Seizure Diagnosis & Treatment

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The Problem

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

- Hippocrates

Four Vital Questions

- Is the event that is witnessed or described likely seizure? (Part 1)
- Is it likely there an underlying cause that can be treated specifically? (Part 2)
- When to treat and with what medication? (Part 3)
Part 1: Seizure vs. Seizure-like

• Discuss definition of a true “epileptic” seizure

• Discuss what we learned from EEG in enhancing your understanding of seizure in terms of:
  a. Distinguishing seizure from seizure-like episodes
  b. Detecting and treating non-convulsive seizure

Simple Questions?

• What is a seizure?

• What is epilepsy?

• Is epilepsy a disorder?

It is official....

“The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have recently agreed that epilepsy is best considered to be a disease”


ILAE - Epilepsy

• At least two unprovoked (non-reactive) seizures occurring >24 h apart (2005)

• One unprovoked seizure and a probability of further seizure of at least 60% over the next 10 years (2014)

ILAE - Seizure

• Transient occurrence of signs, symptoms or both due to abnormal excessive or synchronous neuronal activity in brain

• Best defined by electroencephalography (EEG)

BVNS EEG Program

• Intramural technician certification

• Collaborate with physician expert in human and animal EEG

• Performed during suspect seizure event to detect seizure and guide therapy
**Electrical, Convulsive Seizure**

- Cataplexy, narcolepsy, REM sleep disorder
- Vestibular episodes
- Panic attack
- Metabolic / toxic event
- Episodes of neuromuscular disease or encephalitis
- Myoclonus
- Breed associated movement disorders / Dyskinesia
- Cervical muscle spasm
- Head bobbing / Tremor syndromes
- Feline hyperesthesia syndrome
- Intermittent decerebrate / decerebellate rigidity
- Chiari malformation / syringomyelia associated episodes
- Atlanto – Axial subluxation
- Syncope
- Lip smacking / neck extension from gastric reflux

**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 titters normal
- Clindamycin, prednisone, zonisamide, levetiracetam, phenobarbital and 30 hours later this [video](#)

**EEG Diagnosis – NSSE**

**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

Outcome

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

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
Lucy – The Situation

- Discovered 6:00 AM in crate with large amount of saliva, feces, and urine and twitching of head and legs, right worse than left, unsteady, glazed
- ER clinic, treated for organophosphate toxicity with methocarbamol, atropine, anti-emetics, noted to have knuckling of RTL, eyelid twitch, video

Lucy’s Left Forebrain

Nina
1 year-old, FS, Chihuahua

EEG Diagnosis – normal
Plan – wait-and-see, Keppra
Diagnosis – metabolic encephalopathy

Lucy
3 yr, FS
Shih Tzu

EEG diagnosis – non-convulsive status epilepticus
Plan - MRI +/- CSF, directed therapy, higher doses of AED rapidly
Pathologic diagnosis – Meningoencephalitis of unknown origin

EEG diagnosis – normal
Plan – wait-and-see, Keppra
Diagnosis – metabolic encephalopathy

Lucy
3 yr, FS
Shih Tzu

EEG diagnosis – normal
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Ozzie

14 month, MC
German Shep Mix

Ozzie – The Situation

- 3 am – chewing unfrozen freezer pack
- 7 am - lethargic, not getting out of bed, did not eat well
- 8:45 am - convulsive seizure, T – 107.1, 3 doses valium for seizure
- 10 am – BVNS, seizure at admission, lateral recumbent, non-responsive, eyelid twitching, jaw chomping, tremor / paddling of all 4 limbs

Likely Possible Causes for Ozzie?

- Given age, normal blood work, onset, and that he eats anything, a toxin is likely
- Inflammation of the brain (encephalitis) also fits well
- CSF analysis should define cause because:
  a. Analysis normal with toxin
  b. Increased cells and protein with encephalitis

Prognosis & Plan for Ozzie

- 25% mortality rate with Status Epilepticus
- EEG advised to do the following:
  a. Define events as non-convulsive seizure
  b. Determine type and amount of medication

Ozzie Outcome

Door #1 - EEG, not assessed to be seizure, anti-tremor medication and sedation, home the following day

