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Review

# Clinical presentation, diagnostic findings, prognostic factors, treatment and outcome in dogs with meningoencephalomyelitis of unknown origin: A review

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ABSTRACT

Meningoencephalomyelitis of unknown origin (MUO) encompasses a group of idiopathic, most likely immune mediated, inflammatory central nervous system diseases that cause clinical, diagnostic and treatment challenges to veterinary neurologists. Clinical criteria for obtaining this presumptive diagnosis are currently available, and multiple treatment protocols have previously been investigated in small (prospective or retrospective) case series. As this group of diseases is considered fatal if left untreated, the identification of clinically usable prognostic indices could be of great value. This review provides an overview of recent developments in the clinical presentation, diagnostic findings, possible prognostic factors, treatment and outcome in dogs diagnosed with MUO.



## Introduction

Meningoencephalomyelitis of unknown origin (MUO) encompasses a group of idiopathic, non-infectious central nervous system (CNS) diseases (Talarico and Schatzberg, 2010; Coates and Jeffery, 2014). It noteworthy that the term MUO is synonymous with MUA (etiology) and MUE (etiology), and that all terms are intermingled throughout the literature. This group of idiopathic non-infectious meningoencephalomyelitides (NIME) includes several subtypes, including steroid responsive meningitis-arteritis (SRMA), eosinophilic meningoencephalitis (EME), granulomatous meningoencephalomyelitis (GME) and necrotizing encephalitis (NE; including necrotizing meningoencephalomyelitis (NME) and necrotizing leucoencephalitis (NLE)). As SRMA and EME have fairly distinct diagnostic characteristics, the term MUO is introduced to cover the three specific subtypes of NIME that can only be confirmed based on histopathology, including GME, NME and NLE (Granger et al., 2010; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014). No statistics are currently available regarding overall incidence of MUO in the canine population, but early reports quoted a variable incidence for GME of 5–25% of all CNS disorders in dogs (Braund, 1985; Tipold, 1995).

Generally, a diagnosis of MUO is made based on a combination of signalment, neurological examination results, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) analysis (Munana and Luttgen, 1998; Adamo et al., 2007; Granger et al., 2010; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014), although these findings might vary substantially between studies and patients (Wong et al., 2010).

This group of diseases offers both diagnostic and treatment challenges to veterinarians. As the condition is considered fatal without the initiation of appropriate treatment (Munana and Luttgen, 1998; Granger et al., 2010), recent studies have evaluated different treatment modalities and potential prognostic factors.

### *Etiology*

The exact etiology and pathophysiology of MUO are currently unknown and the most current theories have been discussed in a recent literature review (Coates and Jeffery, 2014). Although MUO most likely has a multifactorial pathogenesis, the combination of a genetic predisposition and factors triggering an excessive immunologic response are considered most important (Kipar et al., 1998; Talarico and Schatzberg, 2010; Flegel et al., 2011; Coates and Jeffery, 2014). Suspected triggers include environmental factors and infectious antigens (Schatzberg et al., 2005; Greer et al., 2010; Barber et al., 2012). This, combined with information with the generally positive response to immunosuppressive treatment, suggests that the conditions comprising MUO are immune-mediated diseases (Wong et al., 2010), and the cornerstone of medical treatment is therefore immunosuppressive therapy (Kipar

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et al., 1998; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014).

*Clinical presentation*

Middle-aged toy and terrier breeds are predisposed to GME (Munana and Luttgen, 1998; Adamo et al., 2007; Talarico and Schatzberg, 2010), while NE predominantly affects younger toy and small breed dogs including Pugs, Yorkshire Terriers, Maltese, Chihuahuas, Pekingese, Papillons, Shih Tzus, Coton de Tulears and Brussels Griffons (Talarico and Schatzberg, 2010; Cooper et al., 2014). However, dogs of any breed and age can be affected (Granger et al., 2010; Coates and Jeffery, 2014); a recent study revealed that 25% of dogs diagnosed with MUO were large breed dogs (>15 kg; Cornelis et al., 2016b).

Statistical analysis of 173 GME cases, 53 MUO cases and 69 NE cases, revealed a significant difference in age distribution between dogs affected with GME and NE; dogs with NE were predominantly <4 years old, whereas the peak age for GME was 4–8 years (Granger et al., 2010). In a series of 60 pugs with NE (Levine et al., 2008), the median age at diagnosis was 18 months. In a series of five Chihuahuas with NE (Higgins et al., 2008), the median age at diagnosis was 5 years. In Pugs, fawn females are significantly more often diagnosed with NME compared to black males (Greer et al., 2010). Although it is widely believed that there is a female predominance in GME (Russo, 1979; Braund, 1985; Bailey and Higgins, 1986; Sorjonen, 1990; Munana and Luttgen, 1998), no statistical difference in female:male ratio has been reported in more recent studies (Talarico and Schatzberg, 2010; Granger et al., 2010; Cornelis et al., 2016a,b).

