Meningoencephalitis of Unknown Etiology in Dogs

Jocelyn Garber, DVM
Definitions

- **Meningitis**: Inflammation of the meninges
- **Encephalitis**: Inflammation of the brain
- **Myelitis**: Inflammation of the spinal cord
**Definitions**

- **MUO**: A non-infectious etiology is suspected but definitive histopathological diagnosis is lacking.

- **GME** (Granulomatous meningoencephalomyelitis): Perivascular accumulations of mononuclear cells in the central nervous system (predominantly white matter).

- **NME** (Necrotizing meningoencephalomyelitis): Prominent necrosis and infiltration of inflammatory cells including lymphocytes, plasma cells and monocytes.

- **NLE**: Lesions are predominant in the white matter.
Reticulosis

- Term used in the 1950’s-1980’s in human medicine
- Reclassified as CNS B cell lymphoma
- Different histopathology in dogs, but termed used though early 1970’s

- 3 Categories
  - Inflammatory
  - Neoplastic
  - Microgliomatosis

- In 1978 Braund et al. reclassified inflammatory reticulosis as GME

Signalment

- Small breed dogs, although can be large breed
  - NME: Pugs, Maltese, Yorkie
- GME: 4-8 years old, NE: <4 years old
- Females > Males
Clinical Signs

Variable depending on the lesions localization:

- Seizures
- Visual Deficits
- Head tilt
- Circling
- Tremors
- Spinal Pain
- Paresis/paralysis
- Cranial Nerve deficiency
- Vestibular signs
- Pain
- Lethargy
- Acute to sub acute to chronic

Sumners et al. Veterinary Neuropathology 1995
3 Forms:

- **Disseminated**
  - Most common
  - Multifocal disease

- **Focal**
  - Single space occupying mass lesion
  - Most likely to confuse with neoplasia

- **Ocular**
  - Visual impairment
  - May progress to disseminated
Diagnostics

#1: Rule out systemic disease
- CBC, Biochemistry, UA +/- Radiographs/Ultrasound
- Common DDX: PSS, SARDS, Toxicity

#2: Characterize the CNS disease
- Advanced Imaging
- CSF Analysis
- Biopsy?!
Differentials for Inflammatory CNS disease

- **Infectious**
  - Viral
  - Protozoal
  - Fungal
  - Parasitic
  - Bacterial

- **Non Infectious**
  - Eosinophilic meningitis
  - SRMA
  - Neoplasia
  - GME, NME, NLE
Steroid Responsive Meningitis-Arteritis

- Beagles, Boxers, Bernese mountain dogs, Weimeraners, Nova Scotia DTR
- 6-18 months old
- CS: Cervical hyperesthesia, pyrexia, depression
- Acute and Chronic forms
- Prognosis: Good
Idiopathic Eosinophilic Meningitis

- Uncommon finding
- Young large breed dogs
- Variable imaging findings
- Prognosis variable
- Infectious etiologies are not commonly identified
- IVDD

Windsor et al. CSF eosinophilia in dogs. JVIM 2009

Raskins canine and feline cytology
Characteristics of MR Images of GME in 11 dogs

Cherubini et al. Vet Record 2007

- Focal lesion in 4 dogs
- Multiple lesions in 6 dogs
- No lesion in 1 dog (per acute onset)
- No meningeal enhancement, but 9/11 had histologic lesions of meninges
- Hyperintensity in T2 weighted and FLAIR sequences in all lesions
- Variable signal intensity on T1
- Variable contrast enhancement
- Irregular margins

A normal MRI does NOT rule out GME
CT Assessment in Canine Meningoencephalomyelitis


- Relatively hyperdense single or multiple focal lesions before contrast
- Impregnating single or multiple focal lesions after contrast
- 100% sensitivity, 71% specificity and 83% accuracy

“CT scan can be considered a valid diagnostic aid in dogs' MEM, when it is impossible to access MRI”
Magnetic Resonance Imaging for the Differentiation of Neoplastic, Inflammatory and Cerebrovascular Brain Disease in Dogs
Wolff et al. JVIM 2012;26:589-597

<table>
<thead>
<tr>
<th>Inflammatory Lesion</th>
<th>Without Clinical Data</th>
<th>With Clinical Data</th>
<th>#dogs</th>
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<tr>
<td>Sensitivity</td>
<td>86.0 %</td>
<td>80.7 %</td>
<td>19</td>
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<tr>
<td>Specificity</td>
<td>93.1 %</td>
<td>95.4 %</td>
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<table>
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<th>GME</th>
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<th>#dogs</th>
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<tr>
<td>Sensitivity</td>
<td>50.0 %</td>
<td>50.0 %</td>
<td>8</td>
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<tr>
<td>Specificity</td>
<td>87.9 %</td>
<td>84.8 %</td>
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<th>#dogs</th>
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<tr>
<td>Sensitivity</td>
<td>53.3 %</td>
<td>66.7 %</td>
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<tr>
<td>Specificity</td>
<td>92.9 %</td>
<td>92.9 %</td>
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CSF Analysis

