Managing Seizures: Etiology & Current Therapy

Jill Hicks, DVM, DACVIM (Neurology)
Associate Veterinary neurologist/neurosurgeon
Animal Neurology & MRI Center
1120 Welch Road
Commerce Township, MI 48390

Before we discuss causes and treatments of seizures in our small animal patients, we have to ask how we recognize seizures.

- **Epilepsy:** recurrent epileptic seizures
- **Epileptic seizure:** = hypersynchronous neuronal electrical activity in the cerebral cortex that manifests as a paroxysmal and transient abnormality of consciousness, motor activity, autonomic function, sensation or cognition

Sound broad? It is, which is why seizures can range from more obvious manifestations to conditions that leave us all unsure.

**Parts of a seizure**

- **Prodrome:** change in mind (anxiety, withdrawal, etc)
  - Long-lasting (hours to a day or more)
  - 11% of dogs in one study
  - Not associated with abnormal EEG
- **Aura:** (repetitive movement/behavior; no impairment of consciousness)
  - Seconds to minutes
  - Most commonly reported type of focal onset (humans)
  - May/may not be associated with abnormal EEG
- **Ictus:** Seizure event
  - Seconds to minutes
  - Involuntary muscle tone/movement and/or abnormal sensations or behavior
  - Abnormal EEG (gold standard)
- **Post-ictal:** Period after actual seizure
  - Minutes to days (length of seizure not associated with severity of post-ictal signs
  - Altered behavior, inappropriate elimination, changes to appetite/thirst

**Seizure types**

- **Focal**
  - +/- alteration in mentation
  - Simple motor seizures versus abnormal behavioral disorder
• “fly-biting,” aggression, vocalization, drooling, hippus, elimination, running, etc
• More often associated with focal intracranial pathology?
  • We have more evidence now that idiopathic epilepsy can also have focal onset frequently

• Generalized
  • Tonic-clonic
    • Increased muscle tone and repetitive muscle movements
    • Frequently includes autonomic signs in small animals
      • Salivation, urination/defecation
  • Clonic
    • Repetitive muscle contractions leading to repetitive movement
  • Myoclonic
    • Sudden contraction of muscles
  • Atonic
  • Absence
    • Loss of awareness without other outward manifestations
    • Not clearly recognized in small animals, but one EEG case report with suggestion in a dog

• Reflex epilepsy syndrome- seizures are precipitated by sensory stimuli
  • Dachshunds with LaFora disease
  • myoclonic epilepsy d/t auditory/visual stimuli
  • Audiogenic seizures in cats

What’s the cause?
Recently, there has been new terminology suggested based on human classifications of seizure disorders. Many people still use the older terms, but the transition may occur.

• Genetic
  • Replaces “Idiopathic” in veterinary medicine for DOGS
  • Known or highly-suspected genetic epilepsy in many breeds
    • Belgian Tervuerens, Vizslas, Keeshonds, Retrievers, Shelties, Border Collies
  • +/- Inherited
    • Single gene mutations frequently identified in humans without inheritance

• Structural/Metabolic/Immune-mediated/Infectious
  • Replaces “Symptomatic”

• Unknown
  • Replaces “Cryptogenic”
  • Presumed to have an underlying cause that is not genetic, but not found

Signalment matters!
For the major causes of epileptic seizures in dogs, age and breed can be some of the most important factor. Age also matters in cats, but in the US breed doesn’t.
Age:
1) Most dogs and cats that present with genetic/idiopathic epilepsy present between 1-6 years (about 75-80% of cases in dogs).
2) Most dogs with new-onset seizures who are >8 years will be diagnosed with a primary brain tumor.
3) Small breed dogs presenting with inflammatory CNS disease as a cause of seizures are also typically young to middle-aged.
4) Although less common causes, stroke is more likely in middle-aged and older dogs and cats, especially with underlying diseases including kidney disease, Cushing’s, hyperthyroidism or primary hypertension.
5) Although less common causes, infectious diseases tend to affect young animals, especially puppies/kittens. (i.e. canine distemper, feline infectious peritonitis)
6) Congenital causes of seizures normally present when animals are very young; hydrocephalus would be the most common cause.

