Seizure Management

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Background and Definitions

Seizures by definition are transient abnormal excessive or synchronous neuronal activity in the brain. Seizures occur secondary diseases that affect the forebrain. The forebrain includes the cerebral cortex and thalamus. Specifically seizures are secondary to cerebral cortex neuronal dysfunction. Refer to the neurolocalization notes for further information on forebrain neurolocalization. Epilepsy is defined as recurrent seizures. Epilepsy is the most commonly treated chronic neurology issue in small animal medicine. Zero point five to 5% of the non-referral dog population suffers from epilepsy. Seizures can be provoked. These types of seizures are referred to as either reactive or reflexive seizures. Reactive seizures are seizures secondary to some stimulus or disturbance in function (example toxin exposure or metabolic disease). Typically, reactive seizures are reversible once the stimulus is removed. Reflex seizures are also secondary to a stimulus such as light or sound or movement. For example, there are descriptions of humans suffering seizures secondary to exposure to strobe lights—the reason behind signs at Disney World on some of the rides wherein bright lights are used to warn individuals who seize secondary to bright lights that perhaps that is not the ride for them. There are also reports of seizures being induced in humans exposed to certain music, singers or songs, etc. My cat growing up had reactive seizures; hers induced by the opening “crinkle” sound heard when the Pounce cat treats were opened. We would open in the adjacent room so as not to induce a seizure then then she would get her treats safely. With both reactive and reflexive seizures if the stimulus is removed the seizures should, theoretically, abate.

The transient abnormal or excessive neuronal activity responsible for seizures are often considered secondary to channelopathies—some sort of dysfunction in the ion channels located within the brain leading to alterations in membrane potentials. There may be abnormalities in the concentration or receptors for certain neurotransmitters (GABA or glutamate, for example) or the ion channels themselves (Cl^-, Na^+, Ca^{2+}, for example). If there is an increase in expression or concentration of excitatory neurotransmitters within the brain—glutamate, aspartate or dopamine—you may be more apt to seizure. If there is a decrease in expression or concentration of inhibitory neurotransmitters within the brain—GABA or glycine—you may be more apt to seizure.

Seizure Classification

Seizures are further classified as self-limiting, cluster or status epilepticus. Self-limiting seizures are single, isolated events. Cluster seizures are those in which more than one is observed in a 24-hour period wherein the individual regains consciousness between each seizure episode. Cluster seizures, many times, are considered medical emergencies. Status epilepticus (SE) is defined as a single seizure lasting greater than 5 minutes or as greater than three seizures in a row without a return to normal consciousness between seizure events. SE is considered a medical emergency and, therefore, necessitates veterinary care.

Seizures are further classified by type based on phenomenology or the look of the seizure episodes. In the more recent years, the International Veterinary Epilepsy Task Force produced a consensus proposal wherein they defined and redefined some for the more standard seizure classifications. In veterinary medicine, seizures are classified as two main categories: focal aka partial seizures and generalized seizures.

Focal or partial seizures used to be further subcategorized as simple partial vs. complex partial. Now it is more acceptable to stratify this category as motor, autonomic or behavioral/psychomotor seizures. Partial seizures are disturbances within a focal area of the brain, typically on one side of the cerebral cortex. Since the left forebrain, for example, controls the contralateral body side, a dog with neuronal misfiring of the neurons within the left cerebral cortex may show twitching or muscle contractions of the right facial muscles during a focal seizure. The neurons responsible for motor function are disturbed during motor focal seizures evidenced by facial twitching or blinking, for example. During an autonomic focal seizure, the neurons in control of the parasympathetic nervous system are diseased leading to dilation of pupils, vomiting or hypersalivation as clinical signs of their seizure event. Behavioral seizures, also known as psychomotor seizures, are episodic abnormal episodes that could be confused with abnormal behaviors such as tail chasing or fly biting. In old terminology, simple partial seizures were those in which a portion of the body was affected but mentation of the patient was not altered during seizure activity. Complex partial seizures were those in which a portion of the body was affected, while mentation was altered and consciousness not normal. With the change in terminology, it is accepted that mentation may or may not be overtly altered during any of the three main subcategories of focal seizure.

