Seizure Very Short Course

William Bush, VMD, DACVIM (Neurology)

bbush@bvns.net
Winter, Sugarloaf, Mountain, Comus, MD
Vital Questions: Seizure Management

• Is the event that is witnessed or described likely seizure?

• Is it likely there an underlying cause that can be treated specifically?

• When to treat and with what medication?
The Problem

All the most acute, most powerful, and most deadly diseases, and those most difficult to be understood fall upon the brain.

- Hippocrates
What is a Seizure?

- Transient occurrence of signs and/or symptoms due to abnormal excessive and/or synchronous neuronal activity in brain
- Best defined with EEG
Did He Say EEG?
BVNS EEG Program

- Intramural technician certification
- Collaborate with physician expert in human and animal EEG
- Discriminates epileptic seizure from movement, psychogenic & metabolic disorders
False Positive

• The transient occurrence of symptoms or signs that is NOT due to abnormal neuronal activity in the brain

• Observed behavior is NOT epileptic seizure but from a **metabolic disorder, movement disorder, or psychogenic problem**
Many Seizure-Like Events

- Cataplexy, narcolepsy, REM sleep disorder
- Vestibular episodes
- Panic attack symptoms
- Metabolic / toxic event
- Episodes of neuromuscular disease or encephalitis
- Myoclonus
- Breed associated movement disorders / Dyskinesia
- Fly Biting / GI Disease
- Cervical muscle spasm
- Head bobbing / Tremor syndromes
- Feline hyperesthesia syndrome
- Intermittent decerebrate /decerebellate rigidity
- Chiari malformation / syringomyelia associated episodes
- Atlanto – Axial subluxation
- Syncope
Bear
1 ½, FS
Labrador Mix
Bear – The Situation

• 16 months of persistent seizure / seizure-like episodes (SLE) during sleep, intermittent seizure in day time, anxiety, no response to bromide & phenobarbital

• Bear videotape

• Bear EEG sleep study
EEG Diagnosis – REM Sleep Disorder
Plan – clonazepam, tricyclic antidepressant
Pathologic Diagnosis – idiopathic / congenital

Bush, et al. Diagnosis of REM sleep disorder with EEG and treatment with antidepressant, JAAHA, 2004
Agi (and owner) 8, FS
Scottish Terrier
Agi – The Situation

• Episodes of collapse and being non-responsive, the episodes are increasing in frequency and severity

• Normal CBC, Chemistry

• Video
EEG Diagnosis – normal
Plan – treat for encephalitis, imipramine, feeding tube, time
Pathological Diagnosis – Narcolepsy based on clinical course
Elmo
11 yr, MC
DSH
Elmo – The Situation

• Diabetic on 2 units of glargine, presents non-responsive, hypoglycemic, facial twitching and tongue movement

• Twitching has persisted for last 30 hours despite normoglycemia, MgSO4, Keppra 25 mg/kg, Q8, midazolam, diazepam, phenobarbital 16 mg/kg and normal electrolyte and pH

• Elmo would twitch during EEG
EEG Diagnosis – normal
Plan – wait-and-see, Keppra
Diagnosis – metabolic encephalopathy
False Negative Possible?

- Abnormal or excessive synchronous neuronal activity within the brain but **failure to recognize the transient occurrence of symptoms or signs**

- Few to no outward signs of the electrical seizure which is also called non-convulsive seizure
Electrical Seizure / Electrical Status

• Ictal discharges consisting of a rhythmic pattern with definitive evolution in frequency, amplitude and/or morphology persisting for at least 10 seconds (seizure) or greater than 30 minutes (status)

• Most electrical seizures are focal or partial in human medicine and this is very likely true in veterinary medicine

• Seizure can be non-convulsive
What is Non-Convulsive Seizure?

