# Perspectives on Meningoencephalomyelitis of Unknown Origin

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**KEYWORDS**

• Necrotizing meningoencephalitis • Necrotizing leukoencephalitis
• Granulomatous meningoencephalomyelitis • Central nervous system
• Immune-mediated • Inflammatory • Immunomodulation

**KEY POINTS**

- Meningoencephalomyelitis of unknown origin (MUO) is a syndrome of idiopathic noninfectious central nervous system inflammatory diseases defined by their clinical presentation, advanced imaging characteristics, and cerebrospinal fluid analysis.
- Genetic and immune-mediated processes underlie the disease, but it likely has a multifactorial pathogenesis.
- Management is focused on remission of clinical signs through judicious use of immunosuppressive therapies, including glucocorticoids.
- Future studies on the therapeutic efficacy of different strategies using a more targeted approach may depend on identification of prognostic indicators and case stratification using molecular genetic discoveries.

## INTRODUCTION

Recent advances in the understanding of noninfectious inflammatory diseases of the central nervous system (CNS) have resulted in an increasing subdivision of this parent category, each with its own specific name. The recognition that specific histologic subtypes cannot be identified on routine antemortem clinical tests has led to the use of an umbrella term: meningoencephalomyelitis of unknown origin (MUO). Because each of the subtype conditions has an extremely unwieldy name, there is

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a plethora of acronyms, and the resulting alphabet soup (which has even been exacerbated though differences in United States and United Kingdom spellings; explaining why this article uses the term "meningoencephalomyelitis of unknown origin" throughout) can be very confusing to navigate.

It is uncertain whether the various breed-specific idiopathic encephalitides of dogs that constitute the cases known as MUO are variations on a common etiologic theme or are truly distinct pathologic entities.[1–3] This review primarily focuses on providing an overview of the subtypes, illustrating how the differences in histopathologic classification and underlying neuroinflammatory responses may have relevance to the therapeutic approach and prognosis.

Clinical signs of noninfectious CNS inflammatory disorders are frequently very similar to those of infectious CNS diseases and even those of neoplasia. Diagnosis in the clinic therefore rests predominantly on advanced imaging, cerebrospinal fluid (CSF) analysis, and serologic tests designed to rule in or rule out infectious disease. In most cases, neoplastic lesions, which are generally unifocal, are easily differentiated from inflammatory disease, which are usually multifocal. Therefore, the major diagnostic decision is between infectious and noninfectious disease. Nowadays in the developed world, noninfectious inflammatory diseases of the CNS, which can affect the brain, spinal cord, and/or the meninges, are much more common.

MUO has long been assumed to have an autoimmune and genetic pathogenesis.[4] In general, major factors that contribute to the development of autoimmunity are genetic susceptibility and environmental factors (eg, infections, tissue injury). Nevertheless, a trigger factor is assumed to initiate signs of disease in each specific dog at a specific time.[5–8] Suspected agents include environmental or infectious antigenic triggers that might activate autoreactive cells in the CNS, although no such agent has yet been incriminated in the development of MUO.[9–12] Susceptibility genes may confer susceptibility or protection for autoimmunity by influencing the maintenance of self-tolerance. Data from inbred rodent studies have identified a strong influence of genetic background as a competing influence in the variability of lymphocyte responses in clearing pathogens from the CNS and promoting neuroprotection.[13–15]

### *Categorization of Noninfectious Inflammatory Disease of the CNS*

Noninfectious inflammatory disease of the CNS can be divided into several subtypes, based mainly on the specific regions of the CNS that are affected and the specific histopathology (**Fig. 1**). These subtypes include steroid-responsive meningitis-arteritis (SRMA), eosinophilic meningoencephalitis, granulomatous meningoencephalomyelitis (GME), and necrotizing encephalitis (NE). SRMA, which affects the meninges only, and eosinophilic meningoencephalitis have fairly distinct disease signatures based on clinical presentation, CSF abnormalities, and histopathology,[16] and are not considered further here.

Recently, the term MUO has been introduced to encompass all clinically diagnosed (ie, dependent on advanced imaging and CSF analysis) cases of noninfectious inflammatory CNS disease.[4,17] MUO thus includes all the specific subtypes of noninfectious inflammatory disease that can be identified through histopathology, including GME, necrotizing meningoencephalitis (NME), necrotizing leukoencephalitis (NLE), and so forth, but does not include the diseases without evidence of overt CNS involvement (such as SRMA). NME and NLE are inflammatory disorders described with neuropathologic nomenclature reflective of the affected region of the brain. However, there is much overlap in clinical signs, signalment, and neuropathology for these conditions and, therefore, the more inclusive term NE, incorporating NME and NLE, is preferred for antemortem diagnosis.[4,18]

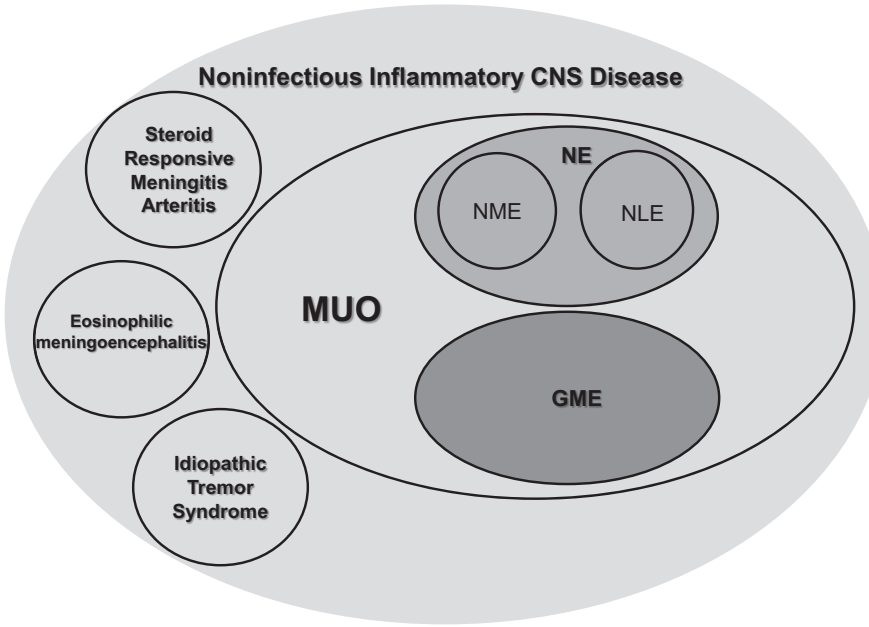



**Fig. 1.** Various noninfectious inflammatory central nervous system (CNS) diseases. Meningoencephalomyelitis of unknown origin (MUO) includes the necrotizing encephalidites, necrotizing leukoencephalitis (NLE) and necrotizing meningoencephalitis (NME), and granulomatous meningoencephalomyelitis (GME). Note that the noninfectious inflammatory CNS diseases, steroid-responsive meningitis arteritis, idiopathic tremor syndrome, and eosinophilic meningoencephalitis stand apart, with the distinctive disease signatures based on cerebrospinal fluid analysis or clinical signs.

## AN OVERVIEW OF NEUROINFLAMMATION

Although many of the general features of CNS inflammation are similar to those affecting other body systems, an important feature of the CNS is its relative isolation from the peripheral immune system, which has important implications regarding the pathogenesis, diagnostic criteria, and therapy for inflammatory CNS diseases. The blood-brain barrier (BBB), usually understood to also include the blood–spinal cord barrier, implies that there is "gating" of the flow of cells and macromolecules from the systemic circulation to the CNS.[19] This selectively permeable barrier is formed through the influence of the endothelial cells and basement membrane, and the neighboring perivascular pericytes, glial cells (astrocytes, microglia), and neurons, and tends to temper the intensity of inflammatory responses within the CNS.[19–21] However, although the CNS traditionally has been considered immunologically privileged, current data confirm that the CNS is immunocompetent and actively interacts with the peripheral immune system.[22] In fact, peripheral inflammation can trigger a neuroinflammatory response involving BBB endothelia, glia, and neurons. Neuroinflammation is characterized by a broad range of immune responses, differing from peripheral inflammation primarily in the principal cells involved, most notably the astrocytes and microglia.[23]

### *Immune-Mediated CNS Disease*

Autoimmune diseases arise from dysregulation of either or both of the innate and adaptive immune systems to produce inflammatory responses leading to cellular

dysfunction and tissue destruction.[24,25] Innate immunity comprises immediate, nonspecific, short-term responses of the immune system usually triggered by distinctive pathogen-derived molecules, known as pathogen-associated molecular patterns (PAMPs) or, in the case of noninfectious inflammatory responses, by damage or danger-associated molecular patterns (DAMPs). By contrast the adaptive immune response, which involves humoral (antibody production) and cell-mediated immunity, is delayed but highly specific, and capable of memory responses.

