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A Literature Review of Paroxysmal Dyskinesias: Canine Epileptoid Cramping Syndrome

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Abstract

This literature review is to gather the relevant information currently known about canine PD/CECS from different sources to discuss the most common presentation of PD/CECS, review the history and background of PD in the canine species, the most likely causes of the CECS, most effective treatment options and highlight areas of research that are missing. The goal of the structure of this review is to provide a comprehensive history of the disease with an insight into effective diagnosis or treatment that could increase the chances of a more successful diagnosis and reduce in prevalence of the disease.

Contents

Abbreviations

AGA IgG anticanine gliadin-IgG

BT border Terrier

CD celiac disease

CECS canine epileptoid cramping syndrome

CT computed tomography

EEG electroencephalography

GWAS genomewide association study

MRI magnetic resonance imaging

NCGS nonceliac gluten sensitivity

PD paroxysmal dyskinesia

PED paroxysmal exertion-induced dyskinesia

PKD paroxysmal kinesigenic dyskinesia

PNKD paroxysmal nonkinesigenic dyskinesia

SNP single nucleotide polymorphism

TG transglutaminase

TG2 IgA anticanine transglutaminase-2-IgA

1. Introduction

In human medicine Paroxysmal Dyskinesia's (PDs) are more clearly described and classified than they are in veterinary literature [1]. Their grouping within human medical literature is differentiated by the factors that trigger the episodes, how often they're occurring, how long they last, characteristics of the episodes and response to use of anti-epileptic drugs [2], [3]. Similarly, to human medicine familial and idiopathic association is suspected to be the underlying pathophysiology of PDs in dogs [4]. Canine Epileptoid Cramping Syndrome can be described as a paroxysmal movement disorder/paroxysmal dyskinesia (PD) [2], [3]. Despite recognition of CECS more recently as a different classification from epileptic seizures, which it was historically thought to be similar to [2][3], it is arguable due to lack of understanding of the true pathophysiology, mode of genetic inheritance and recognition of clinical manifestations it may be misdiagnosed in the veterinary field with treatment efficacy still not being fully understood. This literature review will attempt to look at the different research gathered, summarise findings of previous research and possibly highlight areas

where more research may be beneficial to develop more successful diagnostics and treatment of CECS and other PD.

2: Literature Review

2.1 Paroxysmal Dyskinesia

Canine Epileptoid Cramping Syndrome can be described as a paroxysmal movement disorder/paroxysmal dyskinesia (PD) [2]. In human medicine PD's are more clearly described and classified than they are in veterinary literature [1], [2]. Their grouping within human medical literature is differentiated by the factors that trigger the episodes, how often they're occurring, how long they last, characteristics of the episodes and response to use of anti-epileptic drugs [3], [5]. There are three distinct groups of PDs that have been defined within human medicine these include; PKD – Paroxysmal kinetic dyskinesia, PNKD – Paroxysmal non-kinetic dyskinesia and finally PED – Paroxysmal exertion induced dyskinesia (depicted in table 1 below). Phenotypic studies of CECS has shown it to be most equivalent to PNKD in human medicine [1], [2].

Table 1
Classification system of human dyskinesias [1], [6]

Type of movement disorder	Age of onset	Duration	Frequency	Trigger	Response to AEDs
Paroxysmal kinesigenic choreathetosis (PKC)/Paroxysmal kinesigenic dyskinesia (PKD)	Childhood/early adolescence	Typically <2 minutes	High (up to 100 per day)	Precipitated by sudden movements	Yes
Paroxysmal dystonic choreoathetosis (PDC)/Paroxysmal non-kinesigenic dyskinesia (PNKD)	Childhood/early adolescence	5 minutes to 4 hours	Few per day-none for months	Alcohol, fatigue, caffeine, excitement	Not typically effective
Paroxysmal exertion induced dyskinesia (PED)	Childhood/ early adolescence	5 to 30 minutes	Daily-one per month	Precipitated by prolonged muscle exertion	Not typically effective
Paroxysmal hypnogenic dyskinesia (PHD)	Childhood in familial, adulthood in sporadic	30 to 45 seconds	5 times a night-5 times a year	During non-REM sleep	May be effective

AEDs antiepileptic drugs

2.2 Pathophysiology of Human PD, classification and recognition of PD in Canines

Underlying pathophysiology of human dyskinesias is not yet fully understood, however further research that has taken place more recently has identified certain mutations of genes

to be the reason for the different PD groups. PRRT2 for PKD, PNKD (MR-1) and KCNMA1 for PNKD, and SLC2A1 (GLUT1) for PED [4], [7], [8], [9]. Similarly, to human medicine familial and idiopathic association is suspected to be the underlying pathophysiology of PDs in dogs [5]

Previously PD episodes were believed to be a type of focal epileptic seizure due to their short duration, stereotypical nature, and their encouraging response to anti-epileptic drugs [10]. To understand the difference between true epileptic events and PD episodes there are certain characteristics that have been described by owners, veterinarians and within scientific research which can be used to help differentiate the two. PD (CECS) has been characterised as an episodic disorder, with hypertonicity and involuntary movements [2], [3], which can be distinguished from epileptic seizure disorders due to the lack of autonomic signs (urination, defecation, hypersalivation and post-ictal behaviour), that can be seen during an episode. During said episodes of CECS there is usually no loss of consciousness [3], [11], often one of the differentiating features between PDs and simple focal seizures in human medicine [3]. Finally, there is a lack of interictal (between a seizure/paroxysms) and ictal (during a seizure) EEG (electroencephalography) activity during PDs that may normally be seen during a focal epileptic seizure [3], [8], [12].

