



Understanding Canine Epilepsy

Introduction

Epilepsy is the most common neurological disorder seen in dogs, and has been estimated to affect approximately 0.75% of the canine population³. The term epilepsy refers to a heterogeneous disease that is characterized by the presence of recurrent, unprovoked seizures resulting from an abnormality of the brain. The condition can be inherited (genetic or idiopathic epilepsy), caused by structural problems in the brain (structural epilepsy), or stem from an unknown cause (epilepsy of unknown cause)¹. 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 dogs¹. 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, the International Veterinary Epilepsy Task Force proposed a classification scheme for veterinary seizures, which is similar but not identical to the current human classification system¹. Using this system, a seizure is primarily classified according to where it begins in the brain, with specific features of the seizure used to further characterize the event.

Seizure Classification

Seizure description is the most critical information needed for the diagnosis of canine epilepsies. There are two basic types of seizures, generalized and focal. Generalized seizures involve both sides of the brain at the onset, and are characterized by clinical signs apparent on both sides of the body. Most generalized seizures manifest as bilateral involuntary muscle movements or sudden losses or increases in muscle tone. During a generalized seizure, an individual's awareness of the environment is typically impaired, and salivation, urination and/or defecation can occur. Focal seizures originate in a discrete area of the brain, and are characterized by signs that affect a single side or specific part of the body. Focal seizures can present with abnormal motor activity (facial twitches, chewing movements, paddling of a limb), behavioral signs (fear, attention seeking), and/or changes in autonomic functions (pupil dilation, salivation, vomiting). Awareness may or may not be impaired during focal seizures. A focal seizure can spread to both sides of the brain and become generalized.



Commonly Used Terminology

Automatisms – repetitive motor activity that resembles movement under voluntary control, such as lip smacking, licking or chewing

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; clinically defined as 2 or more seizures within a 24-hour period

Focal seizure – seizures originating from only part of the brain and therefore also only affecting part of the body

Generalized seizure – seizures originating from both hemispheres of the brain

Idiopathic epilepsy – epilepsy without an identifiable structural cause, typically assumed to be genetic.

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 behavioral changes may be observed

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 (i.e. stiffening) lasting up to several minutes

Tonic-clonic seizure – a seizure where the tonic phase is followed by shorter, clonic (jerking) movements

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). Veterinarians and owners should also pay close attention to how dogs behave immediately after a seizure. Although some animals will quickly return to normal, during the postictal period, others will experience difficulties standing or moving; blindness; sedation, anxiety or other changes in behavior. These symptoms may last for varying amounts of time, and can affect treatment choice.



In some cases, seizures can result from exposure to a specific stimulus, such as an illness, exposure to a toxin, or problems with metabolism (reactive seizures). Any potentially precipitating events should be brought to the attention of the attending veterinarian, as such reactive seizures are not generally treated with standard anti-epileptic drugs⁴. 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 dogs⁵.

Types of Epilepsy in Dogs

It is not always possible to identify the cause of seizures in dogs; however, canine epilepsies can generally be classified into one of three categories based on etiology. Idiopathic epilepsy is defined as epilepsy without an identifiable structural cause and having an assumed genetic origin. 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 idiopathic epilepsy⁵. The designation of idiopathic epilepsy suggests that the exact cause of the seizures is unknown, although the condition is presumed to be inherited. However, the cause 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. For example, structural epilepsy can 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 stroke⁵. The brain abnormalities seen with 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 idiopathic epilepsy. Interictal changes are less common in dogs with idiopathic epilepsy.

Epilepsy of unknown cause is used to describe a condition in which a structural cause is suspected, but has not been identified on diagnostic evaluation.

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, because they are not caused by an abnormality of the brain.

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 epilepsies.



Gene mutations have been identified, many of which include a group of diseases known as neuronal ceroid-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 neurons¹. One gene for an inherited epilepsy has been identified in Lagotto Romagnolo dogs. That gene, *LG12*, is similar to the previously identified human epilepsy gene *LG11*, and scientists believe that a number of heritable epilepsies may have similar causes in humans and canines¹. Research into potential similarities between dog and human epilepsies has also led to the identification of several candidate genes that may predict the effectiveness of anti-epileptic treatment in some breeds.

The Etiology of Epilepsy

The specific biochemical mechanisms that cause seizures 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 function⁷, but that explanation is likely to only apply to a subset of idiopathic 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) work primarily by inhibiting the action of excitatory neurotransmitters, stimulating inhibitory pathways, or altering ion channel function in the brain. 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 a dog has unusual or severe signs during the postictal period⁹. 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 effective, relatively inexpensive, well-tolerated, and easily dosed⁹. Serious side effects include blood cell loss (cytopenias) and liver toxicity. Other side effects include sedation, ataxia, and increased appetite and water consumption. Dogs can also develop tolerance to phenobarbital over time, and are susceptible to withdrawal effects as physical dependence can develop⁹.

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 monotherapy⁹. Side effects of bromide include sedation, ataxia, vomiting and increased appetite and water consumption.

Second generation AEDs used in dogs include levetiracetam, zonisamide, felbamate, gabapentin, pregabalin, and topiramate. Of these, levetiracetam and zonisamide are used most frequently.

Levetiracetam is considered to be a particularly safe treatment option with a wide range of dosages, however, its efficacy remains unclear⁹. Side effects are considered mild, with sedation and ataxia reported most commonly. Further, co-administration with phenobarbital can affect how long it remains in the bloodstream⁹. **Zonisamide** is metabolized by the liver and can cause liver toxicity, although this is infrequently observed. Other adverse effects include sedation, ataxia, vomiting and inappetence. 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 combination⁹. The second generation human epilepsy drug lamotrigine is **not** recommended for use in dogs because it can cause heart arrhythmias⁸.

Several third generation AEDs have been marketed for human use within the last few years 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 dogs⁸. **Rufinamide**, a novel AED that is unlike any existing AEDs on the market, may also have some potential for canine treatment⁸. Finally, several other types of drugs are also under investigation for epilepsy treatment, including drugs that decrease inflammation, alter the connections between neurons, and address other brain health concerns, but they are not yet ready for general use⁷.

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 toxic⁹. While measuring serum levels of AEDs is a useful monitoring tool, it is 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 epilepsy⁶. It can occasionally be dealt with by the addition of second or third generation drugs, such as gabapentin, zonisamide, levetiracetam, or pregabalin⁶ 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 therapies 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 populations¹⁰.

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^{1,10}, and drug research has been shown to be beneficial to both species. 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 events⁴.

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^{5,8,10}. Additionally, owners have a limited ability to monitor their dogs' seizures, particularly when compared to how well people can report on their own seizures¹⁰. Still, the extent to which naturally occurring epilepsy in dogs is similar to epilepsy in humans presents a unique opportunity to study canine epilepsy as a model to help dogs and their owners alike.

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