Granulomatous meningoencephalomyelitis, necrotizing meningoencephalitis, and necrotizing leukoencephalitis are common inflammatory conditions of the canine central nervous system. Although each disease has unique histopathological features, these canine disorders collectively seem to be aberrant immune responses directed against the central nervous system. A review of the neurological signs and general neurodiagnostic approach to canine meningoencephalitis is followed by an overview of the specific clinical and neuropathological features of granulomatous meningoencephalomyelitis, necrotizing meningoencephalitis, and necrotizing leukoencephalitis. The aetiopathogenesis of each disorder is explored including potential genetic, immunological, and environmental factors along with the current and prospective immunomodulatory therapies for meningoencephalitis.

INTRODUCTION

Granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE) are common inflammatory conditions of the canine central nervous system (CNS). Whilst each disease has unique histopathological features, these canine disorders collectively seem to be aberrant immune responses directed against the CNS. Despite having been recognised for several decades, the aetiopathogeneses for these disorders remain elusive and gold standard treatment protocols have yet to be established.

The antemortem diagnosis of the specific variants of canine meningoencephalitis (ME) is challenging, since histopathological confirmation is required for a definitive diagnosis. In most cases, a presumptive antemortem diagnosis is achieved via a multimodal approach that includes: assessment of case signalment, neurological signs and neuroanatomic localisation, cerebrospinal fluid (CSF) analysis, cross-sectional imaging of the CNS and infectious disease testing. The antemortem diagnosis is often complicated by an overlap in the neurodiagnostic profiles. Therefore, the terminology meningoencephalitis of unknown aetiology (MUE) may be preferable on an antemortem basis in cases of idiopathic ME where histopathology is lacking (Adamo and others 2007, Schatzberg 2007, Zarfoss and others 2006).

A review of the neurological signs and general neurodiagnostic approach to canine ME is followed by an overview of the specific clinical and neuropathological features of GME, NME and NLE. The aetiopathogenesis of each disorder is explored including potential genetic, immunological and environmental factors along with the current and prospective immunomodulatory therapies for MUE.

ME: CLINICAL SIGNS AND NEURODIAGNOSTIC APPROACH

Clinical signs

The clinical presentation of ME is variable and typically reflects the arrangement and location of the CNS lesions. Although the spinal cord may be affected by CNS inflammation, the clinical signs associated with brain inflammation are considered primarily here. Meningoencephalitis commonly is acute in onset, progressive in nature and is associated with a multifocal to diffuse neuroanatomic localisation. Extraneural signs are rare; however, pyrexia and systemic leukocytosis occasionally accompany CNS inflammation.
Neurodiagnostic approach
The differential diagnosis for dogs presented for an acute onset of multifocal CNS signs includes genetic abnormalities, metabolic derangements, infectious and idiopathic ME, neoplasia, and toxin exposure. To differentiate among these disorders may be challenging; diagnostic testing typically includes: a minimum database (complete blood count (CBC), chemistry panel and urinalysis), survey radiographs of the thorax (+/- abdominal ultrasound) to rule down systemic disease and metastatic neoplasia, advanced cross-sectional imaging via computed tomography (CT) scan or magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) collection and analysis. Although more often utilised for suspected brain tumours, CT-guided brain biopsy and histopathological evaluation of brain tissue may be considered in cases of suspected ME (Koblik and others 1999).

CSF analysis
Cerebrospinal fluid analysis routinely includes cytological evaluation, differential cell counts and total protein measurement. Although pleocytosis commonly is present in cases of ME, cytology rarely provides definitive differentiation among idiopathic, infectious and neoplastic disorders. However, the CSF white blood cell differential, when combined with neuro-imaging (see below), may help the clinician to narrow the differential diagnosis. It is unclear whether the pleocytosis associated with ME is derived from an influx of systemic inflammatory cells or secondary to local production by the CNS macrophage phagocytic system (Kipar and others 1998). Regardless of the origin, inflammatory cells accumulate in the Virchow-Robin spaces surrounding blood vessels that penetrate the brain. The magnitude of CSF pleocytosis does not predict survival time, and in rare cases of ME, CSF cell counts may be misleadingly normal (de Lahun and Glass 2009). Elevated CSF total protein also is typical in ME and may be secondary to increased permeability of the blood CSF barrier, intrathecal immunoglobulin production or both (Munana and Luttgen 1998). Anti-body titres and polymerase chain reaction (PCR) testing for infectious diseases should be considered when CSF analysis and neuro-imaging are consistent with ME.

