Seizure Management for the Small Animal Practitioner
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Learning Objectives:

- Review common etiologies of seizures
- Review emergency seizure management strategies and considerations
- Review indications for and common maintenance anticonvulsant therapies

Seizures are the most common neurological problem in small animals. The incidence of idiopathic epilepsy is 0.5 to 5% of the canine population.[1,2]

Pathophysiology: Seizures result from excessive electrical activity in the cerebral cortex.[1,3] This can be related to excessive excitation (Glutamate and Aspartate), inadequate neuronal inhibition (GABA and Glycine) or a combination of excitation/lack of inhibition that leads to a summation effect that drives a seizure.[1,3] Neurons are intrinsically excitable. When a group of neurons depolarize together and remain depolarized, this is called a paroxysmal depolarizing shift. Over time, a kindling effect can occur where neurons at rest can become recruited into this seizure focus.[1]

Seizure Definitions:[3–5]

- Seizure – sudden onset (paroxysmal) events that represent abnormal forebrain function
- Epilepsy – recurrent seizures
    - Idiopathic Epilepsy – recurrent seizures in young dogs (1-6 years old). This is a diagnosis of exclusion.
    - Cryptogenic Epilepsy – recurrent seizures in an older dog (>6 years old). These too have an unremarkable work up, but it is presumed that there is microscopic disease contributing to the seizures.
- Cluster Seizures – 2+ seizures over a short period (minutes to 24 hours) between which the patient regains consciousness (ie normal inter-ictal)
- Status Epilepticus – any seizure lasting longer than 5 minutes OR 2+ seizures between which the patient does NOT return to normal consciousness; can also refer to a continuous seizure lasting >20-30 minutes
- Refractory Epileptic – poor seizure control in a patient despite adequate plasma drug concentration on 2 or more drugs

Types of Seizures:[1,3–6]

1. Generalized seizures – involve both cerebral hemispheres simultaneously
    - Tonic-clonic (Grand mal) – MOST COMMON. Patient lateral with opisthotonus, limbs extended and paddling. May also hypersalivate, urinate and/or defecate.
    - Tonic – sustained, increased muscle contractions (rigid extension)
    - Clonic – paddling or rhythmic jerks of limbs
    - Atonic – RARE – sudden loss of muscle tone, usually lasts 1-2 seconds
    - Myoclonic – shock-like muscle (solitary or group) contractions
    - Absence (Petit-mal) – in people, brief loss of consciousness with specific electrical activity on electroencephalogram (EEG)

2. Focal seizures: location of seizure focus in brain determines clinical manifestation. Focal seizures are more common in cats.
    - With motor signs – could have rhythmic contractions of face, limb, etc
    - With autonomic signs – hypersalivation, vomiting, gagging, diarrhea, abdominal pain
    - Behavioral – licking, chewing, "fly biting", tail chasing, running in circles
    - Complex focal seizures (Psychomotor seizures) – alteration in awareness - unprovoked aggression, irrational fear. Seizure focus involves the limbic system.
    - **Can evolve into a generalized seizure!**

    *** SIDE NOTE: Cat seizures can be WEIRD…aggression, dilated pupils, hypersalivation, vocalization, etc…

4 Stages of a Seizure:[1,3–5]

1. **Prodrome:** behavior proceeding a seizure (restlessness, hiding, acting fearful, clinging to owner, vocalizing). Can occur hours to days before seizure; may not observe.
2. **Aura:** initial sensation of a seizure before signs are observed. Could see subtle changes in behavior as well as vomiting, salivation or inappropriate urination. Lasts seconds to minutes at the onset of the seizure itself. Would see abnormal activity on electroencephalogram (EEG).
3. **Ictus:** the SEIZURE itself. Usually lasts 30 seconds up to 2 minutes. If lasts longer than 5 minutes, then it is status epilepticus. Occurs most commonly from sleep or at rest.
4. **Post-ictal:** transient changes in brain function following seizure. Signs may include: disorientation, restlessness, ataxia, blindness, deafness, aggression, lethargy, thirst, hunger or inappropriate urinations. Lasts several minutes, but may last up to 2 days.