CNS autoimmune disease responses are targeted at cellular components that are normally shielded, in part by the BBB. Infections or other antigens may also alter the way in which self-antigens are displayed to the immune system, leading to failure of self-tolerance and activation of self-reactive lymphocytes. Antigen-presenting cells may present CNS self-antigen (or foreign antigen that is similar to self-antigen) fragments to CNS-reactive T cells in peripheral lymph nodes where lymphocytes that traffic through the brain will ultimately arrive. Activated T cells then exit the lymph nodes, upregulate molecules that facilitate migration across the BBB,[26,27] and participate in a proinflammatory sequence of events within the CNS. Signals arising from injured neurons and surrounding glia create a milieu of cytokines that activate resident microglia and subsets of T cells.[23,28] Polarization of the response toward neurotoxicity or neuroprotection is dictated by altered activation states of 2 arms of the immune system: (1) T cells and (2) the microglia and infiltrating macrophages (**Fig. 2**). Once an autoimmune reaction develops, amplification mechanisms (eg, cytokines) promote activation of autoreactive lymphocytes, and release of self-antigens from damaged cells leads to epitope spreading and exacerbation of the disease.[24]

### *T-cell responses*

Intra-CNS inflammatory responses tend to be dominated by mononuclear cells. All T cells express surface receptor cluster of differentiation (CD) 3 (CD3) antigen. CD4 surface receptor is found only on T-helper (Th) cells that can recognize and process antigens. CD8 surface receptor is only expressed on cytotoxic T cells that attack and kill abnormal cells. Classic major histocompatibility complex (MHC) class I molecules are required for $CD8^+$ T cells to recognize antigen, whereas CD4 is the receptor for MHC class II molecules on antigen-presenting cells. Cytotoxic and helper T-cell subsets and T-regulatory (Treg) cells are divergent in promotion of protective or deleterious responses to neuroinflammation, and are orchestrated through cytokine release.[29] Th-cell subsets modulate cytotoxicity and dictate anti-inflammatory (eg, Th2, Treg) or proinflammatory (eg, Th1, Th17) phenotypes.[30] Cytokine expression includes the interleukins (IL), interferons (IFN), and members of the tumor necrosis factor (TNF) family.

During disease, cytokines in the CNS exert proinflammatory and anti-inflammatory actions, and cause oxidative stress, neurotoxicity, apoptosis, astrogliosis and microglial activation.[22,29,31] For example, Th1 cells that secrete high levels of IFN-$\gamma$ and TNF-$\alpha$ activate M1 microglia. Th2 and Treg cells tend to contribute to neuroprotection through cytokine mediators (eg, IL-4, IL-10, IL-13 via Th2) that drive M2 microglia and suppress cytotoxic T-cell function. Chemokines are small chemotactic cytokines that guide the migration of immune cells throughout the body, and are key molecules in promoting entry of immune cells into the CNS. Typically chemokines, such as monocyte chemoattractant protein 1 (MCP-1; CCL-2) or fractalkine (CX3CL), have very low physiologic concentrations within the CNS but are strongly upregulated in chronic neuroinflammation.[32,33] Such increased chemokine expression then attracts myeloid dendritic cells, monocytes, and activated T cells.[34,35]

### *Microglial responses*

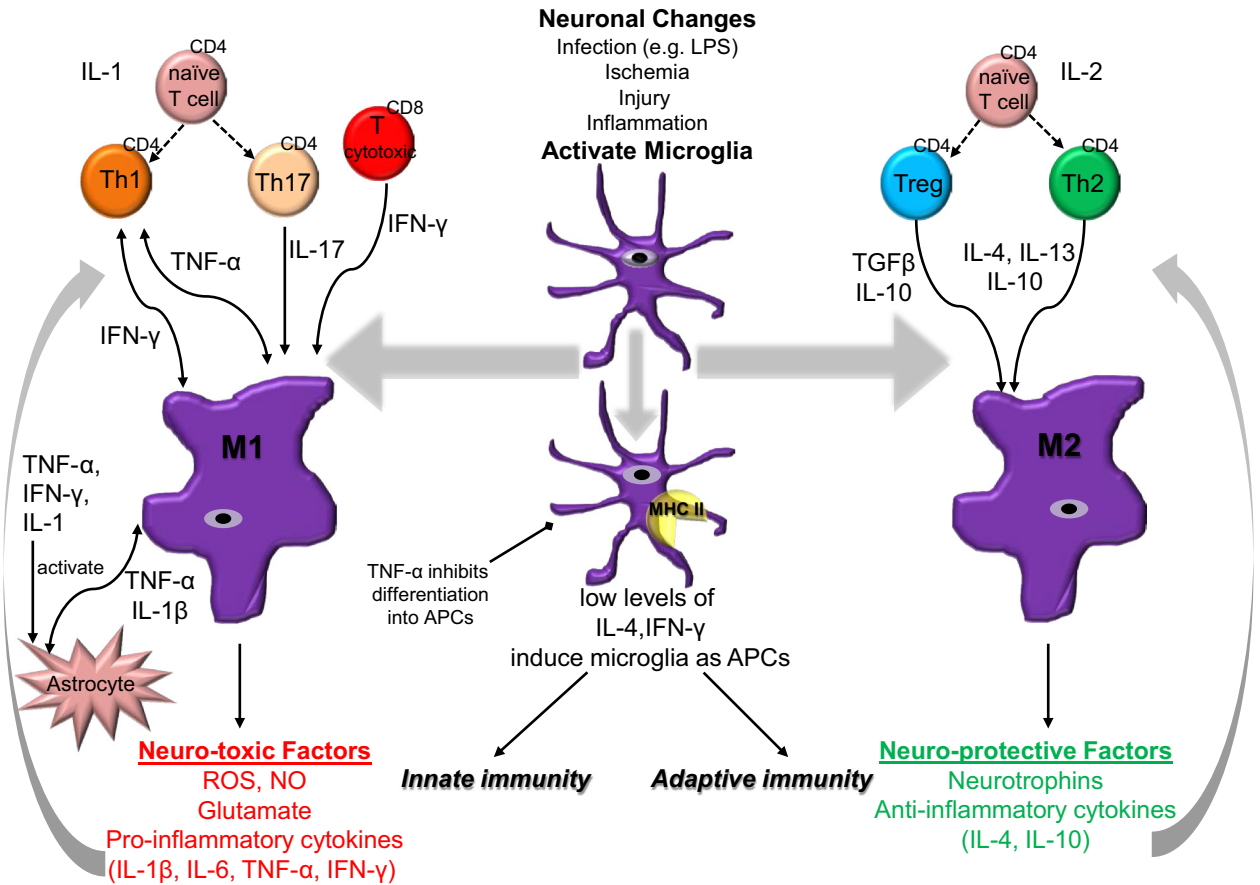
Microglia, the resident macrophages of the CNS, play a crucial role in the process of neuroinflammation. Microglia are derived from a specific embryonic myeloid cell population and invade the CNS during development,[36] where they exhibit regional variation. Microglia display functional plasticity during activation, which involves changes in cell number, morphology, and surface receptor expression, and production of growth factors and cytokines.[37–39] Microglia are the most prominent MHC-expressing cells in the CNS and are capable of processing and presenting antigen by expression of MHC classes I and II, and thereby have a bidirectional interaction with neurons and other microglia.[40] As with macrophages, the cytokine-mediated phenotype switch of microglia directs development of either a proinflammatory (M1) or anti-inflammatory phenotype (M2).[37,41–43] In response to cytokines (eg, high levels of IFN-$\gamma$) and other signaling molecules resulting from acute inflammation or injury, microglia are transformed from an inactivated to an activated phagocytic state, releasing proinflammatory mediators in the process.[28,39,44] M1 microglia increase secretion of proinflammatory cytokines such as TNF-$\alpha$, IL-6, and IL-1$\beta$, reactive oxygen species (ROS), and nitric oxide (NO), and reduce the production of neurotrophic factors, all of which lead to cytotoxicity, astrocyte activation, and neurodegeneration. When induced by a variety of cytokines (eg, IL-4, IL-10) or immune complexes, M2 microglia reduce proinflammatory responses, and produce high levels of anti-inflammatory cytokines (eg, IL-10, transforming growth factor $\beta$) and neurotrophic factors.[41,45] The balance between M2 neuroprotective microglia and M1 neurotoxic microglia fluctuate according to the physiologic conditions they encounter during disease.[37,39,46] Despite advances in the understanding of microglia in the healthy dog, it remains unclear as to whether these cells respond to various disease states stereotypically or if they adapt their responses to the underlying pathologic conditions.[47] In many canine diseases, microglial markers are upregulated to varying degrees and the cells show enhanced phagocytosis.[48,49]