- Patient is not having convulsive movements or classic seizure

- Typically there are only autonomic changes and/or subtle movements

- EEG would demonstrate ictal activity
Squirrel
10, MC
DSH
Squirrel – The Situation

• 36 hours of intermittent 15 second seizure (left side, facial twitching that progressing to generalized twitching, non-responsive, salivation)

• CBC, Chem, MRI, CSF, Infectious titers normal

• Clindamycin, prednisone, zonisamide, levetiracetam, phenobarbital and 30 hours later this [video]
EEG Diagnosis – NCSE
Plan - ???
Pathologic Diagnosis – viral
Mark Stecker, MD, PhD, DABNM, FASNM

- B.A. in Physics, Mathematics, Biophysics, then PhD in Physics from UPENN
- Medical Degree at Harvard Medical School/MIT
- Neurology residency and Dana Fellowship in Neuroscience/Epilepsy at UPENN
Endpoints for Treating Status Epilepticus

- No observable signs of seizure activity
- Reduction or elimination of epileptiform complexes
- Burst Suppression (anesthetic quieting of brain)
1:55, 6 mg/kg PB

4:30 PM, 50 mg/kg PB

11:00 PM, 100 mg/kg PB
Outcome

- Control of the EEG status epilepticus required 100 mg/kg phenobarbital
- Chronic heart condition progressed, developed azotemia and ....

Nina
1 year-old,
FS,
Chihuahua
Nina – The Situation

• 4 days ago – eating, choked, unable to stand, shaking, salivation, lasted 30 seconds, then normal

• 3 days ago – tired, similar episode while chewing on bone

• 2 days ago – occasional trembling, drooling, tired

• 1 day ago – urinated in bed overnight, bed wet with saliva, that afternoon, trembling / shaking, not aware, urinated, salivated, lasted 30 seconds, very dull in between, persisted for 24 hours (maybe 30 episodes total)

• Today – MRI, CSF, valium, keppra, low dose phenobarbital, not waking up from anesthesia  video
EEG Diagnosis - Non-Convulsive Status Epilepticus
Plan – treat GME, titrate treatment to EEG
Pathological Diagnosis - MUE
NCSE is Clandestine

“Clinical detection of NCSE would not have been possible with routine neurologic evaluations without use of EEG monitoring”

NCSE Common in Human ICU

- 50,000 USA cases per year
- 8% of patients hospitalized with unexplained coma
- 52%, 67%, and 79% in NICU or MICU

Foreman B, Hirsch LJ, Epilepsy Emergencies: Diagnosis and Management, Neurol Clin 30 (2012) 11-41,

NCSE in Veterinary Medicine

• JVEECS – 10 cases of refractory SE, 20 mg/kg phenobarbital and all cases noted to have electrical seizure

• BVNS – NCSE seen in 5/15 (33%) cats and 11/89 (12%) dogs that had an EEG with a concern for seizure
NCSE Common & Deadly

- VCU - 164 patients with convulsive status epilepticus that then got EEG

- 14% shown to be in NCSE immediately despite showing no overt signs of convulsive activity and being comatose

- NCSE had a 51% mortality & independently of age and diagnosis, highly statistically significant

NCSE is Deadly

- Mortality in CSE about 30% and about 50% in NCSE

- BVNS - 2/5 cats and 5/11 dogs - 44% in hospital mortality – compared to 21% in controls

- VCU study – subgroup that had better outcome when used EEG as endpoint for aggressive therapy
NCSE Risk Factors - BVNS Study

• Under 3 years of age, seizure within last 8 hours, history of cluster seizures

• No other risk factor could separate cases of electrical seizure from controls
Dilemma When No EEG

• Not all that glitters is gold...there are false positive diagnoses of NCSE without EEG

• Treat because NCSE itself lethal
  a. Keppra 60 mg/kg
  b. Pheno 10 mg/kg boluses up to 60 mg/kg
  c. Clinical endpoint of motionless without autonomic changes (T, HR, RR, Pupil Size)
Part 1: Take Home Points

• There are many events that appear to be seizure that are non-epileptiform events

• Non-convulsive seizure and non-convulsive status epilepticus are serious conditions that are underdiagnosed in veterinary medicine

• EEG pivotal for diagnosis and best treatment of NCSE
Part 2: Structural vs. Unknown

- How do you determine if a seizure patient has structural epilepsy...without referral or MRI
William & Bonapart (BoBo)
Seizure From Forebrain Disease

2 Big Parts of the Forebrain?
What if This Happens?
Hemi-neglect / Hemi-inattention

“With a lesion of the right forebrain the patient is unaware of the left (opposite) side”
Left Forebrain Lesion

- Seizure
- Confusion / Behavioral Changes
- Wide circling or/and head turn to left
- Bumping into things
- Left-side menace, sensory and postural deficits
Your Neighbor Calls ....