Unremarkable differences were noted in a clinical study of CT and magnetic resonance imaging of 7 healthy patients and 17 patients affected with CECS/PD [5]. They also noted no abnormal EEG activity in-between episodes of CECS from 10 affected and 7 non-affected healthy control patients [5]. Within previous studies of EEG activity in dogs that have been diagnosed clinically with epilepsy it has been recorded that they will show abnormal interictal EEG activity in up to 25-65% of cases [13], [14]. In contrast to this, in cases of PD it is much rarer to observe any abnormalities in the EEG activity [15]. This evidence allowed the authors to conclude that the lack of interictal EEG activity and absence of other physiological signs in their patients indicated they were experiencing a PD episode rather than an epileptic event [5]. However, they indicated if they had collected ictal EEG activity may have helped to confirm with greater confidence the difference between PD and true epileptic seizures [5].

Due to a lack of EEG activity during studies from times of rest (sleep) and not at rest [12] there has been suggestion by some authors that the source of the pathophysiological

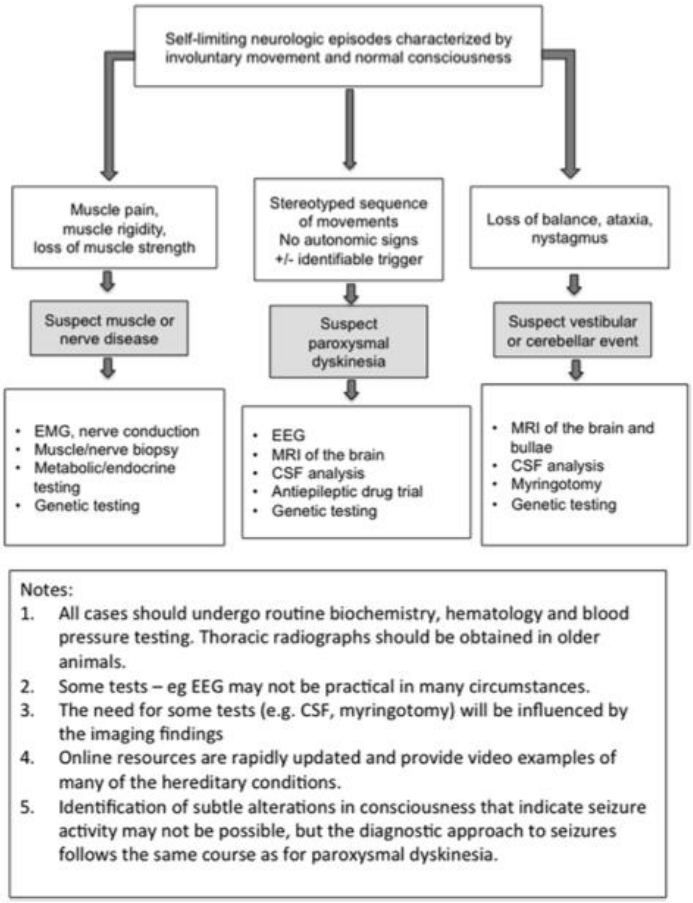
mechanisms of PKD has a subcortical origin, the basal ganglia [16]. Results from a study in 2005 in human patients with idiopathic PKD indicated that a hypoperfusion interictally within the cerebrum, particularly within the posterior parts of the bilateral caudate nuclei, may be actively involved with PKC [17]. The authors could not conclude if the hypoperfusion may be the result of the disease or the cause of disease, and that further investigations of brain perfusion SPECT studies should be undertaken on a larger number of patients to clarify this [17]. As these results are not yielded from canine patients it is not possible to confirm that this is could be the pathophysiology of canine patients suffering with CECS/PDs. It highlights an area where further study within the veterinary field could support further understanding of the epidemiology of CECS.

Over the last 20-25 years there has been an increase in the recognition of PDs within the veterinary field [3], some of these include: Dyskinesia in Bichon Frise [18], paroxysmal dyskinesia in Chinook dogs [19], Episodic Movement Disorder in short haired German Pointer [20]. Despite this the known pathophysiology of PD in animals is not always fully understood, arguably even less so in veterinary medicine than previously discussed is similar PD in human Medicine.

In 2014 Ganokon Urkasemsin et al wrote a paper about PDs increasing in frequency within the canine species. They designed a logical approach to a dog with a movement disorder shown below in figure 1 [3]. They also developed a table to summarise the clinical Manifestaion of recognised PDs in different dog breeds, Table 2 [21].

In this paper they discuss how important clinical manifestation of different PD episodes are in dogs, especially when it comes to categorising them. Which may allow for a more successful diagnosis for future Veterinarians when they come across PDs in their patients. Another significant point they made in their summary was that the if more research is completed into the underlying pathogenesis of the different disorders, genetic factors and influence of inheritance will most likely help to revolutionise a Veterinarian’s ability to diagnose and treat these different PD’s.

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



It was recently discovered a deletion of BCAN gene has been recognised as a cause of a paroxysmal hypertonicity disorder seen in Cavalier King Charles Spaniels, the Episodic Falling Syndrome [22], [23]. Another recent study of Soft Coated Wheaten Terriers diagnosed with canine PD, suggested that it is very likely a mutation in PIGN (a gene which encodes glycosylphosphatidyinositol (GPI)) synthesis enzyme, is the cause of the disease [24].

Table 2. [3] Summary of clinical manifestations of PD in dogs.

