SHAKE, RATTLE AND ROLL: AN APPROACH TO LATE-ONSET EPILEPSY

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Outline

- Case presentation: a tale of 3 Goldens
- Late-onset epilepsy
  - Clinical Signs
  - Differential Diagnosis
  - Diagnostics
  - Treatment
  - Prognosis
"I used to be curious, but searching the internet has answered a lot of my questions."
Golden 1: Harley

- 10 y SF Golden Retriever
- Presenting for a new onset of generalized seizures
- Otherwise healthy

Image Credit: http://buzzsharer.com/2015/07/68-most-popular-golden-retriever-dog-names/
Harley

- Normal physical examination
- CBC/Chemistry/UA: normal
- Chest radiographs: no signs of pulmonary or cardiac disease, no signs of metastasis
- Normal neurological examination
Harley
Harley

- CSF: normal
- Diagnosis: epilepsy with an unknown cause
- Rx: phenobarbital
Golden 2: Allie

- 10 y SF Golden Retriever
- Presenting for a new onset of generalized seizures
- Otherwise healthy

Image Credit: http://dogtime.com/dog-health/general/1220-american
Allie

- Normal physical examination
- CBC/Chemistry/UA: normal
- Chest radiographs: no signs of pulmonary or cardiac disease, no signs of metastasis
Neurological examination:
- Mentation: dull, disinterested
- Gait/posture: compulsively pacing and circling to the right
- Proprioception: delayed in left thoracic and pelvic limbs
- Spinal reflexes: normal
- Cranial nerves: absent menace in the left eye, normal PLR, decreased nasal sensation in the left nostril
- Paraspinal palpation: non-painful

Neurolocalization: right prosencephalon
Allie
Allie

- **CSF: mild albuminocytological dissociation**
  - Protein: 35 mg/dL (< 20 mg/dL)
  - RBC: 3 cells/uL (< 5 cells/uL)
  - WBC: 2 cells/uL (< 5 cells/uL)

- **Diagnosis: hemorrhagic infarction**

- **Rx: phenobarbital**
Golden 3: Bella

- 10 y SF Golden Retriever
- Presenting for a new onset of generalized seizures
- Otherwise healthy
Bella

- Normal physical examination
- CBC/Chemistry/UA: normal
- Chest radiographs: no signs of pulmonary or cardiac disease, no signs of metastasis
- Normal neurological examination
Bella
Bella

- CSF: mild albuminocytological dissociation
  - Protein: 50 mg/dL (< 20 mg/dL)
  - RBC: 0 cells/uL (< 5 cells/uL)
  - WBC: 0 cells/uL (< 5 cells/uL)

- Diagnosis: suspected meningioma

- Rx:
  - Phenobarbital
  - Prednisone (tapering anti-inflammatory dose)
Late-onset epilepsy

It’s definitely a tumor, or is it?!
But first, some terminology…

International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals

But first, some terminology…

- **Epileptic seizure:**
  - A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain
    - Short episodes with convulsions
    - Focal motor activity
    - Autonomic or behavioral abnormalities

Berendt et al. BMC Veterinary Research 2015.
But first, some terminology…

- **Reactive seizure:**
  - A seizure occurring as a natural response from the *normal brain* to a transient disturbance in function (*metabolic or toxic in nature*) — which is reversible when the cause or disturbance is rectified.

Berendt et al. BMC Veterinary Research 2015.
But first, some terminology...

- **Epilepsy:**
  - A disease of the brain characterized by an enduring predisposition to generate epileptic seizures
    - At least 2 unprovoked epileptic seizures > 24 hours apart
  - The most common neurological disease in dogs

Berendt et al. BMC Veterinary Research 2015.
But first, some terminology…

- Idiopathic epilepsy
  - Proven or suspected genetic background
  - Unknown cause and no indication of structural epilepsy
  - Previously termed primary epilepsy

- Diagnosis of exclusion
- First epileptic seizure *typically* occurs before 5 years old

Berendt et al. BMC Veterinary Research 2015.
But first, some terminology…

- **Structural epilepsy**
  
  - Epilepsy caused by an identified *cerebral* pathology
    
    - Vascular events, infections, inflammation, trauma, malformations, congenital defects, neoplasia, degenerative diseases etc.
  
