching the lumbar spine, flexion of both hind limbs	Phenobarbital
Springer spaniel[13]	Paroxysmal dyskinesia	Excitement, exercise	3	NR	NR	NR	Hind limbs rigidity, arching the lumbar spine, fore limbs hypertonicity, falling	NR

The episodic head tremor syndromes are not included in this table.

Abbreviation: NR, not reported.

Data from Refs.[7–10,13,18–29]

triggered by excitement, stress, and exercise. The phenomenology is remarkably similar to that exhibited by Cavalier King Charles spaniels with episodic falling although the authors have worked with several dogs in which mild signs of hind limb spasticity and bunny hopping occur. Episodes last between 5 and 20 minutes. In the majority of dogs, signs decrease in severity with time, with behavior modification or a change in the level of activity and, in those that require medication, fluoxetine and diazepam have been reported to be beneficial.[21,24] Electromyography revealed an increase in interference patterns during episodes but no abnormal spontaneous discharges at rest.[7] No macroscopic or microscopic lesions have been found in the nervous system and muscle of affected dogs, consistent with a primarily functional disorder.[21] A potential role for serotonin in producing episodes is intriguing. Depletion of serotonin with drugs such as methysergide or methionine induces clinical signs, whereas increasing serotonin with fluoxetine, tryptophan, and nialamide reduces or prevents episodes.[23,25,26] However, quantification of brain serotonin content shows no difference between affected and normal dogs,[23,26] and it is unclear whether serotonin has a primary or secondary role in the pathophysiology. Scottie cramp is reported to be inherited as an autosomal-recessive trait.[21] An identical syndrome has also been reported anecdotally in Cairn terriers, Norwich terriers, and West Highland White Terriers, and may be caused by the same genetic disorder given the common lineage of these breeds. Currently, the causative genetic mutation has not been identified, although sequencing of *BCAN* is normal in this breed (Ganokon Urkasemsin and Natasha J. Olby, unpublished observations).

Canine Epileptoid Cramping in Border Terriers

This paroxysmal movement disorder initially went by the name of Spike's disease after the first dog in which it was recognized and is now classified as a paroxysmal dyskinesia.[10] Similar to the condition in Chinooks, episodes do not seem to be triggered by sudden movements or exertion, although some owners report an association with stress or excitement and others report signs during waking from sleep. Age of onset varies widely ranging from 2.5 months to 7 years; typically, events happen in clusters, sometimes separated by months. Episode phenomenology includes difficulty walking that progresses to difficulty standing; dystonia of the limbs, head, and neck; and tremors. Air licking and stretching are also reported. Videos of these episodes can be found at http://www.borderterrier-cecs.com/cecs_videos.htm. A possible link to gastrointestinal disease is intriguing in these dogs. Many owners report borborygmi during an episode and some dogs have episodes of vomiting and diarrhea immediately before or after an episode. This possible association with an autonomic sign may indicate that these episodes are more like seizures in their etiology. Because of discussion about the possible role of food intolerance in this syndrome, most owners alter their dog's diet to a hypoallergenic diet, although there is no evidence that this has any beneficial effect. Treatment with antiepileptic or antispasmodic drugs is ineffective.

Episodic Head Tremor Syndrome

This syndrome is recognized as a suspected hereditary disorder in English bulldogs,[11] and Doberman pinschers[12] and occurs sporadically in a wider population of dogs. Signs typically first appear in young dogs (<2 years of age), but onset can be as late as 9 years of age. There are no specific triggers noted for English bulldogs, although owners usually report their dogs as being quiet when signs appear. Triggers reported in the Doberman pinscher include stress, fatigue, illness, and excitement. Duration of episodes varies from a few seconds to up to 3 hours and frequency ranges from

multiple per day to clusters every few months. The phenomenology of episodes is essentially the same for both breeds of dog; dogs nod their head repetitively horizontally or vertically or both at a frequency of 5 to 8 Hz. They may show mild dystonia of the neck during an episode and, although fully conscious, may show signs of anxiety, irritation, or discomfort, and may yawn, bark, or press their heads against solid surfaces. Numerous videos of these events can be found on the internet simply by searching the term "head bobbing." At least 66% of dogs can be distracted out of the episodes using treats or other interactions and signs are typically not responsive to antiepileptic drugs.[11,12] Approximately 50% of dogs seem to grow out of the condition with time. This disease has been tentatively classified as a paroxysmal dyskinesia, but such isolated head tremors have not been described in people with PD.

SPORADIC REPORTS

Paroxysmal Dyskinesia in a Bichon Frise

Episodic dyskinesia has been described in a 4-year-old Bichon Frise with a 6-week history of episodes.[27] Episodes were unpredictable and occurred at rest, when excited, and with exercise with a frequency ranging from 10 times per day to once a week. The clinical signs were hyperflexion of 1 limb that could progress to additional limbs while disappearing in the first affected limb. Dystonia and rapid flexion and extension of limb were also observed. During the episode, the dog had no change in consciousness. The dog was clinically normal between episodes and brain magnetic resonance imaging and cerebrospinal fluid analysis were normal. Treatment was attempted with phenobarbital but was not effective.

