

# OMG, MUO!

## A Review of CNS Inflammatory Disease

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# OVERVIEW

- Types of CNS Inflammatory disease
- Terminology
- Classic signalment
- Diagnostic testing & histopathology
- Therapies & prognosis
- Role of the general practitioner

# Alphabet Soup

- MUO – meningoencephalomyelitis of unknown origin
- GME – granulomatous meningoencephalomyelitis
- NE – necrotizing encephalitis
- NLE – necrotizing leukoencephalitis
- NME – necrotizing meningoencephalitis
- SRMA – steroid responsive meningitis arteritis

NME

NLE

SRMA

MUO

NE

GME

N M O G N  
L M U M E R M E  
N S E A

# Terminology

Organize your alphabet soup

# Important Greek & Latin Terms

Prefix or Suffix	Ancient Term	Meaning
Leuko-	leukos	White
Polio-	polios	Grey
Myel(o)-	myelós	Spinal cord
Encephal(o)	enképhalos	Brain
- itis	itēs	Inflammation
- malacia	malakia	Softening

# CNS Inflammation

- Leukoencephalitis
- Meningoencephalitis
- Meningomyelitis
- Meningoencephalomyelitis



- Leukoencephalitis
  - White matter, brain – inflammation
- Meningoencephalitis
  - Meninges, brain – inflammation
- Meningomyelitis
  - Meninges, spinal cord – inflammation
- Meningoencephalomyelitis
  - Meninges, brain, spinal cord – inflammation

# MUE, MUA, or MUO?

Meningoencephalomyelitis of Unknown Etiology

Meningoencephalomyelitis of Unknown Aetiology

Meningoencephalomyelitis of Unknown Oorigin



HELP

N M O G N  
L M U M E R M E  
N S E A



# Inflammatory CNS Disease

**Non-infectious**

**meningoencephalomyelitis**

**Infectious**

**meningoencephalomyelitis**



# Non-infectious meningoencephalomyelitis

**NLE**

**GME**

**SRMA**

**NME**

**Eosinophilic  
meningoencephalitis**

**Corticosteroid responsive  
tremor syndrome**

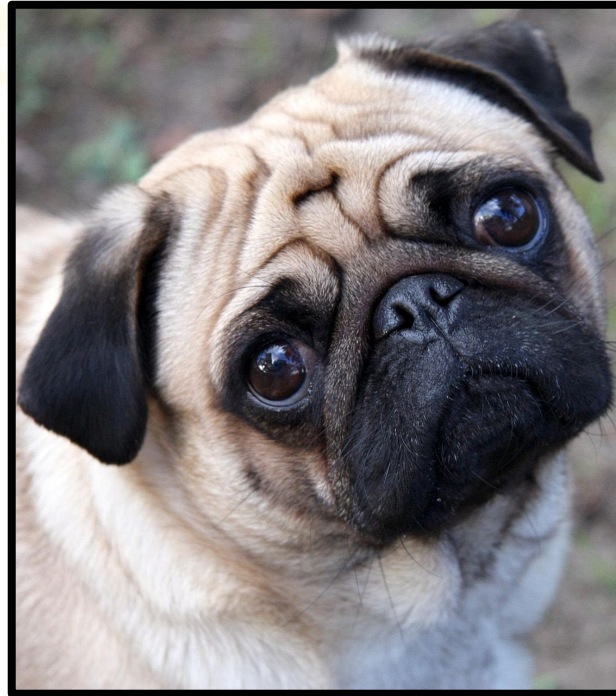
**MUO**

**NE**

**GME**

**NLE NME**

# MUO – Signalment



NLE

MUO

NME





# MUO – Signalment

- Small breed dogs (<15kgs) → 75%
- > 6 months of age
  - Typically < 8 years
- Mean age at onset ~4.5yrs
  - Others report ~2.5yrs

Variable	Small/medium breed dogs (n=83)	Large breed dogs (n=28)
Signalment		
Age (months)	52 (6–146)	60 (10–120)
Male	44 (53%)	17 (61%)
Female	39 (47%)	11 (39%)

Cornelis et al. 2016, Veterinary Record

**ANY breed, ANY sex, ANY age**

# Clinical findings and treatment of non-infectious meningoencephalomyelitis in dogs: A systematic review of 457 published cases from 1962 to 2008

Nicolas Granger<sup>a,\*</sup>, Peter M. Smith<sup>b</sup>, Nick D. Jeffery<sup>a</sup>

	<b>NE</b>	<b>GME</b>
Age	Majority <4 yrs	Majority 4-8 yrs
Female : male ratio	1.7 : 1	1.5 : 1
Lesion Localization	14% multifocal 77% forebrain only	33% multifocal 24% forebrain only

Granger et al. 2010, The Veterinary Journal

# MUO – Clinical Signs

- Rapidly progressive vs. slow/insidious
  - Multifocal\* vs. focal disease
- Reflect the area of the CNS affected
  - Meningitis
  - Encephalitis – seizures\*
    - forebrain and hindbrain
  - Myelitis
- +/- Pyrexia & peripheral leukocytosis

Granger et al. 2010, The Veterinary Journal

# MUO - Pathophysiology

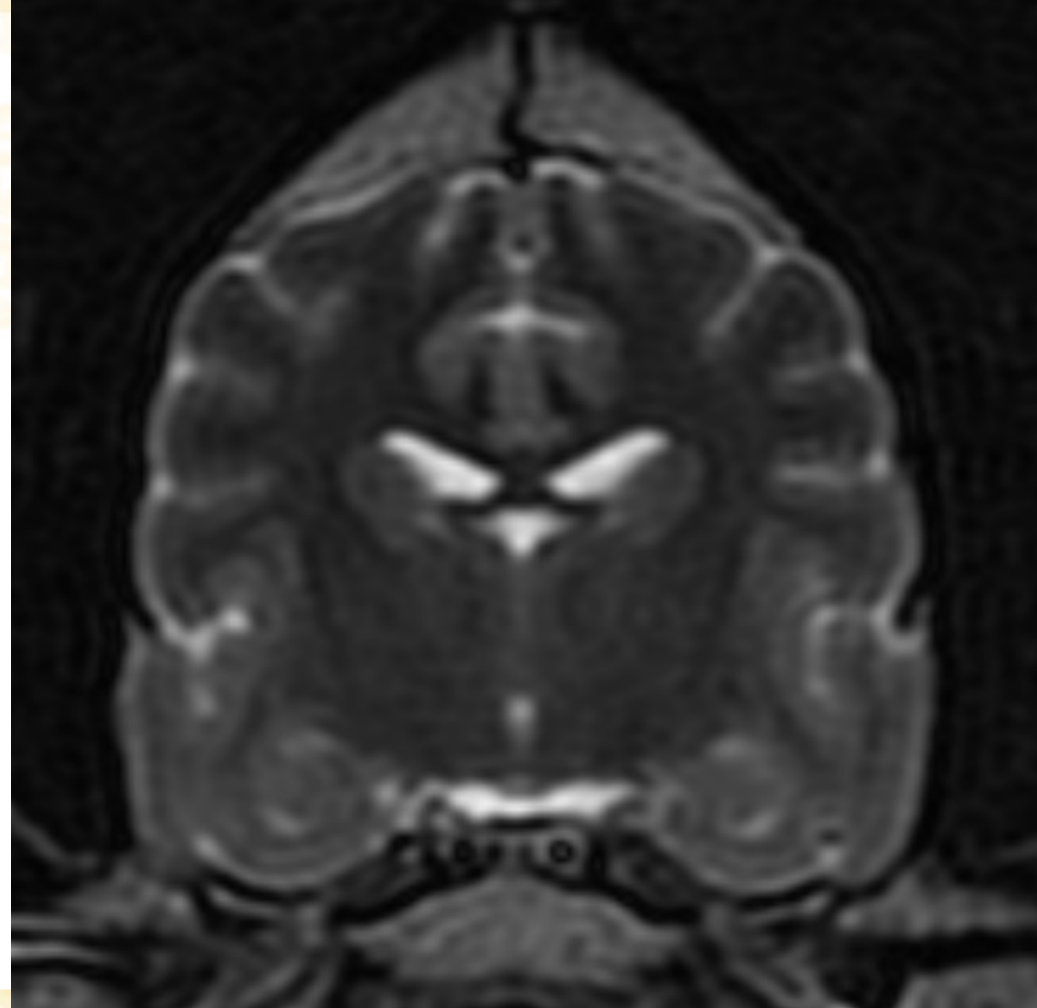
- Not completely understood
- Presumed to be immune-mediated
- Numerous theories, none proven
  - Genetic?
  - Autoimmune?
  - Environmental?
  - Immunological?
  - Infectious stimulus?
  - Neoplastic?

Talarico & Schatzberg 2010, J Sm Anim Prac

# Diagnostic Approach

# MUO – Diagnostic Approach

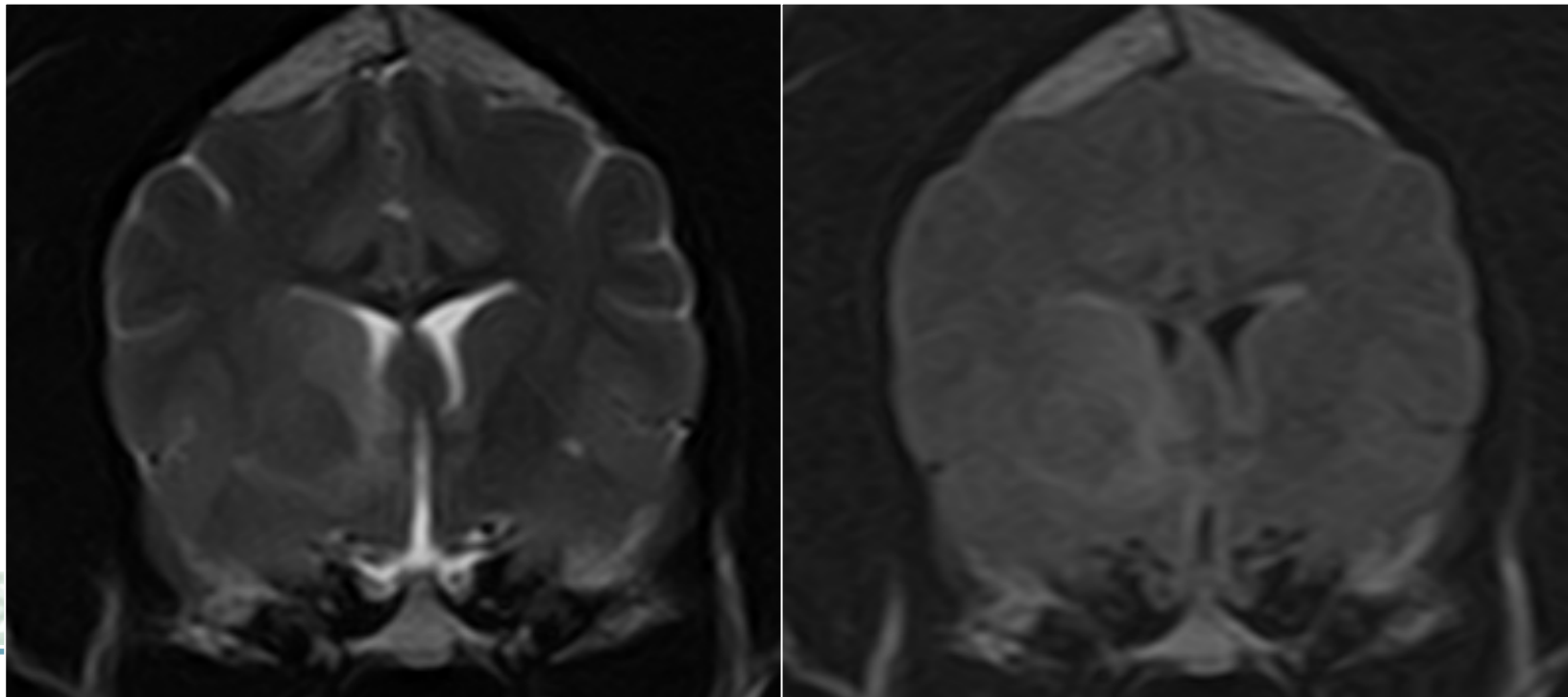
- Signalment & history
- Thorough **neurologic exam**
  - Localize the lesion(s)
- Advanced imaging
  - **Pre-anesthetic testing**
- Cerebrospinal fluid analysis
- Infectious disease testing
- Histopathology \*\*
  - Brain biopsy or post-mortem exam