## *Histopathology of Neuroinflammation*

Immunophenotyping for a variety of cellular markers in the MUOs can assist in determining the inflammatory signatures that influence perivascular and parenchymal hypercellularity, disease distribution between white and gray matter, and disease progression. Canine microglial cells share antigenic markers with macrophages, which has complicated identification of these cells, but the combined analysis of antigenicity, cell size, and cell complexity allows them to be distinguished. In dogs, several differences between resident microglia and infiltrating macrophages have been noted, along with topographic differences within the CNS.[49–51] Although both express $CD18^+$, $CD11b/c^+$, and CD45, microglia have lower levels of expression of CD45.[50] Moreover, stimulated microglia in healthy dogs generate lower levels of ROS.[49,51]

## *Neuroinflammation in MUO*

Although neuroinflammation has been investigated in several spontaneous canine CNS diseases,[48,49,52–54] mechanisms still remain enigmatic for the MUOs. When the normal immune regulatory mechanisms of the CNS are rendered dysfunctional, for instance by age, pathogen exposure, or neurodegeneration, the threshold to initiate CNS inflammation and the ability of the CNS to direct immune effector functions will change.[22] Such alteration may also decrease neuroprotective responses and support controlled proinflammatory responses against pathogens and other insults. Knowledge of what dictates the predominance of neurotoxic or neuroprotective


Neuronal Changes
Infection (e.g. LPS)
Ischemia
Injury
Inflammation
Activate Microglia
IL-1
CD4
naïve T cell
CD4
Th1
CD4
Th17
CD8
T cytotoxic
TNF-α
IL-17
IFN-γ
IFN-γ
M1
TNF-α,
IFN-γ,
IL-1
activate
TNF-α
IL-1β
Astrocyte
Neuro-toxic Factors
ROS, NO
Glutamate
Pro-inflammatory cytokines
(IL-1β, IL-6, TNF-α, IFN-γ)
TNF-α inhibits differentiation into APCs
MHC II
low levels of IL-4,IFN-γ induce microglia as APCs
Innate immunity
Adaptive immunity
CD4
naïve T cell
IL-2
CD4
Treg
CD4
Th2
TGFβ
IL-10
IL-4, IL-13
IL-10
M2
Neuro-protective Factors
Neurotrophins
Anti-inflammatory cytokines
(IL-4, IL-10)

immunomodulation through cross-talk between the periphery (extraneural) and the CNS,[29,55] and how to limit cytotoxicity and enhance neuroprotection, would help identify appropriate targets for immune-based therapy.[56] Immunohistochemistry studies of the MUOs are summarized in **Table 1**.

## SIGNALMENT, NEUROLOGIC SIGNS, AND HISTOPATHOLOGIC FEATURES

Clinical signs associated with GME and NE simply reflect the region of CNS involved; common presenting syndromes include meningoencephalitis, although signs vary widely, even including myelopathy alone.[57] Although the syndrome can affect any dog, small, female dogs aged between approximately 3 and 7 years are most commonly affected by all subtypes of MUO. Although there are some apparent breed predispositions for specific subtypes, those between GME and NE (for example) are indistinct; similar breeds are commonly affected and there are no differences in age or sex predilection between the 2 groups.[58] It is thought that the spectrum of pathologic lesions for the MUOs may represent combinations of genetic influences on the cascade of neuroinflammatory responses.[16]

### *Granulomatous Meningoencephalomyelitis*

GME may represent up to 25% of all canine inflammatory CNS diseases.[16] Neurologic signs of GME are nonspecific and can be localized to forebrain, brainstem, or spinal cord, or appear as a multifocal syndrome.[58] The clinical presentation correlates with 3 pathologic distributions: multifocal (disseminated), focal, and ocular.[59,60] Multifocal GME typically is characterized clinically by acute onset and rapid progression of multifocal neurologic signs.[60–62] In the acute phase, dogs may have fever and exhibit paraspinal hyperesthesia, especially localizing to the cervical region.[59] By contrast, focal GME tends to have a more insidious or slower progression of neurologic signs that may suggest a space-occupying lesion,[59,60] with differential diagnoses including intracranial neoplasia. Forebrain and brainstem signs are reported most frequently with multifocal GME, whereas forebrain signs alone are more frequent with focal GME.[59,62] The third form, ocular GME, clinically manifests with acute signs of visual dysfunction attributable to optic neuritis and is sometimes considered one aspect of disseminated GME.[17,63–67] Anterior and posterior uveitis also can occur.[68]

GME is a distinct pathologic entity in which neuropathologic lesions consist of whorling, perivascular, disseminated, or focal infiltrates of mononuclear cells in the white matter and meninges of the brain and spinal cord (**Fig. 3**).[59,69,70] Originally GME was referred to as inflammatory or neoplastic reticulosis,[71,72] and reclassification as CNS lymphosarcoma or malignant histiocytosis is a viable alternative for some cases.[73] It appears that in acute progressive disease the gray and white matter is equally affected, whereas in more chronic GME white matter is predominantly

**Fig. 2.** A mechanism by which cytokines activate microglia, in response to neuronal changes that thereby promote neurotoxicity (*red*) or neuroprotection (*green*). Low levels of both IFN-γ and IL-4 can induce microglia to express MHC to function as APCs that mediate innate and adaptive immunity. This figure is a simplification of the neuroinflammatory processes based on interpretation of the current literature. The types of cellular responses to the milieu of cytokines/chemokines and cellular contact mechanisms are influenced by other environmental factors and differences between species. APCs, antigen-presenting cells; CD, cluster of differentiation; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NO, nitric oxide; ROS, reactive oxygen species; TGF, transforming growth factor; Th, helper T cell; TNF, tumor necrosis factor; Treg, regulatory T cell.