- Not always attainable
  - Unsafe based on cerebellar herniation
  - Unable to get adequate sample
- Increased cellularity/protein
- Mononuclear Pleocytosis
  - Lymphocytes
  - Monocytes
  - Plasma cells
  - Neutrophils (<20%)
CSF Analysis

- Range 0 to 11,840 cells/µL (normal <5 cells/µL)
- 10-16% of GME dogs had counts WNL (more likely to be focal lesions)
  - 22% of MUO dogs, 12.5% of NME dogs
- 50-70% have mostly lymphocytic inflammation
- ~10% of dogs had neutrophilic inflammation
- Protein range 9-1,848 mg/dL (normal <20)


Should We Biopsy?

- 17 dogs with suspected encephalitis
- 82% attained a diagnosis of a specific type of encephalitis
- An additional 12% had evidence of encephalitis
- Morbidity 29%, indirect case fatality 6%
- Only for a lesion in the forebrain
- 33% had a sampling error and had to be re-sampled
- 3/17 dogs also had necropsy, diagnosis was confirmed in 2/3 (one diagnosed with GME on biopsy had NME)

Diagnostic Yield and Adverse Effects of MRI-Guided Free-Hand Brain Biopsies through a Mini-Burr Hole in Dogs with Encephalitis

Flegel T et al. JVIM 2012;26:969-976
Histopathology

- Angiocentric inflammatory reaction, especially white matter
- Leptomeningeal involvement is common
- Perivascular cuffing involving macrophages, lymphocytes, giant cells, and plasma cells
- Focal, disseminated and ocular distribution
Left parietal lobe. The cerebral cortex has multifocal to coalescing areas of malacia and cavitation with infiltration by large numbers of inflammatory cells. Perivascular cuffing and meningitis are also prominent. The white matter is vacuolated but relatively spared of inflammation. Courtesy of R. Blair
Left parietal lobe. Inflammatory infiltrate is composed predominately of macrophages (circles), with large numbers of lymphocytes (arrowheads/triangles), and occasionally neutrophils (arrows). H&E, 40x objective. Courtesy of R. Blair.
Treatment

- IMMUNOSUPPRESSION and IMMUNOMODULATION
  - Corticosteroids
  - Cyclosporine
  - Leflunomide
  - Cytarabine Arabinoside
  - Procarbazine
  - Lomustine
Corticosteroids

- No prospective study with steroid monotherapy
- Dose range 2 mg/kg BID to 0.25 mg/kg SID

<table>
<thead>
<tr>
<th>Number of Dogs</th>
<th>Median Survival</th>
<th>Survival Range</th>
<th>Reference</th>
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<td>26</td>
<td>36</td>
<td>2-1200</td>
<td>Pooled review</td>
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<tr>
<td>7</td>
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<td>3-63</td>
<td>Parkodzy et al</td>
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<tr>
<td>10</td>
<td>357</td>
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<td>Flegel et al.</td>
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Cyclosporine

- 3 dogs had Cyclosporine adjusted based on blood level and CSF taps (no Cyclosporine was found in CSF)
- 3 dogs placed on Cyclosporine after prednisone side effects or relapse
- Some dogs on ketoconazole, some with prednisone
- Compared dogs with prednisone alone (median 28 days)

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<th>Reference</th>
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<tr>
<td></td>
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<td>Minimum</td>
<td>Maximum</td>
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<tr>
<td>6</td>
<td>240</td>
<td>30</td>
<td>365</td>
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<tr>
<td>10</td>
<td>930</td>
<td>60</td>
<td>1290</td>
</tr>
<tr>
<td>7</td>
<td>423</td>
<td>6</td>
<td>840</td>
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-Parkozdy et al. Survival in dogs with GME with ciclosporin. Veterinary Record 2009
-Adamo & O’Brien. Use of ciclosporine to treat GME in 3 dogs. JAVMA 2004
Procarbazine

MOA: Monoamine oxidase inhibitor, lipid soluble, crosses the BBB, alters DNA, RNA and protein synthesis

