A TALE OF TWO DOGS: MENINGOENCEPHALITIS OF UNKNOWN ETIOLOGY (MUE)

Sarah Trub, DVM
(Resident in Neurology & Neurosurgery)
Meningoencephalitis

- Inflammation of the brain and leptomeninges
- Meningoencephalomyelitis if spinal cord is also involved
Two groups of etiologies

- Infectious
- Immune-mediated
Common infectious etiologies

- Protozoal
  - Toxoplasma
  - Neospora
- Viral
  - Distemper
- Rickettsial diseases
  - E. canis
  - Anaplasma spp
  - R. rickettsii (RMSF)
- Fungal
  - Cryptococcus spp
  - Coccidioides immitis
- Bacterial
Meningoencephalitis of Unknown Etiology

- Encompasses all clinically diagnosed cases of noninfectious inflammatory CNS disease
- Does not include diseases without overt CNS involvement (i.e. SRMA)
- Histopathology is necessary for definitive diagnosis of subtype
Granulomatous meningoencephalitis (GME)

- T-cell mediated delayed-type hypersensitivity reaction with organ-specific autoimmune disease
- Young adults (1-6 yrs), females and small breeds
GME: Distributions

- Disseminated
  - White matter of the cerebrum, caudal brainstem, cerebellum and cervical spinal cord
  - +/- gray matter, leptomeninges, choroid plexus
  - Multifocal signs
  - Acute onset and rapid progression
- Focal
  - Solitary granuloma
  - Most common in cerebral white matter
  - More insidious progression
- Ocular
  - Retinal or post-retinal portions of the optic nerve
  - Acute visual dysfunction
GME: Histopathology

- Whorling, perivascular, disseminated or focal infiltrates of mononuclear cells in parenchyma and meninges of the CNS
- Acutely, equal distribution among gray and white matter
- Chronically, white matter lesions predominate
Necrotizing Encephalitis (NE)

- Necrotic lesions in cerebral white or gray matter
- Rapidly progressive neurologic signs
- 6 mo - 7 yr, mean age 2.5 yr
- Two subtypes: NME, NLE
Necrotizing meningoencephalitis (NME)

- Young, small breeds
- Pugs overrepresented
  - Familial inheritance
NME: Distribution

• Most often affects the cerebrum and/or thalamus
• Lesions most often located at the junction between the gray and white matter
NME: Histopathology

- Extensive asymmetric regions of cerebral necrosis and non-suppurative inflammation
- Leptomeningeal involvement
- Loss of demarcation between gray and white matter
Necrotizing leukoencephalitis (NLE)

- Yorkshire Terrier
- French bulldog
NLE: Distribution

- Forebrain
- Brainstem
NLE: Histopathology

- Nonsuppurative leukoencephalitis
- Multiple necrotic and cavitated regions in white matter
- Minimal leptomeningeal involvement
Clinical presentation

• Varies based on lesion distribution
• Typically, fever is not present
Diagnostics: CBC/Chem

• Typically normal
Diagnostics: MRI

• Multifocal, single, or diffuse, ill-defined, intra-axial variably contrast-enhancing lesions, hyperintense on T2w and FLAIR
• +/- Leptomeningeal enhancement (NME)
• +/- Perilesional edema
• +/- Mass effect suggesting elevated ICP
• +/- Ventriculomegaly
• +/- Cavitary lesions (NE)
• Normal (25%)
Diagnostics: CSF

• Mononuclear pleocytosis most common
  • Other pleocytoses possible
• Elevated protein concentration
  • Due to BBB disruption or intrathecal IgG production
  • Nonspecific indicator of CNS disease
• Normal
Diagnostics: Rule out infection

- *Toxoplasma* IgG/IgM
- *Neospora* IFA
- Distemper PCR or serology
- Tick PCR panel
- *Cryptococcus* PCR or fungal profile
- +/- CSF culture and sensitivity
Diagnostics: Biopsy (101)

- 82-100% accurate
- Methods
  - Stereotactic
  - Ultrasound-guided
  - Endoscopic-guided
  - CT-guided
- 6-29% mortality and morbidity
- Not commonly performed
Treatment: Goal

- Achieve remission
- Minimize adverse effects
Treatment:
Treat the Cause

- Empiric antibiotic therapy
  - Clindamycin
  - Doxycycline or minocycline
- Immunosuppressive therapy
  - Corticosteroid therapy
  - Cytosine arabinoside
  - Cyclosporine
  - Procarbazine
  - Lomustine
Treatment:
Treat the Symptoms

• Anticonvulsant therapy
• Maropitant, meclizine
• Pain medications
• IV fluids
• Nutrition
Prognosis

- MST
  - Multimodal tx: 240-590 d
  - Corticosteroid +/- lomustine: 28-357 d
- 56% die within 2 months of diagnosis
- 31% (70% of those who live >2 m) have good to excellent long-term outcomes
- Patients that survive 3 months tend to live
- Relapses are common (65%)
- Most will require life-long therapy
- Some may achieve remission and be able to be weaned off all medications
Prognosis