Cross-sectional imaging
Whilst CT scan may have diagnostic utility in some cases of inflammatory brain disease, MRI is the gold standard imaging modality for ME. Magnetic resonance imaging may be especially helpful for differentiating among the idiopathic meningoencephalitides, as it often discloses lesions that are reflective of the gross neuropathologies associated with each disorder. Although there are overlapping clinical and histopathological features among the meningoencephalitides, the topographical distribution of the lesions (for example, NME versus NLE) and presence or absence of necrosis (for example, GME versus NLE) may be imaging features that help direct a presumptive ante-mortem diagnosis. Magnetic resonance imaging also has several advantages over CT scan as it provides excellent anatomic detail (especially of the caudal fossa) and allows for acquisition of images in multiple planes (sagittal, transverse, dorsal).

Despite the limited soft tissue detail provided by CT scan, when coupled with CSF analysis, it may help to provide evidence of ME. The imaging features for several inflammatory brain diseases have been described (Plummer and others 1992, Thomas 1998); however, the CT appearance of ME is variable and non-specific. The presence or absence of contrast enhancement with inflammatory brain disease depends upon the degree of blood brain barrier (BBB) breakdown (Plummer and others 1992, Speciale and others 1992). Despite the fact that it cannot definitively differentiate among disease processes, CT scan may be especially useful for localising lesions before brain biopsy. An important limitation of CT scan is that it produces a beam hardening artefact (due to preferential absorption of low energy x-ray beams), most notably adjacent to the petrous parts of the temporal bones. This artefact may obscure the clinician’s ability to interpret brainstem and cerebellar lesions.

GRANULOMATOUS MENINGOECEPHALOMYELITIS

Background
In 1962, Koestner and Zeman utilised the nomenclature “reticulosis”, for a canine ME that is histopathologically consistent with GME (Cordy 1979, Koestner 1975). This term was introduced in human neuropathology in the 1950s, but went out of favour by 1980, with the reclassification of reticulosis as a primary CNS B cell lymphoma (Higgins and LeCouteur 2007). The terminology CNS reticulosis persisted in veterinary medicine despite a lack of similarity to the human lesion (Higgins and LeCouteur 2007). In 1972, Fankhauser divided CNS reticulosis in dogs into three categories: inflammatory, neoplastic and microgliomatosis (Fankhauser and others 1972). Histopathologically, the inflammatory form of reticulosis consists of histiocytic cells mixed with lymphocytes, plasma cells and occasionally other leukocytes; whereas monomorphic leukocytes predominate in the neoplastic form (Summers and others 1995). Inflammatory reticulosis of the brain and spinal cord has since been reclassified as GME (Braud and others 1978, Braund 1985, Sorjonen 1989, Thomas and Eger 1989, Summers and others 1995). Neoplastic reticulosis was reclassified as CNS lymphosarcoma (LSA) or malignant histiocytosis (Vandevelde and others 1981). Microgliomatosis has been reported only rarely in dogs (Vandevelde and others 1981).
out both grey and white matter (Fig 1a). MRI lesions often are distributed throughout the CNS white matter, and have irregular margins. Despite the predilection of the GME for white matter, MRI findings to disseminated GME, and discriminating among these differentials may be challenging.

The focal form of GME may be identified on CT or MRI as a non-specific single space occupying mass lesion (Speciale and others 1992, Kitagawa and others 2004). In ocular GME, the optic nerves may be isointense on T2-weighted images, and may enhance on T1-weighted images with the contrast medium (Kitagawa and others 2009) . The optic chiasm also may appear enlarged, reflecting the gross pathology that may be associated with this form (Fig 2).

Although CT scan is not as sensitive as MRI in delineating parenchymal and meningeval lesions, it may provide evidence of brain inflammation (Plummer and others 1992). Both focal and disseminated forms of GME may be associated with contrast enhancement on CT, and mass effect may be observed by displacement and maturation of blood derived monocytes or histiocytes (Summers and others 1995); however, the origin of the CNS inflammation (intrathecal versus systemic) has not been investigated rigorously. Occasionally, a few neutrophils and multinucleate giant cells also are present. Chronic granulomatous lesions may compress and invade adjacent CNS parenchyma, leading to necrosis and vasogenic oedema formation (Braud 1985, Summers and others 1995). In areas of chronic oedema, the surrounding neurophil may contain astrogliosis.

**Neuro-imaging**

Although not specific for GME, the most common MRI findings for the disseminated form include multiple hyperintensities on T2-weighted or fluid attenuated inversion recovery (FLAIR) sequences scattered throughout the CNS white matter (Cherubini and others 2006, Cherubini and others 2008). Lesions typically assume an infiltrative appearance and have irregular margins. Despite the predilection of the GME for white matter, MRI lesions often are distributed throughout both grey and white matter (Fig 1a). The lesions are variable intensity on T1-weighted images and have variable degrees of contrast enhancement (Cherubini and others 2006). Vasogenic oedema in the white matter is commonly present on T2-weighted images and appears hyperintense to cerebral parenchyma. Meningeval enhancement is not commonly apparent. Mild NME, infectious ME, CNS LSA and less commonly glial and metastatic neoplasms may present with similar clinical and MRI findings to disseminated GME, and discriminating among these differentials may be challenging.

