An Overview of Canine Idiopathic Epilepsy for the Small Animal Practitioner

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Introduction

As a small animal practitioner, seizures are one of the most common neurologic abnormalities encountered. Much of what we know about seizures is derived from the observation and study of human seizure disorders, which have been well recognized since the beginning of recorded history. Once thought to be manifestations of mystical powers or demonic possession, the Greek physician Hippocrates in 400 B.C. theorized that the actual origin of seizures was due to disruptions in the brain itself. Throughout the centuries, seizure disorders have been studied extensively, however, research conducted during the past 80 years on human seizures and epilepsy has greatly increased the understanding of the disorder in animals as well.[1]

Seizure disorders occur frequently in dogs. Estimates of seizure incidence in the canine range from 0.5-5.7% of all dogs.[2] Of all dogs presented with neurologic signs, approximately 14% were related to seizures.[3]

Seizures are a clinical sign of functional (ie. physiologic or metabolic) or structural (ie. trauma, inflammatory, or tumor) cerebral dysfunction. The terms seizure, fit, convulsion, and ictus are used synonymously and refer to any transitory dysrrhythmia of brain cells that begins suddenly and ends spontaneously. Any brief and episodic involuntary event should be considered a possible seizure.[4,2]

Seizures are comprised of four main phases: the prodromal phase (preceding the seizure by hours or days), the aura or preictal phase (minutes to seconds prior to the seizure), ictus (the actual seizure stage), and the postictal stage (minutes to hours following ictus).[4] There are three major types of seizures: generalized, partial, and partial with secondary generalization. Generalized seizures, most commonly tonic-clonic, are the most frequent type seen in dogs. By identifying the type of seizure, oftentimes the underlying cause can be narrowed down. Generalized seizures are most commonly manifestations of primary (idiopathic) epilepsy, toxicity, and metabolic disorders. Partial (focal) and partial with secondary generalized seizures should alert the practitioner to a focal or multifocal structural problem, such as neoplasia, ischemia, encephalitis, or trauma.[4] These seizure types are described in Table 1.[4]

The normal brain is capable of convulsing in response to either internal stimuli (within the CNS) or due to external influences. Most researchers believe that the basic problem lies within the cells of the cerebral cortex. Despite the fact that seizures occur intermittently, these epileptogenic cells persist throughout the interictal period. Although the trigger is unknown, seizures result from the rapid uncontrolled discharge of neurons. Theories for this trigger include abnormal levels of certain neurotransmitters, loss of inhibitory neurons, hypersensitivity to acetylcholine, and glial abnormalities.[4] Days to weeks after a focal seizure episode, the opposite or uninjured side of the brain develops similar abnormal activity and therefore becomes a secondary epileptic focus known as a mirror focus. The mirror focus can become autonomous and is capable of independent seizure activity. Another phenomenon in the progression of seizure disorders is kindling. Kindling is the increased excitability of neurons and potential for seizure activity to occur with repetitive stimulation.[4] Kindling and mirror focus should be considered when dealing with pets that have seizures. If the background is compatible with idiopathic epilepsy, anticonvulsant therapy should be considered after the first or second seizure.[4,2]

Some animals have a lower seizure threshold than others, meaning that their mechanism to control neuronal excitement

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Table 1: Classification of Seizures in Animals

Classification	Comments
Generalized	
Tonic-clonic seizures	- Most common type
Severe form (grand mal)	- Manifests as a loss of consciousness and paddling or extension of limbs.
Mild form	- Manifests as little to no paddling or extention of limbs, and consciousness is usually maintained.
Absence (petit mal) seizures	- Rare or rarely recognized. Brief (seconds) duration of unconsciousness. Animal may stare.
Myoclonic seizures	- Rare. Massive involuntary jerking of muscles of the body.
Partial	
Partial motor seizures (focal motor seizures)	- Common. Caused by an acquired structural disorder. Involuntary movements are usually observed on one side of the body (whisker, ear, eyelid twitch).
Behavioral (psychomotor) seizures (partial seizure with complex symptomatology)	- Occasional. Intermittent bizarre behavior or autonomic signs.
Partial with Secondary Generalization	
Partial seizures that generalize to tonic-clonic	- Common. Caused by an acquired structural disorder. Can be confused with generalized tonic-clonic seizures if the beginning of the seizure is not closely observed.