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

2.3 The emergence of Canine Epileptoid Cramping Syndrome

Canine Epileptoid Cramping Syndrome (CECS) first established its name in 2003, given by Diana Plange, a German veterinarian and Border Terrier breeder, who first described the disease in 1997 [25]. During this year, several Border Terrier owners reported to Plange

similar clinical signs and symptoms in their animals. These reported clinical signs were described as epileptic-type problems, but did not fit the classic epileptic form [25]. Plange organised for over 100 Border Terriers to visit to her surgery and other specialist surgeries to be analysed for any anomalies or abnormalities which may have been used to explore the causes of clinical signs seen in these animals [25]. During testing they sampled the patients' blood, urine and liver. It was initially suggested in her study that liver dysfunction in certain patients could be an indicator for the disease. This was discounted later when more symptomatic patients became apparent with normal liver function.
Plange went on creating articles about CECS in different European magazines and a website, due to which it became apparent that there were more Border Terriers affected with the disease outside of Germany in other areas of the EU but also the USA as well. This was thought to be connected due to the fact that there were also animals imported from the UK into the United States. Plange co-ordinated with Universities across the USA and Europe to increase the number of studies and results on the disease. Owner support lists created online were used to see the effects of changing nutrition of the affected dogs and possible drug treatments that could be used [25].

Emergence of new research by Mark Lowrie et al, [26] has indicated a gluten sensitivity as part of the environmental trigger for the disease, which will be discussed in more detail within later in this chapter. After the results of said research it has been suggested by the authors that a more appropriate name of the disease should be Paroxysmal Gluten-sensitive Dyskinesia (PGSD).

2.4 Prevalence of CECS/PGSD

The prevalence of the disease is not currently well documented. Previous research has attempted to collect some data via questionnaires sent to dog owners asking about PD/Movement disorders but not CECS in particular.
A general Health Surveillance survey was initiated using a general health and behaviour questionnaire in 1998 and repeated in 2004 by the Dutch Border Terrier club [5]. The questionnaires were sent out to 1,494 owners in 2004 to help reveal the prevalence of PD in Border Terriers at the time. The results of the survey reported that between 2003-2006 the prevalence of episodes of movement abnormalities in Border Terriers was 4.8% [5].

In December of 2014 the Kennel Club initiated a Pedigree Breed Health Survey in the UK. These results were reported in 2016 on their Website. However, prevalence of CECS was not mentioned in their summary report. This may have been due to low submission of reports of the disease were collected during the survey. This could indicate that there is an under-reporting issue, perhaps due to minimal recognition of the clinical manifestations of the disease, or a reduced number of Border Terrier owners taking part in the survey. It is also important to note that any data they did report from this survey for breeds that have a lower number of responses cannot be representative of the entire population.

In the last 2 decades, UK Border Terrier Clubs have agreed to set up a Breed Health Group to encourage more up to date health status of the Breed (border terrier health.org). In the last the few years owners that are a part of the UK Border Terrier Clubs and outside of the club were invited to fill out a health status form on a yearly basis. Consequently, it was reported in 2018 10 cases of CECS were reported using the CECS report form; 7 reports were from the UK, 2 from New Zealand and 1 from Belgium. In 2020 of 64 Border Terriers in the UK 10 of those were reported to have CECS, 2021 13 owners reported CECS of 131 Dogs reported on (of which 65 had been deemed healthy by their owners and 66 had been reported to have medical issues). The reliability of this data collection is questionable due to reports coming from owners and not their veterinary surgeons, therefore no clinical diagnosis of CECS has been recognised in these animals.

In the past decade, “cramping episodes” also have been reported by breeders and owners of specific families of Border Terriers in the Netherlands and Germany. During the same time frame, an increasing number of Border Terriers with episodic dystonia was observed in Finland [5].

2.5 Phenotyping CECS

Clinical signs of CECS that are most commonly seen include Chorea: unpredictable muscle movements. Athetosis: a writhing, slow but continuous contraction of the muscles in the trunk of the animal. Choreoathetosis when describing these two symptoms together. Dystonia: a repetitive, involuntary spasm of the muscles. Ballismus: sudden contraction of

muscles in the limbs, which results in a flapping movement of the limb [2]. Most commonly affected muscles are those in the head, neck and limbs of the animal. These symptoms culminate in an animal being unable to walk normally. When observed together these clinical signs are generally described as a dyskinesia [2].

Episodes seen in Border Terriers are not normally triggered by certain precipitating events, which has been indicated in certain PD types in human medicine, like prolonged exercise or sudden movement disorders. In phenotypic reports of the disease owners reported This leads them to be described mostly in the category of PNKD within the human medicine classification [2].

There has been no sex prelidiction suggestion from previous study of CECS and it is believed most BTs will suffer their first attack before they are 3 years of age [2].