The focal form of GME may be identified on CT or MRI as a non-specific single space occupying mass lesion (Speciale and others 1992, Kitagawa and others 2004). In ocular GME, the optic nerves may be isointense on T2-weighted images, and may enhance on T1-weighted images with the contrast medium (Kitagawa and others 2009) . The optic chiasm also may appear enlarged, reflecting the gross pathology that may be associated with this form (Fig 2).
Idiopathic inflammatory disorders of the canine CNS

Aetiopathogenesis

Despite its recognition as a clinical entity for over four decades, the aetiopathogenesis for GME remains unclear. Genetic, autoimmune, infectious, neoplastic and even toxic causes have been theorised. Previous work has demonstrated that females are predisposed to GME which is similar to other autoimmune demyelinating diseases including multiple sclerosis (MS) and experimental allergic encephalitis (EAE) (Munana and Luttgen 1998, Hoffman and others 2001, Herrera and others 2007). The pathogenesis of the female predisposition for autoimmune CNS diseases is unclear, however a connection between sex steroid associated alterations in T-helper cytokines, suppression of regulatory cytokines and X-chromosome susceptibility alleles may be involved (Hoffman and others 2001, Herrera and others 2007).

Kipar and others have suggested that GME is a delayed type hypersensitivity reaction with an autoimmune basis, supported by a predominance of major histocompatibility complex class II and CD3 antigen-positive T-lymphocytes (Kipar and others 1998). Suzuki and others subsequently confirmed a predominance of CD3 positive T lymphocytes and a complete absence of the CD79 (B cell marker) immunoreactivity in four cases of GME (Suzuki and others 2003b). However, the major factors affecting survival were neuroanatomic localisation and focal versus multifocal neurological signs. Dogs with focal GME were reported to survive longer (median 114 days) than those with the disseminated form, which die within a few days to weeks (median eight days) of diagnosis (Munana and Luttgen 1998). This large study suggests that GME has a poor prognosis, with most dogs succumbing to the disorder or euthanased within a few weeks to months after diagnosis, despite steroid treatment. However, the study was limited to post-mortem examination confirmed disease, so survival times and the associated prognosis may be biased towards dogs with severe GME.

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FIG 1. Disseminated granulomatous meningoencephalitis (GME). (a) Transverse, T2-weighted MRI image at the level of the midbrain and cerebral hemispheres. Multiple, infiltrative hyperintensities are scattered throughout the central white matter. These hyperintense lesions likely represent a combination of oedema and inflammation. (b) Subgross GME lesions seen here in the cerebrum and midbrain. (c) The cells in the perivascular cuffs include lymphocytes, plasma cells and large, pale histiocytic cells. The left panel shows coalescing cuffs. When several cuffs coalesce, a grossly visible lesion will be evident. Despite the density of the cuffs, there is little tendency for cells to infiltrate the parenchyma. (d) High magnification view of lymphocytes and large histiocytoid cells in a perivascular cuff. Plasma cells, rare in this image, may also be present.
same group was unable to demonstrate statistical differences in the number of CD-3 positive cells between GME and NME or GME and central malignant histiocytosis (Suzuki and others 2003a, Suzuki and others 2003b). Immunophenotyping studies are in progress, preliminarily showing a consistent pattern among disseminated GME cases (Higgins and LeCouteur 2007). Anti-astrocytic antibodies have also been identified in the CSF of dogs with GME (Matsuki and others 2004). The complete immunological profile of GME, and whether CNS autoantibodies are the cause or consequence of inflammation, remains to be elucidated.

Despite the conventional view that GME is a disorder of immune dysregulation, some veterinary neuropathologists suggest that GME is a “lymphoproliferative disorder” with features of both inflammation and neoplasia (Brian Summers, personal communication). Focal GME is particularly similar to neoplasia, as lymphocytes within the perivascular cuffs often have variable degrees of pleomorphism and mitotic indices (Fankhauser and others 1972). Interestingly, CSF from disseminated GME cases occasionally contains lymphoblasts (Schatzberg, personal observations). It is unclear whether the abnormal lymphocytes within brain lesions or CSF are reactive inflammatory cells or representative of a true neoplastic population.

Potential infectious triggers for GME have been considered in recent years (Schatzberg and others 2005, Schwab and others 2007). Borna virus was reported in several dogs with ME in Japan and Switzerland and has been proposed as a causative agent for GME (Weissenbock and others 1998, Okamoto and others 2002). Borna virus, however, is unlikely to be a common aetiology for GME, given its predilection for CNS grey matter. Schwab and others have demonstrated positive immunohistochemistry (IHC) for West Nile, canine parainfluenza and encephalomyocarditis viruses in severe GME lesions (Schwab and others 2007). The significance of these observations is unclear, as the positive IHC may be due to antibody cross-reactivity with endogenous proteins, as has been described with measles infections (Sheshberadaran and Norrby 1984). Alternatively, these results may support the theory that GME is a non-specific inflammatory response to various antigens, of which pathogens comprise an important subset.