Door #2 – No EEG, managed with seizure medication with endpoint being stopping the twitching, sedative side-effects and additional cost and risk
CLINICAL CHARACTERISTICS AND OUTCOME OF CASES DIAGNOSED WITH ELECTRICAL SEIZURE IN 74 DOGS, 11 CATS

• Determine number and appearance of cases with ES/ESE among all cases that had EEG for seizure

• Determine if there were any characteristics / risk factors in the ES/ESE group that could distinguish them from non-ES/ESE group such that might not need EEG

• Determine mortality rate in ES/ESE and non-ES/ESE

Findings with ES/ESE Study

• 15/86 (17%) had electrical seizure

• Mortality in the ES/ESE group was 40% compared to 21 % in non-ES/ESE group

Findings with ES/ESE Study

• Cats at risk for ESE, younger animals and those with other EEG abnormality were at risk for ES

• Seizure within 8 hours, cluster seizure, and twitching more prevalent in ES/ESE group but not significant

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 diseases that are underdiagnosed in veterinary medicine

• EEG pivotal for diagnosis and best treatment of NCSE — referral to BVNS advised for patients where NCSE suspected

Part 2 – Structural Disease?

• Discuss evolution off classification system for seizure based on underlying cause

• Discuss ways to determine the probability a patient with new onset seizure is likely to have a structural cause for the seizure

Many Causes for Seizure
ILAE Seizure Classification by Cause

1989
- Idiopathic (<6, unknown)
- Symptomatic (tumor, stroke)
- Cryptogenic (>6, unknown)

2005
- Genetic
- Unknown
- Structural / Metabolic

Genetic Epilepsy – 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

Seizure Generated in Forebrain

What if This Happens?

R+ R+

Exam Findings?

MUST REMEMBER THE FOLLOWING

With a left forebrain lesion the patient is unaware of the right side

Right Forebrain Lesion

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

Using Age Alone

• What are the odds this patient will have a structural lesion?

More on Age

• 70% of dogs with first seizure at 7 or older will have structural epilepsy?

• 88 % of dogs with first seizure 10 or older will have structural epilepsy


Cause in Structural Epilepsy

• 72% of the 169 dogs with structural epilepsy had a brain tumor (next most common was stroke at 12%)

• Therefore if 7 or older, 70% chance structural and 50% chance it is a brain tumor

• Are you ready to tell neighbor that Lucky has a brain tumor?

Further Clues on Signalment

• Does considering the breed or weight help you in assessment whether or not this patient has structural lesion?

Breed & Weight

• Boxer, Golden, French Bulldog, and Boston Terrier are at higher risk of brain tumor

• Dogs > 15 Kg are 2.3 times more likely to have a brain tumor

• Pug, Miniature poodle, Maltese, Bichon, Dachshund are at higher risk for encephalitis

What Next to Help Neighbor?

a. Run blood work
b. Perform MRI
c. Refer to neurologist
d. Perform examination
e. Regret not telling neighbor you were grade school teacher

3 Step Neurological Exam

Neighbor’s Dog Exam is Normal

- Does this mean that there is not a structural lesion in this dog?

Accuracy of Exam in Predicting Structural Lesion

- 31% of dogs with Structural Epilepsy (neoplasia or stroke) will have normal exam
- 18% of dogs without a structural lesion will have an abnormal examination
Anything Else to Help Neighbor?

- Is there anything else that you can do to determine if there is a structural lesion and best advise your neighbor?

Historical Findings?

Inappropriate elimination in a dog > 6 typically will often indicate the patient has a brain tumor.

More Historical Findings?

- Underlying cause is suspected based on signalment, exam findings, history or/and when CBC, chemistry do not elucidate cause
- Poor seizure control

Referral When?

