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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