Meanwhile, generalized seizures are seizures that are the result of neuronal dysfunction involving both diffuse involvement of both cerebral hemispheres. Because the entire cerebral cortex is involved, consciousness and mentation are altered. Under the term generalized are tonic/clonic (aka grand mal), tonic, clonic and myoclonic seizures. These

terms are descriptive terms for the phenomenology of the seizure episode. Tonic/clonic seizures are the classic convulsive seizure. Tonic seizures occur when muscles are maintained in a sustained, contracted position. Clonic seizures occur when muscles rapidly contract—the classic “paddling” phenomenology to a seizure. Myoclonic or “jerk seizures” occur when the neck, head and body suddenly jerk almost as if the animal was shocked.

Episodic Events That Resemble Seizure

One of the most important parts of the seizure veterinary visit is getting a good, thorough history and convincing yourself, as the veterinarian, that the episode the patient had at home is in fact a seizure. Many times owners are savvy and take video of the episode. However, if video is not readily available and the episode happened at home, you have to rely on the owner description of the episode to determine if you think it is in fact a seizure the animal experience. Key historical questions to ask include: how long was the duration of the episode, did the pet lose consciousness, what happened from beginning to end during the episode, did the pet act abnormally hours or minutes before the episode, how did the pet act directly following the episode, etc. Several conditions can resemble seizure in look and description; however, these conditions are not secondary to disease involving the cerebral cortex neurons. Examples of episodic events that resemble seizures but are not include syncope, episodes of neck or back pain, narcolepsy/cataplexy, vestibular episodes, behavioral abnormalities, tremor syndromes, paroxysmal dyskinesias (movement disorders).

Syncope is perhaps, one of the most common disease processes mistaken for seizures. One large difference between syncope and seizure is the lack of a post-ictal phase with syncope. Following a syncopal episode the patient is usually immediately ‘normal,’ while animals after having a seizure can experience neurologic deficits such as transient blindness and behavior change. Patients who have episodes of neck and back pain can appear mentally abnormal when the pain acutely strikes. Typically these patients “tweak” their neck or back and once over the pain act normally again. Narcolepsy is acute onset of sleeping and cataplexy is the loss of muscle tone that occurs at the same time. Because narcolepsy/cataplexy is episodic and there is inherently a brief loss of consciousness, it is often mistaken for seizure. Episodes of balance dysfunction can occur secondary to any disease that affects the balance center (vestibular nuclei or nerves). When a patient acutely loses balance, they often fall to the ground and paddle in an attempt to get up—thus resembling seizure. Behavioral abnormalities most closely resemble behavioral seizures. A dog may acutely fly bite because there is a fly in the room, or tail chase if there are fleas as his tail base, rather than because he is having a seizure, for example. Tremor syndrome are not sequela to cerebral cortex dysfunction but can be episodic and involve a portion of the

entire body—thus resembling seizure. Movement disorders of which paroxysmal dyskinesias (PD) are a subtype are a newly recognized type of episode in veterinary medicine. PDs sometimes last longer than seizures, but like generalized seizures, often involve the entire body, and are episodic. Nevertheless, unlike generalized seizures, consciousness is maintained throughout the duration of the episode.

