

Granulomatous meningoencephalomyelitis in dogs: A review

Emma J. O'Neill¹, Darren Merrett² and Boyd Jones¹

¹Department of Small Animal Clinical Studies, Faculty of Veterinary Medicine, University College Dublin, Ireland.

²Melbourne Veterinary Referral Centre, Glen Waverley, Victoria, Australia.

Granulomatous meningoencephalomyelitis (GME) is an inflammatory disease of the central nervous system in dogs that is characterised by focal or disseminated granulomatous lesions within the brain and/or spinal cord, non-suppurative meningitis and perivascular mononuclear cuffing. The aetiology of the disease remains unknown, although an immune-mediated cause is suspected. This article reviewed the typical history, clinical signs and pathology of the condition along with current opinions on pathogenesis. The potential differential diagnoses for the disease were discussed along with current treatment options.

Key words

Dog,
Brain,
Granulomatous
meningoencephalomyelitis.

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Introduction

Granulomatous meningoencephalomyelitis (GME) is an idiopathic inflammatory condition of the central nervous system (CNS) in dogs that was first reported by Braund and colleagues in 1978. Since that report it has been observed worldwide (Cordy, 1979; Glastonbury and Frauenfelder 1981; Alley *et al.*, 1983; Maeda *et al.*, 1993, 1994; Demierre *et al.*, 2001). Early reports quoted a variable incidence of between 5% and 25% of all CNS disorders in dogs (Cuddon and Smith-Maxie, 1984); more recent prevalence information is unavailable.

Pathology

Histologically, GME lesions occur predominantly within the white matter of the CNS, characterised by dense aggregates of inflammatory cells arranged in whorling patterns around blood vessels. These perivascular cuffs (Figure 1) comprise principally macrophages along with varying numbers of lymphocytes, monocytes, plasma cells, and lesser numbers of neutrophils and multinucleate giant cells (Braund *et al.*, 1978; Cordy, 1979; Braund, 1985; Kipar *et al.*, 1998). Lymphocytes and macrophages represent the dominant cell types in the lesions;

however, marked variation is described: some granulomas being principally lymphoid, some not perivascular, and some with eccentric development of a granuloma from an existing perivascular cuff (Alley *et al.*, 1983; Braund, 1985; Kipar *et al.*, 1998). Typically, lesions are widely distributed within the CNS but they occur most commonly within the white matter of the cerebrum, cerebellum, caudal brainstem or cervical spinal cord. Comparable lesions may also be observed in grey matter and there may be lesions involving the vasculature of leptomeninges

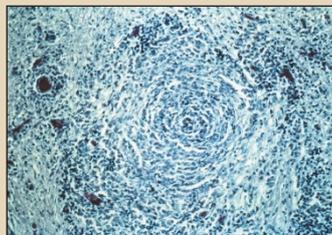
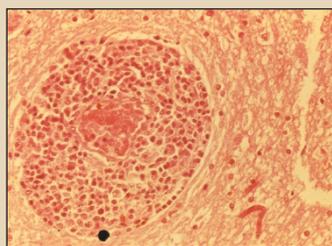


FIGURE 1: Sections from brains of GME cases:
A) Section showing a characteristic perivascular cuff lesion around a blood vessel comprising a predominantly mononuclear inflammatory cell infiltrate. Haematoxylin and Eosin. Original magnification x40 (top left).
B) Section demonstrating characteristic 'whorling' pattern of inflammatory cells within the CNS white matter. Reticulin-staining. Original magnification x20 (bottom left).

Address for correspondence:

Emma J. O'Neill

Department of Small Animal Clinical Studies,
Faculty of Veterinary Medicine, University College Dublin, Republic of Ireland

E-mail: emma.oneill@ucd.ie

Tel: +353 1 716 6025

Fax: +353 1 716 6023

Abbreviations:

CT: computed tomography, CDV: canine distemper virus, CN: cranial nerve, CNS: central nervous system, CSF: cerebrospinal fluid, DTH: delayed-type hypersensitivity, GME: granulomatous meningoencephalomyelitis, MHC: major histocompatibility, MRI: magnetic resonance imaging, PCR: polymerase chain reaction, UMN: upper motor neuron.