is more easily impaired. In these animals, seizures can be triggered by over-excitement, estrus, fever, hyperventilation, fatigue, certain drugs, etc. Most investigators believe that certain dogs have a low seizure threshold that is genetically determined.[4]

Differentials for seizures

Disorders that induce seizures may arise from either outside the nervous system (extracranial) or within the nervous system (intracranial). Extracranial causes can be divided into two categories: causes that come from outside the body (ie. toxins) and causes coming from within the body but outside the nervous system (ie. hypoglycemia.) Intracranial causes can be either progressive (ie. neoplasia) or non-progressive (ie. idiopathic epilepsy.)[5] Table 2 lists the more common causes of seizures, the ages of onset, and the breed predispositions.[5] This paper will focus on primary (idiopathic) epilepsy and therefore, the many other causes of seizures will not be discussed in great detail.

Diagnostic Approach

Determining the cause of a seizure begins with a review of the signalment, history, physical exam findings, and neurologic exam findings. This information can lead the practitioner toward the correct diagnosis. However, in all cases, a minimum database consisting of a complete blood count, serum biochemistries, and urinalysis should be obtained. On the basis of this information, a list of differential diagnoses should be made. Further testing may be required on a case by case basis (i. radiographs, CSF tap, toxicology testing, etc.)[6,2]

The age of the animal is very important. If the patient is one year old or younger, one should consider congenital, hereditary, metabolic, toxic, or inflammatory disorders. If the animal is between the ages of one and five, idiopathic epilepsy would be a likely diagnosis, especially if the seizures occur on an intermittent basis. In an older animal, neoplasia, metabolic, vascular disease (as a primary problem or secondary to diseases

Table 2: Differential Diagnoses of Seizures in Dogs

Inherited or congenital disorders	Usual Age of Onset	Breed Predisposition
Congenital hydrocephalus	<1 year	Chihuahua, Boston Terrier, Maltese, Yorkshire Terrier, Chow Chow, Pomeranian, Toy Poodle
Portosystemic shunt	<1 year	Yorkshire Terrier, Miniature Schnauzer, Lhaso Apso, Shih Tzu, Retrievers, Irish Setter, Irish Wolfhound
Lissencephaly	<1 year	Lhasa Apso, Wirehaired Fox Terrier, Irish Setter
Primary epilepsy	1-5 years	German Shepherd, Saint Bernard, Irish Setter, Golden Retriever, Keeshond, Labrador Retriever, Siberian Husky, Cocker Spaniel, Beagle, Standard and Miniature Poodles, Wirehaired Fox Terrier, Border Collie
Lysosomal storage diseases	<1 year	Beagle, Basset Hound, Poodle, English Setter, Chihuahua, Spaniels, German Shorthaired Pointer
Metabolic disorders		
Hypoglycemia (diet-related)	<1 year	Toy breeds
Hypoglycemia (insulinoma)	>5 years	None
Hyperlipidemia	2-7 years	Miniature Schnauzer
Uremia	Any age	None
Hypocalcemia	Any age	None
Hypoxia	Any age	None
Polycythemia	Any age	None
Neoplasms		
Primary brain tumors		
Meningiomas	>5 years	Dolichocephalic dog breeds
Glial cell tumors	>5 years	Brachiocephalic dog breeds
Metastatic brain tumors	>5 years	None
Inflammatory disorders		
Canine distemper virus	Any age, but usually < 1 year	None
Rabies	Any age	None
Fungal encephalitis	>1 year	Primarily large-breed dogs
Protozoal encephalitis	Any age	None
Bacterial encephalitis	Any age	None
Rickettsial meningoencephalitis	Any age	None
Pseudorabies	Any age	None
Granulomatous meningoencephalitis	1-8 years	Any breed, but especially Poodles and Terriers
Pug dog encephalitis	1-7 years	Pug
Idiopathic conditions		
Springer Spaniel rage syndrome	3 months to 3 years	Springer Spaniel, Golden Retriever
Toxicity		
Lead, organophosphates, Ethylene glycol, many others	Any age, but usually > 1 year	None
Trauma		
Severe head trauma	Any age, but usually > 1 year	None
Vascular disorders		
Ischemia (stroke)	Any age	None
Arteriovenous malformations	Young dogs	None
Parasitic conditions		
Aberrant migration of Cuterebra or Dirofilaria	Any age	None

such as Cushing's disease) or inflammatory disorders are the primary differentials.[6,2]