Seizure Stages

There are three stages to a seizure: the ictus, pre-ictal period and post-ictal period. The ictus refers to the actual seizure event. It typically lasts seconds. The post-ictal period is the period of time directly following the seizures event. This period lasts anywhere from hours to weeks. The average post-ictal period in a dog is 48 hours. That being said, the post-ictal phase, in rare circumstances can last as long as a week. During the post-ictal phase a pet may experience classic “forebrain” signs including transient blindness, circling, head pressing, change in behavior, decreased menace and nasal sensation. The pre-ictal phase is sometimes referred to as the prodromal period. It is the time preceding a seizure. During this phase, pets may have a behavior change, circle or head press, seek attention or what to be by themselves. This period typically lasts minutes to hours. During the pre-ictal, phase humans experience an aura. The aura is a time during which the person realizes that they are going to have a seizure. It is unknown if pets experience this aura. A common question asked by referring veterinarians is, “when do I worry that a patient has true neurologic deficits secondary to a disease process rather than post-ictal deficits secondary to an idiopathic seizure?” Typically, post-ictal deficits are not lateralizing and typically abate within a few days following the ictus.

Diagnosing the Cause of Seizure

To diagnose a seizure, descriptions or video of the episode can be reviewed. An electroencephalogram (EEG) can be performed to objectively diagnose a seizure. During a seizure episode, abnormal paroxysmal burst activity is observed on an EEG. EEG, prior to the use of MRI, was used to diagnose the location and in some cases cause of seizures. Now in veterinary medicine it is more used to determine if a non-classic looking episode is or is not in fact a seizure. In human medicine, it is used to localize the seizure focus. Surgical removal of a seizure focus is a treatment for epilepsy in some people.

The causes of seizure are typically distilled down to intracranial and extracranial causes. To look for extracranial causes blood work is performed including CBC, chemistry panel, electrolytes and blood glucose values are important to obtain. In some cases, liver function testing (bile acid or blood ammonia testing) is also important to perform; **in cats** additional

testing including FeLV/FIV and T4 is recommended. If no overt extracranial cause is determined then advanced cross sectional imaging of the brain is recommended in the form of MRI or CT. MRI is more sensitive and specific for determining the cause of brain disease than CT. That being said it involves anesthesia, while CT can be performed under heavy sedation. The former takes longer than the latter and is slightly more expensive. CSF tap is often paired with brain imaging in order to rule in or out meningitis as the cause of seizures.

Differential Causes for Seizure

As alluded to earlier, the cause of seizures is typically separated into two broad categories of intracranial and extracranial disease. An example of the former is a brain tumor, and example of the latter is hepatic encephalopathy secondary to, most commonly, high blood ammonia levels secondary to liver dysfunction. When developing a list of causes for seizure in dogs and cats it is best to stratify your list based on age: less than 6 months of age, 6 months to 6 years of age and greater than 6 years of age.

The most likely cause of seizures in puppies and kittens is metabolic disease (hypoglycemia) and liver dysfunction secondary to microvascular dysplasia and/or a portosystemic shunt. Electrolyte abnormalities such as hypokalemia, hyperkalemia, hyper and hyponatremia, hypochloridemia, and hypomagnesemia can all cause seizures. Congenital malformations such as hydrocephalus or lissencephaly can also cause seizures in a young animal. Trauma and toxins such as strychnine, lead, theobromine and metaldehyde to name a few can also result in seizure activity. Meningoencephalitis secondary to infectious (viral disease such as rabies and distemper, FIP, FeLV/FIV or protozoal disease such as toxoplasmosis and *Neospora*, bacterial disease, tick borne disease such as rocky mountain spotted fever and ehrlichiosis, fungal disease such as *Cryptococcus*, *Coccidioides*, blastomycoses can also cause infectious meningoencephalitis. Non-infectious meningoencephalitis is not as common in this age group.