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or choroid plexus (Braund, 1985; Sorjonen, 1987a). Three forms of GME have been described, based primarily on the presenting clinical signs, namely: focal, disseminated (multifocal) and ocular (Braund, 1985; Sorjonen, 1987a). However, in both focal and disseminated forms, the lesions are usually widely scattered throughout the CNS; in the focal form there is a coalescence of neighbouring granulomas to give rise to a space-occupying lesion that is responsible for the clinical signs of a focal lesion (Braund, 1985; Gearhart *et al.*, 1985; Sorjonen, 1987b; Thomas and Eger, 1989). Focal lesions are reported to be more common in the cerebrum and brainstem (Braund, 1985; Munana and Luttgen, 1998).

There has been some confusion in the terminology used to describe GME, particularly in earlier reports where the term ‘reticulosis’ was used to describe the disease (Reviewed: Cuddon and Smith-Maxie, 1984). Reticulosis refers to “an abnormal increase in cells derived from, or related to, the monocyte macrophage” (Cuddon and Smith-Maxie, 1984). Since the lesions of GME represent an accumulation of macrophages, by definition GME would represent a subset within the broader category of reticulosis. The historical description of reticulosis involved further classification of cases as either inflammatory or neoplastic reticulosis based on histopathological features such as mitotic index and cellular pleomorphism (Cuddon and Smith-Maxie, 1984). The use of this terminology has been largely superseded; it is generally accepted that GME and inflammatory reticulosis are terms that have been used to describe the same condition (Cordy, 1979; Gearhart *et al.*, 1985; Thomas and Eger, 1989). In addition, as immunohistochemical staining methods have been applied to some of the archived tissue sections, it has been shown that some cases previously classified as neoplastic reticulosis may be more correctly referred to as CNS lymphosarcoma (Vandeveld *et al.*, 1981).

Pathogenesis

The pathogenesis of GME is unknown; however, three possible aetiologies have been considered:

- a) An **infectious aetiology** has been suggested by some authors (Braund, 1985). However, compelling evidence for any one infectious agent has not been presented.
- Several authors have suggested that, in view of the increased

recognition of GME as the cases of distemper decline with routine vaccination (Braund, 1985), GME may reflect an aberrant response to canine distemper virus (CDV), or even a modified immune response after vaccination. However, there have only been sporadic reports in the literature identifying CDV in GME cases, employing either immunohistochemistry (Vandeveld *et al.*, 1978) or serology (Sorjonen, 1987b). In addition to their sporadic nature, these results have not been corroborated by others (Thomas and Eger, 1989; Kipar *et al.*, 1998); nor have newer techniques, such as PCR, provided supportive evidence (Haley *et al.*, 2003). Negri body-like inclusion bodies and *Toxoplasma*-like organisms have been reported within lesions; however, the occurrence of GME within countries known to be rabies-free (Glastonbury and Frauenfelder, 1981; Alley *et al.*, 1983) and negative serology results for protozoal organisms in large studies (Tipold, 1995) would tend to argue against these aetiologies.

- Sutton and Atwell (1982) reported GME in two dogs after treatment with levamisole (a known immunostimulant); along with the reported occurrence of inflammatory CNS lesions following levamisole administration (Vandeveld *et al.*, 1978), this may suggest a reaction to a previously latent antigen, possibly of infectious origin.
- A possible aetiological relationship with LaCrosse virus has been proposed based on similar histopathological findings (Tatum *et al.*, 1999).
- Some authors have speculated on the possibility of a retroviral infection, possibly a vaccine contaminant (Summers *et al.*, 1995).
- A report of GME in two related, co-housed Afghans (Harris *et al.*, 1988) could suggest an environmental, genetic or infectious cause.
- b) An **immune-mediated aetiology** has been suggested by Kipar *et al.* (1998) and by Wong and Sutton (2002). Immunohistochemistry demonstrated that inflammatory cells within GME lesions consisted predominantly of MHC Class II antigen-positive macrophages and CD3 antigen-positive T lymphocytes (Kipar *et al.*, 1998). These findings are suggestive of a T cell-mediated delayed-type hypersensitivity (DTH) reaction.