Rogue, 8, MC, Lab Mix
Many Causes for Seizure

<table>
<thead>
<tr>
<th>Class</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>Lysosomal storage, leukoencephalomalacia</td>
</tr>
<tr>
<td>Anomalous</td>
<td>Hydrocephalus, polymicrogyri, lissencephaly, cyst</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Low thyroid, glucose, calcium</td>
</tr>
<tr>
<td></td>
<td>High triglyceride, PCV, Liver &amp; Kidney Toxins</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Low thiamine</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Meningioma, glioma, metastatic, lymphoma</td>
</tr>
<tr>
<td>Infectious</td>
<td>Parasitic, protozoal, viral, fungal, bacterial, rickettssial</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Genetic / Unknown</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Necrotizing, GME, other immune</td>
</tr>
<tr>
<td>Trauma</td>
<td>Acute, Chronic (post-traumatic)</td>
</tr>
<tr>
<td>Toxin</td>
<td>Ivermectin, strychnine, lead, etc</td>
</tr>
<tr>
<td>Vascular</td>
<td>Infarct, hemorrhage</td>
</tr>
</tbody>
</table>
Age
Breed
Weight

Unknown

Structural
Age

When dogs with first seizure between 7 and 9 about what percentage will have structural epilepsy?

70 %

When dogs with first seizure > 9 about what percentage will have structural epilepsy?

88%

Brain Tumor Breed

What breeds would be suspected of having a brain tumor despite being < 6 years of age at time of first seizure?

Boxer, Golden, Boston Terrier, French Bulldog

True or False:

Big dogs (>15 kg) are at significantly higher risk for brain tumor?

Seizure from Encephalitis

What breeds would be suspected of having encephalitis despite being < 7 years of age?

Pug, Miniature poodle, Maltese, Bichon, Dachshund
(small dogs get encephalitis)
Cause in Structural Epilepsy

Among the 169 dogs with structural epilepsy what percentage had a neoplasia diagnosis?  

72%

What was next most common diagnosis?  

Stroke, 12%

Guideline Onset of 7, 70% structural, 50% tumors
Tell Neighbor Rogue has Brain Tumor?
Brief Exam is Plenty Sufficient!

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Forebrain Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentation</td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td></td>
</tr>
<tr>
<td>Postural Reaction</td>
<td></td>
</tr>
<tr>
<td>Menace</td>
<td></td>
</tr>
<tr>
<td>Neck Pain</td>
<td></td>
</tr>
</tbody>
</table>

### 3 Step Neurological Exam

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left Forebrain Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentation</td>
<td>Confused</td>
</tr>
<tr>
<td>Gait</td>
<td>Circling left</td>
</tr>
<tr>
<td>Postural Reaction</td>
<td>Right side deficit</td>
</tr>
<tr>
<td>Menace</td>
<td>Right side deficit</td>
</tr>
<tr>
<td>Neck / Head Pain</td>
<td>No / Maybe</td>
</tr>
</tbody>
</table>
Friend’s Dog Exam is Normal...
Inappropriate elimination in a dog > 6 typically will often indicate the patient has a brain tumor
More Historical Findings?

**TABLE 2.** Common Behavior Changes in Dogs with Structural Brain Disease

- Aggression
- Inappropriate elimination
- Irritability
- Lethargy/head pressing
- Not greeting owners
- Restless at night
- Sleeping more during the day
Take Home Points Part 2

- Age, breed, weight, exam findings, and history can often determine whether patient has structural vs. unknown cause of epilepsy
Part 3: When, What and How?

- When do you treat?
- What do you treat with?
- How do you treat cluster seizure / status?
When Do You Start Treatment?

AND KNOW WHEN TO SAY WHEN.
Treat after 1-2 in 6-12 months

• What do owners think?

• Seizure begets seizure

• New AED have few to no side effects or toxicity, BID dosing, inexpensive and effective

Evidence (Italian Spinone)

- Treating after 3 (compared to 2) seizure was a significant risk factors for mortality

De Risio L, et al. Idiopathic Epilepsy (IE) in the Italian Spinone (IS) in UK: Prevalance, Clinical Characteristics, and Predictors of Survival and Seizure Remission. JVIM 2015; 29; 917-924
What Do You Do?