Certain breeds of dogs have a higher incidence of idiopathic epilepsy; for example, German Shepherds, Golden Retrievers, Keeshonds, Beagles, Dachshunds, and Belgian Tervurens appear to be prone to the development of idiopathic epilepsy.[6] Seizures generally occur in both sexes with similar frequency, however, males seem to be more commonly affected with idiopathic epilepsy than females. Neutering does not seem to affect this rate.[6]

Historical information is very important in determining a diagnosis. In addition to general questions, the practitioner should ask the owner to describe the seizure episode. It is quite common for owners to confuse an intermittent event as a seizure. Pain, collapse due to a primary problem such as cardiac or respiratory disease, vestibular signs, and syncopy can be misconstrued as seizures. Most generalized seizures are manifested by involuntary movements and loss of consciousness, along with salivation, urination and/or defecation.[6] It is also important to know the duration and frequency of the seizures. Typically generalized seizures last 1-2 minutes and rarely up to 4-5 minutes. Metabolic or toxic causes should be primary rule outs for seizures of a longer duration.[6]

Another historical fact helpful in making a diagnosis is if the animal has had a prior illness resulting in fever (ie. canine distemper) or if the animal is currently ill with an underlying primary disease resulting in hypoxia, hypoglycemia, or inflammation. Exposure to toxicants, such as lead, organophosphates, or ethylene glycol can lead to seizures. Trauma resulting in a head injury can lead to seizures acutely or result in post-traumatic epilepsy weeks to up to 2 years after the initial injury.[6]

Vaccination history, nutritional information, housing and environmental concerns are important to obtain, as is a familial history. Idiopathic epilepsy is considered to be genetic in many cases, therefore if other littermates or one or both of the parents of the patient are affected with intermittent seizures, idiopathic epilepsy would be the top differential.[6]

Physical and neurologic examinations must be performed in all cases. It is important to perform the neurologic exam not only post-ictus, but also during the interictal period. The neurologic exam is often normal during the interictal period in most dogs with idiopathic epilepsy.[6]

The results of a CBC, serum chemistry profile, and urinalysis may be helpful in identifying patients with infectious, metabolic, toxic, or neoplastic disorders. If a primary CNS disturbance, such as idiopathic epilepsy, is the cause of the seizures, then the minimum database will typically be unremarkable.[6,2] Further diagnostic tests may be warranted to aid in determining an intracranial cause. Such tests may include CSF analysis, skull radiographs, CT or MRI of the head, EEG, etc. However, with idiopathic epilepsy, there will likely be no abnormalities in these tests either.[6]

Idiopathic Epilepsy (IE)

Seizures are seen in approximately 14% of all dogs with neurologic symptoms, 80% of which are recognized as being idiopathic.[3] It has been estimated that worldwide, 1% of all dogs suffer from idiopathic epilepsy.[7] The CNS abnormality in animals with idiopathic epilepsy is at the physiologic or biochemical level; therefore the results of diagnostic tests are usually normal.[5] However, studies are being performed in order to assess the use of EEG during the interictal period to diagnoses idiopathic epilepsy.[8] These seizures are caused by functional disorders in which both cerebral hemispheres are affected by paroxysmal neuronal discharges resulting in generalized and symmetrical seizure activity.[2]

The first seizure in dogs with IE typically occurs between 6 months and 5 years of age, with the majority occurring at 1 to 3 years of age.[9] The frequency of seizures is variable, occurring up to once daily to once every 6 months. Grand mal seizures, lasting from 1 to 2 minutes, are seen in 80-90% of all dogs with IE. These are commonly described as tonic-clonic attacks with loss of consciousness, dilated pupils, hypersalivation, and release of urine and/or feces.[7] IE has been described to be more common in males versus females, especially in certain breeds such as the Golden Retriever. Some

studies have indicated the male to female ratio as *3.5:1* and up to *5:1.* Typically the prodromal phase and/or aura are lacking or of short duration in these dogs and the post-ictal phase is usually mild.[3]

As stated earlier, IE has been described to occur more commonly in specific breeds of dogs and therefore a familial predisposition is likely. Based on large scale pedigree analysis, it was found that the disease has a multifactorial autosomal-recessive mode of inheritance with a sex-linked influence in the Beagle, Collie, Keeshond, Golden Retriever, and Labrador Retriever.[7,3] Genetic studies have indicated a clear increase in occurrence of IE in lines that are highly inbred (with several family members affected with IE) and in offspring sired by an epileptic male. However, a simple dominant mode of inheritance is not possible, as the condition is known to jump several generations and certain unaffected parents produce affected descendants.[7] Some estimates indicate that litters from 2 epileptic parents may have 30-100% of their offspring affected with IE.[10]