Courtesy Dr. Dennis O'Brien

# MUO - Magnetic Resonance Imaging

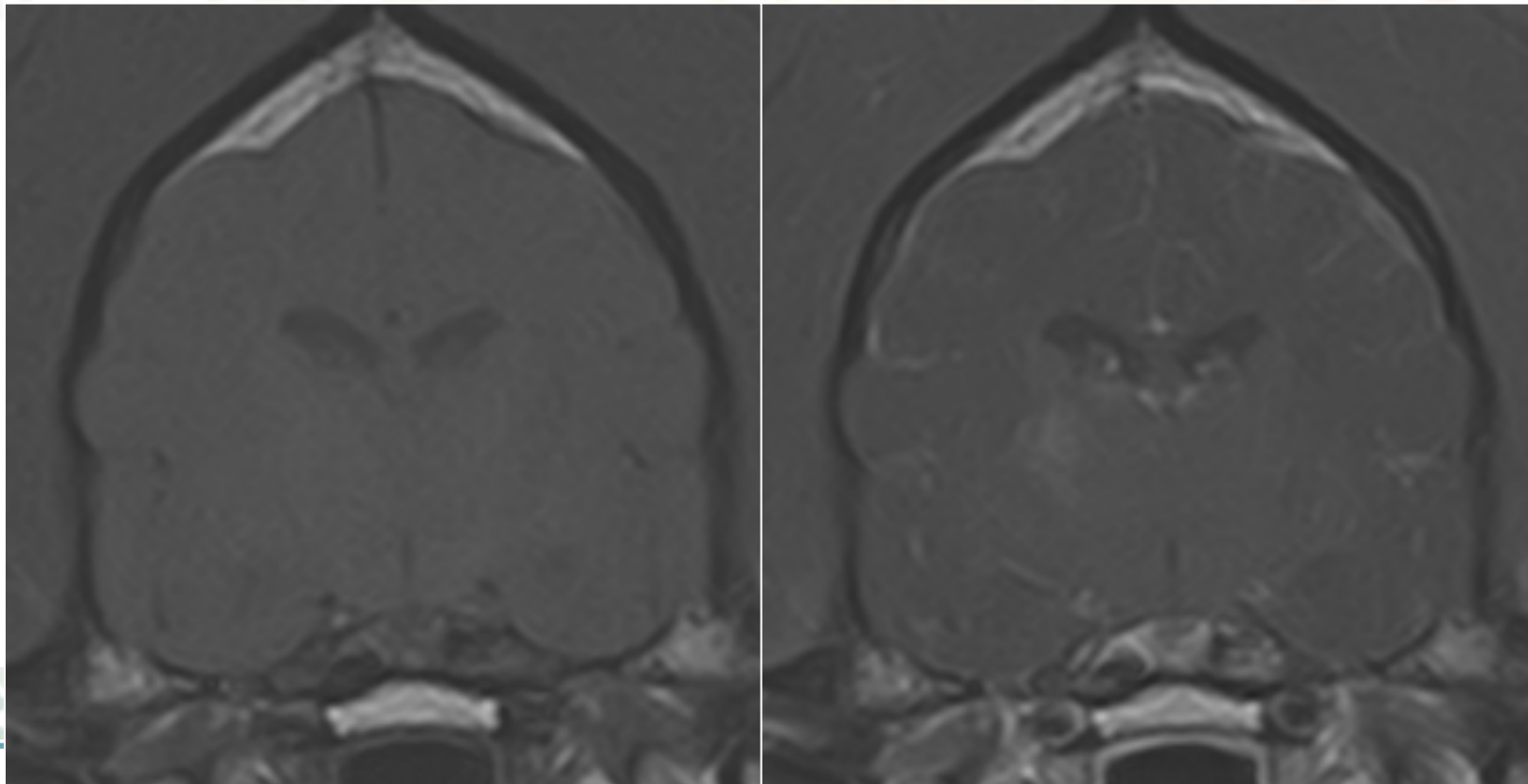
- Multifocal (~70%)
- T2 hyperintensity (up to 93%), FLAIR hyperintensity
- Ventriculomegaly, asymmetry





# MUO - Magnetic Resonance Imaging

- T1 hypo to isointensity
- Post-contrast enhancement variable (69%)



# Breed-Specific Magnetic Resonance Imaging Characteristics of Necrotizing Encephalitis in Dogs

*Thomas Flegel\**

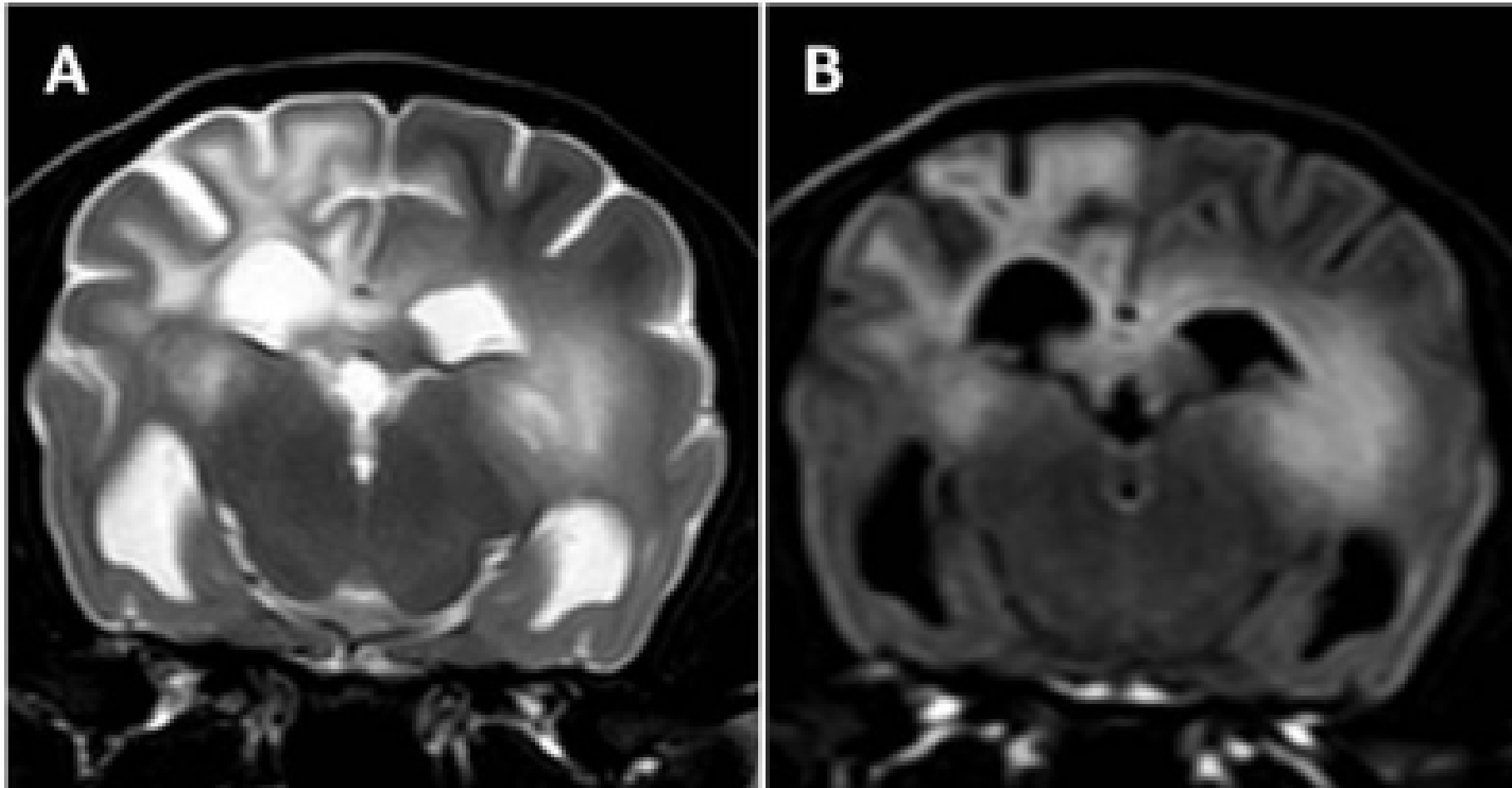
Flegel 2017, Frontiers in Veterinary Science