Historically, three histological distribution patterns are described in dogs with GME: multifocal or disseminated, focal, and ocular (Cuddon and Smith-Maxie, 1984; Braund, 1985; Sorjonen, 1990). Each of these distributions has been associated with a different clinical presentation, including an acute onset and rapid progression in dogs with multifocal GME, a more insidious or slower progression in dogs with focal GME, and acute signs of visual dysfunction in dogs with ocular GME (Braund, 1985; Sorjonen, 1990; Zarfoss et al., 2006; Talarico and Schatzberg, 2009; Coates and Jeffery, 2014).

Extraneural signs are rare, but pyrexia can occasionally accompany CNS inflammation (Talarico and Schatzberg, 2010). Common laboratory tests (complete blood count, biochemistry profile, urinalysis) are often within the reference range (Thomas and Eger, 1989; Sorjonen, 1990; Tipold, 1995).

On neurological examination, disease localization was categorized as follows: a) mainly forebrain, brainstem or multifocal for GME; b) focal (forebrain, brainstem) or multifocal in MUO; or c) mainly forebrain in cases with NE (Granger et al., 2010; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014; Cornelis et al., 2016a). Large breed dogs presented significantly more often with identifiable decreased mentation compared to small breed dogs (Cornelis et al., 2016b). Eight percent of dogs diagnosed with GME presented with neurological deficits suggestive of a myelopathy (Granger et al., 2010). The myelopathy could be localised anywhere in the spinal cord, and there were clinical sings ranging from general proprioceptive ataxia to paresis or plegia; spinal hyperesthesia was a common finding (Griffin et al., 2008; Wong et al., 2010; Cornelis et al., 2017a).

*Diagnostic findings*

As previously stated, MUO is a clinical diagnosis that can be achieved based on a combination of signalment, neurological examination results, cross-sectional intracranial imaging abnormalities and CSF analysis (Munana and Luttgen, 1998; Adamo et al., 2007; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014). Granger et al. (2010) systematically reviewed 457 published cases with NIME (including MUO, GME and NE) and formulated guidelines to recruit cases diagnosed with MUO in the absence of a histopathological diagnosis. The following four inclusion criteria have been established: (1) dogs older than 6 months of age; (2) multiple, single or diffuse intra-axial hyperintensities on T2-weighted (T2W) MR images; (3) pleocytosis on CSF analysis with >50% of monocytes/lymphocytes; and (4) rule out of infectious diseases commonly occurring in the specific geographic area (Granger et al., 2010). As stated previously, a definitive diagnosis can only be obtained by histopathological examination (Uchida et al., 2016).

*Cross-sectional imaging*

MRI has been reported to be 94.4% sensitive and 95.5% specific for detecting a brain abnormality, with similarly high performance for classifying neoplastic and inflammatory disease. In contrast, MRI is only 38.9% sensitive for classifying cerebrovascular disease (Wolff et al., 2012). It is also important to note that up to 7% of dogs in one study (2/25 dogs, one diagnosed with GME and one with MUO) showed no abnormalities on T2W MR images (Talarico and Schatzberg, 2010; Granger et al., 2010), which may cause similar cases not to be included in pro – or retrospective studies if no histopathology is available. Equally for CT imaging, up to 14% (5/36 dogs, specific diagnosis not specified) from studies revealed no abnormalities (Granger et al., 2010). Overall, the sensitivity of imaging in identifying all inflammatory abnormalities suspected from the neurological examination remains quite low (<60%; Granger et al., 2010). Additionally, MRI abnormalities were only observed in 76% of cases with inflammatory CSF findings in one study (19/25 dogs; Lamb et al., 2005). Although the use of cross-sectional imaging might aid in differentiating between the different types of idiopathic meningoencephalitides (Talarico and Schatzberg, 2010), no information is currently available regarding the use of MRI to differentiate between histopathologically confirmed cases of GME, NME and NLE.

One study specifically focused on the MRI findings in 11 dogs with histopathologically confirmed GME (Cherubini et al., 2006). The focal, multifocal or diffuse T2W and fluid attenuating inversion recovery (FLAIR) hyperintensities were located in the forebrain, brainstem or cerebellum (Fig. 1). Abnormalities were scattered throughout grey and white matter, showed variable intensity on T1-weighted (T1W) images, and variable degrees of contrast enhancement. Imaging findings suggestive of vasogenic oedema in the white matter were commonly present on T2W images, where meningeal enhancement was not commonly apparent and minimal if present (Cherubini et al., 2006; Talarico and Schatzberg, 2010; Coates and Jeffery, 2014). The distribution of abnormalities on MR imaging (location in grey or white matter) was consistent with the histopathological findings (Cherubini et al., 2006).