**Table 1**
**Summary of clinical and histologic characteristics of the meningoencephalitides of unknown origin**

| | GME | NME | NLE |
|---|---|---|---|
| Clinical signs | Multifocal (disseminated), focal and ocular; forebrain, hindbrain, spinal cord | Focal or multifocal forebrain; seizures most common | Focal or multifocal; forebrain and hindbrain signs |
| MR imaging characteristics | Multifocal or diffuse lesion hyperintensity on T2W and FLAIR sequences; variable T1W contrast enhancement; gray and white matter lesions; minimal meningeal enhancement; mass effect | Asymmetric, multifocal cerebrocortical gray and white matter lesions; lesions appear iso- to hypointense on T1W and hyperintense on T2W and FLAIR sequences; variable T1W contrast enhancement of parenchymal lesions; meningeal enhancement; mass effect; varying ventriculomegaly | Asymmetric cerebral white matter and brainstem lesions. Lesions appear iso- to hypointense on T1W and hyperintense on T2W and FLAIR sequences; minimal contrast enhancement of parenchymal lesions; lack of meningeal enhancement and mass effect; varying ventriculomegaly |
| Histologic characteristics | Whorling perivascular mononuclear cell infiltrates; white matter, meninges, spinal cord; acute lesions in gray and white matter; chronic lesions in white matter | Asymmetric extensive necrosis and cavitation; mononuclear infiltrates involve cerebral cortex, corona radiata, subcortical white matter; prominent reactive astrogliosis effacing areas of cavitation; inflammation can occur in brainstem and cerebellum; extensive leptomeningeal inflammation | Asymmetric extensive necrosis and cavitation; mononuclear infiltrate and prominent reactive astrogliosis effacing areas of cavitation; predominantly white matter; meninges minimally affected |

| | | | |
|---|---|---|---|
| Immunohistochemistry characteristics | CD3 lymphocytes in perivascular cuffs, parenchymal granulomas, and leptomeninges; CD43 and CD45R$^+$ expression were low; expressions for B cells and plasma cells were low; strong MHC class II antigen expression observed in resting and activated T and B lymphocytes; MAC-387$^+$ common; CD163$^+$ macrophages, epithelioid cells more frequent in perivascular cuffs than NME and NLE and in parenchymal lesions; CCR2 and highest in GME compared with NME and NLE; lysozyme$^+$ histiocytes[6,76,77] | GFAP$^+$ astrocytes distributed widely over cerebrum; CD3$^+$ lymphocytes scattered in meninges, perivascular cuffs, and brain lesions but less compared with GME; MAC-387$^+$ cells limited in NME but mainly in meninges and perivascular cuffs; lysozyme$^+$ cells faint compared with GME; expression of IFN-$\gamma$ and CXCR3 highest in NME compared with NLE and GME. CD163+ macrophages localized in active inflammatory lesions perivascular cuffs and brain parenchyma[1,76,77] | Intralesional GFAP expression; CD3$^+$ T cells dominate in perivascular cuffing and in diffuse histiocytic and lymphocytic infiltrates; rare B cells; MAC-387$^+$ histiocytic cells were detected in lesions of Yorkshire terrier but few in French bulldog; IgG deposits in white matter associated with inflammation; faint labeling IgM and IgA; CD163$^+$ cells diffusely infiltrated the cerebral white matter[77,96,98] |

*Abbreviations:* CD, cluster of differentiation; FLAIR, fluid-attenuated inversion-recovery; GFAP, glial fibrillary acidic protein; GME, granulomatous meningoencephalomyelitis; IFN, interferon; IgA, -G, -M, immunoglobulin A, G, M; MHC, major histocompatibility complex; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; T1W, T1-weighted; T2W, T2-weighted.

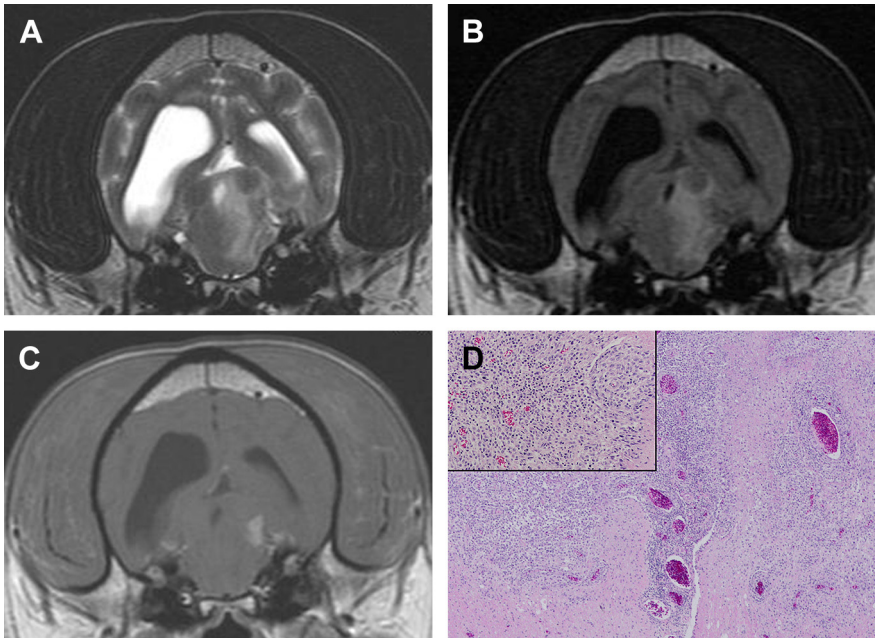



**Fig. 3.** Focal granulomatous meningoencephalomyelitis with ventriculomegaly. (*A*) Transverse T2-weighted magnetic resonance (MR) image at the level of the midbrain, caudal colliculi, and cerebral cortex. Diffuse and right-sided hyperintensity involving the central gray substance, brachium of caudal colliculus, reticular formation, medial lemniscus, and mass effect of the mesencephalic aqueduct. (*B*) Transverse, T2-weighted fluid-attenuated inversion-recovery (FLAIR) image at the same level as in *A*. Edema in the right midbrain is more conspicuous as a result of suppression of signal intensity in the mesencephalic aqueduct. (*C*) Transverse T1-weighted image at the same level as in *A* after intravenous administration of a gadolinium-based contrast medium. The lesion displays variable contrast enhancement. (*D*) Hematoxylin and eosin staining of multifocal perivascular infiltrates consisting of macrophages, histiocytes, plasma cells, and lymphocytes. There is whorling of mixed cell infiltrates around blood vessels (see inset). Original magnification 100×; inset 400× (*Courtesy of* Gayle C. Johnson, DVM, PhD, Columbia, MO.)

involved.[59] Multifocal granuloma can predominate in the cerebellum and brainstem with epithelioid cells in advanced stages,[6,69,74] and tryptase-positive mast cells have been found in the perivascular cuffs, meninges, and CNS parenchyma of dogs with acute forms of GME.[75] Focal lesions represent a coalescence of a large number of perivascular lesions, which commonly involve the pontomedullary region and cerebral white matter.[61,62,66,73] Kipar and colleagues[6] have suggested, based on a predominance of MHC class II and $CD3^+$ T cells, that GME is a result of delayed type hypersensitivity. However, $CD3^+$ immunoreactivity varies little between GME and NME or between GME and CNS histiocytosis.[74,76] Park and colleagues[77] also reported a tendency toward higher numbers of $CD163^+$ macrophages in GME than in NME and NLE.

### *Necrotizing Encephalitis*

NE is a subtype of MUO that appears histopathologically distinct from GME because of characteristic necrotic lesions in cerebral white or gray matter. The onset of

neurologic signs of NE ranges from 6 months to 7 years of age but most commonly occurs in younger dogs with a mean age of 2.5 years.[58] In general, signs associated with NE are rapidly progressive and commonly include seizures, abnormal mentation, vestibulocerebellar dysfunction, central visual deficits, and death. Histology typical of the NEs includes nonsuppurative meningoencephalitis and bilaterally asymmetric cerebral necrosis (see **Fig. 4**). There are 2 subtypes of this category of lesion, namely NME and NLE, which appear to have considerable overlap in breed association and lesion distributions.