TABLE 1: GME cases: the characteristic history and patient data, with variations

	Classically but there is marked variability
Age	Young adults – middle aged dogs (mean approximately 5 years) (Munana and Luttgen, 1998; Braund, 2003)	5 months – 12 years (Sorjonen, 1987a; Thomas and Eger, 1989; Braund, 2003)
Breed	Small breed dog especially toy and terrier breeds and Poodles (Bailey and Higgins, 1986; Braund, 2003)	ANY breed may get GME, e.g., German shepherd dogs, Great Danes, Pointers, Weimeraners (Braund <i>et al.</i> , 1978; Gearhart <i>et al.</i> , 1985; Sorjonen, 1987a)
Sex	GME occurs in both sexes; however, there appears to be a higher prevalence in females (Sorjonen, 1987a; Bailey and Higgins, 1986; Munana and Luttgen, 1998; Demierre <i>et al.</i> , 2001).	

c) Finally, and particularly with large focal GME lesions, a **neoplastic cause** has been postulated since such lesions may have a variable mitotic index and varying degrees of cellular pleomorphism (Cuddon and Smith-Maxie, 1984). It has certainly been demonstrated that, on occasion, focal GME may represent the misdiagnosis of a lesion that is actually CNS lymphoma or neoplastic histiocytic disease (Vandeveldel *et al.*, 1981).

History and patient data

GME occurs most commonly in young adult small-breed dogs (Cuddon and Smith-Maxie, 1984; Munana and Luttgen, 1998; Demierre *et al.*, 2001). However, there is a wide variation in reported patient data. **Table 1** is included to highlight both the ‘classical’ data reported along with variations that have become apparent as more reports of the condition have been published.

Syndromes and clinical signs

As is the case with the majority of CNS diseases, the clinical signs observed in an animal with GME primarily reflect the location of the inflammatory lesions within the CNS rather than being specific for the disease itself. **Table 2a** summarises the typical clinical signs that are observed with lesions in each of the

main regions of the brain. **Table 2b** provides a summary of the clinical signs that have been observed in the GME cases reported in the literature.

Animals with the disseminated form of the disease have signs reflecting dysfunction of two or more of the following: cerebrum, brainstem, cerebellum, spinal cord, meninges, and optic nerves. This disseminated form accounts for approximately 50% of the GME cases and has generally been accepted to occur with acute onset (Russo, 1979; Braund, 1985; Munana and Luttgen, 1998).

The focal form of GME is characterised by signs attributable to a single space-occupying lesion. The more commonly reported signs reflect lesions within the cerebrum and brainstem. However, clinical signs can reflect a lesion at any location within the CNS. Focal GME also accounts for approximately 50% of the presentations and, typically, it has been associated with a slower onset, e.g., three to six months (Braund, 1985; Munana and Luttgen, 1998).

Despite this historical perception that the disseminated form has an acute onset and the focal form has a more chronic presentation, there is considerable variability (Jones, Merrett and O’Neill, unpublished data). In addition, this viewpoint that the disease time course correlates with the focal and

TABLE 2a: Summary of the clinical signs typically associated with lesions in specific regions of the brain (adapted from Braund, 2003)