The most common MRI abnormalities reported in dogs with NME are asymmetrical, multifocal and located in the forebrain (more severe lesions in parietal and occipital lobes have been described); are hyperintense on T2W and FLAIR images; and typically affect the cortical grey and subcortical white matter with loss of grey/white matter demarcation and variable degrees of contrast enhancement of the parenchymal lesions on T1W post-contrast images (Flegel et al., 2008; Young et al., 2009; Talarico and Schatzberg, 2010; Fig. 2). However, cerebellar and brainstem lesions were also detected in 4/18 and 3/18 cases in one study, respectively (Young et al., 2009). Meningeal enhancement can also be present, accompanied by mass effect and varying degrees of ventriculomegaly (Coates and Jeffery, 2014).

In NLE, multiple asymmetrical cerebral white matter and brainstem abnormalities have been detected (von Praun et al., 2006). These abnormalities were typically hyperintense on T2W

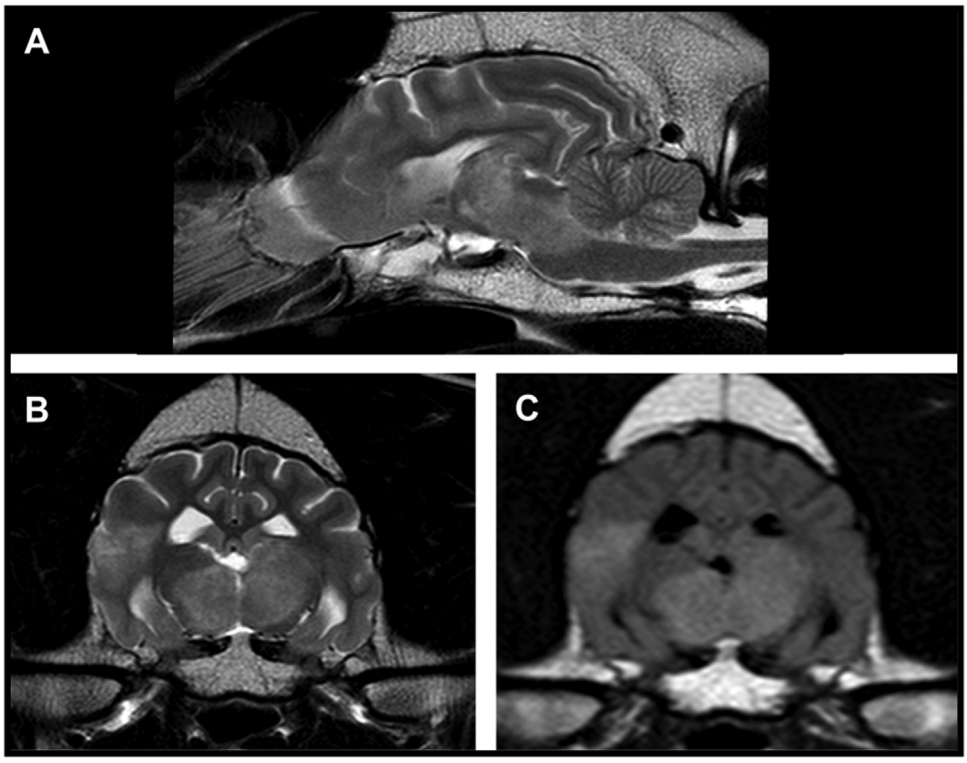


**Fig. 1.** Sagittal (A) and transverse (B) T2W and transverse FLAIR image (C) at the level of the interthalamic adhesion in a 6-year-old female entire Golden retriever with a histopathological diagnosis of GME. Note the diffuse hyperintensities on the T2W and FLAIR images affecting grey (both cortical and deep grey matter) and white matter involving forebrain (temporal lobe) and brainstem (Images courtesy of The Royal Veterinary College, University of London).