***Necrotizing meningoencephalitis***

NME was originally reported as a breed-specific disease in Pug dogs (Pug dog encephalitis),[78] and many other reports have followed.[76,79–84] NME has now also been reported in the Maltese,[76,84,85] Chihuahua,[1] Pekingese,[86] West Highland White Terrier,[87] Papillon,[3,76] Shih Tzu,[3,76] Coton de Tulear,[3] Brussels Griffon,[3] and other

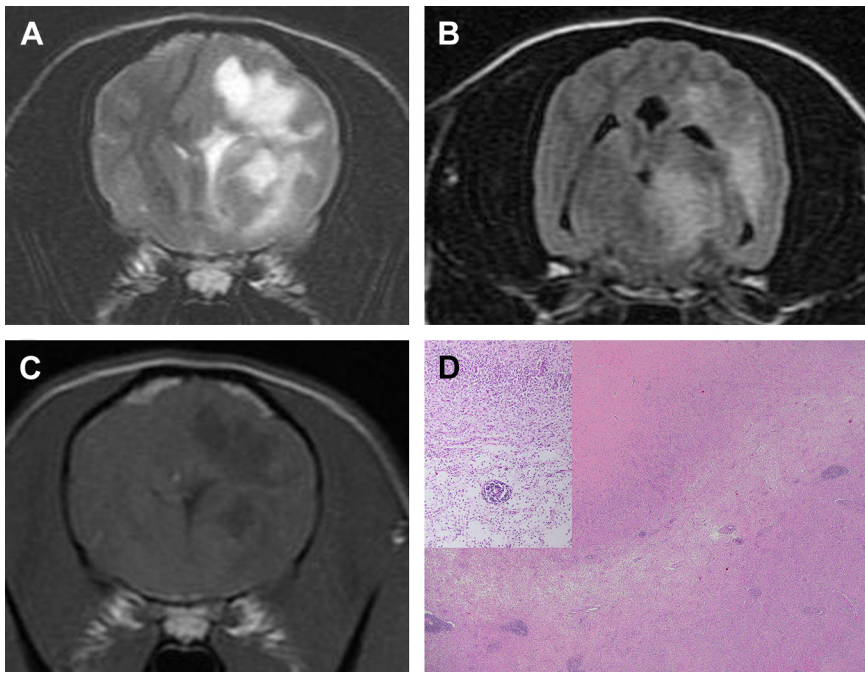



**Fig. 4.** Necrotizing leukoencephalitis. (*A*) Transverse T2-weighted MR image at the level of the caudate nucleus and cerebral cortex. Note the hyperintensity of the white matter (internal capsule, centrum semiovale, and corona radiate) of the right cerebrum. (*B*) Transverse T2-weighted FLAIR image at the level of the thalamus. Edema in the right centrum semiovale and internal capsule is more conspicuous as a result of suppression of signal intensity in the lateral ventricle. Edema is also noted in the region of the right thalamus. (*C*) Transverse T1-weighted image at the same level as in *A* after intravenous administration of a gadolinium-based contrast medium. The lesion displays mild peripheral contrast enhancement and hypointensity, suggestive of necrosis. (*D*) Hematoxylin and eosin staining of internal capsule with edema, dissolution of white matter, and multifocal perivascular cuffing of mostly lymphocytes. Multifocal small areas of white matter surrounding affected vessels are effaced and replaced by foamy macrophages, glial cells, and gemistocytic astrocytes (see inset). Original magnification 100×; inset 400× (*Courtesy of* Gayle C. Johnson, DVM, PhD, Columbia, MO.)

breeds.[4] Dogs with NME commonly manifest forebrain signs, especially seizures, because of lesions in the cerebral cortex.[3,58,80,82] Other forebrain signs include lethargy, anorexia, central blindness, circling, and head-pressing.[78,80] Cervical spinal hyperesthesia may be evident depending on the extent of leptomeningitis.[78]

The hallmark of NME is extensive necrosis, which varies in severity from neuronal necrosis and gliosis in the early stage to gross cavitation of parenchyma in advanced disease.[1,78,84] Lesions, dominated by plasma cells, lymphocytes, and histiocytes, commonly involve the leptomeninges, cerebral cortex, corona radiata, and subcortical white matter, and lead to loss of demarcation between gray and white matter.[78,84] Lesions are most common in the cerebrum, but have also been identified in the brainstem and cerebellum of Pugs and other breeds.[3,80] A distinctive segmental, multifocal pattern of intense meningitis and encephalitis is a consistent finding in Chihuahuas,[1] Maltese,[85] and Pug dogs.[78,83] Park and colleagues[88] divided the histopathologic lesions of NME dogs into 3 phases: mild inflammatory cell infiltration in the acute phase; moderate malacic changes and intense inflammatory reactions, especially in the leptomeninges, in the subacute phase; and extensive malacia in the chronic phase. Lesion topography also includes extensive leptomeningeal inflammation.[3,78,84] Immunohistochemistry studies of lesions in a small cohort of dogs with NME suggest that IFN-$\gamma$ plays a major role in NME.[88]

#### *Necrotizing leukoencephalitis*

NLE has been described in Yorkshire terriers[89–94] and French Bulldogs[95,96] with differing clinical and topographic features. Clinically most dogs with NLE have presented with visual loss, seizures, and central vestibular signs reflecting forebrain and brainstem involvement.[89–91,93,95,96]

Histopathology of NLE is characterized by nonsuppurative leukoencephalitis with multiple necrotizing foci affecting the white matter of the forebrain and brainstem, with subsequent cavitary necrosis and prominent reactive gemistocytic astrogliosis (**Fig. 4**).[91,93,95–98] It is noteworthy that leptomeningeal involvement usually is minimal, in contrast to NME (see previous section). Neurons within gray matter appear to be unaffected despite parenchymal inflammation.[90,97] Areas of necrosis and cavitation with NLE are more extensive in comparison with NME, although the cavitation is less prominent in the brainstem and cerebellum. A recent report of NLE in the French Bulldog described inflammatory changes in the optic nerves and retina,[96] and one case report describes similar lesions in the spinal cord.[91] Spitzbarth and colleagues[96] demonstrated that a dominant T-cell response was associated with a marked upregulation of MHC class II expression, and that resident activated microglial cells rather than blood-derived macrophages play a central role as antigen-presenting and phagocytic cells in NLE of French Bulldogs. Similarly to GME, these findings are suggestive of local antigen presentation and possible immune-mediated inflammation.[6] However, these findings differ from those of GME, in which macrophages represent the dominant cell type of infiltrating lesions.[76,77,88]

## DIAGNOSTIC EVALUATION

MUO is a clinical diagnosis based on neurologic examination, cross-sectional imaging findings, and CSF abnormalities, supplemented by exclusion of infectious diseases.[4,99] For this reason there is no specific noninvasive antemortem diagnostic test, and many-other diseases can mimic the MUOs; definitive diagnosis of noninfectious inflammatory CNS disease requires histopathology.[16,100,101] However, Granger and colleagues[58] used a meta-analysis to formulate guidelines for establishing a presumptive diagnosis of MUO in the absence of histopathologic diagnosis (**Table 2**): In summary, most cases

**Table 2**
**Proposed guidelines for diagnosis of meningoencephalomyelitis of unknown origin**

| Diagnostic Variables | Descriptions |
|---|---|
| Signalment | Dogs older than 6 mo |
| Magnetic resonance (MR) imaging findings | Multiple, single, or diffuse intra-axial hyperintense lesions on T2W MR images |
| Cerebrospinal fluid analysis | Pleocytosis with >50% mononuclear (monocytes/lymphocytes) cells and increased protein concentration |
| Infectious disease testing | Infectious diseases based on geographic area should be ruled out |
| Image-guided biopsy and histopathology | Stereotactic systems, ultrasound-guided, endoscopic-guided, free-hand computed tomography–guided |

*Adapted from* Granger N, Smith PM, Jeffery ND. Clinical findings and treatment of noninfectious meningoencephalomyelitis in dogs: a systematic review of 457 published cases from 1962 to 2008. Vet J 2010;184:290–7; with permission.

diagnosed with MUO have multifocal neurologic signs, CSF mononuclear pleocytosis, and hyperintense lesions on T2-weighted (T2W) magnetic resonance (MR) imaging.[58]

Although some MR imaging features are common to the NEs and GME, none are considered specific for the diagnosis of any disease process. Moreover, the diagnostic efficiency of both CSF analysis and MR imaging is incomplete because some cases lack abnormalities in one or the other test.[1,58] Lamb and colleagues[102] determined that approximately 25% of brain MR images of dogs with an inflammatory CSF revealed no abnormalities, emphasizing that a normal brain MR image does not rule out CNS inflammatory disease.