**NLE**

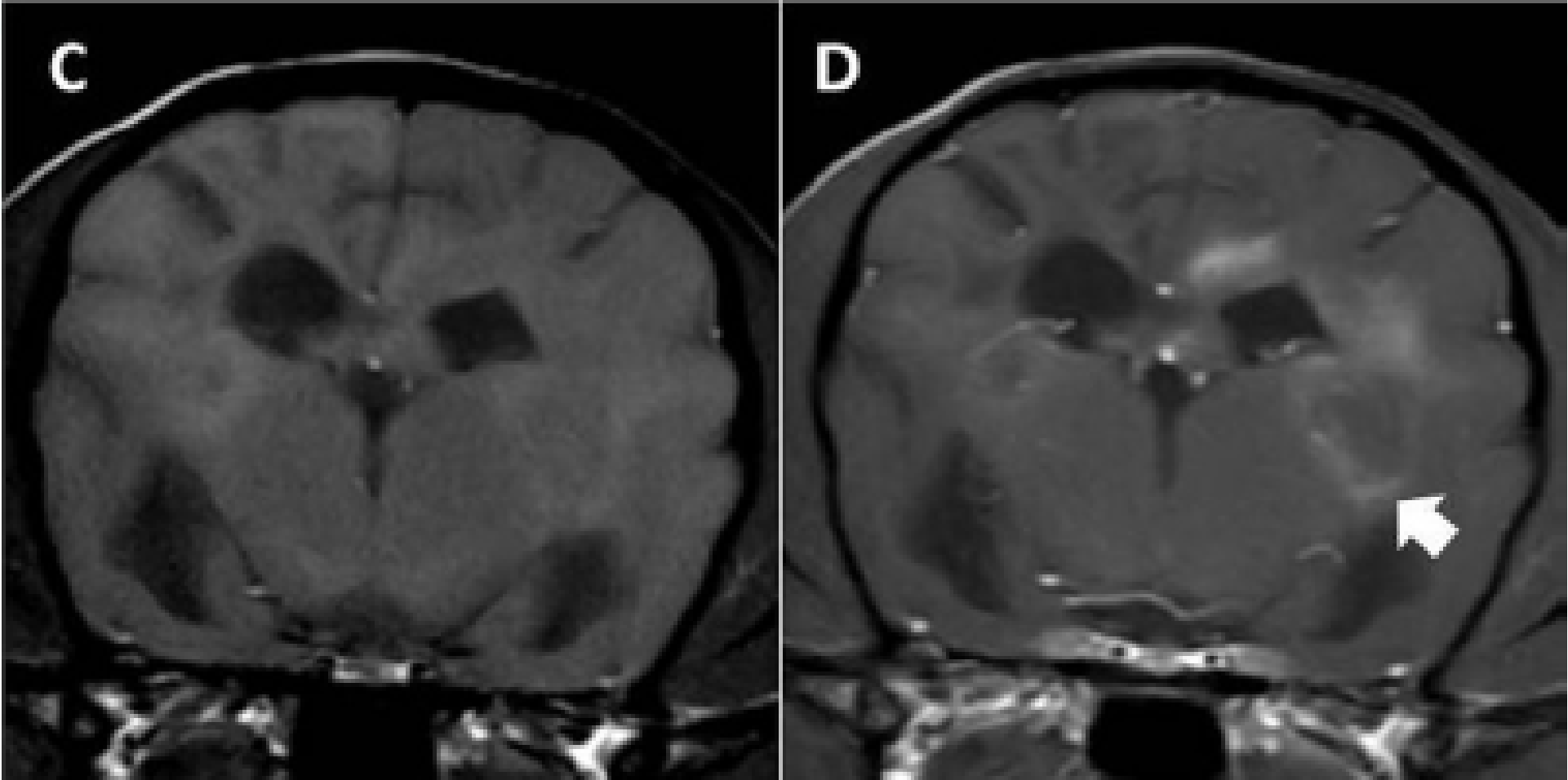
**NME**

# NLE (Yorkshire Terrier)



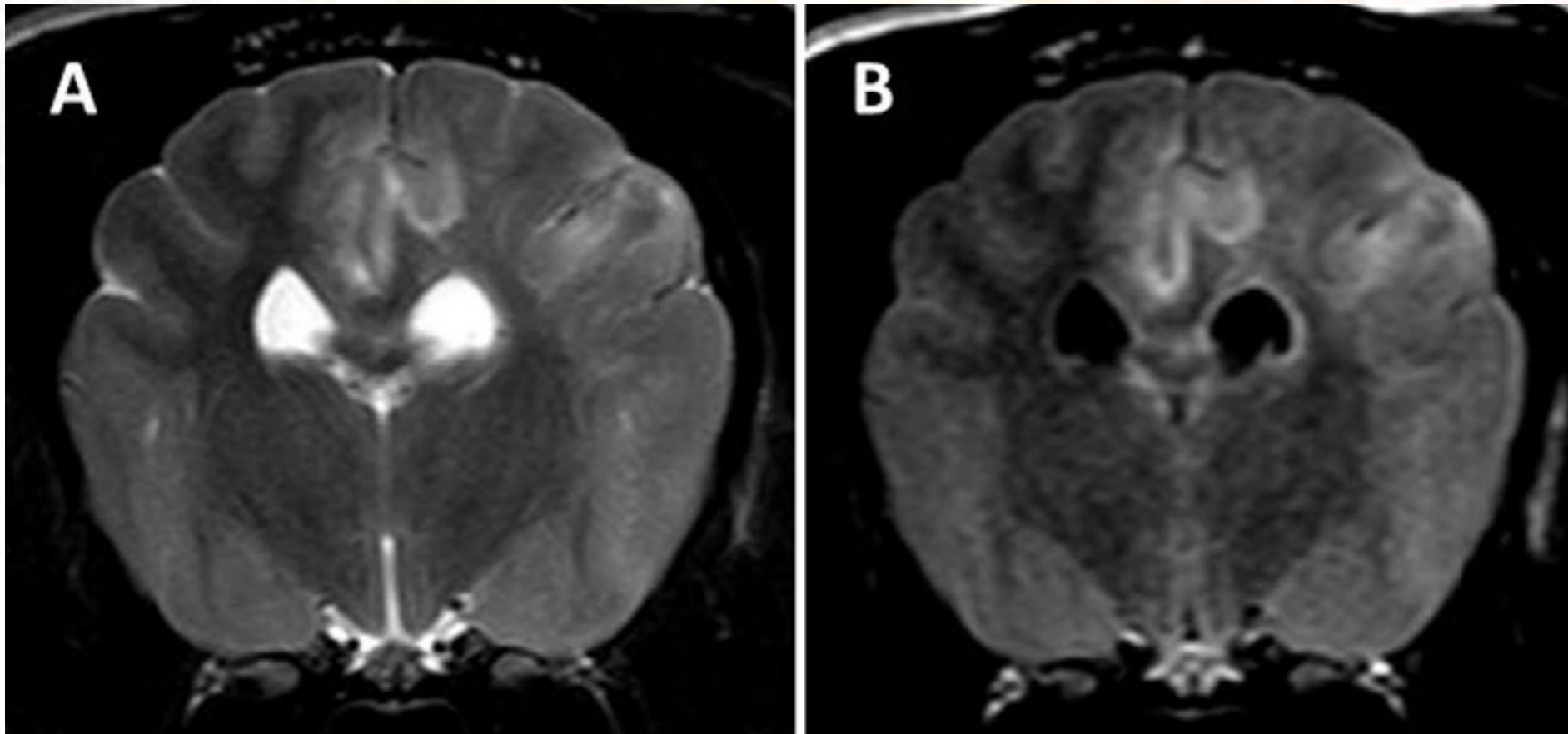
Flegel 2017, Frontiers in Veterinary Science

# NLE (Yorkshire Terrier)



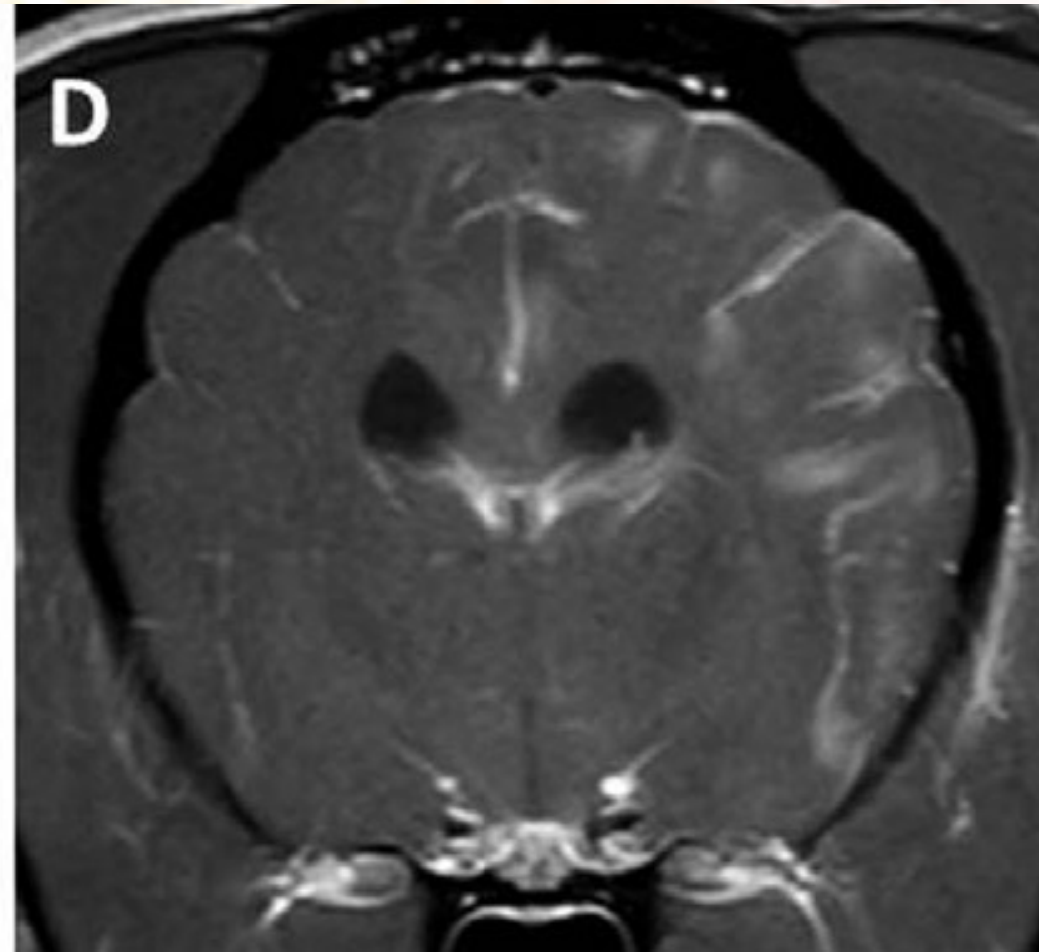
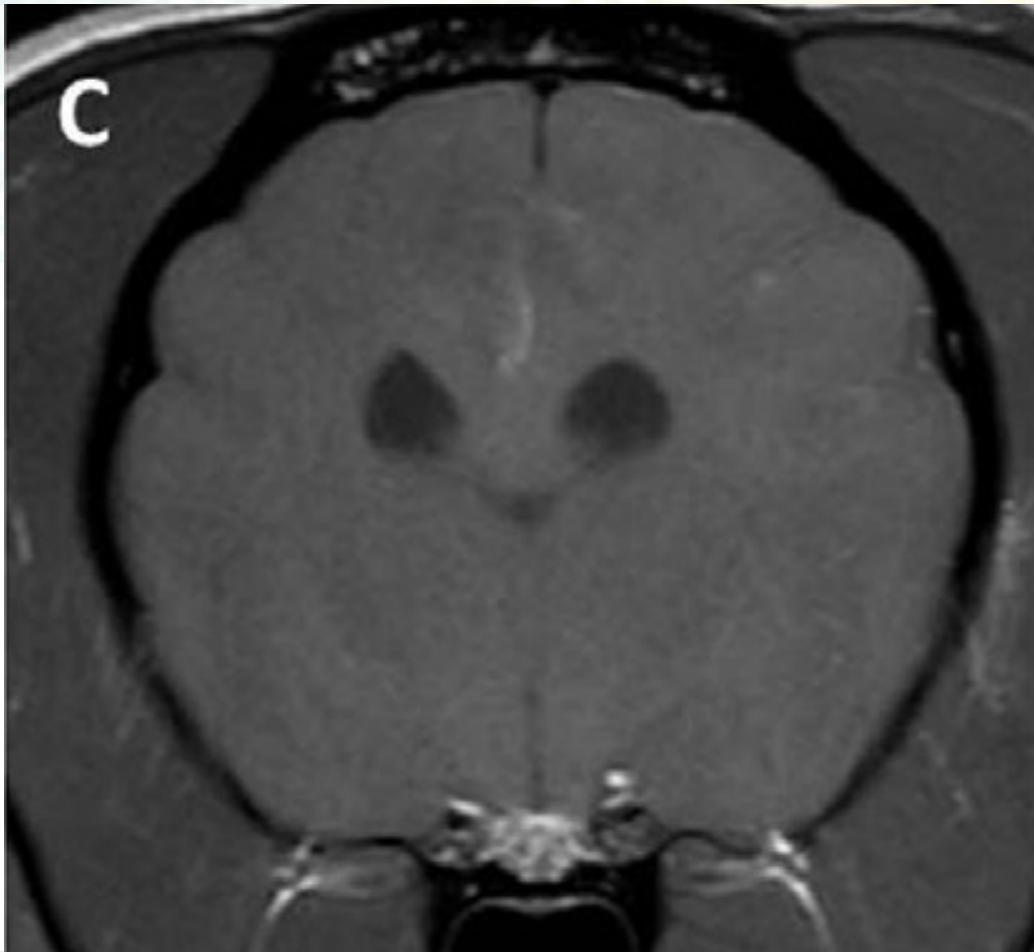
Flegel 2017, Frontiers in Veterinary Science