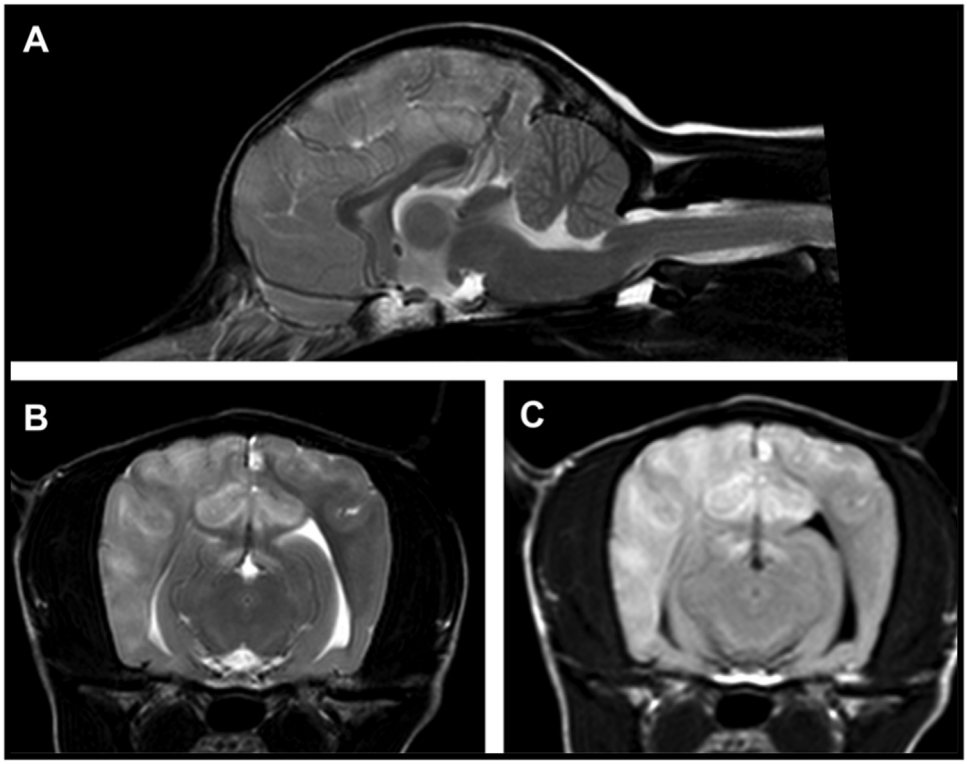


**Fig. 2.** Sagittal (A) and transverse (B) T2W and transverse FLAIR image (C) at the level of the interthalamic adhesion in a 2-year-old female entire Maltese terrier with a histopathological diagnosis of NME. Note the diffuse forebrain hyperintensity affecting the cortical grey and subcortical white matter on the T2W and FLAIR images, involving the frontal, temporal and parietal lobes. Mass effect causing loss of cerebral sulci and occlusion of the right lateral ventricle can be observed. The deep cerebral grey matter, brainstem and cerebellum seem unaffected in the presented case (Images courtesy of The Royal Veterinary College, University of London).

and FLAIR images and often included multiple cystic areas of necrosis. Contrast enhancement of parenchymal abnormalities was minimal in two reported studies (Talarico and Schatzberg, 2010; Coates and Jeffery, 2014). There was lack of meningeal enhancement and mass effect, with varying degrees of ventriculomegaly in a third study (Coates and Jeffery, 2014; Fig. 3).

Fifty-seven dogs with meningomyelitis of unknown origin have been reported, including three dogs with histopathologically confirmed GME (Cherubini et al., 2006; Griffin et al., 2008; Wong et al., 2010; Cornelis et al., 2017a). Imaging findings were available for 36 of the 57 cases, using different types of imaging modalities. Twelve dogs underwent myelography alone or computed tomography (CT) -myelography; there were no abnormalities in 11 dogs and a ventral extradural spinal cord compression in one dog (Wong et al., 2010). MRI was performed in 25 dogs, revealing no abnormalities in three dogs, multifocal poorly demarcated intramedullary T2W hyperintensities with variable contrast enhancement in six dogs, and a focal ill-defined, intramedullary T2W hyperintense and T1W isointense abnormalities with variable contrast enhancement of the parenchymal lesion and/or overlying meninges in 16 dogs (Cherubini et al., 2006; Wong et al., 2010; Cornelis et al., 2017a).

Other imaging modalities, including positron emission tomography (PET) in NME, fluorodeoxyglucose PET (FDG-PET) and single voxel proton magnetic resonance spectroscopy ($^{1}$H MRS) in MUO, and transcranial sonographic findings in GME, were investigated as diagnostic modalities (Eom et al., 2008; Kang et al., 2010; Carvalho et al., 2012; Carrera et al., 2016). However, further studies with larger sample sizes are necessary to evaluate the clinical usefulness of these imaging modalities.

*Cerebrospinal fluid analysis*

Cerebrospinal fluid pleocytosis, defined as an increase in total nucleated cell count (TNCC; reference <5 white blood cells (WBC)/μL), is one of the proposed diagnostic criteria for MUO (Granger et al., 2010). However, the prevalence of CSF cytological abnormalities varies greatly across the literature, possibly due to major differences in methodology and inclusion criteria applied. Additionally, CSF cytology can be normal in 3–57% of dogs with MUO (Menaut et al., 2008; Granger et al., 2010), which is comparable to the results of a study in dogs with GME and NE, where CSF analysis revealed normal cell counts in 16% dogs with GME and 12.5% dogs with NE (Granger et al., 2010). Albuminocytological dissociation can occur in cases with a normal cell counts and increased CSF protein concentrations (Tipold, 1995; Granger et al., 2010). Lymphocytes were the predominant cell type in 42% of GME cases and 71% of MUO cases, whereas monocytes and lymphocytes were found equally in NE; neutrophils were the predominant cell type in <10% of cases in each group (Granger et al., 2010). In summary, most cases had a CSF mononuclear pleocytosis and as such a pleocytosis with >50% mononuclear cells has been proposed as a diagnostic criterion for dogs with MUO (Smith et al., 2009; Granger et al., 2010; Lowrie et al., 2013; Coates and Jeffery, 2014). However, dogs with MRI abnormalities suggesting increased intracranial pressure but where CSF collection is not performed are therefore often excluded from CSF studies, creating a possible bias towards less severe cases (Cornelis et al. 2016a).