### *Cross-Sectional Imaging*

Before MR imaging became widely available, computed tomography (CT) provided some help in the diagnosis of inflammatory CNS disease, especially when combined with CSF analysis.[103] CT imaging characteristics of NE include multifocal areas of hypoattenuation, absence of mass effect, and lack of contrast enhancement.[89] CT abnormalities in GME consist of multifocal or focal distributions, mass effect associated with edema and granuloma, and ventricular asymmetry.[103,104] However, lesions may be difficult to detect using CT if they are located in the caudal fossa or lack contrast enhancement.

MR imaging is a recommended diagnostic tool for all dogs with possible CNS inflammatory disease. Compared with cerebral parenchyma, inflammatory lesions are hyperintense on T2W and fluid-attenuated inversion-recovery (FLAIR) sequences, variably hypointense to isointense on T1-weighted (T1W) sequences without contrast, and have variable degrees of contrast enhancement. Although T2W sequences are sensitive in detecting MUOs, MR imaging does not identify all MUO lesions and lacks specificity in distinguishing the different subtypes of MUO.[58,105] Use of a gadolinium-based paramagnetic contrast agent increases the sensitivity of T1W MR imaging for inflammatory parenchymal or meningeal lesions.[102,106] However, the FLAIR sequence has been reported to have higher sensitivity when compared with T2W and precontrast and postcontrast T1W sequences in detecting brain lesions in dogs with multifocal localization and abnormal CSF analysis.[107] The presence or absence of contrast enhancement with inflammatory CNS disease depends on the degree of BBB disruption or presence of vasodilation or neovascularization, and as such is a nonspecific

finding associated with a variety of CNS diseases[102] and does not distinguish between specific infectious and noninfectious inflammatory diseases.[108] Moreover, lack of meningeal (ie, leptomeningeal) enhancement does not rule out meningeal disease that still can be evident on histopathology.[106,107] None the less, within the subtypes of MUO leptomeningeal enhancement is characteristic in Pug dogs[79,82] and other breeds[3] with NME, but is not a typical imaging feature of GME[107] or NLE.

The histologic characteristics that form the basis of the diagnosis of CNS disease cannot be determined using MR imaging, but a clinical diagnosis may be based on the pattern and number of lesions detected on MR images,[109] which can aid differentiation of intracranial neoplasia and meningoencephalitis.[102,104,107,110,111] Differential diagnoses for multifocal intracranial lesions include infectious meningoencephalitis, cerebrovascular lesions, CNS lymphosarcoma, and glial and metastatic neoplasms. A recent study determined that MR imaging is highly sensitive and specific for identifying brain lesions and classifying disease as inflammatory, but very poorly sensitive for diagnosing cerebrovascular disease.[104]

The most common MR imaging findings in GME include regions of multifocal or diffuse hyperintensity with irregular margins on T2W and FLAIR sequences in any part of the CNS, with variable enhancement after intravenous contrast is administered (see **Fig. 3**).[107,112] Although histopathologic lesions of GME typically are distributed primarily in the white matter, lesions on MR imaging are distributed throughout both gray and white matter[107]; mass effect with a suggestion of increased intracranial pressure also may be observed.[112]

NME is typically associated with asymmetric, multifocal cortical gray and white matter lesions with loss of gray/white matter demarcation and variable contrast enhancement; forebrain predilection, perilesional edema, mass effect, and irregular lesion margins are common.[1,79,82] Lesions appear isointense to hypointense on T1W images and hyperintense on T2W and FLAIR images,[3,79,113] and the mass effect may be sufficient to cause herniation.[1,3,79,82,113] However, although meningeal enhancement, mass effect, and ventricular dilation are frequent in Pugs with NME, NME and GME cannot be differentiated according to these features alone.[79,82] MR imaging characteristics of mass effect and contrast enhancement in NME also share similarities to those of neoplastic lesions; therefore, MR imaging findings common to NME lack specificity.[82,114,115] Increased lesion burden as evidenced on imaging in Pugs with NME has been correlated with increased disease time but not with prognosis.[82,116,117]

NLE lesions on MR imaging predominantly affect the subcortical white matter and brainstem.[91,94,96] Multifocal distribution of lesions and cavitation with mild to absent contrast enhancement in the brainstem are highly suggestive of NLE.[92,95,97] Affected areas appear hypointense on T1W images and hyperintense on T2W and FLAIR images (see **Fig. 4**).[90,97] The hyperintensity on FLAIR sequences within lesions likely reflects higher protein content in comparison with CSF. Varying degrees of ventriculomegaly also can be apparent.[90–92,95]

Especially for necrosis in the NEs, MR imaging can identify lesion topography reflective of the gross types of lesion associated with the different disorders.[1,82] It has been suggested that cavitary lesions, characterized by sharply demarcated T1W hypointensity and T2W and FLAIR hyperintensity without contrast enhancement, may be highly indicative of NE.[91,92,95] However, there was no such correlation in a study of Pug dogs with NME.[82] Brain MR imaging of dogs with chronic NE and necrosis showed widened sulci and dilation of the adjacent ventricle reflective of loss of tissue volume,[90,113] and there is a suggestion that necrotic lesions may imply disease chronicity.[91,116,118]

### *Cerebrospinal Fluid Analysis*

Typically CSF analysis of MUOs reveals mononuclear pleocytosis and elevated protein concentration, both of which may vary considerably in severity. Increased protein concentration is a nonspecific indicator of CNS disease, typically caused by either BBB disruption or increased intrathecal immunoglobulin production. The CSF in GME has been described as containing a mild to moderate lymphocytic, neutrophilic, or mixed cell pleocytosis.[62,119] In dogs with NE, CSF analysis similarly typically consists of a moderate to marked lymphocytic pleocytosis with greater than 80% lymphocytes, but a mixed cell pleocytosis may occasionally be seen.[58,69,80,93] Although CSF analysis is more sensitive than MR imaging in identifying abnormalities consistent with inflammatory disease, normal CSF analysis has been described in cases with histopathologically confirmed inflammatory CNS disease.[5,16,58,75,80,107] Overall, CSF analysis is highly variable in the various types of MUOs but with little difference between these groups.[58,120]

Other analyses of CSF have been studied for CNS inflammatory diseases, but lack disease specificity. CSF protein composition can be further defined by semiquantitative electrophoretic techniques, and abnormalities have been reported to be useful in the identification of inflammatory, neoplastic, and degenerative disease.[121–123] For instance, CSF electrophoresis of dogs with GME may reveal an increase in β- and γ-globulins.[59,122] The lesser degree of BBB disturbance and increased intrathecal production of (autoreactive) immunoglobulins in dogs with chronic GME reflect the immune-mediated nature of the condition.[59] Antiastrocytic autoantibodies in canine CSF were suggested to be specific for NME and GME,[81,124,125] but this seems unlikely because antiastrocytic autoantibodies have also been detected in cases of brain tumors and in clinically normal dogs.[11,124] Flow cytometry and immunophenotyping has been used to identify mononuclear cells in the CSF of inflammatory disorders[126] and identification of lineages of neoplastic cells, but its practical use for CNS inflammatory disease is hindered by the need for large volumes (4–5 mL) of CSF unless the cell count is very high.

