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Review

Classification of involuntary movements in dogs: Paroxysmal dyskinesias

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ABSTRACT

Paroxysmal dyskinesias (PDs) are a group of hyperkinetic movement disorders characterised by circumscribed episodes of disturbed movement, superimposed on a background state in which such abnormality is absent. There is no loss of consciousness. Episodes can last seconds, minutes or hours, and the beginning and end of the movement disturbance are abrupt. Neurological examination is typically normal between episodes. PDs are associated with a broad spectrum of clinical presentations, encompassing various aetiologies. In humans, three main groups of PDs are distinguished, based on precipitating events rather than phenomenology: (1) paroxysmal kinesigenic dyskinesia (PKD); (2) paroxysmal nonkinesigenic dyskinesia (PNKD); and (3) paroxysmal exertion-induced dyskinesia (PED). In recent years, there has been an expansion of the spectrum of manifestations of PD due to the identification of genes associated with PD in humans (*PRRT1*, *MR-1*, *SLC2A1* and *KCNMA1*) and dogs (*BCAN* and *PIGN*). The precise pathophysiological mechanism underlying the clinical manifestations of these reported mutations remains to be elucidated. Progress is also being made in the field of immunology, and links to gluten hypersensitivity in Border terriers with so-called canine epileptoid cramping syndrome (CECS) have been reported. This review aims to synthesise a classification scheme for veterinary PDs by reviewing human systems and applying them to veterinary examples. However, it is anticipated that genetic advancement will greatly aid in future stratification and therapy for PDs in dogs. Therefore, classification systems should be viewed as works in progress that should be modified as necessary.

Introduction

The paroxysmal movement disorders are a group of conditions characterised by episodes of abnormal movement that are self-limiting. Episodes are painless, autonomic signs are absent, consciousness is not impaired and abnormal post-ictal behaviour is not observed. Episodes can last seconds, minutes or hours, with the beginning and end of the movement disturbance being abrupt. In the great majority of cases, neurological examination is normal between episodes. Many of these features help distinguish paroxysmal dyskinesias (PDs) from epileptic seizures, one of the main differential diagnoses for this condition.

Clinical reports of veterinary PDs have expanded our knowledge base over the last decade but no classification system is yet recognised. Although these reports describe varying dyskinesias, each condition is phenotypically indistinct from another when based on observation alone. The extreme heterogeneity in the clinical manifestation and varying degrees of severity of phenotype in humans suggest that many of these disorders can go undetected in companion animals and they might be far more common than the literature reports. Their similarity to epileptic seizures also makes them difficult to diagnose at times. Recognition therefore remains important, because the identification of more unusual clinical signs associated with PD (e.g. tremor, twitches, myoclonus etc.) undoubtedly aids classification and subsequently enables successful therapies to be implemented.

Historically, PDs in humans have been divided according to aetiology (e.g. primary, where no obvious cause is identified, and secondary, whereby pathology is identified that might cause the condition). However, classification systems have evolved, allowing separation of PDs according to their causative mutation or precipitating event, i.e. an environmental or physiological stimulus. We review these classification schemes and propose an aetiological classification for veterinary PDs based on the paucity of reported information on both precipitating factors and genetics.

Pathogenesis in humans

The pathogenesis of PD remains unclear. The two main theories regarding the causation of PD are that they represent either an epileptic disorder or a transient dysfunction of the basal nuclei.

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Support for basal ganglia involvement arises in part because of single photon emission computed tomography studies citing hyperactivity within the basal ganglia during episodes of PD (Berti et al., 2011) and the identification of lesions affecting the basal ganglia in secondary PD (Bax et al, 2005; Dale et al., 2009). However, no conclusive evidence supports this view. Studies have demonstrated that the synthesis and storage of dopamine in patients with PD are decreased, leading to a chronic upregulation of the number and affinity of postsynaptic dopamine receptors. One hypothesis suggests a sudden excessive release of dopamine can be stimulated by alcohol and coffee, resulting in episodes of PD (Lombroso, 1995).