# NME (Pugs)



Flegel 2017, Frontiers in Veterinary Science

# NME (Pugs)



Flegel 2017, Frontiers in Veterinary Science

# CASE

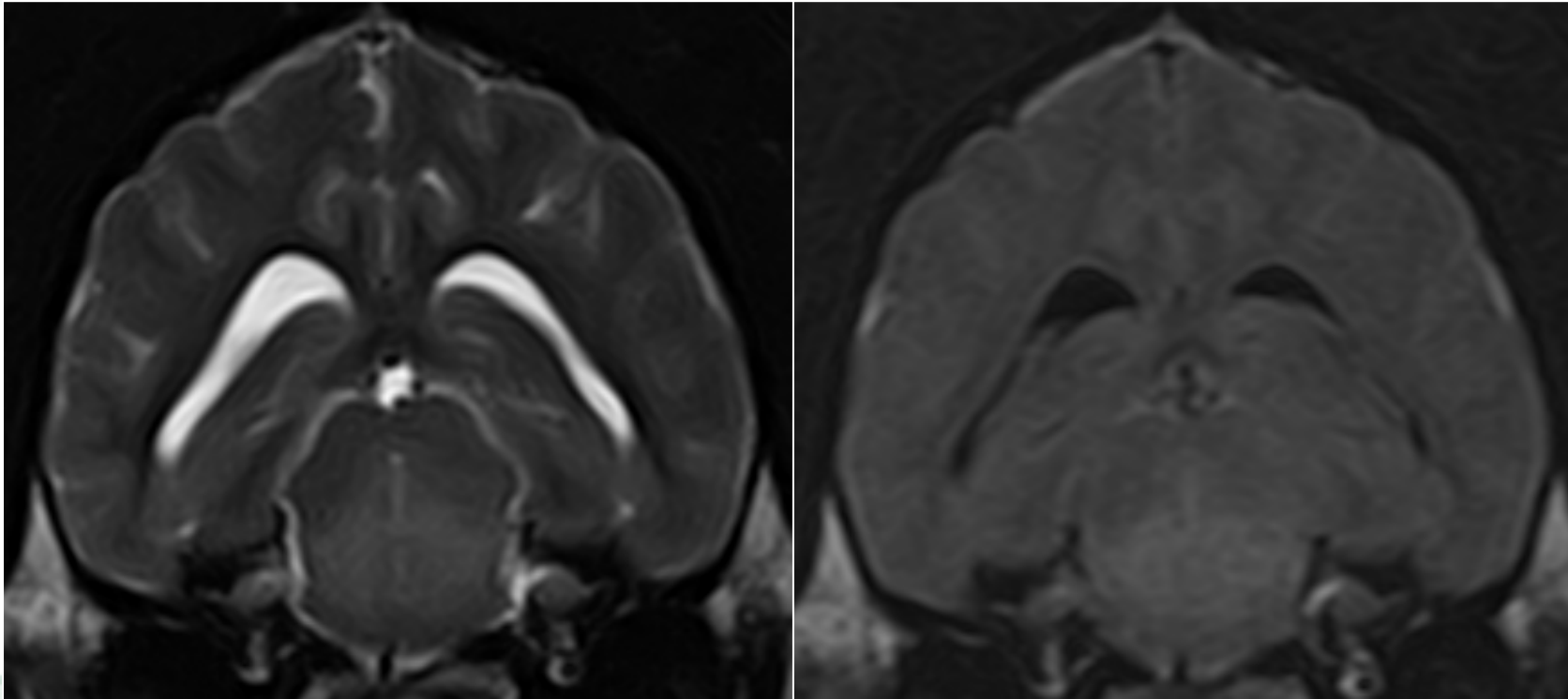
- George – 3 yo M Goldendoodle
- Acute onset, rapid progression
  - Circling, behavioral changes
  - Ataxia, facial asymmetry
- Neurologic examination

**MULTIFOCAL**



# GME Imaging

- Less cavitation
- Mass effect
- Focal, ocular
- Brainstem

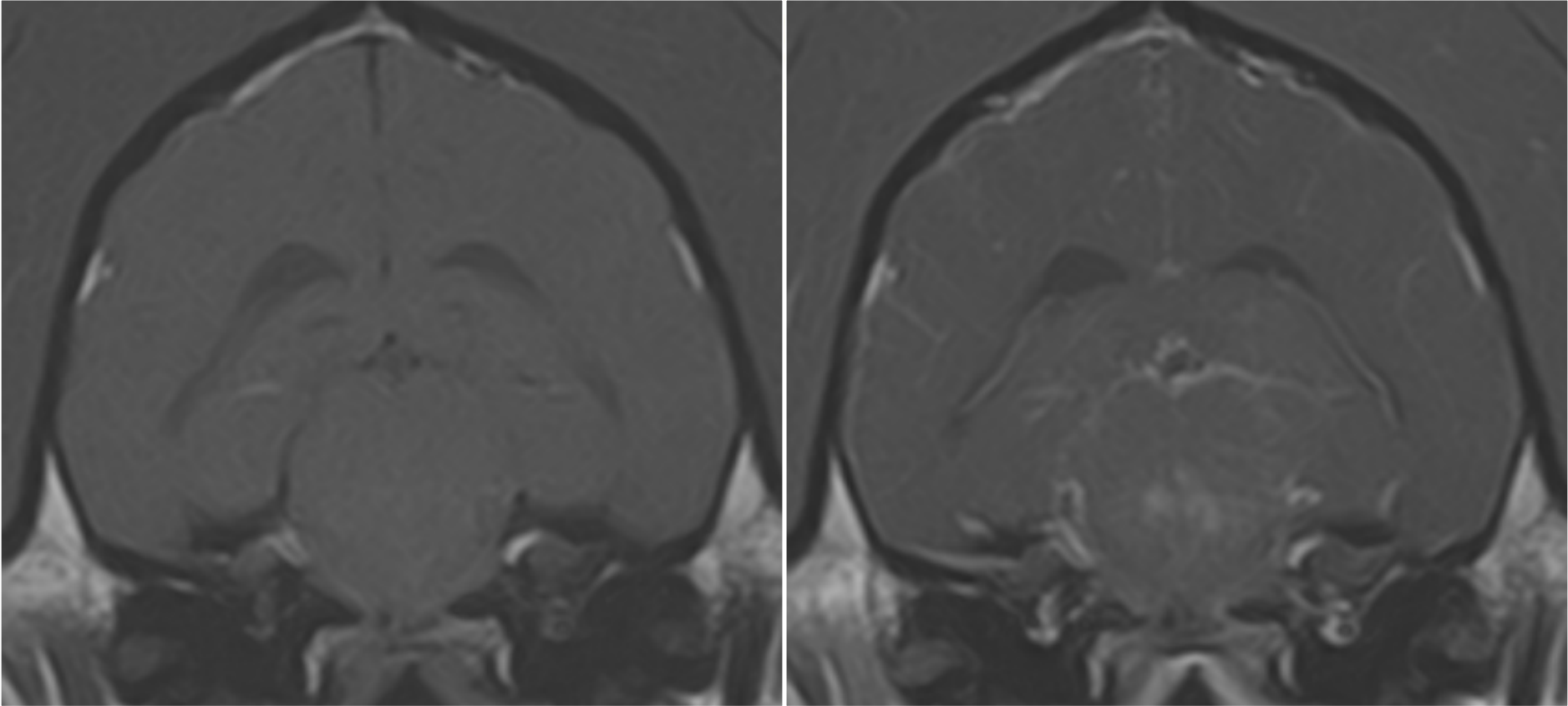


Granger et al. 2010, The Veterinary Journal



# GME Imaging

- Meningeal contrast lacking ??



Talarico & Schatzberg 2010, J Sm Anim Prac

# Magnetic Resonance Imaging

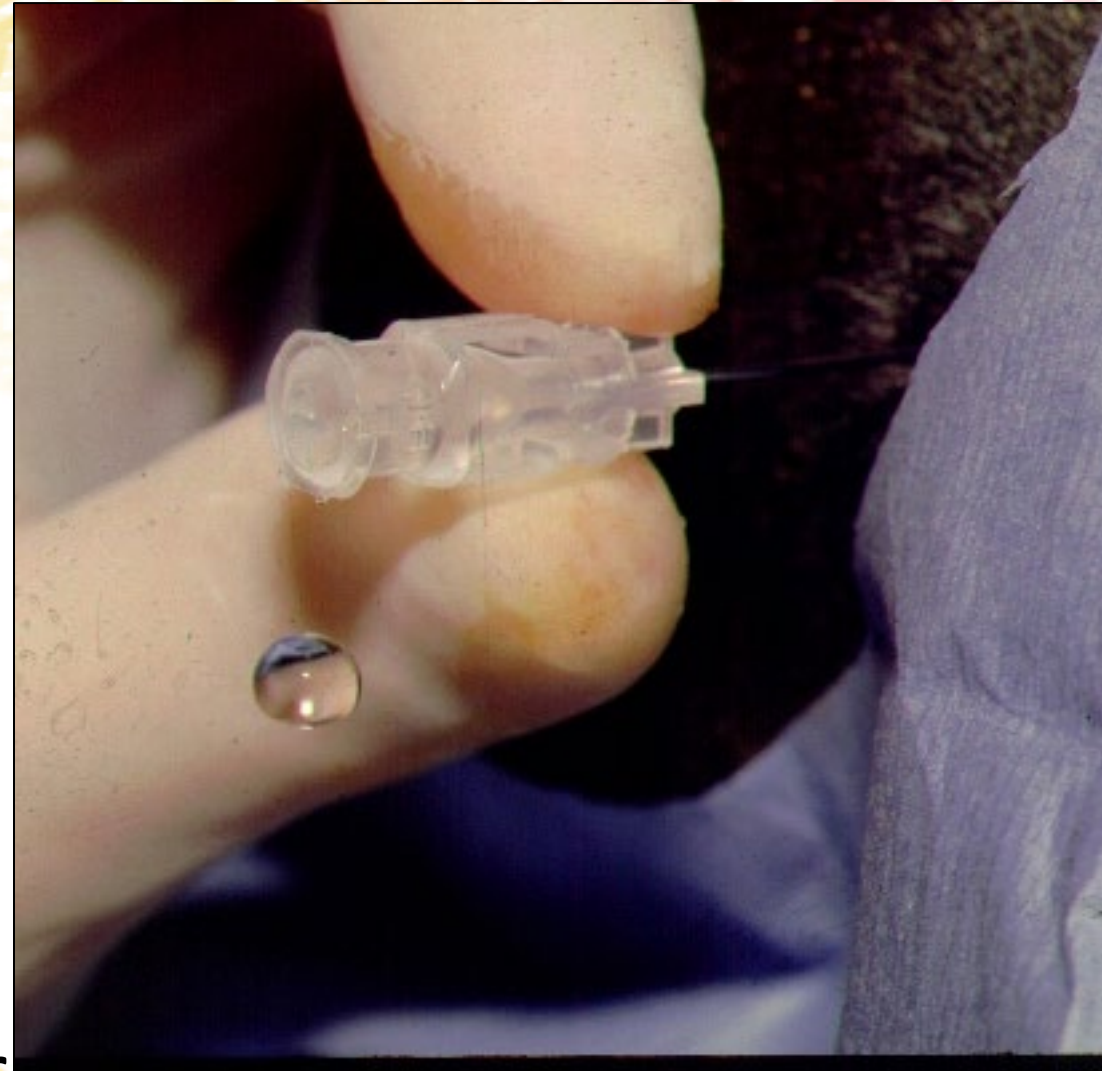
- Bohn et al. 2006, Vet Clin Pathol – 256 dogs total
  - 52 cases presumed inflammatory disease
    - **33%** (17/52) had normal MR images
  - 9 cases definitive
    - **30%** (3/9) had normal MR images
- Lamb et al. 2005, VRUS– 25 dogs with inflammatory CSF
  - **24%** of cases had normal MR imaging

