Canine Meningoencephalomyelitis

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YOU HAVE ASKED...

How is canine meningoencephalomyelitis diagnosed, and what are the treatment options?

THE EXPERT SAYS...

Unlike in humans, an infectious cause cannot be identified in the majority of dogs with meningoencephalomyelitis. Noninfectious inflammatory meningoencephalomyelitis has been described by histopathologic examination as granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME), necrotizing leukoencephalitis (NLE), and eosinophilic meningoencephalitis (EME).

Although different causes may be suspected for GME, NME, NLE, and EME, specific causes have not been identified; therefore, they are classified as noninfectious inflammatory diseases. In the absence of histopathologic examination and without evidence of infectious disease, the term *meningoencephalomyelitis of unknown origin* (MUO) can be used.[1] A diagnosis of MUO signifies that a dog has been clinically diagnosed with inflammatory brain disease and no evidence of infectious disease was found.

How Is MUO Diagnosed?

The clinical presentation of MUO may be acute or chronic and reflect focal or multifocal disease. Clinical signs reflect the location of the lesion(s). For example, dogs with forebrain disease may show signs of compulsive circling, seizures,

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behavior changes, or blindness. Dogs with brainstem disease often show vestibular signs, but other cranial nerves may also be affected.

Small dog breeds are more commonly affected, which suggests a genetic predisposition.[2,3] Recently, genetic markers were identified in pug and Maltese dogs, which indicates a genetic risk for the development of MUO in those breeds.[2,3] Although small dog breeds are overrepresented, MUO has been diagnosed in large dog breeds as well.[4]

Common magnetic resonance imaging (MRI) abnormalities include multifocal hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging with variable contrast enhancement. MRI is normal in some cases, however.[1] Supportive cerebrospinal fluid (CSF) findings include mixed mononuclear pleocytosis with increased protein concentration. Both total nucleated cell count (TNCC) and protein concentration may be normal in some dogs.[5] Biopsy may be pursued in some cases to obtain a histopathologic diagnosis.

Granger and Smith proposed the following criteria for a clinical diagnosis of MUO[1]:

1. Multifocal neuroanatomic lesion localization
2. Age >6 months
3. Intra-axial hyperintense lesions on T2-weighted MRI
4. Pleocytosis with >50% mononuclear cells and increased protein concentration in CSF
5. Negative testing for geographic-specific infectious diseases[1]

MUO Treatment Options

Standard treatment is immunosuppressive glucocorticoid therapy (1 mg/kg twice a day prednisone or prednisone equivalent) because of excellent penetration through the blood-brain barrier, ease of administration, and relatively low cost.[5,6] When standardized glucocorticoid protocols are used, CSF analysis returns to normal in 1 month in 44% of dogs with MUO.[7] A slow taper of medication over months to years is recommended. Some animals may remain on medication for life.

Preferred starting treatment protocols vary depending on the clinician, patient, and financial situation of the client.

Glucocorticoid adverse effects may be intolerable to some owners; therefore, multiple protocols have been investigated using other immunosuppressive agents combined with glucocorticoids (***Table 1***, next page). Preferred starting treatment protocols vary depending on the clinician, patient, and financial situation of the client. In addition, because causes can be multifactorial with possible genetic predispositions, a single treatment protocol has not been shown to be optimal for all dogs. Additional studies are needed to determine if glucocorticoid monotherapy or combination protocols should be prioritized during the first stages of treatment.

Prognostic Indicators

Multiple studies have attempted to identify reliable prognostic indicators for inflammatory brain diseases.[1,8-10] Focal GME may be associated with a better prognosis; however, the published study that concluded this used death as an endpoint; therefore, it is unknown if this finding is valid for dogs surviving with GME.[8] Other imaging features, such as location of the lesion, presence of mass effect, herniation, or high lesion burden, have been variably associated with prognosis but

CSF = cerebrospinal fluid, EME = eosinophilic meningoencephalitis, FLAIR = fluid-attenuated inversion recovery, GME = granulomatous meningoencephalomyelitis, MRI = magnetic resonance imaging, MUO = meningoencephalomyelitis of unknown origin, NLE = necrotizing leukoencephalitis, NME = necrotizing meningoencephalitis, TNCC = total nucleated cell count