- Antibiotic: Doxy- or Minocycline 10 mg/kg, Q24 x 4 weeks & Clindamycin 15 mg/kg, Q12
- Infectious Testing: +/- Titters (PCR CDV, Toxoplasmosis, Neospora, Sarcocystis, Tick serology or PCR, Fungal)
- Empiric Treatment: Prednisone 0.5 mg/kg, Q12 +/- Cyclosporine 5-6 mg/kg, Q12

No Referral – Encephalitis Suspected

- Antibiotic: Doxy- or Minocycline 10 mg/kg, Q24 x 4 weeks & Clindamycin 15 mg/kg, Q12
- Infectious Testing: +/- Titters (PCR CDV, Toxoplasmosis, Neospora, Sarcocystis, Tick serology or PCR, Fungal)
- Empiric Treatment: Prednisone 0.5 mg/kg, Q12 +/- Cyclosporine 5-6 mg/kg, Q12

No Referral – Tumor Suspected

- Prednisone 0.5 mg/kg, Q12 and maybe taper to 0.25 mg/kg, Q12
- Prompt, higher dose AED treatment or multiple AEDs
Part 2 : Take Home Points

Age, Breed / Weight, History, Exam Findings

Unknown

Structural

Part 3 – When and How Treat

• Discuss my perspective on when to treat epilepsy

• Review currently available anti-epileptic drugs (AED) and optimizing their use in treating epilepsy

When To Start Treatment

Under what conditions would YOU start treatment of a seizure disorder?


AED Mechanism of Action

• New AED work by different mechanism from phenobarbital and bromide

• Much different side-effect profile

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

What is Distance to Seizure?

Threshold

Recting
Increased Distance to Depolarization

- Inside more negative by increasing flow of negative ions into cytosol
- Outside more positive by slowing the flow of positive ions into the cytosol

What Do You Do?

In a two-year old dog with genetic/unknown epilepsy that you have decided to treat, which AED would YOU choose?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Mg/kg</th>
<th>Side Effect</th>
<th>Primary Side Effect</th>
<th>Toxicity Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>10-30, B, J 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>Pregabalin</td>
<td>2-8, S</td>
<td>3</td>
<td>PUP/PFP/S/W/A</td>
<td>Less Leth</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>Bravecto</td>
<td>15, 5</td>
<td>5</td>
<td>P/U/P/P/M/S/W/A</td>
<td>Severe Asthma</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5-1, B, 8</td>
<td>3</td>
<td>S,A,W</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Principles of Chronic AEDT

- Use just one medication at a time
- Pick meds with best efficacy, safety, side-effect, cost and ease of administration
- Determine a serum concentration when initiating therapy in hard to control cases and/or before increasing when at high end of dose and poor seizure control
Will An AED Work? What Do YOU Tell Client?

What percent canine epilepsy patients have frequent or severe seizure or intolerable side-effect despite appropriate serum concentration of an AED?

30%

T/F – a majority of canine patients on phenobarbital or bromide become seizure-free (1 year without seizure) without adverse side-effects

False

Honeymoon Phenomenon

T/F - An AED might only work well for 6 months?

True in people, probably in dogs

How often do YOU think a placebo will reduce the seizure frequency in dogs? By greater than 50%?

• 22/28 (79%) demonstrated decrease in seizure compared to baseline
• 8/28 (29%) could be considered responders with a 50% reduction from baseline

Swimming AED Therapy

• Multiple AED will have additive side-effects
• Adequate serum concentrations of at least one AED must be maintained in the transition
• Consider half-life when making transition

Transitioning AED

Pulse Therapy

• Pulse therapy defined as giving additional and/or different AED after one seizure and based on idea that seizure susceptibility waxes and wanes
• Cluster seizure and Status Epilepticus common and life threatening condition
• Define interval between cluster of seizure and ability to swallow to decide – parenteral vs. per os
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


Performing Pulse Therapy

- PO meds should not be given closer than every hour in order to allow for absorption
- Consider trying candidate rescue medication outside of when there is a cluster to assess tolerability
- Any AED with exception of bromide suitable for pulse therapy

Pulse Therapy Examples

Seizure Management With Acepromazine

- Treats toxicity and stress induced seizure in dog and reduces neuronal damage in SE in rat model
- Rapid bolus of Chlorpromazine induced EEG changes in 22/43 dogs and caused seizure in 2 dogs (Holliday, 1970)
- In 2 studies, low dose acepromazine (0.01-0.1 m/kg, IV or 1 mg/kg, PO) in 64/67 dogs hospitalized for seizure or with seizure history did not cause seizure in observation period

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

At Home Parenteral AEDT

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

Hardy BT, Subcutaneous Administration of Keppra in Healthy Dogs. 2011 AVMW Abstract, P-9, p. 142

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
Part 3: Take Home Points

• Newer AED are attractive first choice medications for treating seizure

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

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