Between the ages of 6 months and 6 years, idiopathic epilepsy becomes the most common cause of seizure. In order for idiopathic epilepsy to be considered a likely differential diagnosis for seizures, the pet has to be neurologically normal interictally, be between the ages of 6 months to 6 years at the time of first seizure and have a normal brain MRI and CSF tap. There are three subgroups to idiopathic epilepsy: genetic epilepsy (epilepsy for which a genetic mutation has been proven to be the cause), suspected genetic epilepsy (epilepsy for which a genetic mutation is thought to be the cause but not yet proven in that particular breed of dog) and epilepsy of unknown cause (no genetic cause but like all idiopathic epileptics, a diagnosis of exclusion). **Genetic epilepsy has not been yet proven**

to occur in cats. Meningoencephalitis caused by infectious disease (see above for etiology) or non-infectious disease can also occur. Non-infectious meningoencephalitis is rare in cats but much more common than infectious meningoencephalitis in the adult dog. Non-infectious meningoencephalitis is also known as meningoencephalitis of unknown etiology (MUE) and is thought to be immune-mediated. Subcategories under the blanket term MUE include GME (granulomatous meningoencephalitis), NLE (necrotizing leukoencephalitis) and NME (necrotizing meningoencephalitis). MUE is most common in small breed dogs between the ages of 2–8 years of age. MUE is covered extensively in your spring semester elective course. Neoplasia can be observed as a cause of seizure in this age group as can toxin, metabolic disease, anomalous and traumatic disease. Cerebrovascular accidents (CVAs) also occur in this age group once a patient is of an adult age. CVAs are more commonly recognized in dogs than cats.

In patients over the age of 6 at the time of first seizure, neoplasia becomes the most likely differential diagnosis followed by meningoencephalitis, CVA, metabolic disease (liver failure or electrolyte dysfunction secondary to systemic disease), toxin or trauma. Once older than 6 at the time of first seizure, but in patients with a normal brain MRI and CSF tap and who are normal interictally the diagnosis of cryptogenic epileptic is given. Cryptogenic epilepsy means that the dog looks in every way like an idiopathic epileptic but is “too old” at the time of first seizure to be an idiopathic epileptic. The term is given as there may be something “cryptically” hiding in the brain but the MRI and CSF tap not sensitive enough to detect it at the time of work up.

TREATMENT

Seizures, regardless of cause, are often treated with anti-convulsants. That being said, there are a few exceptions to this rule the most notorious of which is hypoglycemia. If a patient comes in seizing one of the first things to check is a blood glucose level and electrolyte levels. Hypoglycemia is treated with Karo syrup orally and dextrose while electrolyte abnormalities can be treated with fluids and supplementation or treatment of the underlying cause of the electrolyte abnormality. In the heat of the moment, however, when a patient is seizing in the clinic often a benzodiazepine is given while the blood glucose and I-stat performed. Anti-convulsants come in the form of acute treatment and maintenance treatment. An important fact to remember is that anti-convulsants are given to reduce the frequency and severity of seizures, but they rarely stop seizures from ever happening again. All dogs presenting with cluster seizures or in SE have earned themselves a long-term maintenance anti-convulsant upon entering the hospital.

In the case of status epilepticus or when a patient seizures in the clinic, benzodiazepines are administered in order to stop the seizure. The danger of SE is hyperthermia and the sequela to having a prolonged elevated temperature such as disseminated intravascular coagulopathy or multi-organ dysfunction, increased risk of aspiration pneumonia, and hyper excitable neurons. Seizures beget seizures, so the more seizures that occur prior to treatment, the more difficult it may be to hyperpolarize the neurons and reduce further misfiring. Benzodiazepines including midazolam and diazepam are typically used most often in veterinary medicine as a first line seizure treatment in the acute situation. Both work in a similar way to increase the frequency with which the GABA (an inhibitory neurotransmitter) channel is open to allow increased chloride (a negative ion) to flow into the depolarized neuron. The influx of negative ions facilitates neuronal hyperpolarization and seizure abatement. Midazolam can be given IV, IM, orally or nasally. Diazepam is given rectally, IV or nasally. Both benzodiazepines are very safe and thus repeated administration can be performed. That being said, if you have to repeatedly give intermittent boluses of either medicine it is time to switch to a constant rate infusion (CRI) of either diazepam or midazolam and add in a longer activing maintenance anticonvulsant (such as phenobarbital, zonisamide or keppra). If a CRI of a benzodiazepine, in combination with a longer-acting maintenance anticonvulsant, is not working then propofol, as a CRI is recommended. More recent literature shows that propofol does have some anti-convulsant properties. Gas anesthesia such as isoflurane and sevoflurane can also be used but the anti-convulsant properties of these gases are questionable. Often patients in status put on gas still show evidence of seizure activity on EEG. Gas anesthesia stops the muscle contraction and hyperthermia associated with SE, but does not inhibit neuronal depolarization. I, personally prefer using a combination of benzodiazepine intermittent boluses or CRI in combination with a maintenance medication rather than using propofol, if I can. I typically avoid even more so, gas anesthesia. Interpreting muscle contraction and movements when an animal is being weaned off of a propofol CRI can be challenging. Is the patient paddling like a normal patient does after coming out of anesthesia or he or she going into another seizure? That is the problem with propofol more so than with benzodiazepines, in my opinion. Propofol also carries a significantly higher expense to the owner than either benzodiazepine.