Inbreeding not only can increase the rate of IE in offspring, it has been noted to affect the time of expression of the IE. For instance, a puppy produced by the inadvertent mating of 2 related dogs with IE may begin seizuring under 6 months of age. Since most epileptic dogs begin seizuring at 1-3 years of age, these early onset puppies may be difficult to diagnose unless familial history is known. Therefore, in breeds that are known to have a genetic component to the development of IE, genetic counseling may be quite valuable. Certain breed clubs, like the Keeshond Club of Britain, keep detailed records of matings and offspring and therefore are developing recommendations to potential breeders. This is done in the hope that genetic counseling can decrease the number of dogs affected with IE within the predisposed breeds. As clinicians, we should discourage breeding of dogs with IE especially in the breeds known to have a genetic mode of inheritance.

The clinical expression in terms of onset, frequency, and severity is variable, therefore other "triggering" factors are thought to play an important role. Numerous studies have been performed using various exogenous factors to trigger seizures in dogs with IE. It has been decided that factors such as housing, feeding habits, season, time of day, day of the week, weather, etc. play a minor, if any role in triggering seizures in IE.[12]

Treatment

Therapy for seizure disorders depends on accurate determination of the cause of the seizures. Treatment with anticonvulsants is indicated for animals with IE. It is important to note that these drugs reduce the clinical signs of the disease and do not treat the underlying cause.[13] About 30% of dogs with IE do not respond to anticonvulsant therapy and eventually die due to complications caused by recurrent seizures.[13] Anticonvulsant agents are drugs used to stabilize neuronal membranes and decrease the firing associated with clinical seizures. This can occur by altering ion conduction and hyperpolarizing the neuronal membrane or by enhancing the actions of inhibitory neurotransmitters.[13] Early aggressive anticonvulsant therapy is advocated since repetitive seizures may create additional seizure foci (mirror foci.) Also, early treatment in large breed dogs with IE is warranted, since the seizures in these dogs tend to be difficult to control.[13] There is no set number of seizures that appears to be the critical point in which treatment is advocated, however, the decision to treat should be based on severity of the problem.[13]

The overall objective of anticonvulsant therapy is to reduce the frequency, severity, and duration of the animal's seizures. A realistic goal is to reduce seizure frequency to a point that is acceptable to the owner without being intolerable or life threatening to the animal.[13]

Phenobarbital is the drug best suited for seizure control in dogs with IE. Clinical reports indicate that 60-80% of epileptic dogs may be controlled effectively with phenobarbitol used as a single treatment agent. Although it is a controlled substance, it is safe, effective, and an inexpensive anticonvulsant drug for long-term maintenance therapy.[13] Treatment should be instituted at 2.2mg/kg BID or TID. Negative side effects may result such as sedation, ataxia,

polyuria and polydipsia, polyphagia, and weight gain. Tolerance to these effects generally develops within 2 weeks. Occasionally, "paradoxical hyperactivity" may develop, which may resolve with an increased dose. With prolonged use, moderate increases in serum concentrations of alkaline phosphatase, alanine aminotransferase, and glutamate dehydrogenase may occur with the potential for hepatotoxicity. Therefore, every 6-12 months, serum bile acids, albumin, ALT, and ALP values should be evaluated. If hepatotoxicity is suspected, the phenobarbital dose should be decreased accordingly and supplementation with potassium bromide should begin (discussed later.)[13,2]

Because of the long half-life of phenobarbital (24-36 hours), steady state serum levels will not be reached for 10-15 days after therapy is instituted. A practical approach is to increase the dose about 20% (current dose : desired dose = current level : desired level) after a seizure and recheck serum phenobarbital levels in 2 weeks. However, such monitoring is not a substitute for clinical judgment.[2] Maintenance serum concentrations should range between 15-45 ug/ml. Each individual animal has its own optimal level typically within this range. It is important to not administer greater then 10mg/kg BID because toxic serum concentrations may occur at this dosage. Dogs with an acceptable level of seizure activity while being maintained on phenobarbital therapy should be reexamined by a veterinarian every 6 months. A CBC, biochemistry panel, pre and post bile acids, and serum phenobarbitol levels should be performed annually.[13,2]