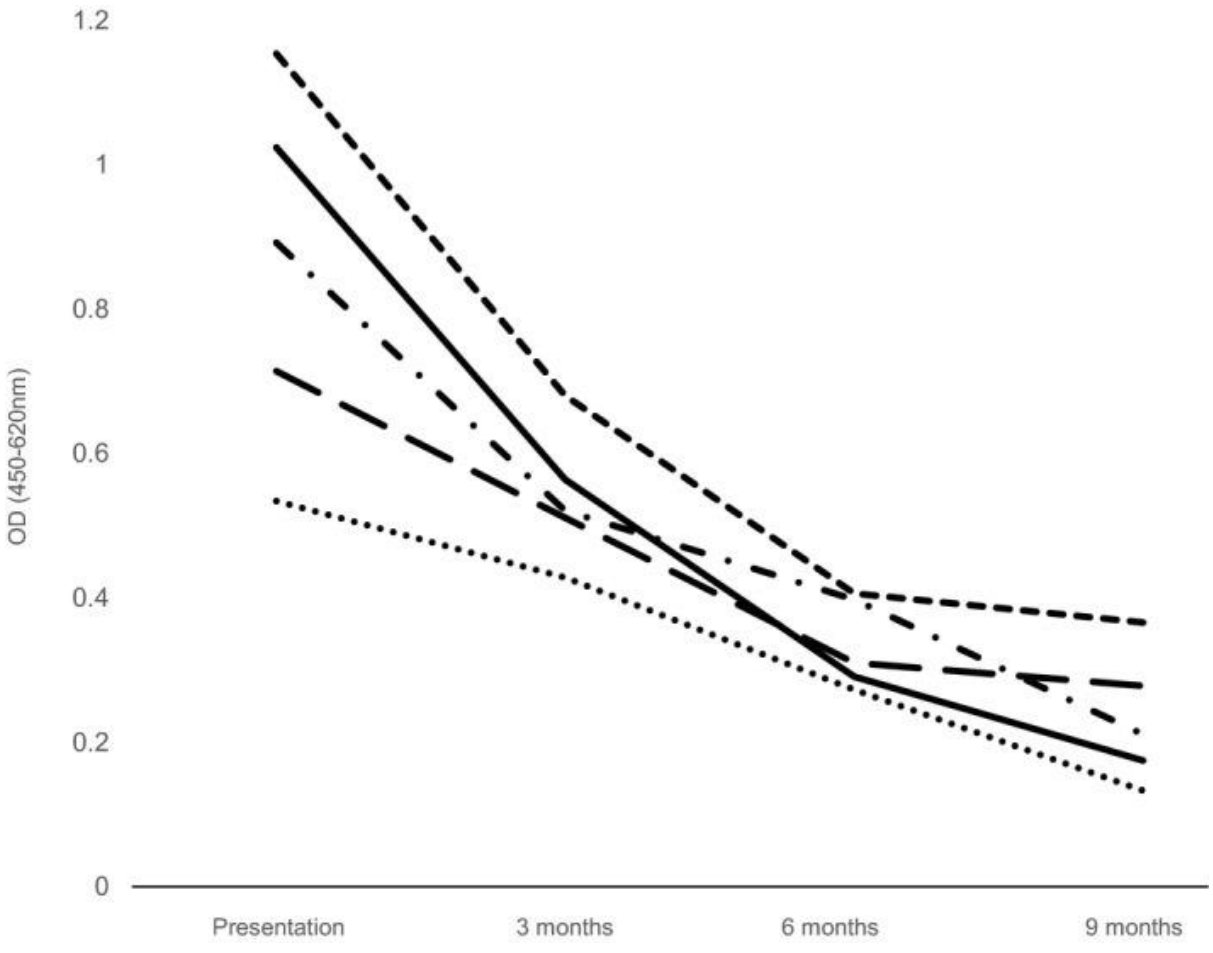
1.6 Gluten Sensitivity and its involvement in CECS/PGSD

In Celiac disease autoimmunity has been identified as one of the integral genetic components of the disease [27]. It can be described as an immune mediated type of enteropathy, which will be triggered when the genetically susceptible individuals ingest gluten. In such patients, an abnormal duodenal biopsy can be obtained. In which there will be an increase in the presence of intra-epithelial lymphocytes and villous atrophy in the presence of an autoantibody against the enzyme that breaks down gliadin, named transglutaminase-2 antibodies, within the serum [27].
In human medicine this has now been given the name Nonceliac Gluten Sensitivity (NCGS), several conditions fall under this umbrella term, which are all characterised with an immune response to the ingestion of gluten [28], [29], [30]. One of these conditions is gluten ataxia (neurological disorder) [31] in which the best diagnostic markers of the disease are autoantibodies to the glial enzyme, the enzyme responsible for gluten sensitivity [32], [33].
A study in 2015 looked at the effects of a gluten free diet for dogs with CECS. They used serological evidence to assess the hypothesis that there is a connection between CECS and gluten sensitivity. The tests were performed on BTs that had been clinically diagnosed with CECS. Samples collected from 6 BT with CECS over a period of 2 years, 2012-2014, collecting samples at presentation, 3 months, 6 months and at 9 months. They were sent to

Davies Veterinary Specialists for analysis. During the trial all the dogs were fed an exclusively gluten-free diet, with no other food to be introduced into the diet during the time of the trial. The owners were instructed to keep a diary of the episodes witnessed during the trial.

