Proceeding of the SEVC
Southern European Veterinary Conference

Oct. 2-4, 2009, Barcelona, Spain

http://www.sevc.info

Next conference:

October 1-3, 2010 - Barcelona, Spain

Reprinted in the IVIS website with the permission of the SEVC
www.ivis.org
DIFFERENTIAL DIAGNOSES OF SEIZURES IN DOGS AND CATS

Michael Podell MSc, DVM, Diplomate ACVIM (Neurology)
Animal Emergency and Referral Center, Northbrook, IL Professor (Adjunct), University of Illinois, College of Veterinary Medicine, Champaign, IL

INTRODUCTION
The approach and treatment of seizure disorders in small animals is similar in many respects to the treatment of various other ailments in veterinary medicine: an antecedent historical problem arises, a proper diagnosis is made to confirm the condition, and therapy is initiated to treat the underlying disease and/or signs of the disease. Important differences arise, however, when approaching the diagnosis and treatment of seizures in the cat and dog. First, a specific underlying etiology is often not identified. Second, the clinician must often make a therapeutic decision based on historical accounts alone. Third, treatment is often initiated when the pet is normal, with little ability to predict frequency of seizure recurrence. Finally, both the pet’s and owner’s quality of life during the interictal period must be balanced with the ability to limit the severity, frequency and duration of future seizure events. This presentation is designed to help clinicians understand the variables for consideration in the treatment of seizure disorders in the cat and dog.

CLINICAL SIGNS AND DIAGNOSIS
Classification of seizures and epilepsy into a universally accepted, coherent, and relevant scheme for clinicians has been an ongoing dynamic process in human epilepsy over the past two decades. The standardized classification scheme for seizures and epilepsy established by the International League Against Epilepsy (ILAE) in the 1980’s, provided the first basis for a taxonomic foundation for an analytic approach in the diagnosis and treatment of epilepsy. This classification scheme, however, is restricted by the following limitations: 1. The reliance on the clinician’s ability to classify seizure types based on the presence of “impaired consciousness;” 2. The reliance on electroencephalographic (EEG) features to classify seizure type; and 3. The difficulty in distinguishing between an “idiopathic” disorder of confirmed undetermined etiology versus a “cryptogenic” cause of highly suspect morphologic disease of the brain. Considering that as veterinarians we rarely perform EEG analysis on affected pets, rely heavily on owner perception of the event to determine if consciousness is “impaired,” and may not always have the opportunity to perform a complete battery of neurodiagnostic tests (including brain imaging), it is no wonder that we are all left in a confused state of trying to describe, classify, and categorize seizures and epilepsy in our patient population.

My goal is to attempt to piece together a rationale categorization for use in small animal epileptic patients adapted on the recent recommendations of the ILAE Task Force on Classification and Terminology. The purpose is to establish a common ground mode of communication to allow diagnostic and therapeutic data to be tabulated for clinical outcome measures. The proposed new diagnostic scheme consists of five levels or axes as follows as proposed by Engel.

Axis 1: Ictal Phenomenology:

A seizure can be defined as a non-specific, paroxysmal, abnormal event of the body. An epileptic seizure is the clinical manifestation of excessive and/or hypersynchronous abnormal neuronal activity in the cerebral cortex. Thus, an epileptic seizure has a specific neural origin. Absolute confirmation that a seizure is epileptic may be difficult, as it requires simultaneous visualization of behavioral and EEG changes. As a result, historical information is often used to diagnose an epileptic seizure. The clinical features of epileptic seizures can be separated into four components. The prodrome is the time period prior to the onset of seizure activity. Owners report that they can “predict” the onset of their pet’s seizures by behaviors exhibited during this time, such as increased anxiety related behaviors (attention-seeking, whining, etc.), reluctance to do normal activity patterns, or increased hiding (in cats). The aura is the initial manifestation of a seizure. During this time period, which can last from minutes to hours, animals can exhibit stereotypic sensory or motor behavior (e.g., pacing, licking), autonomic patterns (e.g., salivating, urinating, vomiting) or even unusual psychic events (e.g., excessive barking, increased or decreased attention seeking). The ictal period is the actual seizure event manifested by involuntary muscle tone or movement, and/or abnormal sensations or behavior lasting usually from seconds to minutes. Following is the post-ictal period, which can last from minutes to days. During this time, an animal can exhibit unusual behavior, disorientation, inappropriate bowel/bladder activity, excessive or depressed thirst and appetite, and/or actual neurologic deficits of weakness, blindness, and sensory and motor disturbances. The latter problems are known as Todd’s paralysis, and are often an indicator of a focal, contralateral cortical epileptic focus. Often owners only observe the post-ictal period as evidence that their pet has had a seizure. Thus, careful questioning is
Seizure types are first classified as either being self-limiting (isolated) or clustered (2 or more within 24 hours) and/or continuous (status epilepticus). Within each category, seizures are divided into being either focal or generalized. Focal seizures are the manifestation of a discrete, epileptogenic event in the cerebral cortex. The focal nature of this seizure type is associated with a higher incidence of focal intracranial pathology. Focal seizures can be elementary motor seizures, commonly seen as facial muscle twitching, or manifested by more abnormal behavioral disorders. Progressive involvement of the facial, neck/shoulder, and/or limb muscles is known as a “Jacksonian” march seizure event. More complex behavior patterns with focal seizures will include impaired consciousness often with bizarre behavioral activity. Previously termed complex partial or psychomotor seizures, these events are now classified as automatisms, or automotor seizures. Animals may show “fly-biting” behavior patterns, become aggressive without provocation, howl incessantly, become restless or exhibit a variety of motor disturbances. Cats may show a variety of abnormal behaviors and/or motor signs, to include drooling, hippos, excessive vocalizations, or random, rapid running behaviors in house. Whenver a focal seizure is suspected, the clinician should be suspicious of a focal cerebral disturbance and plan the diagnostic work up accordingly. Generalized seizures are subdivided into tonic-clonic, clonic, myoclonic, atonic, or absence types. The terms convulsive (“grand mal”) and non-convulsive (“petit mal”) seizures are no longer in use. Generalized seizures originate from both cerebral hemispheres from the start, or progress secondarily from focal seizures. Unlike focal seizures, generalized seizures are not necessarily associated with focal cerebrocortical disease.

Axis 3: Syndrome:
A syndrome by definition is a group of signs or characteristics that define a particular abnormality. Epilepsy syndromes are not well defined in veterinary medicine, although familial epilepsies are now being identified with segregation analysis. A number of purebred dogs have been identified with either proven or highly suspect familial epilepsy, to include Belgian teruvn, Vizslas, and a variety of other breeds. The vast majority of epileptic syndromes in dogs will be idiopathic in nature.

Axis 4: Etiology:
The differential diagnosis of epileptic seizures due to underlying brain disease can be divided into three main etiologic categories: Idiopathic, symptomatic, and probably symptomatic (previously termed “cryptogenic”) epileptic seizures. Idiopathic epilepsy implies that no underlying structural brain lesion is present and is presumed to be genetic in origin. Symptomatic epilepsy is the result of an identifiable structural lesion of the brain. Probably symptomatic epilepsy, or “cryptogenic,” is believed to be the result of a structural lesion of the brain but not identified. Reactive epileptic seizures are due to metabolic disease and therefore are not classified as an etiology for epilepsy, as the brain returns to normal once the underlying inciting change in metabolism is corrected. The differential diagnoses for these categories are presented below.

Axis 5: Impairment from the epilepsy:
Inclusion of signs that are associated with epilepsy allows one to evaluate for persistence of functional and/or structural neurologic changes with associated seizures. The majority of signs in cats and dogs are transient, to include disorientation, visual impairment, salivation, incontinence, altered behaviors, etc. Dogs have been found to demonstrate transient structural changes with cerebral edema of the temporal lobe on MRI scans of the brain, along with altered cerebral metabolism with proton MR spectroscopy after seizures. Symptomatic temporal lobe epilepsy with associated hippocampal neuronal loss, however, appears not to be present in idiopathic epileptic dogs.