Etiology of Seizures: separated into *extracranial* and *intracranial* causes[1,3,6]

Extracranial:

- Degenerative: NONE
- Anomalous/Congenital: NONE
- **Metabolic:**
    - Hypoglycemia - paraneoplastic (insulinoma, leiomyosarcoma, giant hepatoma, lymphoma), insulin overdose, young anorexic toy breed, liver failure, Hypoadrenocorticism (Addison's), hunting dog overexertion, sepsis
    - Hepatic encephalopathy (HE)
    - Hypocalcemia (Ca) – lowers neuronal threshold resulting in hyperexcitability, tremors and/or seizures.
    - Hyper/hyponatremia (Na):
        - Hypernatremia: causes brain cell shrinkage → production of intracellular idiogenic osmoles in chronic condition. Rapid correction causes edema.
        - Hyponatremia: causes brain cell swelling → excretion of osmoles to extracellular space. Rapid correction causes cells to shrink.
    - Uremic encephalopathy
    - Increased viscosity (triglycerides, RBCs)
- Neoplasia: NONE
- **Nutritional:** Thiamine Deficiency (Vitamin B1)

- Infectious/inflammatory: NONE
- **Toxins:** Lead, Ethylene glycol (EG), Organophosphates (OPs)/Carbamates, Pyrethroids, Bromethalin, Chocolate (Theobromine and Caffeine), Illicit Drugs (Amphetamines, cocaine, etc), Strychnine, Metaldehyde (snail bait), Xylitol (due to hypoglycemia), +/- Mycotoxins
- Trauma: NONE
- Vascular: NONE

Intracranial:

- **Degenerative:** Storage diseases – breakdown in metabolism causes accumulation of cellular products within the cell. Signs often present by several months of age with cerebellar signs most common. Diagnosis via metabolic testing (urine and/or blood).
- **Anomalous/Congenital:** Hydrocephalus
- Metabolic: NONE
- **Neoplasia:**
    - Primary: Meningiomas, Gliomas, Choroid plexus tumors, Ependymomas, Histiocytic sarcoma, Lymphoma
    - Metastatic (secondary): Hemangiosarcoma, Melanoma, Lymphoma, Carcinomas
- **Idiopathic Epilepsy (IE):**[1,5,7–10] Recurrent seizures with no brain abnormalities – diagnosis of exclusion. Most common etiology in dogs between 6 months and 6 years of age; can occur in cats. Breeds predisposed to epilepsy (genetic component suspected): Beagle, Belgian Shepherd, Bernese Mountain Dog, Border Collie, Boxer, Cocker Spaniel, Collie, Dachshund, Dalmatian, English Springer Spaniel, Finnish Spitz, German Shepherd, Golden Retriever, Irish Setter, Irish Wolfhound, Keeshond, Labrador Retriever, Lagotto Ramagnolo, Miniature Schnauzer, Nova Scotia Duck Tolling Retriever, Petit Basset Griffon Vendeen, Saint Bernard, Sheltland Sheepdog, Siberian Husky, Standard Poodle, and Vizsla.
    - ~75% of dogs that had first seizure prior to 1 year of age diagnosed with IE[7]
    - 35% diagnosed with IE with onset > 5 years of age[8]
    - Dogs with onset ≥ 7 years of age, 21% had no identifiable cause[9]
- **Non-infectious Inflammatory (autoimmune): MUE** (GME, NLE, NME)
- **Infectious:**
    - Viral: Distemper, FIP, FIV/FeLV, Rabies
    - Fungal: Cryptococcus, Aspergillus, Histoplasma, Coccidioidomycosis, Blastomyces
    - Protozoal: Toxoplasma, Neospora
    - Parasites: Cuterebra migration
    - Tick borne/Rickettsial: Ehrlichia, RMSF
    - Bacterial: penetrating bite wound, sepsis
- **Trauma**
- **Vascular/Ischemic disorder**

General Rules with Regards to Seizures:

- Young dogs more likely have infectious diseases, congenital malformations or toxin ingestions.
- Toy/small dogs more commonly have non-infectious inflammatory disease (MUE).

- Old dogs are more likely to have neoplasia or a vascular event.
    - Brachycephalic breeds more commonly have gliomas.
    - Dolichocephalic breeds more commonly have meningiomas.
- In older dogs where diagnostics are unremarkable, we call them Cryptogenic Epileptics meaning, there is nothing obvious, but suspect microscopic disease could be present.
- Don't forget about your breeds that more commonly get Idiopathic Epilepsy!