It has been argued that PD might be a type of epileptic disorder. Early descriptions of PD used the terminology 'reflex movement-induced seizure' due to the association of episodes with sudden movement or startle (Gowers, 1881). Demonstration that episodes could be relieved by excision of a cortical scar provided support for this hypothesis (Falconer et al., 1963). However, many now believe that although pathophysiological mechanisms involving ion channels might be similar for epileptic seizures and PD, the two conditions remain distinct and could sometimes co-exist. Several paroxysmal neurological disorders that are not of epileptic origin (e.g. episodic ataxia type 1 and 2, familial hemiplegic migraine) have been associated with different ion channel gene mutations, and these same disorders have significant clinical overlap in presentation and treatment when compared to PD (Ophoff et al., 1996). In this context, the co-occurrence of epilepsy and PD in some families suggests that a common genetically determined pathophysiological abnormality of ion channel function is variably expressed in the CNS (Du et al., 2005). The notion that PDs represent channelopathies is supported by the identification of ion channel mutations (*KCNMA1* and *SLC2A1*) in some patients (Erro et al., 2014), which could cause abnormal excitability in the cerebral cortex and basal nuclei under different circumstances. For example, an age-dependent expression of different subunits of ion channels can be observed. However, the recent discovery of the association of PD with non-ion channel mutations (*PRRT2* and *MR-1*), presumably resulting in abnormal proteins that do not mediate channel functions, counters this theory and suggests the possibility of multiple mechanisms contributing to PD (Erro et al., 2014).

Controversies

There is controversy regarding the relationship between PD and epilepsy. Dyskinesia in the setting of epilepsy has been reported as part of a familial paroxysmal movement disorder in the Chinook breed of dogs (Packer et al., 2010). However, according to current veterinary literature, this is the exception rather than the rule and the co-existence of epilepsy and dyskinesia does not imply the two share pathophysiological characteristics; rather, this might represent comorbidities. This is complicated by the clinical differentiation of epileptic seizures and paroxysmal movement disorders, in that they can share similar clinical characteristics (Donaldson et al., 2012). However, the assumption that a diagnosis must either be epilepsy or a movement disorder implies the two conditions cannot coexist. In humans, not only can epilepsy masquerade as a movement disorder, but also paroxysmal movement disorders can be observed which are not easily differentiated from epileptic seizures (Donaldson et al., 2012). This information bias in the published literature has resulted from the stratification of individuals, i.e. a diagnosis was limited to those with the typical signs of the disease. We believe there is far more phenotypic heterogeneity within this category of disease than has so far been reported and that genetic and biochemical disease markers for PD will open the way for more detailed studies of phenotype and the underlying biology.

Identification

The diagnosis of PD is made by the observation of an episode and assessing motor activity, mentation, duration, post-ictal behaviour and the presence of autonomic signs (Donaldson et al., 2012). Because diagnosis by observation is not a robust method and has potential inaccuracies, there is on-going controversy regarding whether a set of clinical signs is more likely to denote an epileptic seizure or a PD. However, biochemical and genetic markers are available for some PDs in dogs (notably canine epileptoid cramping syndrome [CECS] and episodic falling syndrome [EFS] of the Cavalier King Charles spaniel, respectively) and these have only served to confirm the suspicion of PD over epilepsy in these breeds (Forman et al., 2012). As the name implies, all PDs must involve some form of abnormal movement (Donaldson et al., 2012). Typically, involuntary movement of one or more limbs is suggestive of PD (Black et al., 2014). However, these clinical signs are non-specific and are shared with other transient disorders, notably epileptic seizures, although the frequency of such movements is usually markedly decreased in PD compared to that observed with generalised tonic-clonic seizures (GTCS; Donaldson et al., 2012). Several additional clinical signs can be observed in support of a diagnosis of PD. Firstly, there can be preservation of consciousness during generalised episodes, despite motor manifestations in all four limbs (Black et al., 2014). In contrast with subtle lapses in consciousness, typically the dog owner is unable to attract their dog's attention during an episode, for example a name call or offering a bowl of food. However, if the dog can acknowledge such an intervention then consciousness is considered present and a movement disorder would be deemed more likely over a GTCS, for example Black et al. (2014). Secondly, there can be failure of progression from a typical dyskinetic episode into a GTCS during PD episodes (Donaldson et al., 2012). Thirdly, episode duration tends to be much longer for PD than epileptic seizures (up to 2 h), although shorter episodes can occur in both conditions (Donaldson et al., 2012). Finally, there can be lack of a post-ictal phase even after PD episodes lasting hours (Donaldson et al., 2012).