**PATHOPHYSIOLOGY**
Epilepsy represents a heterogeneous disease consisting of diverse etiologies, electrophysiological and behavioral seizure patterns, and responses to pharmacological intervention. As such, the pathogenesis of
epilepsy is multifactorial. Genetically determined “seizure susceptibility factors” play a crucial role in the brain's response to triggering or precipitating factors, also known as the seizure threshold. The seizure threshold in people has been shown to lower during sleep (in particular stage 2 sleep), where the hypersynchrony of sleep facilitates both the initiation and propagation of partial seizures in the parietal and occipital lobes. Seizures in these individuals may be activated from unrecognized changes in neuronal activity, intrinsic neurochemical transmission, or by environmental stimuli that do not cause seizures in the normal brain.

A basic tenet in the mechanism of epilepsy is the presence of an imbalance in excitatory and inhibitory neurotransmission. A seizure develops when the balance shifts towards excessive excitation. Recently, much research has been focused on the role of glutamate, the principle excitatory neurotransmitter in the brain, and its receptor complex, the N-methyl-D-aspartate receptor. Conditions leading to excessive excitation or loss of inhibition will lead to depolarization of neurons without normal regulatory feedback mechanisms. The result is a paroxysmal depolarization shift of a neuronal aggregate. Epileptic foci will then develop with the potential to spread throughout the brain. Recently, ion channel mutations have been linked to a variety of epilepsies considered idiopathic in humans. The majority of genes identified to date for human idiopathic epilepsy are inherited disorders of ion channels, known as channelopathies. Excessive influx of sodium, blockade of efflux of potassium or altered calcium flux can lead to repetitive neuronal firing. Specific functional genetic mutations have been identified for each of these ion channels in people, but not in animals.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of epileptic seizures can be divided into four main etiologic categories: Idiopathic, symptomatic (or secondary), probably symptomatic (cryptogenic), and reactive epileptic seizures. Idiopathic epilepsy (IE) is diagnosed if no underlying cause for the seizure can be identified and presumed to be of genetic origin. This diagnosis is most common in dogs with the first onset of seizures between the ages of 1 to 5 years, a normal inter-ictal neurologic examination, in purebred dogs, and if there is a longer initial inter-ictal period (> 4 weeks). True idiopathic epilepsy is much less common in the cat due to the more diverse genetic background of most cats. As such, all cats should be evaluated for underlying reactive or secondary seizures with appropriate diagnostic testing before a diagnosis of idiopathic epilepsy is made in the cat.

Symptomatic, or secondary epileptic seizures, are the direct result of structural forebrain pathology. Any age or breed of dog may develop this type of epileptic seizures. Younger dogs are more prone to developmental and encephalitic diseases, while older dogs (> 7 years of age) are more likely to develop intracranial neoplasia. As expected with underlying cerebral pathology, these animals are more likely to exhibit focal or multifocal neurologic deficits. However, focal lesions in “silent” cortical areas of the brain (e.g., olfactory, pyriform, and occipital lobes) may have seizures as the only neurologic problem.

**TEN GUIDING PRINCIPLES OF THERAPY**

1. **THE BRAIN IS SIMILAR TO OTHER ORGANS IN THE BODY.** The brain is an organ that can get sick and recover, similar to other body systems. Epileptic seizures are a sign of a sick brain. Thus, all epileptic seizures should be taken seriously, and approached in a similar fashion.

2. **BE CERTAIN THAT EPILEPTIC SEIZURES HAVE OCCURRED.** It is essential to determine a positive diagnosis to ascertain that an epileptic seizure has occurred. Many events may mimic epileptic seizures, such as syncope. The majority of seizures are paroxysmal in onset, have a finite duration, and are followed by a change in behavior from seconds to hours.

3. **IDENTIFY THE SEIZURE ETIOLOGY.** The most important aspect of seizure management is establishing the underlying cause. The differential diagnoses in terms of prevalence of diagnosis differ according to the age of onset of the seizure. Overall, dogs that present at less than 1 or greater than 7 years of age, have an initial interictal interval less than 4 weeks, and/or have a partial seizure as the first observed seizure should carry a high suspicion for an underlying identifiable etiology for their seizures with appropriate diagnostic tests done, to include MRI scanning of the brain.