Things That Can Look Like Seizures to Owners:[1,5,11]

- Syncope
- Acute vestibular disease
- "Sleeping
- Idiopathic head tremor/bob: English and French Bulldogs as well as Boxers have rhythmic side to side wobbling of head "no" movement, whereas Doberman Pinschers have up and down motion "yes". Other breeds can have this too. Usually they can be distracted out of this with play, food, attention (calling their name), etc.
- Pain (especially cervical)
- Dyskinesia (movement disorders)
- Intention tremors
- Neuromuscular disease (ex: Myasthenia gravis)
- Behavioral
- Narcolepsy/Cataplexy
- Idiopathic cerebellitis ("White Shaker Dog")
- Mycotoxin tremors (moldy cheese ingestion)

Questions to Ask the Owner to Differentiate Seizures from other Events:[1,3]

- Ask the owner to describe the event (ie is there paddling, limb rigidity, facial twitching, hypersalivation, urination, etc). Frequency? Length of the seizure?
- How long does it take for the patient to return to normal after the event (post-ictal period)? What does the patient do during this time?
- Is the patient normal between events?
- Any mentation/behavior changes prior to the seizure (pre-ictal period)?
- Are the seizures associated with sleeping, feeding, fasting, exercise or stress?
- Has there been any exposure to drugs or toxins?
- Has the patient been sufficiently vaccinated?
- Is there a prior history of head injury?
- Is there any familial history of seizures?
- Has there been a recent or past illness?
- What is the pet's diet? Any changes in brand? Or how its prepared?
- What previous medications or treatments have been given for the seizures?

When to Work Up These Cases:

- When to wait on brain imaging…first seizure in a dog 1-5 years old with normal physical and neurological exams
- When to move forward with diagnostic imaging (ie brain MRI)…
    - First seizure in a dog < 1 or > 6 years old depending exam/differentials

- Multiple seizures over time with normal exam → to better suggest idiopathic epilepsy as it's a diagnosis of exclusion
- Lateralizing neurological deficits
- Cats

Diagnostic Plan:[3,5,6]

- Systemic health screen (CBC/Chemistry/Urinalysis) +/- T4
- Pre/post-prandial bile acids (vs ammonia level) – good idea in younger dog to help identify a possible portosystemic shunt. Bile acids testing also allows you to evaluate liver function before you start anticonvulsants and establishes a baseline level.
- If a cat, add FeLV/FIV
- +/- Thoracic radiographs (if > 6 years of age, or consider if SE event)
- +/- Brain MRI vs CT scan – prefer MRI for imaging of the brain
- +/- Cerebrospinal fluid (CSF) tap
- +/- Electroencephalogram (EEG)
- +/- Infectious disease testing
- +/- Lead testing, if possible exposure

Maintenance Therapy Considerations:[1,2]

- When to start treatment?
  - Any episode of status epilepticus OR a cluster seizure event!
  - Progressive increase in seizure frequency or severity
- Owners must understand that seizure drugs will NOT stop all seizures but will hopefully reduce the frequency and severity!
- Only about 15% of epileptic dogs become seizure free with drug therapy – uncontrolled seizures are unfortunately a common reason for euthanasia
- What is ideal therapy? Depending on starting seizure frequency, as a minimum, want less than one seizure every 4-6 weeks. Another way to think about it would be to reduce seizure frequency by 50%.
- *See Medication Table 1*- for doses, routes, side effects, monitoring considerations.[1–3,6,12]
- Note about therapeutic range[1]: This is a population statistic for which the majority respond at a given drug concentration. This cannot predict where one individual will best respond. If a patient has a seizure while in the "therapeutic range," this does not mean they have failed therapy. Medication doses should be incrementally increased in an attempt to improve seizure control until it is clear that no further increase will improve seizure control, or the risk of toxicity becomes too great (e.g. Phenobarbital). Once a patient is controlled, a new level should be monitored to establish the patient's "therapeutic range."