In a two-year old Labrador, with genetic/unknown epilepsy that you have decided to treat, which AED would YOU choose?
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>SIDE EFFECT SCALE</th>
<th>PRIMARY SIDE EFFECTS</th>
<th>REPORTED TOXICITY/DYSFUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam*</td>
<td>20–50 mg/kg PO Q 8 H (or Q 12 H for extended release)</td>
<td>1</td>
<td>Ataxia, sedation</td>
<td>None</td>
</tr>
<tr>
<td>Zonisamide*</td>
<td>5–10 mg/kg PO Q 12 H</td>
<td>2</td>
<td>Ataxia, decreased eating, sedation</td>
<td>Affects liver and kidneys Causes urinary calculi</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>10–30 mg/kg PO Q 8 H</td>
<td>2</td>
<td>Sedation</td>
<td>None</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>2–4 mg/kg PO Q 12 H</td>
<td>2</td>
<td>Sedation</td>
<td>None</td>
</tr>
<tr>
<td>Phenobarbital*</td>
<td>2–6 mg/kg PO Q 12 H</td>
<td>4</td>
<td>Ataxia, polydipsia, polyphagia, polyuria, sedation, weakness</td>
<td>Affects liver, bone marrow, skin, and endocrine system</td>
</tr>
<tr>
<td>Bromide*</td>
<td>25–50 mg/kg PO Q 12 H</td>
<td>5</td>
<td>Ataxia, diarrhea, polydipsia, polyphagia, polyuria, sedation, vomiting, weakness</td>
<td>Affects esophagus and pancreas Causes gastritis and panniculitis</td>
</tr>
<tr>
<td>Felbamate</td>
<td>10–40 mg/kg PO Q 8 H</td>
<td>1</td>
<td>Tremors (rare)</td>
<td>Affects liver and bone marrow Causes keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>Topiramate</td>
<td>5–10 mg/kg PO Q 8–12 H</td>
<td>1</td>
<td>Sedation</td>
<td>May cause urinary calculi</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>0.05–2 mg/kg PO Q 12 H</td>
<td>3</td>
<td>Ataxia, polyphagia, sedation, weakness</td>
<td>None</td>
</tr>
</tbody>
</table>

* Serum drug monitoring recommended
Maintenance Choices

- Keppra XR 35 mg/kg, PO, Q12
- Phenobarbital 3 mg/kg, PO, Q12
- Zonisamide 10 mg/kg, PO, Q12
- Bromide 100 mg/kg x 6 days then 50 mg/kg
- Gabapentin 30 mg/kg, PO, Q8
- Topiramate 10 mg/kg, PO, Q8
- Felbamate 30 to 60 mg/kg, PO, Q8
- Clorazepate 0.5 to 2 mg/kg, PO, Q12
Monotherapy with Zonisamide (ZON), Levetiracetam (LEV), or Phenobarbital (PB)

- Retrospective study of 121 cases of idiopathic epilepsy treated with only LEV (16), ZON (40), or PB (65)
- Effectiveness measured as time on monotherapy and all AED equally effective
- Significant difference in side effects with LEV (17%), ZON (36%), PB (78%)

Waldron R, et al. Clinical Outcome With Zon, LEV, or PB Monotherpy in Dogs with Idiopathic Epilepsy. ACVIM Abstract 2015
Keppra XR for Your Hospital

“Keppra 500 XR has actually gone on manufacturer backorder and isn’t available easily. When it’s available, we’ve gotten it from either KeySource Medical or Amatheon”

Diana Steubing, LVT
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Mg/Kg</th>
<th>Side Effect Scale</th>
<th>Primary Side Effect</th>
<th>Toxicity Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin - Pregabalin</td>
<td>10-30, B 1-2, B</td>
<td>2</td>
<td>S</td>
<td>No</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20-40, B-T</td>
<td>1</td>
<td>S, not eating, salivation</td>
<td>Renal (rare)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>2-6, S</td>
<td>3</td>
<td>PU/PD/PP/S/W/A</td>
<td>Less Liver</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>5-10, S-B</td>
<td>2</td>
<td>Less eating, S,V,A,D</td>
<td>Liver /Renal (rare) Urinary Calculi</td>
</tr>
<tr>
<td>Bromide</td>
<td>25, S</td>
<td>5</td>
<td>PU/PD/PP/W/A/T/V/D</td>
<td>Severe Asthma</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5 -1, B</td>
<td>3</td>
<td>S,A,W</td>
<td>Liver</td>
</tr>
</tbody>
</table>
Will An AED Work? What Do YOU Tell Client?