OMG!

A normal MRI  
does NOT rule out  
MUO!

# CSF Analysis

- Cell Counts (reference ranges)
  - TNCC < 4-5 cells/ $\mu$ L  
(Total nucleated cell count)
  - RBC – 0 cells/ $\mu$ L
- Protein quantification
  - < 25-30 mg/dL (normal)
- Cytology
  - Differential Cell Count
  - Predominantly mononuclear



Courtesy Dr. Joan Coates

# MUO - CSF Characteristics



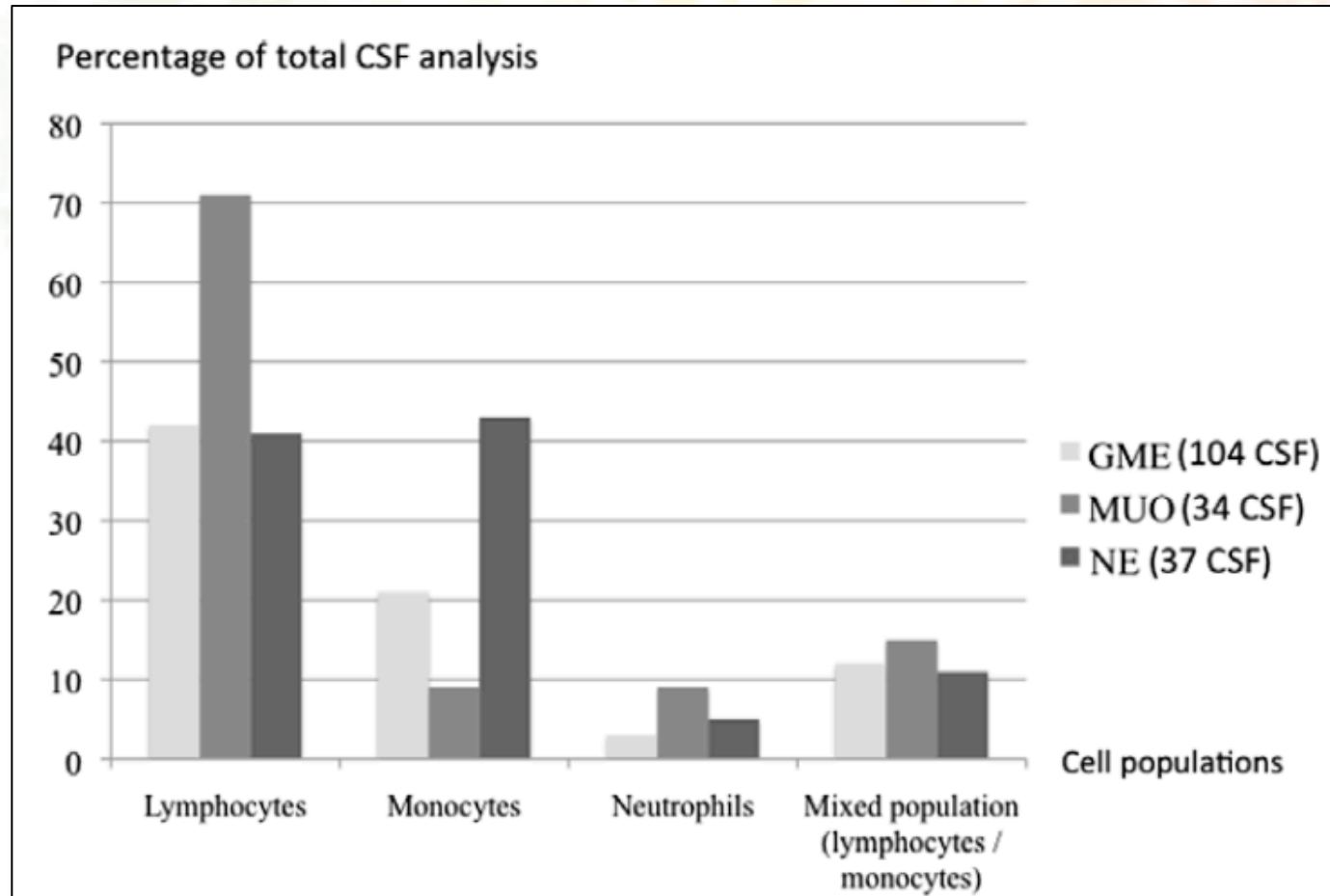
- Elevated TNCC
- Elevated protein
  - Breakdown BBB
  - IgG production intrathecally

George – 3yo M Goldendoodle		
RBC	208 cells/uL	↑
TNCC	56 cells/uL	↑
Protein	36 mg/dL	↑
Cytology	Mononuclear pleocytosis (lymphoid)	

- Cytology
  - Mononuclear pleocytosis
    - Predominantly lymphocytic, may be mixed

Talarico & Schatzberg 2010, J Sm Anim Prac

# CSF cytology – 175 cases



**Fig. 4.** Graphic representation of the predominant cell type in 104, 34 and 37 CSF analyses of GME, MUO and NE cases, respectively.

# CSF cell counts – 222 cases

Distribution of CSF cell counts in GME, MUO and NE cases.

Group	Total number of CSF reported	Number of CSF with a normal cell count (0–5 cells/ $\mu$ L)	CSF cell count range (cells/ $\mu$ L)
GME	145	23 (16%)	0–11840
NE	32	4 (12.5%)	0–630
MUO	45	10 (22%)	0–6860

CSF, cerebrospinal fluid; GME, granulomatous meningoencephalomyelitis; NE, necrotising encephalitis; MUO, meningoencephalomyelitis of unknown origin.

- Albuminocytologic dissociation → 7 with normal TNCC
- Median Protein Concentrations

GME → 70mg/dL    NE → 68mg/dL    MUO → 54mg/dL

# CSF Analysis

- Bohn et al. 2006, Vet Clin Pathol – 256 dogs total
  - 52 cases presumed inflammatory disease
    - **10%** (5/52) had normal CSF analysis

OMG! A normal CSF  
does NOT rule out MUO!

(either)



# Infectious Disease Testing

- **Rule out** infectious disease
  - Geographic location & disease prevalence
  - Travel history
- Antibody titers vs. Antigen tests
  - Serum – protozoal, rickettsial, fungal diseases
  - CSF – viral diseases
  - Urine – fungal diseases



“George” tested negative for:

cryptococcus, toxoplasma, and neospora



**MUO**

# Histopathology

- Needed to obtain a definitive diagnosis

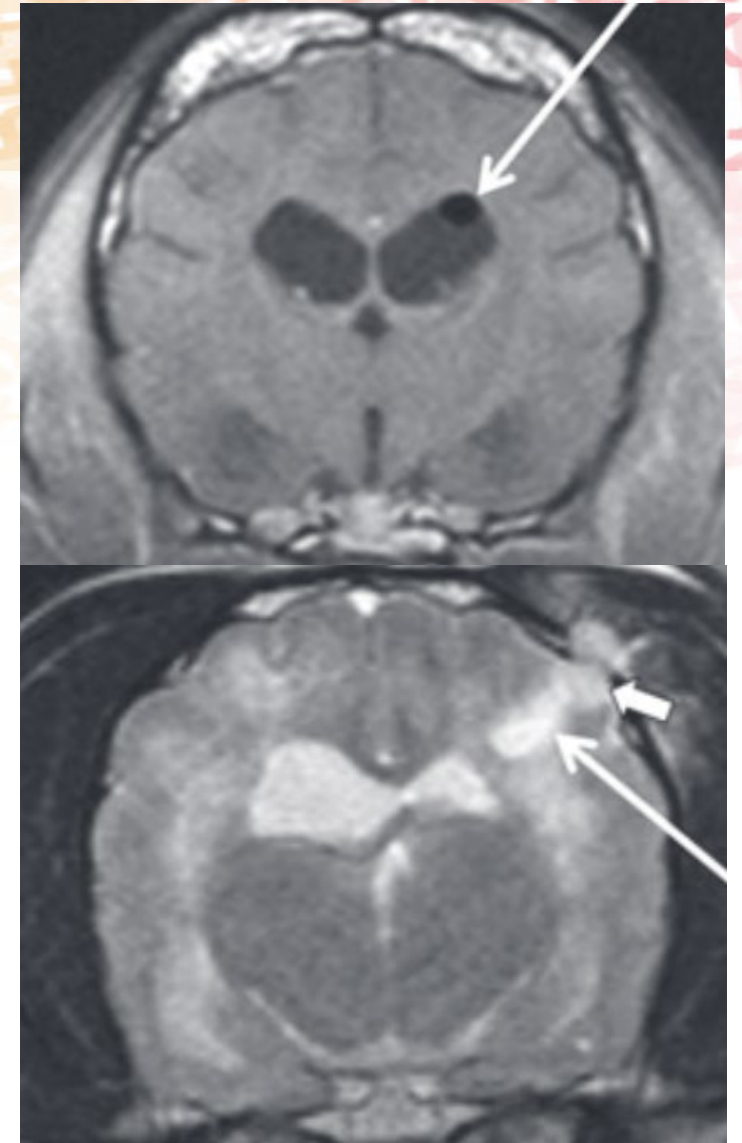
Brain biopsy

VS.