Fore brain: cerebral cortex and thalamus	Cerebellum
Seizures	Ataxia
Behavioural changes (loss of training, failure to recognise owner, aggression, hyperexcitability)	Tremor
Altered mental status (apathy, depression, disorientation, lethargy, coma)	Hypermetria
Abnormal movements, postures (circling, pacing, wandering, head-pressing)	Broad-based stance
Contralateral deficits: postural reactions, vision, menace response, facial sensation	Menace deficits + normal vision
	No weakness
Midbrain	Hypothalamus
Upper motor neuron paresis/paralysis all four limbs or contralateral to lesion	Normal gait
Postural reaction deficits all four limbs or contralateral to lesion	Altered mental status (disorientation, lethargy, coma)
Mental depression/coma	Changes in behaviour (aggression/hyperexcitability)
Ipsilateral oculomotor and trochlear deficits	Bilateral cranial nerve II deficits at optic chiasm
Hyperventilation	Abnormal movements/postures (tight circling, pacing, wandering, head-pressing, trembling)
	Abnormal temperature regulation
	Abnormal appetite
	Endocrine disturbances
	Seizures
Vestibular system (CNS component)	Brain stem
Head tilt	Ipsilateral hemiparesis/asymmetrical tetraparesis:
Nystagmus – positional, vertical, horizontal, rotary	Upper motor neuron signs
Ataxia	Ipsilateral postural reaction deficits
Postural reaction deficits	Cranial nerve abnormalities: V-VII, IX-XII
Altered mental status	Altered mental status: depression
Other cranial nerve signs	Irregular respiration

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FIGURE 2: Cerebrospinal fluid cytology demonstrating mononuclear cell pleocytosis in a case of GME. Original magnification $\times 40$.

disseminated forms has more recently been challenged by Demierre *et al.* (2001) who found that the disease course was not correlated with the size of lesions but rather with the extent of mast cell infiltration.

The ocular form of GME is uncommon and is usually characterised by sudden onset of blindness due to optic neuritis, occasionally with uveitis and more rarely with retinal haemorrhage or detachment (Gelatt, 2000). Typically, the disease is bilateral but it can be unilateral. Some dogs that initially present with the ocular form may later progress to develop other neurological signs (Braund, 1985).

Diagnosis

Routine screening blood tests are often unrewarding for making a diagnosis of GME (Braund, 2003). In some cases mild to moderate leukocytosis is observed (Sorjonen, 1987a; Tipold, 1995), although frequently the rise is within the range encountered with 'stress' responses (Sorjonen, 1987a) and elevations are not seen in the majority of cases (Tipold, 1995). Whilst CSF analysis is the mainstay of diagnosis (Bailey and Higgins, 1986), considerable variation in the findings may be encountered. **Table 3** shows the classical features of GME and variations that may be expected. **Figure 2** shows CSF cytology from a GME case.

Of the few reports of magnetic resonance imaging (MRI) and computed tomography (CT) scanning of GME lesions, most have yielded evidence of space-occupying lesions that cannot be definitively differentiated from neoplastic lesions (Dzyban and Tidwell, 1996; Speciale *et al.*, 1992). In one report of 12 histopathologically confirmed GME cases that underwent CT scanning, the only statistically significant differentiating feature of GME cases was the hyperdense appearance of the lesion prior to contrast enhancement (Gibbons *et al.*, 1999). Variable MRI findings have been reported (Lonbetti and Pearson, 1995). Unsurprisingly, there are no reports of detection of the (microscopic) disseminated lesions.

Brain biopsy is required to make a definitive antemortem diagnosis of GME and, in particular, to differentiate focal GME lesions from neoplastic disease (Summers *et al.*, 1995).

TABLE 2b: The frequency of clinical signs described in 151 GME cases reported in the literature

It should be noted that these numbers represent an approximation only. The major limitation is that papers vary in the details given and in their classification of the clinical signs. Some listed the specific clinical signs, others listed the affected regions of the brain. Here the signs are listed as they were given in the papers (from Braund *et al.*, 1978; Glastonbury and Frauenfelder, 1981; Alley *et al.*, 1983; Gearhart *et al.*, 1985; Bailey and Higgins, 1986; Sorjonen, 1987b; Thomas and Eger, 1989; Munana and Luttgen, 1998; Harris *et al.*, 1988; Speciale *et al.*, 1992; Tipold, 1995; Lonbetti and Pearson, 1995; Dzyban and Tidwell, 1996).

