AKC Canine Health Foundation
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Understanding Canine Epilepsy

Introduction

Epilepsy is the most common neurological disease seen in dogs, affecting up to five percent of the canine population[3,4]. However, this statistic is somewhat misleading as epilepsy is not a single disease. Instead, the diagnosis of epilepsy potentially refers to any one of a number of conditions that are characterized by the presence of chronic, recurring seizures. These conditions may be inherited (genetic, primary or idiopathic epilepsy), caused by structural problems in the brain (structural or secondary epilepsy), result from metabolic problems or a toxic exposure (reactive epilepsy), or stem from an unknown cause[4]. Determination of an appropriate treatment regimen for canine epilepsy depends on an accurate diagnosis of the type and cause of seizures, only after which appropriate therapeutic options can be identified.

Diagnosing and Classifying Canine Seizures

Although classification systems exist for human seizures, there is not yet a widely accepted classification system available for seizures in dogs[3]. While human systems are sometimes used to describe canine seizures, this can be problematic. Human classifications are not always clearly applicable to canines, and there is often confusion about the meaning of specific terminology in the veterinary setting. This is particularly true of those classification elements which require subjective reporting of symptoms. For example, while dog owners may notice a specific behavior that typically precedes a seizure and is indicative of a behavioral change, there is no direct way to determine the presence of a pre-seizure event as sometimes diagnosed in humans.

Recently, a multi-axial classification was proposed for veterinary seizures, which is similar but not identical to the current human classification system. Using this system, seizures would be described based on the seizure characteristics (Axis One); the brain location responsible for generating the seizure (Axis Two); the probable cause of the seizure, if one is known (Axis Three); and other clinical signs caused by the seizure disorder that could affect treatment choice and progress (Axis Four)[3].

Seizure Classification

Seizure description is the most critical information needed for the diagnosis of canine epilepsies, and there are several basic types of seizure. Most seizures that owners observe will be motor seizures. These seizures involve involuntary muscle movements or sudden losses or increases in muscle tone. Motor seizures may affect either localized areas of the body, in which case they are known as focal or partial seizures, or they may be more generalized. Automatisms are another form of motor seizure, involving a repetitive behavior that may look like a voluntary behavior, such as barking, chewing, or paddling the legs[3,4].

Although non-motor, or sensory, seizures may occur in animals they are more difficult to detect. These types of seizures involve the dog perceiving a sensory stimulus that is not actually occurring, which could be reflected in a change in behavioral pattern such as “fly biting” or staring at an empty space. Some dogs also experience seizures involving changes in their autonomic functions, such as their heart rate or ability to control urination[3].

Commonly Used Terminology

Automatisms – repetitive movements that appear to be under voluntary control, but actually reflect seizure activity

Atonic seizure – a sudden loss of muscle tone lasting several seconds or more, not following a tonic or myoclonic event

Cluster seizures – a group of seizures within a shorter than normal interval, such as over the course of a day

Focal seizure – seizures affecting only part of the brain and therefore also only part of the body, also known as partial seizures

Generalized seizure – seizures affecting both hemispheres of the brain

Idiopathic epilepsy* – epilepsy of unknown cause, typically assumed to be genetic. See also primary epilepsy.

Interictal period – the time between seizures

Myoclonic seizure – sudden, brief contractions of a muscle or group of muscles

Postictal period – the time immediately following a seizure, where sensory or behavior changes may be observed

Primary epilepsy* – epilepsy with no identifiable structural or reactive cause, typically assumed to be of genetic origin. See also idiopathic epilepsy.

Refractory epilepsy – seizures that occur even during treatment with therapeutic doses of antiepileptic medication, i.e. the medication stops being effective.

Status epilepticus – a serious condition where seizures follow closely on one another without a break, or where a single seizure lasts more than 5 minutes

Tonic seizure– a sustained increase in muscle tone lasting up to several minutes

Tonic-clonic seizure – a seizure where the tonic phase is followed by shorter, myoclonic, contractions

*The terms idiopathic or primary epilepsy are applied inconsistently in veterinary medicine at the current time. Some veterinary neurologists consider all idiopathic epilepsy to be of genetic origin (similar to human medicine) whereas others consider it to be of "unknown origin," particularly in cases that occur outside of an expected age range for genetic-based epilepsy.

Describing Seizures

When observing seizures, it is important for dog owners to keep a diary of detailed information including: 1) affected body parts 2) when seizures occur 3) how often seizures occur, and 4) how long they last (see attached diary template for record keeping). Doctors and owners should also pay close attention to how dogs behave after a seizure has passed. Although some canines will quickly return to normal, during the postictal period, others will experience difficulties standing or moving; problems understanding visual, aural, or other stimuli; or other changes in behavior. These symptoms may last for varying amounts of time, and can affect treatment choice.

In some cases, seizures will occur as the result of exposure to a specific stimulus, such as an illness, exposure to a toxin, or problems with metabolism. Any potentially precipitating events should be brought to the attention of the treating veterinarian, as such reactive seizures are not generally treated with standard anti-epileptic drugs[4]. Reflex seizures, which are seizures that occur consistently

after a particular exposure, such as to a loud noise, a flashing light, or a more complex movement or behavior, have also been reported in dogs[3,4].