Breed:
1) Although any dog, including mixed breeds, could have genetic epilepsy, the inherited epilepsies tend to occur more so in large breed, working or sporting dogs. Most are either purebred or mixes of at-risk breeds (think: Goldendoodle)
2) Small breed dogs in the “genetic epilepsy” age range much more commonly have inflammatory CNS disease as a cause for seizures. This particularly includes French bulldogs/English bulldogs, Chihuahuas, Maltese and pugs, but any breed or mixed breed could be at-risk.

But what about extra-cranial causes?
Extracranial causes of seizure include any condition that does not originate from the brain itself. We typically think about metabolic, endocrine, electrolyte, blood glucose, ischemic or toxic conditions as extracranial causes of seizures.

Most common causes?
1) Low blood glucose
   a. Young dogs = liver shunt, Addison’s disease, exercise or fasting, xylitol toxicity, hypoglycemia (hunting dogs, toy puppies, respectively)
   b. Older dogs = Insulinoma most likely; hepatic insufficiency, xylitol toxicity
2) Hepatic encephalopathy
   a. Young dogs = liver shunt; rarely other causes
   b. Older dogs = hepatic insufficiency due to fulminant liver disease
3) Hypocalcemia
   a. Young dogs = primary hypoparathyroidism, nursing?
   b. Older dogs = nursing? blood transfusions with EDTA?
4) Toxins
   a. Typically will have other “neuro-excitatory” signs
i. Restlessness, hyper-reactivity, tachycardia, tachypnea, hypertension
b. Tremorogenic mycotoxins, metaldehyde, serotonin syndrome, stimulant medications
c. MANY medications can lower seizure threshold, allowing a dog that would not normally seizure to do so, if exposed. In human hospitals, antibiotics often cause this; we see that cause infrequently.

How do we treat epilepsy?

First, DO we treat epilepsy? Whether we start an anti-convulsant can be a grey area, but therapy should be strongly considered if:

1) Cluster seizures or status epilepticus occurs.
   a. If, in a rare case, it turns out this is due to toxicity, you can always taper and discontinue the medication after a period of seizure freedom (usually six months).
      i. Rationale: These are very severe types of seizures, and need to be prevented in the near and far future, if possible, in these patients. If we cannot abolish cluster seizures, there is at least probable benefit from spacing clusters further apart.

2) More than one seizure episode occurs within 1-2 months
   a. Since the goal of anti-convulsant medication is often to reduce seizure number to a “controlled” level, we often do not start medication unless seizures would be considered uncontrolled. I would consider more than one seizure every two months as uncontrolled.
      i. Rationale: Older studies indicated that starting anti-convulsants earlier resulted in a more mild long-term seizure course. More recently, it seems like seizure density (more seizures in a smaller time period) is the primary factor that causes seizure activity to worsen with time. However, seizures are damaging to the brain, and most anti-convulsants are quite safe.

3) Seizure frequency is increasing
   a. Even if a dog/cat is still having relatively infrequent seizures, if they had had 1-2 per year and are now having 1 every three months, I would start medication.
      i. Rationale: Evidence of seizure course worsening.

4) There is a structural cause of seizures
   a. If a dog/cat has a single seizure, but I find a brain tumor or inflammatory disease, I expect that their risk for another seizure in the near future is high. Additionally, seizures in these patients can cause significant neurologic setbacks that are hard to distinguish from primary disease progression.
**Maintenance anti-convulsants: The big four**

1) Phenobarbital
   a. The upside: The most effective anti-convulsant in both dogs and cats, most frequently evaluated for genetic/idiopathic epilepsy
   b. The downside(s):
      i. Minor: PU/PD/PP, dogs/cats that need higher doses initially or later in disease course will often have a quieter mentation and ataxia.
      ii. Major (but rare): Liver dysfunction (idiosyncratic acutely, or long-term hepatotoxicity), bone marrow dysfunction, aggression/abnormal behavior, rare skin reactions

2) Potassium bromide
   a. The upside: Very effective anti-convulsant, liquid easy to dose if very small dogs, organ toxicity does not occur despite long-term use.
   b. The downside(s):
      i. Minor: Same as phenobarbital; caution with changing diet, giving IV fluids as it effects excretion of the bromide salt
      ii. Major (very rare): Aggression/abnormal behavior, rare skin reactions, +/- pancreatitis. Do not use in cats due to significant risk of allergic pneumonitis.