  - Previously termed secondary or symptomatic epilepsy

Berendt et al. *BMC Veterinary Research* 2015.
Image Credits: http://vetneuroandpain.com/gme-part-2-diagnosis/
But first, some terminology...

- Epilepsy with an unknown cause
  - Suspected structural cause that is not identified
  - Previously termed cryptogenic epilepsy

- Diagnosis of exclusion
  - Normal blood work, MRI and CSF

Berendt et al. BMC Veterinary Research 2015.
Clinical Signs

- Mimics of seizures
  - Syncope
  - Movement disorders
  - Behavioral disorders

Clinical Signs

- **Behavior changes**
  - Dull, disinterested → obtunded → stupor → coma
  - Pacing, circling towards the side of the lesion
  - Head pressing

- **Cranial nerve deficits**
  - Cortical blindness contralateral to the lesion
  - Decreased nasal sensation contralateral to the lesion

- **Proprioceptive deficits**
  - Contralateral to the lesion
Clinical Signs

- Normal exam
  - No structural disease
  - Structural disease in “silent areas”
Objective: To determine if neurological examination findings, results of CSF analysis, or age at the onset of seizures could be used to predict MRI results.

Results:
- Abnormal MRI: 61/115 (53%)
- Neurological exam sensitivity: 77 % (47/61)
- Neurological exam specificity: 91% (49/54)
- Age at onset of seizures was not significantly associated with MRI results.

Bush WW. et al. JAVMA 2002.
Differential Diagnosis

- **Vascular:** ischemic or hemorrhagic strokes
- **Infectious/inflammatory:** MUE, bacterial, fungal, viral
- **Trauma:** traumatic brain injury
- **Anomalies:** hydrocephalus, porencephaly, lissencephaly
- **Metabolic/toxic:** hypoglycemia, hepatic encephalopathy, renal failure, hypoxia, toxins
- **Idiopathic:** genetic mutations
- **Neoplastic:** meningioma, gliomas, hemangiosacroma
- **Degenerative:** lysosomal storage diseases, neuronal abiotrophies

Image Credit: https://foodandhealth.com/getting-enough-vitamin-d-tips-and-tricks/
Objective: To classify the etiology of epilepsy and evaluate use of abnormal neurological examination findings to predict secondary epilepsy in dogs ≥ 5 years of age

Retrospective case series
- 99 dogs included
- Epileptic seizures with an onset of ≥ 5 years of age
- Neurological examination, MRI +/- CSF
Results

35/99: seizures without an identified cause
65/99: lesion identified on MRI and/or CSF
  54/65 (83%): neoplasia

86/99: full neurological exam performed
  53/86: abnormal neurological exam
    42/53 (79%): lesion on MRI and/or CSF
  33/86: normal neurological exam
    15/33 (45%): lesion on MRI and/or CSF

Abnormal neurological exam findings had a sensitivity of 74% and specificity of 62% to predict secondary epilepsy.
Diagnostics

- CBC, chemistry, urinalysis
  - Screen for underlying systemic disease
  - Rule out reactive epilepsy (insulinomas, portosystemic shunts)

- Chest radiographs +/- abdominal ultrasound
  - Metastasis check
  - Screen for underlying systemic disease

- +/- cardiac work-up
  - ECG to evaluate for arrhythmias and possible syncope
  - Echocardiogram

Image Credit: https://www.vettimes.co.uk/icteric-serum/
Diagnostics

- MRI
  - Neoplasia
  - Infections/inflammatory diseases
  - Vascular events
  - Congenital malformations
  - Previous trauma
Diagnostics

- Spinal fluid analysis
  - Infection
  - Inflammation
  - Neoplasia
    - Lymphoma
    - Choroid plexus carcinoma

Treatment: Anti-Epileptic Drugs (AEDs)