Types of Canine Epilepsy

It is not always possible to identify the cause of canine seizures; however, canine epilepsies can generally be categorized into one of three types. Primary epilepsy, or idiopathic epilepsy, is defined as epilepsy without an identifiable structural cause and having an assumed genetic origin (see Commonly Used Terminology for more information about primary versus idiopathic epilepsy). Repeated seizures in 1-5 year old dogs with a normal neurologic examination, where there are no known structural abnormalities of the brain, metabolic diseases, or toxin exposures, are often assumed to be a form of primary epilepsy[4]. The designation of idiopathic epilepsy suggests that the seizures are of unknown origin. However, the causes of such epilepsies can sometimes be determined, for example when seizures are the result of a specific genetic defect known to occur in certain breeds.

Structural epilepsy is the diagnosis for seizures that occur because of observable damage to or malformations of the brain. Structural epilepsy is also referred to as secondary epilepsy, because the condition is the result of another problem rather than the primary disease. For example, structural epilepsy may occur after an inflammatory disease of the brain, growth of an intracranial tumor, or after trauma to the head. It can also be the result of congenital malformations or a vascular event, such as a stroke[4]. The brain changes that cause structural epilepsies can sometimes be detected using an MRI or by analysis of cerebrospinal fluid. Testing for structural epilepsy may be indicated if a dog exhibits neurologic abnormalities between seizures or if the dog falls outside the typical age range of onset for primary epilepsy. Interictal changes are less common in dogs with primary epilepsy.

Reactive seizures, seizures which occur in response to specific stimuli (such as a metabolic derangement or a toxin), are not considered to be a form of epilepsy.

The Genetics of Canine Epilepsy

A large number of genetic mutations have been associated with epilepsy in both humans and mice. In humans, the inheritance of epilepsy is generally complex, meaning that it involves interactions of one or more genes with each other as well as potentially with environmental factors, and this is likely true of epilepsy in dogs as well. However, the extent of inbreeding within specific dog breeds has allowed the identification of certain animals that are at particularly high risk of seizure development. No fewer than 26 dog breeds have shown at least some evidence of heritable, primary epilepsies.

Gene mutations have been identified, many of which include a group of diseases known as neuronal cereoid-lipofuscinoses. These are storage disorders where mutations lead to the abnormal accumulation and storage of a cellular product within cells, eventually leading to the dysfunction or death of neurons[1]. One gene for an inherited epilepsy has been identified in Lagotto Romagnolo dogs. That gene, *LGI2*, is similar to the previously identified human epilepsy gene *LGI1*, and scientists believe that a number of heritable epilepsies may have similar causes in humans and canines[1]. Research into potential similarities between dog and human epilepsies has also led to the identification of several candidate genes that may predict the efficacy of anti-epileptic treatment in some breeds.

The Etiology of Epilepsy

The specific biochemical mechanisms that cause seizures to occur are not yet fully understood in either dogs or humans, although seizures are known to result from dysfunction in the brain's electrical activity. It is generally believed that epileptic seizures are caused by an imbalance between excitatory and inhibitory activity in specific areas of the brain, leading to either excessive brain activity or activity that is unusually depressed. However, in the absence of structural damage or metabolic insults, the causes of such dysfunction are not clear. There is some evidence suggesting that abnormal excitatory processes may be caused by functional abnormalities in neurons, specifically mutations in the ion channels that are essential to cells' electrical function[6], but that explanation is likely to only apply to a subset of primary epilepsies. Further research into the specific causes of various forms of epilepsy is still needed; current understanding is incomplete.

Medical Management Options

The information provided below is for information purposes only and cannot replace the advice of your veterinarian. Do not give your dog any medications without a prescription from a veterinarian.

Anti-epileptic drugs (AED) primarily work by inhibiting the action of excitatory neurotransmitters, stimulating inhibitory pathways, or altering ion channel function. Not all drugs work equally well in all animals, and their safety profiles are somewhat variable. A single, isolated seizure is not usually seen as a reason to begin treatment with AEDs. Treatment with these drugs is usually indicated when multiple generalized seizures have occurred within a 24 hour period, a dog has had at least two seizures within a six month period, or the dog has unusual or severe signs during the postictal period[7].

Once treatment has been declared necessary, the process of choosing the right drug requires balancing effectiveness and tolerability. Although many short-term side effects can be managed by titrating medication dosages, some AEDs have the potential to cause significant adverse effects. Therefore, it is important for medications to be chosen and tested with care and to recognize that not all epilepsies are amenable to drug treatment.

Anti-Epileptic Drugs

Phenobarbital, a first generation AED, is one of the drugs most used in veterinary patients, because it is relatively inexpensive, well-tolerated, and easily dosed[7]. Serious side effects include blood cell loss (cytopenias) and liver toxicity. There is also the potential for long term toxicity with phenobarbital, and dogs are susceptible to withdrawal effects as physical dependence develops over time[7].