Of the 51 reported dogs with meningomyelitis of unknown origin, CSF findings were only available for 22 dogs (Cherubini et al., 2006; Griffin et al., 2008; Cornelis et al., 2017a). Although pleocytosis was seen in all dogs, no definitive conclusions can be drawn as the presence of inflammatory CSF was used as an inclusion criterion in 21 of those dogs (Cornelis et al., 2017a). Total protein measurement was performed in 19 dogs, revealing increased total protein concentration in 17 dogs (ranging from 31–1630 mg/dL; Cherubini et al., 2006; Cornelis et al., 2017a).

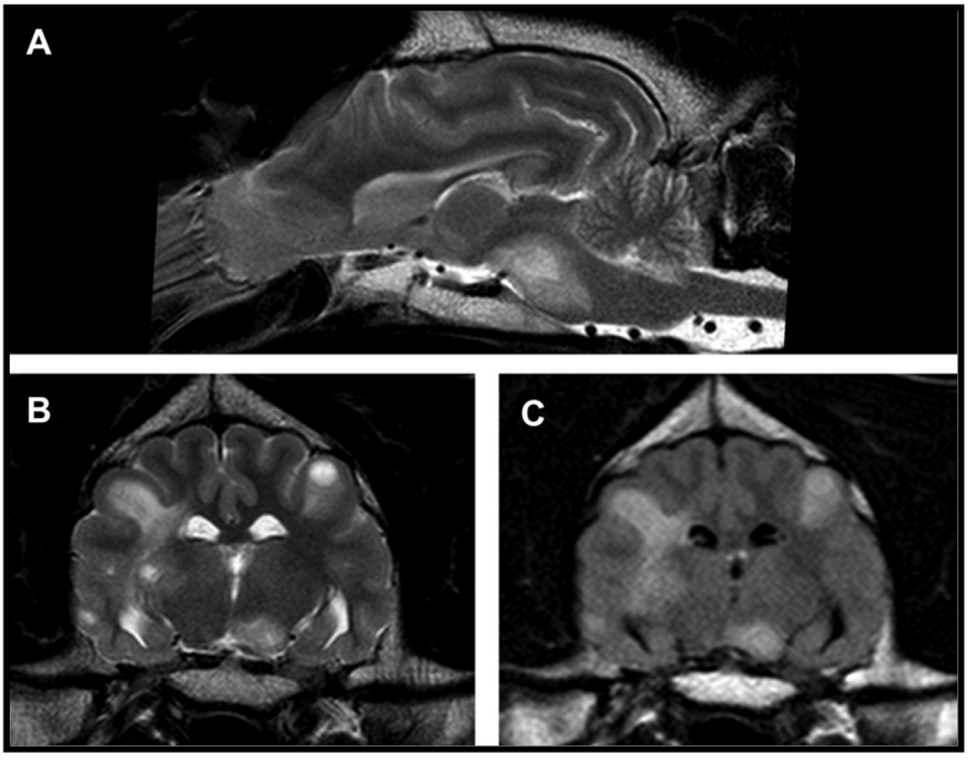


**Fig. 3.** Sagittal (A) and transverse (B) T2W and transverse FLAIR image (C) at the level of the interthalamic adhesion in a 4-year-old male neutered Labrador retriever with a histopathological diagnosis of NLE. Note the multiple hyperintensities mainly affecting the cerebral white matter and the brainstem. Cystic areas were present throughout the forebrain white matter (Images courtesy of The Royal Veterinary College, University of London).

*Biopsy procedures*

Both stereotactic CT-guided brain biopsy procedures (Koblik et al., 1999) and free-hand biopsies through a mini-burr hole (Flegel et al., 2012) have been described in dogs with inflammatory CNS disease, but these are not easily clinically applicable. Diagnostic accuracy ranged from 82% ($n = 17$; Flegel et al., 2012) to 100% ($n = 3$; Koblik et al., 1999), although results should be interpreted with caution due to the relative small sample sizes. None of the dogs died during the procedure. Complications occurred in 12–29% of dogs, including transient epistaxis, transient exacerbation of neurological signs, obtundation progressing to coma, medically uncontrollable seizures, tetraparesis, hemiparesis, ataxia and loss of conscious proprioception (Koblik et al., 1999; Flegel et al., 2012). Most of these signs resolved within 3–14 days (Flegel et al., 2012).

*Treatment*

Although the ideal 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 (Coates et al., 2007; Smith et al., 2009; Coates and Jeffery, 2014). Historically, different inclusion criteria have been used, and because in some studies immune mediated medication was only initiated after results of infectious disease testing were known, resulting in a delay in treatment results, responses and outcomes are difficult to compare (Adamo et al., 2007; Coates et al., 2007; Wong et al., 2010). Additionally, dogs that die within hours of diagnosis (with or without immunosuppressive therapy) are sometimes excluded from enrolment or from further analysis, which inevitably results in improved survival times (Lowrie et al., 2013; Cornelis et al., 2016a; Lowrie et al., 2016). Alternatively, dogs that are treated based on clinical suspicion (lacking a full diagnostic work-up), will also not fulfil the inclusion criteria of most studies, therefore possibly underestimating survival time. Additionally, it is worthwhile mentioning that anesthesia and CSF collection can be associated with side effects, possibly affecting outcome in cases with a complete diagnostic work-up.