To date, molecular investigations at the University of Georgia College of Veterinary Medicine (UGA-CVM) have failed to disclose consistent infectious agents associated with GME; however, work is ongoing to investigate an extremely diverse group of potential viral, bacterial and rickettsial triggers (Schatzberg 2007). Recently, we have identified Bartonella species and Mycoplasma species in sporadic, confirmed cases of disseminated GME (Barber, unpublished). The author’s view is that GME is most likely a non-specific immunological response and multiple environmental triggers (pathogens, vaccinations) and genetic factors are likely to play roles in the aetiopathogenesis.

**Fig 2. Ocular granulomatous meningoencephalitis (GME)/optic neuritis. Involvement of the optic nerves and chiasm can produce the clinical deficits of optic neuritis. Note the brownish discoloration of the cut surface of each optic nerve. The inset displays a subgross histologic view of the optic chiasm revealing extensive perivascular infiltrates**
of 4·5 years (Kuwamura and others 2002). Dogs with both NME and NLE commonly manifest cerebro-thalamic signs due to the predominance of lesions in the prosencephalon; NLE also may cause mid to caudal brainstem signs (de Lahunta and Glass 2009). However, due to the multifocal nature of inflammatory disease, variations may occur with either disorder and clinical signs are primarily reflective of the lesion locations. The signs associated with NE typically are rapidly progressive and most commonly include seizures, depression, circling, vestibulo-cerebellar signs, visual deficits and ultimately death.

**Neuro-imaging**

The characteristic distribution of lesions observed in NME and NLE may aid in the cross-sectional imaging diagnoses (see Neuro-pathology section). Typical MRI lesions associated with NME include asymmetric, multifocal prosencephalic lesions affecting the grey and white matter, with variable contrast enhancement on T1-weighted imaging (Young and others 2009). Loss of grey/white matter demarcation also may be discernible (Flegel and others 2008, Young and others 2009) (Fig 3a). Lesions appear hyperintense on T2-weighted images and isointense to slightly hypointense on T1-weighted images, with slight contrast enhancement. In NLE, multiple, asymmetric bilateral prosencephalic lesions mainly affecting the subcortical white matter have been described (von Praun and others...
The NLE lesions are hyperintense on T2-weighted and FLAIR images and often include multiple cystic areas of necrosis (Fig 4a). These lesions are hypointense or isointense on T1-weighted images and contrast enhancement is variable. Magnetic resonance imaging findings may increase the clinician’s confidence in a presumptive diagnosis of NE.

Computed tomography scan also may support a diagnosis of NE. In the acute stages of either NME or NLE, focal hypodense lesion(s) may be appreciated in the prosencephalon (Thomas 1998). The lesions may or may not enhance with contrast. In chronic NE, the primary lesions on CT scan are characterised by necrosis and cystic changes (Thomas 1998).

**Neuropathology**

The histopathological hallmarks of both NME and NLE include non-suppurative ME and bilateral, asymmetric cerebral necrosis. Necrotising ME commonly affects the cerebral hemispheres and subcortical white matter, with profound inflammation extending from the leptomeninges through the cerebral cortex into the corona radiata (Summers and others 1995) (Fig 3b). The anatomic demarcation between grey and white matter often is lost, a feature identified reliably on gross histopathological examination (de Lahunta and Glass 2009) (Fig 3a and c). Meningeal infiltrates, characterised by plasma cells, lymphocytes and occasionally histiocytes, are most abundant in the cerebral sulci and fissures (Fig 3d).

Areas of malacia, necrosis with liquefaction, and cavitation (similar to those seen in NLE) may be present in NME. Chronic, protracted cases may demonstrate neuronal loss and gemistocyte infiltration.

In contrast, NLE is relatively sparing of the cerebral cortex and meninges, and predominately affects periventricular cerebral white matter including the centrum semiovale, thalamocortical fibres, internal capsule and thalamus (Summers and others 1995) (Fig 4c). Lesions also may occur in the brainstem. The degree of necrosis associated with NLE is related directly to the duration and severity of the disease. Areas of necrosis often coalesce to form larger, more dramatic areas of cavitation with NLE as compared to NME. Within the affected white matter, numerous swollen and necrotic axons, gemistocytes, gitter cells (local macrophages), reactive microglia and occasional perivascular infiltrates may be present (Summers and others 1995) (Fig 4b and d). Interestingly, neurons in the grey matter appear unaffected despite the surrounding inflammation. Small numbers of lymphocytes and plasma cells may be present in the leptomeninges; however, meningeal inflammation typically is minimal.