The consulting room is rarely the best setting for evaluation of human or veterinary patients with these conditions, as many dyskinesias are strikingly situation-specific and variable in severity. For this reason, the advent of smartphone technology has allowed greater recognition of PD (Appendix: Supplementary Video S1). Recognition based on clinical acumen is vital to form a basis for the subsequent diagnostic process, although it remains challenging and misdiagnoses are common (Donaldson et al., 2012). Achieving the correct diagnosis has prognostic implications in humans and this might also be true for dogs. For example, some paroxysmal movement disorders are benign and self-limiting (Forman et al., 2012; Urkasemsin and Olby, 2015; Lowrie and Garosi, 2016a). Lastly, differentiating between the different types of PDs can have important consequences for treatment.

Classification in humans

There is no formal classification in veterinary medicine for PD and as such, attempts to classify according to the three major human classification systems have been performed.

Clinical classification

The clinical manifestation of PD can be complex. The movements observed in humans can be dystonic, athetotic, choreic, or a combination with other clinical signs (Table 1; Demirkiran and Jankovic, 1995). The terms PD and dystonia are often used interchangeably, but they define separate features, with the former being a clinical disease and the latter being a clinical sign (Demirkiran and

Table 1
Clinical signs associated with paroxysmal dyskinesias.

Clinical sign	Definition
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

Jankovic, 1995). Dystonia is a clinical sign that can manifest in different disease processes including PD (Demirkiran and Jankovic, 1995). It is defined as a sustained involuntary contraction of a group of muscles producing abnormal postures (Demirkiran and Jankovic, 1995). Unlike other clinical signs associated with movement disorders in which the action is important for recognition, dystonia is unique in that it is easily identifiable from a photograph or video (e.g. contortions or writhings of the body; Demirkiran and Jankovic, 1995). Some texts confuse dystonia as a category of movement disorder (Richter et al., 2015) but here we use the term PD to encompass all forms of paroxysmal movement disorder, regardless of their phenomenological makeup, in agreement with human nomenclature (Demirkiran and Jankovic, 1995).

Duration of episodes can be highly variable; therefore, the clinical classification of PD in humans as proposed by Demirkiran and Jankovic (1995) is based solely on precipitating factors of the episodes and not phenomenology. This idea stemmed from the observation that each type of PD can manifest with dystonia, chorea, athetosis, or a combination of abnormal movements (Demirkiran and Jankovic, 1995). It was suggested that the term 'choreoathetosis' be replaced with 'dyskinesia', as a variety of movements can be seen in these disorders (Demirkiran and Jankovic, 1995). The classification distinguishes three categories (Table 2), including paroxysmal kinesigenic dyskinesia (PKD; incited by sudden movements), paroxysmal nonkinesigenic dyskinesia (PNKD; occurring spontaneously at rest) and paroxysmal exertion-induced dyskinesia (PED; precipitated by fatigue; Demirkiran and Jankovic, 1995).

After the precipitant is identified, secondary categorisation is based on duration: less than or equal to 5 min (short) or greater than 5 min (long; Lotze and Jankovic, 2003). Tertiary classification is based on presumed aetiology: primary (familial or sporadic) or secondary (Lotze and Jankovic, 2003; see below). This descriptive scheme is helpful in making clinical distinctions and identifying phenotypes for genetic association studies in humans.

Aetiological classification

Most paroxysmal movement disorders in humans are classified as primary, i.e. of idiopathic or familial aetiology, and not part of a degenerative process. The term 'primary' is given to PD that are not associated with neurological signs between episodes and that do not have evidence of pathological abnormalities (Albanese et al., 2013). Other causes in humans include secondary or symptomatic dyskinesia resulting from structural CNS lesions, such as multiple sclerosis (Lotze and Jankovic, 2003). Secondary PDs tend to be accompanied by additional neurological signs that are persistent between episodes (Lotze and Jankovic, 2003).

Genetic classification

Genetic sequencing has identified four causative genetic mutations relating to PD in humans: proline-rich transmembrane protein-2 (PRRT2), myofibrillogenesis regulator-1 (MR-1), calcium-activated potassium channel, subfamily M, alpha member-1 (KCNMA1) and glucose transporter-1 (SLC2A1) genes (Erro et al., 2014). Pleiotropy refers to the diversity of phenotypic expressions that one gene mutation can cause in different affected individuals and this is a common feature of genetic mutations associated with PD (Erro et al., 2014). An example of this is found in the PRRT2 mutation, which can cause various conditions including benign familial infantile epilepsy, infantile convulsions with choreoathetosis syndrome, and PD (Heron and Dibbens, 2013). Other genetic mutations for PDs also show a marked pleiotropy e.g. MR-1 and SLC2A1 (Erro et al., 2014). Furthermore, not all patients presenting with PD have mutations in these genes (Erro et al., 2014). Therefore, the Mendelian notion of 'one gene/one phenotype' should be disbanded in this case, making genetic classification of these disorders challenging. Genetic classification in veterinary medicine is discussed later.