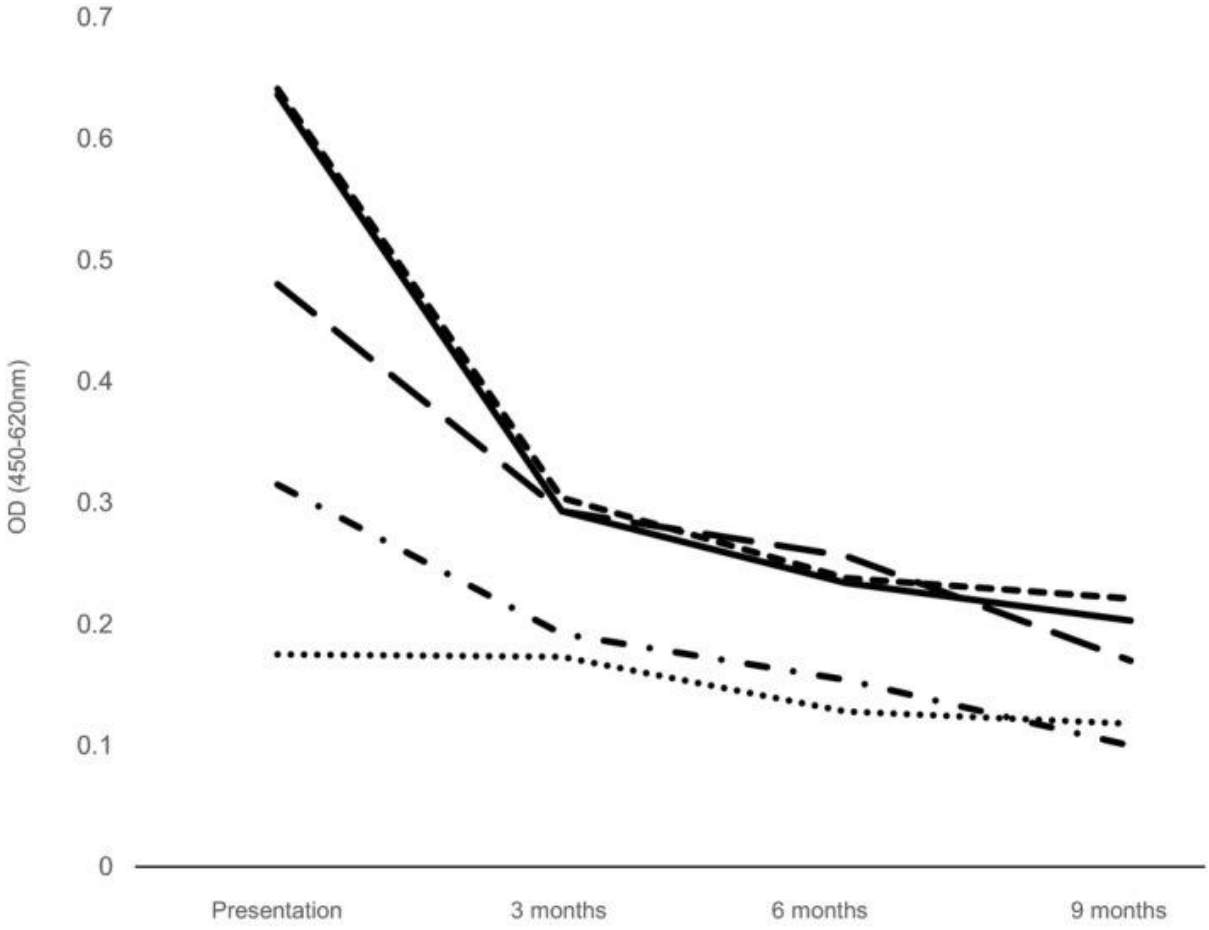
The serum collected was analysed for anticanine transglutaminase-2-IgA (TG2 IgA) autoantibodies and anticanine gliadin-IgG (AGA IgG) antibodies. The results of the serological analysis showed that there was a reduction in the titre of TG2 IgA which correlated to a reduced clinical remission of episodes of CECS reported by the owners. The results are shown in Figure 2 below [26]

Figure 2. [26] Chart demonstrating the serological response of antitransglutaminase-2 IgA to a gluten-free diet in 5 dogs with canine epileptoid cramping syndrome (dog 6 excluded due to failure to adhere to methods). The time periods of monitoring were initial presentation, 3, 6, and 9 months after commencement of a gluten-free diet. Each dog is indicated with a different line. © 2015 The Authors. *Journal of Veterinary Internal Medicine* published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.



They also reported a similar result for the AGA IgG. As shown in figure 3 below [26].

Figure 3: Chart demonstrating the serological response of anti-gliadin IgG to a gluten-free diet in 5 dogs with canine epileptoid cramping syndrome (dog 6 excluded because of failure to adhere to methods). The time periods of monitoring were initial presentation, 3, 6, and 9 months after commencement of a gluten-free diet. Each dog is indicated with a different line [26].



The results of the two tests are strongly support the hypothesis of a possible relationship between the CECS and the gluten sensitivity. Which indicated this to be the first veterinarian PD that has been linked to gluten at the time of this report (2015). To the authors knowledge there is still no other paper reporting on a possible link between PD and gluten sensitivity in the veterinarian literature. This study only sampled a very small proportion of the whole population, therefore more testing and further research should be performed on larger sample size to increase the strength of their hypothesis.

In another study some owners of BTs suffering episodes of CECS described a borboygmi (usually a gurgling sound of the guts) and other gastrointestinal signs including food intolerance [2]. In one of these studies it was reported 11 out of 29 BTs were suspected to be suffering from a food intolerance. Furthermore, 15 of the 29 were also suffering from skin abnormalities. The owners of this study that changed their dog's diet to a (26 out of 29), some choosing hypoallergenic or single protein and carbohydrate source, subsequently reported fewer CECS episodes for the dog. However, the results of the study were only performed in a small population of BTs who were not clinically examined by the authors themselves, so the findings cannot represent the whole population, nor can they confirm that the dogs were clinically diagnosed with these conditions. Furthermore, the Kennel Club's own General Breed Health Survey reported 1.19% of BT registered with them suffer with gastrointestinal problems and 1.79% of BT suffer with skin diseases. Therefore, these findings may be co-incidental [2].

2.7 Genetic importance of CECS

In 2017 owners of 110 affected and 128 unaffected BT were sent a questionnaire regarding the clinical characteristics of their BTs PD [5]. A genome wide association study (GWAS) was performed with DNA of 110 affected and 128 unaffected dogs and in an attempt to determine the most likely mode of inheritance, an inspection of pedigree analysis was performed on affected groups of western European and Finnish BTs, as shown below in figure 4 [5] and figure 5 [5]. Some of the family lines demonstrated a higher prevalence of the disease, whereas others demonstrated they were free from the disease. Segregation analysis of the likely mode of inheritance was not able to be performed due to lack of data about the health status of siblings and parents of affected dogs.