Other Treatment Options:[1,2,6,13]

- Special diets - Purina® Pro Plan® Veterinary Diets NC NeuroCare™. Law et al 2015 revealed a diet rich in medium-chain triglycerides (MCT) can help control seizures (71% of dogs showed a reduction in seizure frequency, 48% of dogs showed a 50% or greater reduction in seizure frequency and 14% of dogs achieved complete seizure freedom).
- Canna-Pet® - more research needed, but potential benefit as adjunct therapy

- Acupuncture
- Digital ocular stimulation (Vagal)
- Vagal nerve stimulation
- Surgery – divide the corpus callosum to prevent generalization

When Seizures Go Awry…

- Status Epilepticus – any seizure lasting longer than 5 minutes OR 2+ seizures between which the patient does NOT return to normal consciousness; can also refer to a continuous seizure lasting >20-30 minutes
    - 60% of IE dogs will require emergency treatment at some point![1,14]
    - 25% overall mortality rate for dogs with SE; 33% euthanized[3,14–16]
    - A status event can be the very first seizure (44-58% of cases)[15,17]
- Cluster Seizures – 2+ seizures over a short period (minutes to 24 hours) between which patient regains consciousness
    - 41% of IE dogs will have cluster events (GSD and Boxers overrepresented)[18]

What To Do During A Seizure:[1,3,6]

- Ideally place an IV catheter or obtain IV access – Save blood for diagnostics and check a blood glucose
- Administer Diazepam/Midazolam 0.5-1.0 mg/kg IV; can give 1.0-2.0 mg/kg rectally or nasally if necessary → can repeat 2-3 times and/or start a CRI (see below)
- Assess your patient…temperature, pulse, respiration, mucous membranes, etc
- Perform a general physical exam and as much of the neurological exam as possible
- Begin active cooling if patient rectal temperature > 104°F. Use wet towels, fans, alcohol on foot pads…do not soak the patient! Stop when ≤ 103°F to prevent reflex hypothermia.
- +/- Dextrose supplementation: If hypoglycemic, treat with 50% dextrose diluted to 25% at 0.5-2 ml/kg (500 mg/kg) IV over 15 minutes.
- +/- Oxygen supplementation

I've Given a Couple Boluses of Diazepam, Now What?

- Need to get started on a maintenance anticonvulsant STAT!
    - Injectable Phenobarbital or Levetiracetam available
- In the meantime, may need to consider a CRI of a shorter-term drug to allow your maintenance medication time to have full effect
- Things to consider for a CRI:
    - Diazepam/Midazolam CRI at 0.1-0.5 mg/kg/hr IV (Usually start at 0.3 mg/kg/hr).
    - Adheres to plastic AND is light sensitive so ideally should change out administration set every 24 hours because will sediment. Wrap syringe and line with vetwrap all the way to the patient catheter.
    - Respiratory depression is possible (be prepared if need to intubate)
    - Once initiated, reduce dose by 0.1 mg/kg every 4-6 hours until can discontinue pending patient remains seizure free. Discharge once off CRI and seizure free for 6-8 hours.
- If the seizure does not seem responsive to Diazepam, you may need to consider different CRI options:

    - Propofol CRI at 1-2 mg/kg IV to effect and be prepared to intubate; continue CRI at 0.1-0.6 mg/kg/min titrated to effect.
    - Ketamine (NMDA receptor antagonist) - 5 mg/kg IV bolus then CRI at 5 mg/kg/hr.
- As a last resort, consider placing the patient under general anesthesia using isoflurane.

- While on CRIs or under anesthesia, you need to provide close monitoring of respiration, tissue oxygenation, blood pressure, hydration, body temperature, etc. Depending on the critical nature of the patient, neurological status should be evaluated every 15 minutes to every 4 hours. Patient should be rotated from side to side every 4 hours. Eyes should be lubricated to prevent corneal ulcers every 4 hours. The urinary bladder may need to be expressed every 4-6 hours.

Neurological Status During/Post-Seizure Monitoring:[3,6,18]

- Pupil size changes can indicate possible changes in intracranial pressure (ICP).
- When sizes are abnormal, need to consider treatment with medications that reduce cerebral edema (secondary to the seizure) – ie increased ICP.
- Mannitol – osmotic diuretic to move fluid from extravascular space to intravascular space to help reduce volume of the brain parenchyma. Also works to scavenge free radicals and increase RBC membrane distensibility. Administer 0.5-1 g/kg IV slowly over 15 minutes. Most effective within 30 minutes and may last up to 3-4 hours.
- Hypertonic (7.5% NaCl) saline 4-6 ml/kg IV over 10 minutes.