- 30% have frequent or severe seizure or intolerable side-effect despite appropriate [AED]

- A majority of canine patients on phenobarbital or bromide will NOT become seizure-free (1 year without seizure) without adverse side-effects
Border Collie

- 2 year average survival from seizure onset
- 94% had cluster seizure and 53% Status epilepticus
- 71% drug resistant and on 2 or more AED

Australian Shepherd

- 30% died, 68% cluster, 60% status epilepticus

- Greater risk when onset under 2 yr, more than 10 in first 6 months, poor seizure control (> 1 seizure/month)

- Focal seizure most common (focal tremor, salivation, dilated pupil, lateral head turn and/or panic attacks, sporadic aggressiveness, pacing, staring)
Italian Spinone

- 32% IE-related mortality rate,

- 73% cluster seizure (CS) and this was strong predictor of mortality

De Risio L, et al. Idiopathic Epilepsy (IE) in the Italian Spinone (IS) in UK: Prevalance, Clinical Characteristics, and Predictors of Survival and Seizure Remission. JVIM 2015; 29; 917-924
Any Dog Really...

- 19/32 (59%) dogs with IE had SE
- Shorter mean life spans in SE
- Significantly shortened shorter survival in SE
Principles: Pulse or Rescue Therapy

• Pulse therapy defined as giving additional and/or different AED after one seizure

• Based on idea that seizure susceptibility waxes and wanes

• CS and SE common and life threatening condition
Performing Pulse Therapy

• PO meds should not be given closer than every hour in order to allow for absorption

• Use candidate rescue medication outside of when there is a cluster to assess tolerability

• Any AED with exception of bromide suitable for pulse therapy
Keppra Pulse Therapy

- Double blinded, placebo controlled, crossover study of 6 epileptic dogs with cluster seizure while on phenobarbital and bromide

- After 1 seizure given placebo or keppra 30 mg/kg, PO, Q8 for 24 hours after last seizure

- Keppra group had 1 seizure per cluster (range 0-2) while placebo had 4 (range 1-7) - p=0.052

### Table 4. AED Pulse Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>10–30 mg/kg PO Q 8 H</td>
<td>For as long as patient is at risk for more seizures</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4–10 mg/kg PO</td>
<td>After every seizure (and/or clorazepate); administer up to Q 1 H, not to exceed 30 mg/kg within 12 H</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>0.5–1 mg/kg PO</td>
<td>After every seizure (and/or phenobarbital)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acepromazine</td>
<td>0.5–1 mg/kg PO</td>
<td>To reduce post-ictal confusion and prevent stress-induced seizures; second dose (0.5 mg/kg) can be given in 1 H if confusion not controlled</td>
</tr>
<tr>
<td>Bromide</td>
<td>Avoid for pulse therapy due to its side effects and long elimination half-life</td>
<td></td>
</tr>
</tbody>
</table>
Acepromazine Helpful

• Excellent for post-ictal confusion as CRI of 0.01 to 0.1 mg/kg/hr or 1 mg/kg PO

• Fewer seizure dogs than expected 3/67 (4%) had a seizure while being hospitalized or treated for seizure

• Owners of Border Collie and Australian Shepherd reported non-specific stress as trigger for seizure

McConnell J, Administration of acepromazine maleate to 31 dogs with a history of seizures. JVECC 2007; 17 (3): 252-267c
Parenteral AEDT Recommendations

- Midazolam 0.5 mg/kg, IM or IN
- Keppra 60 mg/kg, SC or PR
- Valium injectable solution 2 mg/kg, IN, PR (not suppository)

Hardy BT. Subcutaneous Administration of Keppra in Healthy Dogs
2011 ACVIM Abstract, P-3, p. 742
In Hospital Parenteral AEDT

- Valium 1 mg/kg + Keppra 60 mg/kg

- Phenobarbital 10 mg/kg x 2 doses

- Phenobarbital anesthesia 10 mg/kg every 20 minutes up to 70 mg/kg total – end point should be no twitching or abrupt changes in vital signs
What is in your pulse seizure pack?
Take Home Points Part 3

- Newer AED are attractive first choice medications for treating seizure

- Pulse or rescue therapy can limit cluster seizure and status episodes and save lives