Fig 4: Typical pedigree of 76 western European Border Terriers segregating PD. The trait is often seen in littermates and half-siblings. Black symbols: affected; nonfilled symbols: unaffected. Squares: males; circles: females; diamonds with numbers: number of male and female unaffected littermates (status based on questionnaires and breeder reports). *Full siblings from multiple litters.[5]

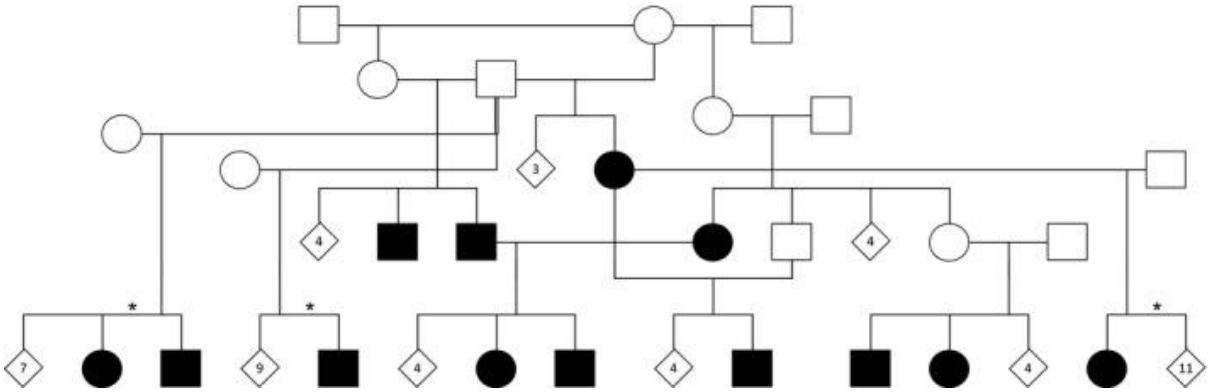
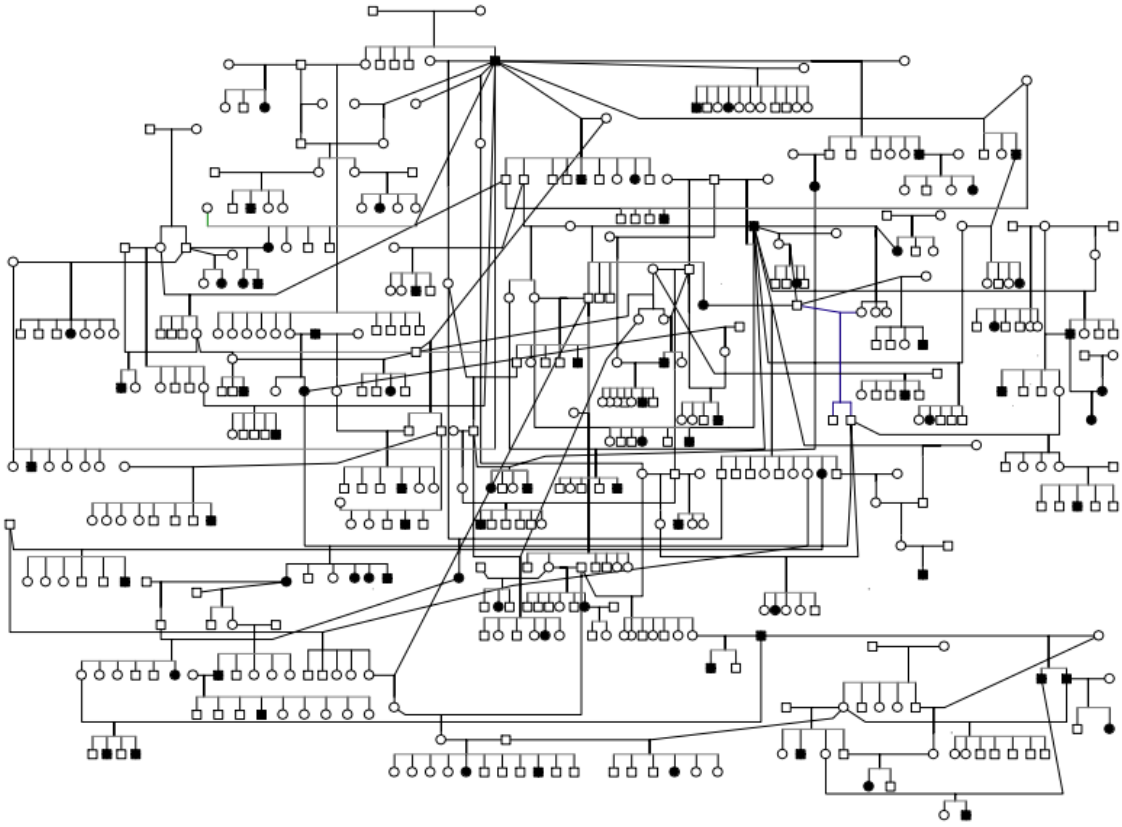
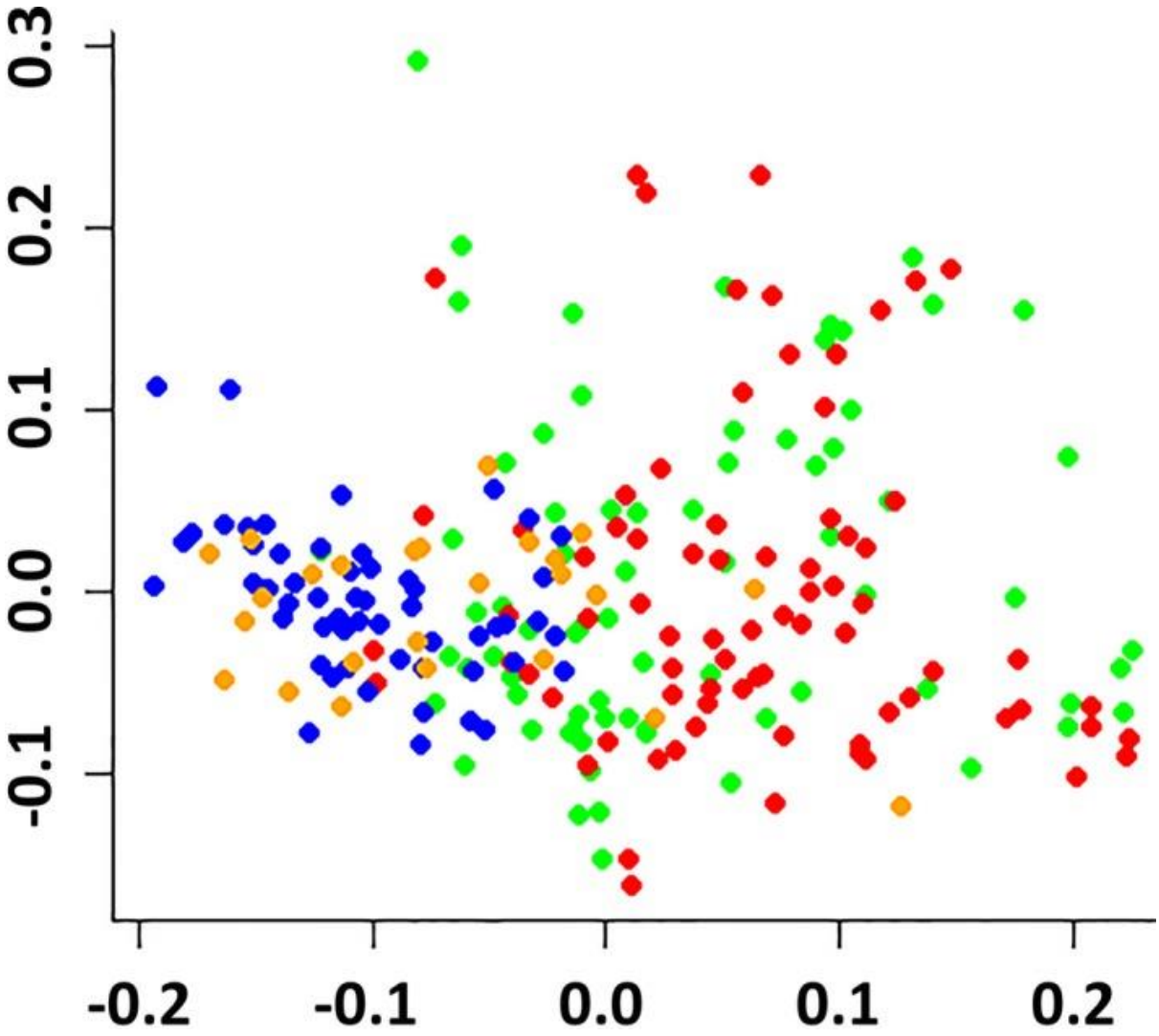