- Monro-Kellie Doctrine (summarized): The skull only has so much room (volume) for the brain, CSF and blood. An increase in one of these should cause a decrease in one or both of the remaining parts. Therefore, small changes can generally be compensated; however, large or rapid changes in volume can become life threatening.
- Cerebral Profusion Pressure (CPP) = Mean Arterial Pressure (MAP) – Intracranial Pressure (ICP)
- Seizures lead to edema – leads to compression of blood vessels in brain – reduced cerebral blood flow (CBF) and secondary ischemia – hypothalamus activates sympathetic nervous system (SNS) – peripheral vasoconstriction to increase cardiac output – increased MAP – stimulates baroreceptors in carotid bodies – stimulating parasympathetic nervous system (PNS) vagal response - resulting in bradycardia
- **Cushings Reflex:** Systemic Hypertension with Bradycardia; *brain herniation possible*
- Decerebrate Rigidity: Results from a lesion of the rostral brainstem (ie possible brain herniation). This posture is characterized by rigid extension of all limbs with opisthotonus. The patient will be stuporous to comatose when this posture is seen.

Systemic Considerations During/Following a Seizure:[3]

- Cardiovascular: susceptible to cardiac arrhythmias due to hypoxia/ischemic damage; hypotension. A MAP of 90 mmHg will maintain CPP > 60 mmHg.
- Respiratory: increased secretions combined with reduced ventilation. Maintain pulse ox readings of at least 95% and PaO2 > 90 mmHg. End tidal CO2 around 35-40 mmHg (PaCO2 35-45 mmHg arterial on room air).
- Brain: can have seizure discharges without physical manifestations

- Skeletal muscle: susceptible to rhabdomyolysis secondary to hyperthermia
- Kidneys: susceptible to poor perfusion – possible acute renal failure (ARF); myoglobinuria from hyperthermic muscle damage.
- Sustained hyperthermia can lead to Disseminated Intravascular Coagulation (DIC)

Diagnostics to Consider During Emergency Treatment of Seizures:[3,6]

- Blood glucose – this is important to check in both young (inadequate nutrition) and old pets (Insulinoma). If hypoglycemic, treat with 50% dextrose diluted to 25% at 0.5-2 ml/kg (500 mg/kg) IV over 15 minutes.
- Arterial blood gas – a metabolic acidosis is common
- Electrolytes or full chemistry panel – evaluate Na^{+}, Ca^{++} and other systemic functions. Should repeat a full chemistry panel in about 48 hours following severe seizure activity to evaluate overall systemic health.
    - Hypocalcemia (Ca^{++}) – Administer 10% calcium gluconate at 0.5–1.5 ml/kg IV slowly over 10 minutes with ECG monitoring to evaluate for bradycardia. Recheck calcium in a day and then every 1-3 days as indicated long-term if oral supplementation indicated.
    - Hyper/hyponatremia (Na^{+}): Correction should not be faster than 0.5 mEq/L/hr!
- Urinalysis – evaluate for myoglobinuria as well as appropriate urine output
- Anticonvulsant serum levels (Phenobarbital and/or KBr, if already on medications)
- Ammonia level/Bile acids – evaluate for a portosystemic shunt/Hepatic encephalopathy
- ECG dependent on status presentation – arrhythmias can occur within the first 72 hours due to myocardial damage
- PT/PTT in severe cases to evaluate for DIC (also separately evaluate platelets)
- Electroencephalogram (EEG): Be mindful that just because you stop the outward manifestations of the seizure does not mean that continued abnormal electrical activity in the brain has stopped while under Propofol or anesthesia….

Seizures can be scary for an owner or during an emergency situation. The most important thing to remember is to remain calm and work to stop the seizure as soon as you can. Anticonvulsant medications are your friend, do not be afraid to use them. When managing seizures long-term, the owner must understand that the anti-seizure drugs will help to decrease the frequency and the severity of their pet's seizures; they will not stop all seizures!

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