Diagnosis of PD in dogs

It is important to first determine whether canine paroxysmal movements truly represent PD. The authors' favoured approach is diagnosis by inspection, clinical history and episode phenomenology.

For the majority of PDs, no specific biological marker is available that can accurately identify the condition. A multitude of diagnostic tests are available (e.g. MRI and cerebrospinal fluid [CSF] analysis), which often require expensive equipment and invasive and time-consuming techniques. Ultimately, the diagnostic value of these procedures over clinical judgment is limited. Scattergun diagnostics provide no haven for clinical indecision due to the high likelihood of obtaining normal results, reflecting the functional origin of many of these disorders (Forman et al., 2012; Lowrie and Garosi, 2016a).

Table 2
Clinical features of human paroxysmal dyskinesia (adapted from Waln and Jankovic, 2015).

Characteristic	PKD	PNKD	PED
Age at onset	Childhood/teens	Childhood/teens	Variable
Precipitating factors	Sudden movement	Coffee, alcohol, fatigue	Prolonged exercise
Nature of episodes	Chorea/dystonia	Chorea/dystonia	Chorea/dystonia
Length of episodes	Seconds to minutes	Minutes to hours	Subside with rest
Episodes per day	Up to hundreds	Up to two to three	Dependent on exercise
Aetiology	Familial cases linked to *PRRT2* (frequently) Can be secondary to brain injury	Some familial mutations due to mutations in *MR-1* gene (frequently), *KCNMA1* gene (frequently, genotype linked to epilepsy), and *SLC2A1* gene (rarely)	Can be idiopathic or familial with mutations of the *SLC2A1* gene (frequently), *GCH-1* gene (rarely) or secondary to Parkinsonian disorders

GCH-1, *GTP-cyclohydrolase-1* gene; *KCNMA1*, *Calcium-activated potassium channel, subfamily M, alpha member-1*; *MR-1*, *Myofibrillogenesis regulator-1*; PED, Paroxysmal exertion-induced dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; *PRRT2*, *Proline-rich transmembrane protein-2*; *SLC2A1*, *Glucose transporter-1* gene.

However, their utility becomes important when considering whether a PD is primary or secondary.

Certain breed-specific features can aid in achieving a definitive diagnosis. The work-up for EFS in Cavalier King Charles spaniels, for example, involves genetic testing, whereas CECS in the Border terrier requires serological testing for gluten-specific antibodies (Lowrie et al., 2015). Although not reported, the authors have diagnosed intracranial lesions associated with PD in two dogs. This might potentially represent secondary PD, although it seems unlikely that these lesions resulted in PD; rather they exacerbated subclinical PD which had the potential to resolve or abate on treatment of the primary condition. Therefore, an MRI scan of the brain and CSF analysis appear to be logical diagnostic choices, although the diagnostic yield of advanced neuroimaging techniques in dogs with video footage and historical data supporting PD, without neurological deficits, is low (Lowrie and Garosi, 2016a). Furthermore, drug-induced dyskinesia has been documented in dogs and there are case reports involving phenobarbital and propofol. Therefore, history taking is crucial before embarking on investigations (Kube et al., 2006; Mitek et al., 2013).

Examples in humans

Paroxysmal kinesigenic dyskinesia (PKD)

In humans, brief dyskinetic episodes (usually less than 2 min) are typically precipitated by sudden movement (Demirkiran and Jankovic, 1995), and affected individuals are more likely to be male (Houser et al., 1999). Most cases are idiopathic and apparently sporadic. Episodes can be induced by a sudden change in position (e.g. from a sitting to standing position) or startle or prolonged exercise. Episode frequency wanes over time, decreasing considerably or abating in adulthood (Bruno et al., 2004). Other features include favourable response to antiepileptic medication, relatively high frequency of episodes and an autosomal dominant family history in about 25% of human cases (Demirkiran and Jankovic, 1995).