**Aetiopathogenesis**

The aetiopathogeneses for NME and NLE are poorly understood. Recently, we evaluated pedigree information on a large cohort of pugs and demonstrated a strong familial inheritance pattern for NME (Greer and others 2008). While this transmission data is not surprising, a simple Mendelian inheritance pattern could not be demonstrated. The latter suggests that NME is a multifactorial disorder. A multifactorial pathogenesis recently has been demonstrated for acute necrotising encephalopathy (ANE) in children, which occurs secondary to influenza and parainfluenza infections (Neilson and others 2009) Missense mutations in the nuclear pore gene RANBP2 have been demonstrated to be susceptibility alleles for familial and recurrent cases of ANE. A similar combination of genetics and infectious triggers may be responsible for canine NE. Molecular studies are ongoing to assess for genetic susceptibility loci and a diverse group of potential infectious triggers that may lead to immune dysregulation in NME and NLE.

Although it is tempting to consider NME and NLE as distinct entities, these disorders may represent a spectrum of CNS injury with similar pathogeneses. Interestingly, neuropathologists have...
evaluated the brains from pugs, several Maltese terriers, and Chihuahuas with lesions that typify NLE (rather than NME as reported in these breeds) (de Lahunta and Summers, personal communication, Higgins and LeCouteur 2007). Conversely, we have studied histopathologically confirmed NME in a Yorkshire terrier. (Schatzberg and Summers, unpublished). Autoimmune encephalomyelitis (EAE) models in rats may provide insights into such variations in lesion topographies within and among different dog breeds. Minor modifications of MHC haplotypes in EAE rats result in different but reproducible patterns of brain inflammation following exposure to a myelin-oligodendrocyte-glycoprotein (Storch and others 2006). Similarly, the histopathologic differences among the NEs may result from minor genetic differences among breeds, modifying genes and/or variations in antigenic exposures.

An autoimmune pathogenesis has been suggested for NME based on the presence of anti-astrocytic and glial fibrillary acid protein (GFAP) autoantibodies in CSF of affected dogs (Uchida and others 1999, Matsuki and others 2004, Shibuya and others 2007). However, similar antibody levels occur in the CSF of dogs with GME, brain tumours and even some clinically normal dogs (Shibuya and others 2007, Toda and others 2007). Whether GFAP autoantibodies are the inciting cause of NME, representative of a breed-specific fragility of astrocytes, or the consequence of prolonged tissue destruction secondarily to infectious disease, requires further investigation.

Because of the neuropathological similarities to viral meningoencephalitides in other species, viral aetiologies have been considered for NE (Cordy and Holliday 1989, Schatzberg and others 2005). The histopathologic lesions associated with canine NME are especially similar to those present in human herpesvirus ME (Cordy and Holliday 1989, Whitley and Gann 2002). As canine herpes virus-1 (CHV-1) may cause encephalitis in neonates (Percy and others 1970, Adams and others 1984, Whitley and Gann 2002), it is conceivable that NE is triggered by a recrudescence of a latent herpesvirus infection. Interestingly, the isolation of a “herpes-like virus” was reported in the NME report by Cordy and Holliday in 1989, but the viral isolate was not retained (Cordy and Holliday 1989).

Further attempts at viral isolation from dogs with NME have been unsuccessful (Summers, personal communication); however, Mx proteins, interferon-induced GTPases associated with viral and inflammatory diseases, have been demonstrated in brain tissues from pugs with NME (Porter and others 2006). To date, broadly reactive PCR assays for herpesviruses have been negative on a large number of paraffinised and freshly frozen NME brains (Schatzberg and others 2005, Greer and others 2008). Moreover, PCR screening of NME brains for an extremely diverse group of deoxyribonucleic acid (DNA) and ribonucleic acid viruses has failed to identify viral nucleic acids (Schatzberg, unpublished). Whilst the lack of viral nucleic acids in NME brains argues against a directly acting, neurotropic virus, this PCR data does not exclude the possibility of a viral trigger for NE via molecular mimicry (Evans and others 1996, Oldstone 1998, Theil and others 2001). Another possibility is that a pathogen is present (but at undetectable levels) in the presence of a self-perpetuating immune response, a phenomenon that has been described for flavivirus infections (Krueger and Reid 1994). Investigations are ongoing to pursue direct acting neurotropogens as well as para- and post-infectious pathogenesis for autoimmune inflammation in canine NE.

**MENINGOENCEPHALITIS OF UNKNOWN AETIOLOGY**

**Background and perspectives**

The majority of retrospective studies evaluating immunosuppressive treatment protocols for canine idiopathic ME include very few cases with confirmed histopathological diagnoses. The various combination protocols published in small cases series have been applied predominantly to cases of MUE (Zarfoss and others 2006, Adamo and others 2007, Coates and others 2007, Menaut and others 2008). Because MUE represents a broad spectrum of disease, it is unlikely that a “gold standard” therapy will be identified. Further complicating the interpretation of published cases is a paucity of prospective data on steroid monotherapy for MUE. As such, the utility of secondary immunomodulation is difficult to evaluate objectively. Standardised corticosteroid protocols also are lacking within and among published reports. Occasionally, standardised dosing and intervals for the adjunctive immunotherapy under investigation are lacking, and “exit strategies” have not been designed for patients that are non-responsive to treatment. In summary, the true efficacy of the various immunosuppressive agents for confirmed GME and NE is presently unknown.