### *Brain Biopsy*

A definitive diagnosis of CNS inflammatory disease is based on histopathology. Antemortem brain biopsy may yield a more definite diagnosis by which to guide treatment approaches, although such procedures depend on obtaining biopsy material from representative portions of the lesion. Minimally invasive techniques such as CT-guided[127–131] or MR-guided[132] stereotactic systems, free-handed techniques that use ultrasound,[133] CT,[134] or MR imaging,[101] and endoscopic-guided biopsy[135] have recently been developed for brain biopsy in dogs. Diagnostic accuracy of brain biopsy in canine CNS inflammatory disease ranges from 82% to 100%, based on the limited available data, and such information highly depends on the population disease types from which the biopsies were obtained.[101,127] Diagnostic yield for biopsy of inflammatory lesions may be influenced by sample size and difficulty in distinguishing between changes in the primary and secondary lesions such as edema and necrosis. Intraoperative cytologic evaluation of the biopsy sample may aid in diagnostic accuracy.[127,136] In addition to limitations in accuracy of diagnosis from biopsy, there are also risks that cannot be easily overlooked; a recent study suggested mortality and morbidity rates of 6% and 29%, respectively.[101]

### *Infectious Disease Testing*

Infectious causes of meningoencephalomyelitis should also be investigated to help differentiate infectious meningoencephalomyelitis from the MUOs and neoplastic

diseases.[99] Microbial culture of CSF has low yield, and culture of blood and urine may also be considered in cases of suspected bacterial infection.[137] More usefully, CSF, serum, or both can conveniently be analyzed for antibodies to infectious diseases, most notably *Neospora caninum*, *Ehrlichia* spp, *Anaplasma* spp, *Rickettsia rickettsia*, and *Coccidioides immitis*, although prevalent diseases vary with global location. Infection by *Cryptococcus* spp is usually detected by antigen testing, and other microbial DNA or RNA can also be detected by polymerase chain reaction (PCR) assays, which have high sensitivity and specificity.[8–10,99] Results should still be interpreted carefully to avoid false positives, and rigorous negative controls must be evaluated in parallel with the clinical sample. A negative PCR result needs to take into account that the nucleic acid may be present but at undetectable levels, the agent may be in the neural tissue but not in CSF, and the disorder may have been triggered by an agent that is no longer present.[99] Nonetheless, specific pathogens in CSF and diseased tissues have not been identified as being associated with the MUOs.[4,8–10]

### *Genetic Testing*

Many autoimmune diseases are complex polygenic traits whereby affected individuals inherit multiple genetic polymorphisms that contribute to disease susceptibility, and consequently act with environmental factors to cause disease.[24] Although strong familial inheritance was reported in Pugs with NME, a simple Mendelian inheritance pattern could not be demonstrated.[138] Along with the wide range of age of onset and variable clinical course, this finding suggested the possibility of genetic modifiers or other influences contributing to the disease phenotype.[80,138] Genome-wide association studies identified CFA 12 near the dog leukocyte antigen (DLA) complex with the development of NME,[12,139] and this region was subsequently focused on the region containing *DLA- DRB1*, *-DQA1*, and *-DQB1* genes.[12] Although the causative mutation had not been identified, fine mapping and candidate gene sequencing implicated linked-allelic homozygosity in the risk of developing NME.[12] Furthermore, it is possible to attain risk assessments for NME by sequencing only the *DQB1* gene that is now being used as a susceptibility haplotype when in the homozygous state.[140] Such findings strongly support the role of the immune system in NME. The strong DLA class II association of NME in Pugs resembles that of atypical variant/fulminant forms in the disease spectrum of human multiple sclerosis (MS).[12] A widely held concept is that MS occurs when certain environmental exposures (eg, viruses), or lack thereof (eg, sunlight and vitamin D), trigger the activation of CNS autoreactive T cells in genetically susceptible individuals, which leads to a CNS inflammatory disease[141,142]; therefore a similar pathogenesis is suspected for NME in Pugs.

## TREATMENT

Once infectious causes have been ruled out, the primary treatment of the MUOs is immunosuppression with corticosteroids or other agents. Initial treatment begins with patient stabilization based on severity of neurologic dysfunction followed by maintenance therapy. If there are seizures, anticonvulsant therapy is also required. Stabilization may necessitate supplementary oxygen for hypoxemia, crystalloid/colloid support to maintain cerebral perfusion and control hypotension, and osmotic therapy (eg, mannitol, hypertonic saline) to reduce elevated intracranial pressure.

Immunosuppression is central to the therapeutic management of MUO, despite the incompletely understood pathogenic mechanisms or triggers. The rationale of immunosuppression for autoimmune diseases is to induce disease remission through the inhibition of inflammation and modulation of lymphocyte function.[143] The ultimate

goal is to achieve disease remission while minimizing adverse effects. Corticosteroids historically have been the first-line therapy for the treatment of MUO. Often anti-inflammatory to immunosuppressive doses of corticosteroids (eg, prednisone, 0.25–0.5 mg/kg by mouth daily) are initiated until review of negative infectious disease testing, and then increased to immunosuppressive doses (2–4 mg/kg by mouth daily) for 2 to 4 weeks; after which the dose is gradually reduced or tapered every 4 weeks when clinical signs stabilize or improve. The ultimate goal is alternate-day therapy at the lowest effective dose to maintain remission of clinical signs or discontinuation of the drug.[144] Animals often will respond initially, but relapses are common; sustaining remission thus may require long-term high-dose corticosteroids, or administration of alternative immunosuppressive agents whereby the undesirable side effects of high-dose corticosteroid therapy can be avoided. Adverse effects of high-dose corticosteroids include gastric ulceration, steroid hepatopathy, alopecia, urinary tract infection, muscle weakness, and iatrogenic hyperadrenocorticism (see the article on corticosteroid therapy elsewhere in this issue by Jeffery).

Reported second-line immunosuppressive drug therapies for MUO include leflunomide,[145] procarbazine,[146] cytosine arabinoside,[17,147–152] lomustine,[144,153] mycophenolate mofetil,[154] azathioprine[155]; COP[149] (cyclophosphamide, vincristine, prednisone), and cyclosporine (**Table 3**).[118,155–159] Radiation therapy has also proved to be effective for focal GME lesions.[62] Not uncommonly, second-line therapies may be introduced early in the disease process in response to severe neurologic signs or rapid neurologic deterioration. Many of these secondary immunosuppressive agents have potential risks for myelosuppression, hepatotoxicity, gastrointestinal disturbances, and other drug-specific systemic effects; therefore, regular monitoring of complete blood count and serum biochemistry is recommended. A systematic review suggested a benefit, based on median survival, of prednisone combined with other immunosuppressive agents.[58] Overall median survival for dogs treated with corticosteroids plus a second-line immunosuppressive protocol ranged from 240 to 590 days. By comparison, survival in dogs treated with corticosteroids alone ranged from 28 to 357 days. However, in dogs with GME and NE, oral administration of lomustine and prednisolone or prednisolone alone had similar efficacy.[144]

Selection of a specific immunosuppressive protocol depends on the clinician's decision, the patient's clinical status, and the pet owner's financial considerations. In accordance with guidelines from other studies,[17,147,148,151] a common protocol is daily administration of prednisone at an immunosuppressive dose combined with cytosine arabinoside administered at 50 mg/m$^2$ every 12 hours as a subcutaneous bolus for 2 consecutive days, or by intravenous infusion at 200 mg/m$^2$ over 8 hours. The treatment cycle is repeated every 3 to 4 weeks for 3 cycles. Subsequently the interval between treatment cycles is increased by 1 week for 3 cycles at the new treatment interval. The treatment cycles are gradually extended to every 6 weeks. Concurrently the dose of prednisone is gradually tapered to a low-dose administration every other day. Intravenous administration of cytosine arabinoside has been described at higher doses (up to 600 mg/m$^2$) in severe cases of MUO.[152,160] The route of cytosine arabinoside administration and protocol likely to be most effective has been controversial. A pharmacokinetic study comparing subcutaneous bolus administration versus intravenous infusion revealed that based on Fick's first law of diffusion, intravenous infusion may produce a more prolonged exposure of cytosine arabinoside at cytotoxic levels in plasma in comparison with the concentrations after subcutaneous administration.[161] However, further study in dogs with MUO is needed to identify whether the sustained concentrations produced by intravenous infusion would improve penetration of cytosine arabinoside across the BBB and produce higher