Post-mortem exam

# Brain Biopsy

- Free-Hand biopsy
- 17 dogs - suspected encephalitis
- Diagnostic yield - 82%
  - Additional 12% nonspecific encephalitis
- Adverse effects - 29%
  - Death - 6%
  - Seizures
  - Neurologic deterioration

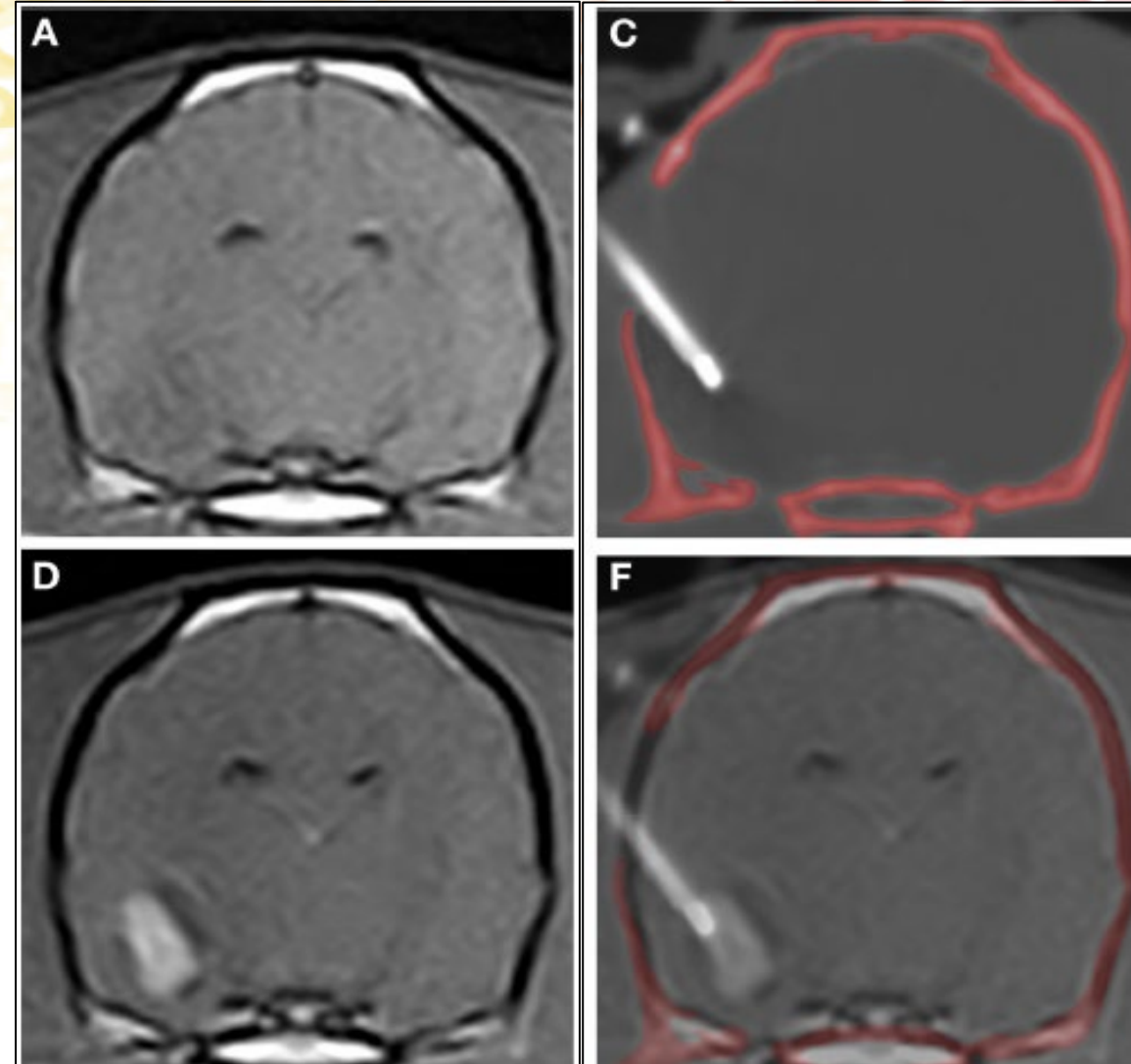


Flegel et al. 2012, JVIM

# Frame-based stereotactic biopsy of canine brain masses: technique and clinical results in 26 cases

*John Henry Rossmeisl<sup>1,2,3\*</sup>, Rudy T. Andriani<sup>1,2</sup>, Thomas E. Cecere<sup>4</sup>, Kevin Lahmers<sup>4</sup>, Tanya LeRoith<sup>4</sup>, Kurt L. Zimmerman<sup>4</sup>, Denise Gibo<sup>3</sup> and Waldemar Debinski<sup>3</sup>*

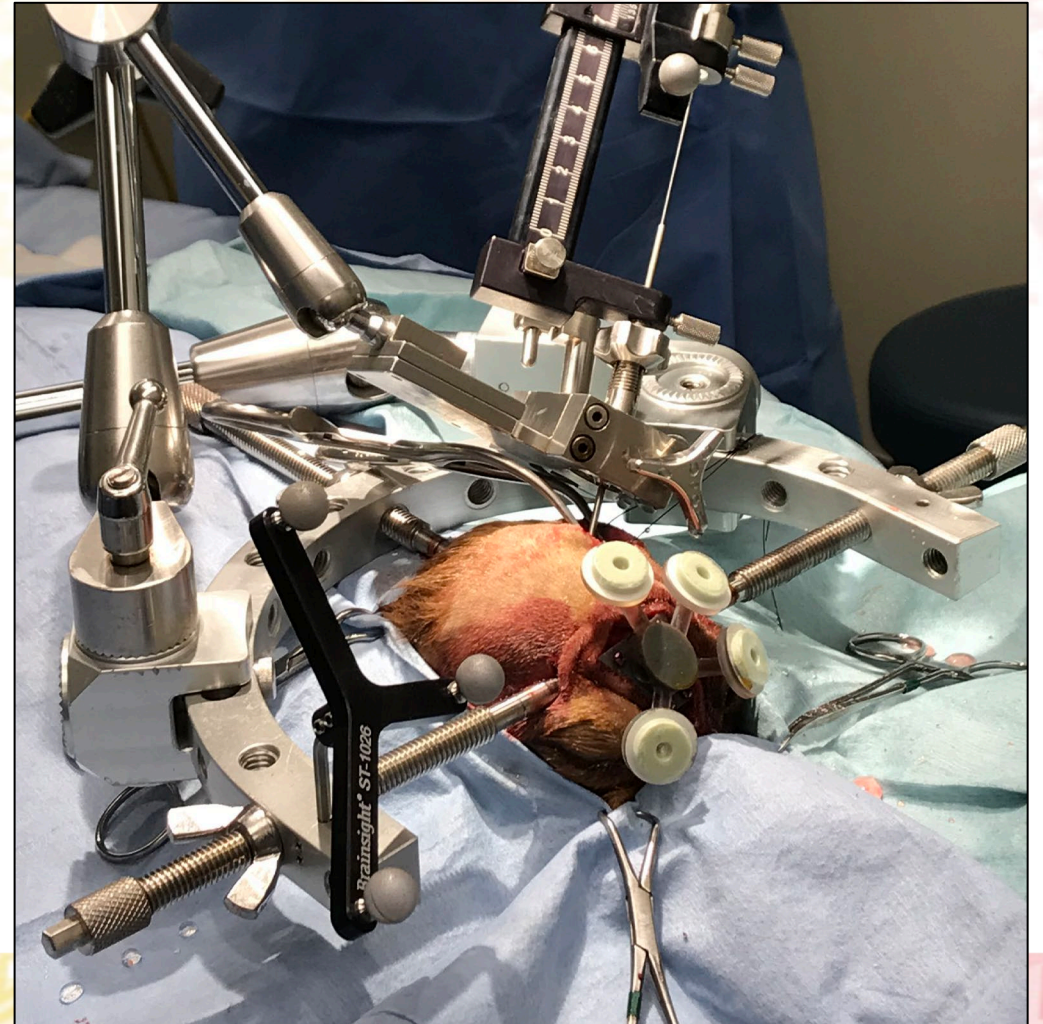
- Diagnostic yield - 94.6%
- **Adverse effects - 27%**
  - Death - 5.2% (1/26)
  - Hemorrhage
  - Ventricular penetration
  - Seizures
- Transient deterioration



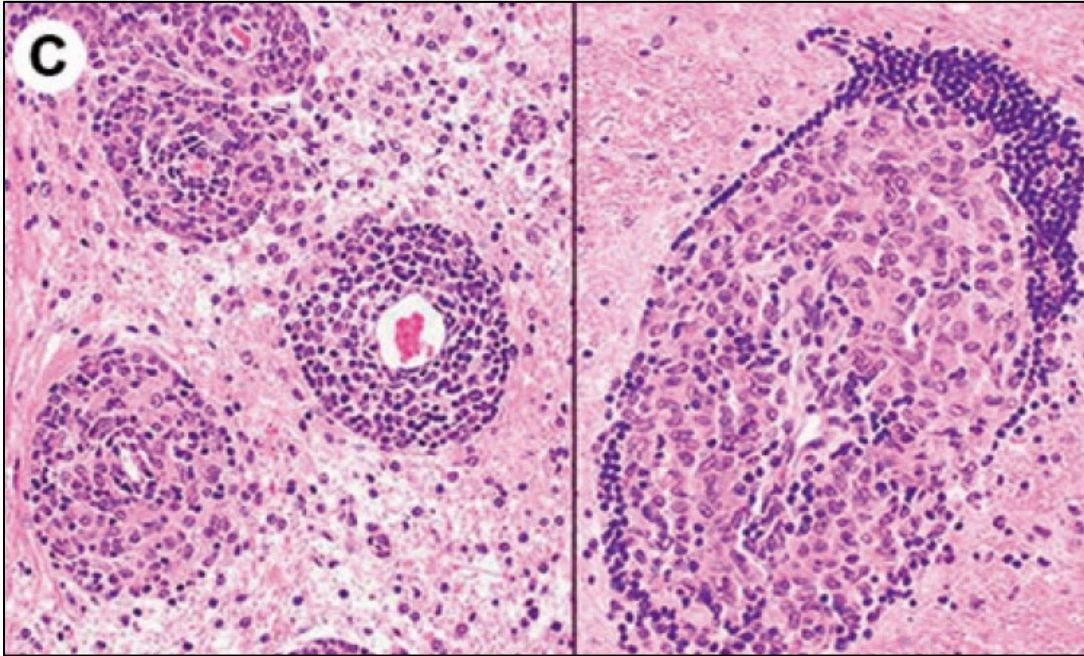
Rossmeisl et al. 2015, Frontiers Vet Science