Genetic analysis has revealed mutations in *PRRT2* associated with PKD (Erro et al., 2014). Around one third of patients harbouring this mutation have a family history of both PD and epilepsy (Erro et al., 2014). A further third will have features of PD only. The remaining third have epilepsy and are diagnosed with infantile convulsions in association with choreoathetosis syndrome (Heron and Dibbens, 2013).

Paroxysmal non-kinesigenic dyskinesia (PNKD)

In humans, PNKDs usually occur spontaneously, but episodes can be precipitated by stress, tiredness or consumption of caffeine or alcohol (Demirkiran and Jankovic, 1995). Following onset, episodes are indistinguishable from PKD, although their duration is longer, lasting minutes to hours. Episode-free intervals can last for days to months. Males are more likely to be affected, although this is not so marked as with PKD. Familial cases have an autosomal dominant mode of inheritance with reduced penetrance (i.e. a gene defect does not always lead to a PD phenotype), but symptomatic cases have been reported (Demirkiran and Jankovic, 1995).

Molecular studies have identified a link between PNKD and mutations in the *MR-1* gene on chromosome 2q (Lee et al., 2004; Rainier et al., 2004; Chen et al., 2005; Ghezzi et al., 2009). A second genetic mutation is described in the *KCNMA1* gene in individuals with PNKD (Du et al., 2005). Clinical characteristics of this condition are indistinguishable to those seen in *MR-1* patients, but a key defining feature is the presence of epilepsy in some individuals, which has not been reported in patients with the *MR-1* gene (Erro et al., 2014).

Paroxysmal exercise-induced dyskinesia (PED)

PED is characterised by episodes of involuntary movement that are induced by prolonged sustained exercise. Episodes can last between 5 min and 2 h and movements are restricted to the exercised limbs. Episode frequency varies from daily to monthly. The onset of symptoms is usually in childhood, but can range from 1 to 30 years and there is a female predisposition (Jankovic and Demirkiran, 2002). An autosomal dominant mode of inheritance has been reported. Secondary PED is very uncommon, with the only reports occurring following traumatic brain injury (Demirkiran and Jankovic, 1995; Lim and Wong, 2003). Treatment remains challenging, and is based on the avoidance of sustained exercise and the potential beneficial effects of antiepileptic medication (Demirkiran and Jankovic, 1995).

Around 20% of patients with PED have a mutation in the *SLC2A1* gene (Schneider et al., 2009). A defining feature of patients with this mutation is that they can have inter-ictal abnormalities including ataxia, epilepsy, learning difficulties and haemolytic anaemia (Weber et al., 2008). A GTP-cyclohydrolase 1 (*GCH-1*) gene mutation is associated with PED, although this same mutation can also cause other movement disorders in the same individuals (Dale et al., 2010).

Veterinary classification

The earliest reports of PD in dogs date back to the late 1960s (Meyers et al., 1969). The limited number of cases from this period is more likely indicative of lack of recognition rather than reduced incidence, as smartphone technology has enabled dog owners to record episodes at home. Breeds reported with PD include the Border terrier, Boxer, Cavalier King Charles Spaniel, Chinook, Dalmatian, German Shorthaired pointer (GSHP), Golden retriever, Jack Russell terrier, Labrador, Norwich terrier, Scottish terrier, Shetland Sheepdog and Soft-coated Wheaton terrier (Meyers et al., 1969; Woods, 1977; Herrtage and Palmer, 1983; Nakahata et al., 1992; Ramsey et al., 1999; Penderis and Franklin, 2001; Harcourt-Brown, 2008; Packer et al., 2010; Lowrie et al., 2015; De Risio et al., 2016; Kolicheski et al., 2016; Lowrie and Garosi, 2016a; Royaux et al., 2016).