3) Zonisamide
   a. The upside: Effective in some dogs/cats, low-side effects in most animals
   b. The downside:
      i. Minor: Sedation, ataxia and decreased appetite can occur
      ii. Major (very rare): Liver toxicity, KCS or other immune-mediated disease, as this is a sulfa-based drug. Aggression/behavior changes possible.

4) Levetiracetam (Keppra)
   a. The upside: No visible side effects in many animals. Can be effective in some dogs, and possibly more so in cats.
   b. The downside:
      Minor: Sedation, ataxia can occur, and sometimes reduced appetite in cats, particularly. Q8h dosing for regular form, and extended release only available for medium to large dogs
      i. Major (very rare): Aggression/behavior changes possible.

**Why didn’t I mention diazepam?**

In dogs, diazepam has a very short half-life and can’t be used as a maintenance drug. Dogs also seem to adjust to the medication quickly and it stops being effective in many. In cats, there is a small (but published) risk of acute hepatic toxicity leading to irreversible liver failure. Since we have other options for cats, it’s not typically recommended anymore. Diazepam is our go-to treatment for
emergency seizure treatment, but it doesn’t really have a place in maintenance anti-convulsants.

What happens when seizures are difficult to control?
Up to half of dogs are considered to have drug-resistant epilepsy. If seizures continue frequently despite starting a maintenance anti-convulsant drug, these steps can be taken:

1) Maximize the potential efficacy of the first drug. Especially if the drug is likely to be effective (like phenobarbital), you should think of the initial dose as a jumping-off point. Many dogs (and cats) will respond to an increased medication dose without significantly increased side-effects. I often increase doses by 25-50% each time. As long as quality of life can be maintained, pets with better-controlled seizures are less likely to be euthanized.
2) Add another maintenance anti-convulsant. This is a good option if a pet has already started to show significant side effects from a medication and either you or the owners are concerned about raising the dose.
3) If cluster seizures are the major issue, try reducing the number of seizures in the cluster. This can often be done by adding a “cluster buster” medication such as chlorazepate or even Keppra. These are only given following an initial seizure and continued for about two days to try to ‘break” the cluster.

Can we ever stop medications?
I almost never do. Most of the time, the risk of recurrent, possibly severe seizures outweighs the potential risk of the medications. But there are some cases where I will do so.
1) There is an organ toxicity likely related to the drug. This would be most likely with phenobarbital, but it’s very rare, even in that case. If the organ toxicity is immediately life-threatening, the drug has to be stopped immediately and another anti-convulsant is chosen to replace it. Otherwise, slow tapering is recommended.
2) The initial seizure event was likely related to toxicity. If a maintenance drug was started, I’d typically continue it until the pet is seizure-free for six months and then slowly taper them off over 1-2 months.
3) The pet was a puppy when seizures started. In some cases of juvenile epilepsy, especially, the dog may grow out of the condition. After a minimum of six months without seizures, I would consider tapering the medication.
4) The owner is unwilling to continue medications. While I would discuss the risks of tapering/stopping anti-seizure medications in this case, including the small but real risk of seizures recurring and being much more difficult to control, I would rather taper medications under my supervision than have the owners cold-stop the drug. Especially in the case of phenobarbital, sudden discontinuation may cause severe seizures.
5) I added a drug to a dog with difficult to control epilepsy, and there was no noticeable change in seizure activity despite dosage adjustments. In this case,
I would consider tapering and stopping the medication so that I am not adding side effects and cost without any benefit in a patient.

Final thoughts
Anti-convulsants are life-saving drugs for animals with seizures. Seizures are associated with shorter survival times for dogs with genetic epilepsy, brain tumors, and even inflammatory CNS disease. Preventing seizures is paramount for quality of life, but must be balanced with adverse effects of medications.