Clinical signs	Number of cases
Head tilt	6
Circling	7
Nystagmus	1
Seizures	11
Behavioural changes	7
Depression	10
Ataxia	22
Gait abnormalities	16
Proprioceptive deficits	16
Postural reaction deficits	5
Dysmetria	11
Exaggerated reflexes	8
Tremors	6
Hyperaesthesia	15
Pelvic/thoracic limb paresis	17
Cranial nerve deficits	17
Blindness/optic neuritis	15
Facial paralysis	1
Febrile	19
Cervical pain	37
Forebrain	25
Brainstem	15
Vestibular	13
Cortical	11
Cerebellar/vestibular	10
Myelopathies	7
Spinal cord	4
Cerebellar	3

Differential diagnoses

As discussed above, the observed clinical signs most typically relate to the location of the lesion rather than to its nature (Braund, 2003). Hence, the list of differential diagnoses to be considered is often large. The clinical detection of a diffuse CNS disease is most suggestive of infectious, inflammatory or neoplastic disease. Signs of a focal CNS lesion can occur with any space-occupying lesion (e.g., neoplasm, inflammatory granuloma, cyst, or infarct). Furthermore, there are numerous potential causes of optic neuritis. Hence, the clinical findings are far from specific.

CSF analysis demonstrating a mononuclear pleocytosis may be consistent with:

a. Viral encephalitides (e.g., canine distemper)

In order to rule out canine distemper, one must perform canine distemper virus antibody titres or canine distemper virus PCR on CSF samples.

b. Protozoal encephalomyelitides (e.g., toxoplasmosis, neosporosis)

These diseases represent major differential diagnoses (Braund, 2003) and in order to differentiate them from GME one should carefully assess the patient for extra-CNS disease. In addition, serum titres for antibodies or CSF/serum PCR for organism can be evaluated.

c. Fungal encephalomyelitides (e.g., cryptococcosis)

Fungal CNS infection typically gives rise to a greater eosinophilic component in the CSF and fungal elements may be identified in the CSF (Braund, 2003).

d. Necrotising meningoencephalitides

There are several sporadic reports of clinically acute and severe, multifocal, diffuse CNS diseases; typically characterised by non-suppurative necrotising meningoencephalitis. Such ‘syndromes’ are recognised as clinical entities affecting particular breeds: for example, pyogranulomatous meningoencephalitis of Pointers (Braund, 1980) and Pug dog encephalitis (Cordy and Holliday, 1989), which is recognised also in Maltese terriers (Stalis *et al.*, 1995), Pekingese (Cantile *et al.*, 2001) and Yorkshire terriers (Jull *et al.*, 1997). These separate disease entities are typically associated with a particular constellation of clinical signs and would be suspected in dogs of the relevant breed demonstrating compatible clinical signs and changes in the CSF.

e. Neoplasia

Some cases of CNS lymphoid or histiocytic neoplasia are misdiagnosed as “GME” (Vandeveldel *et al.*, 1981; Cuddon and Smith-Maxie, 1984; Suzuki *et al.*, 2003). This is not surprising since the CT/MRI appearance can be identical and, on occasion, particularly with meningiomas (Gibbons *et al.*, 1999), there can be significant overlap between findings on CSF analysis (Tippold, 1995).

Treatment

The traditional mainstay of therapy has been corticosteroids, in particular prednisolone used at immunosuppressive doses (2 mg/kg/day) tapered with response over the following months to achieve the lowest dose possible that controls signs (Platt, 2002). It is uncommon for corticosteroid therapy to be terminated. Patients often have a good initial response, but as the dose is tapered, or with time, signs often recur and subsequently prove difficult to control with an increased dose of prednisolone. Sometimes, reducing the dose of prednisolone that had resulted in control of clinical signs can result in a severe recurrence of signs and it has not always been possible to regain control (D. Merrett, unpublished data).