4. **ALWAYS TREAT THE UNDERLYING DISEASE.** Symptomatic or reactive seizures can be viewed as a sign of the overall disease. This sign can potentially be eliminated or greatly reduced by directing specific therapy to the primary diagnosis.

5. **START AED TREATMENT EARLY IN THE COURSE OF DISEASE...** The earlier antiepileptic
drug (AED) therapy is started, the better the potential outcome may be for seizure control. The decision to initiate AED therapy is based on the underlying etiology, seizure type and frequency, and diagnostic evaluation. Reasons to start monotherapy include: 1) Identifiable structural lesion present; 2) Status epilepticus has occurred; 3) More than 3 generalized seizures occurred within a 24 hour period; 4) Two or more cluster seizure events (2 or more seizures) occur within an 1 year period; 5) Two or more isolated seizure events occur within 6 month period; 6) The first seizure was within one week of head trauma; 7) Prolonged ictal events (> 5 minutes), regardless of frequency; and 8) Prolonged, severe, or unusual post-ictal periods occur.

6. START WITH THE APPROPRIATE AED. Limiting total AED intake is advantageous and a goal in treating epileptic dogs. With any AED drug, there is a balance between seizure control and quality of life afforded. As such, monotherapy is recommended to reduce adverse effects, allow better owner compliance, and reduce overall costs. Phenobarbital (PB) and bromide (BR) are the most widely used initial AEDs. The appropriate starting dose of phenobarbital is 2.5 mg/kg PO BID for the dog and 2.5 mg/kg/day for the cat. If BR is to be used as monotherapy the initial maintenance dose is 40 mg/kg/day. Intravenous loading dose is described under emergency treatment of seizures. Bromide is NOT recommended for use in cats due to the potential for allergic bronchitis to develop.

7. MONITOR SERUM CONCENTRATIONS. The goal of drug monitoring is to establish a proactive, yet individualized plan for long-term efficacy and quality of life treatment strategies. Serial serum trough PB concentrations should be evaluated at 14, 45, 90, 180, and 360 days after the initiation of treatment, at 6 months intervals thereafter, if a dog has more than two seizure events between these times, and/or at 2 weeks after a dosage change. BR serum concentrations should be taken at 3 weeks (the first elimination half-life), and at the first steady state concentration (3 months). Blood samples are best taken prior to dosing and in a fasted dog. Blood samples should be submitted in non-serum separation tubes to avoid factitious decreases in drug concentration.

8. KNOW HOW AND WHEN TO ADJUST THE DOSAGE. The most effective trough therapeutic PB range for the dog is 20-35 µg/ml and 10-20 ug/ml for the cat. Five µg/ml increments are beneficial if seizures are occurring at an equal frequency or worsening after 30 days of therapy. Adjustments of the trough phenobarbital concentration can be calculated with the following formula:

\[
\frac{\text{Desired concentration} - \text{Actual concentration}}{\text{Total \# mg phenobarbital/day}}
\]

The optimal therapeutic range for monotherapy BR treated patients is 1500-2500 mg/L. The new maintenance dose can be calculated with the following formula: (Css=steady-state concentration)

\[
\begin{align*}
\text{(Target Css – Actual Css) \times (Clearance/Bioavailability) =} \\
(2000 \text{ mg/L} – \text{Actual Css}) \times 0.02 = \\
\text{added mg/kg/day to existing dose}
\end{align*}
\]

9. MAKE SURE THERE IS GOOD OWNER COMPLIANCE IN DOSING AND MONITORING. All owners should be sent home with a specialized calendar to record seizure events, adverse effects, and changes in drug dosing.

10. KNOW WHEN AND HOW TO ADD OR CHANGE MEDICATIONS. Antiepileptic drug therapy should be changed when either no improvement in seizure control is seen despite maximal trough therapeutic serum concentration and/or when toxic effects are developing.

REFERENCES