**Treatment protocols**

At present, immunosuppression is the mainstay of therapy for MUE. Most clinicians treat MUE with corticosteroids (prednisone or dexamethasone). Depending on the severity of signs and the index of suspicion for infectious disease, some specialists will initiate therapy with anti-inflamatory steroids (0.5 to 1.0 mg/kg prednisone) and await serology and PCR results for regional infectious diseases. If the index of suspicion is extremely high for idiopathic inflammatory disease (for example, pug with MRI lesions consistent with NME), the authors directly initiate immunosuppressive therapy. Response to corticosteroids is variable and may be temporary, but dogs often have a favourable, initial response to steroid monotherapy. Additional immunosuppression is considered on a case by case basis, but the authors typically utilise secondary immunomodulatory agents upon review of negative serology and PCR results. At such time, we utilise the below prednisone protocol (based on clinical experience and not published data), often in combination with one or more of the immunomodulatory drugs. Cytosine arabinoside (CA), procarbazine, cyclosporine, lomustine (CCNU), leflunomide, mycophenolate mofetil (MMF) and azathioprine (Tipold and Schatzberg, in press) have been reported as adjunctive therapies.

**Prednisone**

- 1.5 mg/kg twice a day for three weeks
- 1.0 mg/kg twice a day for six weeks
- 0.5 mg/kg twice a day for three weeks
- 0.5 mg/kg once a day for three weeks
0.5 mg/kg every other day indefinitely (may reduce to 0.25 mg/kg every other day).

As mentioned earlier, steroid monotherapy has not been investigated prospectively as a treatment for MUE. With disseminated GME, 23 cases were reported retrospectively with a survival range of 8-41 days (Munana and Luttgen 1998). In a clinical setting, steroid monotherapy may resolve signs associated with MUE in some dogs, but insufficiently or only transiently provides resolution in others. Moreover, long-term, high-dose corticosteroid therapy often causes adverse effects including polyuria-polydipsia, polyphagia, weight gain, hepatotoxicity, gastrointestinal ulceration, pancreatitis and iatrogenic hyperadrenocorticism. These combined factors have led to a recent focus on complementary immunomodulatory drugs to treat MUE.

Cytosine arabinoside Cytosine arabinoside is a chemotherapeutic agent used to treat several neoplastic conditions in both human and veterinary medicine. Over the past several years, CA has been utilised for its immunosuppressive properties as an adjunctive therapy for MUE (Zarfoss and others 2006, Menaut and others 2008). Cytosine arabinoside is a synthetic nucleoside analogue, which crosses the BBB in dogs, undergoes enzymatic activation, competes for incorporation into nucleic acids and competitively inhibits DNA polymerase in mitotically active cells (Scott-Moncrieff and others 1991). Cytosine arabinoside also causes topoisomerase dysfunction, prevents DNA repair, and inhibits ribonucleotide reductase and glycoprotein synthesis (Griffin and others 1982, Garcia-Carbonero and others 2001). Cytosine arabinoside is metabolised via deamination in the liver, plasma, granulocytes and gastrointestinal tract. Side effects are dose dependent and include myelosuppression, vomiting, diarrhoea and hair loss (Scott-Moncrieff and others 1991).

Cytosine arabinoside is administered as a subcutaneous injection at a dose of 50 mg/m² every 12 hours for two consecutive days and repeated every three to six weeks, indefinitely (Zarfoss and others 2006). Previous reports of CA treatment regimes for MUE showed survival ranges of 46 to 1025 days (Zarfoss and others 2006) and 78 to 603 days (Menaut and others 2008). The authors commonly use CA as an adjunctive therapy for MUE in combination with prednisone as described earlier. Typically, a CBC is performed 10 to 14 days after the first course of CA therapy and then periodically throughout the course of treatment. In our experience, side effects have been minimal and dogs with MUE have a fair long-term prognosis with combined CA/prednisone therapy.

With combined CA/prednisone therapy, the CA dosing interval is gradually increased over several months and the steroids are tapered to the lowest dose possible, which often ameliorates clinical signs and minimises systemic side effects (Zarfoss and others 2006). Recurrence of clinical signs with steroid dose reductions may occur, so the authors gradually taper steroids as per the above section. After four months of a steroid taper, we typically maintain dogs indefinitely on 0.5 mg/kg prednisone PO once daily or every other day depending on the resolution of neurological signs. Relapses are treated aggressively as they may be refractory to treatment. Recently, intravenous (iv) rescue CA protocols (iv constant rate infusion of CA at 200 mg/m² over 48 hours) have been described for the initial treatment of severe MUE, which at UGA-CVM also has proven useful for severe relapses (de Stefani and others 2007). With relapses, some dogs also may require tertiary immunomodulatory drugs for the control of clinical signs.