As previously stated, the exact etiology and pathophysiology of MUO remains unknown, but the cornerstone treatment modality is generally agreed to be immunosuppressive therapy. Several treatment protocols using different inclusion criteria resulting in different long-term survival times have been reported as a result (Sisson et al. 1989; Gregory et al., 1998; Munana and Luttgen, 1998; Adamo and O'Brien, 2004; Gnirs, 2006; Zarfoss et al., 2006; Adamo et al., 2007; Coates et al., 2007; de Stefani et al., 2007; Feliu-Pascual et al., 2007; Uriarte et al., 2007; Jung et al., 2007; Menaut et al., 2008; Pakozdy et al., 2009; Smith et al., 2009; Granger et al., 2010; Kang et al., 2010; Wong et al., 2010; Flegel et al., 2011; Jung et al., 2011; Jung et al., 2013; Lowrie et al., 2013; Beckmann et al., 2015; Mercier and Barnes Heller, 2015; Barnoon et al., 2016; Cornelis et al., 2016a; Lowrie et al., 2016; Cornelis et al., 2017b).

Overall, treatment effect is monitored by clinical response and resolution of neurologic deficits, and occasionally by repeated CSF analysis and MR imaging (Coates and Jeffrey, 2014). In a small cohort of dogs, Lowrie et al. (2013) suggested that a combination of MR imaging and CSF analysis provided greater sensitivity for prediction of relapse than one modality alone. However, repeating those examinations might be difficult to justify because of the risks associated with anesthesia and CSF collection.

Glucocorticoids such as prednisolone remain the mainstay of treatment initially and in the longer term, are mostly combined with other immunosuppressive drugs as cytosine arabinoside or ciclosporine. A summary of these treatment options can be found in Table 1.

*Other immunosuppressive agents*

Other immunosuppressive agents have been described in combination with prednisolone for treatment of MUO, including azathioprine (Wong et al., 2010), procarbazine (Cuddon, 2002; Coates et al., 2007), lomustine (Uriarte et al., 2007; Flegel et al., 2011), vincristine and cyclophosphamide (Smith et al., 2009), leflunomide (Gregory et al., 1998), and mycophenolate mofetil (Feliu-Pascual et al., 2007; Barnoon et al., 2016).

The following side effects were described in those studies: myelosuppression (19%) and hemorrhagic enteritis (15%) with procarbazine (Coates et al., 2007); leukopenia, severe thrombocytopenia and hemorrhagic gastro-enteritis with lomustine (Flegel et al., 2011); myelosuppression, hemorrhagic cystitis and pyometra with vincristine and cyclophosphamide (Smith et al., 2009); and hemorrhagic diarrhoea within the first 2 weeks of treatment with mycophenolate mofetil (Feliu-Pascual et al., 2007; Barnoon et al., 2016). The side effects encountered with the combination of vincristine and cyclophosphamide were unacceptable to the authors, who excluded this protocol from further investigation (Smith et al., 2009). On treatment with azathioprine ($n = 40$), major adverse events were infrequent but included poor coat or thin skin (13/40), urinary tract infection (3/40), vomiting (3/40), corneal ulcers (2/40), diabetes mellitus (2/40), renal failure, keratoconjunctivitis sicca, cruciate ligament rupture, hepatic mass, mammary gland adenoma, lymphoma, demodectic mange and septic

**Table 1**
A summary of the most commonly used treatment options in dogs with meningoencephalomyelitis of unknown origin (MUO).

| Drug | Number of dogs included | Dose | Side effects | Median survival | References |
|---|---|---|---|---|---|
| Only prednisolone | 116 | 0.5–30 mg/kg/day | Polyuria, polydipsia, panting, muscle weakness, dermatological changes, predisposition to infections, muscle atrophy, insulin resistance, hyperglycemia, vacuolar hepatopathy, and hypercoagulability | 28–602 days | Coates et al., 2007; Pakozdy et al., 2009; Granger et al., 2010; Flegel et al., 2011; Mercier and Barnes Heller, 2015; Cornelis et al., 2017b |
| Cytosine arabinoside | 158 | CRI: 100–300 mg/m$^2$ over 8–24 h SC: 4 SC injections of 50 mg/m$^2$ in 48 h | Myelosuppression, gastro-intestinal upset, transient post-treatment lethargy, dysphagia or limb tremors; mild coat and skin changes (increased shedding or alopecia, mild localized dermatitis; transient to intermittent pelvic limb weakness; infiltrative lung disease; anterior uveitis; calcinosis cutis and deep pyoderma at the injection site | 26–1063 days | Cuddon, 2002; Zarfoss et al., 2006; de Stefani et al., 2007; Menaut et al., 2008; Smith et al., 2009; Lowrie et al., 2013; Lowrie et al., 2016 |
| Ciclosoporine | 26 | 3–15 mg/kg PO every 12 h | Hypertrichosis; transient lymphopenia; vomiting; severe gastro-intestinal adverse effects with life-threatening anemia | 236–930 days | Adamo and O'Brien, 2004; Gnirs, 2006; Adamo et al., 2007; Jung et al., 2007; Pakozdy et al., 2009; Kang et al., 2010; Jung et al., 2013 |