**Table 3**
**Summary of immunomodulatory therapies for meningoencephalomyelitis of unknown origin**

| Drug[a] | Mechanisms of Action | Dosages |
|---|---|---|
| Azathioprine[155] | Alters purine metabolism by inhibiting DNA synthesis and mitosis; chromosome breaks; interferes with lymphocyte proliferation, reduces lymphocyte numbers, decreased T-cell–dependent antibody synthesis | 2 mg/kg PO, every 24 h for 2 wk, then decrease to 2 mg/kg every 48 h indefinitely; goal is to achieve alternate-day therapy with prednisone |
| Cyclosporine[155–159] | Inhibits T-cell activation through intracellular target calcineurin; decreases IL-2 and other cytokines preventing proliferation of T-cell and B lymphocytes; also decreases IL-3, IL-4, and TNF-$\alpha$ | 3–15 mg/kg PO every 12 h; or 5–12 mg/kg PO every 24 h when used in combination with ketoconazole 8 mg/kg PO every 24 h. Therapeutic target: trough levels between 200 and 400 ng/mL |
| Cyclophosphamide, vincristine, prednisone (COP)[149] | Cyclophosphamide is alkylating agent; introduces alkyl radicals into DNA strands of cells<br>Vincristine inhibits microtubule function and leads to a disruption in the mitotic spindle causing metaphase arrest and cytotoxicity | Cyclophosphamide: 50 mg/m$^2$ PO, every 48 h for 8 wk, then given in alternate weeks<br>Vincristine: 0.5 mg/m$^2$ IV, every 7 d for 8 wk, then every 14 d<br>Prednisone: 40 mg/m$^2$ PO, every 24 h for 7 d, then 20 mg/m$^2$ every 48 h for 7 wk, then same dose given in alternate weeks |
| Cytosine arabinoside[17,147–152] | Inhibits DNA polymerase; causes topoisomerase dysfunction and prevents DNA repair; cell cycle (S phase) | 50 mg/m$^2$ SC, every 12 h for 2 consecutive days, then repeat every 3 wk for 4 cycles; treatment interval is lengthened by 1 wk every 4 cycles with a maximum interval of 6–8 wk<br>Alternatively dose at same interval using IV infusion at 200 mg/m$^2$ over 8 h |
| Leflunomide[145] | Pyrimidine synthesis inhibitor; tyrosine kinase inhibition; targets B and T lymphocytes | 1.5–4.0 mg/kg PO every 24 h and adjusted based on blood levels (20–40 $\mu$g/mL) |
| Lomustine[144,153] | Alkylating agent; induction of intrastrand and interstrand DNA cross-linking; suppresses B- and T-cell proliferation | 60 mg/m$^2$ PO every 6 wk |
| Mycophenolate mofetil[154] | Purine synthesis inhibitor; selective to lymphocytes (B and T) via depletion of guanosine and deoxyguanosine nucleotides; suppresses dendritic cell maturation and reduces monocyte recruitment | Initial dose of 10–20 mg/kg PO every 12 h (lower dose, eg, 5 mg/kg, may be administered if concern for gastrointestinal side effects); after 1 mo reduce to 5–10 mg/kg every 12 h |

(*continued on next page*)

**Table 3**
**(*continued*)**

| Drug[a] | Mechanisms of Action | Dosages |
|---|---|---|
| Prednisone[151] | Targets macrophages via downregulating Fc receptor expression, decreases responsiveness to antibody-sensitized cells and decreases antigen processing; suppresses T-cell function and induces apoptosis of T cells; inhibits B-cell antibody production | 1 to 2 mg/kg PO, every 12 h for 3–4 wk; 0.5–1 mg/kg every 12 h for 6 wk, then 0.25–0.5 mg/kg every 12 h for 3 wk, then 0.25–0.5 mg/kg every 24 h for 3 wk, then 0.25–0.5 mg/kg every 48 h indefinitely |
| Procarbazine[146] | T-cell specific; monoamine oxidase inhibitor; cell cycle nonspecific with cytotoxicity in the S and G2 phases, DNA methylation, and free radical production | 25–50 mg/m$^2$ PO every 24 h |

*Abbreviations:* IL, interleukin; IV, intravenously; PO, by mouth; SC, subcutaneously; TNF, tumor necrosis factor.

[a] Immunomodulatory drugs are administered in combination with prednisone, which is gradually tapered.

*Data from* Refs.[17,144–159]

efficacy for the treatment of MUO. Alternative approaches include prolonged use of oral leflunomide or cyclosporine in combination with prednisone tapered over approximately 6 to 12 weeks.

Treatment effect often is monitored by clinical response and resolution of neurologic deficits, and occasional repeated CSF analysis and MR imaging. Serial MR imaging has been used to monitor resolution of clinical signs or evolution of lesions in dogs with meningoencephalitis.[91,102,116,117] In a small cohort of dogs presumptively diagnosed with MUO, Lowrie and colleagues[151] suggested that a combination of MR imaging and CSF analysis provided greater sensitivity for predicting relapse than one modality alone, although an abnormal CSF analysis at the 3-month reexamination, despite normal MR imaging findings, was associated with an increased risk of relapse. However, discontinuing treatment before MR-identified lesions resolved always resulted in relapse, suggesting that treatment can be tapered according to MR imaging or CSF findings.

## PROGNOSIS

Prognostic indicators and effects of the treatment of MUO have not been well characterized, but typically focus on the underlying disease process and severity of clinical signs. Focal forebrain lesions have been associated with a significantly longer survival time than those with multifocal/disseminated or brainstem lesions,[62] although subsequent studies have been unable to corroborate this finding.[146,151] Dogs presenting specifically with seizures have been found to have a significantly reduced survival time.[162] However, selection bias for (poor) prognosis also exists for series of dogs that must include a postmortem diagnosis, and may account for some reports of poor prognosis.[62,146] None the less, approximately 15% of dogs with GME die even before being treated.[58]

MR imaging may offer a broader assessment by which to guide therapy in dogs with MUO. MR imaging abnormalities of foramen magnum herniation, loss of cerebral sulci, or mass effect attributable to MUO have been associated with reduced survival time.[151] By contrast, postcontrast hyperintense lesions, rostral fossa involvement, caudal fossa involvement, and transtentorial herniation were not associated with mortality.[151] Lowrie and colleagues[151] also determined that none of the described MR imaging findings was associated with relapse or was predictive of long-term outcome. Others investigating MR imaging findings also report that contrast enhancement or lesion burden was not predictive of survival time.[82,94] Familiarity with MR imaging and CSF abnormalities indicating a poorer prognosis may facilitate more aggressive therapy and follow-up in these patients to improve survival.[151] However, these prognostic variables need further validation in the context of more tightly controlled prospective studies.

Determining prognosis based on the treatment effect for recovery in dogs with MUOs is challenging because of the difficulty in making definitive diagnoses, disease heterogeneity, treatment variability, and low sample size.[57,58] Outcomes described in dogs treated for MUO by various treatment regimens often are based on survival time, and the probability of long-term survival increases with increased disease duration.[149] Of note, Pugs with NE only receiving an anticonvulsant had mean survival intervals similar to those for dogs with other subsets of MUO.[58,80] Described risk factors in determining outcome or relapse are often based on post hoc analyses with multiple comparisons of low case numbers, which increases the potential for type I error, low power, and inability to take into account other confounding influences (eg, pet owner's decision, concurrent medical problems, financial considerations, indications to treat). Validated outcome measures (eg, neurodisability score) specific for the MUOs are needed to allow novel treatments to be tested objectively over a relatively short time scale.[149] There is still a need for a gold-standard treatment against which a new treatment can be tested. Although the criterion-referenced standard for a clinical trial is a randomized, placebo-controlled, double-blinded, prospective study, it is generally accepted that use of a placebo control treatment group is unethical because dogs with MUO have a poor outcome without treatment.[62,146] Nevertheless, treatment trials comparing 1 or more protocols would be simple to establish, although they would require multicenter collaboration. The lack of data acquisition using well-designed clinical trials means that treatment recommendations for MUO still remain empiric. It will be important to expand our understanding of the pathogenesis of MUO to enable the development of more targeted therapies for improved survival times and sustained remission.

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