Procarbazine Procarbazine is an antineoplastic, alkylating agent with multiple sites of action, and also has been used extensively to treat MUE. It is lipid soluble, crosses the BBB, and alkylates DNA at the O6 position of guanine, inhibiting insertion of essential DNA precursors. Procarbazine also disrupts ribonucleic acid (RNA) and protein synthesis. For treatment of MUE, procarbazine is given PO at a dose of 25 to 50 mg/m²/day (Cuddon and Coates 2002). Side effects include myelosuppression, nausea, vomiting, hepatic dysfunction and neurotoxicity.

Procarbazine has been used as an adjunctive therapy with corticosteroids and as a sole immunomodulatory agent for MUE. The use of procarbazine and prednisone as combination therapy was investigated in 20 dogs with MUE and compared with an untreated group of 11 dogs with confirmed GME (Coates and others 2007). The prednisone dose was reduced or discontinued in 17 dogs and median survival time was 15 months. The authors recommended monitoring a CBC once weekly for the first month of therapy and monthly thereafter. If improvement was noted after the first month, the procarbazine dose was reduced to every other day, provided that relapses were not observed.

Cyclosporine Cyclosporine is an immunosuppressive agent that can be used as a monotherapy but more typically is combined with prednisone and/or ketoconazole to achieve remission in cases of MUE (Adamo and others 2007). Cyclosporine acts by directly suppressing T lymphocyte activation and proliferation (Bennett and Norman 1986). In addition, cyclosporine prevents synthesis of several cytokines including interleukin-2, which indirectly inhibits T-cell proliferation. The rationale for its use in the treatment of MUE/presumptive GME is based on the suggestion that GME is T-cell-mediated delayed-type hypersensitivity (Kipar and others 1998). Although cyclosporine has poor BBB permeability, ME may allow the drug access to the CNS compartment. Moreover, cyclosporine likely concentrates effectively in the cerebral endothelial cells and choroid plexus (Begley and others 1990). Lesions associated with GME and NE are primarily perivascular; therefore, a therapeutic concentration of cyclosporine likely reaches the intracellular compartments of the lymphocytes and macrophages in affected areas of the CNS in these disorders (Adamo and O’Brien 2004).

Cyclosporine works rapidly and reaches effective steady state blood levels within 24 to 48 hours of initiation of therapy (Adamo and O’Brien 2004). When used as the sole therapeutic agent for MUE, a starting dose of 6 mg/kg PO every 12 hours of cyclosporine has been recommended to achieve therapeutic serum concentrations (Adamo and others 2007).
The microemulsified form (Neoral®), or its generic equivalent (cyclosporine modified), is recommended, as a uniform blood level is attained at lower doses compared to Cyclosporine USP, Sandimmune® (Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936) (Gregory 2000). The most common adverse effects include diarrhea, anorexia and vomiting, all of which typically subside when the dose is divided more evenly throughout the day. Occasionally, gingival hyperplasia, papillomatosis, hirsutism, excessive shedding and insulin resistance may occur, requiring discontinuation of therapy (Robson 2003). Rare side effects include nephrotoxicity and/or hepatotoxicity.

Cyclosporine is metabolised by cytochrome P-450; thus, phenobarbital will decrease cyclosporine blood levels as it induces the P-450 enzyme (Robson 2003). If the use of cyclosporine is cost prohibitive, it may be combined with ketoconazole. Ketoconazole significantly lowers the dose of cyclosporine needed to achieve effective blood levels by inhibiting the cytochrome P-450 enzymes and decreasing the systemic clearance of the drug. The recommended combined doses for combination therapy are 5 mg/kg po once a day cyclosporine and 8 mg/kg po once a day ketoconazole (Adamo and others 2007) Side effects associated with ketoconazole include anorexia, vomiting and diarrhea. Hepatotoxicity has been reported rarely, and it is noteworthy that ketoconazole is teratogenic.

In 2007, Adamo and others retrospectively evaluated the utility of cyclosporine for the treatment of MUE. Ten cases of MUE were evaluated including dogs treated with cyclosporin monotherapy and cyclosporin in combination with corticosteroids and/or ketoconazole. The overall median survival time for all dogs in the study was 930 days (range, 60 to more than 1290 days). Side effects were minimal and included excessive shedding, gingival hyperplasia and hypertrichosis.