arthritis of a single joint. However, many of the adverse effects, including weight gain, poor coat, hypertriglyceridemia, thrombocytosis, and elevated liver enzyme activities, could have been associated with concurrent administration of glucocorticoids (Wong et al., 2010).

Median survival times (MSTs) were available for some studies and are as follows: 425 days for procarbazine (Coates et al., 2007), 150–740 days for lomustine (Uriarte et al., 2007; Flegel et al., 2011), 198 days for vincristine and cyclophosphamide (Smith et al., 2009), 250 days for mycophenolate mofetil (Barnoon et al., 2016), and 1834 days for azathioprine (Wong et al., 2010).

*Radiation therapy*

Three studies comprising 17 dogs examined the additional effects of radiation therapy (Sisson et al., 1989; Munana and Luttgen, 1998; Beckmann et al., 2015). This resulted in MSTs of 404–476 days, without any early or late radiotherapy reactions (Munana and Luttgen, 1998; Beckmann et al., 2015).

*Prognostic factors*

As MUO is generally considered a fatal disease (Munana and Luttgen, 1998), multiple studies have attempted to identify prognostic factors for dogs diagnosed with MUO. Unfortunately, as most studies have included relatively small numbers of dogs receiving different treatment regimens, conflicting results have been reported, making the majority of findings difficult to apply in a clinical setting.

Younger age at time of diagnosis was significantly associated with improved survival in 52 dogs with MUO (Oliphant et al., 2017). In 42 dogs with GME, Munana and Luttgen (1998) reported significantly longer STs with focal (21 dogs) vs. multifocal (21 dogs) neurological signs. Additionally, dogs with focal forebrain signs had a significantly longer STs compared to dogs with focal signs related to other areas of the CNS. Dogs with focal forebrain signs that underwent radiation therapy had a significantly longer ST compared to dogs with focal forebrain signs that did not undergo radiation therapy (Munana and Luttgen, 1998). The finding of increased survival for dogs with focal neurological signs was, however, not repeated in more recent studies, including a total of 187 dogs with MUO (Coates et al., 2007; Lowrie et al., 2013; Cornelis et al., 2016a). Dogs presenting specifically with seizures or altered mentation had significantly shorter STs (Bateman and Parent, 1999; Coates et al., 2007; Granger et al., 2010) and a significantly higher risk of dying within the first week after diagnosis (Cornelis et al., 2016a). A significantly longer MST was recorded in 25 dogs that were presented within 7 days of onset of clinical signs, compared to those presented after more than 7 days, suggesting that early diagnosis and treatment might influence survival time (Barnoon et al., 2016).

One study identified a lower CSF TNCC as significantly associated with improved survival in 52 dogs with MUO (Oliphant et al., 2017), while others found that neither CSF TNCC nor protein concentration had an effect on survival time in 148 dogs with MUO (Coates et al., 2007; Cornelis et al., 2016a). The study by Lowrie et al. (2013) failed to demonstrate an association between normal CSF analysis and improved outcome, but did find an association between abnormal CSF analysis and relapse or poor outcome in 39 dogs with MUO (Lowrie et al., 2013). In the study by Mercier and Barnes Heller (2015), CSF analysis was repeated 1 month after diagnosis in 16 dogs with MUO, and results suggested that serial CSF analysis might be a valid tool for monitoring success or failure of treatment in dogs diagnosed with MUO and treated with glucocorticoid monotherapy. It should be noted that CSF analysis always carries a risk of complications, including neurologic deterioration and/or death, and the clinician should always weigh any benefits against potential risks. Additionally, repeat CSF analysis is performed under general anesthesia and can be cost-prohibitive.

Various findings on MR imaging have been evaluated for their possible prognostic value, but to date midline brain shift in 52 dogs with MUO (Oliphant et al., 2017), contrast enhancement on T1W images, and lesion burden in 18 Pug dogs with NME (Young et al., 2009), and the presence of focal, multifocal or diffuse abnormalities, including anatomical localisation, mass effect, brain herniation, parenchymal and meningeal contrast enhancement in 116 dogs with MUO (Cornelis et al., 2016a) were not associated with survival. However, mass effect, loss of identifiable cerebral sulci and foramen magnum herniation were all significantly associated with increased risk of mortality in dogs with MUO, but the association with prognosis was poor for these findings and none were predictive of long-term outcome (Lowrie et al., 2013; Lowrie et al., 2016). Resolution of MRI abnormalities 3 months after diagnosis was associated with a good outcome in 39 dogs with MUO (Lowrie et al., 2013).