Canine dyskinesia syndromes have a remarkable degree of phenotypic variability and phenotypic overlap is frequent. All share clinical features comparable with PNKD in humans with the exception of the GSHP, which has a PD reminiscent of PKD (Harcourt-Brown, 2008). As such, clinical classification according to human criteria is difficult, as the diversity of conditions reported in humans has not been recognised in animals. It is uncertain if human classifications will be useful in veterinary patients, although disorders resembling PKD and PNKD have been reported in dogs (Meyers et al., 1969; Woods, 1977; Herrtage and Palmer, 1983; Nakahata et al., 1992; Ramsey et al., 1999; Penderis and Franklin, 2001; Harcourt-Brown, 2008; Packer et al., 2010; Lowrie et al., 2015; De Risio et al., 2016; Kolicheski et al., 2016; Lowrie and Garosi, 2016a; Royaux et al., 2016). However, since the vast majority of canine reports are compatible with PNKD, this classification should be adopted for veterinary medicine, with the caveat that PNKD might require further sub-classification as our understanding expands. Veterinary classification according to genetic mutations remains in its infancy and there are only two PDs in which a causative mutation has been identified (Gill et al., 2012; Kolicheski et al., 2016). As such, this system is likely to become more relevant as further mutations are identified. Consequently, we propose a clinical classification with a subclassification system according to the likely aetiology. Known causes of PD in dogs are thus far limited to genetic (Forman et al., 2012; Gill et al., 2012; Kolicheski et al., 2016), drug-induced (Kube et al., 2006), and dietary factors (Lowrie et al., 2015). The authors' observations are that secondary PDs occur, but are much less common.

Proposed classification system in dogs

We describe and classify the conditions below by highlighting those disorders with defining clinical signs rather than listing signs that are similar.

Genetic causes

The first genetically mapped PD in companion animals was EFS in Cavalier King Charles Spaniels (Forman et al., 2012; Gill et al., 2012). Episodes were triggered by stress or excitement and were characterised by progressive hypertonicity in the thoracic and pelvic limbs, resulting in a characteristic 'deer-stalking' or 'praying' position. EFS is a PNKD with clinical onset from 14 weeks to 4 years of age (Herrtage and Palmer, 1983). The mutation has been characterised as a deletion affecting the brevican gene (*BCAN*) which encodes a brain-specific component of the extracellular matrix proteoglycan complex and has an autosomal-recessive mode of inheritance (Forman et al., 2012; Gill et al., 2012). This complex is thought to be involved in homeostasis, and mutations of this protein result in a disruption of axonal conduction and synaptic stability (Forman et al., 2012; Gill et al., 2012). There have been two reported cases of asymptomatic homozygous individuals and there are two possible explanations for this. Firstly, these dogs might have had lower levels of activity and therefore not have been exposed to the required exercise threshold to trigger an episode of EFS. Alternatively, they might have compensated for their condition by lowering their activity levels. Rodents harbouring the mutation lack clinical signs (Forman et al., 2012), which could suggest an absence of episode triggers in their environment. Interestingly, EFS is self-limiting in some cases (Forman et al., 2012). It has been suggested that compensatory pathways involving upregulation of other proteoglycans could account for this apparent resolution.

There has been a report of Soft Coated Wheaten Terriers with PD that is reminiscent of PNKD (Kolicheski et al., 2016). This condition shares many features of other PD in dogs, although recently, a mutation in the *PIGN* gene has been associated with this condition (Kolicheski et al., 2016). The disease is inherited in an autosomal recessive manner (Kolicheski et al., 2016). The *PIGN* gene encodes glycosylphosphatidylinositol anchors that attach many different proteins to cell surfaces (Kolicheski et al., 2016). In humans, this same mutation causes a distinct phenotype known as multiple congenital anomalies-hypotonia-seizures syndrome 1 (MCASH1; Kolicheski et al., 2016). To date, the mutation of the *PIGN* gene has not been associated with PD in humans.

Dietary causes

CECS is the name formerly given to a type of PNKD in Border terriers (Black et al., 2014). This term is a misnomer and it now appears more appropriate to apply the name paroxysmal gluten-sensitive dyskinesia (PGSD; Lowrie et al., 2015). Episodes are observed in dogs as young as 6 weeks and up to 7 years of age (Black et al., 2014). PGSD consists of episodes of difficulty walking, ranging from ataxia to a complete inability to stand, tremors, and dystonia of the limbs, head and neck (Appendix: Supplementary Video S2). Episodes can last minutes or hours with dogs being normal in between (Black et al., 2014). Mild to severe gastrointestinal signs such as borborygmi, vomiting or diarrhoea can be observed in between episodes (Lowrie et al., 2015).

A recent prospective study of six Border terriers with PGSD reported clinical improvement when an exclusive gluten-free diet was provided (Lowrie et al., 2015). Furthermore, this apparently reversible gluten sensitivity was measured using serological markers to gluten, anti-transglutaminase-2 and anti-gliadin antibodies, which decreased on adherence to a gluten-free diet. Two of these dogs had signs suggestive of gastrointestinal disease, although only one was investigated with endoscopic biopsies; no histological abnormalities were identified (Lowrie et al., 2015).