TABLE 1

COMPARISON OF SURVIVAL DATA & IMMUNOSUPPRESSIVE AGENTS FOR DOGS DIAGNOSED WITH MUO

Reference	Treatment*	Initial Dose	Number of Dogs	Median Survival (Min–Max) [Days]
Mercier, Barnes Heller (2015)[4]	Prednisone	1 mg/kg (0.8–1.2 mg/kg) twice a day PO, tapered after 4 weeks	16	320 (45– >654)
Flegel, et al (2011)[13]	Prednisone$^{\alpha}$	0.17–2.5 mg/kg twice a day PO, tapered after 1 week	11 (GME) 8 (NE)	323 (39–542) 91 (7–494)
Menaut, et al (2008)[14]	Cytosine arabinoside Prednisone	50 mg/m^2 twice a day SC × 4 doses, repeated every 3 weeks 1–2 mg/kg twice a day PO, tapered after 1 week	11	ND (78–603)
Lowrie, et al (2013)[10]	Cytosine arabinoside Prednisone	50 mg/m^2 twice a day SC × 4 doses, repeated every 3 weeks 1 mg/kg twice a day PO, tapered after 4 weeks	39	26 (0–2250)
Adamo, et al (2007)[15]	Cyclosporine Corticosteroids	3–15 mg/kg twice a day PO Dose unknown	10	930 (60– >1290)
Pakozdy, et al (2009)[16]	Cyclosporine Corticosteroids	3 mg/kg twice a day PO 1-30 mg/kg/day, taper unknown	14	620 (3–870)
Flegel, et al (2011)[13]	Lomustine$^{\alpha}$ Prednisone	44-88 mg/m^2 PO every 6 weeks 0.17-2.5 mg/kg twice a day PO, tapered after 1 week	14 (GME) 10 (NE)	457 (107–709) 329 (98–628)
Coates, et al (2007)[11]	Procarbazine Prednisone	25-50 mg/m^2 once a day PO 0.25-2 mg/kg twice a day PO, taper unknown	21	420 (ND)
Wong, et al (2007)[17]	Azathioprine Prednisone	2 mg/kg once a day PO, then decreased to every 2 days after 2 weeks 1 mg/kg twice a day PO, tapered after 4 weeks	40	1834 (50–2469)
Munana, et al (1998)[8]	Radiation Prednisolone	40-49.5 Gy, fractionated 0.25-2 mg/kg twice a day PO, taper unknown	7	>404 (ND)
Beckmann, et al (2015)[18]	Radiation Prednisolone	30 Gy, fractionated 1.9-4 mg/kg/day PO, variable taper	6	ND (ND)

*All dogs received corticosteroids alone or in combination if a combination protocol was used. Caution should be exercised when extrapolating data to clinical patients because of the variable dose, duration, and type of corticosteroid used.
α = dogs with granulomatous meningoencephalomyelitis and necrotizing encephalitis divided into 2 groups, Gy = gray unit, ND = not determined

currently are not reliable predictors of survival.[9,10]

An increased TNCC in CSF at the time of diagnosis is associated with poorer survival (Oliphant and Barnes Heller, manuscript in preparation), in contrast to a previous study.[11] However, the time to normalization of the CSF TNCC and protein concentration has been variably associated with survival.[10,12] When repeat MRI and CSF findings have been assessed concurrently, the capacity to predict relapses increases.[9] Median survival ranges from 26 days to >1800 days (***Table 1***). Unfortunately, comparison across studies is difficult because different drug protocols were used for each study. Overall, prognosis is guarded-to-fair and, at this time, is based chiefly on a dog's response to immunosuppressive treatment.

MUO suspected, but clients cannot pursue referral to a neurologist: What should be done?

For small-breed dogs >6 months of age with progressive, multifocal CNS signs without systemic signs of illness, clinical suspicion of MUO is high. Other differential diagnoses are infectious meningoencephalomyelitis and neoplasia. If the dog is <2 years of age, congenital and degenerative diseases (eg, storage disorders, hydrocephalus) should also be considered. Without MRI and CSF analysis, diagnosis is presumptive at best. A candid conversation with the client about the advantages and disadvantages of immunosuppressive treatment without a definitive diagnosis is critical before initiating treatment.

Literature support for a specific immunosuppressive protocol is likewise lacking. Therefore, consultation with a local neurologist should be considered before starting treatment. Informed consent should include acknowledgment of the risks of immunosuppression with unknown infectious disease status as well as risks and adverse effects of the recommended drugs.

Initially, prednisone (1 mg/kg twice a day PO) should be used along with antimicrobial coverage for protozoal and some bacterial infections with clindamycin (15 mg/kg twice a day PO), or sulfadimethoxine ormetoprim (15 mg/kg twice a day PO), ± doxycycline (5–10 mg/kg twice a day PO) for possible tick-borne infections, depending on the region. Clinical improvement may be anticipated within 72 hours for dogs with MUO; however, dogs may remain clinically static or worsen during this time frame. If improvement occurs, prednisone should be continued for 30 days and then gradually tapered over 2 to 18 months to an alternate-day dose or to discontinuation. Antibiotics are empirically discontinued after 2 to 4 weeks. If worsening occurs after discontinuation of the antibiotics, an infectious cause should be highly suspected.

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Other supportive therapy (eg, anticonvulsant drugs, hospitalization for IV fluid therapy, nutritional support) should be initiated as needed. Pursuing a diagnosis by MRI and CSF analysis is not recommended while on immunosuppressive therapy because of the

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risk of false-negative CSF results; therefore, it is important to eliminate the possibility that the client may pursue MRI or CSF analysis before initiation of therapy.

Conclusion

Treatment of MUO typically starts with immunosuppressive glucocorticoids, but multiple drug protocols have been used. Rapid referral to a neurologist is strongly encouraged so that advanced imaging and CSF analysis can be used to support the diagnosis and immunosuppressive therapy can be initiated quickly. Future studies of possible genetic or environmental triggers, better prognostic indicators, and more targeted treatment approaches are ongoing and will hopefully result in improved management and survival.

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