Paroxysmal Dyskinesia in the Boxer

Two litters of boxers were examined for a paroxysmal dyskinesia.[28] Episodes consisted of briefly sustained hyperflexion of a single thoracic or pelvic limb, with unilateral dystonia of the neck, face, and trunk. Dogs would fall if the episode occurred during movement. The age of onset was 2 months and the frequency of episodes ranged from 10 episodes per day to 2 episodes per 6 months. Episodes were more severe and more frequent in males than females. Excitement seemed to trigger some episodes, but they could also occur randomly. The episodes lasted for 1 to 5 minutes and frequency and duration decreased with age. During the episodes, the dogs remained conscious and responded when the owner called their name. Stroking and calmly talking to the dog shortened the duration of episodes. There was a rapid recovery and no neurologic deficits between episodes.

Paroxysmal Dyskinesia Reported in Other Breeds

There are brief clinical descriptions of paroxysmal dyskinesias affecting Springer spaniels and Wheaton terriers.[13] In Springer spaniels, the age of onset was 3 months and the triggers were exercise or excitement. The clinical signs of progressive hypertonicity were characterized by pelvic limb rigidity, arching of lumbar spine, thoracic limb hypertonicity, and falling. Resting helped to resolve the signs. In Wheaton terriers, signs started around 1 to 2 years of age. The main clinical signs included sustained flexion or rigidity of hind limbs and back spasms. Diazepam may have reduced severity of clinical signs.

Phenobarbital-Responsive Paroxysmal Dyskinesia

Most dogs affected by paroxysmal dyskinesia do not respond to antiepileptic drugs. However, a rapid reduction of frequency and severity of clinical signs were reported in a German shorthaired pointer with suspected paroxysmal dyskinesia after

phenobarbital administration.[29] This dog exhibited typical muscle hypertonicity, including arching of the lumbar spine and flexion of both hind limbs that was triggered by excitement and prolonged exercise. Episodes lasted from 10 minutes to 3 hours. The dog had symmetric signs in both pelvic limbs and was conscious during episodes, although partial seizure activity was not ruled out with EEG.

Phenobarbital-Induced Dyskinesia

There are few reports of acquired dyskinesias in veterinary medicine, but there is a description of a dyskinesia associated with phenobarbital therapy in an epileptic Chow Chow.[4] The dog showed progressive twitching of the facial, neck, and shoulder muscles, impairing its ability to walk and worsening as the dose of phenobarbital increased. EEG evaluation during an episode was normal and withdrawal of phenobarbital resulted in complete resolution of the signs.

OTHER INVOLUNTARY MOVEMENT DISORDERS

Jack and Parson Russell terriers suffer from a complex cluster of hereditary neurologic conditions including hereditary ataxia, myokymia and seizures (see elsewhere in this issue by Urkasemsin and Olby). Because of the variation in clinical manifestations, classification of this syndrome has been compared with hyperkinetic movement disorders and peripheral nerve hyperexcitability syndromes in humans.[30] Myokymia is characterized by rhythmic undulating muscle contractions producing vermicular movement of the overlying skin or rippling muscles, and accompanied by spontaneous discharges on EMG originating from the motor neuron. The clinical signs may progress to cause collapse and generalized rigidity (neuromyotonia). Affected Jack Russell terriers develop hyperthermia from sustained muscle contractions that can be life threatening.[31] Based on the recent discovery mutation in *KCNJ10* gene in a group of Jack Russell terriers (age of onset between 2 to 12 months) affected by cerebellar ataxia with or without myokymia, seizure, or both,[32] this clinical complex is now classified as a hereditary ataxia.

Startle disease or hyperekplexia has been reported in 2 Irish wolfhound littermates.[33] This dramatic disorder is characterized by muscle rigidity that can be severe enough to cause apnea. In humans, these diseases are caused by abnormal glycinergic neurotransmission. Clinical signs in the puppies started from 5 to 7 days after birth and were triggered by noise, touch, and handling. Nursing caused cyanosis. Affected dogs were normal at rest. A mutation in *SLC6A5* gene encoding presynaptic glycine transporter GlyT2 was identified.[33] Thus, besides the different types of triggers, age of onset, and duration of signs, genetic investigation is also useful to distinguish hyperekplexia from paroxysmal dyskinesias.

SUMMARY

Paroxysmal dyskinesias are being described with increasing frequency in dogs and may start to fall into groups based on clinical signs, triggers, progression, duration, and frequency of episodes. Precipitating factors and duration of episodes are central to categorizing paroxysmal dyskinesias in the human and are helpful in therapeutic decisions.[3,5] None of the canine disorders described seem to fit well into the human category of paroxysmal kinesigenic dyskinesia, and sometimes triggers are hard to identify in dogs. As more syndromes are described, clinically useful categories of disease may start to be developed based on clinical presentation. However, with the rapid increase in our understanding of the genetic basis of canine neurologic disorders, it is reasonable to hope that these diseases will be classified according to their

mutation and the pathophysiologic mechanism underlying them in the near future. To date, only a single mutation in the gene *BCAN* has been identified as a cause of canine PNKD. Genetic investigations in other breeds are ongoing and will likely revolutionize our ability to understand and treat these disorders.

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