Lomustine Lomustine (CCNU) is an antineoplastic agent with potent immunosuppressive properties that relate to its toxic effect on lymphocytes. Lomustine is a highly lipid soluble, nitrosourea compound. It readily crosses the BBB and alkylates both DNA and RNA. Bone marrow suppression (leukopenia and delayed thrombocytopenia) and gastrointestinal upset (vomiting and diarrhea) are the most common side effects. Hepatotoxicity also has been reported in dogs when used at very high doses (90 mg/m² every three to four weeks concurrently with other hepatotoxic drugs) (Kristal and others 2004). Serum chemistry monitoring is recommended after the first treatment, then every three months thereafter. Although the use of lomustine for MUE is common, and anecdotally effective (Dr Allen Sisson, personal communication), there are no peer reviewed manuscripts that have evaluated its utility in this application.

In 2007, investigators on two separate abstracts reported that when combined with low-dose prednisone to treat MUE (23 cases total), lomustine resulted in longer survival times compared to prednisone alone (Flegel and others 2007, Uriarte and others 2007). Flegel and others reported a dose of 60 mg/m² po every six weeks to be effective, with minimal side effects (Flegel and others 2007). Further evaluation of lomustine as an adjunctive therapy for MUE is needed.

Mycophenolate mofetil Mycophenolate mofetil is a lymphocyte specific immunomodulatory drug that decreases the recruitment of inflammatory cells and has been preliminarily reported in five dogs as an adjunctive therapy for MUE (Felini-Pascual and others 2007). An initial dose of 20 mg/kg po twice a day was recommended; after one month of treatment, the dose was decreased to 10 mg/kg twice a day. Side effects included haemorrhagic diarrhoea, which subsided with dose reduction and/or discontinuation of the drug. Neither bone marrow suppression nor hepatotoxicity were reported in the limited dogs treated. Although initial responses are encouraging, the authors concluded that larger, prospective studies are needed to evaluate the efficacy of MMF in the treatment of MUE.

Leflunomide Leflunomide is an immunomodulatory drug that has efficacy in experimental models of autoimmune diseases (Gregory and others 1998). The active metabolite of this drug, teriflunomide (A77), inhibits T- and B-cell proliferation, suppresses immunoglobulin production and interferes with cell adhesion. In addition to its immunosuppressive effects, leflunomide has both in vitro and in vivo antiviral properties (Chong and others 2006). The recommended dose range of leflunomide is 1.5 to 4 mg/kg po once a day; however, this dose may be adjusted, based on A77 blood level measured 24 hours after administration (Gregory and others 1998). In human beings, A77 reaches peak blood levels in 6 to 12 hours, has a long half life of approximately two weeks, and can take up to two months to reach steady state. Dose adjustments should be made to keep blood levels in a safe, therapeutic range (20 to 40μg/ml). Adverse side effects are seemingly rare in dogs; however, they may include thrombocytopenia and haemorrhagic colitis.

In 1998, Gregory and others reported on five dogs with MUE that were treated with leflunomide due to a poor response or side effects associated with prednisolone therapy (Gregory and others 1998). All dogs, treated over 4 to 11 months, had good to excellent improvement in their neurologic status with no reported side effects. Post-treatment MRI of two dogs showed partial to marked resolution of cortical lesions. Further studies are needed to critically evaluate the potentially useful role of leflunomide in MUE.
prognoses among GME, NE, infectious ME and neoplasia. Until more rigorous studies are performed, however, the best therapies and prognoses for the specific disorders will remain unknown.

It is noteworthy that Schwab and others recently evaluated CNS tissues for the presence of pathogens in 53 dogs with MUE (Schwab and others 2007). On an antemortem basis, these cases would have fit our criteria for immunosuppressive therapy. Interestingly, the investigation revealed a causative agent in 26 per cent of MUE cases including porcine herpes virus-1, Escherichia coli, a new disease pattern of parvovirus infection, West Nile virus, canine parainfluenza virus and encephalomyocarditis virus (EMCV). Recent pan-viral PCR studies have identified bunya-polyoma- and paramyxoviruses in CSF from cases of canine MUE (Schatzberg, unpublished). It is possible that antiviral therapies will ultimately play a role in improving the treatment of canine MUE.

CONCLUSIONS

Despite having been recognised for decades, GME, NME and NLE continue to challenge the veterinary community. Collectively, these idiopathic meningoencephalitides seem to be CNS disorders of immune dysregulation, each with relatively unique neuropathologies. From a treatment perspective, it currently is unclear whether we should continue to focus on the similarities or shift our attention to the differences among these disorders. Optimal treatments for the individual disorders remain unknown, because the vast majority of cases are treated with empirical immunosuppression without definitive diagnoses. At present, although treatments vary by institution, most cases of MUE within individual specialty hospitals are treated similarly to one another. The prognosis for canine ME, in general, seemingly has improved with adjunctive immunomodulatory therapies. A more basic understanding of the aetopathogeneses (for example, genetic, immunological and pathogenic components) remains critical for targeted therapies and ultimately for improving survival times for these elusive, and often life threatening disorders.

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References

Coxson, P. & Coates, J. (2002) New treatments for Granulomatous Meningoencephalitis. American Conference of Veterinary Internal Medicine, Dallas, Texas, USA