25-50 mg/m2

Procarbazine significantly improved survival

SE: myelosuppression, GI upset

Median survival for Prednisone + Procarbazine was 14 months

Mentation change and seizures were associated with a shorter survival

Coates et al. JVIM 2007;21:100-106
Azathioprine

Evaluation of treatment with a combination of azathioprine and prednisone in dogs with meningoencephalomyelitis of undetermined etiology: 40 cases (2000-2007)

- Purine analogue that inhibits DNA synthesis and mitosis
- 2 mg/kg q24 h for 14 days, then q48h
- Median survival 1,843 days (range 50-2,496)
- Significant difference in response with dogs that had a complete response (1,916 days) vs incomplete remission (678 days) and dogs that did not relapse (1,961 days) vs had a relapse (472 days)
Cytosine Arabinoside

- **Synthetic nucleoside analogue**
- **Crosses the BBB**
- **Competitively inhibits DNA polymerase in mitotically active cells**
- **Causes topoisomerase dysfunction and prevents DNA repair**
- **Time dependent drug, ideally given as a CRI**
Cytosine Arabinoside

- Median survival 531 days (46-1025)
- 50 mg/m2 q 3 weeks for 4 months then q4 wks x 4 months etc...

Treatment of 11 dogs with meningencephalomyelitis of unknown origin with a combination of prednisolone and cytosine arabinoside
Menaut et al. Vet Record Feb 2008

- Survival range: 78 – 603 days
- Probability of survival at 2 years = 58.4%

Combined cytosinide arabinoside and prednsione therapy for meningencephalitis of unknown etiology in 10 dogs
Zarfriss M et al. J SAP 2006. 47, 588-595
Other options

- Leflunomide
- Lomustine
- Mycophenolate
- Radiation therapy

In dogs with seizures associated with GME, an anticonvulsant is often used.
Mycophenolate Mofetil

- **MOA:** Inhibits IMPDH which is critical in the de novo synthesis of purines
- **Most common side effects:** Diarrhea, weight loss
- **Concurrent use with Azathioprine is not recommended due to similar MOA**
- **Drug interactions:** PPI, fluoroquinolones/metronidazole, cyclosporine, glucocorticoids
- **Dose:** 10 mg/kg BID
What is Leflunomide?

- **MOA:** Selective pyrimidine synthesis inhibitor, possible inhibitor of tyrosine kinase inhibitor
- **Most common side effects:** Bone marrow suppression, GI upset, lethargy
- **Dose:** < 4 mg/kg SID
Leviteracetam (Keppra)

- **MOA:** Modulates the release of neurotransmitters by selective binding to the presynaptic SVA2
- **Oral bioavailability is 100%. Peak concentration in dogs is 2 hrs/cats 1.7 hrs. Half life in dogs 3-6 hrs/cats 3 hrs.**
- **Urinary excretion**
- **DOSE:** 20 mg/kg PO q 8 hrs, extended release q 12
- **SIDE EFFECTS:** Sedation, ataxia
Levetiracetam Rectal Administration in Healthy Dogs. RK Peters et al. JVIM 2014;28:504-509

- Rectal absorption obtained drug levels within 10 minutes of administration.
- Feces decreased absorption
- 40 mg/kg

Double-Masked, Placebo Controlled Study of Intravenous Levetiracetam for the Treatment of SE and ARS in Dogs. BT Harvey et al. JVIM 2012 26; 334-340

- 30-60 mg/kg IV, slow bolus over 5 minutes
- Decreased subsequent seizure activity
Prognosis

“Most cases progress even with aggressive treatment. The prognosis for permanent recovery is poor.” Meric SM. JVIM 1988;2:26-35

“GME is recognized as a disease with a progressive course that is commonly fatal.” Munana & Lutttgen JAVMA 1998

“GME has a poor prognosis. Most studies offer the generalization that dogs with multifocal disease typically have a short survival (up to 6 weeks) and dogs with focal disease have a longer survival (3-6 months.)” Neill et al. Irish Vet J 2005
Prognostic Factors for Dogs with Granulomatous Meningoencephalomyelitis: 42 cases (1982-1996)
Munana et al. JAVMA Vol 212 June 1998

- Significant difference in survival:
  - Focal vs multifocal signs
  - Focal forebrain vs focal in another location
  - Radiation therapy

- Median survival for all dogs was 14 days
  - Focal: 114 days
  - Multifocal: 8 days
Unanswered Questions

- Monitoring
- Treatment of Choice
- Prognostic Factors
- Underlying etiology
Challenges in my patients

- Drug Choice
- Aggressive Therapy
- Seizure Management
- Common complications
  - Hepatopathy
  - Corneal ulcerations
  - Prednisone intolerance
Thank you! / Questions?