In one study, relapse was recorded in 65% of 39 dogs within a median of 210 days after diagnosis (Lowrie et al., 2013). This study revealed that abnormal CSF analysis at 3 months was associated with higher risk of relapse, but the combination of MRI and CSF analysis provided greater sensitivity for predicting relapse than one modality alone. Discontinuation of treatment before resolution of MRI abnormalities always resulted in relapse (Lowrie et al., 2013).

*Outcome*

Published studies suggest that 15% of dogs with GME die before being treated (Munana and Luttgen, 1998; Granger et al., 2010). Despite the initiation of appropriate and aggressive immunosuppressive treatment, 56% of dogs in one study died or were euthanased because of MUO, and 33% of these dogs did so within 3 days after diagnosis (Lowrie et al., 2013). Cornelis et al. (2016a) reported similar results; 25% of dogs in a study of 116 dogs died or were euthanased within 7 days after diagnosis, despite initiation of appropriate treatment. Levine et al. (2008) reported that dogs with NME that had received any form of treatment had a significantly longer mean ST than those that received no treatment. Most dogs with MUO or GME that die, do so within the first 3 months after diagnosis (Thomas and Eger, 1989; Smith et al., 2009; Lowrie et al., 2013). Eighteen of nineteen dogs (95%) survived for 1 month in one study (Smith et al., 2009), but only one of those dogs failed to survive for 1 year. Additionally, dogs that survived for 1 year often lived for a relatively long period beyond this, suggesting that animals alive after 1 month might have a relatively good chance of living several more years (Smith et al., 2009).

In the published literature, 57 dogs with MUO have been described and follow-up information was available for 50 dogs. Overall, 30/50 dogs (60%) died or were euthanased because of their disease, and 18 dogs were alive at time of data capture (Griffin et al., 2008; Wong et al., 2010; Cornelis et al., 2017a). Spontaneous death in cases diagnosed with meningomyelitis of unknown origin might have been caused by progression of the disease with involvement of the brain, although further studies are needed to confirm these findings.

*Closing remarks*

MUO is a disease entity that is characterised by variable pathologies, and many questions remain about its pathogenesis, diagnostic criteria, the most appropriate treatment protocol, short and long-term prognosis and outcome. From a clinical point of view, performing all diagnostic tests to reach a (more certain)

diagnosis may be cost prohibitive, could result in neurologic deterioration and even possibly delay appropriate treatment. Additionally, brain biopsy to obtain a definitive diagnosis is limited in availability and is associated with significant risk of adverse outcome. Why do some animals survive for years with or without therapy in a disease that is considered often fatal? Was the initial diagnosis inaccurate? What is the best treatment option, if this exists? What is the best way to evaluate the effect of therapy? Is it better to evaluate treatment outcome by clinical improvement or by means of further quantitative investigations? Does repeat CSF sampling and/or MRI give an accurate reflection of therapeutic success and is the benefit of repeated anesthesia and CSF collection worth the risk of collection? Different inclusion criteria make interpretation of and comparisons between previous studies difficult and consideration should be given to revisiting the strict diagnostic criteria used. This might enable multicentre clinical studies to further characterise the clinical presentation, diagnostic findings, treatment outcome and prognosis in dogs with presumed MUO, by accepting the possibility that not all dogs will have met all the inclusion criteria in previous studies. Further investigation of genetic factors and possible triggers should also be undertaken.

## Conclusion

As a histologic diagnosis is not generally available ante mortem, the clinician should rely on previously established clinical diagnostic criteria used for the diagnosis of MUO. MUO is the most common cause of meningoencephalitis in dogs in countries where canine distemper virus infection is rare and it is generally considered to mainly affect young to middle aged, medium to small breed toy and terrier breed dogs. However, the results of recent studies indicate that dogs of all breeds and all ages can be affected. MRI is considered the imaging modality of choice for the diagnosis of intracranial or spinal cord abnormalities that are consistent with inflammatory CNS disease. Criteria for differentiating different pathologic forms of MUO (GME, NME and NLE) have not been determined on the basis of MRI findings, and the importance of this distinction clinically or with respect to pathogenesis, treatment and outcome has not been determined. Immunosuppressive drugs are recognized as the main treatment for MUO. Several studies have reported on long-term outcome in MUO, and reported MSTs range from 28–1834 days. Two studies suggested that 25–33% of dogs will die within 1 week after diagnosis, despite the initiation of appropriate treatment. It is currently unclear why some dogs respond favourably to treatment, while others do not, despite appropriate treatment. Further studies are necessary to explore the underlying etiology and pathophysiology of MUO, to identify diagnostic indicators that may standardize clinical diagnosis, to develop evidence-based treatment protocols, and to identify clinically reliable prognostic indicators.

## Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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