# Stereotactic neuronavigation

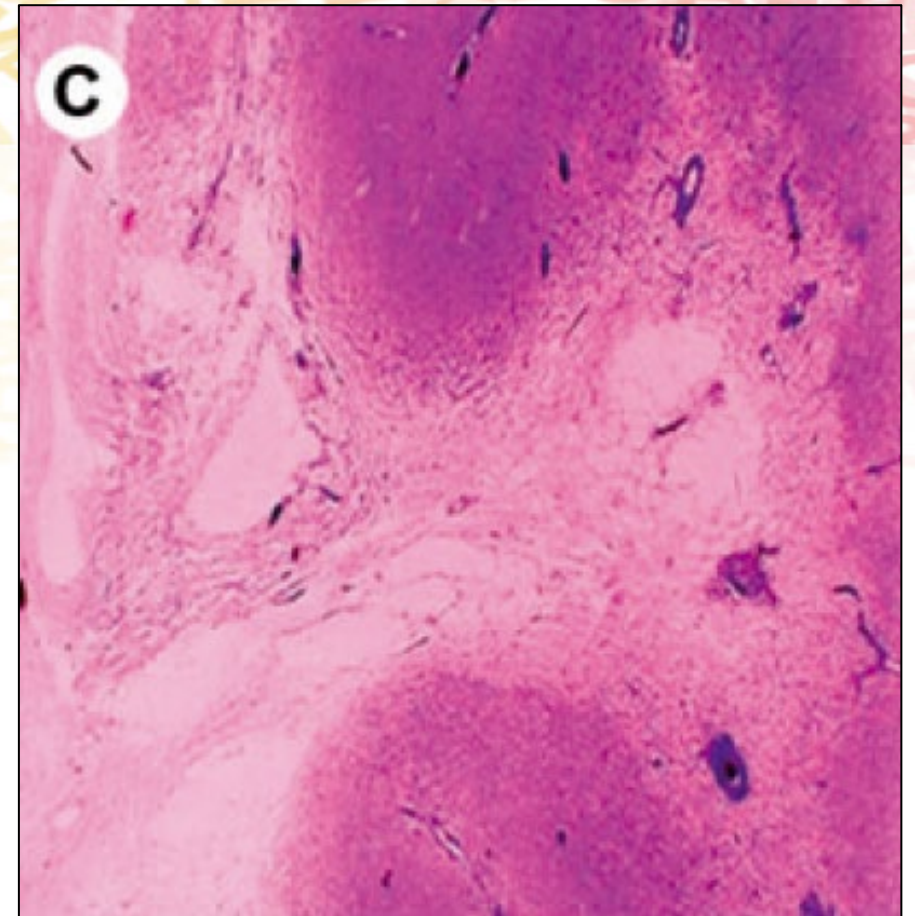
- Limitations
  - Cumbersome
  - Expensive equipment
  - User expertise
  - Fiducial markers
    - Natural or artificial
  - Linking of anatomic space & image space



# Histopathology



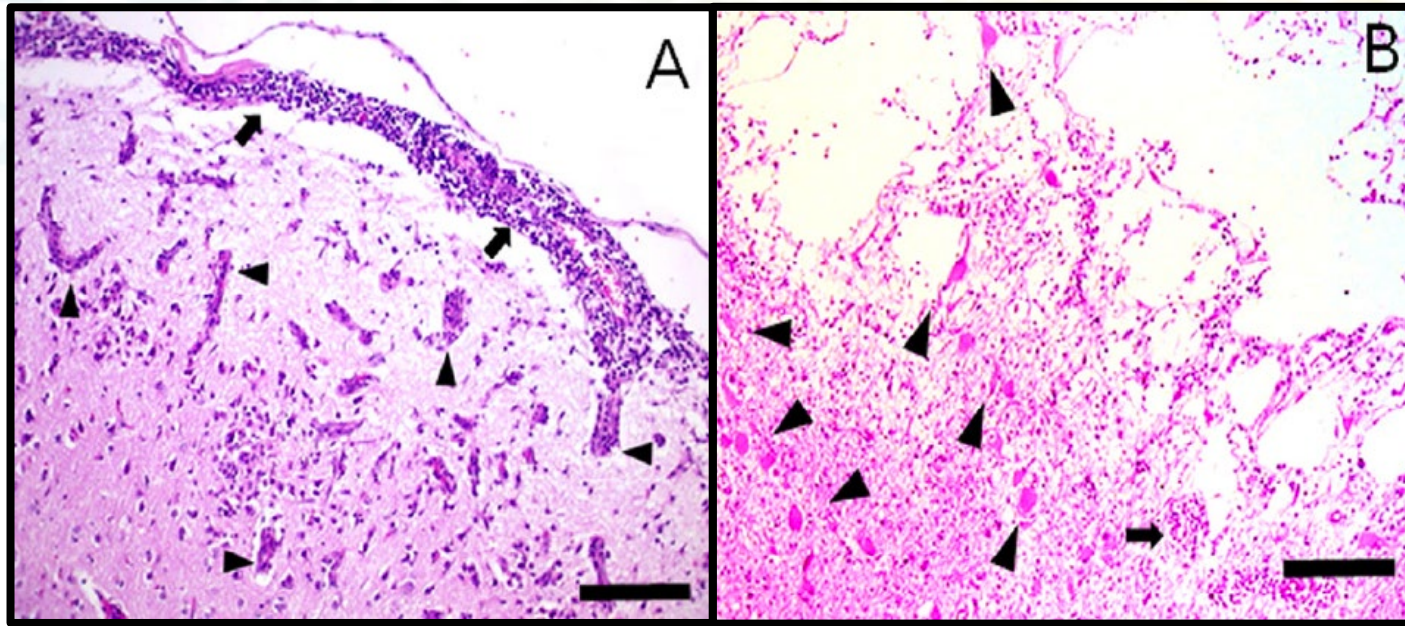
**GME**



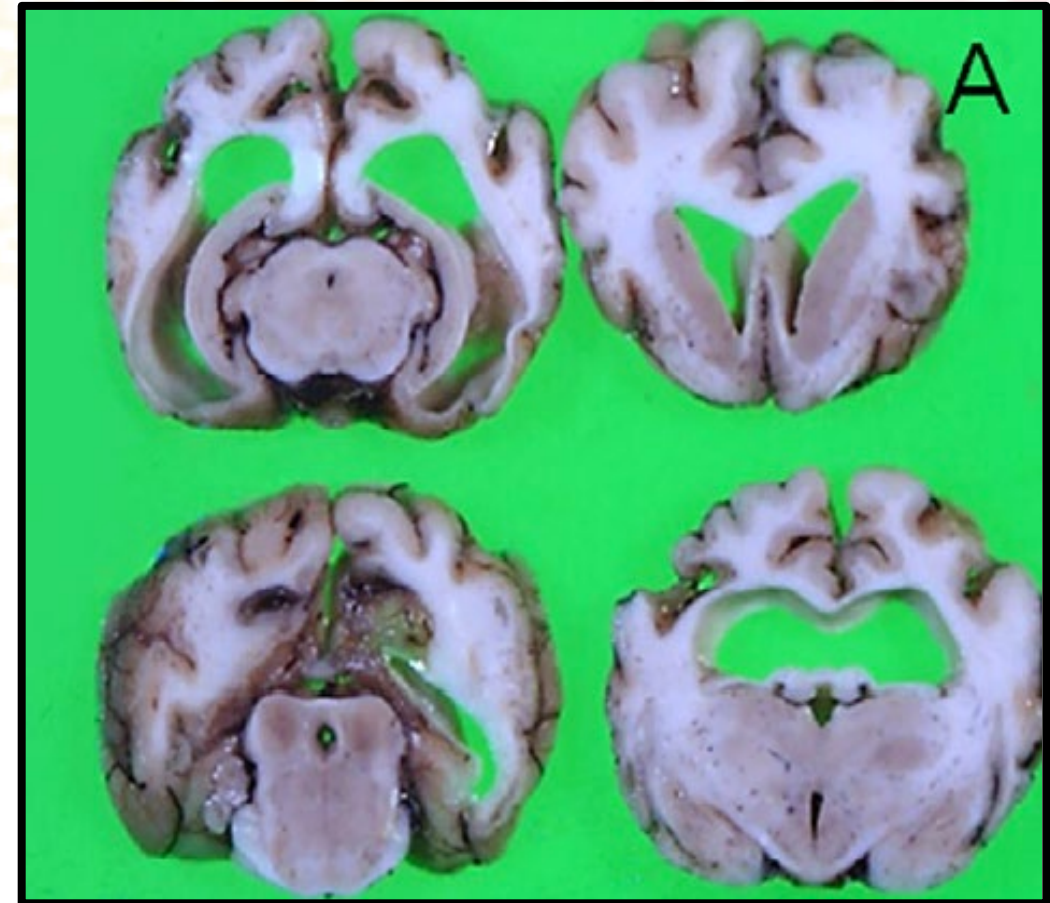
**NLE**

Talarico & Schatzberg 2010, J Sm Anim Prac

# Histopathology



NME



Uchida et al. 2016, The Veterinary Journal





SAVE  
ME

# Treatment of MUO

Immunosuppression

# Treatment - Immunosuppression

- Corticosteroids
- Cytosine Arabinoside (Cytosar)

+/- adjunct meds if needed



# Prednisone

- Immunosuppressive dose
- Initial dose → 2-3mg/kg/day
- SLOW Taper every 4-6 weeks as clinical signs & follow up tests dictate
- Monotherapy **NOT** recommended
  - May only partially or transiently resolve signs



# Cytosine Arabinoside

- Chemotherapeutic agent (cytosar)
- Synthetic nucleoside analogue
  - Cross BBB → Incorporate into nucleic acids
- 200mg/m<sup>2</sup> CRI over 8h \*\*\*
- Administered every 28 days for 3mo
  - SLOWLY increase interval
  - CBC before administration

**CAUTION**  
**Chemotherapy**  
**Waste**



**BIOHAZARD**

**Dispose of Properly**  
**Handle with Care**

# Cytosar – SQ vs. CRI

- Pharmacokinetics
- Crossover study
  - 6 healthy dogs

CRI → achieved steady state

SQ → did not achieve steady state when given Q12h, eliminated quickly

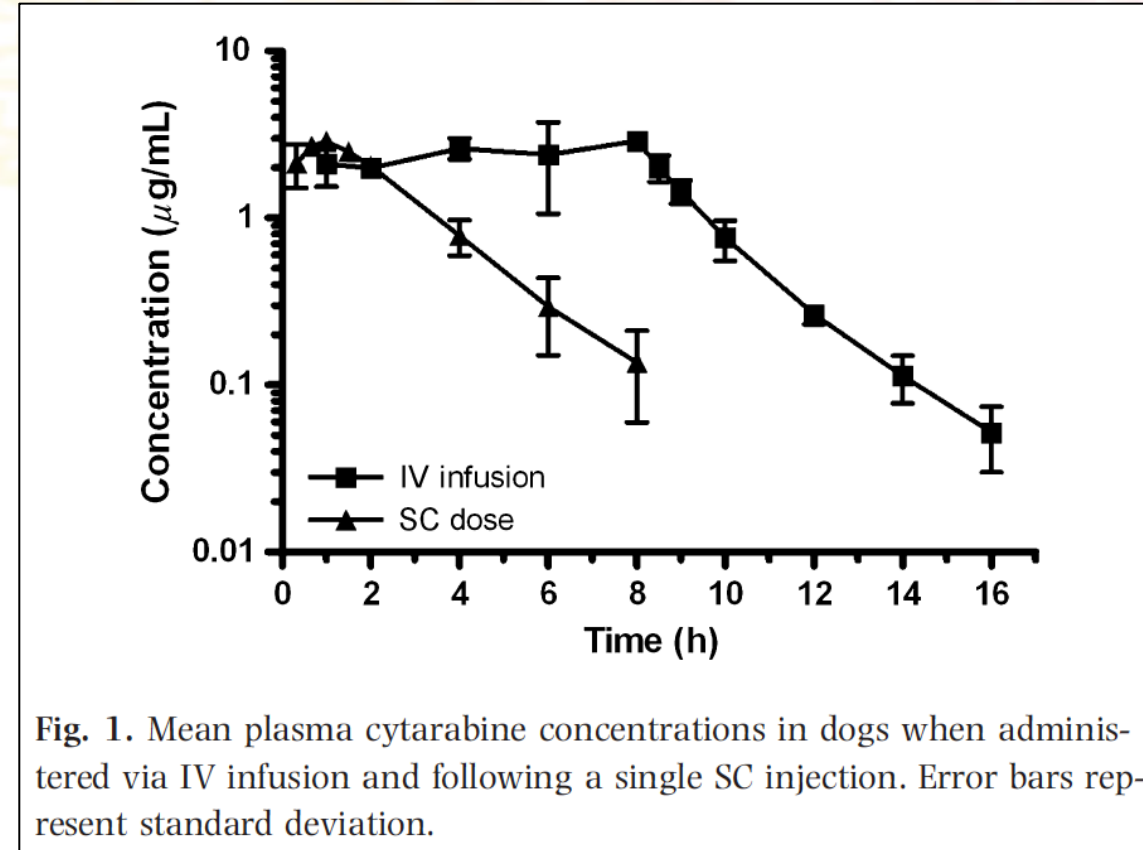


Fig. 1. Mean plasma cytarabine concentrations in dogs when administered via IV infusion and following a single SC injection. Error bars represent standard deviation.