Gluten sensitivity defines a state of increased immune responsiveness in genetically susceptible individuals to gluten (Marsh, 1995). Gastrointestinal signs resulting from inflammatory bowel disease (coeliac disease) were considered the most common feature of gluten sensitivity in humans. However, evidence now suggests that the gastrointestinal tract might not be the sole target in gluten sensitivity and organ-specific manifestations can present alone or in combination with one another (Marks et al., 1966; Sapone et al., 2002). Given the recent evidence that gluten sensitivity can present with multisystemic disease in dogs (Lowrie et al., 2016b), this protein might be a potential antigenic stimulus for other conditions, both neurological and non-neurological.

Secondary causes

Drug-induced causes include phenobarbital administration, which was reported to elicit PNKD in an epileptic Chow Chow (Kube et al., 2006). The pathophysiology is unknown, but clinical signs were reversible on cessation of the medication. Propofol has also been reported to cause PNKD in a Golden retriever (Mitek et al., 2013).

Structural intra-cranial disease must also be considered. We are aware of two cases of secondary PNKD in a dog and a cat. These animals had abnormal neurological examinations inter-ictally, which was supportive of forebrain disease. On MRI, multifocal forebrain lesions were identified with minimal to no contrast enhancement and CSF analysis revealed a mild lymphocytic pleocytosis. These changes were suggestive of meningoencephalitis of unknown origin. On management with prednisolone and cytosine arabinoside the dog improved and there was no further evidence of PD. It is our suspicion that the PD was not caused by the MUO, but was precipitated by it. However, this is not proven and remains open to debate.

Unidentified causes (presumed genetic)

Familial PNKD has been described in chinooks and was characterised by an inability to stand, head tremors, and involuntary flexion of one or more limbs (Packer et al., 2010). In keeping with the characteristics of other PNKD, affected dogs had episodes lasting minutes or hours, demonstrated no autonomic signs, maintained normal awareness, and appeared normal in between episodes. Based on pedigree analysis, the condition is considered to have autosomal-recessive inheritance (Packer et al., 2010). The original study investigated a family of 189 Chinook dogs, of which four had GTCS; three of these also exhibited signs of PD (Packer et al., 2010). It is uncertain if GTCS are a variant of the Chinook PD phenotype or a completely separate condition. In humans, the two can coexist (Packer et al., 2010) and so it will be interesting to see if this transpires in the veterinary literature.

Another syndrome of intermittent exercise, stress or excitement-induced PD has been described in Scottish terriers ('Scottie cramp'). Episode onset occurs between 6 weeks and 18 months of age, and the duration of signs is up to 20 min; severe episodes can last hours (Urkasemsin and Olby, 2015). Pathophysiology can be different from other PD in that the administration of serotonin antagonists (e.g. methylsergide) can evoke episodes, whereas serotonin agonists (e.g. fluoxetine) can abolish episodes (Meyers and Clemmons, 1983; Geiger and Klopp, 2009). Analysis of brain serotonin concentrations has not identified a significant difference between affected and normal dogs and so the exact role of serotonin is uncertain (Meyers and Schaub, 1974). The classical disease was first described by Meyers et al. (1969), with dogs exhibiting changes in pelvic limb gait when running, progressing to severe generalised cramp. However, recently a milder phenotype has been described that is confined to the pelvic limbs and manifests as skipping, bunny-hopping and kicking while running, but without collapse and lasting no more than 20 min (Urkasemsin and Olby, 2015; Appendix:

Supplementary Video S3). An autosomal recessive mode of inheritance is considered plausible, although this would not explain the high proportion of affected female dogs (75%; Urkasemsin and Olby, 2015). Improvement is seen over time, and in the majority of dogs with severe signs, fluoxetine appears to be efficacious (Geiger and Klopp, 2009). These findings suggest that Scottie cramp is analogous to PNKD in humans.

The Labrador retriever and Jack Russell terrier were the most common breeds presenting with PNKD in one UK referral clinic, perhaps in part due to the popularity of these breeds in the UK (Lowrie and Garosi, 2016a). A long-term follow-up study identified key features of the condition in these two breeds and also the natural history of the disease (Lowrie and Garosi, 2016a). Affected dogs had early onset of clinical signs (median 2–4 years, range up to 10 years), were triggered by startle or sudden movements, and there was a male bias (75% were male). One third of dogs had cluster episodes (defined as more than one episode in a week), but episode duration and frequency varied widely, even within individual dogs. The natural history was self-limiting, and just under a third of dogs underwent clinical remission; improvement was observed in 75%. Episodes reduced in frequency and duration, but remission rates were lower in dogs with cluster episodes (Lowrie and Garosi, 2016a), suggesting cluster episodes might have predictive value for prognostication.