Figure 5: Pedigree of Finnish Border Terriers segregating PD. Black symbols: affected; nonfilled symbols: unaffected. Squares: males; circles: females [5].



The GWAS analysis of the BTs used in this project unfortunately did not highlight any large differences between the affected BT and the non-affected BT (case control group) (results shown in figure 6 below [5]). It was also found that there was no obvious association with the regions of the genome affecting the previously mention genetic factors of human PD; *PNKD, KCNMA1, PRRT2 and SLC2A1*.

Figure 6: Multidimensional scaling plot based on DNA data of individual Border Terriers. A principal component analysis of the SNP data of the dogs was performed with GenABEL software. Red dots represent western European cases, orange dots Finnish cases, green dots western European control dogs, and blue dots Finnish control dogs. Within each population, cases and controls are similarly distributed in the plot.[5]



2.8 Diagnosis of CECS

There is no determined genetic test or DNA for CECS discussed in veterinary literature. As there is no true known pathogenesis of the disease it is difficult to suggest tests that may be used to diagnose the disease at the present time.

Research into PGSD in BTs in 2015 [26] did suggest serological testing for anti-transglutaminase-2 and anti-gliadin antibodies might be useful for diagnosing CECS. It could also be used for monitoring the dietary compliance especially in those dogs which are not adhering to the suggested gluten-free diet.

2.9 Treatment options of CECS

There are contrasting reports about the efficacy of anti-epileptic drug use from owners with CECS affected BT [5]. Therapeutic trials performed in one report from 2014 [2], indicated that there was no positive effect (reduction of frequency of an CECS episodes) of phenobarbital, potassium bromide or suppository diazepam. Doses of the medication were within therapeutic range during the trial therefore thought to be adequate for all cases in which they were utilised.
A later report from 2017 found Diazepam in a suppository form has been shown to have a positive response (reducing symptoms of an episode) in 100% of cases [5]. 50% of owners reported that there was a reasonable or good response to phenobarbital injections. 47% of owners reported no change at all in signs or symptoms with their affected BT on antiepileptic medications. In human medicine it has also been reported that there is a benefit to using anti-epileptic medication for PD [10], [34].

Probably one of the more consistent factors mentioned by the owners of affected BTs is a reduction in frequency of CECS episodes when they have changed the diet of their animal. Hypoallergenic and more specifically a gluten-free diet has reported to markedly improve the condition [2], [5], [26].

3. Objectives

The objective of this literature review is to gather the relevant information currently known about canine PD/CECS from different sources to discuss the most common presentation of PD/CECS, review the history and background of PD in the canine species, the most likely causes of the CECS, most effective treatment options and highlight areas of research that are missing. The goal of the structure of this review is to provide a comprehensive history of the disease with an insight into effective diagnosis or treatment that could increase the chances of

a more successful diagnosis and reduce in prevalence of the disease. The prediction of the author is that due to very little veterinary literature into the subject over the last 20 years it will highlight areas of further research needed, also that there will be a high prevalence of gluten free diets having a positive effect on reducing the frequency of CECS episodes throughout research that has been done.