• Repeat diagnostics are helpful
  • MR + CSF more sensitive for predicting relapse
  • Discontinuing tx before resolution of MR lesions always resulted in relapse
  • Abnormal CSF at 3 mo associated with increased risk of relapse
Sophie

- 5 yo FS Yorkshire Terrier
- Presents for circling
History

• 1 week prior, unwilling to navigate stairs and would lose balance/tumble when attempted
• Progressed to worsened incoordination, leaning to the right, head tilt, lethargy, shaking, excessive panting, vomiting
• 1 day prior began circling tightly to the right
Examination Findings

• Alert and appropriate, excitable
• Moderate head tilt (predominantly right-sided), undulating head and neck movements, intermittent predominantly right-sided head turn
• Ambulatory, moderate vestibulocerebellar ataxia with circling both tightly and widely in both directions (predominantly to the left), hypermetria x4
• Inconsistently slow placing and hopping on the left side
• Inconsistent menace OU (OD>OS)
• Decreased palpebral OD
• Intermittent spontaneous horizontal nystagmus (FFL) and positional vertical nystagmus
• Head pain
• T 103.1 F
Neurolocalization

• Central vestibular with paradoxical and dynamic signs, caudal fossa +/- forebrain
Differentials

- Meningoencephalitis
- Congenital malformation
- Neoplasia
Diagnostics: Preliminary

- CBC: Hct 59.51%, rbc 8.97, Hgb 18.2 g/dL
- Chem: BUN 26 mg/dL, Glu 153 mg/dL
- BP: 100 mmHg
Diagnostics: MRI
Diagnostics: MRI

- Multifocal, ill-defined lesions involving the right frontal lobe, left occipital lobe and pons, hyper intense on T2w and FLAIR images, moderately contrast-enhancing; most suggestive of inflammatory or neoplastic disease
- Meninges contrast-enhance
- Mass effect with leftward shift of the medulla and mild FMH
- Mild to moderate COMS, likely exacerbated by suspected inflammatory disease
- Hyperintense signal on T2w images within the cervical spine, likely presyrinx formation or extension of inflammatory disease
- Moderate hydrocephalus, likely congenital
Diagnostics: CSF

• Not performed due to mass effect and considerable brainstem disease
Diagnostics: Infectious Diseases

- *Cryptococcus* Ag: neg
- *Toxoplasma* IgM/IgG: neg
- *Neospora* IFA: neg
Treatment

- Cytosar CRI
- Corticosteroid therapy
- Doxycycline
- Clindamycin

- IV fluids
- Maropitant
- Gabapentin
- Famotidine
Progress

• Gradual improvement
• At discharge 48 hr later
  • Mild, slow positional nystagmus (horizontal, FFL)
  • Circles widely to the left
  • Hypermetric
  • Right-sided head tilt and turn
  • Mildly decreased palpebral and menace OD
• 5d post-discharge
  • Near normal at home
Progress

• 12d post-discharge
  • Recurrance of vomiting, trouble jumping, lethargy, hugging walls, rubbing face on furniture
  • Recheck exam: circling widely in both directions, tightly towards the left, mild positional ventral strabismus OS
  • Added in cyclosporine
• Gradual return to normal, still doing well today!
Ralphie

- 4 yo MN Chihuahua
- Presented for fever and head bobbing
History

• 1 month ago fever and diffuse spinal pain, improved on gabapentin and meloxicam
• Signs recurred once meloxicam was discontinued, started prednisone and improved
• With tapering of prednisone, lethargic, inappetent, staring off, coughing, febrile, head bobbing
• Restarted prednisone, started doxycycline and clindamycin
• Yesterday, tachypnic and hacking cough
• Previous CBC, chem, 4DX, AUS and rads wnl
Examination Findings

- Hypersalivation
- Ambulatory, occasionally lifts up LTL
- Inconsistent menace OU (OD>OS)
- Head and cervical pain
Neurolocalization

- C1-C5
- Forebrain
- +/- Cerebellum
Differentials

- MUE
- Neoplasia
- Congenital malformation
- Metabolic
Diagnostics: Preliminary

- CBC: wnl
- Chem: ALT 483 U/L, Glu 131 mg/dL
Diagnostics: MRI

• Multifocal contrast-enhancing lesions throughout white matter of all regions of the brain, hyperintense on T2w and FLAIR images
Diagnostics: CSF

- Protein: 300 mg/dL
- Cell count: 2376 wbc/uL
- Cytology: 44% lymphocytes, 30% neutrophils, 26% monocytes
- Mixed/mononuclear pleocytosis
Diagnostics: Infectious Diseases

- Cryptococcus Ag: neg
- Distemper PCR: neg
Treatment

- Cytosar CRI
- Prednisone
- Cyclosporine
- Clindamycin
- Doxycycline
- IV fluids
- Gabapentin
- Famotidine
Progress

• Signs waxed and waned for the next couple of months
• In general, steady decline
  • Persistent cough
  • Vestibular ataxia
  • Decreased gag
  • Dull
  • CP deficits
Progress

• Repeat CXR wnl
• Repeat MRI
Outcome

• Ralphie was euthanized
References

Acknowledgements

- Dr. David Brewer
- Sophie and Ralphie’s committed owners