Of late there seems to have been a noticeable increase in the number of alternative agents that have been used to manage this condition. Unfortunately, each treatment typically involves small numbers of cases, making it impossible to draw significant conclusions on the efficacy or advantage of each individual agent. Some of the agents that have been used for GME are listed below:

- Azathioprine has been administered in combination with corticosteroids to allow the dose of the steroid to be reduced to avoid undesirable side effects of prolonged steroid

TABLE 3: CSF in granulomatous meningoencephalomyelitis: the classical findings, variations and the responses to treatment with corticosteroids

	Classically but there is marked variability
Leucocyte count (cells/μL)	50 – 900 (Braund, 2003)	0 – 11,840 Occasional cases (~10%) may have normal leucocyte counts (Thomas and Eger, 1989).
Cytology	Mononuclear pleocytosis usually consisting of lymphocytes (60 to 90%), monocytes (10 to 20%) and variable numbers of large macrophages with lacy cytoplasm (Braund, 2003)	Occasional cases (~10%) may have up to 50-60% neutrophils (Bailey and Higgins, 1986; Munana and Luttgen, 1998). Some cases with relatively fewer lymphocytes than monocytes (Bailey and Higgins, 1986).
Protein (g/L)	40 to 400 (Braund, 2003)	9 to 1,848 (Munana and Luttgen, 1998) Occasional cases (~5 to 10%) may have normal protein concentrations (Tippold, 1995).
Corticosteroid response	In one study, eight dogs were treated with corticosteroids prior to CSF analysis and the mean WCC and protein content of the CSF of these dogs did not differ significantly from non-treated cases (Bailey and Higgins, 1986). In another study of 16 CSF samples analysed, the only two samples that were normal were in dogs previously treated with corticosteroids (Demierre <i>et al.</i> , 2001). <i>However, it should be noted that the great variability of dose, the nature and the timing of prior therapy make it impossible to draw conclusions other than to say that prior treatment with corticosteroids can possibly have “some” effect on CSF analysis.</i>	

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administration (Jones, Merrett and O'Neill, unpublished data).

- Cytosine arabinoside – an antineoplastic agent that acts on dividing cells by blocking pyrimidine synthesis and causes premature termination of the DNA chain. This drug has been used to treat lymphoma and myeloproliferative diseases and recent reports demonstrated success in controlling GME signs (Cuddon *et al.*, 2002; Nuhsbaum *et al.*, 2002).
- Procarbazine – an antineoplastic agent that damages DNA and affects protein and RNA synthesis. This agent has also been recently reported to have a positive effect on control of GME lesions (Cuddon *et al.*, 2002).
- Cyclosporine, a potent suppressor of T cell function, has also been used with some benefit in a small number of cases (Adamo and O'Brien, 2004).

Radiation therapy, either focally directed or whole brain, has been described in a few papers. In one study, seven of 42 dogs received radiation therapy, of which six had focal forebrain signs and one dog had multifocal signs (Munana and Luttgen, 1998). The dog with multifocal signs did not respond and was euthanased shortly after completion of the course of radiation therapy. The six irradiated dogs had significantly longer survival times than the other dogs with focal forebrain signs that did not receive radiation therapy (treated with corticosteroids): the median survival time of irradiated dogs was more than 404 days (longest surviving patient more than 1,215 days), whereas the median survival time of dogs not irradiated was 41 days (longest surviving patient approximately 800 days).

Prognosis

GME has a poor prognosis. Most studies offer the generalisations that dogs with multifocal disease typically have a short survival (e.g., up to six weeks after diagnosis) and dogs with focal disease usually have a longer survival (e.g., three to six months). There are single case reports of dogs responding for longer periods. However, large prospective studies monitoring clinical responses to the newer treatment modalities are lacking and are greatly needed to allow an accurate prognosis to be given. It is the authors' perception that the current literature provides a more negatively biased impression of the disease. Whilst the disease does carry a guarded prognosis, some individuals will respond to treatment for a considerable period of time.

Conclusions

- The presentation of GME can be extremely variable. Patients can present with acute or chronic, focal or multifocal CNS signs, suggesting pathology at many levels of the CNS.
- GME is a difficult disease to definitively diagnose since there are many differentials for the presenting signs and the finding of a mononuclear pleocytosis in CSF.
- Corticosteroids currently remain the mainstay of therapy but, because of the less-than-ideal survival time, there is active interest in a number of other agents.

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