Crook et al. 2012, J Vet Pharmacol Therap

# Cytosar – SQ vs. CRI

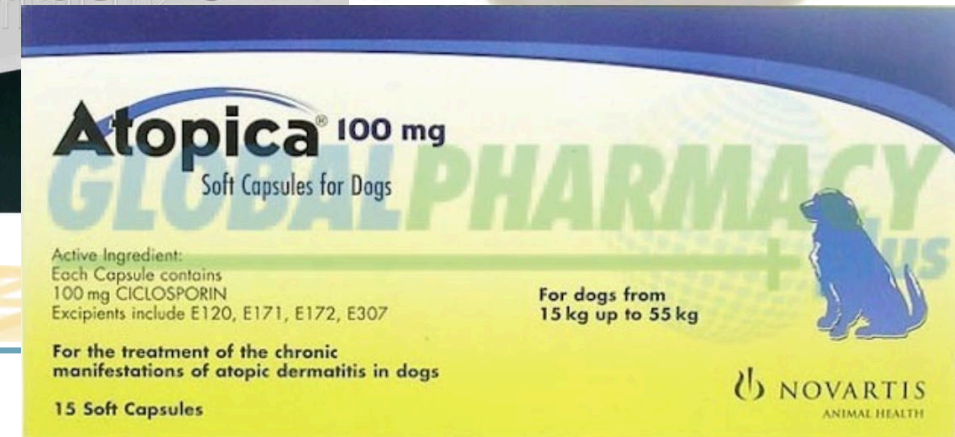
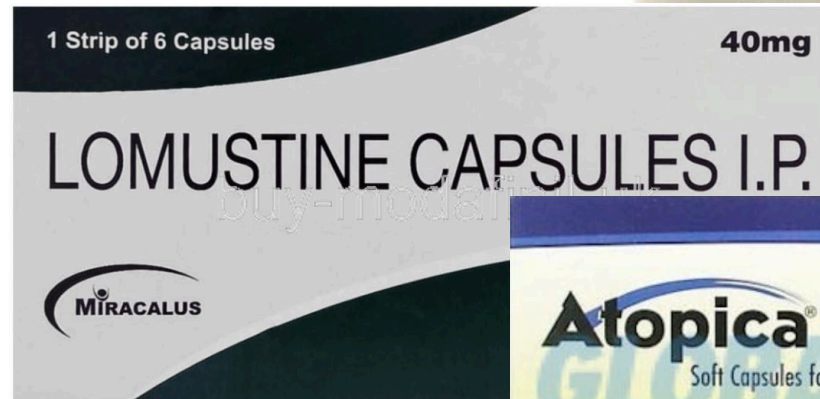
- Clinical efficacy
- Prospective study (2006-2015)

Treatment	Cases	Survival 3m	Survival 12m	Recheck MRI	Recheck CSF
50mg/m <sup>2</sup> SQ Q12h x 4 doses	39	44%	100% (44%)	41% normal	58.8% normal
100mg/m <sup>2</sup> CRI over 24h	41	90%	100% (90%)	92% normal	97.3% normal

Lowrie et al. 2016, The Veterinary Journal

# Additional Treatment Options

- Cyclosporine
- Azathioprine
- Mycophenolate mofetil
- Leflunomide
- Lomustine
- Procarbazine
- Radiation





# Prognosis

“Rule of thirds”

# MUO - Prognosis

- Retrospective study (2006-2015) – 116 dogs
  - 26% survive < 7 days
    - Decreased mentation
    - Seizures
    - Increased percentage of neutrophils on CSF

Cornelis et al. 2016, The Veterinary Journal

# MUO - Prognosis

- VARIABLE PROGNOSIS
- Prospective study – 39 dogs
  - Median survival time 26 days
  - 33% died within 72 hours
  - 56% of patients died (all within 52 days of diagnosis)
  - 31% good to excellent outcome
  - Risk factors for mortality → herniation, loss of sulci
  - Risk factor for relapse → abnormal CSF @ 3 mo recheck

Lowrie et al. 2013, Veterinary Record

# MUO - Prognosis

**1/3 - 1/3 - 1/3**

# MUO - Prognosis

- Postencephalitic seizures → recurrent unprovoked seizures
  - Occur > 1 week after diagnosis, not with relapse
- Retrospective study – 61 dogs
  - 14 dogs (23%) developed postencephalitic seizures
    - 21% were drug-resistant
    - Shorter overall survival time (median 16 months)
  - More likely to occur in younger dogs, seizures at onset, hippocampal lesions

Kaczmarska et al. 2020, JVIM

# Roles of the General Practitioner

1. Identify suspect cases
2. Recommend referral & establish client expectations
3. Provide ancillary care during treatment

# Identify Suspect Cases

- Signalment
- History
- Neurologic examination → multifocal disease

# Establish Client Expectations

- Recommended diagnostic approach
  - Estimate
- Likely treatment course
  - Immunosuppression, multimodal drug therapy, expense
- Long-term treatment & follow up
  - Follow up with neurologist → typically ~ monthly
  - Risk of relapsing disease
  - Risk of postencephalitic epilepsy



# Providing ancillary care

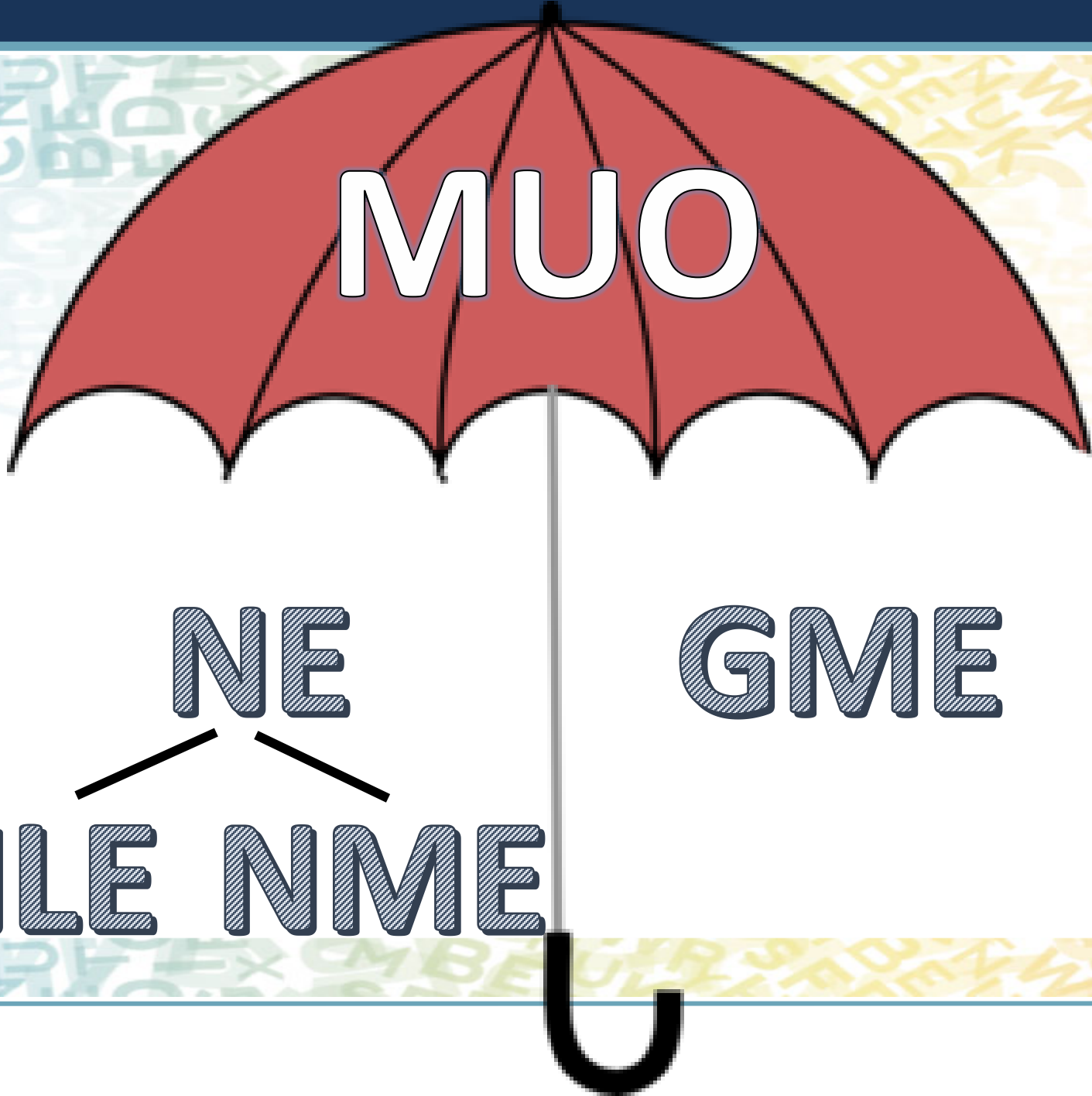
- Risks of immunosuppression
  - Urinary tract infections
  - Skin infections
  - Husbandry recommendations

# To vaccinate or not to vaccinate?!

- Very controversial
- Nobody REALLY knows!
  
- Weigh pros & cons
- Discuss with neurologist if concerned

# TAKE HOME POINTS

- Don't get lost in the alphabet soup!
- Classic signalment, clinical signs, neurolocalization
- Rule out infection
- Histopathology for definitive diagnosis
- Treatment & prognosis
- Important roles of the general practitioner in case management



**MUO**

**NE**

**GME**

**NLE NME**

**Corticosteroid responsive  
tremor syndrome**

**SRMA**

**Eosinophilic  
meningoencephalitis**

**Infectious  
meningoencephalitis**



# References

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