One case report documented a PKD that was responsive to phenobarbital in a GSHP (Harcourt-Brown, 2008). This is the only report of a PKD in companion animals and recently we have observed the same clinical signs in another GSHP (Appendix: Supplementary Video S4) that entered full remission after phenobarbital treatment (3 mg/kg q12h PO). The presence of this condition in the GSHP breed in the UK strongly supports a genetic basis.

Treatment

When there is a positive response to a medication, it is important to consider other diagnostic possibilities and comorbidities. As many medications used to treat PD have sedative effects, it is possible that precipitating factors such as stress are addressed simply by the addition of such a medication. Even counselling an owner might help them to understand the condition and potentially reduce episode incidence by minimising exposure to potential triggers.

A short-term response to treatment should not be taken as confirmation of efficacy because the natural course of PD is intermittent single or multiple episodes interspersed by weeks or even months of normality (Packer et al., 2010). Furthermore, the condition is non-progressive in Jack Russell terriers and Labrador retrievers (and therefore potentially in other breeds), with improvement in the majority and resolution in a minority (Lowrie and Garosi, 2016a).

Medications

Medications used in the management of PD have variable and often limited efficacy. In humans, carbamazepine is the drug of choice for kinesigenic dyskinesias (Demirkiran and Jankovic, 1995) and clonazepam for the non-kinesigenic forms (Unterberger and Trinka, 2008). A major difference between PNKD and PKD in humans is that PNKD is relatively refractory to therapy. In dogs, successful treatment of PNKD has been reported, albeit uncommonly, with clonazepam, acetazolamide and fluoxetine (Gill et al., 2012; Royaux et al., 2016). Acetazolamide was also very effective in the management of EFS in Cavalier King Charles spaniels (Gill et al., 2012).

The PEDs are also notoriously difficult to control with medication in humans (Demirkiran and Jankovic, 1995). One canine report described the successful management of presumed PKD with phenobarbital (Harcourt-Brown, 2008).

Diet

Recent reports suggest a 40% response rate in humans with PED to a ketogenic diet (Ramm-Pettersen et al., 2014). The rationale is that ketone bodies serve as an alternative energy source for the brain, thereby managing neuroglycopaenia. However, the avoidance of precipitating events such as prolonged physical exercise might also prevent episodes. The effectiveness of a ketogenic diet in dogs with PD remains unreported.

Isolated neurological dysfunction with clinical and serological evidence of gluten sensitivity in the absence of gastrointestinal signs is not uncommon in Border terriers with PGSD (Lowrie et al., 2015). Therefore, a gluten-free diet is recommended for this condition and has shown promise thus far (Lowrie et al., 2015). There have been sporadic case reports of paroxysmal movement disorders (including chorea and dystonia) that were eradicated with a gluten-free diet in humans, although pathogenetic mechanisms have not been elucidated (Pereira et al., 2004; Hall et al., 2007; Walker, 2011; Andrade et al., 2015).

Prognosis

Although often refractory to medication, PD is non-progressive in humans (Waln and Jankovic, 2015). Recent long-term follow-up studies in dogs suggest that some breed-specific PDs can be benign and self-limiting (Forman et al., 2012; Urkasemsin and Olby, 2015; Lowrie and Garosi, 2016a). The upregulation of compensatory pathways might account for clinical resolution, although the exact nature of the relevant mechanisms is unknown (Forman et al., 2012; Lowrie and Garosi, 2016a). This improvement over time is in contrast with the natural course of epilepsy and suggests PDs are not a type of epileptic seizure.

Conclusions

PDs exhibit a broad spectrum of clinical presentations which encompass various aetiologies. The precise pathophysiological mechanisms underlying the clinical manifestations of the mutations reported remain to be elucidated. The extreme heterogeneity of this group of disorders and their phenotypic severity suggest that many of these disorders might go undetected; therefore, they could be more common than current published evidence suggests. The classification presented herein aims to facilitate the clinical recognition of PD and offers insights into some established causes in both humans and companion animals.

Conflict of interest statement

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

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.tvjl.2016.12.017.

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