Supportive care is also very important in cases of SE. One-third (1/3) of patients who present in status die in hospital, but that means 2/3 of them we can be saved! Oxygen therapy, temperature monitoring are keys. It is also a good idea to get a blood pressure assessment.

A basic knowledge of pharmacokinetics is important when trying to figure what maintenance anti-convulsant is best for your patient. Things to consider are drug bioavailability and route of drug elimination. The half-life of a drug is the time it takes for the drug to lose half of its

activity. Remember that it takes about five half-lives for a drug to reach its steady state in the blood stream. Some drugs have short half-lives (hours in duration) some have longer half-lives (days in duration). Half-life needs to be considered when choosing an anti-convulsant. Half-life and the associated time to reach steady state for a drug also determines when serum blood levels are performed. An example is phenobarbital. The half-life of this medication is 2–3 days, thus in 10–14 days for the drug to reach a steady state in the blood stream—that is when blood level monitoring is recommended. You must consider the patient's seizure frequency when deciding which anticonvulsant is best. Also consider the health of the animal and the blood work including organ function. A dog who seizes every 2 hours should not be started on a maintenance anti-convulsant, which takes months to reach steady state. A dog with liver dysfunction should not be started on a maintenance anticonvulsant that is metabolized via the liver.

Refractory epilepsy is defined as epilepsy for which more than one anti-convulsant is needed for successful control. Twenty-five to 30% of epileptic dogs are refractory, requiring more than one anti-convulsant in their lifetime. It is best to get maximum relief from one anti-convulsant before adding a second medication. Therefore, if a reported blood level exists, as in the case of bromide or phenobarbital, make sure the patient is at the high end of accepted blood level before adding a second drug. In the case of keppra or zonisamide, make sure the patient is at the high end of acceptable dosing ranges before adding a second medication. Owner compliance and faith in anti-convulsant treatment is lessened with the addition of a second and third anticonvulsant. The other time to add a second drug would be if the side effects of the first at the current dose were considered too severe.

In addition to oral medications, homeopathic remedies have been utilized including herbal medications and essential oils for seizure control. Acupuncture is also recommended for certain patients. Dietary adjustment in the form of a medium-chain triglyceride diet or ketogenic diet has also been explored in dogs as a way to combat seizure activity. Many ongoing studies now are pursing the use of cannabinoids for seizure treatment.

References

1. Berendt M *et al.* International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *Vet Res*. 2015; 11: 182.

2. Bhatti S *et al.* International veterinary epilepsy task force consensus proposal: medical treatment of canine epilepsy in Europe. *Vet Res*. 2015; 11: 176.

3. Ekenstedt K *et al.* Inherited epilepsy in Dogs. *Topics in Comp Anim Med*. 2013; 28: 51.

4. Sanders S. Antiseizure medications. In: *Seizures in Dogs and Cats*, 1st ed. 2015; 166.

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