4. Method

The majority of papers sourced for this literature review were found from online sources; Google Scholar and the PubMed Library. Articles from scientific journals of relevant topics were also used. Finally, some information reported onto UK Kennel Club website and UK Border Terrier Health club website were also sourced for this review.
Criteria for inclusion of papers for this review was their relevance to the goal stated in the objective of this literature review. Phenotypic descriptions of PD in human and veterinary medicine, Canine PD and their pathophysiology, BT CECS data collection and analysis. Some were sourced as they helpfully described relationship between PD in human and veterinary medicine, hypotheses on how they could be related and what research from human medicine may be useful to implicate in veterinary research.
To correctly define canine PD/CECS papers reviewed within this thesis needed to include medical testing to help prove that there is a difference between Epilepsy and PD episodes i.e. studies of ictal EEG activity seen in Epilepsy vs studies of PD.
Random control trials and non randomised studies were eligible for inclusion. All years of relevant data were included if an English abstract was available.

5. Discussion and conclusion

From this literature review it is evident that there is a large lack of data about the prevalence of the CECS in BT. This has been highlighted from the lack of surveys carried out in the UK to thoroughly assess the number of BTs experiencing symptoms of the CECS or other movement disorders. It is hard to tell whether this is due to a low prevalence of the disease or under reporting, as there hasn't been many surveys used, but in surveys that have been used the prevalence has not been very high. The reason for lower prevalence then expected may be to lack of BT owners receiving or taking part in previous surveys. It has highlighted that it

may be prudent in the future to create a more specific survey for CECS aimed towards BT owners on a wider scope (Kennel Club registered animals as well as non-Kennel Club registered animals).

This literature review looked at papers that reported important clinical information regarding CECS and provided similarities between their findings. Therefore, strengthening some of their hypotheses. Majority of the papers reviewed demonstrated a clear differentiation can be made between Epilepsy and canine PD/CECS. Historically they were believed to be within the same medical category but with results of interictal and ictal EEG activity analysis in human and veterinary medicine this should now be discounted.

A precise, common clinical manifestation of the disease was presented across the different papers reviewed. The duration of the episodes was described as being less than 30 minutes in the majority of clinical presentations, with unpredictable intervals between episodes (days, weeks or months)[2], which has also been recognised in the other movement disorders recognised in other breeds [35], [18], evidence that CECS can be described as a waxing waning disorder as it is.

The papers reviewed all similarly indicate that there is no genetic or sexual predisposition for the disease. The lack of any result from GWAS tests probably indicates that there is a complicated inheritance background for CECS [5]. However, the lack of research in this area of the disease is something that has been highlighted throughout the different papers reviewed. An increased number of studies, with an increased sample size would help to provide a more comprehensive study of this in the future. The aim of this kind of genetic analysis on a wider pool of BTs would be to reach a similar concise, definite genetic association responsible for the CECS as indicated by authors Gil JL et al [22] for Episodic Falling syndrome in Cavalier King Charles Spaniels (BCAN microdeletion mutation). This type of association may help to aid and revolutionise the future diagnosis of the CECS.

In conclusion due to lack of prominent diagnostic genetic test, if a BT is suffering with clinical signs and symptoms, it may be more important to diagnose using a rule of eliminating other life-threatening diseases, determination of gluten sensitivity and switching to a gluten-free diet.

The contradicting evidence seen across papers regarding efficacy of anti-epileptic drugs towards CECS indicated that there is a need for further research into this topic. There are important side effects of antiepileptic drugs that should be considered before using them in any animal [36]. So, if there is evidence that owners do not see any improvement this should

be further investigated to reduce unnecessary drug use which put animals at risk of side effects. In some of the therapeutic trials different dosages and treatment protocols used made it difficult to draw meaningful conclusions from their data. Furthermore, a substantial placebo effect, manifested as a decrease in seizure frequency, has been identified in epilepsy treatment trials in dogs [34]. This probably also is applicable to other paroxysmal disorders. Consequently, to evaluate the efficacy of medical treatment on PD in Border Terriers, prospective double-blind placebo-controlled studies are required [5].

Several limitations were recognised across the papers that were reviewed in this literature review. Some patients had not been physically examined by the authors. This may have led to inconsistencies in the data collection process due to bias, subjective opinion or lack of understanding of the question being asked. Diagnostic work up was inconsistent between some of the BTs used in medical trials (medical records and dosages of antiepileptic drugs were not available in all cases). The small number of cases analysed throughout the different papers also means that it is impossible to draw any strong conclusions with regard to the poor response to dietary changes or medications used, as their population of dogs may purely represent a cohort of noncompliant dogs. If there had been a larger number of cases that had received appropriate drugs trials of known dosages and therapeutic concentrations with a poor response to treatment across different papers this would have added weight to the conclusion that there is little efficacy in antiepileptic drug treatment for CECS in Border Terriers [2], [5].

6. Summary

In summary the results of the systematic review have highlighted there is a common positive response to a gluten-free diet and reduced frequency of CECS episodes across different research. It also indicated there is room for further research into a more accurate genetic association to the disease. This would revolutionise the diagnosis of the disease and could reveal the true prevalence of the disease within the BT population not only in the UK but worldwide. It is unclear as to whether there is in any efficacy in the use of antiepileptic drugs in CECS. Further prospective double-blind placebo-controlled testing would be indicated to understand the true efficacy of the drugs as a possible treatment.

7. References

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