Potassium bromide, or bromide, is another first generation AED that is often used to treat canine epilepsy. When used in combination with phenobarbital and other AEDs that are metabolized in the liver, dosages of those drugs can potentially be lowered to reduce the risk of liver damage. Bromide may also be useful in resolving some cases of epilepsy that do not respond to phenobarbital monotherapy[7].

The final class of first generation AEDs are the **benzodiazepines**, which include diazepam and clonazepam, although these drugs are less commonly used in dogs[6,7]. When needed, clonazepam is a longer acting variant of diazepam and allows veterinarian to avoid some of the problems associated with that drug, such as a short half-life. However, chronic use of benzodiazepines in dogs comes with a significant risk of withdrawal seizures, and patients on these drugs can develop tolerance to the medications over time.

Second generation AEDs used in dogs include levetiracetam, zonisamide, felbamate, gabapentin, pregabalin, and topiramate. **Levetiracetam** is considered to be a particularly safe treatment option with a wide range of safe dosages, however it efficacy remains unclear[8]. Further, co-administration with phenobarbital can affect how long it remains in the bloodstream[6,7]. **Zonisamide** is metabolized by the liver and can cause liver toxicity, although this is rarely observed. It is well absorbed, works via multiple mechanisms, and has shown to be effective against a variety of seizure types in humans. Because it interacts with phenobarbital, zonisamide doses should be increased when the two drugs are used in combination[7]. **Topiramate** is another human epilepsy drug that can be used in dogs. Its half life is quite short, although most adverse events are mild[7].

Felbamate has been used to treat seizures in dogs. It has the potential to cause both blood and liver toxicity, therefore monitoring with complete blood counts and chemistry panels is recommended on a regular basis[7]. **Pregabalin** has been suggested as a potential add-on drug for refractory seizures in dogs, with limited, recognized adverse effects[7]. The second generation human epilepsy drug lamotrigine is **not** recommended for use in dogs because it can cause heart arrhythmias[7].

Several third generation AEDs are currently under development and may turn out to be useful in the treatment of canine epilepsy. **Lacosamide** has been shown to be well tolerated in people, and some canine-specific data exist to support its use in dogs[7]. **Rufinamide**, a novel AED that is unlike any existing AEDs on the market, may also have some potential for canine treatment[7]. Finally, several other types of drugs are also under investigation for epilepsy treatment, including drugs that directly address inflammation, synaptic plasticity, and other brain health concerns, but they are not yet ready for general use[6].

Drug Dosing

Determining the appropriate dose for an AED is an extended process. While initial dosing is determined by weight, different dogs metabolize these drugs in different ways. Therefore, a series of blood tests are often needed to evaluate serum drug levels over time in order to make certain that levels remain high enough to be therapeutic but low enough not to be toxic[7]. While serum level of AEDs is a useful monitoring tool, drug levels are not a substitute for clinical assessment when determining the appropriate drug type and dose for any individual dog.

Refractory Epilepsy

Drug resistant, or refractory, epilepsy presents additional treatment challenges both in terms of dosing and in drug choice. Refractory epilepsy is diagnosed when treatment with two appropriate AEDs has failed and occurs in 30-40% of all dogs with epilepsy[5]. It can occasionally be dealt with by the addition of second or third generation drugs, such as gabapentin, zonisamide, levetiracetam, or pregabalin[5] in a multi-drug regimen. There are some dogs for whom seizure control may remain elusive.

The Future of Canine Epilepsy

Researchers continue to investigate the causes of canine epilepsies, both inherited and acquired, along with new treatments to more safely and effectively treat canine seizures. Furthermore, they do this not only to improve the health of dogs with epilepsy, but also to help their human counterparts. Epilepsy in dogs and humans is similar enough that canine epilepsy research not only has direct impacts on dog health, it also has the potential to improve the lives of human epileptic populations[9].

Translational research elements, those that bridge the species gap, can be observed across a broad range of clinical areas. Many of the types of familial epilepsy seen in dogs are similar to those that cause inherited human seizures[1,9], and drug research has been shown to be beneficial to both

species[5,7]. Canine epilepsies have also been used as a testing ground for new therapeutic options that can help dogs and humans alike. For example, preliminary research on intracranial electroencephalography (iEEG) in dogs suggests that the technique might be a way to predict seizures, which has the potential to be incredibly helpful for individuals who currently suffer from seemingly random epileptic events[2].

There are limits, of course. Canine epilepsy isn't identical to human epilepsy, and several drugs have already been shown to have differential toxicity in dogs and humans[5,7,9]. Additionally, owners have a limited ability to monitor their dogs' seizures, particularly when compared to how well people can report on their own seizures[9]. Still, the extent to which naturally occurring epilepsy in dogs is similar to epilepsy in humans presents a unique opportunity to use canine epilepsy as a research model to help dogs and their owners alike.

Acknowledgements

The AKC Canine Health Foundation thanks Drs. Chris Mariani, Ned Patterson and Mary Smith for review and editing of this educational document.

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Seizure Diary

Date	Time	Affected Body Parts	Duration of Seizure (minutes)	Notes
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			
	AM/PM			

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