- Indications to begin AEDs
  - More than 1 seizure every 4-6 weeks
    - Focal seizures count!
  - Seizures that are becoming more severe or more frequent
  - Prolonged or severe post-ictal state
  - Structural brain disease (suspected or confirmed)
Treatment: AEDs

- Indications to load AEDs
  - Status epilepticus
    - 2 or more epileptic seizures without full recovery of consciousness
    - Continuous epileptic seizure lasting more than 5 minutes
  - Cluster seizures:
    - 2 or more epileptic seizures in 24 hours
    - Focal seizures continuing

Image Credit: [https://www.drugs.com/pro/phenobarbital-sodium-injection.html](https://www.drugs.com/pro/phenobarbital-sodium-injection.html)
Treatment: Phenobarbital

- Pros:
  - Cheap, readily available, effective, twice daily dosing

- Cons:
  - Lethargy, ataxia, polyphagia, polydipsia/polyuria
  - Hepatotoxicity, myelosuppression, superficial necrolytic dermatitis
  - Drug interactions

- Contraindications:
  - Patients with significant hepatic dysfunction

Image Credit: http://www.keyword-suggestions.com/cGhlbm9iYXJiaXRhbA/
Treatment: Bromide

- **Pros:**
  - Cheap, readily available, effective
  - No hepatic metabolism

- **Cons:**
  - Long half-life → steady state at 2.5 – 3 months
  - Variability of serum concentrations: diet, intravenous fluids
  - Lethargy, ataxia, sedation, polydipsia/polyuria, pancreatitis
    - Increased sensitivity with concurrent phenobarbital administration

- **Contraindications**
  - Do not use in cats – eosinophilic pneumonitis
  - Use caution with renal insufficiency

Image Credit: http://www.1800petmeds.com/K+BroVet+Potassium+Bromide-prod11164.html
Treatment: Levetiracetam

- **Pros:**
  - Well tolerated, wide therapeutic range
  - Minimal hepatic metabolism
  - IV formulations available

- **Cons:**
  - Dosing every 8 hours vs extended-release ($$)
  - Decreased serum concentrations with phenobarbital use
  - Honeymoon period?

- **Contraindications:**
  - No known contraindications

Image Credit: http://www.vetrxdirect.com/product/view/levetiracetam
Treatment: Zonisamide

- **Pros:**
  - Generally well tolerated
  - Steady-state achieved in 4 days

- **Cons:**
  - Sedation, ataxia, vomiting
  - Hepatopathy, renal tubular acidosis, neutropenia

- **Contraindications:**
  - Use caution with carbonic anhydrase inhibitors or with known sulfonamide sensitivity

Treatment: Adjunctive Therapies

- **Infarctions**
  - Treat underlying causes: hypothyroidism, hyperadrenocorticism, PLE/PLN, hypertension

- **Infectious/inflammatory**
  - Screen for infectious diseases
  - Immunomodulation

- **Neoplasia**
  - Steroids
  - Surgery
  - Radiation therapy

Image Credit: http://www.1800petmeds.com/Prednisolone-prod238154.html
Prognosis

- **Epilepsy with an unknown cause**
  - Good prognosis, likely to respond to AEDs

- **Vascular**
  - Good prognosis, can have persistent deficits and seizures

- **Infectious/inflammatory**
  - Guarded

- **Neoplasia**
  - Palliative care: MST 69 days (18-201 days)\(^1\)
  - Surgery: MST 7 months (0.5-22 months)\(^2\)
  - Surgery and radiation therapy: MST 16.5 months (3-58 months)\(^2\)
  - Radiation therapy: MST 19 months (1-64 months)\(^3\)

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Summary

- Up to 35% of patients with late-onset epilepsy have epilepsy without a known cause
  - These patients have a good prognosis for survival with adequate seizure management

- Structural epilepsy carries a guarded prognosis
  - MRI +/- CSF analysis are required for a definitive diagnosis
  - A normal neurological examination does not rule out structural epilepsy
Questions?
References