Primidone (Mysolin®) is a non-controlled analog of phenobarbital with phenobarbital being one of its primary metabolites. It is estimated that greater than 85% of the anticonvulsant effects of primidone are due to the phenobarbital metabolite. Therefore, there seems to be little benefit from using primidone over phenobarbitol. Primidone is also significantly more expensive than phenobarbital and more commonly causes hepatotoxicity.[13]

It is important to remember when treating an animal with phenobarbital that the concentration of other drugs metabolized by the liver (ie. Digoxin, antibiotics, quinidine) may be reduced. This is due to enhanced biliary excretion and increased activity of hepatic microsomal enzymes caused by barbiturates such as phenobarbital.[13]

In general, a single anticonvulsant agent is best to control seizures, however, if an animal is resistant to phenobarbital alone, potassium bromide may be added. Bromide acts by potentiating the effects of GABA (an inhibitory neurotransmitter) and thus hyperpolarizes neuronal membranes, thus working synergistically with phenobarbital in raising seizure threshold.[14] Approximately half of dogs refractory to phenobarbital alone benefit from the addition of KBr. One study indicated that 83% of dogs in this study showed a decrease in number of seizures over a one year period after addition of KBr to the phenobarbital.[14] Also, because KBr does not induce hepatic enzymes or undergo hepatic metabolism, it is the drug of choice for IE dogs with concurrent liver disease.[13]

A loading dose of 100mg/kg BID for 2 days is used prior to implementing the maintenance dose. The recommended oral maintenance dosage of KBr is 20-40 mg/kg SID or divided BID to achieve a serum concentration of 0.5-2mg/ml and up to 5mg/ml. The original phenobarbital dose can remain the same (unless serum levels are greater than 40 micrograms/ml), however, some authors advocate that it should be decreased by 50% when adding KBr. The decrease should occur gradually over 3 weeks. Careful monitoring is necessary during the transition phase.[13]

Bromide toxicosis (bromism) can occur in dogs. Typically it manifests as personality changes (irritability, attention-seeking behavior, pacing, sedation, etc.), polyuria, and polydipsia. Phenobarbital and KBr have been associated with the development of pancreatitis, however the relationship is unknown. Vomiting, anorexia, and constipation have also been associated with bromide therapy. Rarely, stupor, ataxia, depression, anisocoria, and muscle pain may occur in extreme cases.[15]

Bromide must be obtained from a chemical supply house and a solution made to dispense to the owner. Informed consent should be obtained prior to beginning

therapy, as human toxicities may result.[15]

One consideration when using bromide as a single agent to control seizures due to IE or in combination with phenobarbital is dietary influences. One study indicated high-chloride diets can increase bromide elimination, decrease serum bromide concentrations, and lead to a loss of seizure control in dogs with IE. Certain calculolytic diets used in treatment of urinary calculi have high chloride levels. This increased chloride enhances bromide elimination. Therefore, when treating seizures with KBr, a dietary change may be necessary in order to decrease the intake of chloride.[16]

Although anticonvulsant drug therapies are beneficial for seizure control in many affected dogs, there remains a subpopulation of animals with IE whose seizures can not be well controlled. Typically, these animals are euthanized. Alternatives to drug therapy are few, but many are being studied. One alternative is surgical longitudinal division of the corpus callosum. This surgery has been successfully performed in human epileptics for decades. This theoretically decreases the possibility of mirror focus and kindling which often increase the frequency, severity, and duration of seizures. Approximately 50-70% of patients that have undergone this procedure have improved seizure control and in some cases, the seizure condition has been eradicated entirely. The possible complications are many and the feasibility of this procedure in dogs is not great; however, continued experiments are being performed.[17]

As acupuncture and homeopathic remedies are becoming more widely accepted in the medical and veterinary communities, they may become viable therapeutic options as well.

Conclusion

The causes and treatment of seizures in dogs are very variable, emphasizing the need for a logical and systematic approach to this problem. The importance of obtaining a thorough history and performing a complete physical and neurologic exam cannot be overstated.

The most frequent cause of generalized seizures in the canine without an etiopathological correlation to an organ disorder is idiopathic epilepsy. As a small animal practitioner, a basic understanding of idiopathic epilepsy is essential as it is a disorder that is commonly encountered.◆

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